Medicinal Chemistry
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Computers in Medicinal Chemistry

So, welcome back, in today's lecture we will look at how computers or computational modelling plays a major role in medicinal chemistry. So, in the past few lectures we have been trying to figure out how to generate libraries of compounds and once we generate these libraries of compounds, then we screen them, either, you know, we do combinatorial chemistry which gives us a mixture of compounds or we can do parallel synthesis which will give us single compound but many number of those.

And we compared the pros and cons of each of these methods and so on. Okay, so these will help us with generating libraries of molecules. And so this approach is somewhat less rational because we really do not know what exactly the area where it is going to bind or the interactions that are going to happen, so we sort of make this library and then we start screening for inhibitors or modulators. So, parallely we can also look at rational approaches. So, in rational approach, what we mean is that if you have a target and if you want to model your compound or make your library such that you are trying to access the binding sites in the target, then that would be a rational approach.

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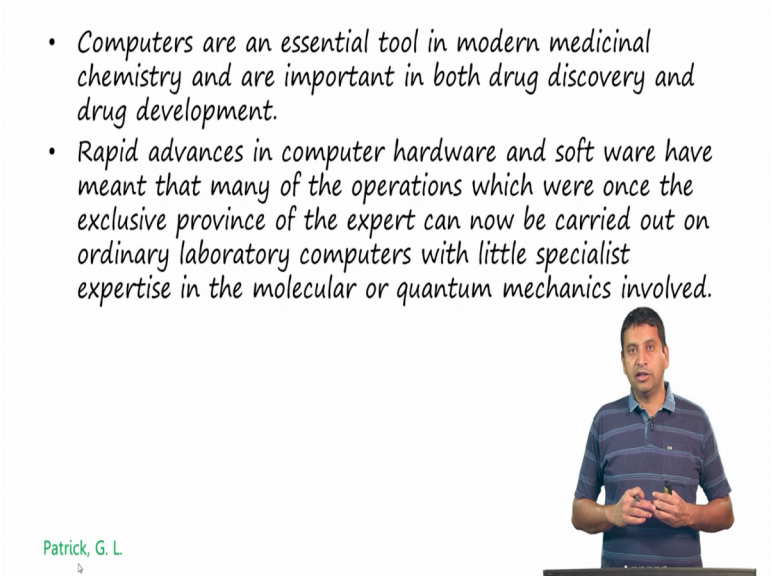

So, here computers become very important. And, in fact in most medicinal chemistry projects or in pharmaceutical industries, computation forms a very important part of the drug

discovery effort and in fact it may even be in some cases very major component of certain drug discovery efforts. So, it is a very essential tool in modern medicinal chemistry. And of course, it is not just important for drug discovery but also for drug development. Because what people have done is to develop new protocols by which you can actually model even pharmacokinetics.

So, based on existing data that we have, you can always look for various ways to find out how the molecule is going to distribute, okay. So, this is being supported by rapid advances in the capital hardware as well as software. And so which were maybe 20-25 years back, these kinds of processes were really not accessible to the drug discovery people, but now even ordinary lab computers can help you, you know, sort of do simple molecular or quantum mechanics-based calculations.

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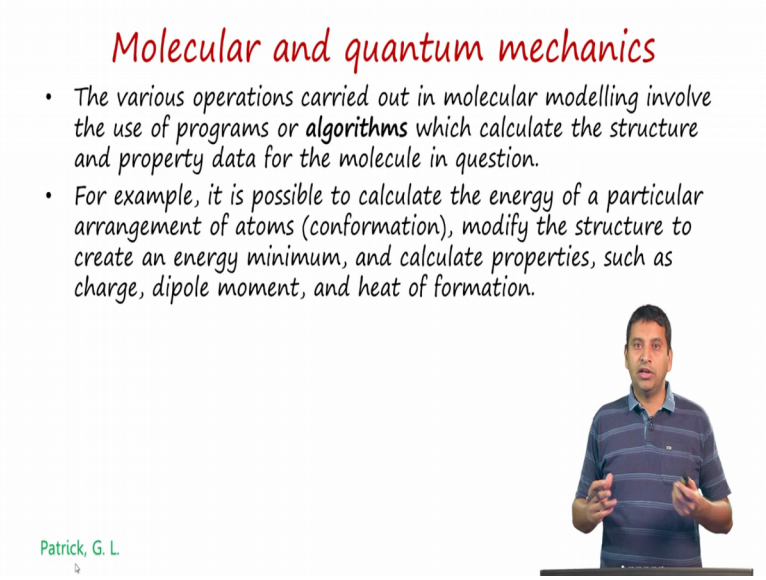

So as I mentioned just now, there are 2 major types of approaches here in computation. And these are the molecular and quantum mechanics. Now, the various operations carried out in molecular modelling involves the use of programs or algorithms, okay. And these are the ones that help with calculating the structure and property data. So, the key words here are structure and property data. Okay. So, once we have a, let us say we want to make a library of all we have a library of molecules and we want to prioritise them as to which one they want to synthesise 1st.

So, we could use these types of calculations to prioritise. So if you were small molecule, it is possible to calculate the energy of a particular arrangement of atoms, which is also known as

conformation, okay. We can also modify the structure to create an energy minimum. That means that a particular conformation that we can draw out does not necessarily have to be the minimum energy conformation. And then we can also calculate properties, we can calculate charge, we can calculate dipole moment, we can also calculate heat of formation. So, these are all possible with computational approaches.

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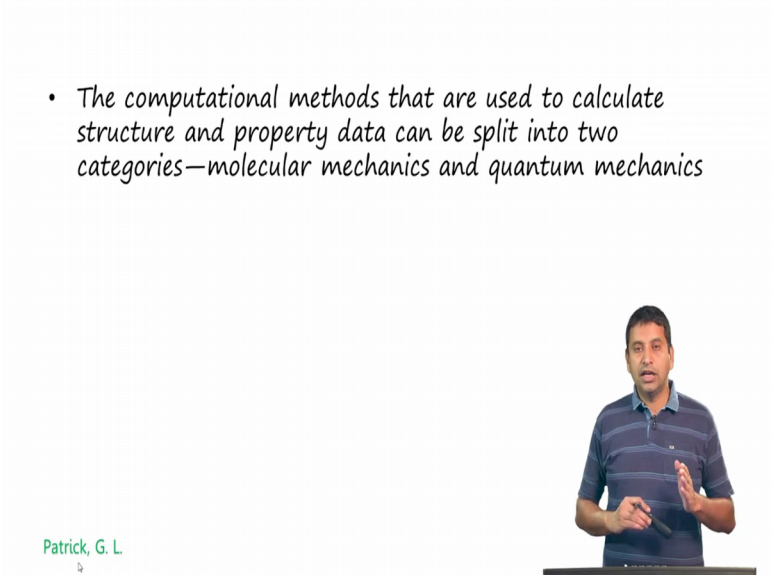

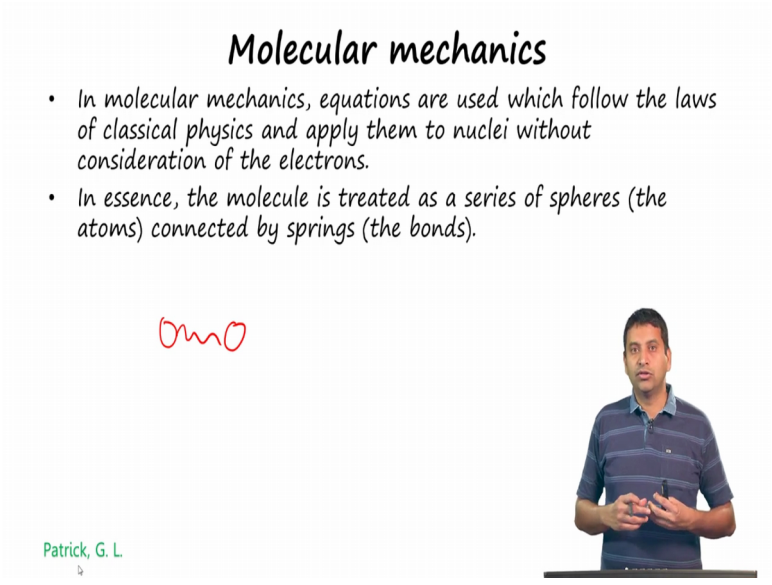

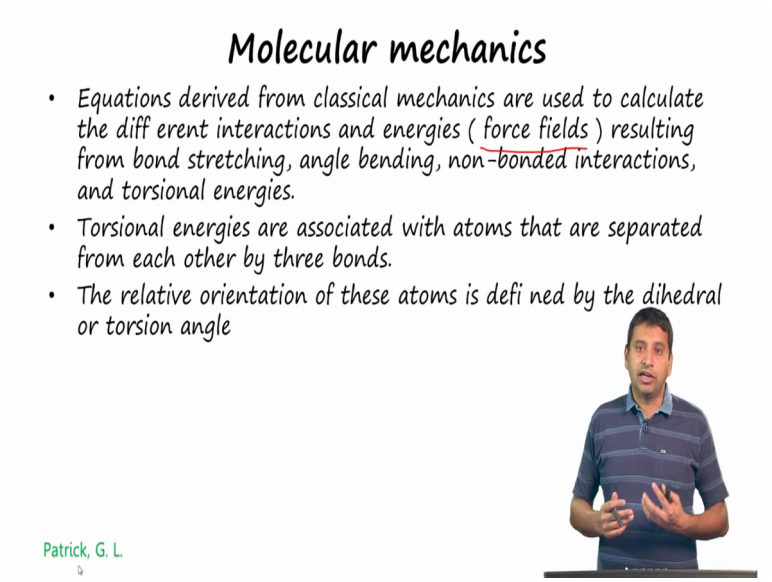

So, there are 2 categories as I just mentioned, one is called the molecular mechanics, and the other one is called quantum mechanics. So, in the 1st approach that is the molecular mechanics approach, here we use equations which follows the laws of classical physics, okay. So, you know these are applied to nuclei without consideration of electrons. So, here what we would assume is that there is a, you know there is a sort of a spring with 2 different nuclei which are connected by springs for example, which bonds and then these spheres are going to be the basis for your calculations.

So, we assume that these are nuclei and they are connected by bonds which are springs and they can vibrate and bend and so on. So, equations derived from classical mechanics are used to calculate the different interactions and energies. So, these energies are also referred to as force fields, okay. And these amenities which result from bond stretching, angle bending, that is if you are at 108 , then you can go down to 107 or go up to 109. And then also you can think about non-bonding interactions, so for example you can have very weak interactions that can happen and torsional energies, that is these are energies which are associated between items which are separated by 3 bonds.

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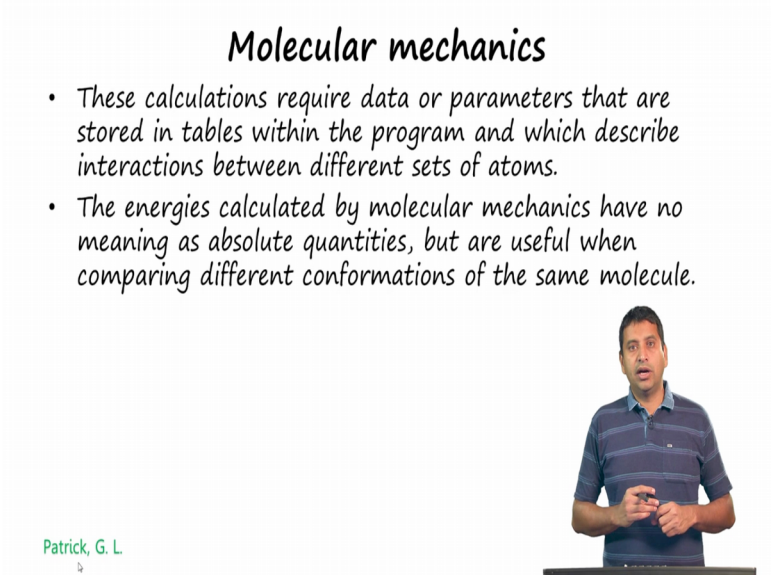

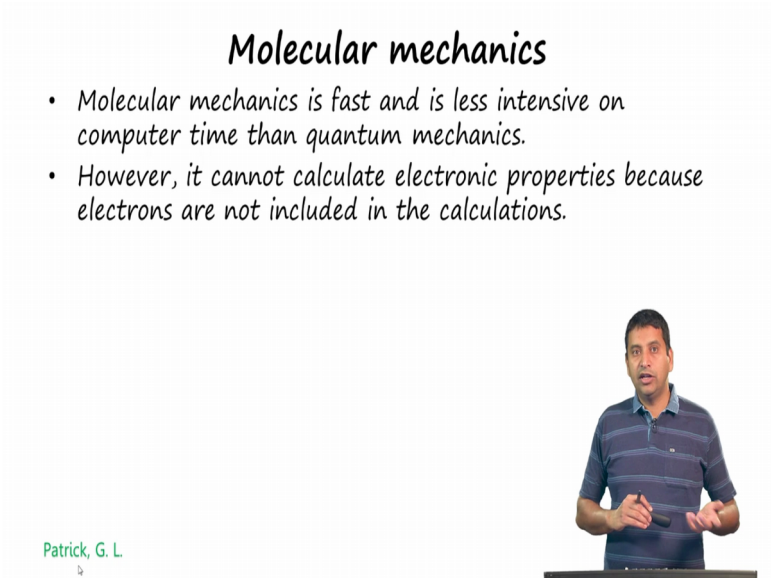

So the relative orientation of these atoms is defined by the dihedral or torsion angle. So, these are things that are taken into account during molecular mechanics calculations. These calculations required data or parameters that are stored in tables within the program, okay. And which then describe interaction between the different sets of atoms. So, the energy is calculated by molecular mechanics have no meaning as absolute quantities. So when we do these calculations, we always understand that these are relative, okay.

So we will have to compare between 2 molecules as a relative term rather than absolute terms, okay. But when you have different confirmations of the same molecule, something that has a lower energy can be considered to be more stable than the one which has a higher energy. Okay. So the advantages of molecular mechanics is that it is quite fast, and it is less

intensive on computer time when compared with the mechanics. However, a major drawback with molecular mechanics is that it cannot calculate electronic properties because electrons are not included in the calculations.

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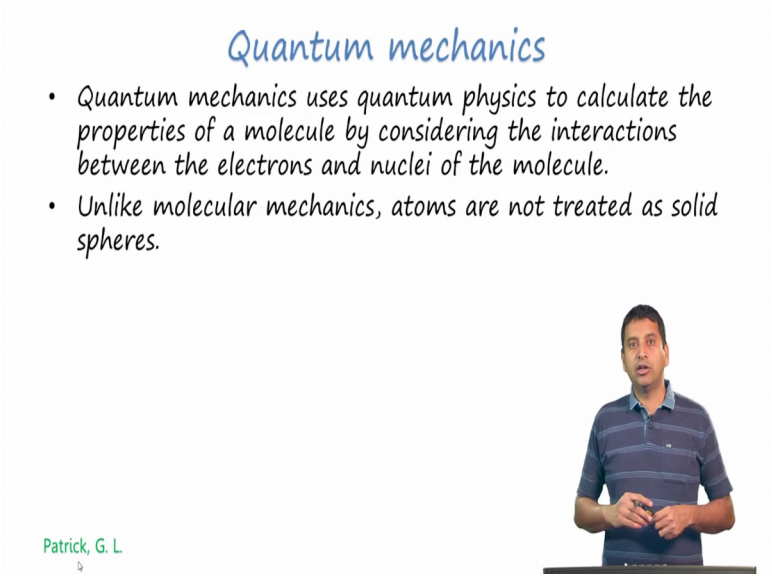

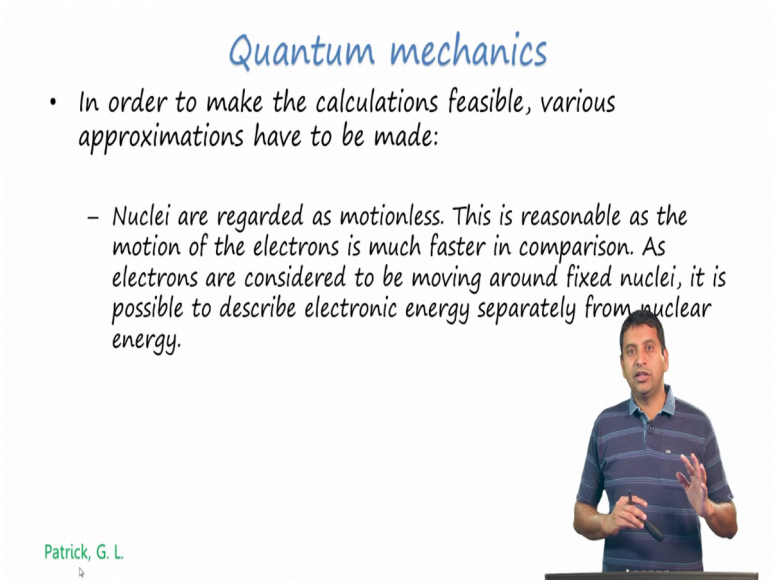

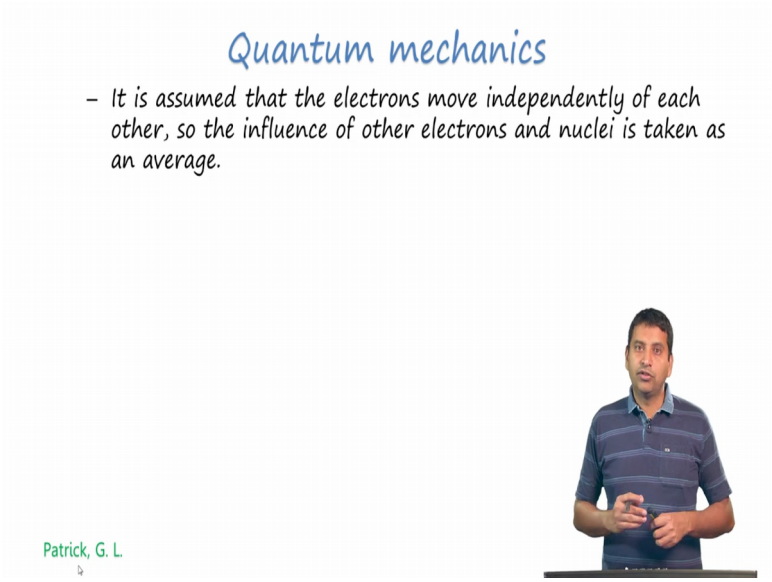

So what we can calculate is to get force fields and we can get some level of information about conformation. On the other hand quantum mechanics uses quantum physics to calculate properties of a molecule. And here the interaction between electrons an APR of the molecule are taken into account. Unlike molecular mechanics, atoms are not treated as solid spheres. So, in order to make these calculations feasible, various approximations have to be made, otherwise it is going to become quite intensive from the computational standpoint.

So the 1st approximation is that nuclei are regarded as motionless, that means they do not move. This is quite reasonable because the motion of electrons is much faster in comparison with that of nuclei. So, as electrons are considered to be moving around fixed nuclei, it is possible to describe electronic energy separately from nuclear energy. It is also assumed that the electrons move independently of each other, so the influence of other electrons are nuclei is taken as an average. Okay. So these are the couple of assumptions that are made in quantum mechanics calculations so that we can produce the computational effort.

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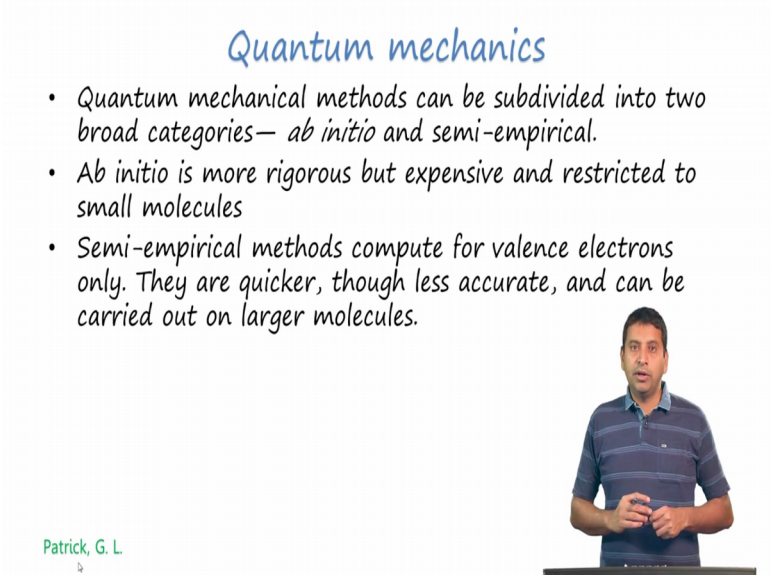

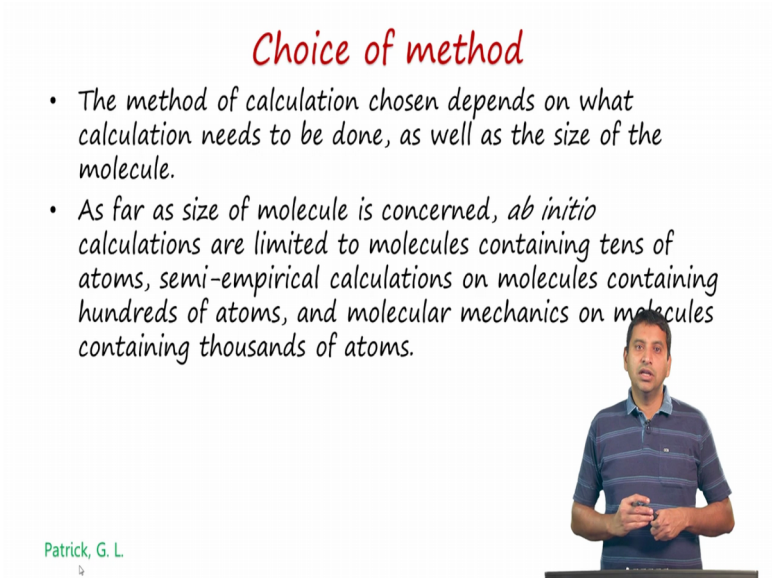

So, quantum mechanical methods can be subdivided into 2 broad categories, the 1st one is called the ab initio methods and the 2nd one is called semiempirical methods. So, ab initio, as the name suggests is starting from 1st principles, okay. So, here the, the method is very rigorous, but computational very expensive. And so we are typically restricted to really small molecules, with molecular weight less than 300 or something like that. Semiempirical methods on the other hand are accessible and they are very computational less intensive.

However they are less accurate because there are far more approximations that are made and however they can be used on larger molecules, okay. So, depending on the need we would resort to either ab initio or semiempirical calculations. So, based on the size of the molecule, we can choose either ab initio or semiempirical. As far as size of the molecule is concerned,

ab initio calculations are very limited the molecules containing tens of items whereas semiempirical contain hundreds of atoms and molecular mechanics can work with thousands of items.

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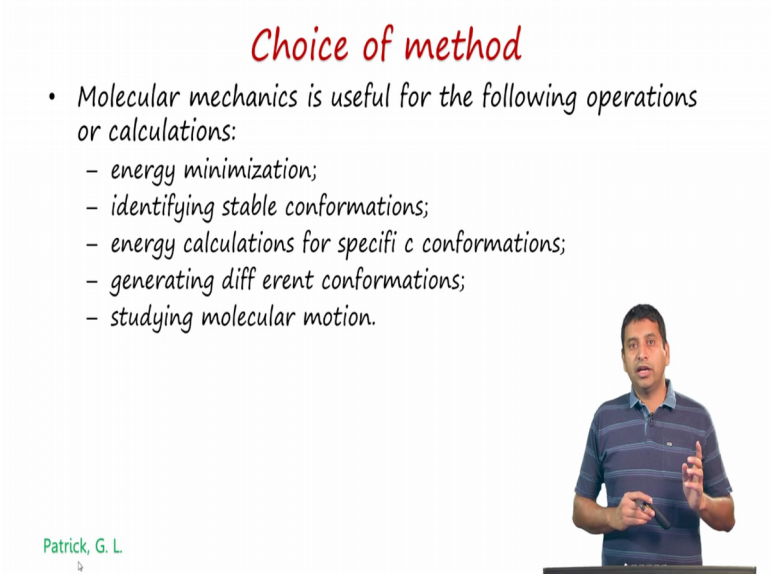

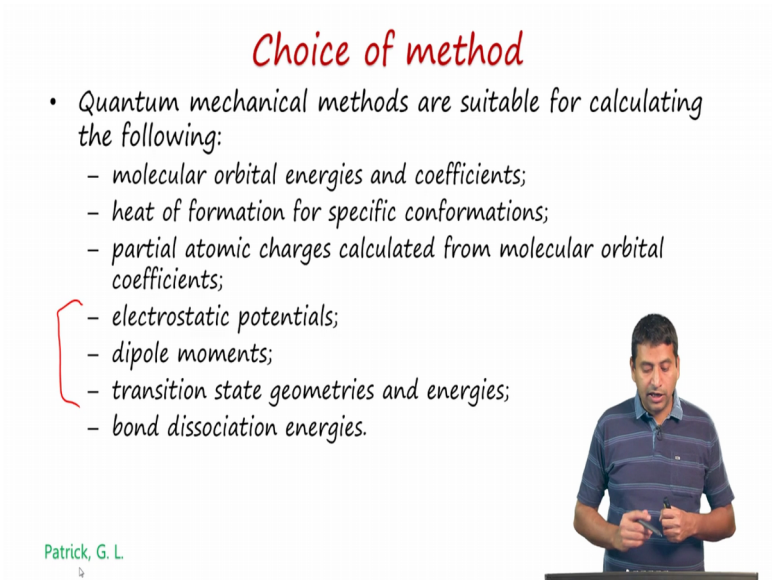

So here is the scale that we are going to work with. So, molecular mechanics is useful for the following operations. 1, energy minimisation, so here you find identify the most stable conformation among the various possible conformations. And then you can also calculate energy for specific conformations, right. And you can also generate different conformations and assign a energy value to it. It is also useful to study molecular motion.

Quantum mechanics is more suitable for calculating molecular orbital energies and coefficients. And it can also be used for heat of formation for specific conformations. So you

have to define the confirmation and then you can calculate the heat of formation. But it can importantly calculate partial atomic charges and electrostatic potential. These both become very important when we are looking at interactions between the let us say a protein active site and the molecule.

It can also calculate dipole moment, transition state geometries and energies. And lastly it can give you an idea about bond dissociation energies. So, these 3 aspects, that is electrostatic potentials, diaper moments and transition state geometries are very important, especially when we are looking at how the reaction proceeds. And so if we are looking at trying to figure out a mechanism of a reaction, then these become important. Also, dipole moments and electrostatic potentials play crucial roles in binding.

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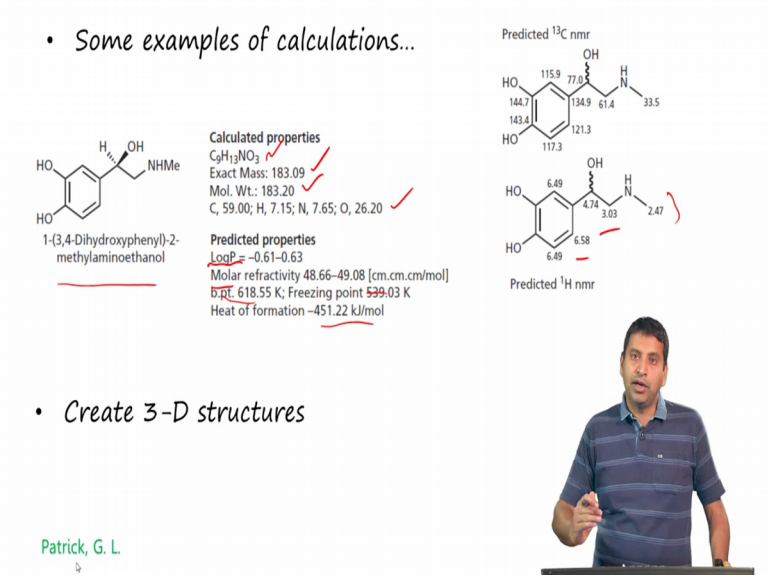

So, here are some examples. So, what we can do is, we can use the commercially available software Chem Draw and what we can calculate very simple properties using Chem Draw. So, for example molecular formula, exact mass, molecular weight and elemental analysis. So, the 4 can be done using Chem Draw. Based on this you have, this software is available in many computers, you can also calculate the partition coefficient which is log P, okay. So, for this molecule for example, the log P value is found to be -0.61.

So here the idea is that we want to be able to have a database, using this database we can actually calculate the properties of a molecule. Now, we can look at bowler reflectivity, we can calculate the boiling point and the freezing point using this software. And we can also calculate the heat of formation. In addition to this, NMR data can be predicted, so you can

have detailed description of the NMR chemical shifts, proton in this case. Or even carbon 13 chemical shifts.

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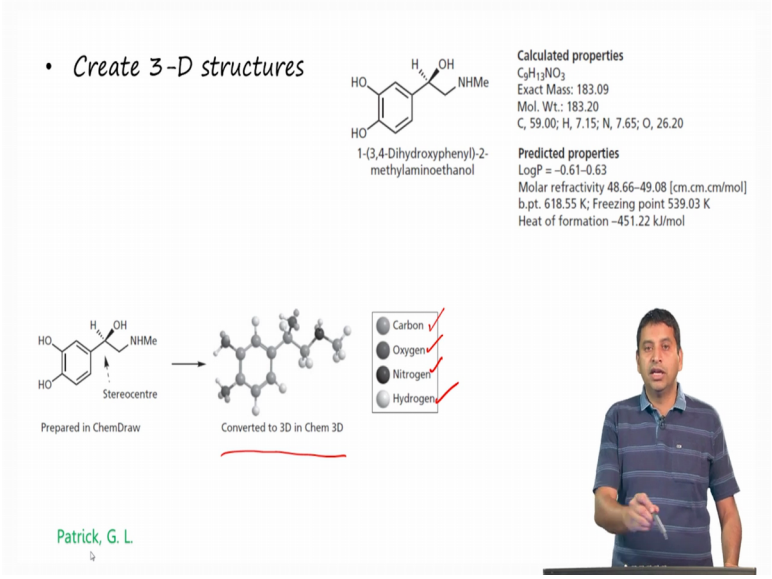

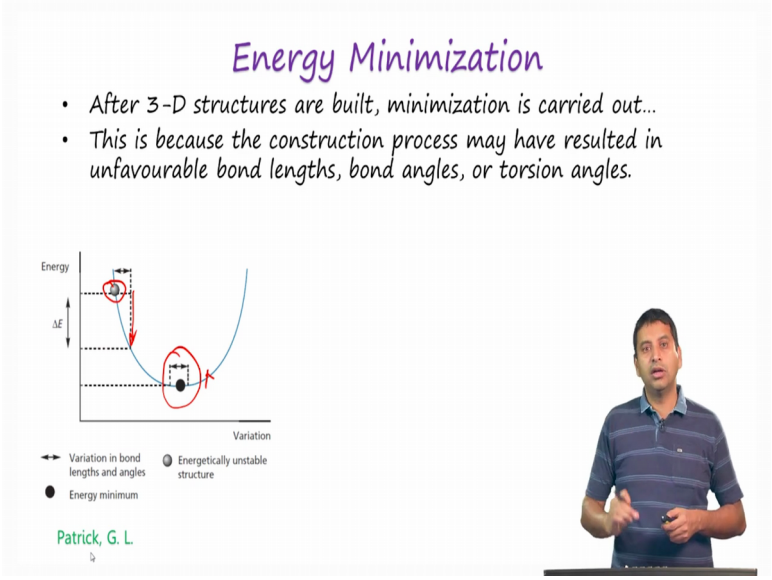

Again these are arrived upon by using algorithms value already field and existing data and then based or that it is able to predict. Now, one of the things that can be done using this kind of software is to create 3-D structures. So the way we would create 3-D structures is that you prepare the structure in a software like Chem Draw and then use what is known as Chem 3-D, which is basically a software which gives you the, attempts to give you the structure in 3 dimensions.

So here you will get a structure like this, which is, here is the carbon, oxygen, nitrogen, hydrogen of these molecules. And you can see that these are located at these as spheres. Then,

what we do is that we need to do what is known as energy minimisation. So, here the process of energy minimisation is important because there can be in the original structure that you draw, there can be various unfavourable bond lengths, bond angles or ocean angles. So the hypothesis going in here is that there is molecule has a set of conformations which are of lower energy compared to another set of conformations which have higher energy.

So, if we start sampling this energy profile, then we would be able to arrive at a situation where the most energetically stable structure can be arrived, we just call the energy minimum. So, here if you start from this point here, small variation in the structure can result in a large energy shift. Whereas if you start from here for example, then a small variation in structure will only result in a small energy shift. Okay. So therefore using this kind of a map of one can arrive at the energy minimum for the molecule.

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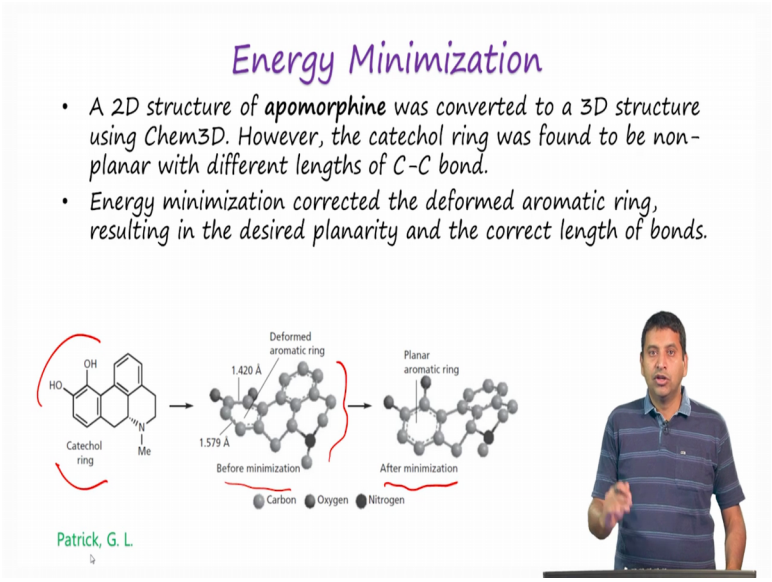

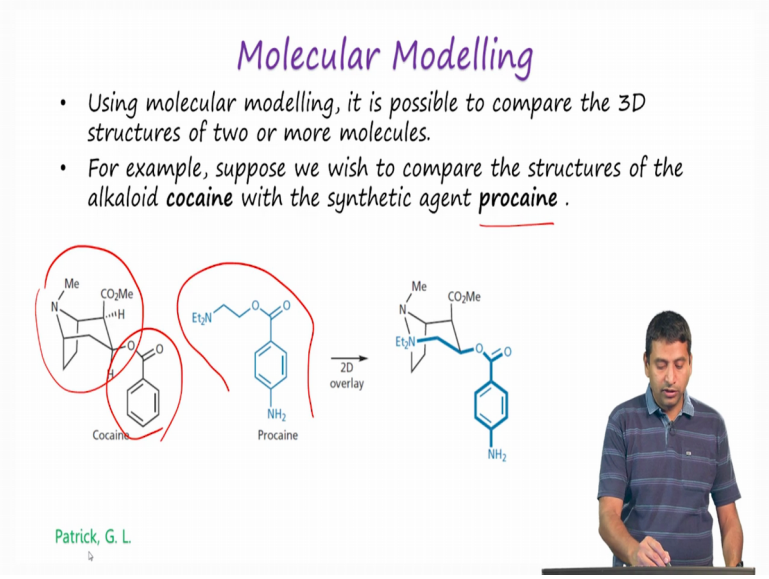

So, here is an example, so we can take it to the structure of apomorphine and then we convert it into 3-D structure using Chem 3-D. However, if you see here, that here is a structure and it has a catechol ring over here and if you see here, before you minimise the molecule, you have a catechol structure and this less of the molecule is actually nonplanar and which has different carbon carbon bond lengths. Now, when you do the energy minimisation, you can actually correct the deformed aromatic ring either result and then the desired plurality and the correct length of bonds can be arrived.

So here is the structure of molecule after you do the energy minimisation. So, therefore this energy minimisation helps us arrive at conformation which is quite stable. No, another example of molecular modelling, is that we take the cocaine which, whose structure is shown here and here you have a heterocyclic molecule which has by Sacklecha ring and a ester, okay. No, there is another molecule or analog which is a synthetic agent called as procaine. So this is the structure of procaine.

So, just by doing an overlay, 2-D overlay, what you will find is that this aromatic ring here will overlap with this aromatic ring. And this structure here will actually sit nicely over here. Okay. So this is what we would arrive at name, using a tedhe overlaying of the 2 structures, which is shown here, okay. Now, is this really accurate?

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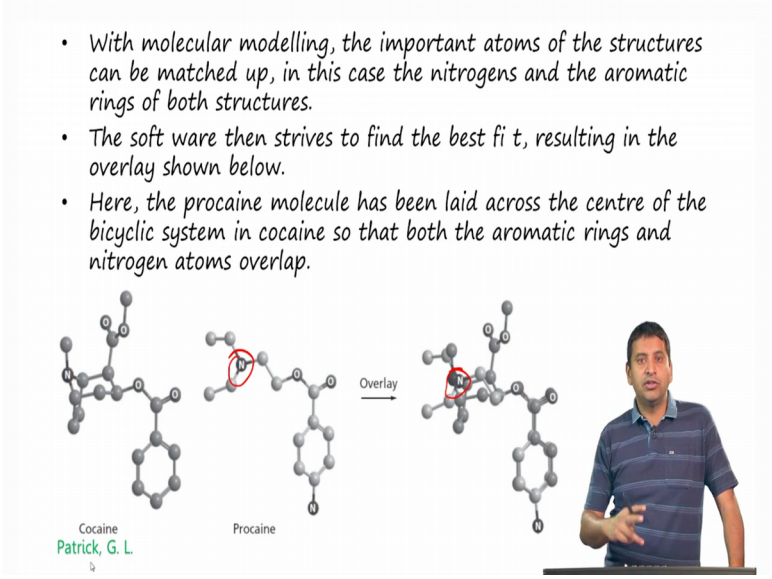

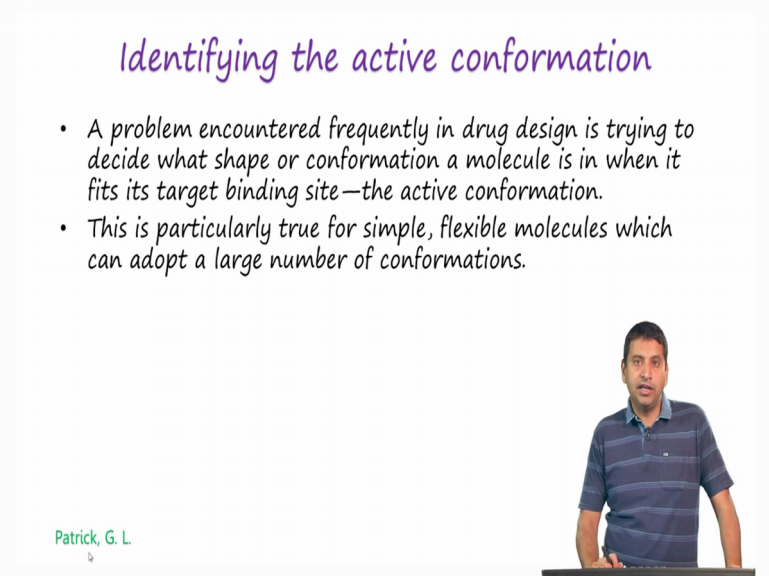

When you actually do molecular modelling, what happens is that you can actually match it up based on the energy minima. So, then what happens is that this software will then strive to find the best fit, okay. So, when you do the best fit, you actually see that this nitrogen of procaine exactly overlaps with the nitrogen of cocaine. So, here the nitrogen is actually lead a dissenter of the bicyclic system in cocaine so that both the aromatic rings and the nitrogen overlap. So, here is a significant difference between the 2-D overlay and the 3-D overlay.

So using this kind of a methodology, you can now imagine that a number of these comparisons of across structures can be made. Once you do these comparisons, you will start deriving maps which can be useful for designing new analogues. Next important problem is in identifying the active conformation. So, frequently in drug design what happens is that a

particular shape our conformation is going to be more important than another shape or conformation. So, the one that actually binds to the structure is called the active conformation.

However the active conformation need not be the energy minimum. And it becomes a big problem, especially when we are looking at highly flexible molecules which is very simple in nature. So, here these types of molecule can adopt a large number of conformations and it becomes very difficult for us to map out what would be the potential active conformations.

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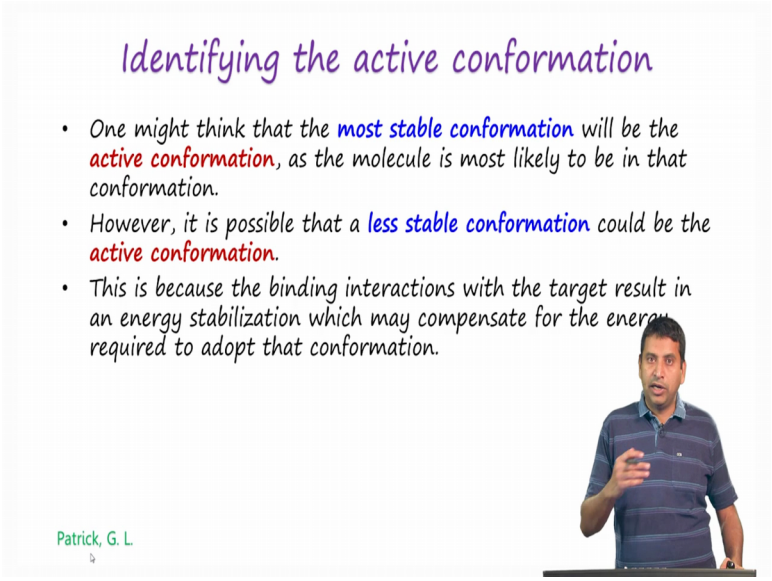

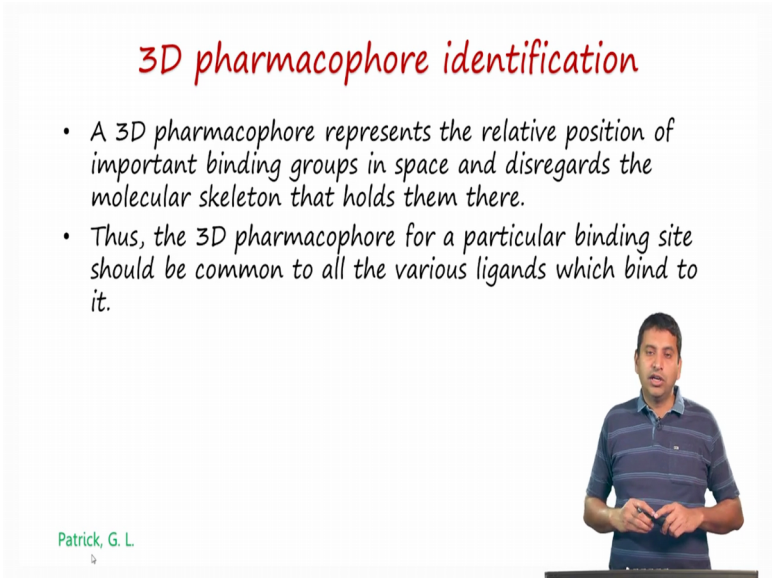

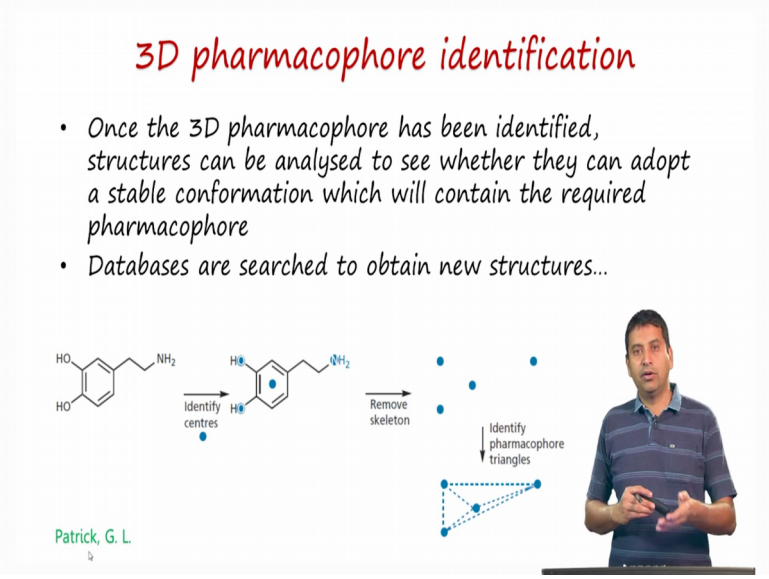

So, in one way to do this is to predict that the most able confirmation will be reactive conformation, okay. But although it is, one would think that it is likely, but it is not necessarily true. It is possible that a less stable conformation could be reactive conformation. This is because the binding interactions with the target can result in some sort of a stabilisation which will compensate for the energy required to adopt that confirmation. So, these are going to be little difficult for us to predict using our intuition.

So a 3-D pharmacophore is useful. A 3-D pharmacophore represents the relative position of the important binding groups in space and disregards the molecular skeleton that holds them there. So, we were already seen previously the, how to construct this pharmacophoric triangles and these are going to be useful here, right. So, this 3-D pharmacophore for a particular binding site should be common to all the various ligands which buy into it.

So for example here, we have already seen that for this molecule you have 3 major functional groups, that is you have the, you know the aromatic ring and you have 2 hydrogen bonding centres, acceptance and donors and then you have an amine. Right. So, now using this we can construct a pharmacophoric triangle. So, that is here is the formation points which are going to bind and using this we can actually construct these 3 triangles or 4 triangles over here. Okay. So, this becomes our pharmacophore.

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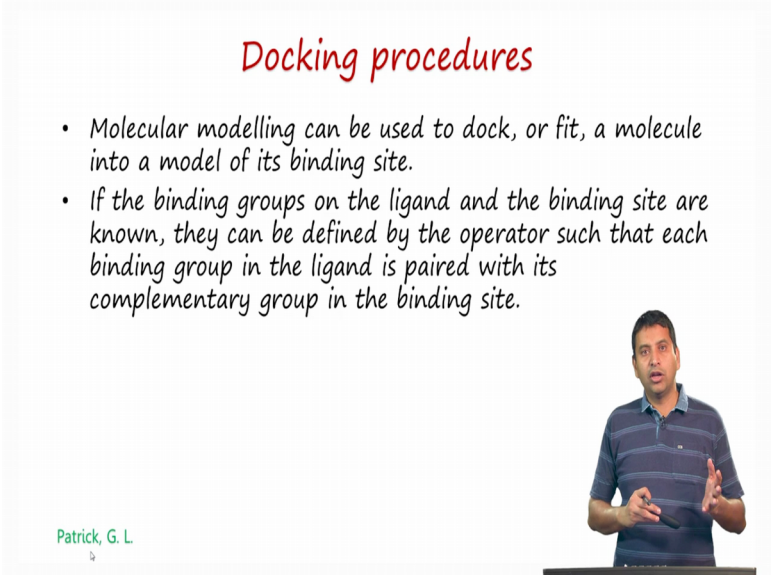

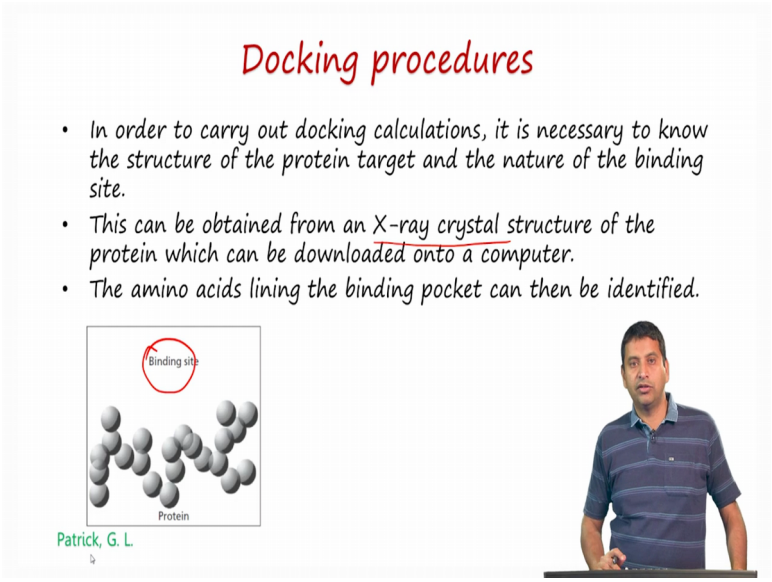

Then molecular modelling can be used to dock, which is also called fitting into a model of its binding site. So, you have binding site model and then you start looking at whether this liquid actually goes and binds to it. If the binding groups on the le get and the binding site are known, then they can be defined by the operator such that each binding group is the liquid is bad with its complementary group in the binding site. Okay. So, this is assuming that we already have maybe x-ray crystallographic data with the ligand and the binding site together.

So the next major aspect is using docking. So, docking is a way to actually find out whether ligand is going to bind to a protein and whether, whether the binding is favourable. Again this gives us a relative score. So, I nodded to calculate this docking calculations, it is needed or it is necessary to know the structure of the protein target and the nature of the binding site. So,

here again, x-ray crystallography becomes very useful because we can then, since the crystal structure of the protein is known, it can be downloaded on a computer and this can be used for identifying the various amino acids lulling the binding pocket.

So, here for example is the binding site that has been identified and here is the various amino acids in the protein. Now, what we can do is to then define the molecular surface of the binding site. So, if you can do this while looking, you go defining the surface of the various site chains that are involved in the protein. Okay. So, each binding site has a Van Der Waal's radius, so this Van Der Wal's radius can be used to define the results in an expensive surface area.

So, keep in mind that much of this surface area is actually inaccessible to the ligand. So, only certain areas of this are actually accessible to the ligand. So, using this method you can then arrive at the major, most favourable interactions that can occur and you can also assign a score for each religion. So, docking is very commonly used in identifying which inhibitor is better in terms of binding compared to another.

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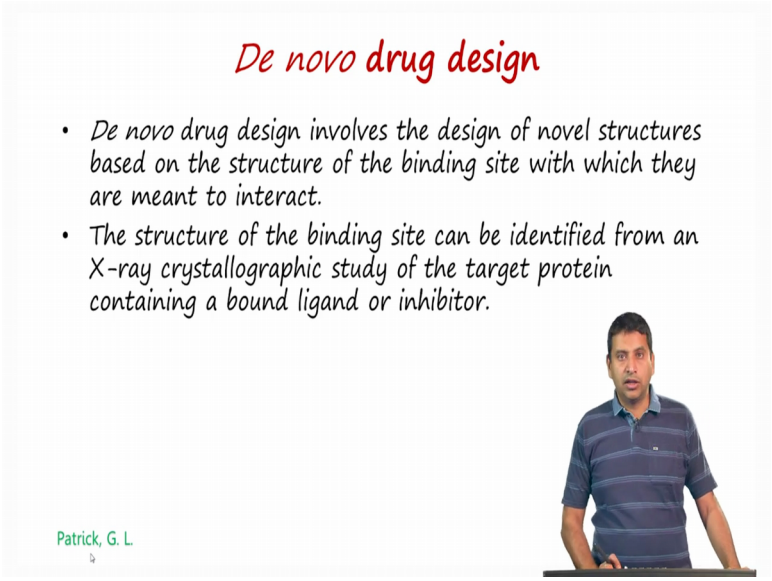

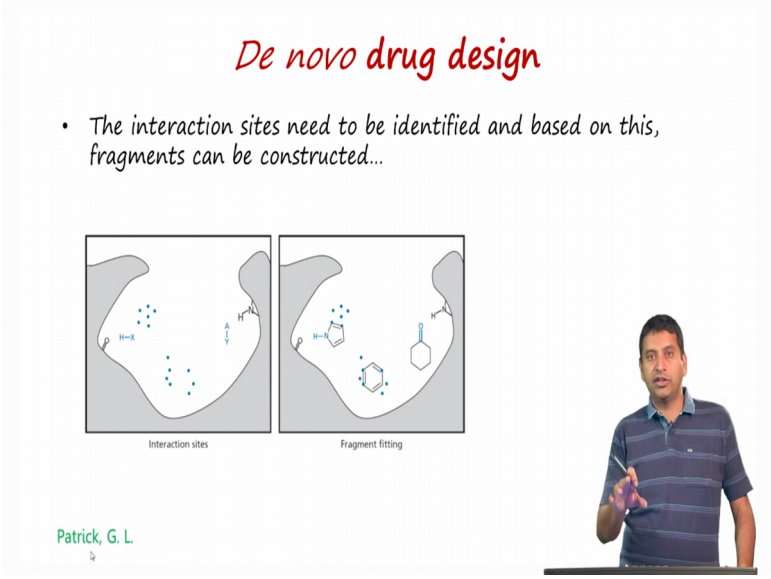

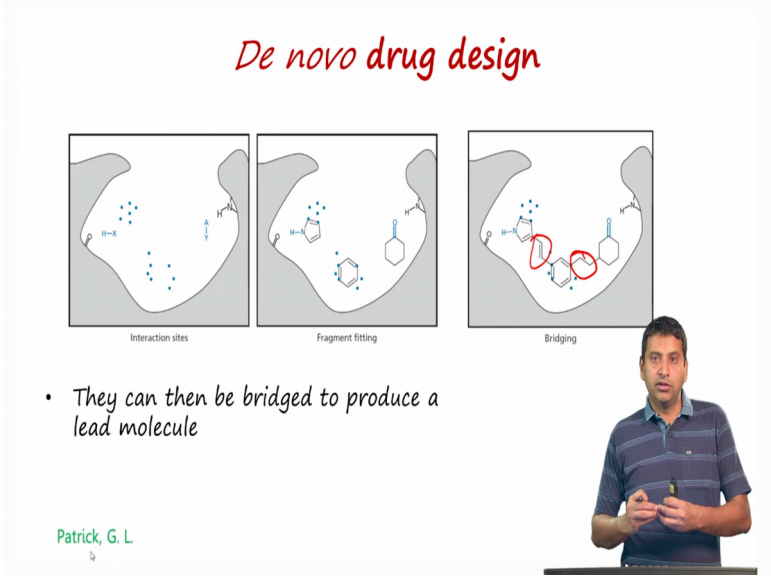

Another concept that can be used is de novo drug design. So, here as the name suggests, that de novo drug design involves a design of new structures based on the structure of the binding site, okay. So, here again we would need x-ray crystallographic structure of the target protein, preferably with the bound ligand or inhibitor. So, here, using this we can identify all the major interactions that are happening between the ligand and the active site. So, then the position of the ligand is that it defies where the binding site is in the protein and also identifies any induced fit that might have occurred as a result of its binding.

Now, using this structure of protein ligand complex, we can then download it on a computer and start looking at how to find out new drugs. The way we would do this is that after you download it on the computer, you delete the ligand and now it leaves only the empty binding site. Now, since we know the binding interactions, we can start constructing molecules which

can be new. So, here is an example. So, this is the example of an active site and here are the major interactions.

So, for example you have an NH here, you have a Carbonyl here and you have other interaction sites as defined here. Now, based on this you can start constructing fragments. So, for example you may want to put a group here, such as ketone which can bind to this NH. Similarly, you have a hydrophobic interaction here for which you can start putting a benzene ring, right. And here is a carbonyl, which can interact through hydrogen bonding and for that carbonyl you can put the Pyrrole ring, okay.

So, this is some of the fragments that we can start constructing. Now, what we can do is then once you start constructing these fragments, then you connect them. Okay, so now you need to connect them using appropriate sort of, you know, linkers. And here, after you connect these with linkers, this can become your target molecule for synthesis.