Structural Biology
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Lecture – 46
Why We Need MD Simulation

Hi, everyone, and welcome again to the structural biology course. Today, we will discuss a completely different thing than what we have discussed before. We discussed sequences and structures, but all of them were in static mode. Today, I am going to introduce you to the world of dynamics.

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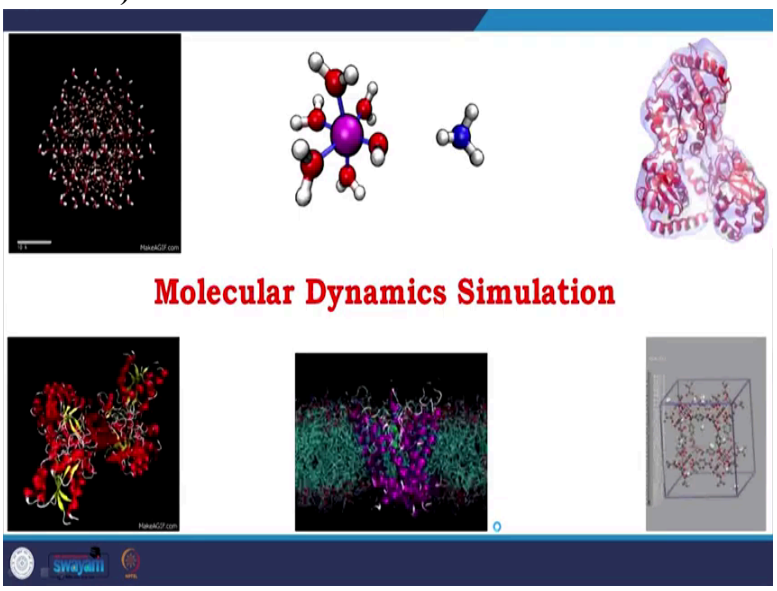

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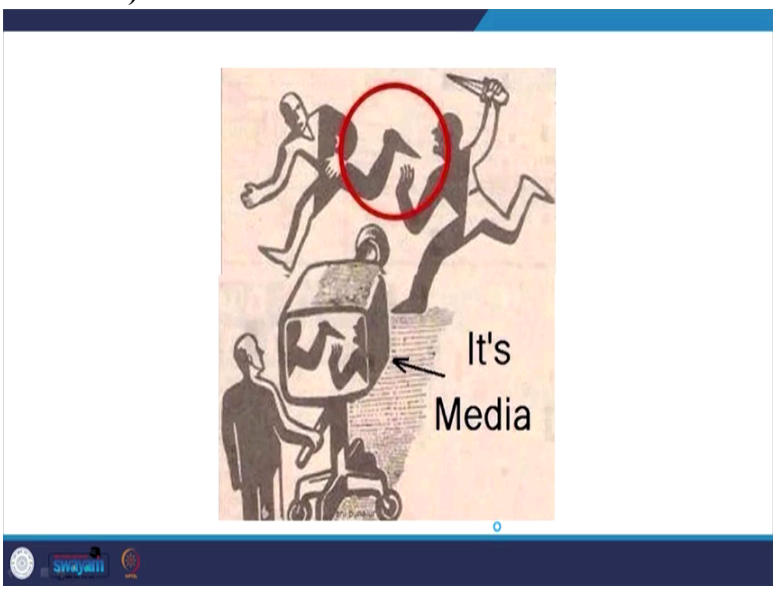

So, this is the first class of molecular dynamics simulation. To start with, I have posted a question that might be in your mind: why do we need dynamics? Here is a crude example,

which will tell you how the pictures are not always giving us the true story; you are looking in this picture, a man is running, and another man is chasing with a dagger. But the scenario could be oppositely represented, and sarcastically, we say it is media. Still, it is true that by taking pictures, many things could be represented very differently than reality.

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So, as I told pictures could be wrongly projected. Let us look at some pictures people have taken and tell you the story, which is not in the scene. So, I told them the picture could be wrongly projected. You might argue that videos could also be wrongly projected in this highly technological world. I agree, but pictures could be wrongly projected very quickly. Even the common people without technological expertise could have done that.

Also, in this picture, where Steffi Graf is facing a tennis ball, you would want to know what happened next. So, the picture sometimes, as I told, tells us wrong stories, but the picture also sometimes tells us incomplete stories, and as I told, with the help of dynamics, we could have solved this problem. You see the few figures I have presented here and how ammonia is coming to the complex and forming a bond. It was impossible to present this scenario, the series of events, using static structures.

Similarly, in any complex, if there is a movement, it is difficult, how the solvent is moving. It is difficult, how a membrane protein interacts with the membrane. It isn't easy to understand how in a crystal, the molecules are moving. How the change of conformation of the protein could be defined is difficult. So, molecular dynamics simulations have solved all these problems. But it also has its challenges.

If you follow my class, you already know that in previous classes, we discussed the PDB file and the coordinate information, and you see that the PDB file is so big for a protein structure. Now start imagining the movement of the atoms of the molecule. There will be further changes in the coordinates, and you will get many coordinates. So, how difficult would it be to handle or manage those huge data? How or what other information do you need, like when you are presenting coordinate, but now we were setting change.

So, you have to present the change of coordinates for time. When presenting a coordinate, most of the time, you present it at the lowest energy. Now, they might be the change of energy, all those things, you have to include these module contains 5 classes, it would not make you an expert in molecular dynamic simulation, but it would be a humble effort from my side to give you a basic knowledge of the process of the terms regarding the molecular dynamics simulation of macromolecules mostly taking proteins.

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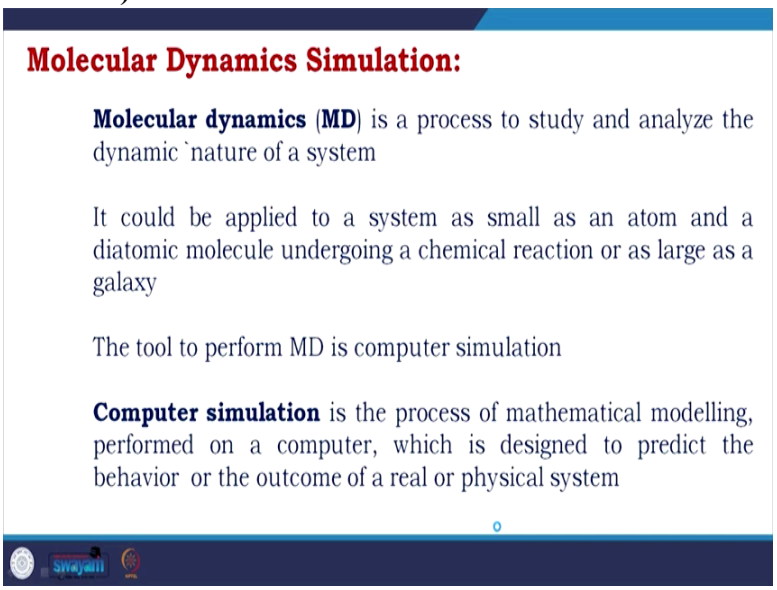

So how to define molecular dynamic simulation is a process of studying and analyzing the dynamic nature of the system. As I told you earlier, it could be applied to a system, that is what the beauty of this technique is as small as an atom and diatomic molecule which are undergoing chemical reactions or as large as the galaxy, and you could do anything in between them, the tool to perform MD or molecular dynamics is called computer simulation.

So that is why it is called molecular dynamics simulation. So, computer simulation is the process of mathematical modeling performed on a computer, designed to predict the behavior

or the outcome of a real or physical system. Definitions are always, you know, confusing. So, let me define it more elaborately.

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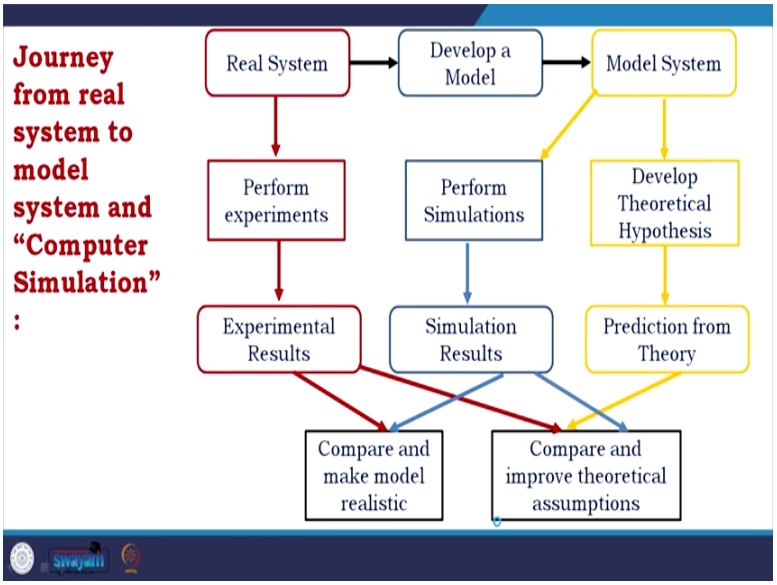

The journey from a real system to a model system and defining computer simulation: So, you have a real system, and now, when you want to apply theory, you have to develop a model. That is the initial criteria to go for computation or anything theoretical. So, you have a real system, and you develop a model, you get a model system, there is a real system, there is a model system, the real system because it is in your hand, you could perform the experiment, whereas, in a model system, you could perform simulation.

That is a computer simulation, or you could develop a theoretical hypothesis and make some hypotheses by looking at the model system. When you experiment, you get experimental results, pretty straightforward. When you perform a simulation, you get the simulation results, and when you develop a theoretical hypothesis, you get some predictions from the theory.

So, what happens ultimately, you compare them. You make your model realistic by the help of the experimental result comparing with the simulation results. In contrast, you could improve it by comparing and improving your theoretical assumptions. You have the experimental and simulation results, but you also take the prediction from theory.

The more you combine more you make your model system close to reality, and why it is essential because then you could perform experiments, experiments means simulation

experiment or theoretical experiment. You do not have to spend money, or there are many things we are discussing in brief again, and the experiment is impossible. It might be expensive, and it might be dangerous we will talk about.

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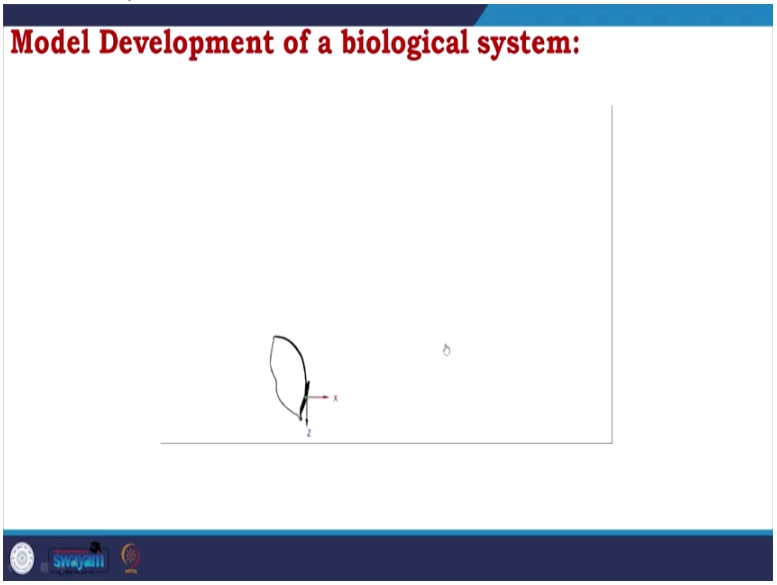

So MD simulation in the biological system: Let me introduce you to a biological system and show you how people have developed models. This is a very interesting video from science where you see the movement or flying of a butterfly. You see, the butterfly is moving, and they have done the video recording and take 1000 frames per second, that is the speed, and then analyze that top view and side view, and from all those, they have developed the model of how a butterfly is flying.

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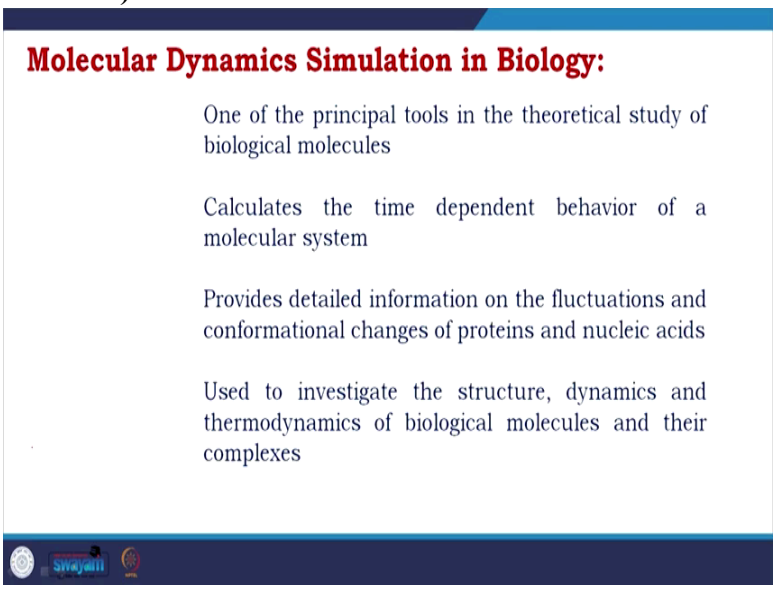

So, in molecular dynamics, MD simulation is one of the principal tools in the theoretical study of biological macromolecules. As I told you to look at biology is very dynamic, and

until a very long time, we have been trying to study biology. You are trying to understand biology by ignoring these dynamics. The introduction of molecular dynamics simulation has given us that opportunity.

It calculates the time-dependent behavior of a molecular system as a protein, protein complex, DNA, protein DNA, or anything you could calculate. It provides detailed information on proteins and nucleic acids' fluctuation and conformational changes. How they move, their atomic coordinates change, and, more importantly, how those changes are related or correlated to biology used to investigate the structure, dynamics, and thermodynamics of biological molecules and their complexes.

So, we already know the challenges or problems in biology, but, among them, few are understood in a much better way by introducing this theoretical process called MD simulation. One of them is protein folding.

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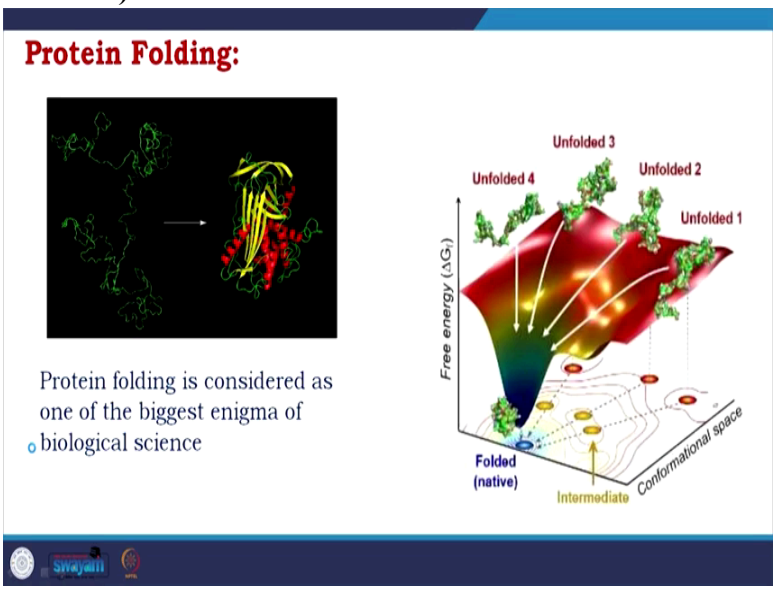

Protein folding after so many years of research, as I have told in the protein structure section, normal structure section when I talk about protein every time I was talking about because this is considered one of the biggest enigmas of biological science. And I have also talked multiple times. If we could understand the detailing of protein folding, it could have given us interesting people to understand a lot of diseases.

It would help us understand the biological process details mechanism and would be critical for many fields of biomedical science. As you see here, how there are intermediate states in

the protein folding, identifying them, and correlating them with the function, because we now know from all our discussions the protein is not restricted to one conformation.

So, this shift between their conformation even more interestingly, when this should be static, they are still dynamic. There are vibrations and stretching and all those things going on. Understanding them, calculating them, and identifying the changes gives us a lot of advantages towards understanding biology better.

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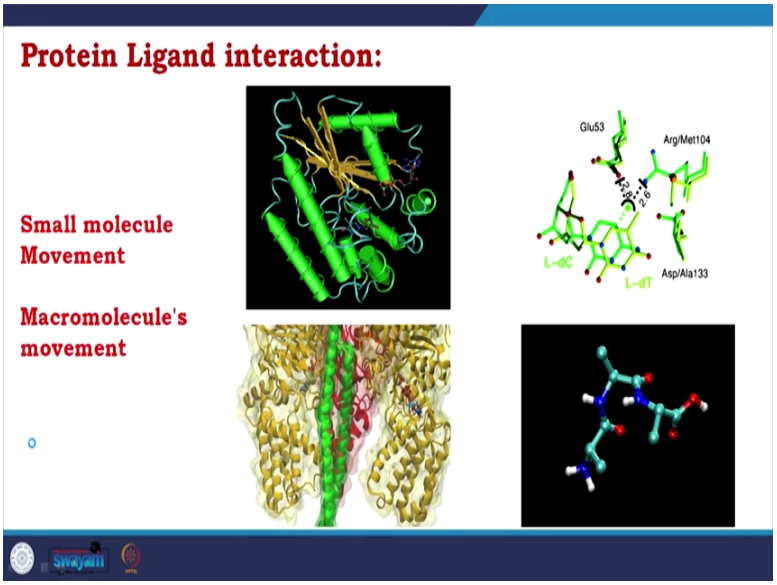

Also, if you look at protein-ligand interaction, which is critical to understanding many disease processes and drug designing, here is an example of a protein deoxycytidine kinase. I am not going into detail, but the protein has a substrate. The enzyme has a substrate called deoxycytidine which converts to deoxycytidine monophosphate. The enzyme looks like it cannot convert deoxy thymidine to deoxythymidine mono phosphate showing selectivity.

But when we started the mutational analysis, we saw that what is not possible is possible, and by solving 2 crystal structures, as you see here, they have optimized their positions, and that is why they could prevent themselves from the steady class. So, it takes us the development of mutants, the development of 2 crystal structures and kinetic analysis, and a lot of time and money.

But if we; could have developed models where the dynamic small molecules are present or movement of the proteins, if we see small molecule movement or macro molecule movement, that would help us save time and money already getting the understanding through the study

of theory. And as I said, the beauty of the theory is if you could develop a realistic theoretical model for your system, you could have done countless experiments because then you could use your computer. You do not need to do the actual experiments.

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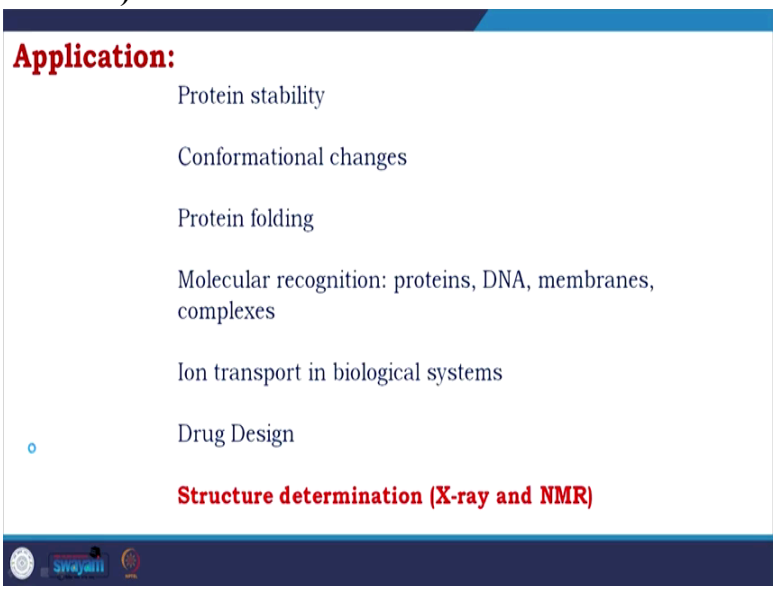

There are some applications; the best is protein stability. I would talk about these in the case study because protein stability of protein engineering is one of my application topics, which I will discuss at the end. Dynamics Molecular dynamics have contributed very significantly. Change your confirmation as I continuously talked about proteins in the cell. It is like a factory, but there is no regulator, and the only regulation or the major regulation comes through the change of conformation of the protein.

So, understanding them is extremely critical to understand the function, which is our major goal in protein folding. I have already discussed molecular recognition proteins, DNA, membrane, all the complexes, iron transport in the biological system, and drug designing. These are all very interesting areas where significant progress is now happening with molecular dynamic simulation's help.

Last but again, not least, and very interestingly, MD simulation also contributes to the structure determination, especially on X-ray and NMR. We have undergone refinement when we are doing the model building I talked about. Because we are doing the manual building, mistakes or something might happen, which could be corrected by running refinements cycles.

Refinement cycles define the actual criteria bond length, bond angle, and all these things, which are already in the library pushing the already made model towards energy minimization, and that is where we use MD simulation, how energy minimization happened in MD simulation, we will talk about in the next 2 classes. We cannot ignore the famous scientists Richard Feynman when discussing molecular dynamics, special in biology.

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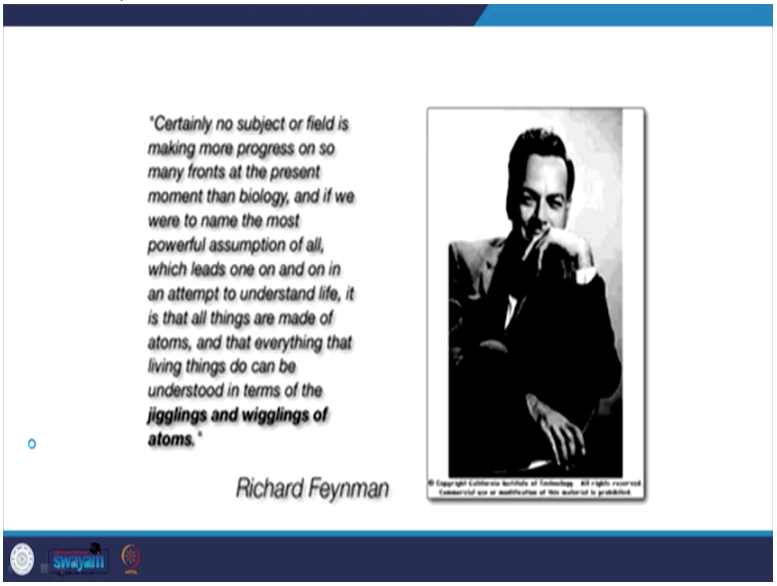

I have already talked about this, but I want to repeat this to show you how beautifully he imagined the progress. So, in his language, certainly, no subject or field is making more progress on so many fronts at the present moment than biology, and if we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that all things are made of atoms, the concept of atom and that everything that living things do can be understood in terms of the jiggling and wiggling of atoms.

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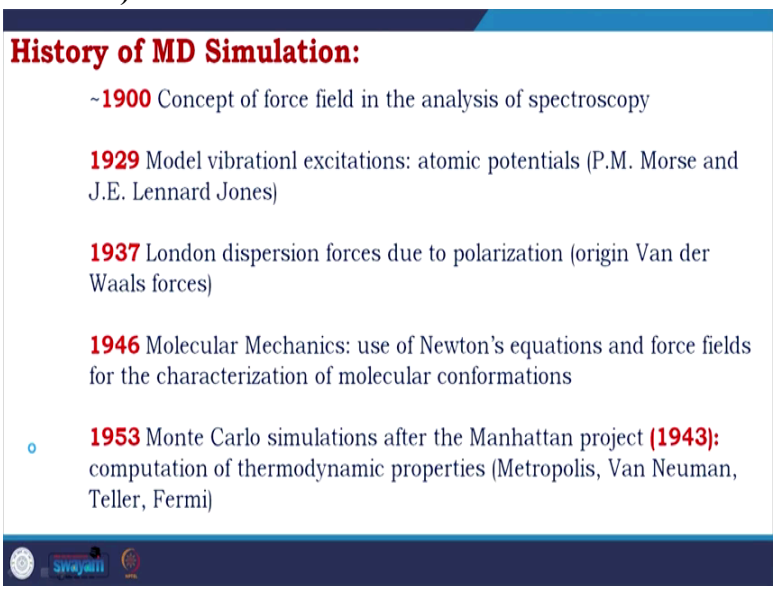

Before going into detail, let us look at the history which has made the backbone of the MD simulation technology. In 1900 when people were developing spectroscopy, the concept of force field came, and that is very important because when you are doing dynamics, you are putting your system in a force field, and you are putting a force. In 1929, model vibrational excitation atomic potentials, which are P.M. Morse J.E. Lennard Jones even today, are successfully used.

1937 London dispersion force due to polarization is the origin of Van der Waals we will discuss.1946 molecular mechanics used Newton's equation and force fields to characterize molecular conformation. So, we are going to the computational process from a force field. That journey was coming around the 1950s when the Manhattan Project and I am coming into.

So, in 1953 Monte Carlo simulation after the Manhattan Project which helps to generate computational use a lot, where the computation of thermodynamic properties Metropolis, van Neumann, Teller, and Fermi are the significant contributor.

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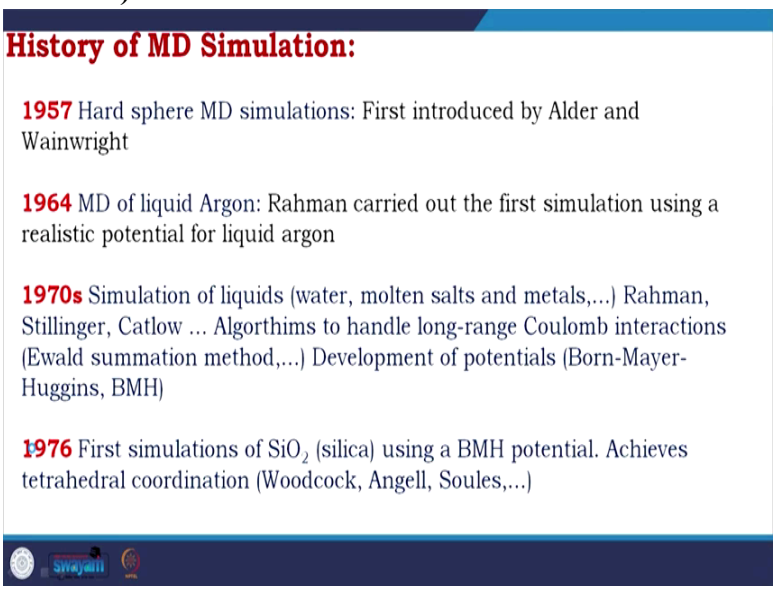

In 1957, hard sphere MD simulation was first introduced by Alder and Wright. Further significant step MD of liquid Argon, Rahman carried out the first simulation using a realistic potential for liquid argon. 1970 is a critical simulation of liquids water, molten salts, and metals again. Rahman was there, and Stillinger and Catlow developed numerous algorithms to handle long-range Coulomb interactions.

So, non-covalent bonds could be handled using the Ewald summation method. Development of potentials Born-Mayer-Huggins or BMH. This BMH helps in the first 1976 simulation of silica using this BMH potential. They also have achieved tetrahedral coordination. Woodcock, Angell, and Soules are significant contributors.

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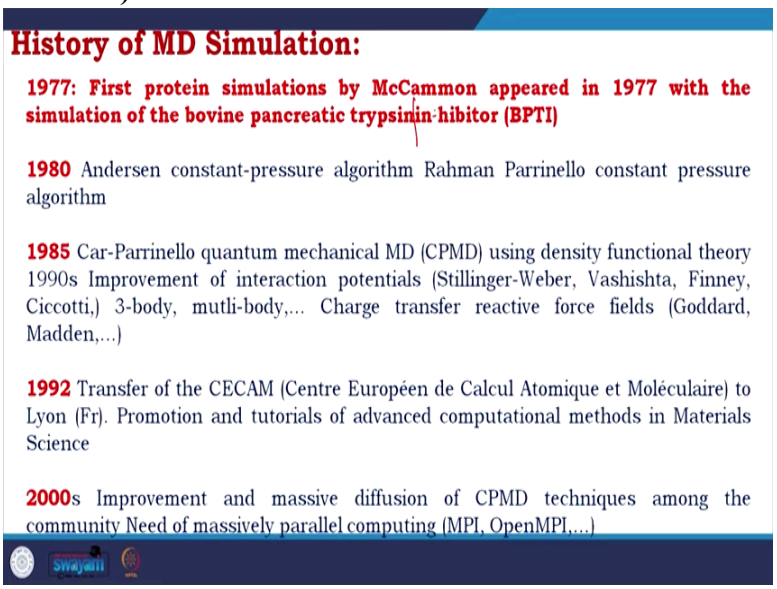

1977 was a year that was very significant first protein simulation by McCammon appeared in 1977 with a simulation of the protein bovine pancreatic trypsin inhibitor or BPTI. Here there should be a gap inhibitor. In 1980, Anderson's constant pressure algorithm Rahman Parrinello's constant pressure algorithm then Car-Parrinello. This is the quantum mechanical MD using density functional theory. We are now going into the ability to calculate the reactions.

1990s improvement of interaction potentials Stillinger-Weber, Vashishta, Finney, Ciccotti, 3-body, multi-body, charge transfer reactive for spills Goddard Madden, a lot of significant improvements. 1992 rather than development, it could say institutional update transfer of Sikkim to Lyon, which promoted and showed advanced computational methods in material science.

In the 2000s, there were improvements and massive diffuse and CPMD, which is Car-Parrinello quantum mechanical MD techniques among the community need of massively parallel computing. So, the bigger molecules are coming into play now. Bigger molecules are coming the content many 100s of atoms.

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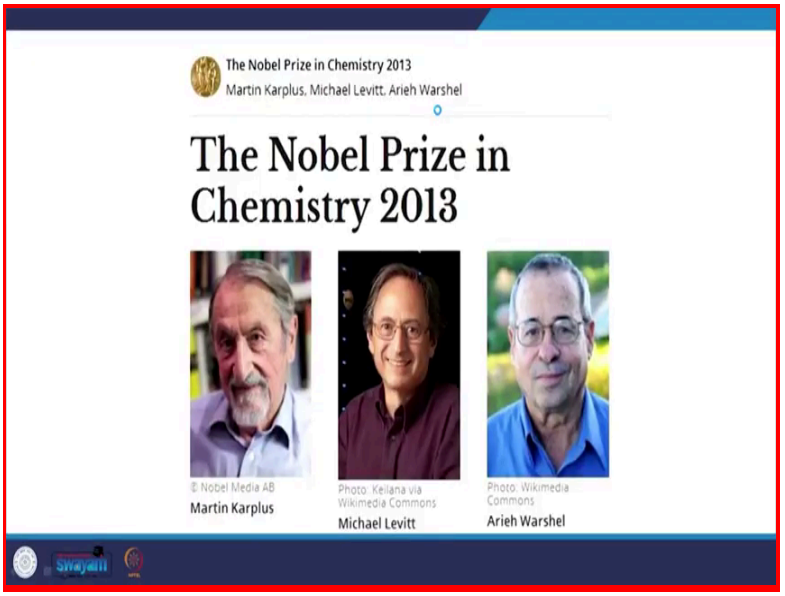

So the requirement for computer power is increasing day by day. As a result, in 2013 Nobel Prize in Chemistry was given to Martin Karplus, Michael Levitt, and Arieh Warshel. I am not going into details, but a few things would be significant to discuss. Martin Karplus, this is the first time a Nobel Prize is given to acknowledge a field development, not an individual innovation.

Just take an example PCR was invented by Carrie Mullins, so a person and the product. Sanger sequencing by Sanger, not here. These 3 guys were given a Nobel Prize because the scientific community wanted to acknowledge this technique's contribution, especially in chemistry, physics, and biology. Martin Karplus is the person who helped bring others by taking all the different programs people have written and writing that into one program package called CHARM.

Michael Levitt has developed the physics backbone, and Arieh Warshel significantly contributed to spatially QM MM models, where you get a very interesting opportunity. Now, you could study how an enzyme behaves while reacting. So, these innovations are significant, but more importantly, this was an acknowledgment of the field.

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I always talk highly about Richard Feynman. So, in his Nobel laureate lecture in 1984, he asked how small you can make machinery or smaller you are going in further development you are making. To answer him, in 2016, Sauvage Stoddart and Feringa were awarded the Nobel Prize in Chemistry, and you might say how this relates to MD simulation. So, let us look at what they did. They have developed the smallest molecular machine.

If you look at this machine, they call it an auto-driving car and nanomotor, and they have developed an idea that it is a long work, a huge contribution, a development of catenin, a development of rock octane and a development all this coming into. But what helped them is the huge background of molecular motors study using molecular dynamics simulation technology.

Those backgrounds have not only inspired them but also given them direct information to develop a synthesized motor. If I talk about now standing in 2020 in these few years already, these motors are used in target-specific drug designing and many other applications. So, why do we do simulations? I have talked about this before in a broader way. But now, we want to replace the experiment we want to design or provoke a new one.

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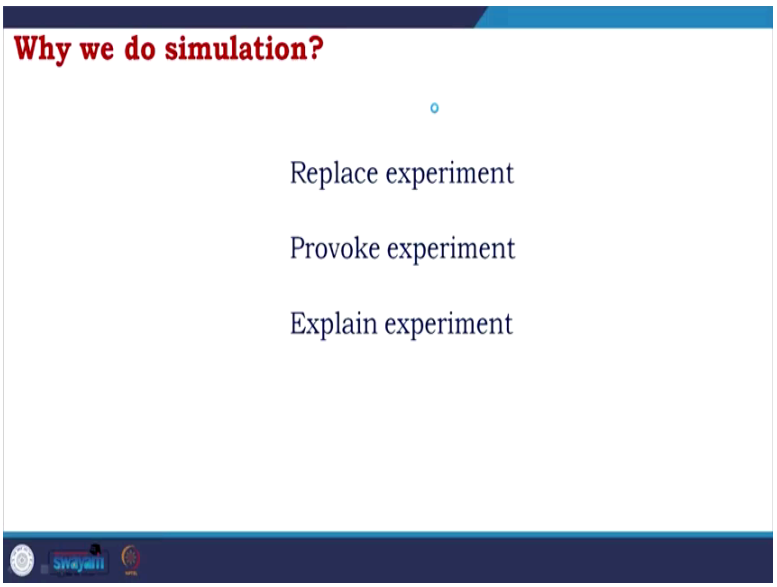

And sometimes, we want to explain some experiments where we do not understand what is there and why the outcome is like that. So, more going into the mechanical details, we want to experiment.

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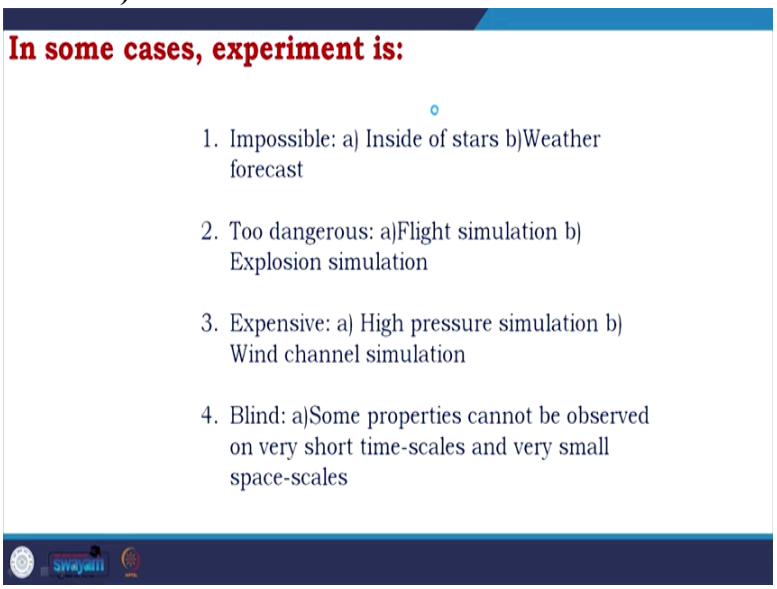

Sometimes, impossible experiments, like inside the stars and weather forecasts, are too dangerous, like flight and explosion simulations. Sometimes they are very expensive high-pressure simulations and wind channel simulations. Sometimes it is blind, and we have no idea some properties cannot be observed on very short timescales and small spatial scales. So we need to develop models for them. So, why is molecular dynamics simulation? There are The most popular 3 dynamic methods used one is Brownian movement, the second is Monte Carlo, and third is this molecular dynamic simulation.

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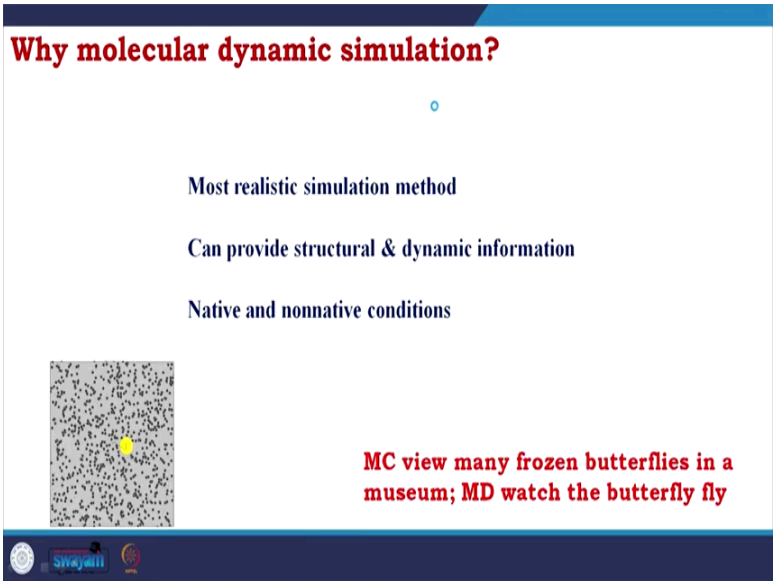

This is the most realistic simulation, and it could provide structure and dynamic information. We start from structure, so atomic coordinates and all are there. So, we have total control here, and it could work on native and non-native conditions. Like as I was talking about, there is an explosion going on. So how you could catch and understand it, you have to create the further explosion.

You have to make a lot of damage. But by molecular dynamic simulation you could have performed, there is a very popular story we had heard when the American soldiers were back from the work field, because of tent staying for a long time, the work base, many of them had problems in hearing. But the doctors had not much idea how to treat them. So, in Pittsburgh's supercomputing center, they have created a model by developing models of physical human bodies.

Specifically focusing on the 3 bones which are needed for hearing those tiny bones, how they are affected, and how the system is affected by the war situation where the sound decibels are high. By developing this model, they have understood what they have worked on, and by those understanding, the surgeons and the medical surgeons have done minor operations and minor surgeries, and most of the soldiers got their hearing back.

As I was talking about the Brownian movement, most models are unfit, especially atomistic models. Monte Carlo has contributed significantly. I am not going into details as I told you in an introductory class. I am just giving you an example of how to differentiate between Monte Carlo and MD simulation, and we are talking about the butterfly movement. If you consider

the movie of a butterfly movement, that is MD simulation, but if you take the photographs, which are freezing the butterfly movements, good enough to explain the entire flying mechanism that is Monte Carlo.

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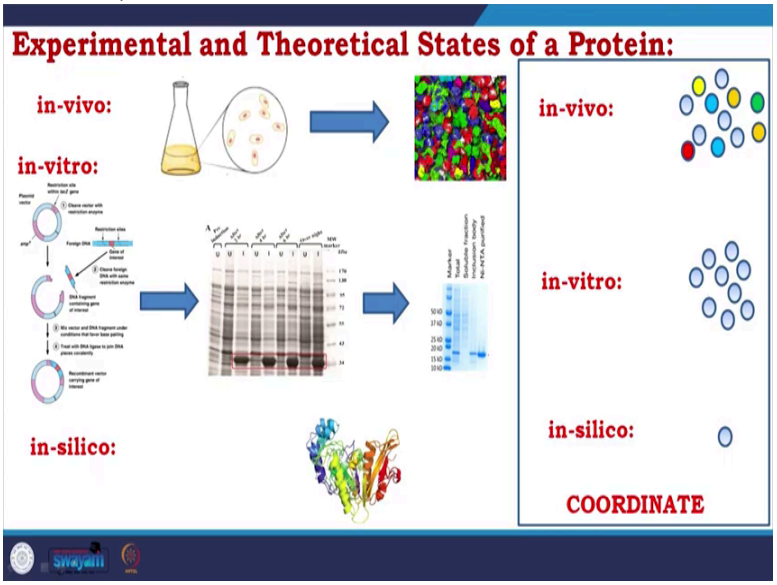

So, if you look at the advantages, I am talking about 3 situations. In in-vivo, where you have your cell, your culture your cell, and you get a lot of proteins. In in-vitro, where you target a specific protein, you do the cloning and purification, but you still get your protein in high numbers. So, the copies of your proteins are very high. But in in-silico, you get only one or a few proteins you want to set up your experiment.

So, if we compare them in in-vivo, you get your proteins which are the blue dots, but you get many other proteins with this. In in-vitro, you again get the purified protein in multiple copies. In in-silico, you will get one or a few according to how you set up or how you want to set up, and more importantly, you will get the information about the coordinates. So, by having these 2 controlling the number and controlling the coordinate, you apply force fields. So, you see the changes in the coordinates. You have a lot of controls in the MD simulation experiment.

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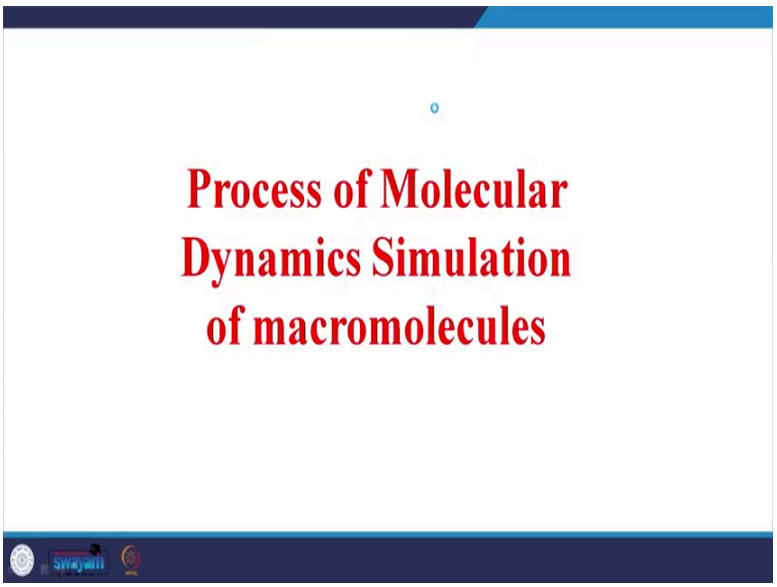

We are coming to the process of molecular dynamics simulation of macromolecules.

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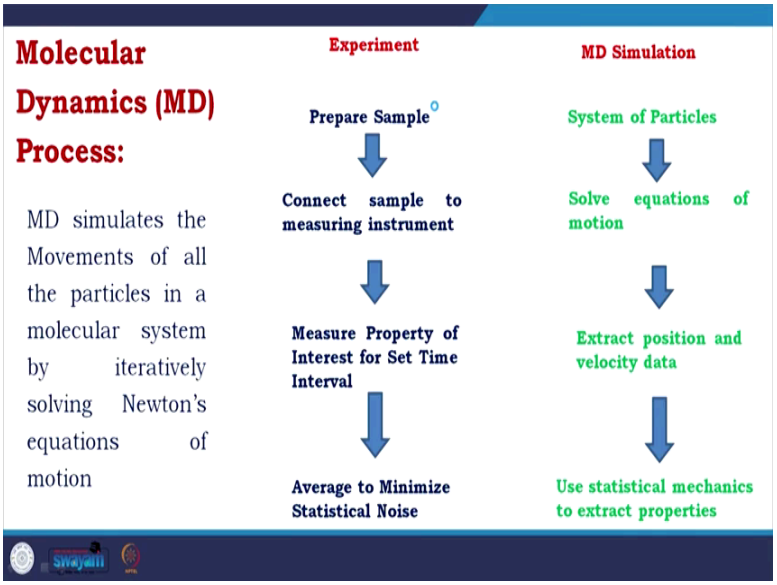

So, suppose you compare molecular dynamics simulation process with an experiment. In that case, you prepare a sample. Here you prepare the systems, and I will talk about how you prepare the system, especially for protein. After preparing the system, you connect the sample to the measuring instrument. For example, if you have a protein solution, you want to do spectroscopy, connect it to the spectroscopy instrument, and do the measurement.

Here you solve the equation of motion. In the experiment, you measure the property of interest of set time interval after connecting. Here you extract the position and velocity data coordinate and the coordinate change with the velocity time. In the experiment, you average to minimize the statistical noise you get the data. Here you use statistical mechanics to extract

properties. So, molecular dynamics simulate the movement of all the particles in a molecular system by empirically solving Newton's equation of motion.

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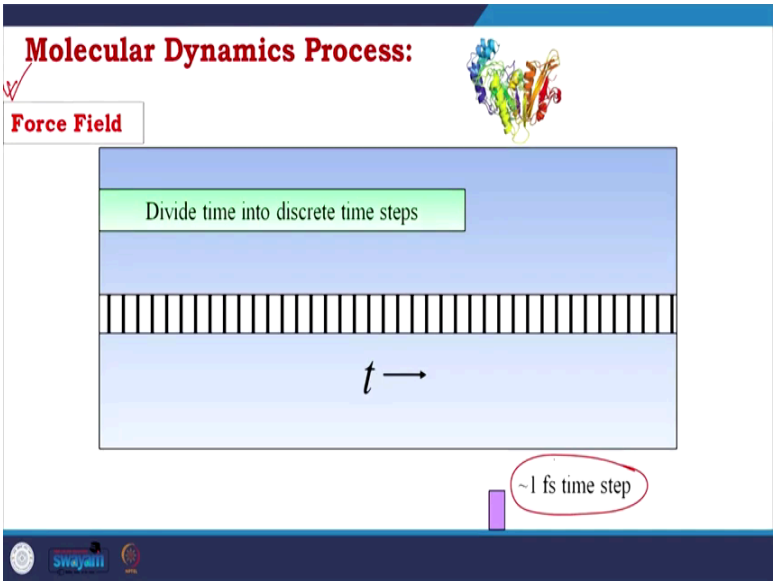

So what we need here, very important, is a force field. Then in the force field, we divide the time into discrete time steps. Like a very reasonable time, the step is one femtosecond time step, and then we have our coordinate system and apply force to that.

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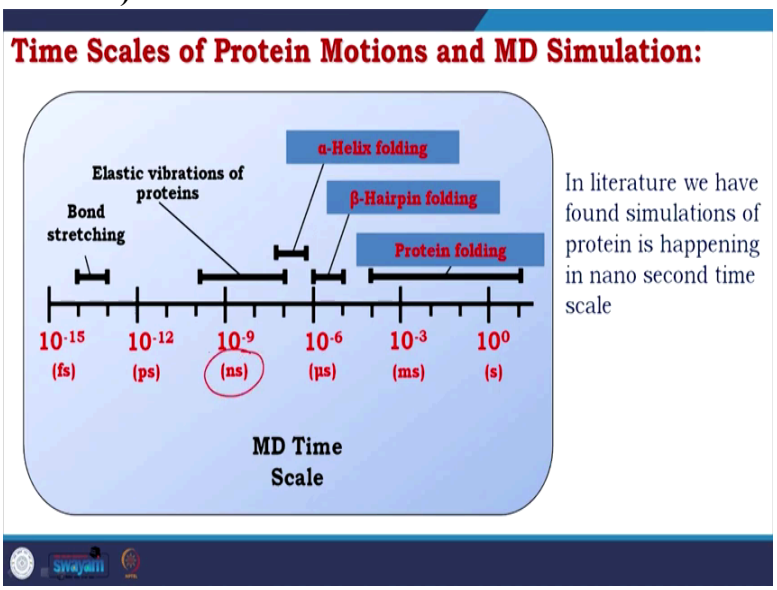

So, I talked about the time step. Let us look at the time scale of protein motion and MD simulation. So, bond stretching; is a stretch between 2 atoms in the scale between femtosecond and picosecond. Elastic vibration is special; your protein is coming on that nanosecond level. Alpha helix folding is coming between nanoseconds to microseconds. Beta hairpin folding is around at the microsecond level.

Protein folding, which we are looking for, is around millisecond to second level. So, suppose you look at this and know about MD simulation. In that case, you know that from the literature, we see that the simulation of protein generally happens at the nanosecond timescale. Still, all protein folding events happen in the higher order of time scale. So, quite how it is feasible.

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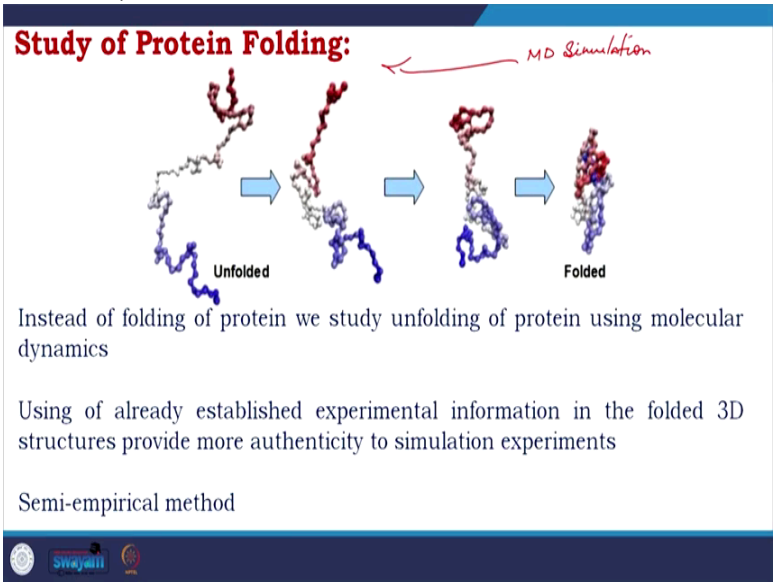

It is very interesting, and we study protein folding. Here in MD simulation, the major focus of the system goes through. Instead of folding the protein, we study the unfolding of the protein. So, we go in the reverse direction in MD simulation, and if you see it, we will talk about disadvantages and all. But if you see the advantage directly, when you were going from folded to unfolded, you already have the folded information coming from the experiment. That is why MD simulation, even a theoretical method, is called a semi-empirical or semi-experimental.

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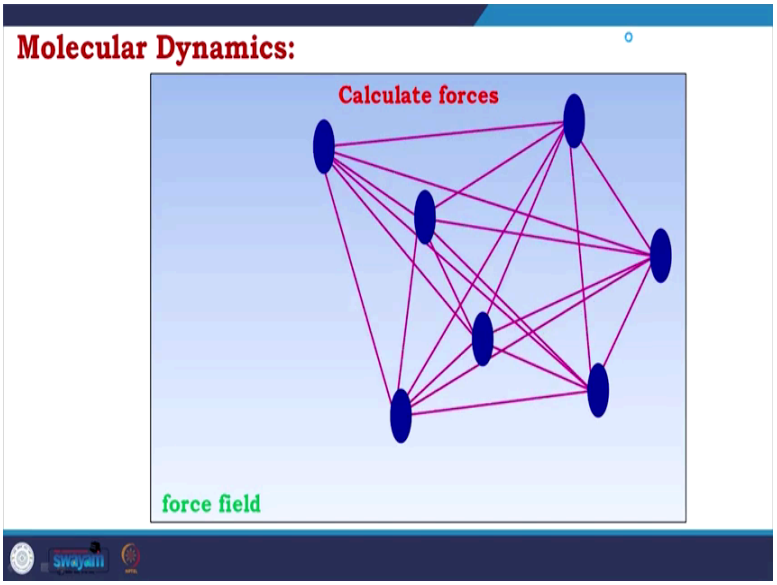

So, as I told you, in molecular dynamics, we have a force field, and we will calculate the forces.

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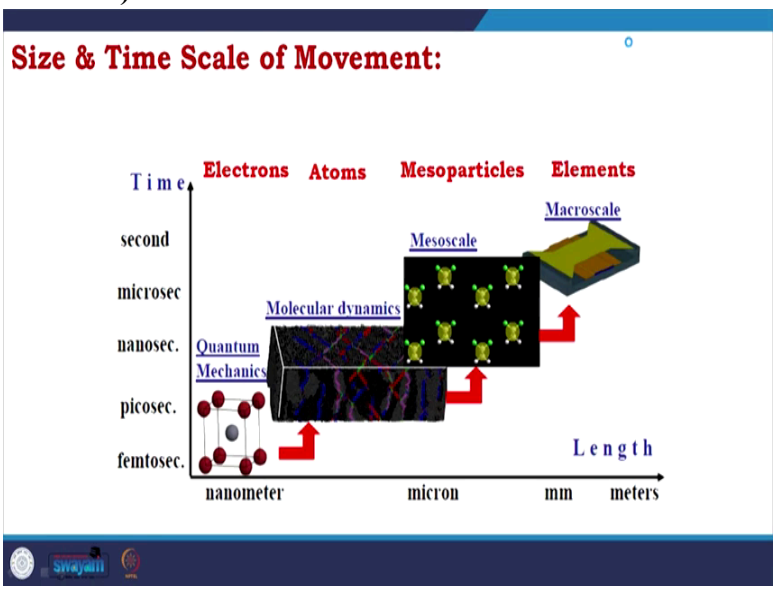

What is the size and time scale of movement? At the nanometer level, we do quantum mechanics where the electrons are there. It is mostly femtosecond and picosecond levels. In relatively higher nanosecond atoms are there, we do molecular dynamics. In higher mesoscale, we use the simulation of or movement of measure particles, and in the macro skill, we treat the elements.

As I told you, we know that we are applying classic Newtonian physics for protein, but it needs the force field to calculate the effects of the protein component. So let us look at the development of the force field because this is one of the most critical things to understand.

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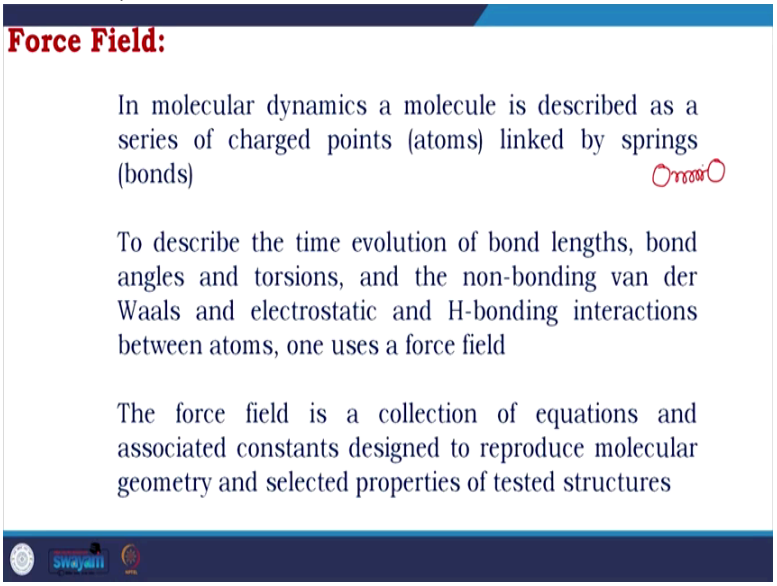

In molecular dynamics, a molecule is described as a series of charging points, which are atoms linked by springs. So you have 2 atoms connected with the spring. That is what the model is. To describe the time evolution of bond length, you get the bond length, angle, and torsion. Torsion is the dihedral and the non-bonding Van der Waals electrostatic and hydrogen bonding interaction.

So in bonded, there is bond length, angle, and torsion dihedral. In non-bonding, there is Van der Waal, electrostatic and hydrogen bonding. The force field is a collector-similar equation and associated constant designed to reproduce the discrete structure's molecular geometry and selected properties. So, you have 6 components, look at them and understand their physics development equation. So, you have 6 component equations. Now, you apply the force field and see how it deforms the atom, changing the coordinates and all the associated parameters.

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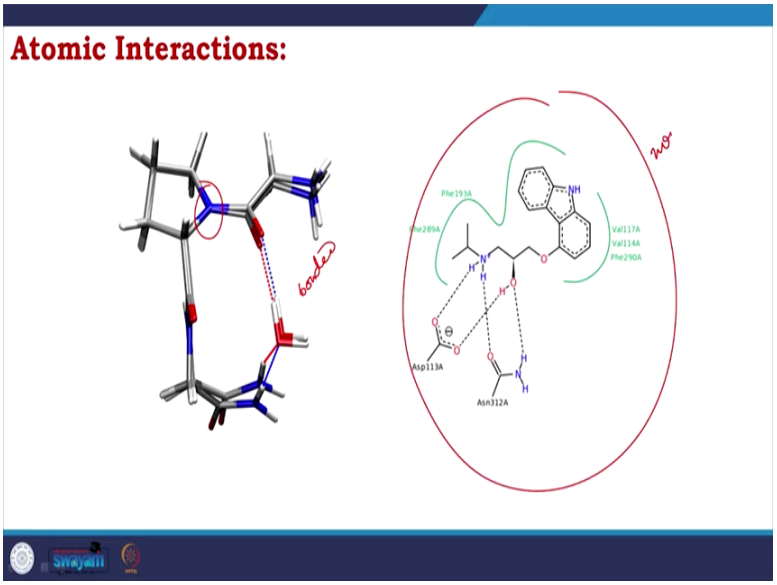

So, coming to the atomic interactions, I said there are bonded and non-bonded interactions. So, bonded and non-bonded.

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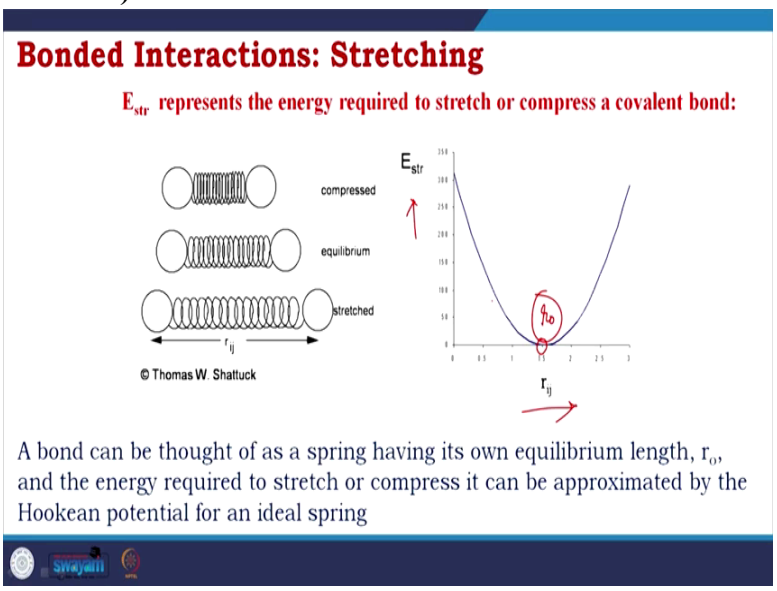

In bonded interaction, there is stretching. As I told you, consider them connected in the spring. So, if you have a spring at 2 atoms and put a force, they will be expanded; if you release it, they will be contacted. So, they would be like doing this and then come to a bond length equilibrium. So, if you put energy and the distance, the equilibrium r 0 would be the bond length energy of stretching the presence of the energy required to stretch or compress a covalent bond.

So, again because it is a spring, they would be approximated or calculated with the like model of Hookean and the potential of an ideal spring. So, a bond can be considered a spring with

its equilibrium length, r 0, and the energy required to stretch or compress it can be approximated by the Hookean potential for an ideal spring.

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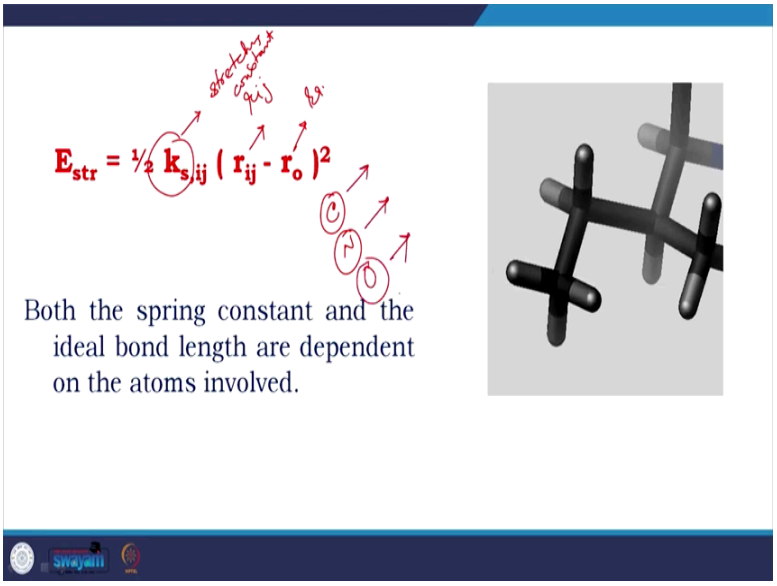

So, the energy would be half k s is k s is the stretching constant r ij is any position you take it you put a force it expanded then you release it is doing that. So, any position is our ij when i and j are 2 atoms and r 0 is the equilibrium position half k s r ij - r 0 whole square. This is the model of a realistic situation, how the bond stretching happened in a protein, this is the spring constant stretching constant, and the ideal bond length would depend on the atoms involved. So, carbon, nitrogen, and oxygen have their own spring constant and bond length.

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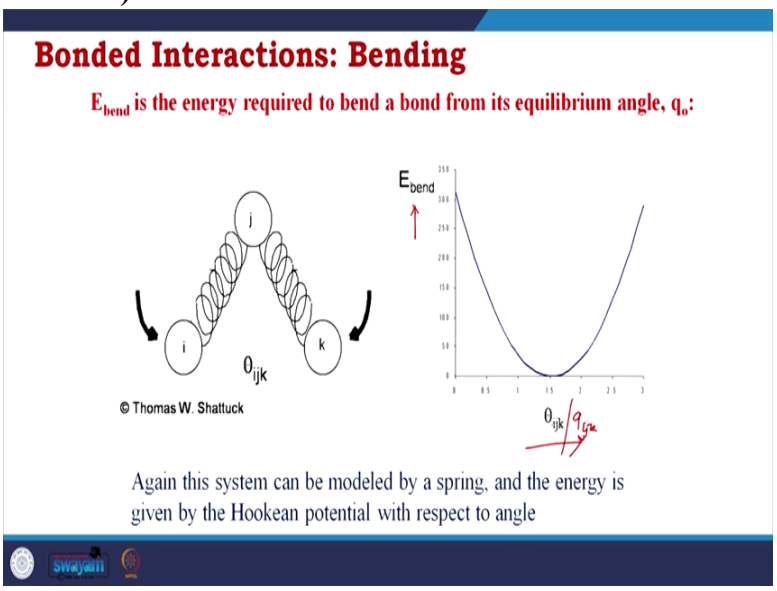

Bending is similar to up stretching, but instead of 2, you have 3. So, you will do in this the curve is the same instead of energy stretching, there is energy bending instead of bond length, and there is the bond angle which is theta, or q. Anything you could be presenting Ebend

again is the energy required to bend a bond from its equilibrium angle q 0. If you consider q ijk, it is q 0 theta j k theta 0. Again this system can be modeled by a spring, and the energy is given by the Hookean potential with respect to the angle similarly.

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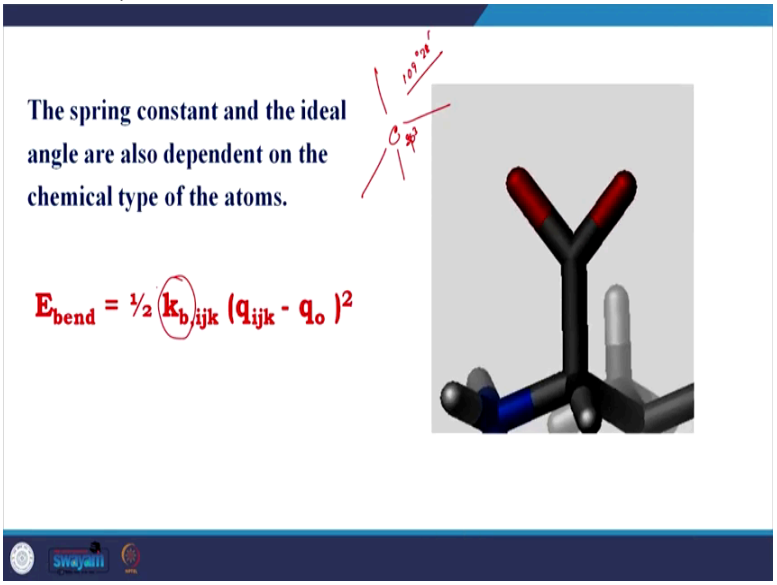

The spring constant and the ideal angular also depend on the atom's chemical type. So, when you consider carbon, it forms bonds. If it is sp3 hybridized, remember I talked about this angle would be 109 degrees 28 minutes. In that way, you will get every bond I have already explained. E bend similarly is half k b where k bis the bending constant and q ijk is anybody sent q 0 is the equilibrium position. So, this is a realistic situation.

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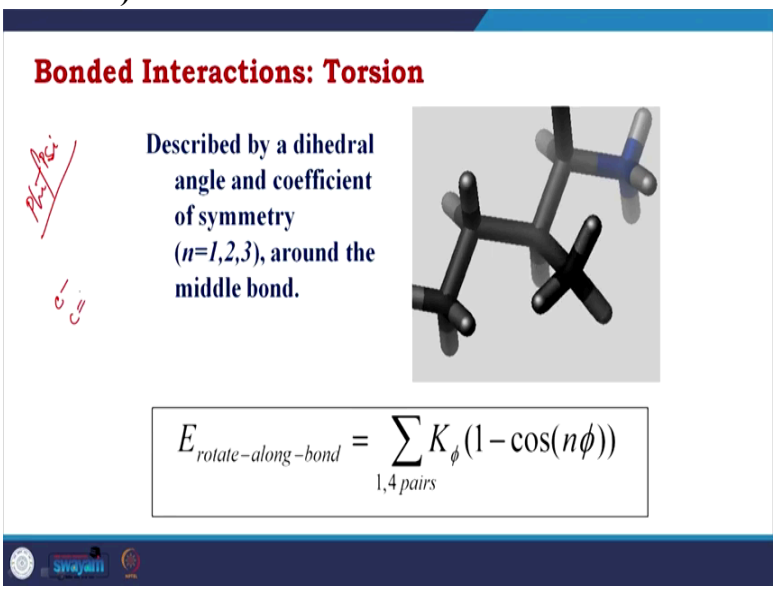

Coming to the torsion, a dihedral angle would describe it. You already know that phi and psi are extremely important for protein, and by understanding the change of phi and psi, you could have determined the conformation and whether a model could be validated or not. So,

energy would be K phi 1 -cos n phi, where n is the symmetry. The symmetry again depends on how the geometry of the atom involved. So, like when I was talking about carbon, it is a single bond. It has one with a double bond it has one backward.

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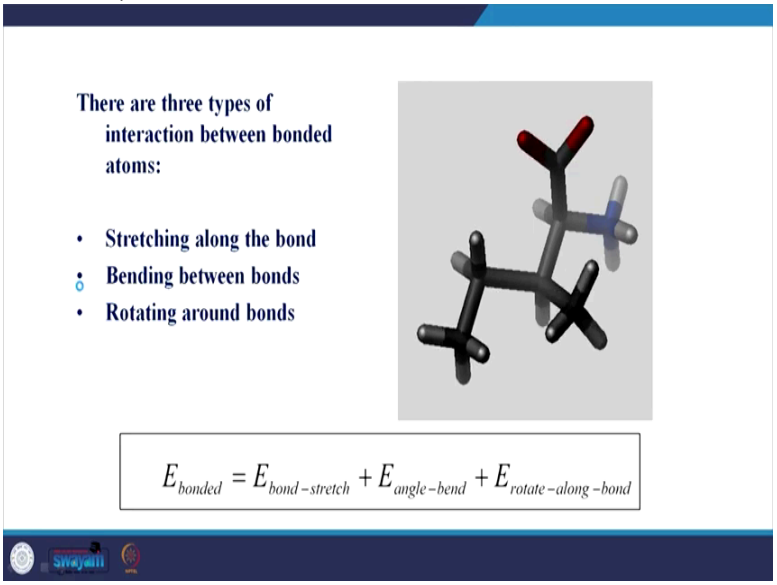

So, as I told there are 3 types of interaction between bonded atoms stretching along the bond, bending between the bond, and rotating around the bonds, and this is the entire picture

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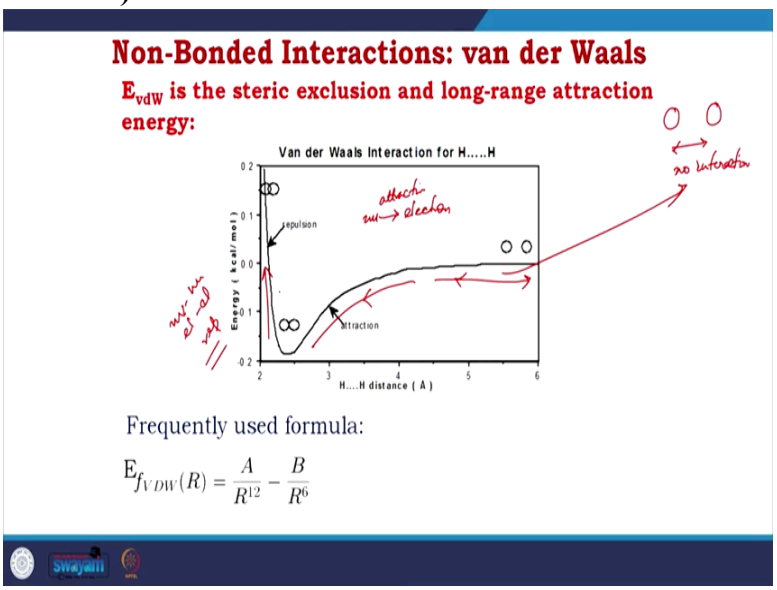

Coming to non-bonded interaction Van der Waals if you have 2 atoms initially, they will have no interaction. So, you see that flat curve where no interaction happens, then when they are coming closer, nuclei of one would attract other electrons. So, the energy would be released reduced, and after some distance, when they are closer, there would be nuclei, and electron-electron repulsion, which the enhancement of the curve will define.

The energy would be defined at A / R to the power 12 -B / R to the power 6, where it is defined as the distance E Van der Waal is the steric exclusive and long-range attacks in energy, this is non-covalent, and this tells where the steric class could be prohibited.

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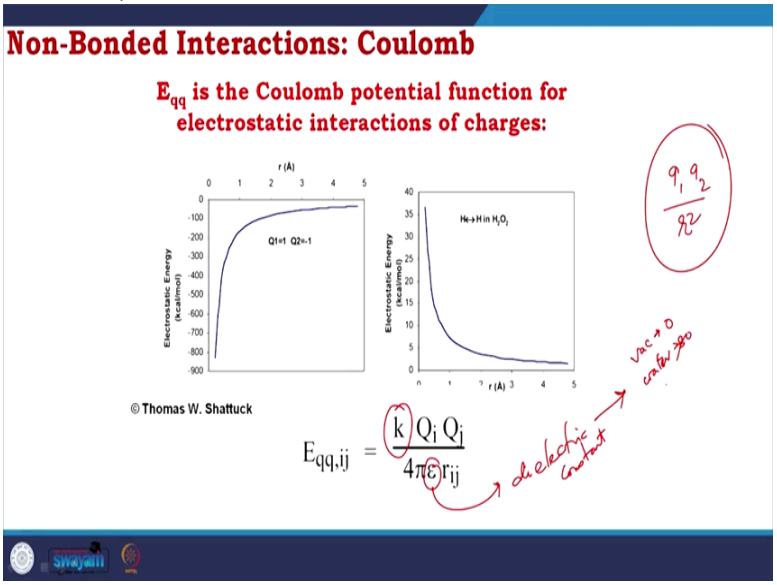

Coulomb, as you know, Columb is in charge. It is the Columb potential function for the electrostatic interaction of charges. So, if you see the electrostatic energy with the distance and it is the same as you know in the charge field is Q 1 Q 2 / r square which we have studied in our tenth, plus 2 level is same here Q i Q j is Q 1 Q 2 and r ij is the distance only the k is Coulomb constant, and epsilon is important, this is a dielectric constant which is in vacuum 0, and when it comes to the water, it is 80. So, each of the solvents has its characteristic dielectric constant.

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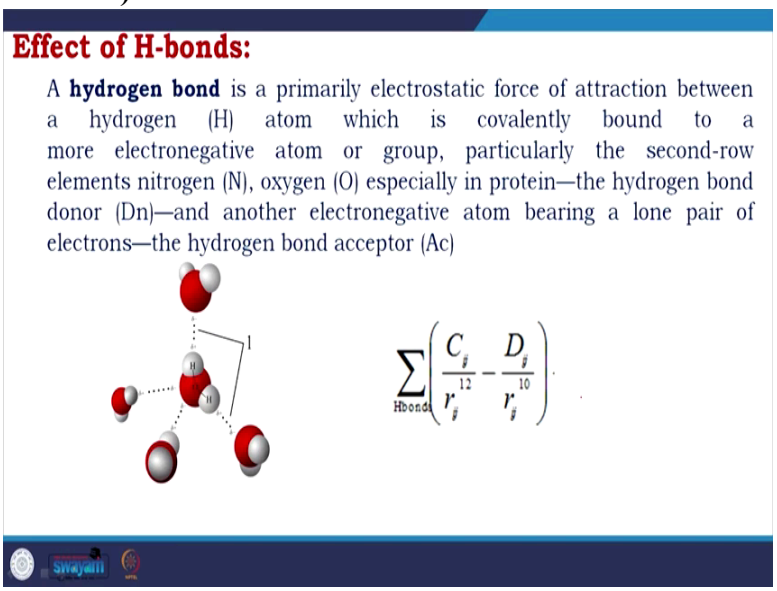

Coming to the hydrogen bonds, which we have already talked about. A hydrogen bond is a primarily electrostatic force of attraction between a hydrogen atom covalently bound to a more electronegative atom or group. In the case of protein, it is only nitrogen and oxygen. One would be the donor, and another would be the acceptor. The physics behind it is like Van der Waals, but here instead of so, it is C / r to power 12 like that, but instead of B / r to power 6, it is r to power 10. That is the difference.

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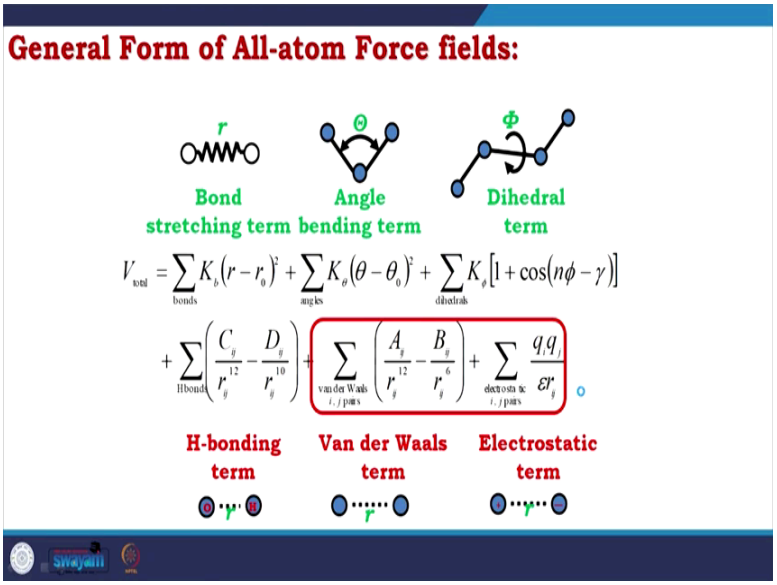

So, a general form of an all-atom force field is a bond stretching term, angle bending term, dihedral term, hydrogen bonding term, Van der Waals term, and electrostatic term.

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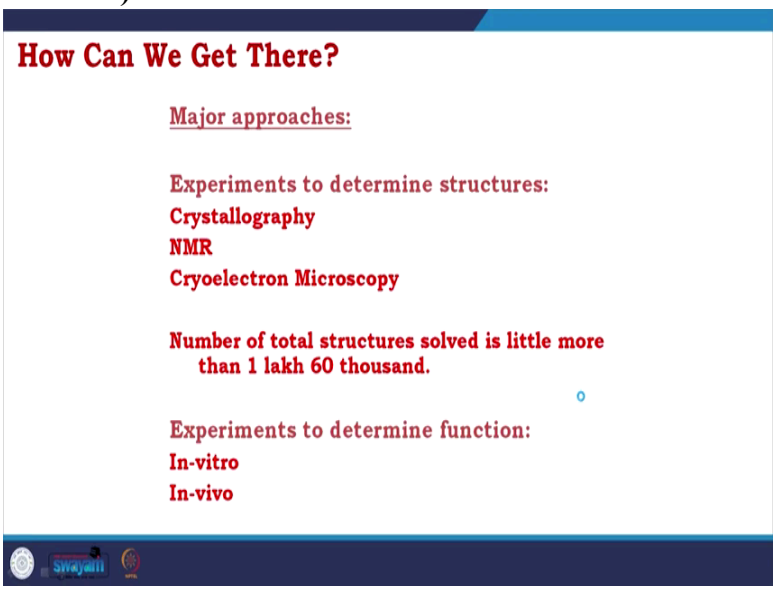

The first requirement is to get the coordinate we could get from all the techniques we have discussed in high-resolution structure determination, crystallography, NMR, and electron microscopy. We could also get experimental information from in-vitro and in-vivo data.

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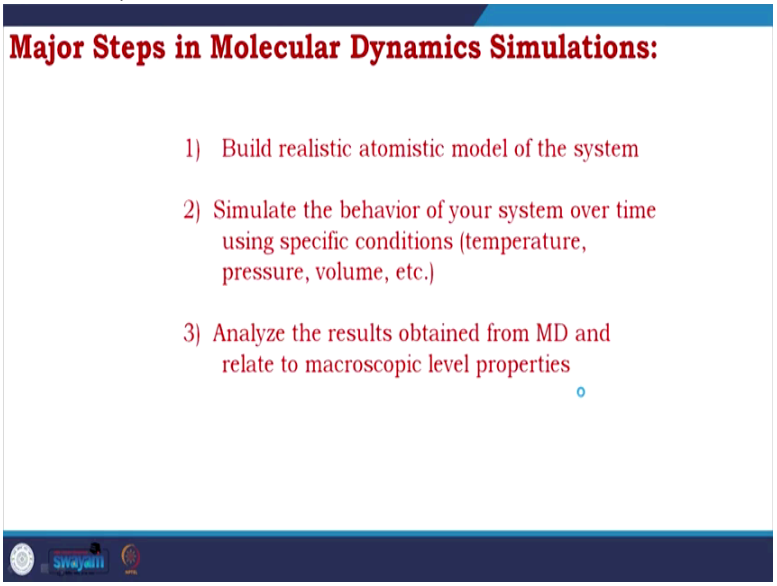

We have now come to a major step in performing molecular dynamics simulation. We will build a realistic, atomistic model of the system. We will simulate the behavior of your system over time using specific conditions, and then we will analyze the results obtained from MD and relate because, as I told you, in MD, we take microscopic properties and relate them to the macroscopic level properties.

So, today in this introduction class, I have introduced the basic requirement and reasons behind molecular dynamic simulation, why it is required in biology and why it is essential for biological experiments, how it has played a critical role and what its application is, and more importantly, how the process would be related to the experiment, how the process is performed and how the algorithm would be applied in a force field using the Newtonian physics.

And we ended up with what is the force field, what the parameters are, and how the parameters contribute to that total equation. So, thank you very much for listening.