Out of equilibrium dynamical systems, the path from A to B.

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Summary

In recent work, we have shown how to understand the properties of a slow, out-of-equilibrium system by studying dynamical properties – namely an ensemble of trajectories. These studies were two pronged, first they involved physical insight into the basic nature of glassy systems as well as development of methods to study such ensembles of trajectories. The true nature of glasses is far from being agreed upon, but progress in this arena has allowed us to bridge gaps between various methods of calculating thermodynamic and dynamic properties towards a unified picture of supercooled liquids. In this statement I propose to further this work not only to study glasses but also to extend the methods developed to study these systems to other systems such as the biophysical problem of crowded cellular environments. Moroever, beyond applying these methods, I propose to extend these methods even further, thus allowing us to not only learn more information about the physical world we live in but also gain new ways to engineer models and novel materials to preform desired behaviors.

1 The Glass Transition

Supercooled liquids and the glass transition are a much debated and poorly understood physical phenomenon. The nature of supercooled liquids is inherently out of equilibrium as the equilibrium state (crystalline solid) is avoided by a slow cooling protocol that frustrates the previously in-equilibrium liquid. In recent work, we have shown how it is possible to take a wide range of experimental data for molecular glass former transport properties and collapse them onto a single curve. Many of the data taken on supercooled liquids originate from measurements that involve probe particles - guest particles that are used as 'thermometers' for their host liquid which can be used as recorders of transport properties as well as dynamic heterogeneity. One behavior that has yet to be fully understood is to what extent these probes can record useful information about their host solvents. Conventionally, probe particles are made to be as "inconspicuous" as possible to mimic the behavior of the host. I would like to investigate how far this can be pushed. For example, can the probe size be swelled until the probe is on the order of the size of dynamic heterogeneities. Once the probe size is of that order it should recover the mean field behavior of an average liquid – for example, the diffusion constant and the relaxation time should be coupled as per the Stokes-Einstein equation, even when the host supercooled liquid shows decoupling. I intend to study the effects of probe particles on host liquids by use of molecular dynamics and Monte-Carlo simulations of glass-formers. Through these studies, it can be understood to what extent the probe particle can be used as a molecular thermometer for the host and, moreover, to what extent and in what regime does the probe actually disturb the normal dynamics of the host liquid. These insights are useful to experimentalist who often assume that the probe acts only as a 'passive' recorder of the host solvent's dynamics. The extent to which this assumption is valid, is something that should be further tested.

2 Crowded Environments

Recently, many have touted the analogy between crowded cellular environments and the colloidal glass transition. By increasing the osmotic pressure inside a cell, experimenters were able to 'jam' the interior environment, just as they would a dense colloidal or granular material. While this pressure was applied in a laboratory, this increase in pressure is also felt during rapid tumor formation as cells become more

and more densely packed due to rapidly dividing cells. Since cells are crowded out of equilibrium environments they share many features with supercooled liquids – also dense packings of molecules, only on a different scale. Recent numerical work and simulation technique advances have been used to shed light on elementary motion in such supercooled environments. By exploiting the similarity, large molecular simulations of a dense cellular work coupled with new techniques can be used to further study basic motion of small proteins as they diffuse in such a crowded environment. These simulations would use techniques of transition path sampling to characterize the ensemble of possible moves as a protein escapes its environment by exiting its cage. Questions about the nature of these motions – and to what extend they resemble the facilitated motions in granular and colloidal materials – would help us understand the physical environment of the biological material that makes up a cell.

Intracellular materials are not the only biological system with analogies with jammed materials. Recent work in microfluidic devices have shown how sickle-cell disease manifests itself when cells change their shape and form clots is small chambers (veins). The geometry of the cells as they "sickle" has been shown to play an important role in acute attacks of the disease. Understanding basic elementary processes about how clots form and break apart can be of use to creating new treatment for the disease. For example, it has been shown that a small molecular inhibitor can be used to break up such clots, however that inhibitor was carbon monoxide – a toxic chemical. Molecular simulation may be useful in understanding what kind of guest molecules would be best at preventing and treating these clots. Perhaps by elucidating which size and shape molecules can be used to frustrate the formation of such clots. Again being able to single out elementary steps using transition path sampling techniques will help elucidate the key steps to the formation and destruction of such clots.

3 Sampling Methods

In a recent interview, when asked what the greatest challenges for computational materials science is, pioneering researcher Michele Parrinello stated that "...sampling is really the most important aspect to be improved...". To that end, I will develop methods to improve sampling and design in materials. The first aim of this work is to use a new parameter space sampling technique to investigate ensembles of trajectories. This method would investigate rare events in complex dynamical systems with increased computational efficiency. The second aim is to use a novel method to optimize parameters to select for a certain dynamical behavior. This second technique would allow us to engineer models which strike a balance between thermodynamics and dynamics. Both methods have applications for studying glass formers, biophysics, and designing novel materials.

To investigate behaviors of rare events , we have used advanced sampling methods developed to study ensembles of trajectories. The most significant of these was transition path sampling (TPS) This method has allowed people to probe a diverse set of dynamical problems from supercooled liquid dynamics to biological self-assembly. While current methods can investigate trajectory space for fixed parameters very well, few techniques exist which allow for crossing large barriers in parameter space. Traversing dynamical barriers in trajectory space suffers the same pitfalls as traversing barriers in configurations space: barriers in space-time can prove too high to climb in a given parameter set, meaning that important regions of trajectory space may go unexplored. If this is the case, the TPS ensemble will be poorly converged and may not reflect the true nature of the underlying dynamical free energy landscape. In fact, even with our simple models, straightforward sampling leads to a large number of rejected trajectories.

Up until now, parameter space methods for parallel tempering have been limited to swapping static configurations with different parameters by taking into account the relative probabilities of these states. I propose and extension of this method to trajectory space which can mix both dynamical order parameters (which characterize a trajectory) as well as thermodynamic parameters (such as the temperature). This issue has only recently become tractable with advances in computing – both in advances in hardware as well as architecture designed to take advance of the parallel nature of supercomputers. In order to make such a trajectory space parallel tempering method fully functional, one has to calculate the path

probability for the entire trajectory - requiring storing each and every step and the current state of the system. Using this technique, the path probability can be reconstituted with any new arbitrary set of parameters and thus parallel tempering like swaps can be attempted between two trajectories run with different thermodynamic and dynamical parameters. This work can be extended to not only look at swaps between different thermodynamic variables but also between different protocols. One can imagine a trajectory whose temperature changes as a function of time, as long as the path probability of that trajectory can be computed for any arbitrary protocol, swaps can be made not only assuming that the trajectory has one unique value of temperature but any arbitrary time protocol. I will test these methods on two simple lattice models, the simple glass former models (KCMs) already known to exhibit interesting dynamical behavior as well as simple lattice models of proteins which have also been shown to be rich with unexpected dynamic phenomena.

Material Design

In the last twenty years, nanoparticles and their applications have come to the forefront of scientific consciousness. Many of these nanoparticles can be used for self-assembly: they spontaneously form aggregated complex structures. Many believe that the future will hold a wide array of uses for particles capable of self-assembly. Some have speculated that they will be useful for targeted drug delivery, optics , and surfactants. The exact structure of the final, assembled, group depends on the interactions between the nanoparticles and how those interactions dictate kinetic pathways to assembly. It has been noted that interactions should be strong but *not too strong* so that an unassembled system has enough time and energy to bind but also to anneal out defects. Unfortunately, targeted computational methods that optimize specified assembly pathways (and final structures) at viable conditions are not yet known.

Tuning interactions until they produce a desirable effect involves developing a method to allow trajectories to explore parameter space. For specific parameters of interest (which characterize, say, a biological system) we can get insight into dynamics by sampling other regions of parameter space. This allows us to sample not only the most probable values of our ensemble distribution but also the extremes.

Once this information is gathered, I use an ensemble of trajectories to optimize parameters that select for a particular behavior in a system with two basins, A and B. An example of such a system would be a self-assembly process where A is an unassembled state and B is an assembled state. We seek to optimize the probability of seeing a trajectory that goes from A to B given that the trajectory starts in A; that is, optimize, relative to the thermodynamic parameters, the probability of ending in state B given that the system started in state A.

Optimization methods for these kinds of problems have been recently promoted and are generally referred to as "maximum likelihood estimators". These methods can be then used iteratively until an ideal set of parameters is found that increases the probability of going from A to B. This method would act as a kind of conjugate-gradient method for path probability in parameter space. These results can be informed by real thermodynamic control parameters that experimentalists can actually tune – such as the interaction strength between particles (experimentally, say, by changing the solvent or tuning some magnetic field).