Computer Aided Drug Design
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Lecture – 38
Docking

Hello everyone, welcome to the course on a computer aided drug design, we will continue on the topic of docking. In the previous class, I talked about how to use auto dock of course and there is another software called Swiss dock also. So, I do not have time to show that but you can use that software as well okay.

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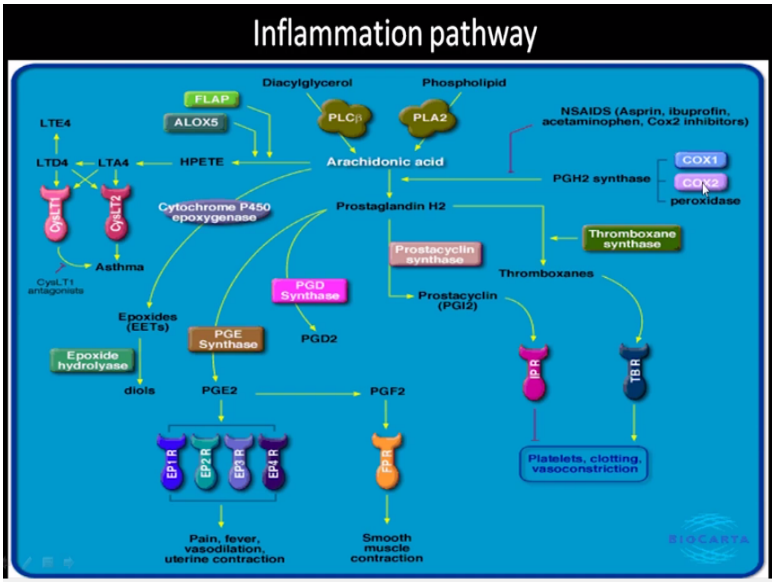

Okay, so let us go to this inflammatory pathway, so we have the Arachidonic acid produced us or which gets converted to prostaglandin H2 by the Cox 1 and Cox 2 enzymes okay and Arachidonic acid also getting converted to the leukotrienes by the lipoxygenase enzymes.

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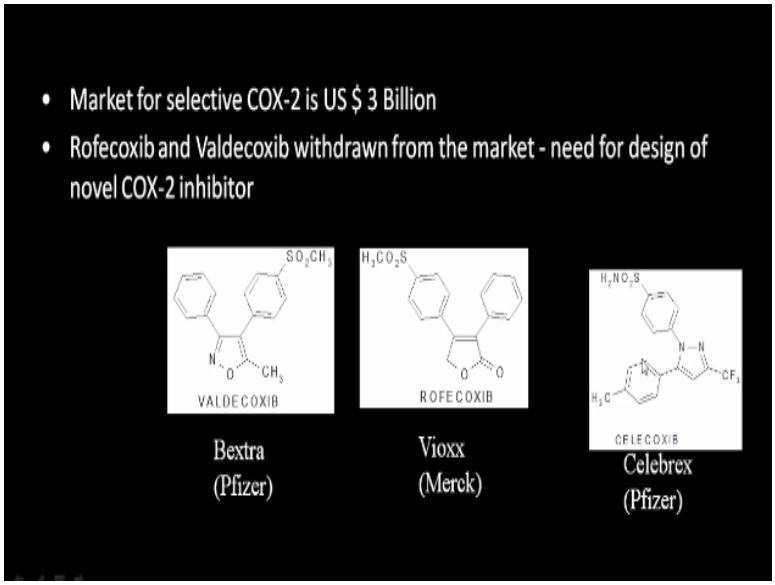

So, there are drugs which are very specific towards the Cox 2, okay which are in the market like a Valdicoxib, Rofecoxib, Celecoxib, so we can download the structure of Cox 2 okay.

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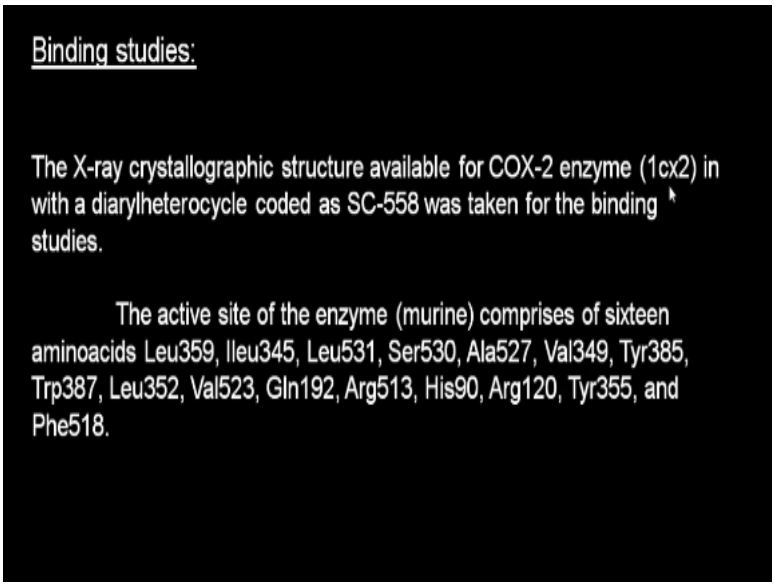

This is the structure of Cox 2 enzyme; it is called 1cx2.

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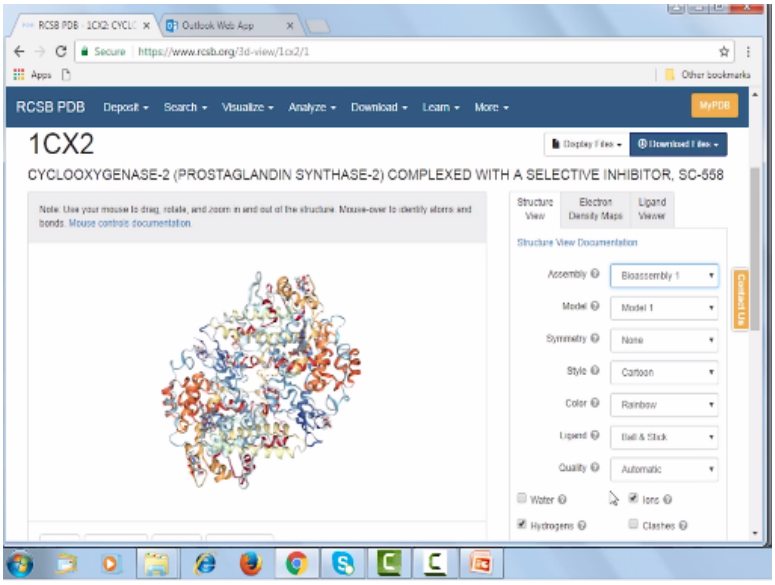

So, if you look at your pdb, 1cx2; you can see cyclooxygenase 2, which is also called PG synthase 2, okay, this is v1, it is there, you can see this and you see the (()) (01:38) as well, then okay so this 1, okay, the enzyme cycle of cx2 and there is elegant and okay, so selective inhibitor; SC 558; SC 558 is a selective inhibitor of these cycle, cx 2, okay. Now, then we can use a software like Auto dock or remove the active site of this particular enzyme, where these are the amino acids present in the active site.

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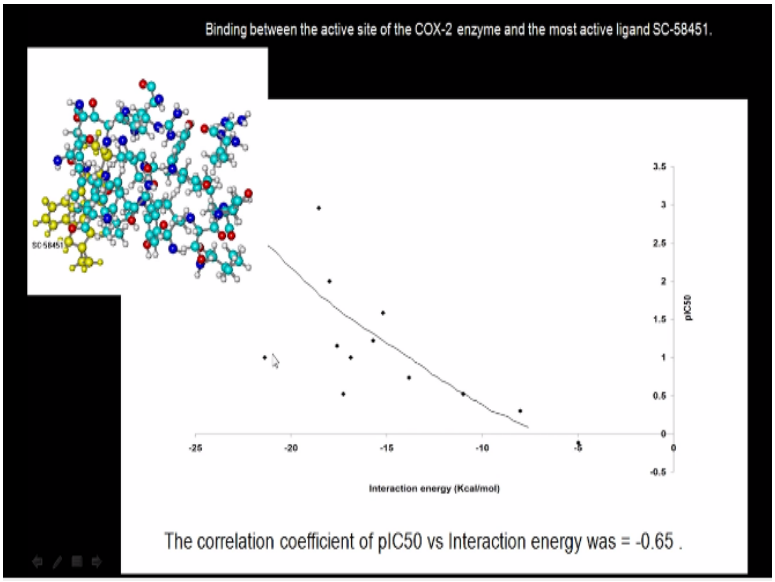

So, when we do binding of each one of these molecules okay, there are about almost 12 molecules which we have selected, which are known to have selective and some of them are not so selective but we know the activity of them, there is IC 50, so we get the binding energy or interaction energies using Auto dock for these; 12 all these molecules and here we plot their activity okay, as you can see here.

And we see there is a very good negative correlation, so as the binding energy increases the activity also increases okay, so this is quite good correlation coefficient. So, what is the use of this? Suppose, we have another molecule which we think we can design on which may be better active, we can bind it to this cox 2 enzyme and we can see where the binding energy or interaction energy that comes.

And then we can sort of predict its IC 50, whether if it comes here, here and so an actually, okay, so this can be used as IC predictive 2, okay.

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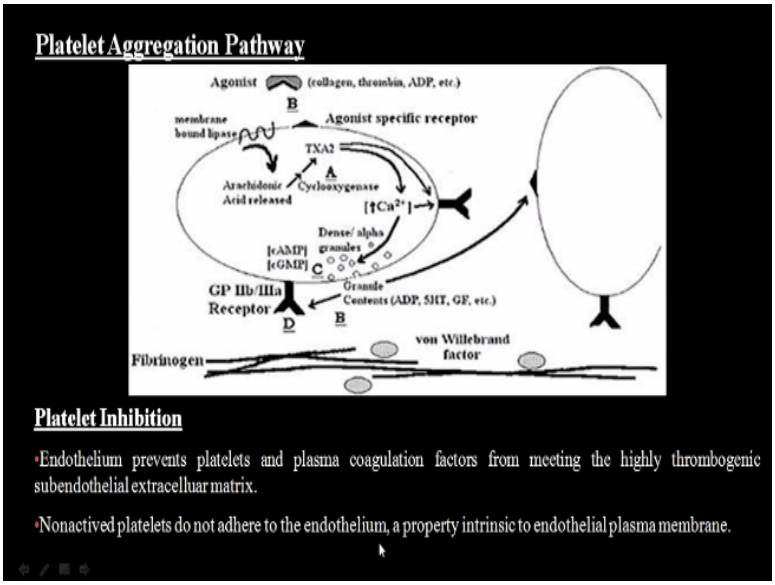

Now, let us look at another example you know, the platelet aggregation; platelet aggregation is a very serious issue which leads to thrombosis okay. Platelet inhibition; endothelium prevents platelet and plasma coagulation factors from meeting the highly thrombogenic sub endothelial extracellular matrix okay. So, non-activated platelets do not adhere to the endothelium okay, so activated platelets adhere, okay that is the big problem.

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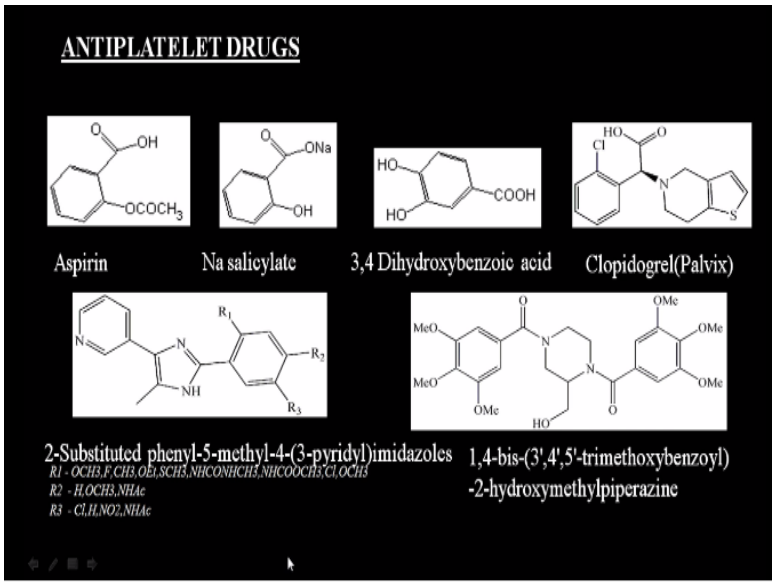

There are many drugs which are given for antiplatelet aggregation, nowadays aspirin it seemed to be you know; pseudo salicylate, dihydroxybenzoic acid, Clopidogrel, okay and so on actually a lot of substituted phenyl systems and all are there, so antiplatelet activity of many of these drugs have been reported in the picture.

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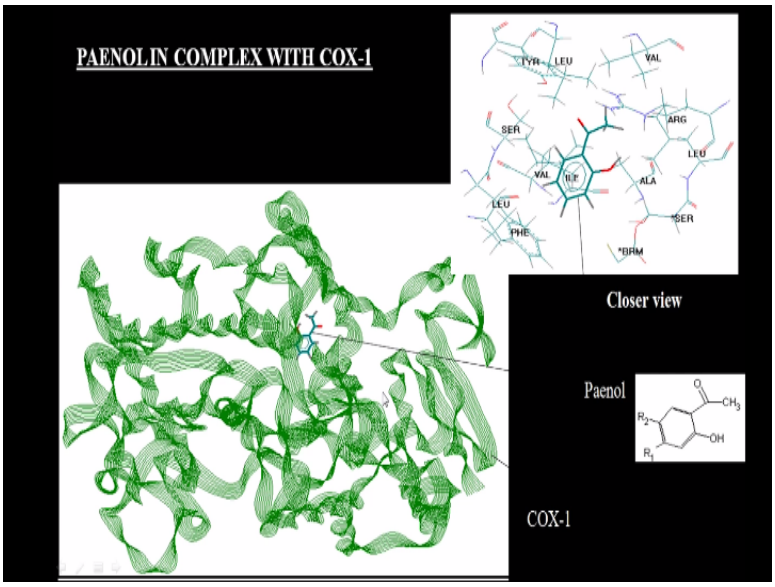

And we also have looked at some compounds like this, they are called Paenol, okay then look at it, it is almost like aspirin; R1 and R2, we can put a lot of substitutions here, so we can get a huge number of derivatives, we can look at antiplatelet activity of these and Cox 1 is an enzyme which is known to be involved in the platelet aggregation, as you can look at the pathway here, where here comes the cyclooxygenase okay.

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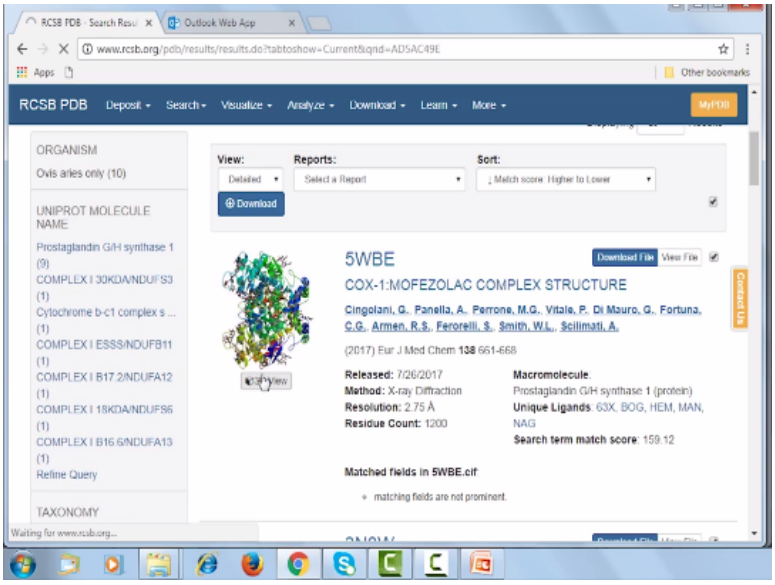

So, Cox 1; we need to inhibit, so I mean, if you look at the pdb, very nice 3d structure available of Cox of Cox 1, so we can take that and then we can as you can see, there are many coxines there; this is Cox 1, it is complex with Mofezolac, this is Cox 1, okay you can be profound, there are many Cox ones are there, in the picture okay, we can download based on unoccupied, so based on our requirement, okay, just to our requirement, we can download.

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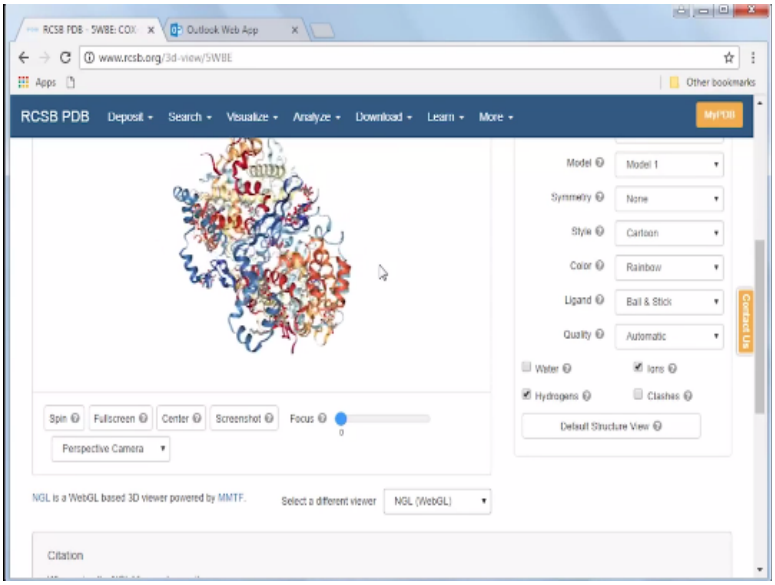

This is the structure from the PDB, now of course, we can use the Auto dock and we have large number of molecules, which we have synthesized, if they all derivatives okay, so we can find bind of them or drop all of them as you can see your docking to the cox 1, okay docking to the cox 1 here, this is the cyclooxygenase 1, large number of molecules docking to that.

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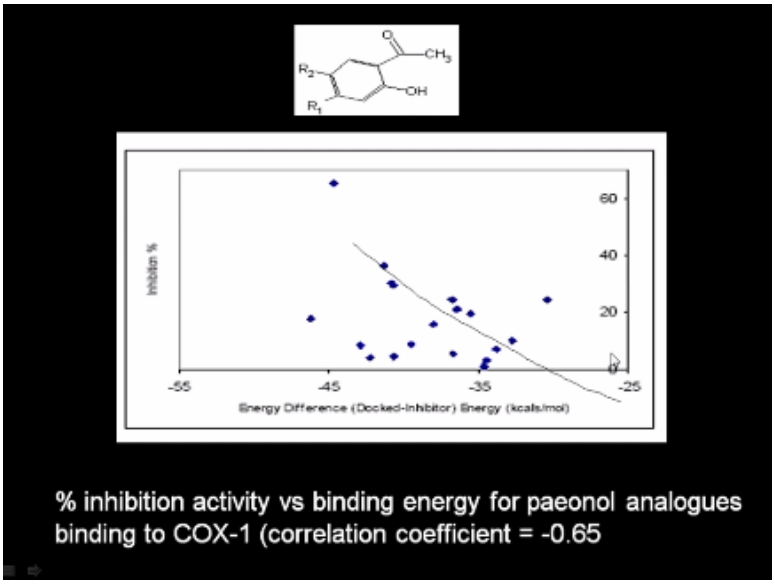

% inhibition activity vs binding energy for paeonol analogues binding to COX-1 (correlation coefficient = -0.65

So, we can get a relationship between the binding energy or interaction energy as we call it or energy difference being docked and undocked and then this is your percentage inhibition of platelet aggregation again, you see a nice negative correlation okay as the binding or interaction increases, the activity or a percentage inhibition also increases. So, we can use this type of target based design also for designing new molecule.

So, new molecule if I come up with the new structure, I can dock it to the same enzyme and then based on the docking energy or binding energy or interaction energy, I can predict what will be its activity okay.

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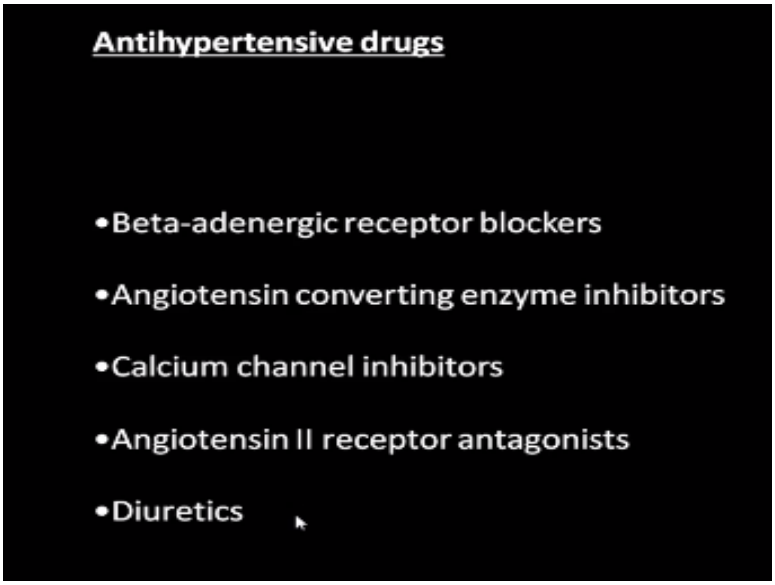

Okay, let us look at another example, antihypertensive drugs; these drugs are used widely for reducing your hyper blood pressure, okay. There are certain beta adrenergic receptors okay,

there are some angiotensin 2 receptors okay, angiotensin converting enzyme inhibitors of course, diuretics. Generally, these are very, very popular of course, doctors also prescribe diuretics as well.

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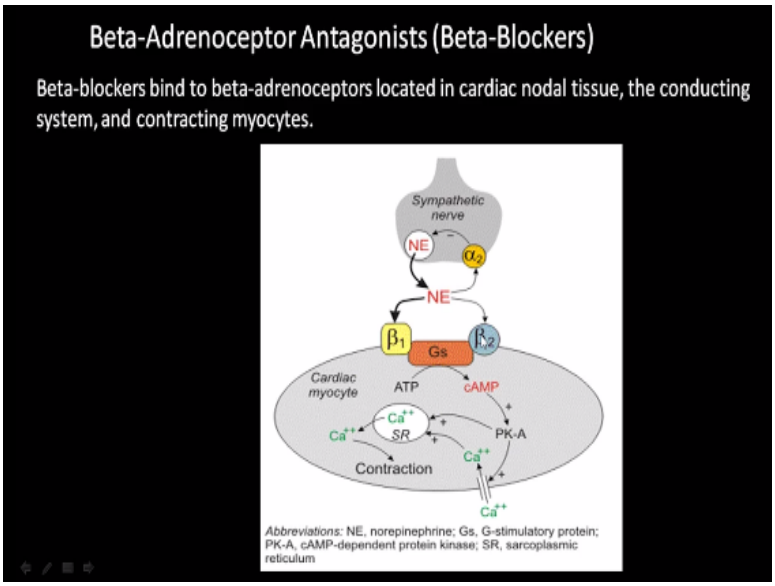

So, look at this beta adrenoceptors antagonists okay, there are 2; beta 1 and beta 2 okay, so there are non-selective drugs, they are called beta blockers which may bind up the both; beta 1 and beta 2.

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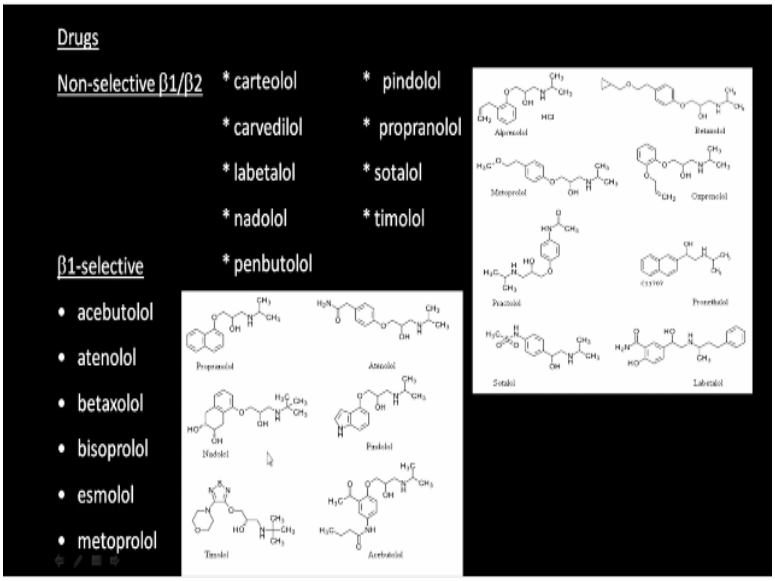

Or they are selective ones that is non selective; carteolol, pindolol, carvedilol, propranolol, and there are beta 1 selective also; acebutolol, atenolol, betaxolol and so on actually okay. There are non-selective beta 1 and beta 2 or there is selective beta 1 okay so, as you can see in synaptic

sympathetic nerve comes in here okay and then which goes here and then we have the cardiac myocytes.

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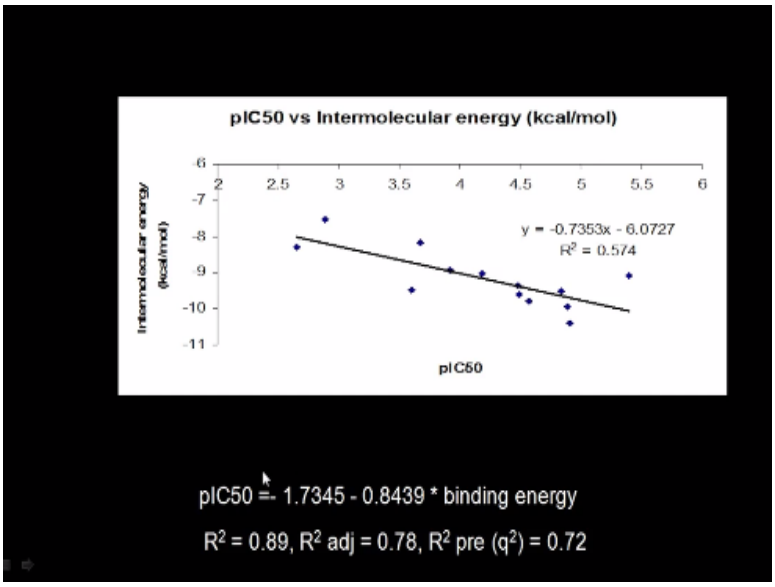

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So, it basically blocks the beta 1 or it blocks both beta 1 and beta 2, okay so again, there are structures available which; beta blocker as you can see here, so there are many beta blockers; lot of beta blockers as you can see almost 25 of them are there. Beta blocker; we have the drug propranolol bound to that okay, so a lot of drugs are there; lot of drugs.

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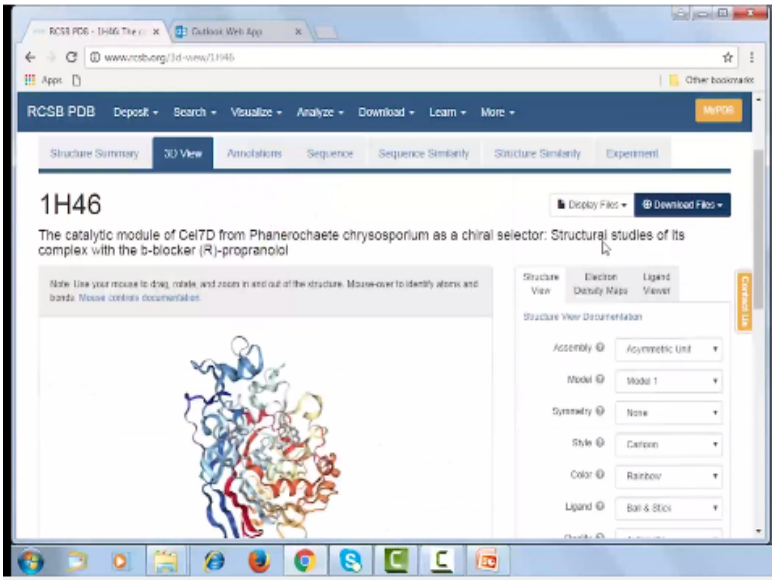

Very nice 3d structure available of Cox, drug called propranolol bound to the beta blocker, okay and so once we drop all these drugs to the active side of; and then we plot the IC50, PIC 50, which got from literature and then this we call it the intermolecular energy or binding energy or interaction energy, again you see a nice and the correlation more negative okay that means, the activity is negative, less the activating, so very nice okay.

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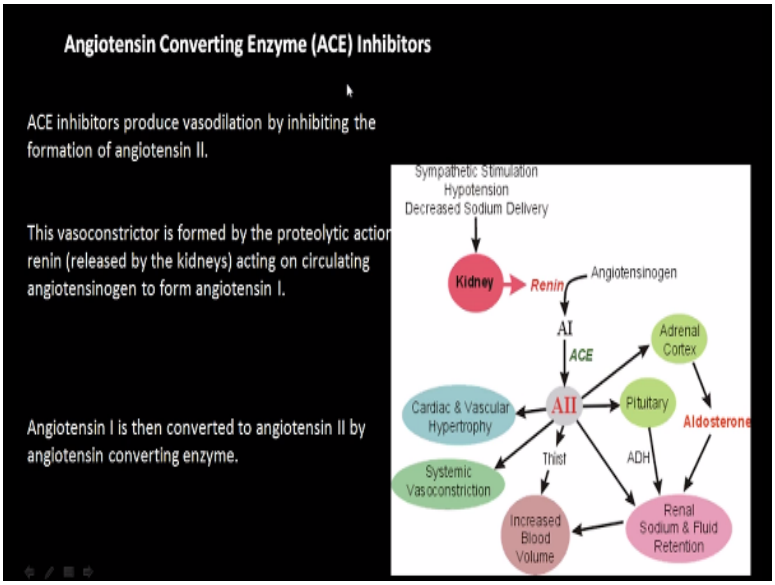

Then, again involved in the hypertension, there is another enzyme called angiotensin converting enzyme okay. So, these ACE inhibitors produce vasodilation means, so what happens is; we have ACE enzyme which converts A1 to A2, okay which leads to Vasoconstriction, increased blood volume all these things okay, so A1 one is called angiotensin 1 which leads to angiotensin 2 by this enzyme ACE; angiotensin converting enzyme.

So, there are drugs which block this particular enzyme ACE and so A1 one does not get converted to A2, okay, so the vasoconstriction does not happen, so this is how these drugs work.

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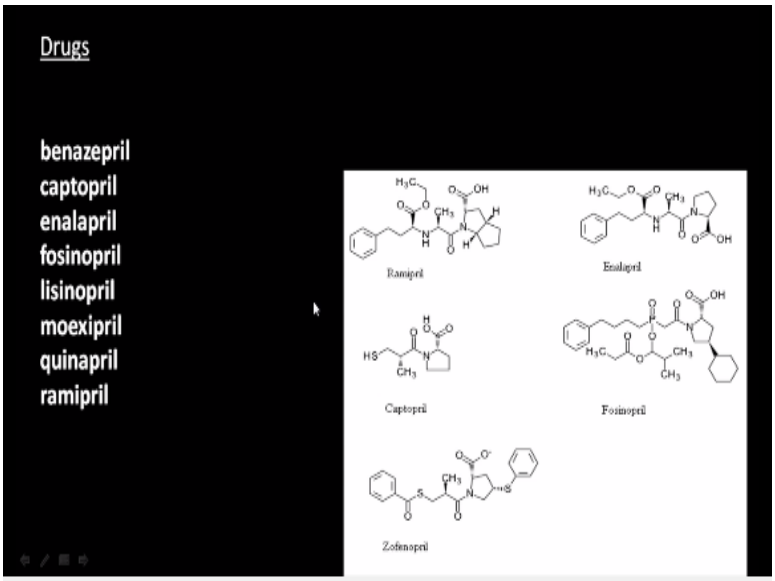

ACE is called the ACE inhibitors, there is a lot of drugs; benazepril, captopril, enalapril, fosinopril, lisinipril, ramipril and so on, so all these drugs work towards blocking this particular enzyme called ACE okay, angiotensin converting enzyme okay.

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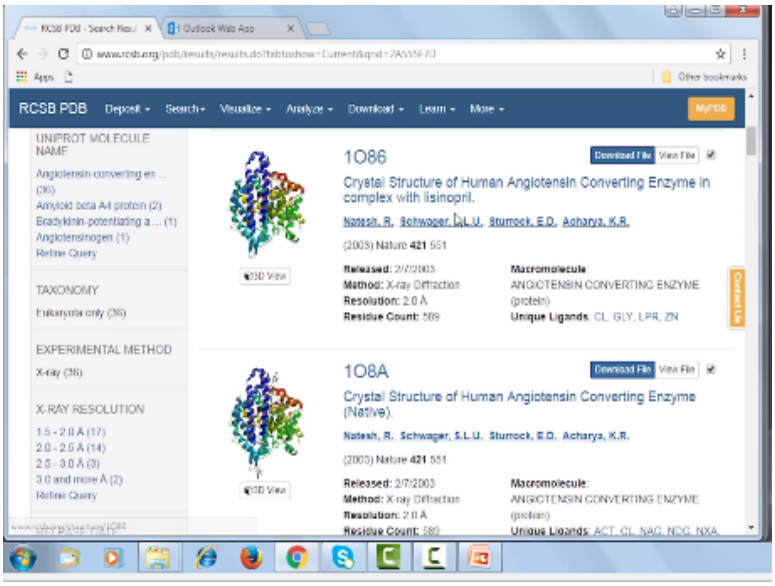

Again, there are many ACE, just type ACE, so as you can see there are many, many structure of ACE here, (()) (11:45) ACE here, so you can be more selective towards what you want to have okay, as you can see; angiotensin converting enzyme in complex with lisinopril, this is the drug which is binding to this particular enzyme okay.

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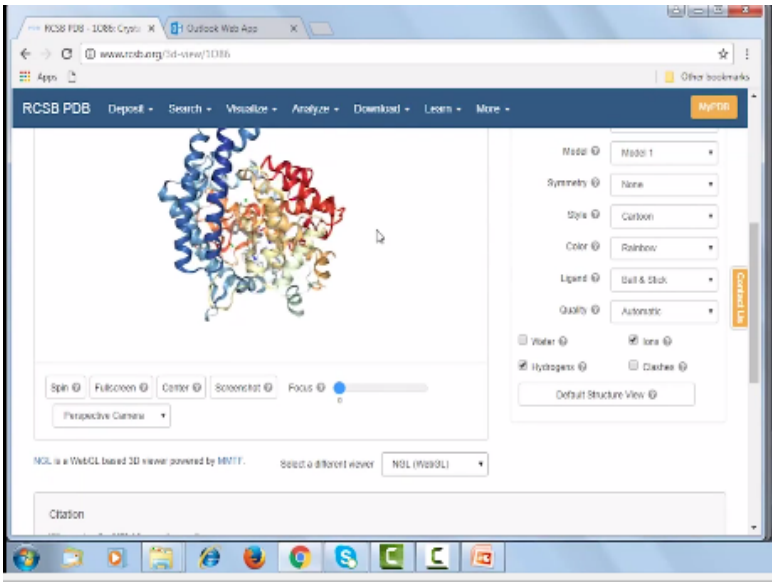

So, we can see the lisinopril, may be here, you can see the drug here, okay so ACE inhibitors and there is literature data on the activity of these jobs towards the ACE percentage inhibition.

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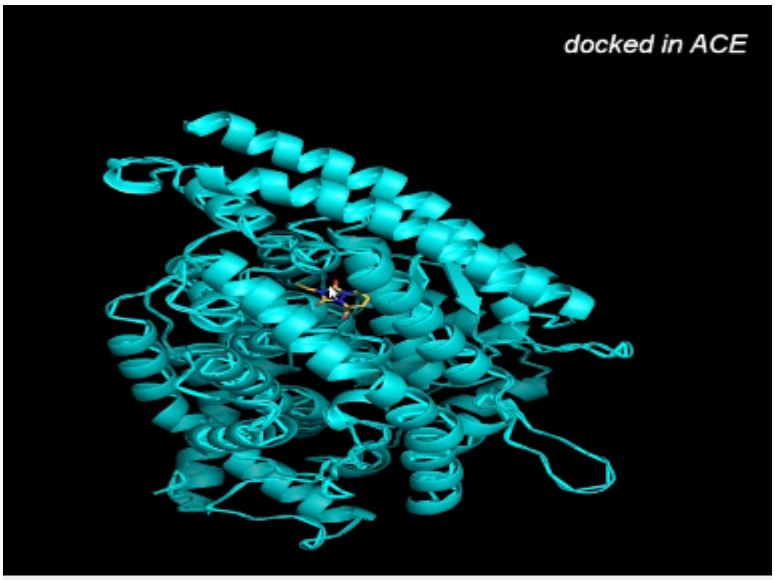

Also, you can see this docked in ACE; okay the drug docked in ACE, okay.

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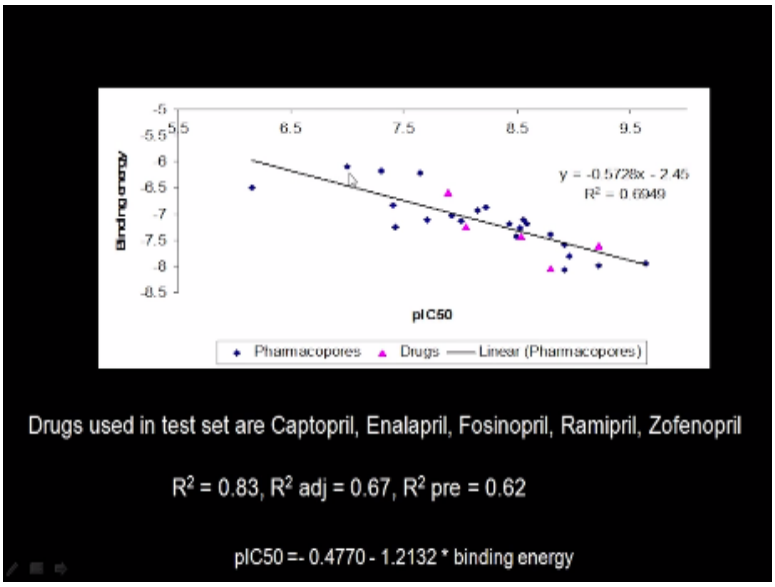

So, as you can see here, this is the binding energy, more the binding higher is the activity, this is the activity on this axis, so a lot of ligands and these triangles are the drug, drugs here, okay and so you get a nice reasonably good straight line with R square of 0.7 which is not bad, so as the binding energy increases the activity also increases. So, if you are trying to design a new molecule for ACE inhibition to prevent the angiotensin 1 getting converted to angiotensin 2.

All you have to do is; a design and start docking each one of them and see where the binding energy comes and from there you will be able to predict what would be its activity and all this data is obtained from literature. So, from the literature data you get this graph and then when you start designing new molecules, we can use this graph for predicting the activity of new compounds, so that is the beauty of target based drug design.

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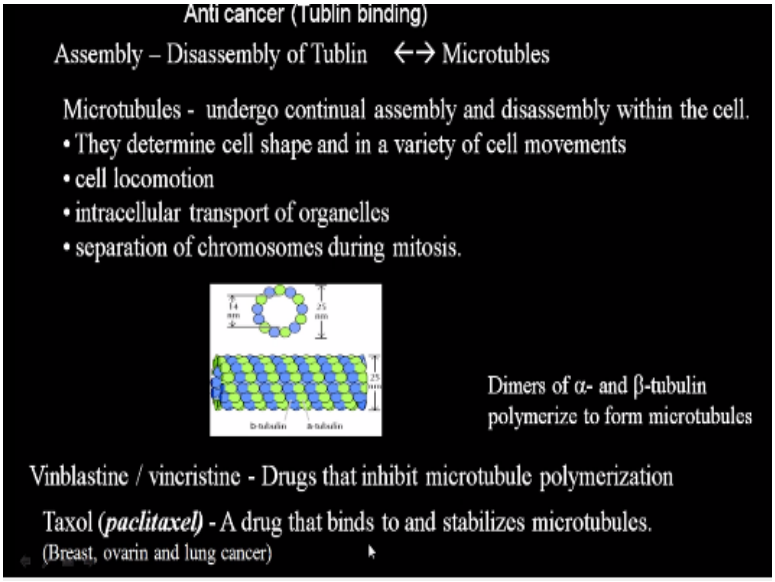

So, another example we will look at this is my tublin; tublin assembles and disassembles to form a microtubule; okay, microtubules undergo continual assembly and disassembly within the cell, they determine the cell shape in a variety of cell moments okay, cell locomotion, intracellular transport organelles, separation of chromosomes during mitosis, okay, so there are drugs which prevent the assembly, there are drugs which prevent the disassembly okay.

Vinblastine, vincristine; these are drugs that inhibit microtubule polymerization okay, so it does not allow the assembly, whereas Taxol; paclitaxel, that drug binds to and stabilizes the microtubule okay, so it prevents disassembly. So, taxol is used in breast cancer, ovarian cancer, lung cancer okay, so you assemble, disassemble, perform these microtubules, so there are drugs which prevent the assembly, there are drugs which prevent disassembly also okay.

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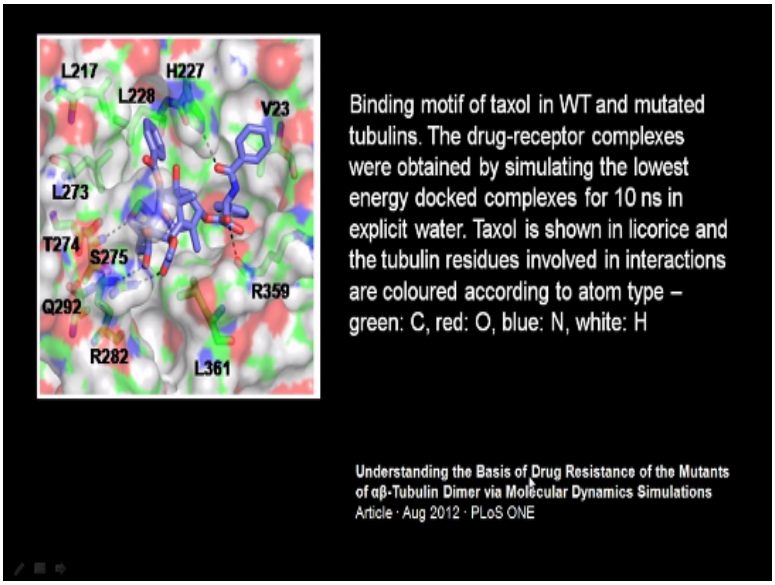

Okay, so as you can see taxol binding to certain tubulin is taken from this particular reference okay.

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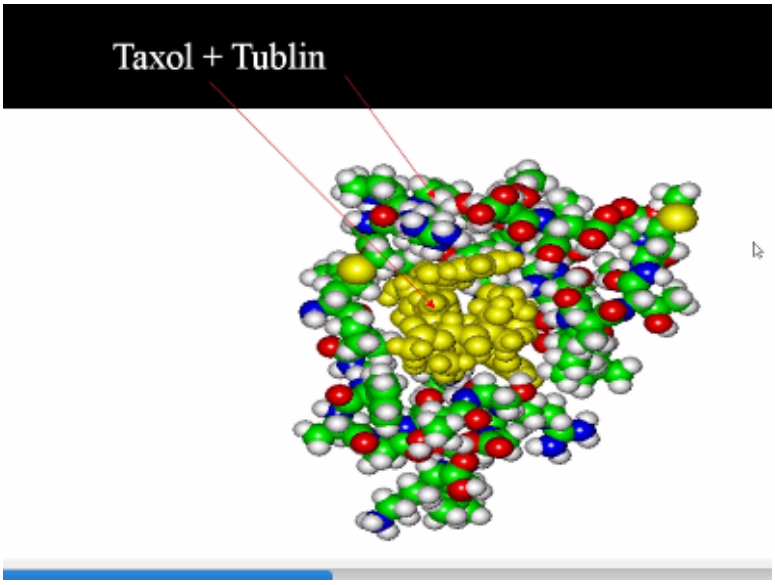

So, this is; we have the active site shown in this picture, taxol binding in the active site okay, the red ones are oxygen, blue ones are nitrogen, green are carbon and whites are hydrogen okay.

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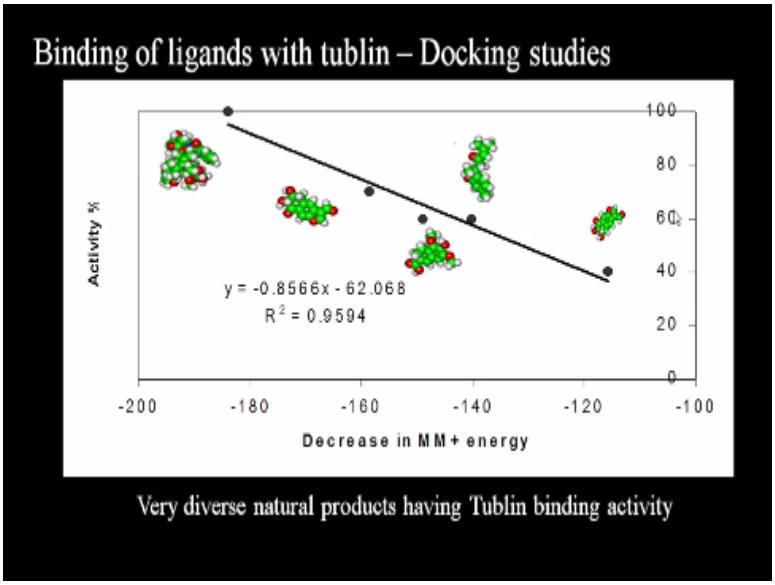

So, we have several molecules binding to the particular protein and again you can see, you call it decreasing energy or increasing the binding in a negative more binding activity, so that activity keeps increasing and then as it becomes more better binding, more interaction, more decreasing of the binding or the activity value also keeps increasing. So, I am shown you lot of examples of target based drug design, where we can, okay do the binding of various ligands, once you have the protein of our interest.

Protein of our interest can be obtained from your PDB data Bank, okay and then we can perform the docking and I showed you in the previous class how to do the docking, of course there is an auto dock is a very good software.

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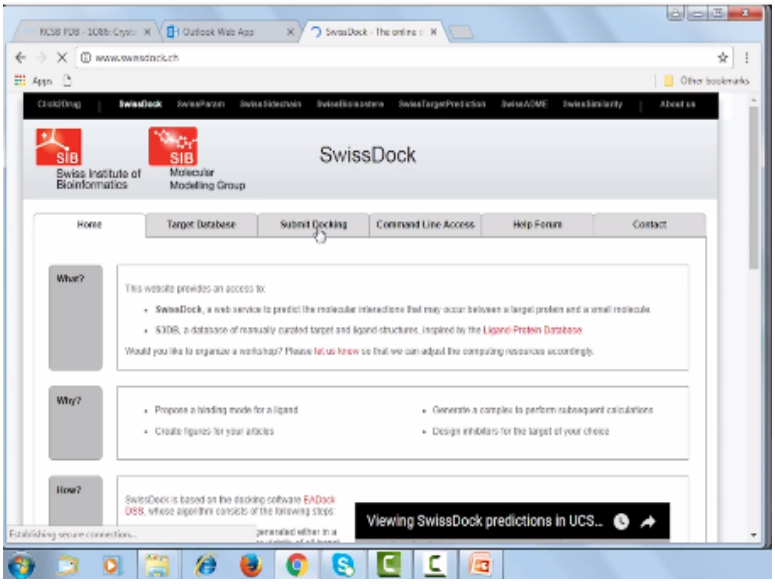

And also this Swiss dock is also there, which can also do a good job. It is done through a web server and all the software belong with this yeah, so we can do a docking here also, so you can submit the docking, I do not want to spend too much time.

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So, here we give the target, so we can give 3, 9, yeah, so we have this particular protein and then here, in that place we can put the ligand and then we can submit for docking, you set up and then here we can put out ligand okay; ligand name okay, so we can load the ligand and so we can load the ligand and so we have loaded both aspirin mol 2 file, 3v99 is a file lox file.

And then we can give the job name, aspirin dash file lox and then we can give my email id here and then the results will come to you, okay, the results will come to you, okay you can start docking, results will come to you okay.

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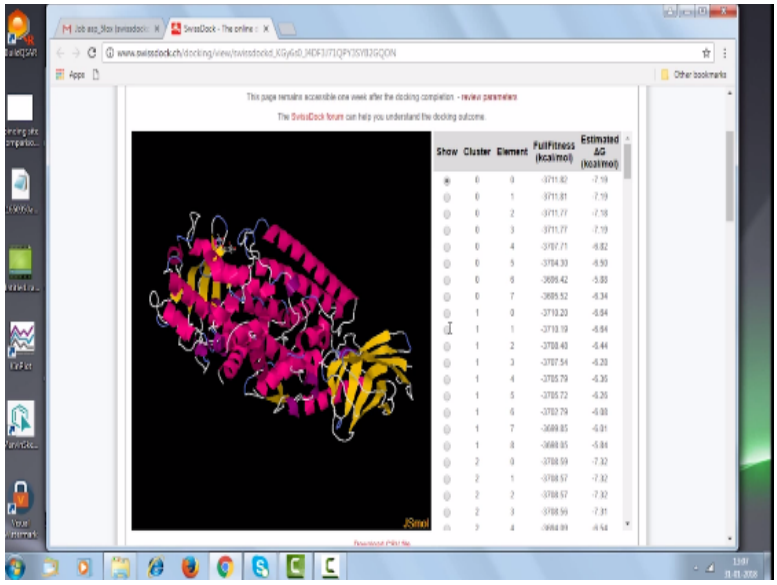

The results from Swiss dock comes to your email okay like this okay, if you click on the results as you can see here, you can see the binding energies between aspirin and file lox in fact, that is what we gave, the 3v99 and aspirin, we gave an aspirin in mol 2 format as a PDB, so we can see this and here you can see that estimated delta G, this gives the highest negative binding energy, this is all the cluster 0, okay.

And then the cluster 1, cluster 2 and so on actually, so you can see here, we can click on different clusters okay, so we can see the aspirin here, as you can; can you see the aspirin here? Aspirin is seen here, okay the aspirin is 0, somewhere here, are you able to see the aspirin? Yeah, you can see the aspirin here and this is the file lox enzyme okay, this is the output from the Swiss dock.

So, it gives you large number of results and different clusters also it gives you, so you can see how the aspirin binds okay, you can look at different clusters and okay, so aspirin has come down there, so in different locations; starting locations and then it binds okay, you can see the aspirin here okay.

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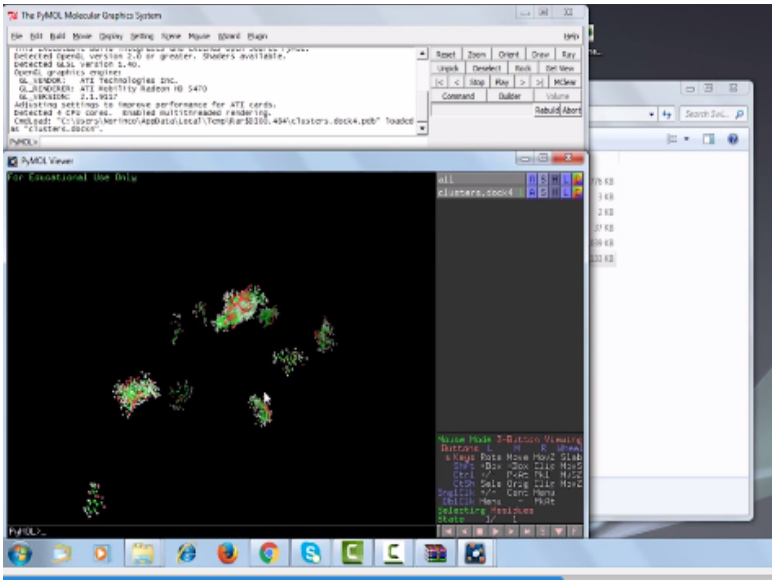

So, we can download some; we can download some of these prediction files, we can look at them in more detail, which I have downloaded okay, so we can look at the; okay, so this how the aspirin; various clusters.

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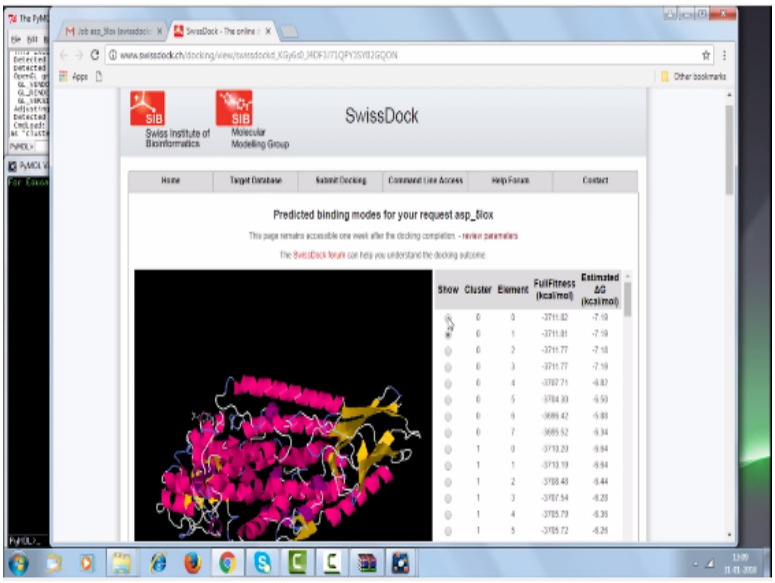

So, generally this clusters seems to be the highest that must be cluster 0 and cluster 1, okay, so predominantly aspirin seems to be binding in these places more than any other places okay, so this is the aspirin as you can see here, okay. So, the other cluster is a cluster 1 okay, where aspirin is bound more, yeah here, here so, cluster 0 and cluster 1 is seen here, so predominantly cluster 1; cluster 0 and cluster 1, we can view them okay.

So, Swiss dock is another interesting program, which can be used for docking ligands to protein and it gives you the estimated delta G in kilocalories per mole okay.

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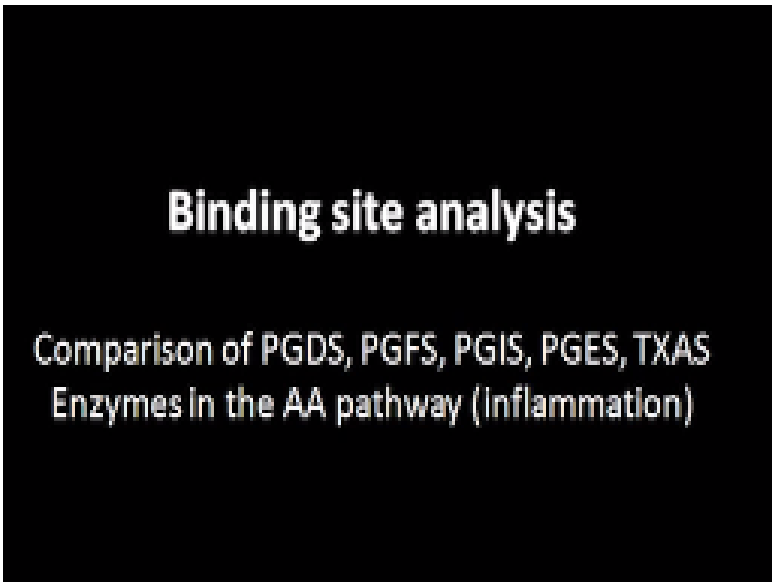

There are other software's which are also; which looks at the binding site analysis, there are suppose you have many proteins and you are interested to know what is the relationship between those routine active sites, there are some software's okay.

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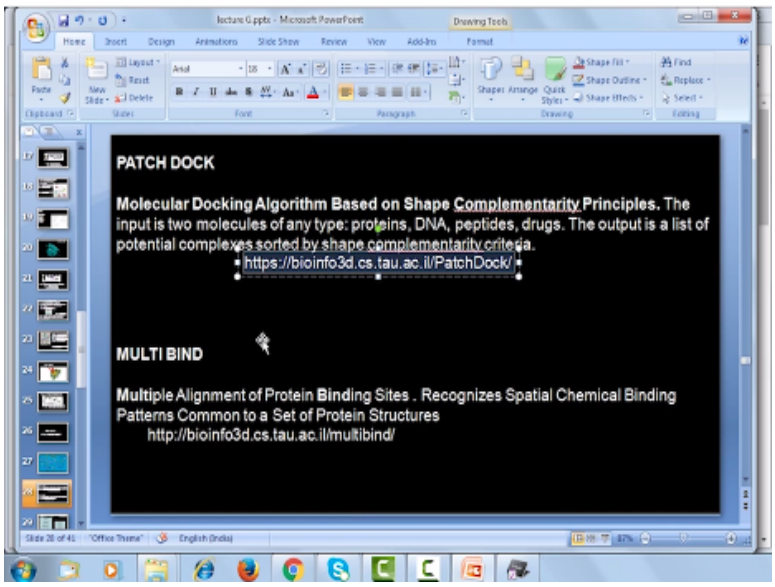

And there is a software called a patch dock, and there is another software called multi bind. Patch dock is molecular docking, it could have been based on shape, complementarity principles, so I can put a protein and then I can put a ligand and if you try to find what is the shape complementarity. So, I can take the same ligand as a probe and then I can look at different proteins that is called a patch dock okay.

Another software called multi bind, so it aligns multiple alignments of protein binding size; sites and then recognize a spatial relationship or common binding patterns of set of proteins, okay, so that is called multi bind, okay.

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Multi bind looks at different proteins, or we can have included as zip file, so it compares different proteins, okay and if you find out common chemical patterns okay.

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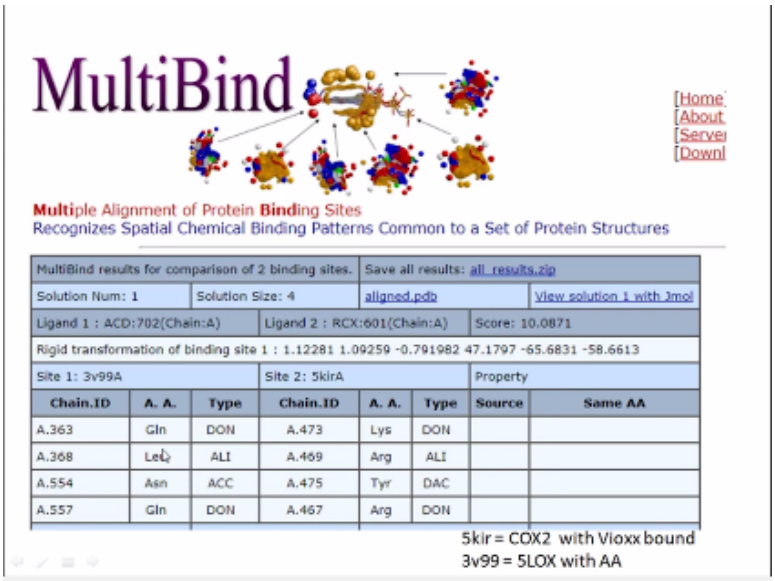

The results of multi bind again comes to your email ID as seen here, we can click on that and basically multi bind looks at; basically, compares different proteins okay, it compares different proteins and see what are the common features okay, in their active sites, this is very useful if you are looking at families of protein and basically, in the example, we looked at the 3v99; looked at 3v99 and we looked at 5k IR.

3v99 is; yeah 3v99 is a 5 hypooxygenase protein with the arachidonic acid bound to it and 5 KR is cyclooxygenase 2, enzyme with Vioxx bound to it, cyclooxygenase 2 is involved in prostaglandins and file lox hypooxygenase is involved in leukotrienes okay, so get result like this okay, so the 2 proteins; 3v99 okay, which is the 5 lipoxygenase protein and the other one is 5 KR which is a cycloxygenase protein, it has Vioxx bound to it and 3v99 has a arachidonic.

So, these 2 protein active sites are being compared and hydrogen bond donors, aliphatic, acceptors is there, donor is there okay and you get a score of about; it gives you score as well, score of 10.0, which is low okay, higher the score that means higher this there, comparison, whereas lower the score lower is the value okay. So, this software is useful if you are looking at comparing different active sites of protein is useful.

Yeah this is useful if you are going to have a comparison of different proteins and see whether the same drug may be acting on these active sites of these 2 proteins okay because they may have similarities in their active sites structural features.

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Table 3: Pairwise Alignments of PGH2 Binding Sites using MultiBind

Compared Proteins	No. of detected features	Score
PGFS-PGIS	18	41.2
PGDS-PGFS	13	38.0
PGES-PGIS	15	35.2
PGES-PGFS	12	33.7
PGES-PGDS	10	30.7
PGDS-PGIS	12	28.9

For example, there are some proteins in the arachidonic acid pathway, prostaglandin, called PGFS, PGIS, PGDS, just like PGES, so you can compare between, then it seems there are some common features, PGFS verses PGIS, PGDS verses PGFS, PGES verses PGIS, PGES verses PGFS, so it can give some sort of a score and say these are the common features between protein, okay.

Yeah so these are the PGES, PGDS, PGIS, okay so what is the common feature between these 4, so we can use the software called multi bind and then the software may give results like this, okay commonality between these proteins, so pairwise comparison, then say there is a score, so these proteins; PGFS and PGIS have a common score, what is that PGIS and PGFS? Like I mentioned here, they all come in the arachidonic acid pathway okay.

Okay, so we have this is PGIS, PGDS, okay PGIS, PGES, PGDS and so on, okay, so these are; what are the commonality between all these proteins that is what this particular software will be able to tell; multi bind. If you look at the other one, the patch dock, what it does is say; it takes a molecule like a ligand and then it takes it as a probe and see what is the shape similarity between that ligand and particular molecule of interest; I am sorry, protein.

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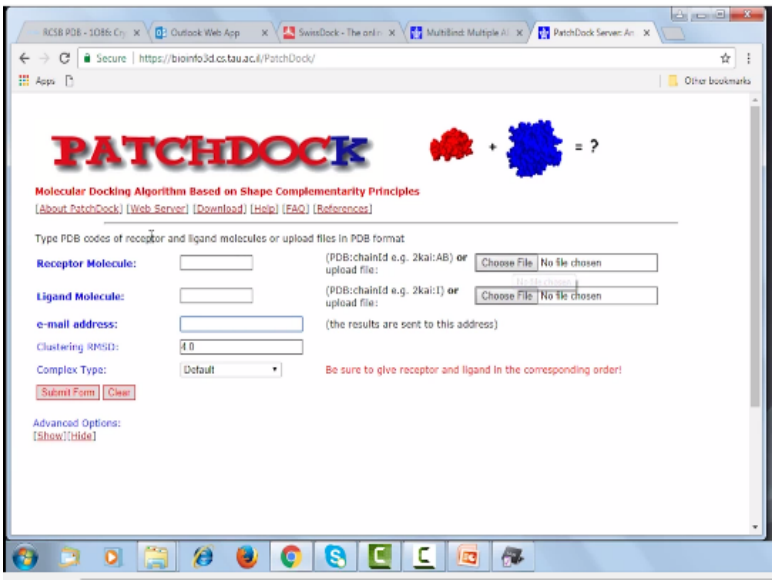

So, it tells you shape complementarity criteria, it is based on a; it is called the patch dock, so this software is also very, very useful so it does not do a docking, so it gives you a receptor protein molecule, it gives you a ligand molecule, it gives the email address and then it does the job; 3v99, sorry, we can give like this; so we can give a choose 5 here this, so we can give like this, so we can again give a choose 5 here for your ligand.

And then we give the email address okay and then it does the job here, so it gives basically looks at the shape complementarity between the ligand and the protein okay, so the receptor molecule we can choose from our file, 3v99, we have been looking at it for a long time, okay PDB, 3v99, so we can give a PDB chain ID in (()) (31:39), so you can say 3v99, been here the ligand molecule, we can give aspirin as you all know okay.

Aspirin mol 25 is accepted here I think it is mol 2, then I give my email id and then default, okay that is how it is done. So, the results of patch dock, which is a software that compares the structural features of the ligand and the protein that means basically whether it is got concave regions and convex regions, whether they have a complementary regions and predict whether the ligand will go and bind to that protein that is given by patch dock.

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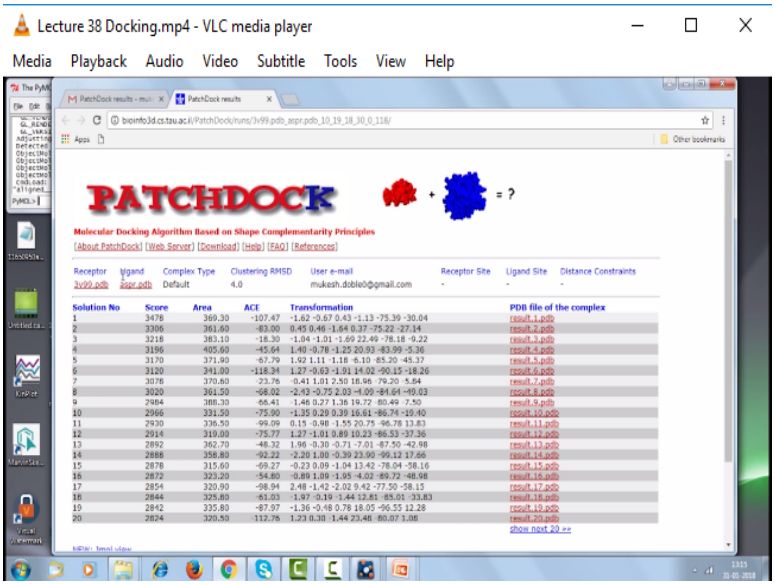

And the results again come to your email and as you can see here we were looking at the aspirin and we were looking at 5 lipoxygenase protein; 3v99, so it tries to see and try to give a score okay, big score, small score and so on actually, so patch dock that is sort of comparison of a ligand like aspirin in this particular case and protein 3v99 that is a 5 lipoxygenase.

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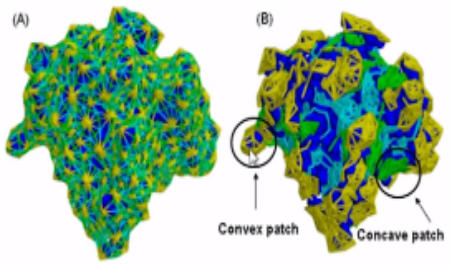
PatchDock is an algorithm for molecular docking. The input is two molecules of any type: proteins, DNA, peptides, drugs. The output is a list of potential complexes sorted by shape complementarity criteria.



So, patch dock can be used for molecular talking, so it sees whether there is a convex patch, concave patch and whether there is a complementing convex and concave patch in the ligand, so we can say possibly they could be interacting at a place, so it could be protein ligand, it could be 2 proteins, it could be drug protein, DNA, so many things we can do that actually. So, it is just based on shape, complementarity criteria.

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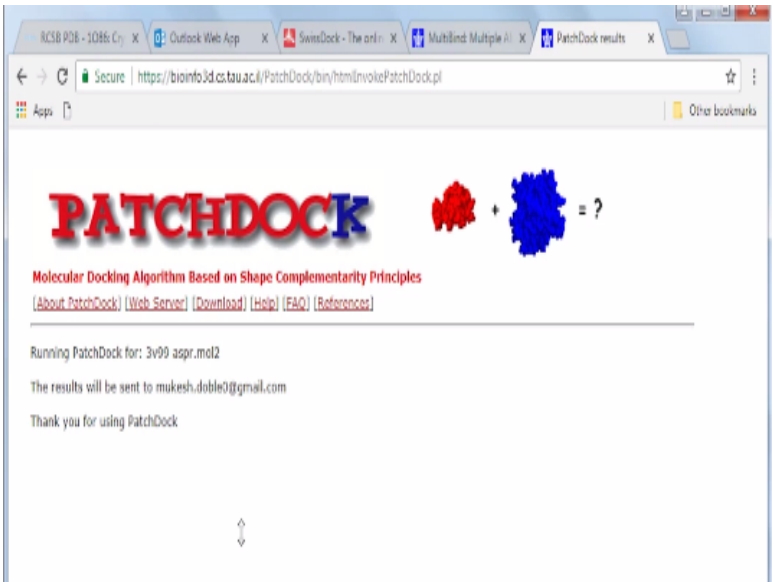

So, if you have a concave and if the another ligand has a convex and the matching, so we can say there could be a interaction or binding here. So, this sort of gives you the score okay, so this is another software, which is useful when you are looking at ligands and proteins, will be send to this particular ID. So, this is also a very useful software, okay so this multi bind looks at several protein binding sites.

And then it says what is the similarity like principles like hydrophobic, hydrophilic, polar nonpolar and so on, whereas a patch dock looks like ligand and target protein and see what is the commonality based on the shape okay. As you can see they are all with server based, so we upload our problem and the results will come to your email id and you can start analysing them. So, they are all free of charge okay, so we will continue more on the topic of computing in drug design in the next class as well, thank you very much for your time.