Advanced Thermodynamics and Molecular Simulations
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Lecture - 55
Multiple Histogram Method; Umbrella Sampling; Thermodynamic Cycle; Potential of Mean Force; Pulling Simulations; Meta-dynamics; Tackling Time Scale Issues.

Hello all of you, so in the last lecture we have been discussing the free energy calculations and where we ended was the overlapping distribution method where in what exactly we do is If I want to look at two systems 0 and 1 I compute the energy change between the two systems and this is then canonically averaged over both systems 0 and system 1 that is we find the probability distribution using system 0, p_0 (ΔU) and then using system 1 that is $p_1(\Delta U)$ and using these we construct essentially two functions f_0 and f_1 as a function of ΔU, which are basically based on simulations performed in system 0 and 1 respectively.

$$\Delta U = U_1 - U_0$$

and, then let us say if this is my f_0 and this is my f_1 the difference gives us the free energy.

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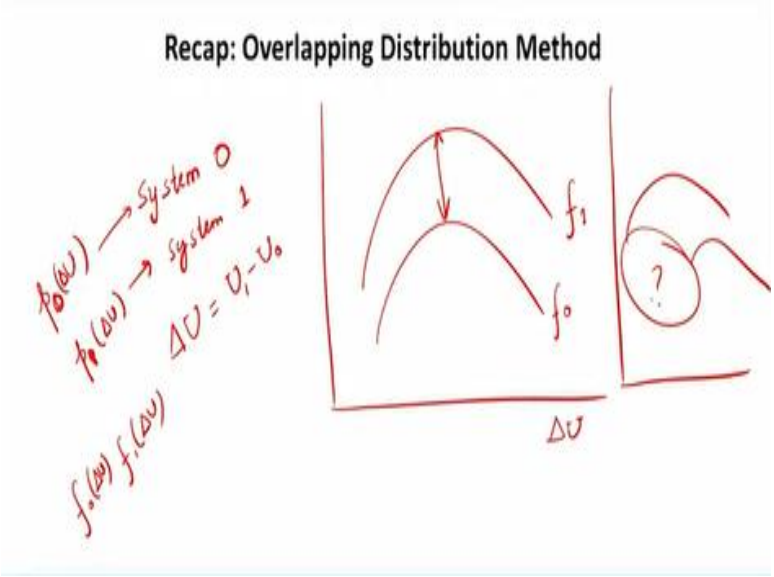

Now, the only problem in that approach as we had discussed is when there is not sufficient overlap between the two distributions. Let us say for example, the two distributions look like this in that case, there is not much overlap in the regime where we do not have the values for one of the distributions and, in that case, how can we find the offset and therefore the free

energy change is only available for the regime where there is overlap.

So, this has been the motivation for a method called the multiple histogram method that is an extension of this idea where instead of using two systems we define a sequence of systems between 0 to 1 such that there is always an overlap between successive I can say windows or successive distributions that we are analysing and that makes your that we always have the overlap with a catch that we have to do many, many simulations.

So, one of the reasons why that is strategy works is because we are looking at systems which are relatively closer to each other; then for example, system 0 and 1 which can be far apart in terms of their behaviour and configuration if we think of systems which are like intermediate then they will so some intermediate behaviour and therefore we can expect substantial overlap between the two distributions. And, therefore the more windows we are going to put the more systems we study in the sequence we are going to have better accuracy in terms of free energy calculation at the expense of, of course more calculations because, even in the overlapping distribution case we have to simulate both in system 0 and system 1.

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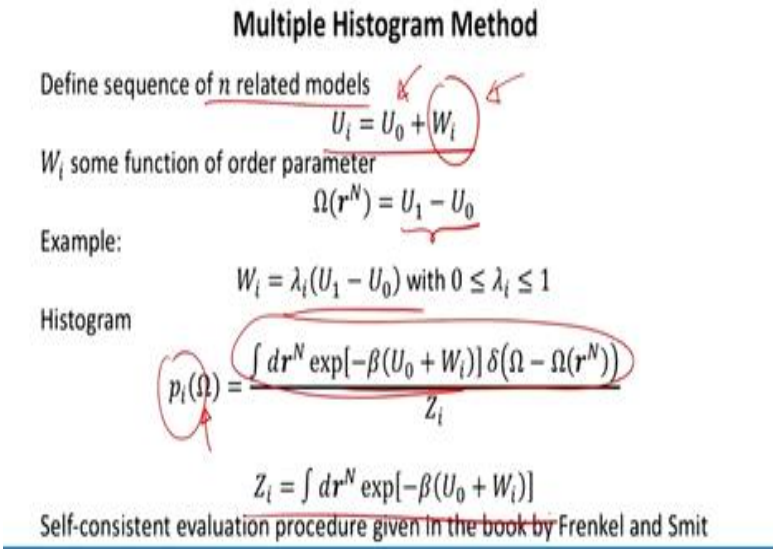

Now, if I define n such windows then we have to perform n simulations in all of these windows, but nonetheless the model goes like this- so, I define a sequence of n related models where the energy in these models is given by-

$$U_i = U_0 + W_i$$

and W_i in general can be a general function of the order parameter here and that order parameter in this case is U_1 - U_0, that is the energy difference between system 1 and system 0.

$$\Omega(r^N) = U_1 - U_0$$

The two limits of the behaviour I want to analyze. For example, we can consider a function like this where λ_i is going from 0 to 1 that is a linear function of the energy difference

$$W_i = \lambda_i(U_1 - U_0) with\ 0 \leq \lambda_i \leq 1$$

and, clearly when λ_i is equal to 0 in that case we will get W_i equal to 0 and U_i equal to U_0, when λ_i is equal to 1 then in that case W_i will be U_1 - U_0 and U_i will therefore be U_1.

So, now we can construct a histogram for the order parameter that we have defined for each of these individual windows and therefore we define a p_i as the probability distribution in the ith window and in there again-

$$p_i(\Omega) = \frac{\int dr^N \exp[-\beta(U_0 + W_i)]\ \delta(\Omega - \Omega(r^N))}{Z_i}$$

we will have a modified definition of the probability density for each of these windows and we have to define a partition function that is defined over that particular distribution in the sequence.

$$Z_i = \int dr^N \exp[-\beta(U_0 + W_i)]$$

Now there is a self-consistent procedure to get the p_i value and the Z_i values I will not details there. If you are interested you can refer to the book by Frenkel and Smit understanding molecular simulations, but this is one example of this so in this case, I am showing you the simulations perform using multiple windows.

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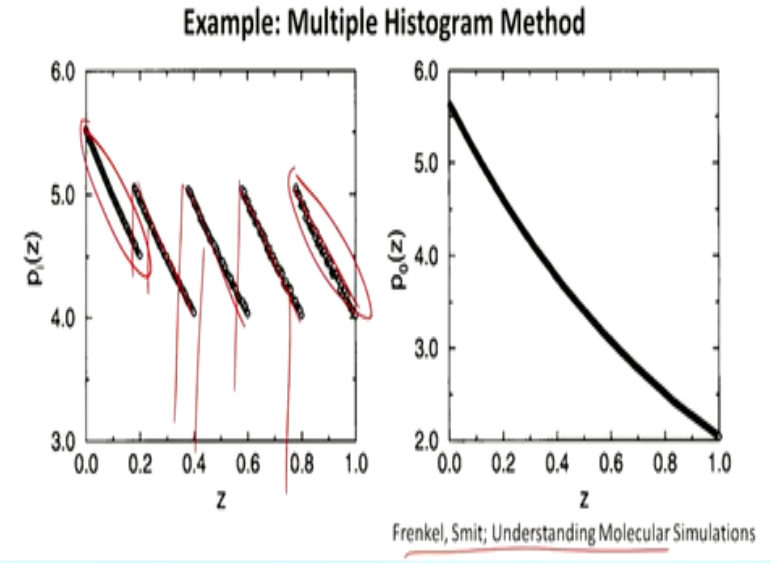

So, you see now the sequential probability distributions, they have significant overlap regions. So, the limiting distribution these two we are not overlapping but all the intermediate ones are such that successive probability distributions are overlapping with each other and using these sequences we can basically reconstruct the p_0 that is the probability density in zero and, that is a self-consistent procedure referring to and you are selected to refer to this particular book for more on that.

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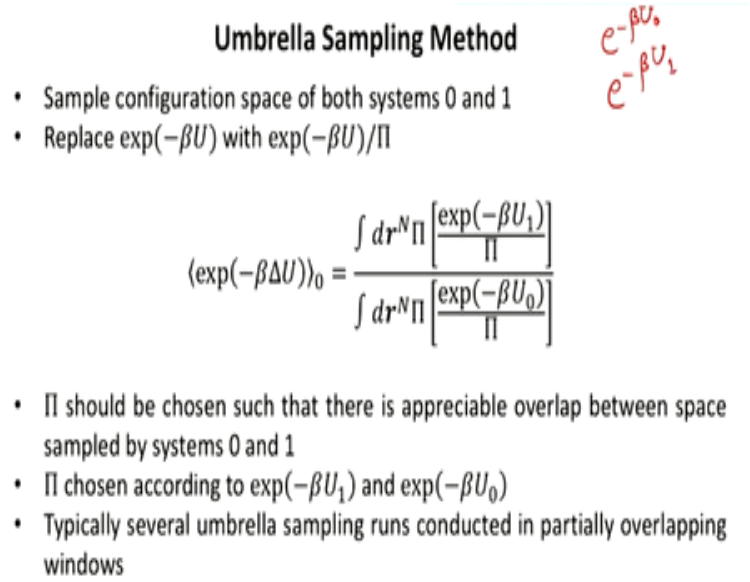

There is something else that we can do if we want to look at systems which do not have appreciable overlap between each other. So, that means that when I am sampling one of them using their Boltzmann weight that is giving rise to a very different sampling than the other system. So, exponential of - βU_0 is giving me a distribution or giving me a configuration space that is very different from that sample using exponential of - βU_1. So, in that case, essentially

what we do is we give away with that metropolis condition that we will sample according to the Boltzmann weight and we add some kind of a bias so as to speak that is called Π.

$$\langle \exp(-\beta \Delta U) \rangle_0 = \frac{\int dr^N \left[\frac{\exp(-\beta U_1)}{\Pi}\right]}{\int dr^N \Pi \left[\frac{\exp(-\beta U_0)}{\Pi}\right]}$$

So, that now as simple with a modified weight that is exponential of - βU_1 by Π an exponential of - βU_0 by Π and what this Π does is that ensures that we have appreciable overlap between the state samples by simple by system 0 and system 1 and, this is how we can possibly choose Π we have to choose in a manner that we are able to sample spaces that are sampled both by exponential of - βU_0 and exponential of - βU_1, that is the Boltzmann weight of system 0 and system 1.

Again, just like the multiple histogram method one can do multiple umbrellas sampling windows in order to get partially overlapping windows and that will be more efficient than doing with fewer windows. It turns out the umbrella sampling is one of the most commonly used methods for it is inherent simplicity the only difficulty is to get the actual expression of Π which is not always very trivial to get. So, we have to really ensure that whatever Π we choose is actually able to sample distributions covered by both systems 0 and 1, but there are methods for doing that and again you can refer to more references on that.

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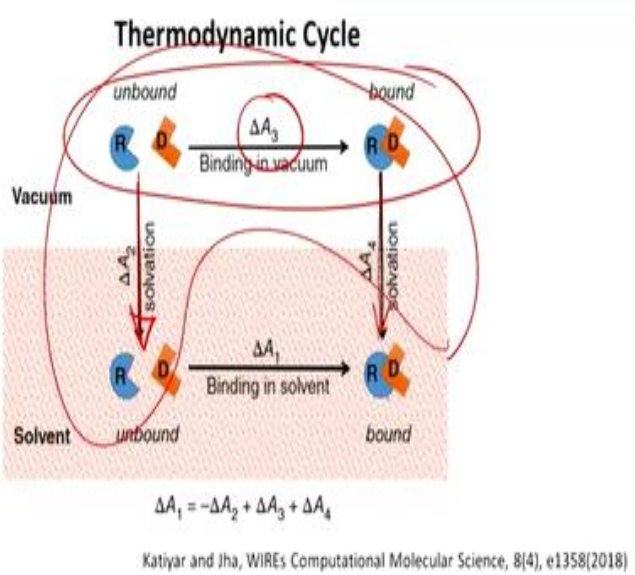

Katiyar and Jha, WIREs Computational Molecular Science, 8(4), e1358(2018)

The other approach that is particularly useful in certain cases, especially when looking at the free energy of binding is the idea of a thermodynamic cycle and let us say for example we are

interested in the binding of a ligand to a receptor or binding of enzyme to a receptor hunting of that kind of a problem, where two molecules have to come together and bind each other.

Now, typically that happens in a solvent and the presence of solvent makes the computation very difficult or expensive. So, in that case what will really happen in most typical time scales you can simulate in MD or Monte Carlo is that you will spend plenty of time simulating the solvent motions and therefore it will take forever for the drug and the ligand to come together or the receptor elegant to come together or enjoyments ligand to come together and in those cases if for example, we do a simulation without solvent but clearly the simulation will be much more cheaper in comparison and that can be easily done and then once we have done that kind of a binding process without solvent we can use the idea of thermodynamic cycle to get the binding energy in the solvent and next example I am showing in here.

So, this is the binding process that we can simulate in vacuum that is without the solvent just continuing the receptor and the drug or the whatever ligand that you have and we compute let us say ΔA_3 as the free energy change in that particular process and, then in a separate simulation we look at the solvation of the unbound drug and receptor in a separate simulation we also look at the solution process of the bound drug and receptor and by solvation process I mean here is we start with vacuum and we compare to a case when it is filled with solvent.

So, in that case the configuration of the drug and receptor will not change only the solvent will be added to the system and now once we have done these three simulations since the final state are going to be the same. If we basically sum over the free energy changes in these three simulations the two solvations simulations and one binding simulation conducted in vacuum, it will basically give me the free energy for binding in solvent and therefore basically compute these three free energy changes ΔA_2, ΔA_3 and ΔA_4 and that gives me the free energy change of the binding in the solute.

$$\Delta A_1 = -\Delta A_2 + \Delta A_3 + \Delta A_4$$

There are other variations to this method depending on the problem in the hand, we can choose any appropriate thermodynamic cycles again once we choose thermodynamic cycle it does not have to be like borrowed from what is happening in the experiment. Since, the free energy is a state function we can define any arbitrary thermodynamically valid cycle, so we can conduct the simulations in different conditions and then add the free energies for those of them and,

using the sum of the free energies we can get the free energy for the process trying to simulate.

So, our choice of the cycle is really something that can be like, there can be many choices we have to pick the one that will give me the more a most efficient simulation it does not have to be something that can be experimentally realized. Let us say in this case the drug receptor will may not mind in vacuum that is not the kind of experiment that or you can easily conduct or is required to be able to use these kind of simulations.

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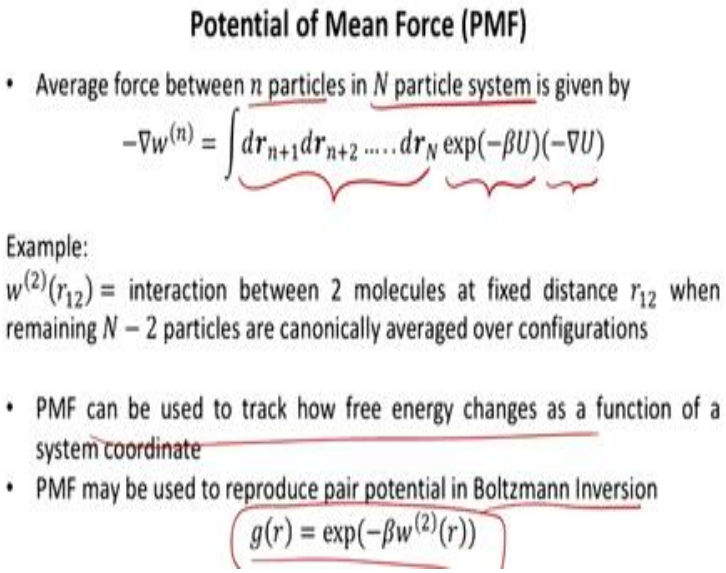

The next things that have been used a lot is the idea of the potential of mean force that is again some sort of an estimate of the free energy change along a coordinate of a system or the reaction coordinate so as to speak and in this case what we do is we find the average force between some particles in the system. Let say a small n is the number of particles and we want to compute the average force between them in a large n particle system. In that case, I can basically average over all the particles other than small n particles multiply with the Boltzmann weight and multiply with the ΔU that is the force that is coming between the n particles.

$$-\nabla_w^{(n)} = \int dr_{n+1} dr_{n+2} \ldots \ldots \ldots \ldots \ldots \ldots . d_{r_N} \exp(-\beta U)(-\nabla U)$$

For example for small n = 2 what we have is the interaction between 2 molecules which are at a fixed distance and the remaining n - 2 molecules are canonically averaged they can move we can do simulations and we look at how the interaction between the two molecules are changing and as a function of the changes in the configuration of the other molecules and we average

over all of that and we get the effective force or the potential of mean force between the two particles.

So, this is one measure of how the free energy changes as a function of system coordinate, but more importantly this can also be directly used to produce the pair potential when we are using the Boltzmann inversion process, we will discuss the method inward detail later. So, do some approximation the g of r can be approximated as-

$$g(r) = \exp(-\beta w^{(2)}(r))$$

and just like we have done for 2 particles, we can extend to 3 particles, 4 particles, 5 particles and so on. And, therefore we will have many, many potential of mean forces defined over a collection of particles.

One other thing that we can do particularly in cases where simulation is taking too long and we are interested in states which are far apart is perform some kind of a cooling simulation. Just to give an example, let us say for example, we have an aggregate of some surfactant or some other molecules and we want to find what is the free energy change? If I pull a molecule out of the aggregate clearly that cannot be done in the typical particular dynamics because the molecules will take forever to come out of the aggregate but this can be done if I for example apply some bias that pulls the molecule out of it and this is precisely is done in the pulling simulation, we apply some bias potential in this case I am showing you some kind of a harmonic spring that is pretty much acting in a manner that the molecule is pulled apart from the aggregate and we compute the energy change for that and of course we correct for the bias potential that we have added and we get the free energy change for that.

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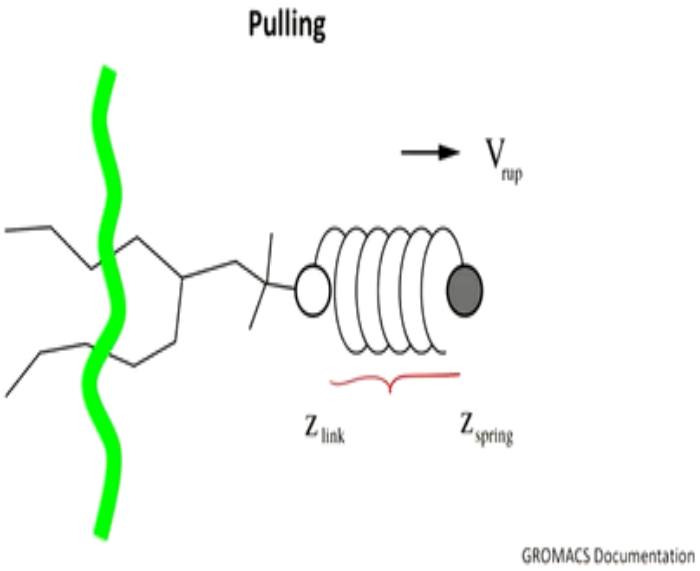

It is particularly useful in the context of whenever we are doing any kind of an aggregation process by looking at what is the free energy of the aggregate. For example, or how much energy do you have to apply to pull a molecule form the aggregate or what is the dissolution energy that is required to dissolve the aggregate and so on because all these processes may take very long in a typical molecular dynamics and in many cases the free energy barriers are so large that it will almost never happen because the fluctuations will never be large enough to bring the molecule out of the aggregate.

Then there is one more method that is relatively recent that is the method of meta-dynamics because of Parrinello and Leo and in this method the idea is let us say this is my free energy landscape which I am trying to prove. The problem I was mentioning is that I can be stuck easily in one of those local minima's. So, let us say for example, I am stuck here, then in that case it will take me forever or it may never happen that the system will get large fluctuations, so that it can enter other minima's. So, even though, this particular minima is much higher in comparison to this minima or that minima the system will be kind of trapped in there.

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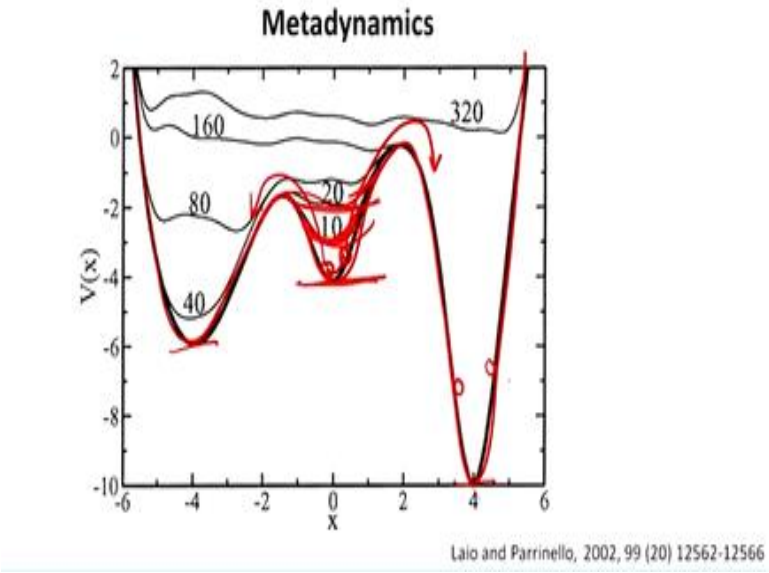

So, in meta dynamics, what we do is completely opposite off what we do in a typical detailed balance kind of Monte Carlo simulation, but we do here is equivalent of saying that I do not revisit the points that I have already visited. So, we somehow keep memory of where all I have been in a manner that we do not go back there. That is like can imagine it like filling sands wherein we wherever we go so that once the sand is filled then we do not go back there to just to keep track of like I have already been to these states.

So, I should not revisit those states again and again, this is done by using the bias potential but the key idea here is I keep on adding some bias potentials and try to come out of the well, making sure that I try not to visit the states that we have only visited or give lesser importance to visiting the states already visited and try to basically visit newer states in some kind of like as an explorer trying to visit what all is there for the system to explore.

So, in this case, for example in the first fill, we are at 10. So, there the system starts from the second minima and it comes to still the second minima, but we are slightly above the well. In 20, we are now exploring the first minima. In 40, we are trying to fill the first minima as well at 80 and these are the value of the biases that I am basically filling in. At 80, we are filling both first and second minima. At 160, we are already in the third minima as well and at 320 we have pretty much explored all the minima's in the free energy. This is a very nice method particularly when the free energy landscape is very difficult and there are multiple minima's there by keeping a memory of where all we have been we can pretty much explore the entire free energy landscape scale.

There is an alternative version of this method called the well-tempered meta-dynamics where the essential idea remains the same, but I do not keep filling once the all the minima have been identified we stopped at a particular time and it provides me a better estimate of the free energy differences or the free energy landscape. Again, these are this is very rudimentary introducing the method you are suggested to read more references, if you are being interested in learning more about this particular method.

So, with this particular idea I now want to move on to somewhat different kinds of simulations that are trying to tackle time, so in a slightly different manner than the free energy calculation or whatever you have discussed.

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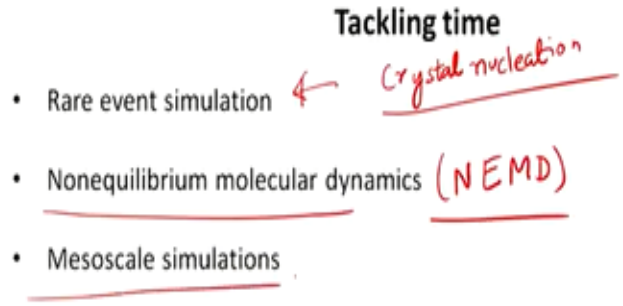

So, one of the class of methods are referred as the rare event simulations- in these cases what we are interested in the events that has very less probability to happen. For example; if we look at the crystal nucleation the physical time scales for these phenomena can be very, very large.

So, any typical molecular dynamics or Monte Carlo will never be able to grow it and there has to be some specific class of methods that can pretty much jump the time scales and we able to simulate these kinds of phenomena and there are methods like transition path methods which come under the status, then there are class of methods that comes under the non-equilibrium molecular dynamics or NEMD and in here we are essentially not interested in the systems at equilibrium, we are interested in systems out of equilibrium for example under the presence of an external field and in that case the molecular dynamics algorithm is modified or the equation

of motion is modified account for the external field.

The last class of method and probably most important to our discussion are the mesoscale methods in which our goal is to pretty much study phenomena at much larger length scales and time scales typically to the level where we can study mesoscale system that is beyond the typical molecular scales that the MD or Monte Carlo simulated for atomic systems.

So, methods in that category include coarse graining methods and we will discuss that but they also include some other methods called for example, the Langevin dynamics method in which case we pretty much remove the solvent molecules from the system and try to simulate only the solute molecules. Brownian dynamics is another version of the Langevin dynamics in the limit of high friction and, there are methods known as the dissipative particle dynamics and is stochastic rotation dynamics which are one step beyond and also the accounts for the effect of hydrodynamics and finally, there are class of methods called the lattice Boltzmann method that does have thermodynamics to I would say a molecular scale analog of stoke's equation.

So, we will discuss that in the coming week, thank you.