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

Yael S. Elmatad

Summary

Increasingly, statistical physics has had to grapple with scientific questions in which techniques of classical, equilibrium thermodynamics have to be stretched in order to apply to inherently slow and often driven systems. As these systems are out-of-equilibrium, it does not suffice to simply study ensembles of configurations. Instead, we are forced to examine dynamical ensembles of trajectories. One such problem is the glass transition. Reconciling the apparent disparity between the microscopic, disordered nature of glass and its macroscopic rigidity has confounded physicists for years. However, we have recently shown how studying a simple model in trajectory space can shed light on the true nature and universality of molecular glassformers. While these simple models have given us new insight into glasses, I propose to further my study of glasses by investigating the effects of probe particles on supercooled liquids. Specifically, I would like to understand to what extent probe particles are recorders of the dynamics of the host. I will use techniques developed to study supercooled liquids (eg. transition path sampling) to study other out of equilibrium processes such as motion in a crowded intracellular environment and clot formation in sickle-cell anemia. Beyond these applications, I will investigate new dynamical sampling methods. One such method would allow for parallel tempering in trajectory space – helping improve sampling efficiency in path ensembles. Another would allow create a protocol for designing novel materials by optimizing model parameters to create an ideal process for observing a desired effect (say, self assembly). In effect, this method would shift the focus from studying a set of trajectories given particular parameters, to studying a set of "models" given a desired process. Inverting the question allows us to not only learn more about the physical world we live in but also to gain new ways to engineer models and novel materials to perform 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 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 glassformer 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 material – acting as recorders of transport properties. To what extent these probes can record useful information about the material in which they are embedded is poorly understood. Conventionally, probe particles are designed to be as "inconspicuous" as possible to best mimic the behavior of the host. However, this passivity is often taken *a priori* and unverified. I propose to investigate this claim as well as see how far this can be pushed. For example, swelling the probe size might tell us something about inherent length scales. Once the probe size is of the order of the typical distance between dynamic heterogeneities (a hallmark of 'glassy' dynamics), 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 while the host supercooled liquid exhibits decoupling. I intend to study the effects of probe particles on host liquids by use of molecular dynamics and Monte-Carlo simulations. 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 experimentalists who often assume that the probe acts only as an ideal 'passive' recorder.

2 Crowded Environments

Recently, many have touted the analogy between crowded cellular environments and the colloidal glass transition. By changing the osmotic pressure, 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 change in pressure is similar to the pressure change during 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 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 system coupled with new techniques can be used to 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 macromolecular cage. These techniques have been used to study elementary cage hops in granular materials and are related to techniques I used to study simple glassformer models. Borrowing these techniques, we will be able to answer questions about the nature of these motions within a cell – and to whether or not they resemble the facilitated motions in granular and colloidal materials. This information would lead to a better physical understanding of such a complex, crowded environment.

Beyond intracellular material, analogies with jammed materials are also observed when examining *extra*-cellular materials. Recent work in microfluidic devices have shown how sickle-cell anemia manifests itself when cells change their shape and form clots is narrow veins. The geometry of the cells as they "sickle" has been shown to play an important role in acute attacks of the disease. Understanding elementary processes about how clots form and break apart can be of use to create new treatment for the disease. It has already been shown that a small chemical inhibitor that binds to red blood cells can alleviate clot formation. Unfortunately, this inhibitor is toxic. Alternatively, another treatment method might be to add an intruder which does not bind chemically, but rather frustrates the formation of such clots geometrically. The important elementary steps of formation and destruction of such clots can be studied using techniques of transition path sampling. The information from these simulations would add insights about this physical phenomenon that has devastating medical consequences. Moreover, this knowledge may help us understand what size and shape molecules would be best for treatment, perhaps offering a non-toxic alternative to chemical binding.

3 Sampling Methods

The problem of efficient and accurate sampling methods for complex systems is one that continues to challenge researchers even in the face of great technological and algorithmic gain. 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 glassformers, biophysics, and designing novel materials.

To investigate behaviors of rare events, we have used advanced sampling methods developed to study ensembles of trajectories. One of the most significant of these is 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 extending 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). 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. This computational demand has only recently become tractable with advances in computing – both in hardware as well as architecture designed to take advance of the parallel nature of supercomputers. Using this technique, the path probability can be reconstituted for any 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" (eg. cooling a liquid toward its glass transition). Take, for example, 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 attempted between these protocols. I will test these methods on two lattice models, the glassformer models (KCMs) I have already shown to exhibit interesting dynamical behavior as well as lattice models of proteins which are also 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. It is increasingly clear that the future will hold a wide array of uses for particles capable of self-assembly such as for targeted drug delivery, in optics, and as 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 will 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 maximization 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 host material or tuning an external field).