Glassy Arrest in Colloidal Fluids with Size Polydispersity

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Short-range attraction between colloidal particles such as proteins can drive a glass-like structural arrest. For monodisperse systems, mode-coupling theory affords a simple asymptotic prediction of the transition. Here, using a depletion mapping framework, we extend this result to incorporate size polydispersity. For comparison, we also give an energy landscape formulation of the transition. We comment on the relevance to subcellular crowding, recombinant protein expression, and osmotic stress in microbial organisms.

Experimental studies of glass formation in colloidal suspensions are strikingly concurrent with the predictions of mode-coupling theory, a scheme that sets out to reduce the exact equations of particle motion to tractable form by focusing only on dominant relaxational modes of the system. Insofar as these dominant modes are inferred from the radial distribution function $g(r)$, the basic equilibrium-structural specification of the system, the mode-coupling approach can be said to unite kinetic and thermodynamic aspects of the glass transition.

The radial distribution function in turn depends on the nature of particle−particle interactions. For many colloidal systems such as proteins, the interaction can be coarsely divided into a hard-core volume exclusion and a short-range attraction. The core underpins the classical caging mechanism for glass formation at high concentration, while a "reentrant" onset of the glass occurs at lower concentration, driven independently by the attractive part.[1] This latter behavior is relevant in particular to the colloidal volume fractions $\varphi = 20 - 40$ % associated with physiological crowding, for example, in blood cells and microbial cytoplasm.

Motivated by the fact that physiological[2] and other colloidal systems in general comprise a mixture of different sized components, we wish to address here the role of size polydispersity in modulating reentrant onset of the glass. The current theoretical status is that while the mode-coupling equations can be fairly easily solved for various model interactions in the monodisperse case, they are somewhat more complicated for mixtures.[3] Our strategy will be to bypass this problem by exploiting the familiar concept of "depletion", the entropic renormalization of the effective interaction between colloidal particles that occurs because of volume exclusion when secondary components such as polymer are added.[4] Specifically, we map the attractive hard-sphere mixture to a Yukawa form for the effective single-component interaction potential

$$u(r) = \begin{cases} \infty & 0 < r < d \\ -\dfrac{\epsilon}{r/d} \exp^{-z(r/d-1)} & d < r \end{cases} \qquad (1)$$

where d is the effective particle diameter, ϵ parametrizes the effective strength of attraction, and the screening parameter z reflects its inverse range. The mode-coupling equations have been studied previously for this model.[5] For large z and low volume fraction φ, it can be shown that the temperature onset of the reentrant glass transition scales with the model parameters as $T_g \sim \epsilon z^{-1/2} \varphi^{1/2}$. Hence, the effect that polydispersity has on the glass transition can be gauged straightforwardly from its relation to ϵ and z.

In order to make this relation explicit, a pertinent choice of mapping identity is to equate the respective fluid−fluid critical points of polydisperse mixture and monodisperse Yukawa (the reentrant glass and critical point are phenomenologically connected insofar as both are driven by attractive interaction[6]). We first set up a more or less standard equation of state to describe the mixture and determine its critical point, distinguishing hard-core versus attractive bond contributions to pressure, that is, $p = p_b + p_{hs}$. To lowest order in the degree of polydispersity Δ (standard deviation divided by the mean) with respect to particle diameter, the equation of state for normal-distributed hard spheres is given by the well-known scaled particle theory[7]

$$\frac{p_{hs}}{\rho kT} = \frac{1}{1-\varphi} + \frac{3\varphi(1-2\Delta^2)}{(1-\varphi)^2} + \frac{3\varphi^2(1-3\Delta^2)}{(1-\varphi)^3} \qquad (2)$$

where ρ is the particle number density.

For the attractive contribution, if each particle shares an average n reversible bonds with neighbors in its immediate contact shell then the associated free energy per particle is $F/N = -\epsilon_b n/2$, where ϵ_b is the bonding energy. Let us write $n = 4\pi\rho g_{cs} a \langle d^2 \rangle$, where a is the width of the contact shell, $\langle d^2 \rangle$ is the mean-square particle diameter, and g_{cs} is the value of the radial distribution function in the contact shell. In the spirit of a perturbation approximation, it is reasonable to adopt the known result for hard spheres[8] $g_{cs} \simeq 1 + 5\varphi/2$. Combining these

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TABLE 1: Effective Yukawa Parameters: Inverse Screening Length z and (Reduced) Attractive Strength $\epsilon' = (\epsilon/\epsilon_b)\langle d\rangle/a$, Calculated by Matching to the Critical Point of the Mixture at φ_c and Reduced Temperature $T'_c = (kT_c/\epsilon_b)\langle d\rangle/a$ [a]

Δ	φ_c	T'_c	z	ϵ'	$f(\Delta)$
0	0.197	2.51	3.6	5.77	1
0.1	0.198	2.50	3.65	5.75	0.99
0.2	0.199	2.46	3.7	5.66	0.97
0.3	0.203	2.39	3.75	5.50	0.93
0.4	0.208	2.28	3.8	5.24	0.88

[a] From the Yukawa parameters, we obtain the modulating factor $f(\Delta) = (1/\sqrt{3.02})\epsilon'z^{-1/2}A^{-1}$, where $A = (1/\sqrt{3.02})(\epsilon'z^{-1/2})_{\Delta=0}$.

definitions with $\varphi = (\pi/6)\rho\langle d^3\rangle$ and $\langle d^2\rangle/\langle d^3\rangle \simeq (1 - 2\Delta^2)/\langle d\rangle$, we arrive at

$$\frac{p_b}{\rho kT} = \frac{\rho \partial_\rho F}{NkT} = -12a(\epsilon_b/kT)(\varphi + 5\varphi^2)(1 - 2\Delta^2)/\langle d\rangle \quad (3)$$

For monodisperse fluids, the spinodal onset of phase separation corresponds to the locus of zero inverse compressibility $\partial_\rho p = 0$. The situation is more complicated for mixtures because the appearance of daughter phases will in general be accompanied by fractionation,[9] but this need not greatly concern us here. We are merely interested in the critical point as an expedient mapping device. In Table 1, we have tabulated the nominal critical point just as the extremum of the $\partial_\rho p = 0$ locus.

Inverse compressibility of the corresponding Yukawa fluid follows from Waisman's integral equation treatment.[10] The result for the spinodal is

$$\epsilon/kT = \frac{\gamma}{48\varphi\eta z^2}[\kappa - \lambda(2\gamma + \eta)]^2 \quad (4)$$

where for compactness

$$\gamma = \frac{1 + 2\varphi}{z(1 - \varphi)}; \qquad \eta = (\gamma + \sqrt{1 + \gamma^2})^{-1}$$

$$\kappa = (e^{-z} - 1)(z^2 + 2z + 4) + 4z;$$

$$\lambda = (e^{-z} - 1)(z^2 + 2z) + 2z^2 \quad (5)$$

This completes the details of the mapping. By matching the respective critical points, the parameters $\{z, \epsilon\}$ of the effective Yukawa potential are determined easily for given $\{\epsilon_b, a, \langle d\rangle, \Delta\}$ of the mixture. The upshot is that the $\varphi^{1/2}$ asymptotic scaling of the Yukawa glass transition[5] may be expanded in size polydispersity Δ; that is, as $T_g \propto f(\Delta)\varphi^{1/2}$ where $f(\Delta) = 1 + c_1\Delta + c_2\Delta^2 + ...$. Using the calculations of Table 1, we infer finally the robust expression

$$\frac{kT_g}{\epsilon_b} \simeq A\varphi^{1/2}\frac{a}{\langle d\rangle}(1 - \Delta^2) \quad (6)$$

where the value of the constant is $A = 1.75$.

An intriguing counterpart to MCT is afforded by the energy landscape definition of an "ideal" glass; a low-lying basin where the system may become trapped in thermodynamically self-consistent fashion.[11] To formulate this mechanism for attractive colloidal mixtures, we proceed as follows. We assume that at the base of the landscape there exists a single nondegenerate glassy state in which each particle shares an average n_{IG} bonds with its neighbors. With corresponding system energy $E_{IG}/N = -n_{IG}\epsilon_b/2$, this is the lowest energy state available to the system overall. The highest energy states, on the other hand, are those in which there are no bonds whatsoever; that is, $E = 0$. There
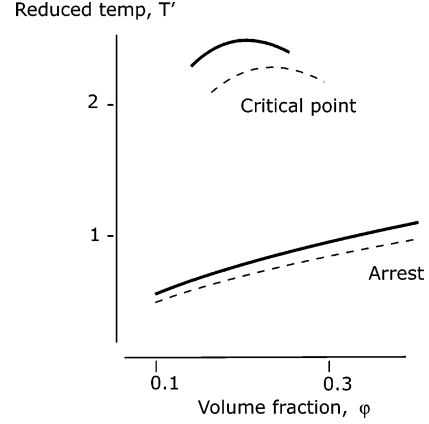

Figure 1. Phase diagram showing trend with increasing polydispersity from the monodisperse limit. Solid, $\triangle = 0$; dashed $\triangle = 40\%$. Reduced temperature is defined as $T' = (kT/\epsilon_b)\langle d\rangle/a$.

are many such states; hence, a system with zero E has high configurational entropy, call this S_0. To interpolate between S_0 and $S = 0$ for the ideal glass we follow the Gaussian convention of previous workers,[11] $S(E)/S_0 = 1 - (E/E_{IG})^2$. This is sufficient to formally establish the connection between landscape topology and thermodynamics because the Helmholtz free energy $F = E - TS(E)$ is now defined. Solving the thermodynamic condition for stability of the glassy state $(\partial F/\partial E)_{E_{IG}} = 0$, the ideal glass transition temperature is given by

$$\frac{kT_g}{\epsilon_b} = \frac{n_{IG}}{4}\left(\frac{S_0}{Nk}\right)^{-1} \quad (7)$$

Coupling of the transition to volume fraction φ and polydispersity Δ enters via the zero-energy entropy; that is, $S_0 = S_0(\varphi, \Delta)$. To work out S_0, we need to sum the partition function over the constrained set of system configurations in which no two particles lie close enough to form an attractive bond, that is, within the bonding range a. Since this is exactly the partition function for polydisperse hard spheres with diameters renormalized to $d + a$, we need look no further than the scaled particle equation of state, eq 2. Volume integration yields to leading order $S_0/Nk \approx C - 5\tilde{\varphi} + 6\Delta^2\tilde{\varphi}$, where $\tilde{\varphi} = \varphi(1 + 3a/\langle d\rangle)$ is the renormalized volume fraction ($a \ll d$), and where we assume intermediate volume fraction $\tilde{\varphi} \sim 0.5$ to deal with the logarithmically diverging ideal term. Let us fix the integration constant C by requiring that S_0 go to zero in the monodisperse nonattractive limit of random-close packing $\varphi_{rcp} = 0.64$. Substituting into eq 7 we have then

$$\frac{kT_g}{\epsilon_b} \approx \frac{n_{IG}}{20\varphi_{rep}}\left[1 + \frac{\varphi}{\varphi_{rep}}\left(1 + \frac{3a}{\langle d\rangle}\right)\left(1 - \frac{6}{5}\Delta^2\right)\right] \quad (8)$$

Comparison with the mode-coupling prediction of eq 6 is interesting. We see that the energy landscape recovers a broadly similar qualitative response of the glass transition temperature to the parameters ϵ_b, a, and d governing interactions in the mixture. Of particular note is our finding that the modulating factor introduced by polydispersity appears near identical.

We mentioned above that the attractive sphere mixture is a useful model with which to study crowding in cytoplasm. It is clear from the phase diagram plotted in Figure 1 that in fact for physiological volume fractions the glass is always preempted by the phase separation. Alternatively, it has been suggested both theoretically[12] and experimentally[13] that microbes may be able to alleviate the threat of phase separation via circulation
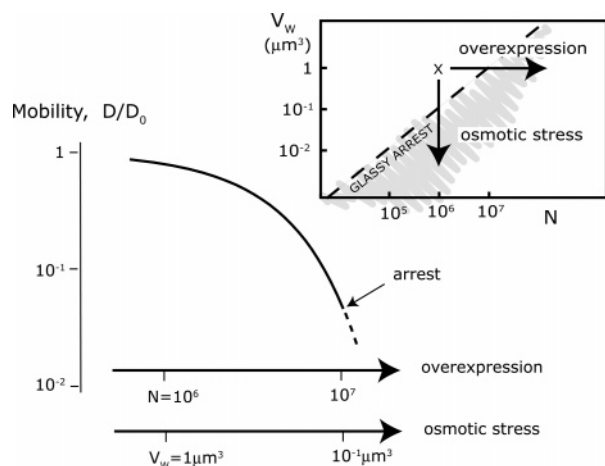
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Figure 2. Experimentally measured[17] diffusive mobility of proteins in cytoplasm is of order $D = O(1\mu m^2/s)$, well below a Stokes−Einstein estimate $D_0 \approx 100\ \mu m^2/s$ for proteins in dilute solution. This situation is captured qualitatively by Rosenfeld's scaling argument plotted in the main panel. An increase in crowding, due to increased expression and/or osmotic stress, further impairs mobility, arguably leading ultimately to a glass-like structural arrest at some critical $\varphi_g = N\nu/(N\nu + V_w)$, where ν denotes mean specific volume per macromolecule. For this illustration, we set $\varphi_g = 50\ \%$, $\nu = 100\ nm^3$.

of compatible osmolytes, small molecules notable for their subtle volume exclusion character.[14] This of course begs the difficult question of to what extent compatible osmolytes might also interfere with glassy arrest, which we defer to a future study. Suffice it to say for the time being that, in alleviating phase separation, it seems entirely feasible that the organism instead lays itself open to glassy arrest. Substitution into eq 6 of rough order of magnitude guesses[15] for the strength and relative range of attraction between cytoplasmic macromolecules, respectively, $\epsilon_b/kT \sim O(1)$ and $a/d \sim O(10^{-1})$, confirms qualitatively the possibility of a glassy cytoplasm above some critical volume fraction φ_g within the physiological range. As sketched in Figure 2, this would correspond to a straight line in the physiologically important phase space of cytoplasmic water (V_w) versus abundance of expressed macromolecules (N). This straight line locus we can interpret as an absolute limit to crowding, noting that it is likely to be preempted as an effective limit, insofar as a strong pretransitional slowdown in macromolecule mobility conceivably undermines physiological function somewhat prior to the onset of arrest proper. Figure 2 plots the slowdown as predicted by a semiempirical thermodynamic scaling argument originally due to Rosenfeld.[16] We have labeled the two principal thermodynamic approaches to the glass, respectively, "osmotic stress" and "overexpression" so as to underscore their relevance to experimentally familiar threats to homeostasis: a bacterium losing cytoplasmic water to a saline environment is seen to be subject to glassy arrest, as is a bacterium used as an expression host for large amounts of genetically engineered recombinant protein.[18]

Statistical mechanical considerations have suggested previously that the size polydispersity of cytoplasmic components has a negligible bearing on their miscibility.[15] This turns out to be similarly the case here in respect to the glass transition. Gel

electrophoresis data from lysed cells indicate that the degree of polydispersity with respect to molecular weight, call this δ, lies typically in the range 30−50% (see ref 19). Provided it can be assumed that sphere-like weight-diameter scaling $w \sim d^3$ holds reasonably, then the relation to the size polydispersity parameter of our discussion is $\Delta \approx \delta/3$ (this is derived using the moment generating function for a normal distribution). Hence, substituting $\Delta \sim 10\ \%$ the associated modulating effect on eq 6 is seen to be rather minor. Note that for this degree of polydispersity our use of lowest order expansions eqs 2 and 3 is reasonably valid. Note also that the asymptotic scaling prediction on which we have based our discussion, while not expected to be quantitative, has nevertheless been found in previous work to perform well against more detailed numerical calculations at the intermediate fractions relevant to cytoplasm.[5] Having said this, it certainly breaks down in the approach to very high crystalline-like volume fractions around 60%, which might at a pinch be accessible to cytoplasm along some high-temperature crowding-thermodynamic trajectory of our Figure 1. Here, the alternative repulsive "caging" mechanism for glass formation might become relevant (see ref 1), a distinct "jam-packing" limit to crowding.

References and Notes

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(16) Diffusive mobility scales according to Rosenfeld exponentially with the nonideal (excess) part of the entropy per particle s_{ex}. In the figure, we have plotted $D/D_0 = \exp(bs_{ex}/k)$, substituting the scaled particle result for s_{ex}. Calibration against the dilute limit of Batchelor $D/D_0 \approx 1 - 2\varphi$ sets the constant to $b = 1/2$. See Rosenfeld, Y. *Phys. Rev. A* **1977**, *15*, 2545; Mittal, J.; Errington, J. R.; Truskett, T. M. *J. Chem. Phys.* **2006**, *125*, 076102.

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(18) The obtainable yield of a recombinant protein is often found experimentally to be limited by the formation of insoluble precipitate (see e.g., Niiranen, L.; Espelid, D.; Karlsen, C. R.; Mustonen, M.; Paulsen, S. M.; Heikinheimo, P.; Willassen, N. P. *Protein Expression Purif.* **2007**, *52*, 210), which our Fig 2 interprets more specifically as glassy precipitate. Note that with overexpression of a specific single protein there occurs a significant narrowing of the expressed weight distribution. A corollary of our conclusion that polydispersity does not greatly supress the glassy state is that this narrowing does not in itself drive precipitate formation.

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