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PAPER

Nature and interrelations of fast dynamic properties in a coarse-grained glass-forming polymer melt

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Recent experimental studies have demonstrated that the dynamics of glass-forming liquids on fast picosecond timescales are directly relevant to developing effective formulations for protein drug preservation. In these systems, short-time dynamic properties, including the Debye–Waller factor, non-ergodicity parameter, and the ‘fast beta’ relaxation time, are ‘tuned’ by the addition of antiplasticizer additives, with associated improvements in protein preservation. We employ molecular dynamics simulations of a coarse-grained polymer melt with and without the addition of an antiplasticizer additive to characterize how these fast dynamic properties interrelate and how they are altered by the addition of antiplasticizer additives. We find that the Gaussian approximation for the van Hove correlation function holds to an excellent approximation at short times, facilitating the establishment of precise interrelations between these properties and the characterization of their temperature and composition dependence. Following previous studies, we first fit the fast relaxation process to an empirical ‘stretched Gaussian’ form ($\exp[-(t/\tau)^\beta]$) with $1 < \beta < 2$ and find that β equals 3/2 over a wide range of temperature for the post-inertial relaxation process. We then consider a more theoretically motivated description of fast beta relaxation inspired by an earlier model for the relaxation of a fractal network of elastic clusters in glass-forming colloids, and we find that this description provides an excellent fit to the entire short time relaxation over a large range of temperatures with physically meaningful parameters. Finally, we show that it is possible to tune the fast beta relaxation process with antiplasticizer additives, resulting in effects that rationally enhance protein preservation in glassy sugar matrices.

Introduction

Recent experiments have revealed that the preservation of proteins in glassy sugar matrices strongly correlates with molecular dynamics on picosecond timescales.^{1–4} In particular, it has been shown that the Debye–Waller factor $\langle u^2 \rangle$, which can be interpreted as a particle ‘cage’ size or localization scale on a picosecond time-scale, correlates strongly with protein preservation lifetime. The surprising finding that long-time protein degradation correlates more directly with dynamics on picosecond timescales than with protein degradation timescales (weeks or months) indicates a pressing need to understand and control the nature of relaxation of glass-forming liquids in the picosecond time range and to understand the reasons why this time-scale of relaxation is so important for protein preservation.

Several physical models have been advanced to describe the ‘fast’ dynamics of glass-forming liquids. The simplest picture is that relaxation is purely inertial until roughly the average inter-particle collision time.⁵ Alternatively, the mode coupling theory (MCT) argues for a power-law relaxation in time on these “microscopic” time scales.⁶ In a third view, the ‘coupling model’^{7–10} simply assumes a Debye spectrum (*i.e.*, simple exponential decay process) at short times, yielding exponential relaxation prior to a crossover time t_c . At longer times, corresponding to alpha (α) relaxation, the decay of correlations is generally assumed to take the form of a stretched exponential, $\exp[-(t/\tau_I)^\beta]$ with ‘stretching exponent’ $\beta < 1$.^{7–10} The present work freshly examines the fast relaxation process to determine which, if any, of these models conforms to molecular dynamics simulations of a model glass-forming polymer melt. This dynamical regime is particularly attractive for molecular dynamics study since its timescale is quite accessible computationally.

Transient caging

A key phenomenon in the short-time dynamics of glass-forming liquids is the emergence of particle caging as the glass transition

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temperature is approached from above. As shown in Fig. 1, this caging manifests as a plateau in the mean square particle displacement and becomes pronounced at a ‘crossover temperature’ (or mode-coupling temperature) T_c that lies somewhat above the glass transition temperature T_g . The Debye–Waller factor mentioned above is essentially the height of this plateau.

The emergence of caging in glass-forming liquids is closely connected to the emergence of elasticity. An inverse relationship between the high frequency modulus G_∞ and the Debye–Waller factor, $G_\infty \propto kT/\langle u^2 \rangle$, is frequently assumed¹¹ and has been derived on the basis of a simple Maxwell model of liquids.¹² This provides a basis for a correlation between the Debye–Waller factor and protein preservation: reduced $\langle u^2 \rangle$ correlates with increased elastic modulus, and the resultant retardation of solvent-facilitated degradative protein motions results in enhanced protein preservation. The Debye–Waller factor also correlates with the free volume as measured by positron annihilation^{13,14} and by molecular dynamics (MD) simulation of a glass-forming polymer melt.¹⁵ A decrease in $\langle u^2 \rangle$ in the glass state thus corresponds to a reduction of free volume and to a consequent reduction in the rates of diffusion of reactive species that contribute to protein degradation.

Although these trends provide qualitative insight into why the fast dynamics of sugar glasses are key to their preservation of proteins, the exact nature of the relationship between the cage size and the dynamics of the glass remains unclear and is a central target of the present investigation.

Antiplasticization

The phenomenology of protein preservation in glasses suggests a new method of interrogating and controlling dynamics at the picosecond timescale. Namely, the addition of antiplasticizer additives to a sugar glass alters $\langle u^2 \rangle$ and correspondingly strongly

correlates with improved protein preservation.¹⁶ This effect suggest that these additives non-trivially tune fast glass dynamics. As a consequence, they provide a probe for the relationship between caging, other fast dynamic properties, and protein preservation times.

Antiplasticizers are additives that reduce the glass transition temperature T_g of the material to which they are added while simultaneously stiffening its glass state.^{17–19} This stiffening effect is seen in the elastic,²⁰ bulk, and shear moduli of the glass¹⁹ and is associated with a densification of the glass. This densification implies that antiplasticizers generally improve packing efficiency¹⁹ (note that the reverse is not always true – densification upon addition of an additive does not imply that the additive is necessarily an antiplasticizer).

The above effects of antiplasticizers have been shown in non-crystallizing systems to be associated with a reduction in fragility of glass formation,^{18,22} a measure of the non-Arrhenius character of the structural relaxation process.²³ This trend indicates that the additives change the fundamental character of glass formation in these systems rather than merely shifting the glass transition temperature; in particular, they increase the temperature breadth of the glass transition while stiffening the material in its glass state.

Overview

The above observations indicate that changes in fast dynamics are characteristic of antiplasticizer additives. Accordingly, we focus on the interrelations between fast dynamics properties and the effect of antiplasticizing additives on these relations, in order that measurements in this dynamic regime can be used to more reliably engineer better protein preservative formulations. This study also affords an opportunity to better understand this aspect of glass-formation from a fundamental perspective. In particular, we address the following questions:

- 1) How is particle caging affected by antiplasticization?
- 2) What functional form describes structural relaxation at these short timescales, and what is the nature of the molecular motions of which short-time relaxation is comprised? Is the relaxation purely inertial or does it deviate from inertial behavior in some way? Does one of the other relaxation functions argued for by the coupling model or mode coupling theory hold?
- 3) What is the nature of the tuning of fast dynamics in glass-forming liquids by antiplasticizer additives over a wide range of temperatures?
- 4) How do the various measures of dynamics at this time scale (Debye–Waller factor, non-ergodicity factor, time dependence of the structural relaxation) interrelate?
- 5) More broadly, how can answers to the above questions point the way toward improved protein preservation *via* tuning of fast dynamics by antiplasticizer additives?

In order to answer these questions, we conduct molecular dynamics simulations of two systems: a coarse-grained Lennard–Jones polymer melt and the same system with the addition of an antiplasticizer additive. We begin by examining the effect of antiplasticization on the Debye–Waller factor over a wide range of temperatures. We then investigate the accuracy of a simple approximation (the Gaussian approximation) for the distribution of particle displacements at short times and employ this

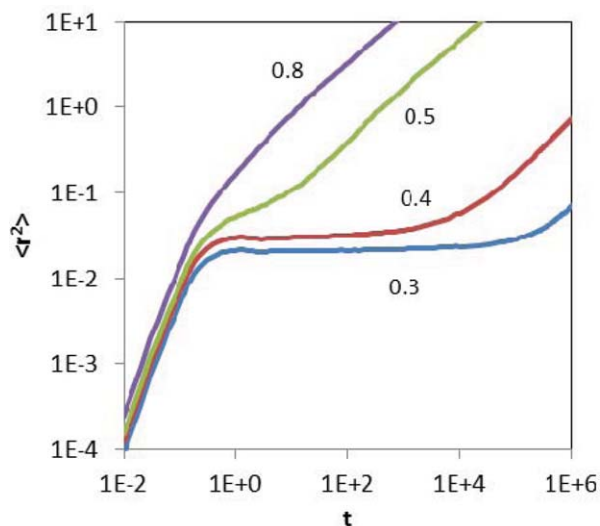


Fig. 1 Monomer mean square displacement as a function of time for the pure polymer system studied in this paper, at a variety of temperatures. The number next to each curve denotes the corresponding temperature. All numbers here and throughout all figures are in reduced Lennard–Jones units, as commonly defined in the literature.²¹ Details of the systems are described in the methodology section.

approximation in examining the implications of an empirical fit frequently employed in the study of fast dynamics. Finally, we suggest a new model for the dynamics of molecular glass-formers at this timescale based on the relaxation of a fractal elastic network.

Methodology

Simulations

The pure polymer model considered in this work consists of 50 polymer chains, each comprised of 32 Lennard-Jones (6–12) monomers with radius $\sigma = 1$ and a mass of unity. These beads are bound by stiff harmonic potentials with force constant $2000 \epsilon/\sigma$. This system has been described previously and is known to yield glass formation rather than crystallization.²⁴

The antiplasticized system additionally contains 674 antiplasticizer particles (5% by mass or about 30% by mole), which are monomeric 6–12 Lennard-Jones (LJ) particles with half the diameter of the polymer monomers ($\sigma = 1/2$). The mass of these particles is one eighth that of the monomer particles, consistent with their volume ratio. The self-interactions of both species and the cross-species interaction are characterized by the same Lennard-Jones energy parameter ϵ , equal to unity. For the cross interaction, we take $\sigma = 3/4$. All LJ interactions are cut off at a distance of 2.5, and the potentials are shifted such that they go to zero at this cutoff.

The overall behavior of this pair of systems has been characterized in previous work,^{18,22} with characteristic temperatures of glass formation summarized in Table 1²² (the temperatures in this table and throughout this paper have the following physical meanings: T_A demarcates the beginning of the glass formation regime and the first emergence of cooperative motion; T_c is a crossover temperature separating high and low temperature regimes of glass formation and below which caging effects become pronounced; T_g characterizes the temperature below which aging and non-equilibrium effects become significant on a laboratory timescale; and T_0 represents a low temperature end of the glass formation regime²⁵). The addition of the particles antiplasticizes the melt, decreasing the glass transition temperature T_g while increasing the shear modulus and density in the glass state.¹⁸ These effects have furthermore been shown to correspond with a reduction in the fragility of glass formation of this model polymer melt as determined by multiple measures.¹⁸

Simulations were conducted with the LAMMPS²⁶ (Large-scale Atomic/Molecular Massively Parallel Simulator) molecular dynamics simulation package using a RESPA (reversible reference system propagator algorithm) timestepping scheme. Thermo- and baro-stating were performed with the Nose-Hoover thermostat and barostat as implemented in LAMMPS, with temperature and

pressure damping parameters of 2τ for both, consistent with previous use of this model, where τ is the LJ unit of time (equal to 2.16 ps for argon²⁷). All NPT runs were performed at zero mean pressure. For the pure system, the time step for LJ interactions was 0.01τ . The time step for the harmonic bonds was 0.0025τ . For the antiplasticized system, the time step for LJ interactions was 0.004τ and the time step for harmonic bonds was 0.001τ . The shorter time-step for the antiplasticized system was necessitated by the smaller particle size (and hence steeper LJ repulsion) of the antiplasticizer particles. With these time-steps, total energy fluctuations were on the order of one percent or less.

Systems were initially equilibrated in the NPT ensemble for 10^4 LJ time units at $T = 1$, where T is defined to be the temperature in LJ units. Systems of varying temperature were then produced by cooling in the NPT ensemble at a rate of $10^{-5}/\tau$ to a minimum temperature of $T = 0.1$. Each configuration was then equilibrated for an additional time, specified in Table 2, in the NPT ensemble. This variable-equilibration-time methodology was used to accommodate the slower structural relaxation at lower temperatures. Where possible, the equilibration time was chosen to be on the order of 100 times as long as the alpha relaxation time of the system as determined from the self-intermediate scattering function calculated at the mean interparticle distance. For the coldest systems, the simulation-time demands of this scaling are prohibitive, and a maximum equilibration time of $10^6 \tau$ was chosen, corresponding to 100 million and 250 million time steps for the pure and antiplasticized systems, respectively. We estimate that this corresponds to a duration in real units on the order of one microsecond.

Based on these NPT equilibration runs, the density was determined at each temperature. Configurations were then rescaled to this density over $10^3 \tau$ and given an additional $10^3 \tau$ to equilibrate in the NVT ensemble. Production runs were then conducted from these configurations in the NVT ensemble. This methodology was chosen to reproduce the proper temperature dependence of the experimentally common constant pressure condition.

Using the above methodology, we conducted runs extending to temperatures well below T_g . Trajectories from several independent configurations were studied at each temperature in order to generate better overall statistics. In general, results below T_c , where the system tends to fall out of equilibrium, must be interpreted with care. However, given the short time scales of interest and the relatively very long equilibration times employed in this work, it is reasonable to expect that results will not be affected by equilibration issues for the relatively fast times that are the focus of the present paper. Furthermore, in several checks, no equilibration time sensitivity was found for the properties under consideration here for equilibration times of up to one order of magnitude less than those ultimately used.

Determination of the Debye–Waller factor

It has previously been argued that the appropriate time for determination of the Debye–Waller factor $\langle u^2 \rangle$ in polymeric

Table 1 Characteristic temperatures of glass formation, reproduced from earlier work.²²

	Pure	Antiplasticized
T_A	0.59	0.51
T_c	0.42	0.34
T_g	0.37	0.26
T_0	0.36	0.23

Table 2 NPT equilibration time after cooling

T	0.7 to 0.9	0.6	0.5	0.475	0.1 to 0.45
τ	10^3	10^4	5×10^4	10^5	10^6

systems is fairly constant and is equal to τ for simulated systems similar to those considered here.^{5,15} On this basis, $\langle u^2 \rangle$ is here determined as the mean-square displacement at a fixed time of 0.950τ for the pure polymer system and 0.948τ for the antiplasticized polymer system. These are the times closest to 1τ recorded in the two systems, and they are in the time regime of caged behavior for all systems studied in which a pronounced cage is present. The small difference in the two times is due to the different time step for the two systems and is not expected to significantly affect the results.

Results and discussion

Debye–Waller factor

As expected, antiplasticization is found to have inverse effects on the Debye–Waller factor in the glass and liquid states. Our results provide the first simulation evidence of a crossing in the effect of antiplasticizers on the Debye–Waller factor from the glass to the fluid above T_g . As shown in Fig. 2, antiplasticization ‘softens’ the fluid above T_g (increases the Debye–Waller factor) and stiffens it (decreases the Debye–Waller factor) when well into the glass state. This correlation is consistent with the expectation that the Debye–Waller factor should have a roughly inverse relationship with the high frequency modulus,¹¹ which likewise exhibits an inversion of the effect of antiplasticization from the glass to liquid states. The crossover between these regimes is not actually at T_g , but at some temperature below it. Earlier experimental studies have suggested that this ‘antiplasticization’ temperature (obtained from relatively high frequency dielectric and mechanical spectroscopy measurements) is around the Vogel–Fulcher^{28,29} temperature T_0 for the pure system.³⁰

The temperature-scaled inverse form of the Debye–Waller factor shown in Fig. 2 also has the interesting property of

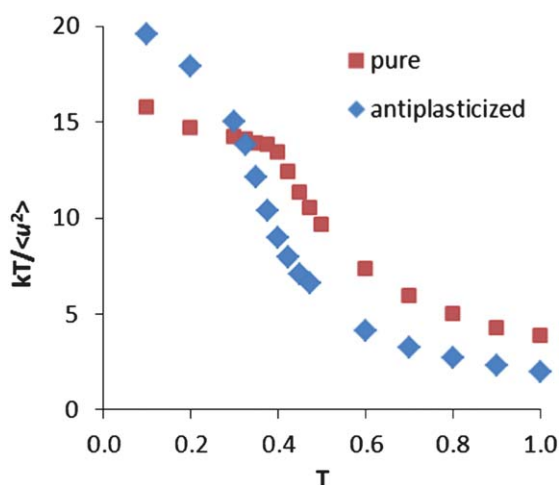


Fig. 2 Temperature-scaled inverse Debye–Waller factor, corresponding to local material ‘stiffness’. For all points, standard deviations are smaller than data points. It should be noted that the interpretation of the Debye–Waller factor as a particle caging size somewhat breaks down above T_c as pronounced caging ceases to be present. The values shown in this plot for that temperature range are a naive continuation of the constant-time definition of the Debye–Waller factor described in the text.

exhibiting a pronounced ‘kink’. The location of this kink is consistent with T_g for these systems as determined from the structural relaxation time in previous studies. In particular, a kink is plainly seen for the pure system between $T = 0.375$ and $T = 0.400$, in agreement with the previously determined T_g of 0.37 .²² For the antiplasticized system, a slightly less pronounced kink is seen between $T = 0.200$ and $T = 0.300$, also in agreement with the previously determined T_g of 0.26 .²² This result reflects the expected reduction in the glass transition temperature with antiplasticization. More broadly, this provides support for the notion that it is possible to determine T_g based on a kink in the Debye Waller factor.³¹

Gaussian approximation

In answering the questions posed in the introduction, some simple physical interrelation between particle displacement statistics and system relaxation would be of great value. In this case, ‘system relaxation’ will be characterized by the self part of the intermediate scattering function $F_s(q, t)$, defined as

$$F_s(q, t) = \frac{1}{N} \sum_k \langle \exp[-iq \cdot r_k(0)] \exp[iq \cdot r_k(t)] \rangle, \quad (1)$$

where q is the wavenumber, t is time, $r_k(t)$ is the position of particle k at time t , N is the total number of particles, and brackets denote an ensemble average (we follow the usual convention of choosing q to be the wavenumber corresponding to the mean interparticle distance determined from the first peak in the structure factor). Such an interrelation is suggested by the Gaussian approximation for particle displacements, which assumes that the distribution of particle displacements about the mean is Gaussian in form. Provided that this relation holds to a good approximation at the short times under consideration here, we have

$$F_s(q, t) = \exp \left[-\frac{q^2}{6} \langle r^2(t) \rangle \right], \quad (2)$$

where $\langle r^2(t) \rangle$ is the mean square displacement determined from the simulation itself.

As illustrated by Fig. 3, the Gaussian approximation for the self-intermediate scattering function, given by eqn (2), is excellent at short times up to the caging time. We find that it holds down to the lowest temperatures considered below T_g . This simple relationship leads to sharply defined relationships between fast dynamic properties.

Given that the Gaussian approximation holds at short times and applying the Maxwell–Boltzmann distribution for velocities, the inertial decay expected asymptotically at short times should take the form³²

$$F_s(q, t) \propto \exp[-(t/\tau_I)^2] \quad (3)$$

The temperature dependence of τ_I , based on the Maxwell–Boltzmann distribution, should be $\tau_I \propto T^{-1/2}$. Note that the Gaussian decay predicted by eqn (3) is in contrast to both the power-law decay for the ‘microscopic relaxation’ argued for by the mode coupling theory⁶ and the exponential decay predicted by the coupling model.^{7–10}

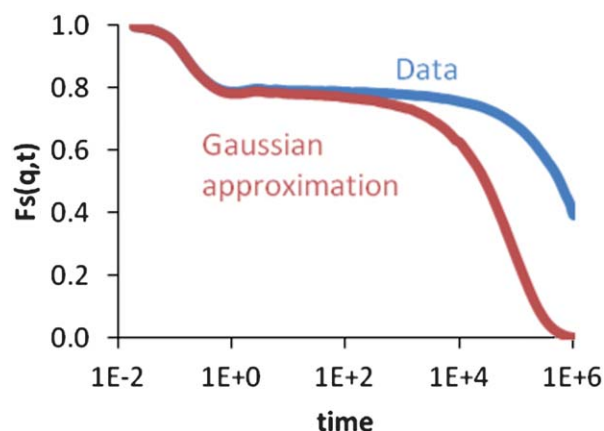


Fig. 3 Comparison of self-intermediate scattering function data to self-intermediate scattering function obtained from the mean square displacement *via* eqn (2), for the pure polymer system at $T = 0.400$. The standard deviation of the data curve as computed from multiple runs is roughly within the thickness of the curve over the entire range of data.

Stretched Gaussian fit to fast relaxation process

In a variety of systems, including dusty plasmas³³ and colloidal gels,³⁴ the fast relaxation process has been empirically modeled as a ‘stretched Gaussian’ form:

$$F_s(q, t) \propto \exp[-(t/\tau_\beta)^\beta]. \quad (4)$$

This approach is based on an analogy with the stretched exponential form of the alpha relaxation at longer times. Given its empirical nature, β should be viewed only as an effective exponent, and its value depends on the time range examined. This purely empirical approach to quantifying the short-time decay of $F_s(q, t)$ is somewhat unsatisfying, and below we suggest a model for the fast relaxation process that is based on the emergent elasticity of glass forming liquids. First, we explore the ‘conventional’ approach encapsulated by eqn (4).

At very short times, we find that relaxation follows the inertial form given by eqn (3) above (*i.e.*, β goes to two as time goes to zero). This result verifies the intuitive expectation that at very short times particles behave in an essentially noninteracting ballistic manner. However, by about 0.1τ the relaxation smoothly transitions to a distinct regime characterized by eqn (4) with β equal to an effective value of $3/2$. This value of the stretching exponent provides a reasonable fit for the approximate high frequency time range of 0.1 to 0.2τ over the entire range of temperatures studied (eqn (4) was fit to the time range $0.09 \tau < t < 0.18 \tau$, and for all cases correlation coefficients greater than 0.99 were obtained). We again emphasize that this is a purely empirical description of the fast relaxation data that is sensitive to the specific nature of the intermolecular potential. As such, β is not a universal parameter. After this intermediate time, β smoothly drops to zero, signalling a crossover to caged behavior. The inertial, fast decay, and caging time regimes are depicted in Fig. 4 as A, B, and C, respectively.

As shown by the bottom part of Fig. 4, the $3/2$ stretching exponent for the self-intermediate scattering function accords with the apparent scaling for the mean square displacement in the same time regime, consistent with the Gaussian

approximation. Specifically, an apparent $3/2$ power law is found for the mean square displacement in the same time range, consistent with fractional Brownian motion^{35–37} over the limited range of the beta relaxation time regime. Again, we emphasize that fast dynamics itself exhibits sensitivity to the form of the intermolecular potential, and we expect this effective β to more generally range from 0 to 2 .

For temperatures below T_c , this apparent ‘stretched Gaussian’ relaxation terminates with the transition to ‘caged’ particle dynamics (*i.e.*, corresponding the plateau in $\langle u^2 \rangle$ shown in Fig. 4). For considerably higher temperatures, the beta relaxation and alpha relaxation (*i.e.*, the secondary structural relaxation following the plateau in Fig. 3) overlap substantially and become difficult to distinguish.

The decay form given by eqn (4) has also recently been introduced to describe the fast beta relaxation of a simulated colloidal gel.³⁴ It has also been seen, albeit with a lower value of β , in the fast

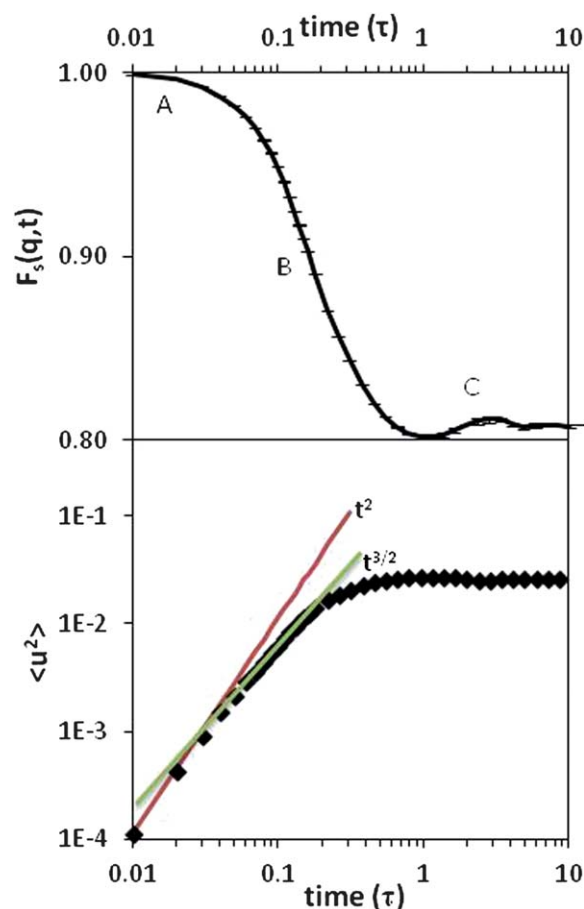


Fig. 4 Self part of the intermediate scattering function at q corresponding to the first peak of the structure factor (top) and mean square displacement (bottom) for pure polymer system at $T = 0.375$ for short times. Region A corresponds to the time domain in which the inertial behaviour given by eqn (3) fits to a reasonable approximation. Region B is the time-range in which the empirical $3/2$ stretched Gaussian decay form is found to hold. Region C denotes the crossover to fully caged behaviour. The line labelled t^2 denotes the scaling of the MSD in the short-time inertial regime, while the line labelled $t^{3/2}$ denotes the scaling of the MSD in the fast beta regime. Error bars denote the standard deviation based on several runs.

beta relaxation of a simulated dusty plasma.³³ This variability of the stretching exponent β in differing systems again suggests that its value may not be universal. Indeed, we find that the apparent value of β can be altered by changing the bond strength of the chain backbone. We emphasize that this effect should not be viewed as artifactual; rather it suggests that the underlying fast relaxation is influenced by the presence of fast gamma relaxation processes associated with bond vibrations and rotations. The details of these gamma relaxations alter the apparent stretching exponent describing the beta relaxation process.

As shown in Fig. 5 for the pure polymer melt, the time constant for the inertial decay has the expected inverse 1/2 power law temperature dependence that universally characterizes inertial relaxation (the inertial time constant is obtained from a fit to eqn (3) for $t < 0.05 \tau$). The time constant for the apparent stretched Gaussian fit to the 'fast beta' time regime given by eqn (4) also has a power law scaling with T , but with a higher inverse power law exponent. We stress that this temperature dependence is unlike many other high frequency processes,³⁰ such as the Johari-Goldstein beta relaxation,³⁸ which exhibit Arrhenius temperature dependence.¹⁶ The temperature dependence of the relaxation time instead more closely resembles that seen in gases, suggesting that molecular motions comprising the fast relaxation are mainly not activated in nature but are rather dominated by inertial particle motion.

Interrelations between fast dynamic properties

The Gaussian approximation provides a straightforward interrelation within the glass state between the Debye–Waller factor and the fast relaxation time $\tau_{\beta f}$ from eqn (4). In particular, combining eqn (2) for the Gaussian approximation with eqn (4) for the fast relaxation process suggests that, if the Gaussian approximation holds and the fast beta relaxation is the dominant relaxation at the time the Debye–Waller factor is defined, then the Debye–Waller factor should obey the relation

$$\langle u^2 \rangle \propto \tau_{\beta f}^{-3/2}. \quad (5)$$

As shown by Fig. 6, this relation indeed holds for the pure and antiplasticized polymer systems, both below T_g and to

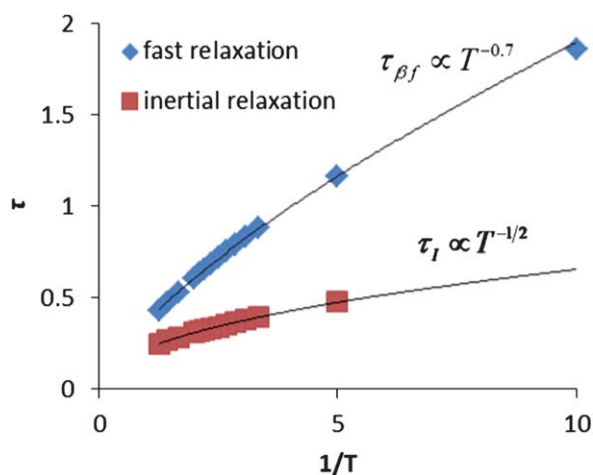


Fig. 5 Temperature dependence of time constants for inertial and fast beta relaxations in the pure polymer system.

a reasonable approximation until around T_c (above this temperature the fast beta begins to overlap with the alpha relaxation and so eqn (5) cannot be expected to hold). Furthermore, the *same* relation between these two measures of fast dynamics describes both systems, suggesting the possibility of a universal low-temperature relationship between the fast beta relaxation time $\tau_{\beta f}$ and $\langle u^2 \rangle$ based on the Gaussian approximation. It should also be noted that eqn (2) and (4) imply a strict relationship between the temperature dependencies of $\tau_{\beta f}$ and $\langle u^2 \rangle$, namely that the power law exponent of the temperature dependence of $\langle u^2 \rangle$ should be $-3/2$ times that for $\tau_{\beta f}$. This relationship is found to hold as well up to about T_c .

As shown by Fig. 7, there is also an apparently general relationship between $\langle u^2 \rangle$ and the height h of the caging plateau in the intermediate scattering function, which is known as the 'non-ergodicity parameter' (h is determined as the value of $F_s(q, t)$ at $t = \tau$, consistent with our determination of the Debye–Waller factor at this time). This relationship again holds up to about

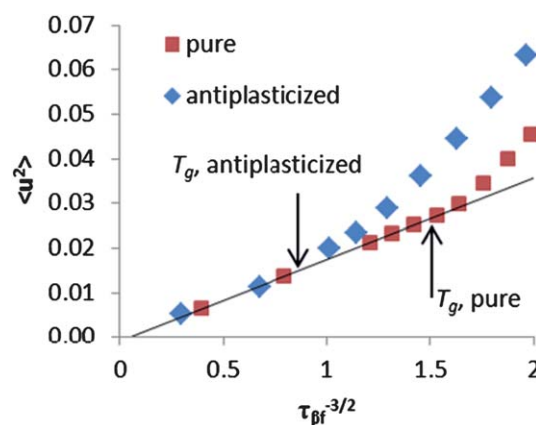


Fig. 6 Expected relation between Debye–Waller Factor and time constant for the fast beta relaxation from fit to eqn (4). The black line represents a linear fit to sub- T_g data.

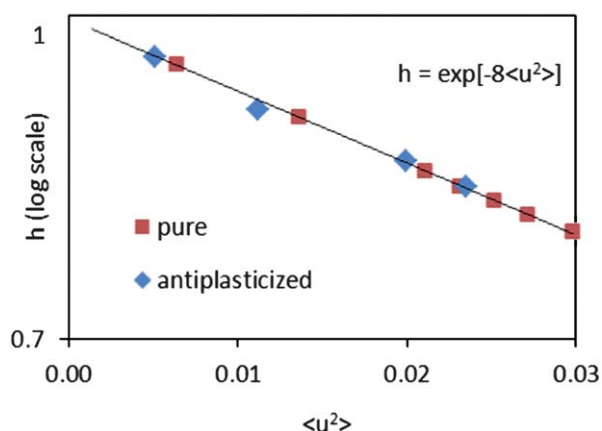


Fig. 7 Height of the caging plateau in the self-part of the intermediate scattering function on a log scale versus the Debye–Waller factor for temperatures less than T_c for each system. Diamonds and squares correspond to the pure and antiplasticized systems, respectively. The line is a fit to the data for the pure system, with the equation shown in the plot.

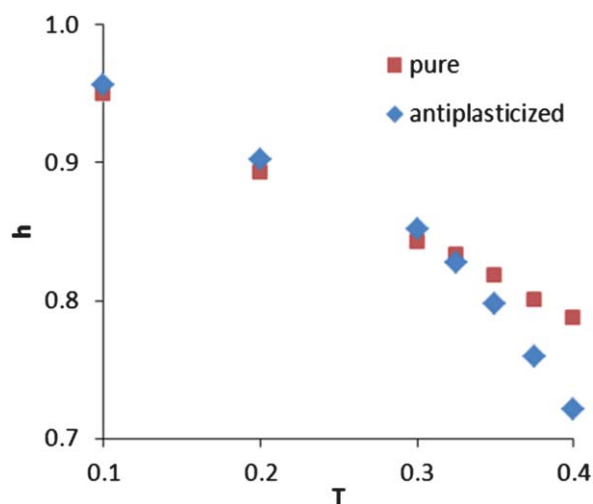


Fig. 8 Non-ergodicity parameter versus temperature for pure and antiplasticized systems.

T_c , where the caging plateau begins to vanish and the fast beta relaxation process is not distinct from the alpha. In essence, this demonstrates that the height of the caging plateau can be predicted from the Gaussian approximation and the Debye–Waller factor. This is an important result, as this relationship is in fact assumed to hold in the calculation of the Debye–Waller factor from scattering data.^{39,40}

Somewhat surprisingly, the relationship demonstrated by Fig. 7, combined with the observation from Fig. 2 that the Debye–Waller factors for the pure and antiplasticized systems cross from high to low temperature, implies that the non-ergodicity parameter should likewise exhibit a crossover with antiplasticization from the liquid to glassy states. As shown by Fig. 8, this indeed occurs; the addition of antiplasticizer decreases the non-ergodicity parameter at high temperature but increases it at low temperature.

The non-ergodicity parameter provides a measure of the strength of the fast relaxation of the self-intermediate scattering function. The observation from Fig. 8 that antiplasticization increases the non-ergodicity parameter in the glass state is consistent with prior observations of a positive correlation between fragility and the strength of other relatively ‘fast’ relaxation processes, including the Johari–Goldstein ‘slow’ beta relaxation process.³⁸ We point out that some authors have recently defined the non-ergodicity parameter based on the intermediate scattering function for relatively low q -values,⁴¹ in which case the non-ergodicity parameter is related to the compressibility of the fluid. In contrast, our non-ergodicity parameter is defined for a length scale corresponding to the interparticle spacing and is thus naturally related to the Debye–Waller factor.

Effect of antiplasticizers on inertial and fast beta relaxation processes

In order to understand the effect of antiplasticization at these short timescales, we examine the temperature dependence of the time constants for the inertial and fast beta relaxations for the pure and antiplasticized systems. A crossing in the relaxation

time curves for the pure and antiplasticized systems can be understood as being characteristic of antiplasticizer physics; a lack of such a crossing suggests that antiplasticizers do not tune the associated relaxation process in an interesting way.

The temperature dependence of the time-constant of the inertial relaxation process lacks the characteristic crossing behavior seen in $\langle u^2 \rangle$. In particular, the addition of antiplasticizer particles to the melt reduces the inertial relaxation time τ_I of the system at all temperatures, as shown by Fig. 9, with little to no change seen when the relaxation time is appropriately rescaled by the mass as suggested by the Maxwell-Boltzmann distribution and eqn (2). This trivial outcome does not appear to have any direct relationship with the more complex crossing-over behaviors of the system elastic moduli and Debye–Waller factor that result from antiplasticization. This implies that modification of the inertial relaxation process is *not* a direct mechanism by which antiplasticization alters experimentally relevant properties of the glass-former.

In contrast to the inertial effects of antiplasticizers, these additives cause the fast beta relaxation process to become faster in the liquid state but slower in the glass state, as illustrated in Fig. 10. This inversion is consistent with the effects of antiplasticization seen in the shear modulus⁴⁹ and Debye–Waller factor (see Fig. 2), which likewise show an inversion from the glass to liquid state. This correspondence between antiplasticizer effects on the fast relaxation time and the Debye–Waller factor supports the hypothesis that the fast beta relaxation is relevant in sugar formulations’ effect on protein preservation and indicates a relation between this relaxation time and the Debye–Waller factor.

More generally, the correspondence seen here between the fast beta relaxation and the Debye–Waller factor raises the question of whether any more fundamental form for the fast relaxation process than that offered by eqn (4) can be obtained by

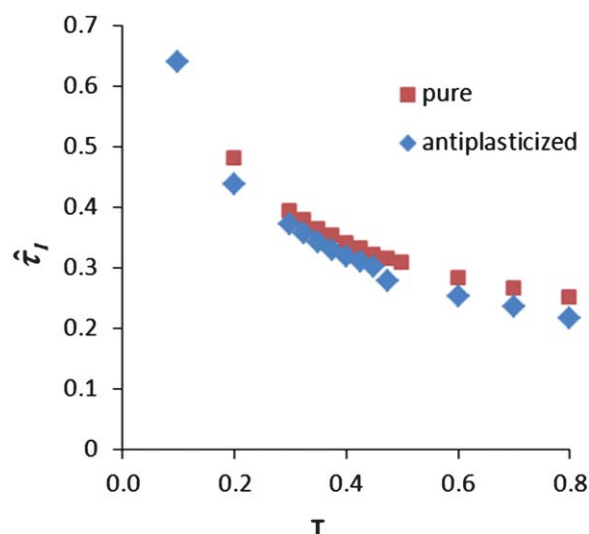


Fig. 9 Temperature dependence of mass-rescaled inertial relaxation times for pure and antiplasticized systems. The rescaled tau is given in accordance with the Gaussian approximation and the Maxwell-Boltzmann distribution by $\hat{\tau}_I = \tau_I / \sum_i m_i x_i$, where m_i and x_i are the mass and mole fraction of species i , respectively.

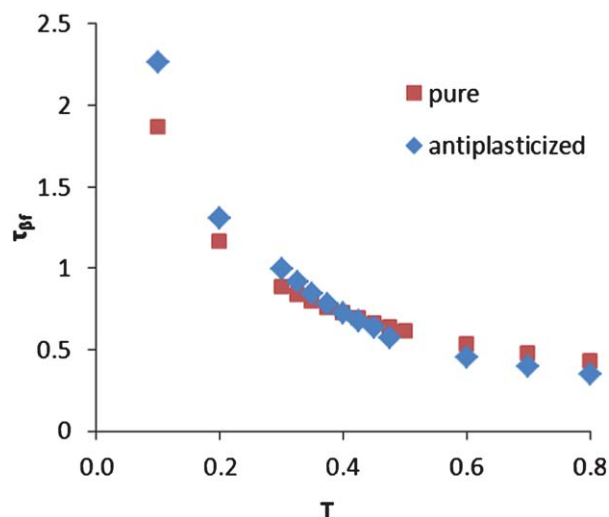


Fig. 10 Time constant for fast beta relaxation as a function of temperature for pure and antiplasticized systems.

employing the close relationship between the caging size and the fast dynamics timescale. This issue is addressed in the following sections, where we seek a more fundamental description of the fast beta relaxation process based on the emergence of elasticity as the glass transition is approached.

Other proposed forms for the fast beta relaxation

We begin the discussion of a more general form of the short-time relaxation with an examination of the power-law decay form suggested by mode-coupling theory.⁶ We find that a power law decay indeed approximately holds over the same time range to which we have fit a stretched Gaussian decay form. However, a widely varying power is required to fit the data over the range of temperatures studied, an effect not predicted by that theory. The apparent power law required to fit the data varies by an order of magnitude – from -0.025 at the lowest temperature studied up to -0.25 well above the glass formation region. Previous fits of experimental data over a large temperature range have noted a similar necessity to take the power law exponent to have a strong temperature dependence,⁴² in qualitative agreement with our fitting to this relation. The present stretched Gaussian form has the relative advantage of yielding an unambiguous relaxation time for the fast beta relaxation – an outcome which is not obtained in the case of a variable power law. However, as noted above, this relation is rather phenomenological.

Given the narrowness of the time window over which both of these forms are seen to hold, it is not possible to empirically establish any single equation as a unique fit to the relaxation. However, we can exclude the universally exponential decay form predicted by the coupling model^{7–10} as being evidently inconsistent with the stretched Gaussian form above. The problem remains of establishing a more general mathematical and physical form of β relaxation.

General form for short-time relaxation

Krall and Weitz have developed a model for the fast beta relaxation in colloidal glass-formers based on the idea that $\langle r^2 \rangle$ at

short time is dominated by localization of particles into relatively rigid and irregular ('fractal') clusters.⁴³ In these colloidal systems, the very short-time dynamics are Brownian rather than inertial, but we suggest below that the essential nature of particle caging is the same in both classes of glass-forming materials. On this basis, we extend these arguments to molecular glass formation.

The mean square displacement of a particle undergoing a Gaussian path process within a strongly confining local harmonic potential is given by^{43,44}

$$\langle r^2 \rangle \cong \langle u^2 \rangle [1 - \exp(-\hat{t})], \quad (6)$$

where \hat{t} is the reduced time variable associated with the Gaussian path process. Pure Brownian and inertial motion are both Gaussian processes (see Fig. 3 for the molecular case), so that eqn (6) is formally applicable both to colloidal and molecular systems, provided that the reduced time variable \hat{t} is chosen appropriately. Specifically, Brownian motion requires that $\hat{t} \equiv t/\tau_f$, whereas short-time inertial motion requires that $\hat{t} \equiv (t/\tau_f)^2$. In both cases, τ_f is a characteristic time after which $\langle r^2 \rangle$ approaches a constant average value $\langle u^2 \rangle$ that scales inversely with the force constant localizing the particle. Eqn (6) provides a reasonable model for particle localization in a *homogenous* system; however, this is not the situation for glass-forming liquids.

Krall and Weitz extend the argument leading to eqn (6) to account for dynamic heterogeneity in colloidal glass forming liquids. They start from the observation that elasticity in these systems emerges from the growth and increasing lifetime of irregularly shaped clusters of highly localized particles (which are directly observable *via* microscopy). They argue that the degree of localization must vary within these 'fractal' clusters. Inspired by the Rouse model of polymer chain dynamics, they numerically average eqn (6) over the distribution of local relaxation strengths implied by this model to obtain the numerical approximant:

$$\langle r^2 \rangle = \langle u^2 \rangle [1 - \exp(-(\hat{t})^p)]. \quad (7)$$

In this relation, the exponent p is related to the fractal dimension of the emergent 'immobile' particle clusters and, more generally, quantifies the distribution of local elastic constants within these clusters. Later work by Weitz and coworkers has further quantified the properties of these growing immobile particle clusters and their relation to the emergent elasticity of the glass-forming liquid.⁴⁵ Observations by Hobbie and Stewart on another colloidal fluid confirm this physical picture.⁴⁶

Simulation studies of glass-forming liquids provide extensive evidence for the growth of fractal clusters of immobile particles that are apparently similar in geometry to those in colloidal glass-forming liquids.^{47–55} This similarity is natural since both systems are characterized by emergent elasticity. It is thus natural to describe relaxation in colloidal and molecular glass formers from a unified perspective.

Before attempting to apply this approach to molecular fast relaxation, we note that the approximant for $\langle r^2 \rangle$ given by eqn (7) is problematic at short times. In particular, eqn (7) implies the non-analytic short-time scaling $\langle r^2 \rangle \sim \hat{t}^p$ rather than the correct scaling $\langle r^2 \rangle \sim \hat{t}$. To resolve this consistency issue, we propose the modified approximant

$$\langle r^2 \rangle = \langle u^2 \rangle [1 - \exp[-(\hat{t})^p]]^{1/p}, \quad (8)$$

which by construction exhibits the correct asymptotic behavior at short times. Notably, this new relation is compatible with eqn (7) at intermediate to long times; Krall and Weitz' physical picture of fast relaxation is thus preserved. Accordingly, p retains its physical interpretation in terms of the fractal dimension of the emergent elastic network. We now apply eqn (8) to fast relaxation in a molecular glass-forming liquid.

Since we have shown that the Gaussian approximation holds very well at these short times, the self-part of the intermediate scattering function is obtained explicitly by combining eqns (2) and (8):

$$F_s(q, t) = \exp \left\{ -\frac{q^2}{6} \langle u^2 \rangle \left[1 - \exp[-(\hat{t})^p] \right]^{1/p} \right\} \quad (9)$$

As shown by Fig. 11, this form yields an excellent fit to the entire short-time relaxation (from $\tau = 0$ through the caging time) over the entire glass formation range, from deep within the glass state up to T_A . There is some loss of fit quality at long times at the most highly elevated temperatures, but this is an expected consequence of mixing of the short-time beta relaxation process with the alpha relaxation process. We note that the time range over which this fit holds is much broader than those for both the MCT power law fit and the empirical stretched exponential fit considered above.

Fig. 12 indicates that the values of both p and τ_f are roughly constant to within statistical error in the glass state. More specifically, for the pure polymer $p = 0.48$ and $\tau_f = 0.14$ are found to provide excellent fits to the entire short-time decay for all temperatures less than T_g and to provide reasonable fits up to the crossover temperature T_c . As mentioned above, this temperature domain corresponds to that in which caging is well established. Above this range, p should be interpreted as being related only to

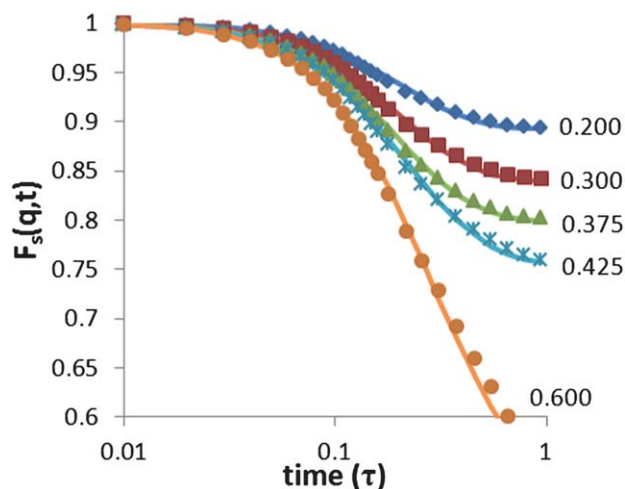


Fig. 11 Fit of eqn (9) (solid lines) to self-intermediate scattering function data (points) for the pure polymer system. The number next to each data set indicates the corresponding reduced system temperature. Fits of data below T_c are based on the average temperature independent values of p and τ_f observed at low temperature, as discussed in the text. Fits at higher temperature are based on optimized values of p and τ_f at that temperature.

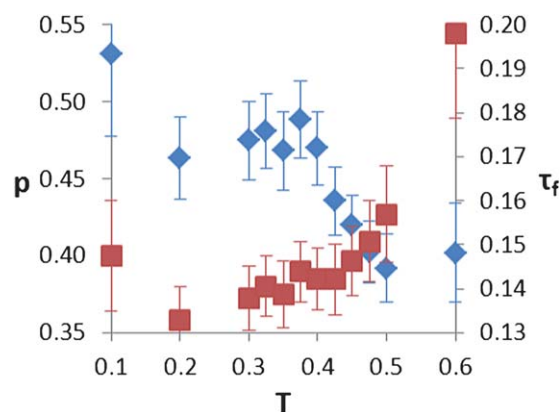


Fig. 12 Fit values of p (blue diamonds) and τ_f (red squares) as a function of temperature for the pure polymer system. Error bars denote 95% confidence intervals.

an *effective* fractal dimension of the transient elastic clusters forming in the cooled or concentrated fluid.^{46,48,51–55} In this higher temperature range, we see that p decreases with increasing temperature up to T_A .

This result suggests that the fractal structure of the elastic network of immobile particles, as characterized by p , is a temperature-independent property of the system below T_c , as is τ_f . Evidently, the only parameter that changes significantly with temperature below T_c is the size scale $\langle u^2 \rangle$ of the cages, and changes in short-time dynamics with temperature should thus purely reflect the change in cage size with temperature.

Consistency of the above result with the separate temperature dependence of the inertial dynamics illustrated in Fig. 5 requires that the inertial effects are subsumed by $\langle u^2 \rangle$. In other words, for a given system, the slower inertial dynamics at lower temperature must yield a correspondingly lower $\langle u^2 \rangle$ such that all explicit dependence of $\langle r^2 \rangle$ and $F_s(q, t)$ on temperature is lost. This result can be understood in the context of earlier work suggesting that the Debye–Waller factor reflects a competition between inertial and elastic effects.¹⁵

Conclusions

We have employed coarse-grained molecular dynamics simulation of a glass-forming polymer melt to study the nature of fast relaxation in glass formers, with the following conclusions regarding the questions posed in the introduction.

(1) How is particle caging affected by antiplasticization?

With the addition of antiplasticizers, the Debye–Waller factor decreases at low temperature (signifying enhanced particle caging) but increases at high temperature (signifying weakened particle caging). The reduction in Debye–Waller factor in the glass state by antiplasticizing additives can be expected to correspond to increased material stiffness. Indeed, previous simulations¹⁹ have demonstrated a corresponding increase in shear and bulk moduli for the same model. The present work is the first simulation study to observe this ‘stiffening’ effect in terms of the Debye–Waller factor. This consistency reinforces the interpretation of $kT/\langle u^2 \rangle$ as a basic measure of material elasticity.

(2) What functional form describes structural relaxation at these short timescales, and what is the nature of the molecular motions of

which short-time relaxation comprised? Is the relaxation purely inertial or does it deviate from inertial behavior in some way? Does one of the other relaxation functions argued for by the coupling model or mode coupling theory hold?

We find that an empirical 'stretched Gaussian' fit to short-time relaxation yields important physical insights into the fast relaxation process. However, our analysis suggests that the apparent 3/2 exponent observed in this and other studies is not universal and depends both on the nature of the system's gamma relaxations (other relatively high frequency relaxations associated with local molecular motion) and of the short-range interactions between particles in the system. In particular, this apparent stretching exponent can be tuned by modifying the polymer backbone bond strength. We find that fitting to the power law form predicted by the mode coupling theory⁶ requires that the power have an appreciable temperature dependence, an effect not predicted by that theory. The coupling model is also found to give an unsatisfactory fitting description of our data.

A new model for the fast relaxation is proposed based on domination of the short-time response by emergent elasticity and by the formation of fractal elastic clusters. This form for the relaxation, deduced from a modest extension of the model for fast dynamics of colloidal glass-formers by Krall and Weitz, exactly recovers by construction the correct limiting behavior at long and short times and provides an excellent fit to the entire short-time relaxation at all temperatures examined. Below the crossover temperature T_c , the only temperature dependent parameter is the Debye–Waller factor, implying that for a given system short-time relaxation in the glass state is a function of particle caging-size scale only. This result points to the essential nature of the fast relaxation: it reflects a balance between inertia and elasticity. The elasticity grows out of the formation of large-scale clusters, and relaxation in this regime is thus expected to be highly finite size dependent, as has been observed experimentally.⁵⁶

(3) *What is the nature of the tuning of fast dynamics in glass-forming liquids by antiplasticizer additives over a wide range of temperatures?*

We find that antiplasticization has an inverse effect on the fast beta relaxation time, as determined from the empirical stretched-Gaussian fit, at high and low temperature. This 'crossing' parallels the same behavior in both the Debye–Waller factor and various moduli, suggesting that the fast beta decay, unlike the inertial process, is sensitive to antiplasticization and is expected to play a central role in the improvement of protein preservation with antiplasticization.

More broadly, the model proposed in this paper suggests that the tuning of the short time dynamics has two basic origins: modification of the particle caging size and alteration of the fractal dimension of the elastic network. Simply by reducing cage size, the addition of antiplasticizers should slow the fast beta relaxation.

(4) *How do the various measures of dynamics at this time scale (Debye–Waller factor, non-ergodicity factor, time dependence of the structural relaxation) relate?*

We show that the short-time success of the Gaussian approximation for the distribution of particle displacements results in clear interrelations between the Debye–Waller factor, the non-ergodicity parameter, and the fast beta relaxation time as

determined from an empirical stretched-Gaussian fit. At temperatures below roughly the crossover temperature T_c , for which the Debye–Waller factor is well defined, the interrelations between these properties appear to be universal for our systems.

(5) *More broadly, how can answers to the above questions point the way to improved protein preservation via tuning of fast dynamics by antiplasticizer additives?*

Many of the studies in this area consist of purely empirical correlations between various fast dynamics properties and protein preservation times. While these correlations appear to be phenomenologically well-founded, their physical origins remains obscure. There is a considerable need to understand from a fundamental standpoint the interrelations between these fast dynamics properties. The present work is a step in this direction.

A number of recent studies have identified a strong empirical correlation between the measured non-ergodicity parameter (defined on a picosecond timescale) and protein preservation time (timescale on the order of days to months). This correlation has been rationalized on the basis of a presumed relationship between the non-ergodicity parameter and the Debye–Waller factor. In this study, we have confirmed the validity of this relationship. Moreover, we have extended this reasoning to demonstrate that the empirical fast beta relaxation time should provide an additional measurement target for the identification of systems with improved preservative properties. However, to our knowledge this expected relationship has not been exploited in the design of enhanced protein preservation formulations. We also expect that the Boson peak frequency should correlate with protein preservation (and other fast dynamic properties) on the basis of the Gaussian approximation, and we plan to examine this expectation in subsequent work. Future experimental research on protein preservation should validate and leverage these new interrelations between fast dynamic properties.

Our results also support an emerging understanding of the physical origin of protein preservation enhancement by antiplasticizers. Previous experiments have indicated that antiplasticizers reduce the Debye–Waller factor in the glass state, and the present study provides the first clear simulation evidence for this effect. A reduction in Debye–Waller factor has been shown to imply a reduction in free volume¹⁵ and it is natural to expect that this should suppress the diffusion rate of gases and other small species that can react with the proteins. As noted above, the reduction in Debye–Waller factor by antiplasticizing additives also corresponds to increased material stiffness in the glass state. Additionally, we find that antiplasticizers increase fast beta relaxation time in the glass state. These facts support the hypothesis that a reduction in the amplitude of local molecular motions translates into improved protein stability through a coupling between the glassy matrix and protein dynamics.

Beyond these immediate conclusions, we expect that our unified model for the fast dynamics of colloidal and molecular glass forming liquids should have broad implications for the physics of glass formation. For example, we expect that the parameter p from eqn (9), relating to the fractal dimension of elastic clusters, should depend on fragility and intermolecular potential, and a future study will examine this possibility. We also plan to study whether the temperature dependence of this parameter at temperatures above T_g correlates with the temperature dependence of the stretching exponent

characterizing the alpha relaxation. The temperature dependence of this latter exponent has been shown to be highly dependent on the intermolecular potential⁵⁷ and other factors that influence the fragility of glass formation.⁵⁸ This comparison should aid in developing an improved understanding of the interrelation between the beta and alpha relaxation processes, which has previously been discussed based on relaxation time data alone.^{5,59}

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