Role of $\alpha$ and $\beta$ relaxations in Collapsing Dynamics of a Polymer Chain in Supercooled Glass-forming Liquid

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Understanding the effect of glassy dynamics on the stability of bio-macromolecules and investigating the underlying relaxation processes governing degradation processes of these macromolecules are of immense importance in the context of bio-preservation. In this work we have studied the stability of a model polymer chain in a supercooled glass-forming liquid at different amount of supercooling in order to understand how dynamics of supercooled liquids influence the collapse behavior of the polymer. Our systematic computer simulation studies find that apart from long time relaxation processes ($\alpha$ relaxation), short time dynamics of the supercooled liquid, known as $\beta$ relaxation plays an important role in controlling the stability of the model polymer. This is in agreement with some recent experimental findings. These observations are in stark contrast with the common belief that only long time relaxation processes are the sole player. We find convincing evidence that suggest that one might need to review the the vitrification hypothesis which postulates that $\alpha$ relaxations only long time relaxation processes are the sole player. We find convincing evidence that suggest that one might need to review the the vitrification hypothesis which postulates that $\alpha$ relaxations control the dynamics of biomolecules and thus $\alpha$-relaxation time should be considered for choosing appropriate bio-preservatives. We hope that our results will lead to understand the primary factors in protein stabilization in the context of bio-preservation.

INTRODUCTION

Many organisms can survive in dehydrated state for long period of times by accumulating large amount of sugars (sometime 20 – 50 % of the dry weight) [1, 2]. These carbohydrates (mainly trehalose and sucrose) stabilize proteins and membranes in dry state [2]. There are many hypotheses for this protein stabilization and they mainly focus on the vitrification of the stabilizing sugar matrix along with the biomolecules and water replacement from the neighbourhood of the biomolecules by the sugar [2] [4]. In the water replacement hypothesis, it is believed that water molecules are replaced by sugar which provides appropriate hydrogen bonds to polar residues of macromolecules thereby stabilizing them thermodynamically. A slightly refined hypothesis is water entrapment hypothesis, in which it is argued that interfacial waters provide stabilization of local conformations of biomolecules. Some regions on the surface of the biomolecule are more hydrophilic than others which leads to preferential binding of water molecules at biomolecule-sugar interface.

On the other hand, vitrification hypothesis is purely based on kinematics. It is assumed that the carbohydrates form glasses at high concentrations or in dry state and thereby slow down the degradation process of biomolecules. This hypothesis mainly focuses on how glassy materials relaxes at longer time scale. A well-known example of such a phenomena is the preservation of insects in amber for millions of years, suggesting that vitrification is one of the best choices for nature for bio-preservation. A recent hypothesis which is a variant of the vitrification hypothesis, suggests that the shorter time-scale $\beta$ relaxation rather than slower and longer time $\alpha$ relaxation of the glass-forming liquid is actually responsible for the degradation of the biomolecule in sugar glasses [5, 6].

All of these hypotheses suggest rather different approaches to design appropriate sugar glass model to optimally increase the stability of biomolecules for preservation. A clear understanding towards this direction warrants consideration of all the relevant relaxation processes in glass forming liquids, which is summarized below.

Relaxation of density fluctuations in supercooled liquids is hierarchical and happens in multiple steps as the putative glass transition temperature is approached. After a fast initial decay the correlation functions approaches a plateau and then at subsequent long-time it decay to zero. The relaxation that happens in the plateau like regime is called $\beta$ relaxation and the longer time decay from the plateau to zero is called $\alpha$ relaxation [7] [10]. It is well-known that the $\alpha$-relaxation is very heterogeneous and cooperative in nature with a associated growth of a dynamic heterogeneity length scale [5, 6] [11]. On the other hand $\beta$-relaxation is believed to be more local process without any significant growth of correlation length [12], but recent studies have suggested that shorter time relaxation processes are probably also cooperative in nature with length scale that grow very similarly as the long time dynamic heterogeneity length scale [13] [14].

This indicates that if cooperative motions are required for certain relaxation process to happen in a molecules embedded in supercooled liquid, then both short and long time relaxation processes will probably play equally important role. For example, if $\alpha$-relaxation plays a key role in degradation of protein molecules in glassy matrix due to its cooperative nature to induce mobility in these biomolecules which are much larger compare to the solvent molecules, then shorter time $\beta$-relaxation process will also be able to induce such mobility especially at
lower temperatures where the time scale related to $\beta$-relaxation does not become super exponentially larger compare to $\alpha$-relaxation time. Indeed in a recent experiment, it is suggested that $\beta$-relaxation plays very important role in the preservation of protein in sugar glasses [5, 6].

Although the physical and chemical processes that degrade a macromolecule is known, the microscopic mechanisms of how glassy matrix helps to slow down these physical and chemical degradation process of a biomolecules is not clearly understood. A clear understanding of these microscopic mechanisms will reduce the trial-and-error aspect of lengthy and tedious long-term stability studies in many fields such as food, pharmaceuticals. The goal of this work is to understand how the dynamics of biomacromolecule might couple to the dynamics of supercooled liquids and how rates of different processes are modified by the embedding liquid as it is supercooled with decreasing temperature. In this regard, we have quantified the collapse dynamics of a model polymer chain [15] in a well-known glass forming liquids[16] using extensive molecular dynamics simulations. The use of a homopolymer as a system of choice avoids the inherent molecular heterogeneity of diverse amino-acids in a protein, where isolating individual contributions to a glassy-matrix induced change in stability is a difficult task and also provides an incentive for exploring the action of glassy matrices on hydrophobic interaction, one of the central driving forces for protein folding. The model helps us to clearly understand how crowding due to the dense packing of embedding glassy liquid molecules particularly influence the dynamics of model biomolecule and whether the dynamics of the biomolecule can be slaved to the dynamics of the supercooled liquids. We find that indeed the dynamics of a polymer chain can be slaved to the dynamics of the supercooled liquid even when the polymer interacts very weakly with the liquid molecules.

The rest of the paper is organized as follows. First we will discuss about the models studied and the details of the simulations and then introduce correlation functions that we have calculated to characterize the relevant relaxation processes in glass forming liquids. Finally we show our results and discuss the implications of these results in the context of bio-preservation.

MODELS AND METHODS

We have studied the well known Kob-Anderson 80:20 binary glass former Lennard-Jones mixture [16] as the solvent. The interaction potential in this model is given by,

$$V_{AB}(r) = 4\epsilon_{AB} \left[ \left( \frac{\sigma_{AB}}{r} \right)^{12} - \left( \frac{\sigma_{AB}}{r} \right)^{6} \right]$$  \hspace{1cm} (1)

where $\epsilon_{AA} = 0.997$, $\epsilon_{AB} = 1.4955$, $\epsilon_{BB} = 0.4985$, $\sigma_{AA} = 0.34$, $\sigma_{AB} = 0.272$, $\sigma_{BB} = 0.2992$. The units of $\epsilon$ is kJ/mole and unit of $\sigma$ is in nm (all are transformed to real unit in terms of Argon).

This binary mixture works as a solvent for a 32 bead model polymer. The polymer model closely resembles that of Berne and coworkers [15]. The constituent polymer beads are connected to the covalently bonded neighbor by a harmonic potential, with an equilibrium bond length of 0.153nm (the same as CH2-CH2 bond length). The angle between adjacent covalent bonds is represented by a harmonic potential, with an equilibrium angle of 111° (the same as CH2-CH2-CH2 bond angle). The polymer is uncharged and the beads interact among themselves and with their environment via Lennard-Jones potentials. The bead diameter is fixed at $\sigma_b = 0.4 nm$ and the bead-bead interaction is fixed at $\epsilon_b = 11$ kJ/mol. Non-bonded interactions between a bead and its first and second nearest neighbors were excluded, and no dihedral interaction terms were included. The hydrophobic character of the chain can be tuned by varying the intermediate interaction between polymer beads and particles constituting glassy matrices using geometric combination rules. Specifically, the polymer-glass interaction potential is given by $\sqrt{\epsilon_p} * \epsilon_{AA}$ and $\sqrt{\epsilon_p} * \epsilon_{BB}$, where we have independently varied the value of $\epsilon_p = 0.1, 1.0$ and 3.0 kJ/mol in separate simulations for tuning polymer-liquid interactions. In essence, $\epsilon_p$ denotes the polymer contribution towards the inter polymer-glass interaction. On the other hand, the inter-polymer-glass interaction-range has been calculated by $\sqrt{\sigma_b * \sigma_{AA}}$ and $\sqrt{\sigma_b * \sigma_{BB}}$. A cutoff of 1.2nm was used to treat the nonbonding interactions and periodic boundary condition condition was

FIG. 1: Extended Configuration of the polymer inside the binary mixture. The actual size of the solvent glassy molecules have been scaled down in the figure for clarity.
implemented in all dimensions. The temperature range studied for this model is $50 - 120K$. Number of particles we have chosen for the binary mixture is 9600 in a cubic box of dimension 6.8 nm. The same average density was maintained throughout the simulations.

All the molecular dynamics simulations have been performed using GROMACS 5.1.4 software. We have solvated the energy-minimized extended configuration of the polymer chain into the energy-minimized binary mixture for each case. The systems were first energy minimized by steepest descent algorithm and then equilibrated for 100 ps at 260K in NVT ensemble and then in NPT ensemble for 200 ps. The systems were then annealed to desired temperatures at a cooling rate of 0.5 K/ps and then subjected to a NPT equilibration for 20 – 1500 ns depending on the temperatures. Note that equilibration runs for each temperatures are at least $100\tau_\alpha$ or more longer. $\tau_\alpha$ is the $\alpha$ relaxation time (defined later) of the solvent glass forming liquid. Finally the systems were subjected to production run in NPT ensemble. The reference pressure for NPT simulations in last part of equilibration and production run was the average pressure obtained from the equilibrated binary mixture without the polymer. The integration time step used is $dt = 0.002$ ps. Berendsen and V-rescale thermostat has been used respectively during equilibration and production runs to maintain the average temperature. On the other hand Berendsen and Parrinello-Rahman barostat to keep pressure fixed during equilibration and production runs respectively.

**RESULTS AND DISCUSSION**

All our simulations start with an extended configuration of the polymer (Radius of gyration $R_G = 1.2nm$) as shown in Fig.1 in a well equilibrated supercooled liquid state of the solvent mixture at different studied temperatures in the range $T \in [50K, 120K]$ and we explore the transition of the polymer from extended to collapsed conformation during the course of the simulation. Time profile of Radius of gyration of the polymer is calculated (as shown in top right panel of Fig.2 for $T = 50K$) to quantify the collapse-dynamics of the polymer and the collapse time, $\tau_c$ (defined later) is estimated by identifying the time of sharp transition from extended to collapsed conformation at different supercooling temperatures. This collapsing timescale is then compared with the intrinsic relaxation time scale ($\tau_\alpha$) of the glassy liquid. In left top panel of Fig.2 we have shown one such instance of the collapsed configuration of the polymer. The solvent binary supercooled liquid molecules are also shown by reducing their actual size for clarity.

The choice of a large intra-bead interaction parameter ($\epsilon_b = 11kJ/mol$) renders a strong propensity for the polymer-collapse and hence allows us to observe the collapse behavior of the polymer for entire range of temperature of interest $T \in [50K, 120K]$ within simulation time scale. So in gas phase the polymer collapses very quickly with a very low temperature dependence as shown in bottom left panel of Fig.2 (green square symbols). The reason for choosing such polymer parameters is to explore whether dynamics of supercooled liquid can slave the dynamics of the polymer even when the polymer interacts weakly with the liquid compared to its own interaction strength. We also have shown a comparison of the collapsing timescale in the same panel (red circle) when the polymer is immersed in supercooled liquids with particular interaction (discussed in details later). The changes in the collapsing timescale compare to the gas phase timescale is really dramatic. This clearly proves why glassy matrices are chosen for bio-preservation.

We have used three different $\epsilon_p$ value to control the interactions between glass molecules and polymer beads. The $\epsilon_p$ values for polymer-liquid interactions are 0.1, 1.0 and 3.0kJ/mol. Before going in to discussing our main observations, we will briefly discuss how characterization of the supercooled liquid is done. Relaxation time is measured from the decay of a modified version of the two point density-density correlation function $Q(t)$, also known as overlap correlation function [11]. It is defined
percooled liquid and the collapse time, \( \tau_c \) coupling between \( K \) timescales are found to be equal to 38 for details). The VFT divergence temperatures for both the

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\tau_\alpha \text{ and } \tau_c \text{ are found to be close to } 38K \text{ suggesting a strong coupling between the dynamics of supercooled liquid and the collapsing dynamics of the polymer chain. Note that the polymer chain collapse very rapidly in gas phase, whereas its dynamics now is slaved to the dynamics of the solvent glassy liquids.}

Next we compare \( \alpha \)-relaxation time, \( \tau_\alpha \) of the supercooled liquid and the collapse time, \( \tau_c \) for a situation where the solvent supercooled molecules interacts somewhat strongly with the polymer chain molecules. Specifically the polymer-solvent intermediate interaction is tuned by using \( \epsilon_p = 3.0 \text{kJ/mol} \), keeping polymer bead-bead interaction fixed at \( \epsilon_b = 11 \text{kJ/mol} \). In Fig.3 we have plotted collapse time of the polymer along with the \( \alpha \) relaxation time of the liquid for different temperatures for this particular choice of the parameter. It is clear that, at least in the studied temperature regime, \( \tau_\alpha \) controls the degradation rate, supporting the “Vitrification Hypothesis”. One may infer that better stability needs larger value of \( \tau_\alpha \) of the preservative. We have fitted both \( \tau_\alpha \) and \( \tau_c \) by Vogel-Fulcher-Tamman (VFT) formula [17], defined as \( \tau = \tau_0 \exp (A/(T - T_0)) \), where \( \tau_0, A \) and \( T_0 \) are free parameters. \( T_0 \) is known as VFT divergence temperature and is very closed to the Kauzmann Temperature [18]. The divergence temperatures for both \( \tau_\alpha \) and \( \tau_c \) are found to be close to 38K suggesting a strong coupling between the dynamics of supercooled liquid and the collapsing dynamics of the polymer chain. Note that the polymer chain collapse very rapidly in gas phase, whereas its dynamics now is slaved to the dynamics of the solvent glassy liquids.

Next we look at the other extreme in which we choose an interaction parameter such that the polymer chain interacts very weakly with the solvent liquid molecules. We choose the value of \( \epsilon_p \) contributing to solvent-polymer interaction to be 0.1kJ/mol, so in this limit polymer dynamics will be mainly affected (if at all) by the crowding effect of the solvent glassy molecules. In Fig.4 we show the temperature dependence of the two timescales and surprisingly, they cross each other at some intermediate temperature, \( T \sim 55K \) in this case. The corresponding VFT fits also suggest that the extrapolated divergence temperatures are very different from each other. This is now in contrast with our previous observation, where both the timescales are more or less proportional to each other. This new result suggests that only \( \alpha \)-relaxation time is not the main controlling parameter, especially at lower temperatures, where a much faster relaxation process, probably \( \beta \)-relaxation process seems to play a role in the dynamics of the polymer chain. This is in complete agreement with recent experimental observations [5, 6], where it is suggested that protein preservation in sugar glasses is directly linked to high frequency \( \beta \)-relaxation process as protein stability seems to increase almost linearly with \( \tau_\beta \) when \( \tau_\beta \) is increased by adding anti-plasticizing additives. These additives are found to increase the \( \beta \)-relaxation time even though it decreases \( \alpha \)-relaxation time [2].

In a bid to further understand whether it is the glassy dynamics that is slowing down the collapsing dynamics of the polymer chain, we performed quenching studies in which we decrease the temperature of the supercooled liquid rapidly from its initial equilibrium temperature. It is well known that if we quench a glass forming liq-

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Q(t) = \sum_{i=1}^{N} w(|\vec{r}_i(0) - \vec{r}_i(t)|) \tag{2}
\]

where \( \vec{r}_i(t) \) is the position of particle \( i \) at time \( t \), \( N \) is the total number of particles. The window function \( w(x) = 1 \) if \( x \leq a \) and 0 otherwise, where \( a \) is a cut-off distance at which the the root mean square displacement (MSD) of the particles as a function of time exhibits a plateau before increasing linearly with time at long time. The precise choice of \( a \) is qualitatively unimportant. This window function is chosen to remove any de-correlation that might happen due to vibrational motions of the solvent particles inside the cages formed by their neighbours. In this study we have taken \( a^2 = 0.006 \text{nm} \). The relaxation time \( \tau_\alpha \) is defined as \( \langle Q(t = \tau_\alpha) \rangle = 1/e \), where \( \langle \ldots \rangle \) refers to ensemble average.

The collapse time \( (\tau_c) \) of the polymer chain is obtained from the time dependence of the radius of gyration \( (R_G) \) of the polymer chain. In top panels of Fig.2 we have shown the \( R_G \) as a function of time closed to the collapsing transition for \( T = 50K \) as an illustrative collapse profile. In all our analysis, we have considered the chain to be in the collapsed state when \( R_G \) became 0.50nm. In bottom right panel of Fig.2 we have shown the temperature dependence of the collapsed time for three different cutoff radius of gyration for collapsed state of the polymer as 0.45, 0.50 and 0.60nm. As evident, a different choice of the cut off radius gyration to define the collapsed state does not change the results qualitatively.
uid to low temperature then it shows aging and initially it relaxes almost at the same timescale as that of the initial temperature from which it is quenched. The relaxation time then gradually increases with increasing waiting time. Now, if the dynamics of the polymer chain is slaved to the dynamics of the supercooled liquid, then if we quench the whole system, the polymer should still be able to collapse in a timescale which is almost same as the initial temperature from which it is cooled. In Fig.4, we show that collapse time (referred here as $\tau^c_q$) seems to depend on the initial temperature ($T = 120K$) from which it is quenched, irrespective of the final temperatures (green diamonds, $T = 70, 60, 55, 50K$ respectively). In all these quench studies, the equilibrium collapse time is many orders of magnitude larger than the time obtained if the system is quenched to these temperatures from high temperature. This observation seems to corroborate with an old experimental finding [19], where it was noted that survival probability of frozen and thawed yeast is orders of magnitude more if it is cooled very slowly.

We then increase the polymer-solvent interactions a bit more by increasing the value to an intermediate value $\epsilon_p$ to $1kJ/mol$ and $\epsilon_p=3$ kJ/mol for the temperature of range of interest. The lines are the fit to the VFT formula (see text). $\tau^b_q$ is the collapsing time obtained in the quench studies (see the text for further details).

![Image](image1.png)

**FIG. 4:** Comparison of timescale for a polymer with $\epsilon_p=11$ kJ/mol and $\epsilon_p=3$ kJ/mol for the temperature of range of interest. The lines are the fit to the VFT formula (see text). $\tau^b_q$ is the collapsing time obtained in the quench studies (see the text for further details).

In conclusion, we have shown that dynamics of supercooled glass forming liquids play a major role in controlling the collapsing dynamics of a polymer chain at various temperature. At certain polymer-solvent interaction strength, the polymer can be completely slaved to the long time $\alpha$-relaxation of the glassy liquid, on the other hand at low polymer-solvent interaction strength, at which the polymer is passive to the liquid and only packing of the solvent molecules around the polymer molecule is relevant, both short time $\beta$ and long time $\alpha$ relaxations play intricate role at different temperature regimes. We also have shown that coupling between the solvent dynamics and polymer becomes weak if one does quenches from high temperatures due to aging in the glassy liquids. This suggests that flash freezing might not be a good method if one wants to preserve a biomolecules in glassy matrix. Thus “Vitrification Hypothesis” although might be valid for some biomacromolecules, need serious revision to include the effect of shorter time scale processes like $\beta$-relaxation in order to better understand bio-preservation in glassy sugar matrix. In a recent work [20], it is shown that reaction kinetics of polymer collapsing dynamics depends on viscosity of supercooled liquids with a fractional power. This again supports our findings reported in this work very strongly. Finally, in our model studies all complicated interactions like hydrogen bonding and complex structural aspects of the biomolecules are not incorporated, thus it will be important to do further studies to understand how these different parameters influence the results reported here.

![Image](image2.png)

**FIG. 5:** Temperature dependence of $\alpha$-relaxation time and collapse time for the case of $\epsilon_p$ equal to 1.0 kJ/mol. The cross over temperature is now shifted to lower temperature compare to the case when $\epsilon_p$ was 0.1 kJ/mol.

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