Thermodynamics for Biological Systems:
Classical and Statistical Aspects
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Lecture – 75
MD Simulation Examples

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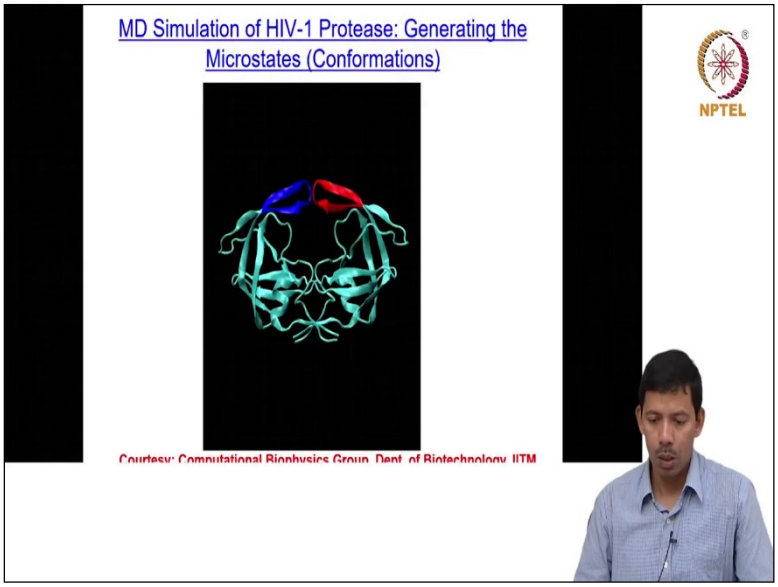

So, I will show you an example here, so this is the data centre in my laboratory in computational biophysics group at IIT Madras, Department of Biotechnology. And this is the data for MD simulation of a protein HIV-1 protease. This protein HIV -1 protease is an important enzyme in the life cycle of HIV virus and we are interested to know how this particular enzyme works. So, we carried out any simulation of this particular protease of this particular protein to generate the different microstates are the different conformations.

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So as so this is a movie so if I play it you will basically see that starting from this particular conformation the protein evolves over different conformations. So, we start today we start from one conformation and then it goes on as you see that no part of the protein is static every part of the protein is moving particularly this region of the protein is the most flexible they called the flaps and they these two flaps they basically make the gate for a substrate or an inhibitor to come and sit into this active site pocket.

So, here as you see that the flaps are pretty mobile and they can change the confirmations they can change the confirmation from different time. so if I play it again so here you can see the blue is kind of towards us and red is kind of behind and over the time you know there is a change there is change of conformations and this flaps are basically opening up so there is now there is gate are open, so gate is now open starting from the close state and now so through this open gate the ligand can enter. So, what I am trying to tell you is basically what this computer simulation has generated is a set of different conformation of the protein.

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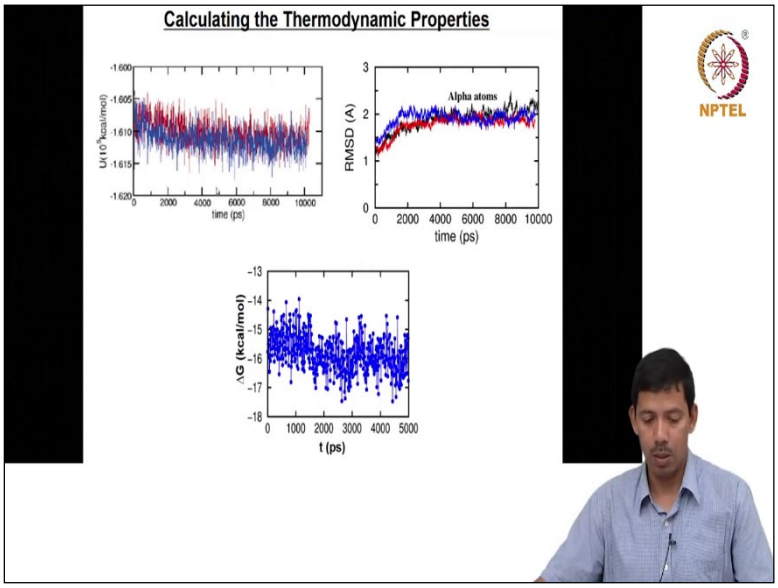

So if you plot them up what you see is this so if you now plot potential energy of the protease of the protease molecule over time you see the potential energy is changing over time. So, the potential energy at each point corresponds to the different conformation of the protein. So, each conformation so each point in the movie corresponds to each point here and each conformation or each microstate of the protein is giving different energy values and those energy values are put up here as a function of time.

This shows the root mean square displacement. So, root mean displacement is basically how the protein is changing over time starting from initial confirmation to the other confirmations. So, this tells that how the how different confirmations of the proteins are captured. Here is another important thermodynamic quantity calculated over time which is a change in free energy. So, this change in free energy was basically due to the binding of a ligand into the protein active site.

And when we attempted doing a simulation of the ligand binding to the protease at different microstates you can see we get a different free energy value. So, from the different microstate or

the different conformation of the protein if you if you bind the ligand molecule into the active site and calculate the Delta G values from here you can find out which is the best ligand bound protease conformation having the least energy some over here.

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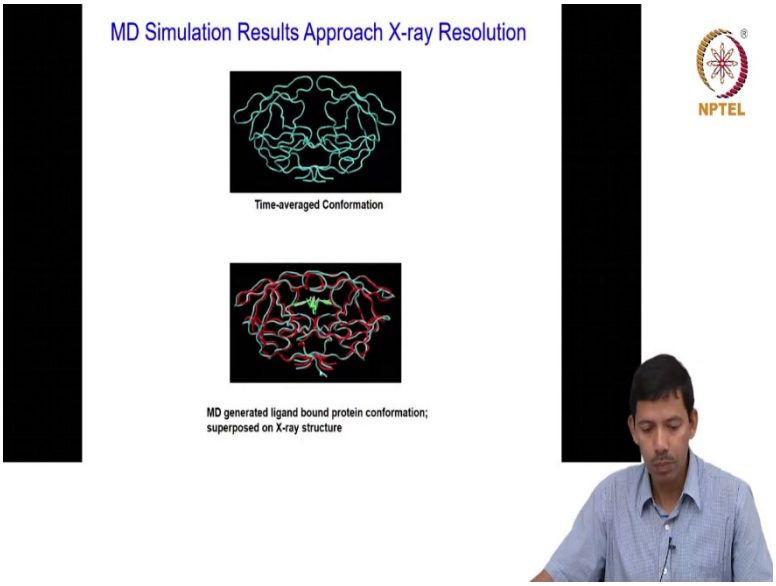

From the from the movie so movie the movie was made basically by put by stitching together all the different microstates what we had generated. so he had generated different microstates and so each microstate was defined by the distribution by different distributions of the atoms and when you put all these distributions together you see the whole protein molecule so this is this is the distribution of the atom and that that is that gives the conformation of the protein and this conformation and the conformation.

The next another confirmation the next when I stitch them together I make a movie and that movie shows how the conformation of the protein changed over time. So, and that is what this time evolution about. Now from here I can see where my system becomes stable. As you can see here the energy started decreasing from this point to this point and after kind of 4,000 Pico second the system was kind of stable so if I want to get the average property if I want to get an average U the average potential energy of the system what I will do I will just take the time average over this region from let us say 4,000 to 10,000 I will take the time average over this and that will be my average U.

And that U should match well with experimentally measurable U and that is the example I am showing you here so when we simulated HIV protease free wild-type HIV protease confirmation from different starting conformation we ended up getting a confirmation which is this which is a

time average conformation so this time average conformation is obtained by running the simulation for a long period of time and then taking the average over the time and that is the time average conformation which you know matches with the crystal structure.

And this is another example where the red is the MD generated ligand bound protein Proteus conformation and when you superposed to the x-ray structure which is in red as you can see the time averaged conformation of the protein is so well matching with the crystal structure and that is the strength of MD simulation that you not only get the average structure very similar to the experimental structure but do you also have the information at every time instant here.

So, if I go back to my movie and I want to pick up this particular conformation around the conformation I can just go here and pick that particular microstate and analyze and see how this particular microstate is different than the microstate here who are very different in their potential energy. So, this is basically showing that how statistical mechanics could start good match how statistical mechanical theory could help you getting the microscopic information and from the microscopic information can give you the macroscopic property which are as good as the experimenter the measured quantities.

So, here the structure of the protease the structure of the protease is matching very well often from MD with the structure often experimentally. So, obviously when you calculate certain thermodynamic quantity like Delta G here you know this must match very well with experimentally measured quantity and in fact this -17.5 which we obtained from MD simulation was very, very close to the experimental data of -18.02 kilo calorie per mole.

Or the same ligand which we simulated but here we basically got the information how this ligand is bound how it is interacting what are the residues of the protein are involving the interactions and those information's sometimes difficult to get experimentally. Also here you see the dynamics how the some interactions are present throughout the simulation run versus some interactions which are not that strong which may can break that you will also be able to capture here from MD simulation technique.

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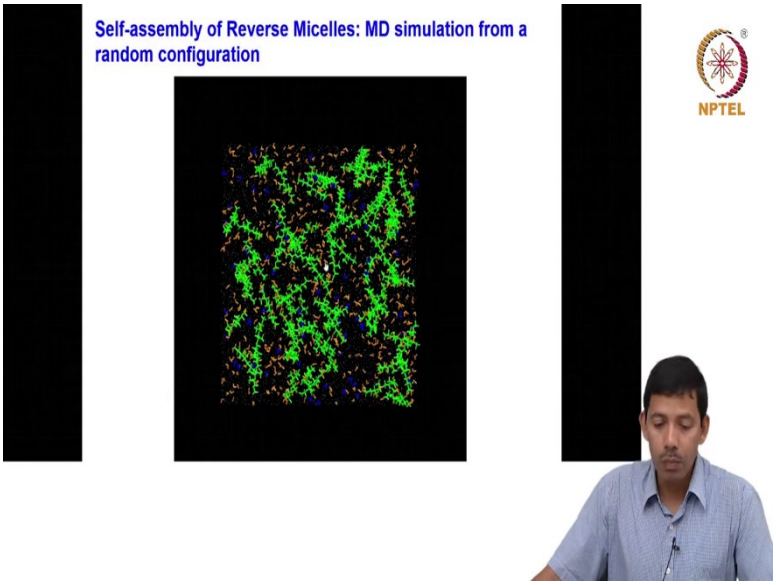

This is another example to show you that the different microstates what you generate from MD simulation they can be very different from your statistical conformation. So, the HIV protease problem what I showed you so there the microstates are not too different from one to the other so certainly there are changes in into the flap region more than any other regions but there are problems where you have large changes there microstates are very different from one to the other and those different microstates also you can capture by molecular dynamics simulation and that is an example I am going to show here.

So, here basically this experiment this MD simulation was done based on our experimental setup. So, experimentally people have found out that when they mix up water and CO2 molecules liquid CO2 is basically CO2 is gas but then when you raise the when you go to the supercritical state of CO2, CO2 becomes liquid. So, there was an experiment where people attempted mixing up water and supercritical CO2. So, the two liquids they did not mix because water is having a polarity or as if you remember if you recall us here to structure CO2 is a linear molecule OCO double bond C double bond O.

And due to the linear structure of CO2 it has zero dipole moment CO2 something like this and bond dipole they cancel each other and therefore CO2 has a zero dipole moment and therefore when they attempted mixing of liquid water with liquid CO2 the mix up. Then when they added certain surfactant molecules or certain lipid molecules they find that the turbid waters here to mixture now become homogeneous, it becomes transparent.

So, that means waters CO2 now have mixed by the subject and other lipid molecules. So, they had no clue what happened by which my water CO2 turbid each mixture certain suddenly became so homogeneous and that is where MD simulation cannot give us a lot of information. So, here we is simply following the experimental setup we took water into the simulation we took CO2 into the simulation and we try to generate certain microstates and we see that the water and CO2 they become separate all water molecules come to one side and all CO2 molecules go to the outside on my simulation system.

But when I put up this molecules the surfactant molecules here and we find something interesting and that is what I play now. So, here the orange molecules are the water molecules and the white dots what you see they are the CO2 molecules and the cream they are the surfactant molecules. And the surfactant molecules do have a polar head group and those polar head groups which was negative in this case those polar head groups have a counter ion and those counter ions are shown in blue.

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So, we mix up water CO2 and the surfactant molecules randomly and from the random mixture we started observing what is happening so as you can see there are aggregations there are aggregates. So, in the aggregates if you see so to start with there are smaller aggregates and then smaller aggregates are also coming together those small aggregators are joining further together now we have 1 2 3 aggregates those 2 aggregates join and now we have big one, one small and over the time we see that those all aggregates joined together and at the end we get a single aggregate where the water molecules are inside the inside a pool made by the surfactant molecules.

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So I will just played one second for you so to start with everything was random and then those random molecules come together in a particular fashion the particular fashion is you see the CO2 molecules are all out the surfactant molecules do have a hydrophobic tail those hydrophobic tails they are pointed out or outward they are solvated in CO2 and the subject end had a head group which were polar. Those polar head groups they make a cavity and in that polar cavity the water molecules get inside and it forms a reverse micelle.

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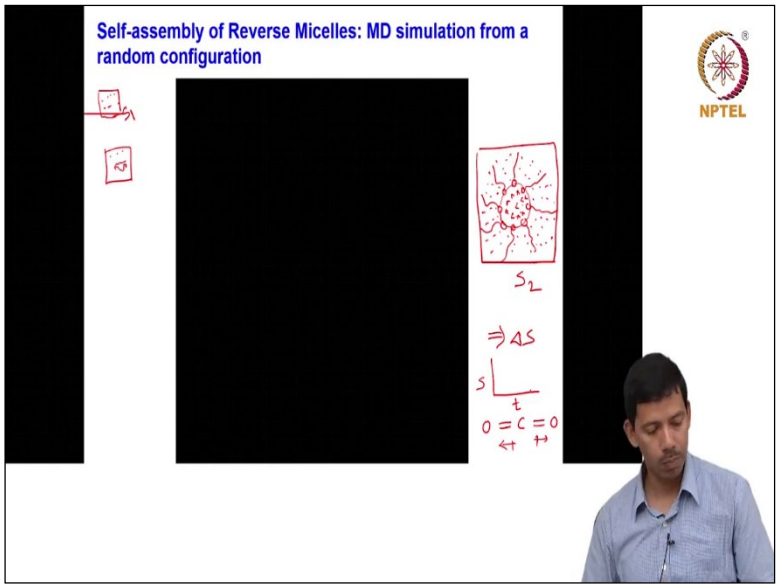

So, basically what we saw here is that surfactant head groups which are shown by spheres so they are the surfactant head groups. So, surfactant head groups they do not; they are polar and they do not like the non-polar CO2 so they come together and they form a cavity and in this cavity with so this is a polar cavity in this cavity the water molecules come in. So, water molecules are now happy in this polar cavity and the surfactant head groups which are hydrophobic they are now the surfactant hydrophobic tails are now solvated in CO2.

CO2 is non polar I should have drawn the CO2 and water the other way so these are the water molecules which are inside solvated in the polar core and the outside that non-polar CO2 making the hydrophobic surfactant happy and therefore what we found is the reverse Micelles, so this is the reverse micelles is an example reverse micelles where the polar head groups are inside and the hydrophobic tails or outside in a non-polar medium.

So, because of this formation of reverse micelles the water and CO2 now become soluble due to the surfactant molecules. So, what you saw here in this particular example that we started from our differ microstates. So, here the microstate the first microstate was all random to the different microstate where there are certain level of ordering and then we get a microstate where things look much more ordered than the very random configuration or conformation already started from.

So in this solution can basically capture those large-scale conformational changes and also from there you can calculate the different thermal or in quantity how you know entropy of the system

was and what is the change in entropy and such as entropy in S1 and S2 and then from there you can calculate the Delta S or we can also calculate how the entropy changes over time.