

Tuning of cytoplasmic effective viscosity via active noise

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The mechanical properties of cytoplasm are crucial for cellular functions. While active processes significantly alter cytoplasmic viscoelasticity, the physical mechanisms remain elusive. Here, we model the cytoplasm as a colloidal suspension subject to passive and active noise, quantified by an effective temperature. We demonstrate that a jammed cytoplasm undergoes a transition from solid to liquid phase at a critical effective temperature. Intriguingly, the simulated complex shear modulus at the critical state exhibits a $1/2$ power-law scaling with frequency and quantitatively matches the experimental data of live cells, given that the cytoplasmic volume fraction is slightly above the jamming transition. We further reveal the biological significance of the cytoplasm being slightly above jamming: It is a regime in which the effective viscosity, the magnitude of complex viscosity, is sensitive to changes in the effective temperature. Our results suggest that cells actively regulate their volume fraction into the sensitive regime, where they can efficiently tune cytoplasmic viscoelasticity through active processes.

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Introduction. The mechanical properties of cytoplasm are crucial determinants of cells' physiological functions in diverse biological contexts [1–7]. Understanding the factors that regulate the viscoelasticity of the cytoplasm is thus paramount for comprehending cell behavior and function. Experiments have suggested that cytoplasm is a crowded suspension of biomolecules resembling colloidal systems of deformable particles [8–10]. A critical feature that distinguishes cytoplasm from passive systems is the active, energy-consuming processes inherent to living cells. Experiments have measured the viscoelastic properties of cytoplasm for mammalian cells [11–20]. Interestingly, at low frequencies, the storage modulus of live cells is significantly lower than that of ATP-depleted cells, which means that active processes fluidize the cytoplasm from a solidlike state. This phenomenon has also been observed in bacteria [7]. Furthermore, both the storage and loss moduli exhibit a power-law scaling with frequency and are approximately equal over a large range of frequency: $G'(\omega) \approx G''(\omega) \sim \omega^{1/2}$ [18,20,21]. In this sense, the cytoplasm is in a critical state, neither solid nor liquid. However, the physical origin of the $\omega^{1/2}$ scaling is still unclear and controversial [18,22]. Furthermore, the volume fraction of cytoplasm as a colloidal suspension remains unknown, and whether this volume fraction is regulated to an optimal value in live cells is even more elusive.

In this work, we investigate the impact of cytoplasmic density and active noise generated by intracellular processes

on the viscoelastic properties of cytoplasm (Fig. S1(a) in the Supplemental Material [23]). We model the cytoplasm as a suspension of soft, spherical particles (Fig. S1(b) in the Supplemental Material [23]), incorporating both passive and active noise, which is coarse-grained by an effective temperature. We compute the complex shear modulus as a function of the effective temperature and volume fraction ϕ (the relative volume occupied by particles). At zero temperature, this simple model exhibits a jamming transition to the solid phase at the jamming volume fraction, where $\phi_J \approx 0.64$ for monodisperse systems in three dimensions [24–26]. We show that systems above jamming with $\phi > \phi_J$ can be fluidized by noise and exhibit a transition from solid phase to liquid phase at the critical effective temperature $T_{\text{eff},c}$. At $T_{\text{eff},c}$, the shear stress upon a constant strain relaxes as a power-law function of time, $\sigma(t) \sim t^{-1/2}$ regardless of whether the active noise is modeled as Gaussian or as an Ornstein-Uhlenbeck process, in analogy to the critical state at ϕ_J and $T_{\text{eff}} = 0$ [27,28]. Surprisingly, the simulated complex shear modulus at $T_{\text{eff},c}$ quantitatively matches the experimental data of mammalian cells as long as we take a volume fraction slightly above ϕ_J . We find that the active part dominates the effective temperature, in concert with the nonequilibrium nature of cytoplasm [19,20,29,30].

To understand whether there is any biological significance for cells to be slightly above jamming, we compute the effective viscosity, the magnitude of the complex viscosity, which reflects the cytoplasmic response to external shear due to both elasticity and viscosity. Intriguingly, we reveal a regime of volume fraction slightly above ϕ_J in which the effective viscosity is sensitive to the effective temperature. We propose that cells actively regulate their volume fractions to operate in this regime, allowing them to efficiently tune their effective viscosity through a slight change in the intensity of intracellular active processes, thereby achieving specific biological functions. Furthermore, the active noise also makes

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the effective viscosity less sensitive to changes in volume fraction.

A particle-based model of cytoplasm. We model the cytoplasm as a colloidal suspension of soft spherical particles whose dynamics follow the overdamped Langevin equation:

$$\eta_i \frac{dr_{i,\alpha}}{dt} = -\frac{\partial U}{\partial r_{i,\alpha}} + \xi_{i,\alpha}. \quad (1)$$

Here, $i = 1, 2, \dots, N$, where N is the number of particles, and $\alpha = x, y, z$, the directions in the Cartesian coordinate. η_i is the friction coefficient, which is related to the viscosity of the background solvent through the Stokes' relationship, $\eta_i = 6\pi\nu a_i$. Here, a_i is the radius of the particle i , and ν is the solvent viscosity. We use a 50–50 mixture of particles with a size ratio of 1:4 to prevent crystallization [24,31]. Particles interact through the “one-side spring” model $U = \sum_{i>j} k(a_i + a_j - r_{ij})^2 \Theta(a_i + a_j - r_{ij})/2$, where $r_{ij} = |\mathbf{r}_i - \mathbf{r}_j|$, k is the spring constant, and Θ is the Heaviside function. The volume fraction quantifies the crowdedness of the cytoplasm, defined as $\phi = \sum_{i=1}^N 4\pi a_i^3/3V$, where V is the system volume. The fluctuating force $\xi_{i,\alpha}$ is modeled as Gaussian noise and its autocorrelation function satisfies [32]

$$\langle \xi_{i,\alpha}(t) \xi_{j,\beta}(t') \rangle = 2\delta_{ij} \delta_{\alpha\beta} \eta_i k_B (T_p + T_a) \delta(t - t'). \quad (2)$$

Here, k_B is the Boltzmann constant and T_p is the passive temperature, i.e., thermodynamic temperature. We introduce T_a as the active temperature, an effective variable that coarse-grains the effects of active intracellular processes, such as ATP-consuming processes. Here, δ_{ij} and $\delta_{\alpha\beta}$ are Kronecker delta function and $\delta(t - t')$ is Dirac delta function. Details of parameters and numerical simulations are provided in the Supplemental Material [23]. We also model the active noise as colored noise using the Ornstein-Uhlenbeck process, and our main conclusions remain unchanged, as shown later.

We remark that the strength of thermal noise is proportional to the particle radius because the friction coefficient is proportional to the radius in Eq. (2). It is shown that the strength of active noise may be proportional to the cube of particle radius [33]. When modeling active force as Gaussian noise, we simplify the model by combining the thermal noise and active noise together and define $T_{\text{eff}} = T_p + T_a$ as the effective temperature incorporating both thermal and active fluctuations. We nondimensionalize the system such that the length unit is the radius of the small particles a_0 , the time unit $t_0 = 6\pi\nu a_0/k$, and the energy unit $E_0 = ka_0^2$. In the following, all variables are dimensionless unless otherwise mentioned.

Noise fluidizes jammed cytoplasm. In the following, we study the viscoelastic response of the cytoplasm model. In this section, we do not specify the contribution of passive and active noise to the effective temperature. We later show that the experimental data of live mammalian cells suggest that the active part dominates the effective temperature [18]. We first let the system relax to the equilibrium state and then apply a strain ϵ to the system through the Lees-Edwards boundary condition: particles initially at (x, y) are displaced to $(x, y + \epsilon x)$ [34]. We compute the stress as $\sigma(t) = \sum_{i>j} F_{ij,x}(y_i - y_j)/L^3$, where $F_{ij,x}$ represents the elastic force of the particle i on j and monitor the stress relaxation as a function of time. We introduce the relaxation modulus $G(t) = \sigma(t)/\epsilon$, from which

we compute the complex shear modulus [35,36] as

$$G^*(\omega) = i\omega \int_0^\infty G(t) e^{-i\omega t} dt. \quad (3)$$

The complex modulus can be written as $G^* = G' + iG''$, where G' is the storage modulus and G'' is the loss modulus (expressions are provided in the Supplemental Material [23]). Our results agree with previous works for the zero-temperature case: The bidisperse system exhibits the jamming transition at a critical volume fraction $\phi_J \approx 0.648$ [24]. Below jamming ($\phi < \phi_J$), the shear stress relaxes to zero; above jamming ($\phi > \phi_J$), the shear stress relaxes to a finite value σ_∞ ; at the jamming point ($\phi = \phi_J$), the shear stress decays as $\sigma(t) \sim t^{-1/2}$ (Fig. S2 in the Supplemental Material [23]) [28]. We note that the $1/2$ power-law decay comes from the abundance of soft modes of the Hessian matrix $H_{i\alpha,j\beta} = \partial^2 U / \partial r_{i\alpha} \partial r_{j\beta}$ [37]; in particular, the distribution of relaxation rates over eigenmodes satisfies $D(s) \sim s^{-1/2}$ for $s < 1$ at the jamming point [27,38]. Therefore, one can approximate the stress as

$$\sigma(t) \sim \int_0^1 e^{-st} s^{-1/2} ds \sim \begin{cases} 1, & t \ll 1, \\ t^{-1/2}, & t \gg 1, \end{cases} \quad (4)$$

where we assume that the contribution of each eigenmode to stress is comparable. For systems above jamming, the $1/2$ scaling of stress crossovers to a finite plateau in the long-time limit (Fig. S3 in the Supplemental Material [23]) [28].

We next study jammed systems with $\phi > \phi_J$ to demonstrate the fluidization effects of noise. We fix ϕ and tune the effective temperature T_{eff} over two decades and calculate the relaxation curve of stress [Fig. 1(a)]. Interestingly, we also find a transition from solid phase to liquid phase as T_{eff} increases. At the critical temperature $T_{\text{eff},c}$, the stress also decays as $\sigma(t) \sim t^{-1/2}$: The stress exhibits the same power-law decay at $T_{\text{eff},c}$ as at the jamming point without noise. Similar results are obtained if we fix T_{eff} and tune ϕ (Fig. S4 in the Supplemental Material [23]). Given the interaction form between particles, the elastic energy scales with the distance to the jamming point as $U \sim (\phi - \phi_J)^2$ [37]. The simplest scenario is that the average energy barrier for escaping a stable state has the same scaling as the energy itself, leading to the following scaling between the critical temperature $T_{\text{eff},c}$ and volume fraction ϕ :

$$T_{\text{eff},c} \sim (\phi - \phi_J)^2, \quad (5)$$

confirmed by our simulations [Fig. 1(b)]. This quadratic scaling appears consistent with previous studies [39–41].

We note that modeling the active noise as white noise is an approximation, which presumably does not affect the long-timescale behaviors. To test the robustness of our results in the presence of a finite correlation time in the active noise, we introduce an Ornstein-Uhlenbeck process to characterize the active noise with the same active temperature as the Gaussian active noise but with a finite correlation time τ_R (see the Supplemental Material [23]) [20,30,42,43]. We find that the fluidization effects of active noise appear only when the observation timescale is above τ_R , and the finite correlation time does not affect the critical long-time scaling $\sigma(t) \sim t^{-1/2}$ (Fig. 2).

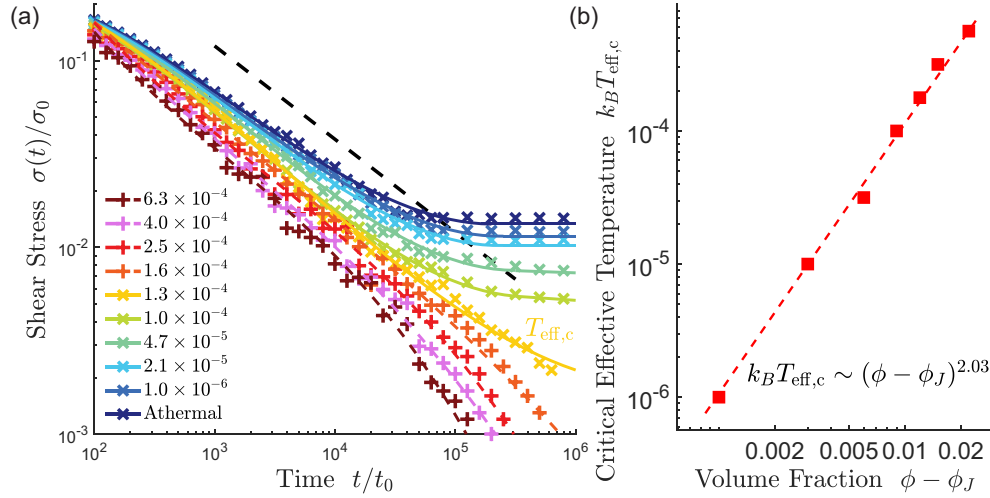


FIG. 1. (a) A jammed cytoplasm with $\phi = 0.660$ is fluidized by noise such that the stress relaxes to zero at a high enough effective temperature. σ_0 is the initial stress when the shear is applied at $t = 0$. The critical effective temperature $k_B T_{\text{eff},c} \approx 1.3 \times 10^{-4}$ in this case. The black dashed line has a slope of -0.5 in this log-log plot. The colorful dashed lines represent a cubic spline interpolation of the simulated data. (b) The scaling between the critical effective temperature $T_{\text{eff},c}$ and $\phi - \phi_J$ on a log-log plot, where ϕ_J is the volume fraction at the jamming transition at zero temperature.

Live cells have jammed cytoplasm and resemble critical jamming system. Recent experiments of active microrheology have measured the viscoelasticity of live cells in which one inferred the complex shear modulus by applying a force on a probe particle and measuring its displacement [18–20]. Interestingly, Ebata *et al.* found that the storage modulus of ATP-depleted cells is significantly higher than that of live cells at low frequencies ($\omega < 10$ Hz): The cytoplasm behaves like a solid if cellular activities are suppressed and becomes fluidized by active noise. Similar phenomena have also been observed in bacteria [7]. More interestingly, both the storage and loss moduli of live cells exhibit approximately power-law scaling with frequency, $G'(\omega) \sim \omega^{1/2}$ and $G''(\omega) \sim \omega^{1/2}$ at low frequency. We remark that the $\omega^{1/2}$ scaling of shear

moduli comes from the stress scaling $\sigma(t) \sim t^{-1/2}$ after a constant strain according to Eq. (3), which suggests that the volume fraction of cytoplasm is likely above jamming, but the system still resembles a critical system due to active noise [Fig. 1(a)].

To verify our hypothesis, we compare the simulated complex moduli at the critical effective temperature with the experimental data. We find that simulated data match the experimental data well with $\phi = 0.660$ and $k_B T_{\text{eff},c} \approx 1.3 \times 10^{-4}$ for both the storage modulus and the loss modulus [Figs. 3(a) and 3(b)]. We also infer $k_B T_p \approx 2.5 \times 10^{-5}$ from the fitting of ATP-depleted cells given the same ϕ . We therefore infer that active noise dominates the effective temperature, independent of ϕ in the sensitive regime (Fig. S5

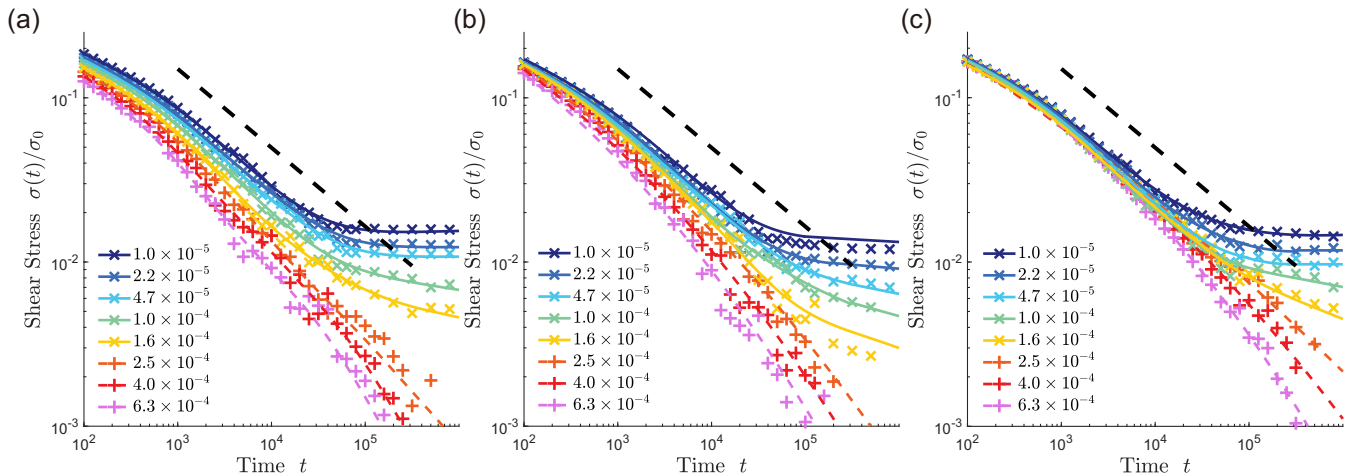


FIG. 2. The relaxation curves of systems with Ornstein-Uhlenbeck active noise. Here, we set $\tau_R = 1$ (a), $\tau_R = 10$ (b), and $\tau_R = 1000$ (c) with $\phi = 0.660$. The curves of different temperatures begin to diverge only when the observation time is above τ_R . The critical effective temperature $k_B T_{\text{eff},c} \approx 1.6 \times 10^{-4}$ and long-time scaling $\sigma \sim t^{-1/2}$ at the critical states remain the same. The black dashed line has a slope of -0.5 in this log-log plot. The colorful dashed lines represent a cubic spline interpolation of the simulated data. In this figure, we set the passive temperature $T_p = 0$ for simplicity.

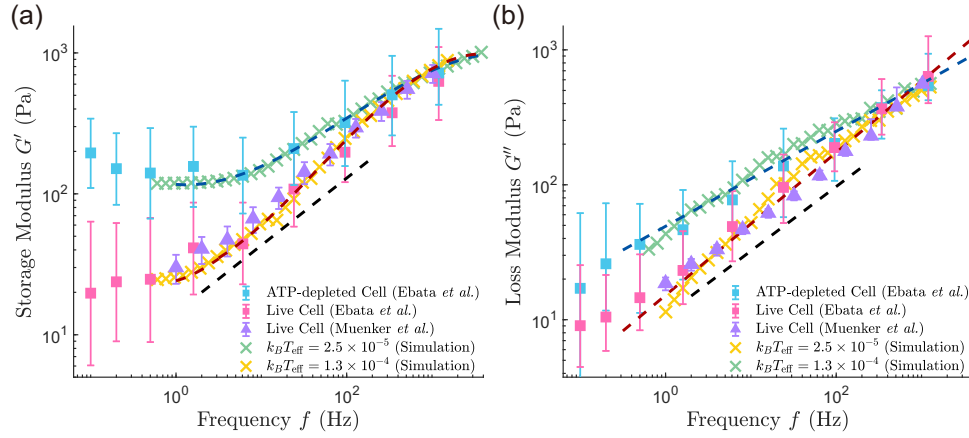


FIG. 3. The simulated complex moduli with $\phi = 0.660$ at the critical temperature $T_{\text{eff},c}$ match the experimental data well, including the storage modulus (a) and the loss modulus (b). Given the same ϕ , we infer the passive temperature $k_B T_p \approx 2.5 \times 10^{-5}$ from the fitting of ATP-depleted cells. Here, to match the simulated and experimental data, we set the time unit $t_0 \approx 4 \times 10^{-7}$ s and modulus unit $G_0 = k/a_0 \approx 1.2 \times 10^5$ Pa. By taking the length unit $a_0 = 10$ nm, we estimate the energy unit $E_0 \approx 10^{-19}$ J. The experimental data are from Refs. [18,20]. The colorful dashed lines represent a third-order polynomial fitting of the simulated data, and the black dashed lines have a slope of 0.5 in the log-log plot.

in the Supplemental Material [23]) [19]. Furthermore, by quantitatively matching the simulated and experimental data, we estimate the physical values of the units employed in the simulations: $t_0 \approx 4 \times 10^{-7}$ s and $E_0 = G_0 a_0^3 \approx 10^{-19}$ J by taking $a_0 = 10$ nm. Given these values, we further estimate the spring constant as $k \approx 10^{-3}$ N/m and solvent viscosity as $\nu \approx 2 \times 10^{-3}$ Pa s. The estimated solvent viscosity is consistent with experiments [7,44]. Interestingly, both models of white and correlated active noise fit the experimental data of complex moduli reasonably well, suggesting a minor influence of τ_R (Fig. S6 in the Supplemental Material [23]).

Our results suggest that the volume fraction of cytoplasm should be slightly above the jamming point. If the volume fraction is too high, an unreasonably high temperature is required to match the experimental data (Fig. S7 in the Supplemental Material [23]). On the other hand, if the volume fraction is below the jamming threshold, increasing the effective temperature makes the system more solidlike (Fig. S7 in the Supplemental Material [23]), which we discuss in the next section.

Sensitivity of cytoplasmic viscosity to active noise. What is the biological function of active noise, and why the volume fraction of cytoplasm is slightly above jamming? To better quantify the cytoplasmic response to external shear caused by both elastic and viscous mechanisms, we introduce the complex viscosity: $\eta^* = G^*/i\omega = G''/\omega - i(G'/\omega)$, and the effective viscosity as the magnitude of the complex viscosity [45–47]:

$$\eta_{\text{eff}} = \sqrt{\left(\frac{G'(\omega)}{\omega}\right)^2 + \left(\frac{G''(\omega)}{\omega}\right)^2}. \quad (6)$$

The effective viscosity captures both the yield stress of a viscoelastic solid and the viscosity of fluid (detailed discussion in the Supplemental Material [23]). For solid, it is dominated by G' ; for fluid, it is dominated by G'' . Intriguingly, we find a sensitive regime slightly above ϕ_J [Fig. 4(a)], in which the effective viscosity exhibits a significant change near the

critical temperature [Fig. 4(b)]. Therefore, we propose that cells adjust cellular activities to lie at the critical state, the border between the solid and fluid phases, allowing efficient tuning of cytoplasmic viscosity, in agreement with the $\omega^{1/2}$ scaling of shear moduli in live cells [18,20]. On the other hand, the cell volume can change in response to osmotic or mechanical perturbations; the resulting change in volume fraction alters the effective viscosity and affects cellular physiology globally. A finite active noise also makes the system less sensitive to the change in volume fraction [Fig. 4(c)]. For a system slightly below jamming, we observe that the effective viscosity increases with the effective temperature (Fig. 4), consistent with the rise in yield stress as temperature increases in the glassy phase [48]. Meanwhile, a volume fraction well above jamming is also evolutionarily disadvantageous, for which a very high effective temperature is required to tune the effective viscosity in a limited range [Fig. 4(b)]. Furthermore, diffusion remains suppressed in the cytoplasm far above jamming even with considerable active noise (Fig. S8 in the Supplemental Material [23]), which is unfavorable for cellular biochemical reactions, although it has been shown that active noise can enhance diffusion (Fig. S9 in the Supplemental Material [23]) [49].

Discussions. In this work, we model the cytoplasm as a suspension of repulsive particles. We apply the concept of jamming transition to cytoplasm and directly compare the simulated shear moduli with experimental measurements. We predict that the cytoplasm of a live cell is slightly above jamming and poised to the critical state by active noise. Furthermore, we reveal the evolutionary advantage of being at the critical point, which allows the cell to efficiently adjust its effective viscosity by tuning the level of active intracellular processes. Therefore, cells can effectively tune their stiffness and adapt to different environments, essential for biological processes such as tumor invasion and cell dormancy [50,51].

Reference [42] has shown that increasing the persistence time of active noise may promote glassy dynamics, but the system's general features of nonequilibrium glassy dynamics

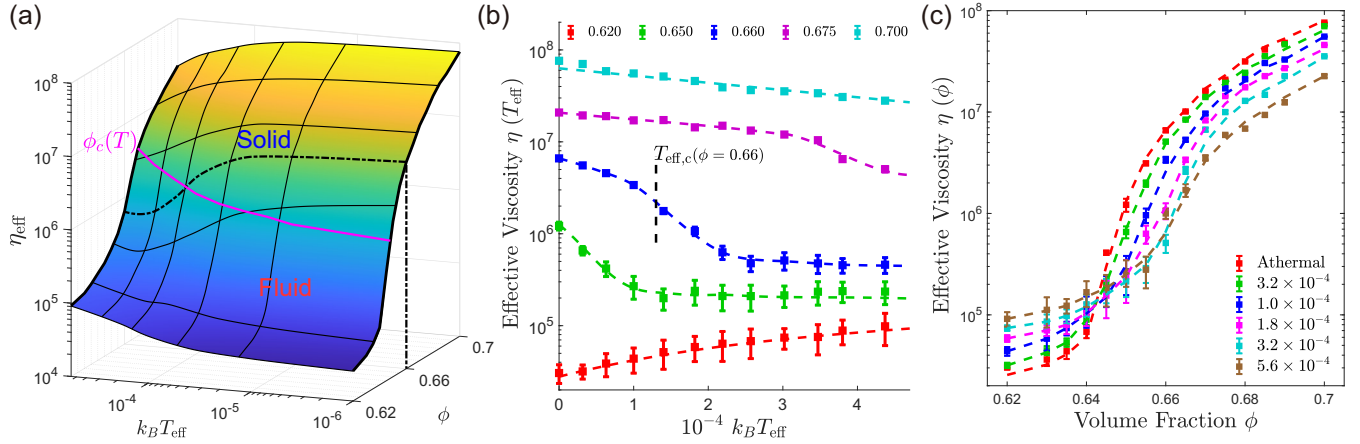


FIG. 4. The relationship between the effective viscosity with the volume fraction and effective temperature. Here, we take $f = \omega/2\pi = 1$ Hz as a biologically relevant timescale. (a) Phase diagram of viscosity where the dash-dotted line represents the viscosity at $\phi = 0.660$ and the pink line is the critical effective temperature $T_{\text{eff},c}$. (b) Viscosity vs T_{eff} under different volume fractions. Below the jamming point, the viscosity increases with temperature. Well above jamming, the viscosity decreases mildly with effective temperature. Slightly above jamming, the viscosity exhibits a sharp slope at the critical effective temperature (the vertical dashed line). (c) Viscosity vs ϕ under different effective temperatures. A finite active noise makes the viscosity less sensitive to the change in ϕ near jamming transition. The colorful dashed lines in panels (b) and (c) represent a cubic spline interpolation of the simulated data.

remain qualitatively unchanged. In Ref. [52], the authors numerically studied the shear rheology of a binary mixture of soft active Brownian particles. They found that the viscosities in the zero-shear limit are compatible with those obtained from the Green-Kubo relation once the Brownian temperature is replaced by an effective temperature that depends on the active Peclet number. These observations justify our simplified assumption of white active noise.

We notice that experiments based on osmotic perturbations estimate the volume fraction of osmotically inactive components to be about 30% [53], which is lower than the jamming volume fraction of purely repulsive systems. One possibility to reconcile our results and the measured volume fraction is to take account of attractive interactions among the molecular species [54,55], which make the system gel-like with lower jamming fraction. To test the predictions, we simulate the system where the interaction between particles has attractive region (Figs. S10–S13 in the Supplemental Material [23]) [56,57]. We find that the jamming volume fraction is lower and our main conclusions remain the same, including the $1/2$ temporal scaling of stress relaxation and the $\omega^{1/2}$ scaling of shear moduli at critical states.

Apart from attractive interaction, the mismatch between repulsive volumes and osmotically inactive volumes may also help reconcile the discrepancy between the measured volume fraction and model predictions. We note that the repulsive volumes of proteins in solution are determined by their gyration radii; meanwhile, the osmotically inactive volumes are presumably set by the volumes considering proteins as compact molecules [58]. Furthermore, due to the widely existing intrinsically disordered regions across the proteome, many proteins have a large fraction of unfolded regions [59]; therefore, their gyration radii can be much longer than the estimates considering proteins as compact molecules.

We note that when using the estimated E_0 , passive temperature $T_p \approx 2.5 \times 10^{-5} E_0$ is much lower than expected. We suggest that one possible reason for this discrepancy

is the underestimation of particle sizes. Due to attractive interaction and gelation, biomolecules may move as large clusters [54]. Taking $a_0 \approx 100$ nm as an example, we estimate $k_B T_p = 2.5 \times 10^{-5} G a_0^3 \approx 2.5 \times 10^{-21}$ J, where $T_p \approx 200$ K is reasonable considering the order of magnitude. In this case, the spring constant $k \approx 10^{-2}$ N/m and the solvent viscosity remains the same.

We also simulate systems with heterogeneous particle sizes to test the robustness of our results [49]. We take different distributions of particle radii in which the radii vary over one order of magnitude (Figs. S14 and S15(a) in the Supplemental Material [23]). Although the jamming volume fraction ϕ_J changes, our main conclusions regarding the scaling of the stress relaxation at the critical states, $\sigma(t) \sim t^{-1/2}$, remain valid (Fig. S15(b) in the Supplemental Material [23]), since the distribution of radii presumably does not affect the distribution of relaxation rates [27,60].

One should note that in this work, we study the viscoelasticity of cytoplasm and compare our data with microrheology experiments in which the cytoskeleton does not affect the probe particle [18,20]. It has been shown that the cytoskeleton can reduce the exponent between the shear modulus and frequency from 0.5 to 0.1 [22], consistent with measurements involving the cytoskeleton [3,8,11–15]. We note that in Ref. [22], the authors proposed an alternative model using a self-similar network of springs and dashpots to explain the origin of the $\omega^{1/2}$ scaling of the complex modulus. We remark that besides rationalizing the $\omega^{1/2}$ scaling of complex modulus, our colloidal model also predicts that the cytoplasm of a live cell is likely to be slightly above jamming and poised to the critical state by active noise, which allows the cell to efficiently adjust its effective viscosity; a finite active noise also makes the cytoplasmic viscosity less sensitive to changes in volume fraction. Furthermore, our conclusions are equally valid in two dimensions (Figs. S16–S18 in the Supplemental Material [23]) [61]. Finally, tuning active noise is not the only way to change the cytoplasmic viscosity. For

example, Ref. [62] showed that budding yeast can modulate viscosity by regulating the synthesis of glycogen and trehalose. The variety of regulation mechanisms suggests the complexity behind viscosity adjustment and requires further investigation.

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Data availability. The data that support the findings of this article are openly available [63].

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