INDIAN INSTITUTE OF TECHNOLOGY ROORKEE

NPTEL

NPTEL ONLINE CERTIFICATION COURSE

Biomedical Nanotechnology

Lec - 09
Bio-Nanomachines

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Hello everyone I welcome all to the 9th lecture of this course this 9th lecture is on bio nano machines.

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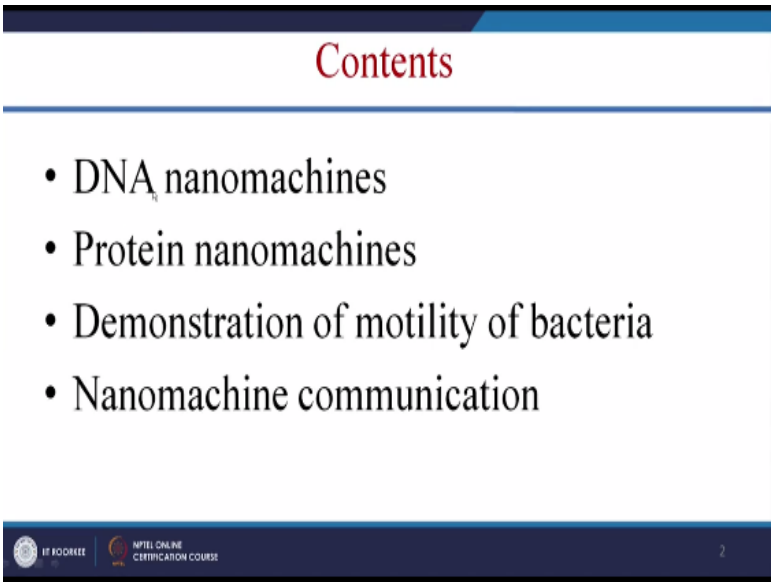

So in this lecture we will learn about DNA based nano machine and the protein based nano machine I will also demonstrate a simple experiment to study the motility of bacteria and wec will also learn about the nano machine communication.

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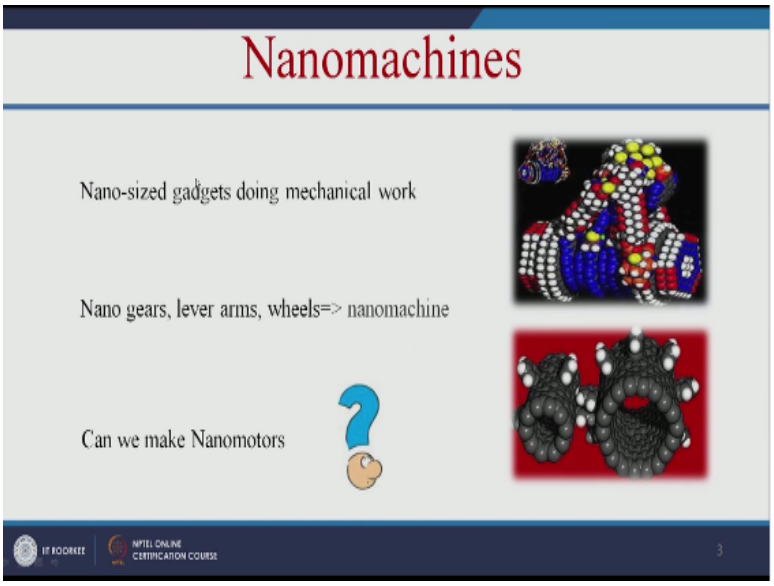

So first we will see what is nano machine it nano machines are nano size gadgets it is doing mechanical work, the examples are like nano gears and nano wheels the question is can we make nano motors and if you want to make nano motors what are the approaches available.

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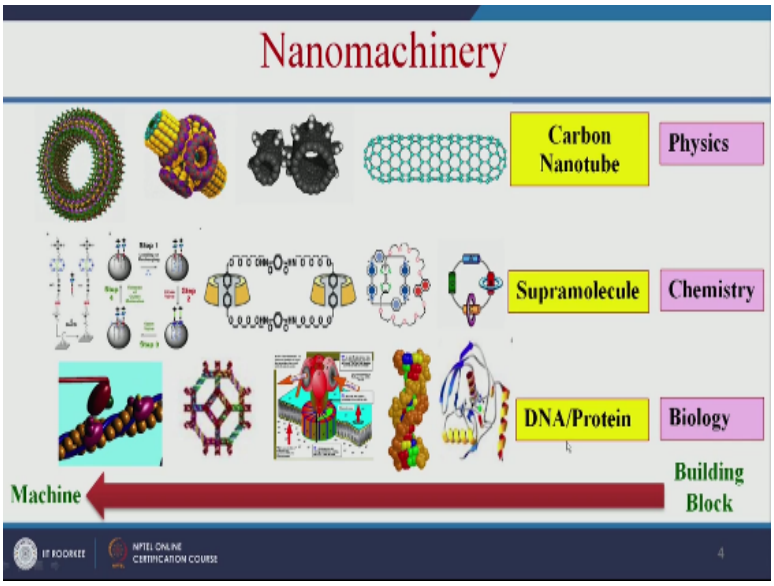

If you see here there are three approaches physics based chemistry and biology based and physics based approach we can use carbon nano tubes and we can make nano machines are nano motors and in the chemistry based approach we can use as supra molecular chemistry and we can make small nano size machine also nano size switches okay and in the biology based approach we can use a DNA and protein for making various nano size machine or rotor.

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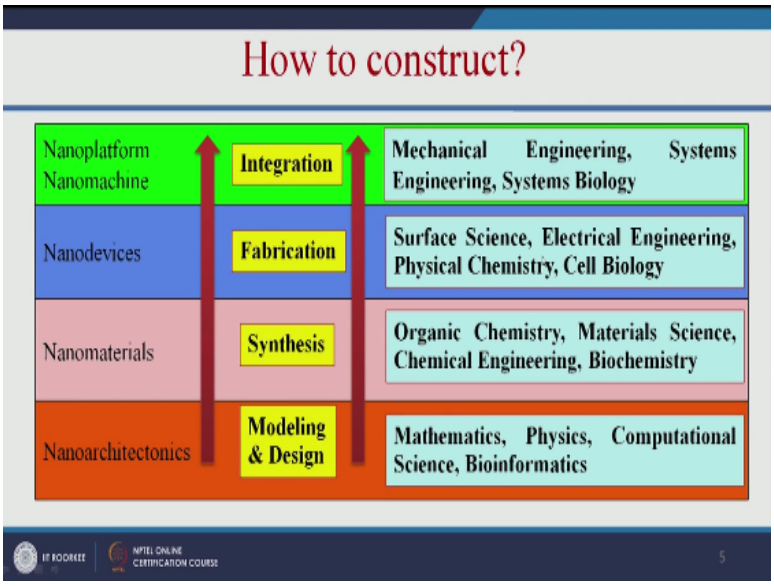

So how to construct this nano machine the first step for constructing nano machine is modeling and design so which comes under nano or electronics and these are the fields contributing to this modeling and design and for synthesis of nano materials mainly the chemistry bio chemistry these fields contributes in the synthesis of nano materials and the next step is fabrication, so for fabrication of nano devices we need the contribution from this cell biology and other fields and finally we have to integrate and make the complete nano machine okay. So what would be the application of this nano machine let us see an example.

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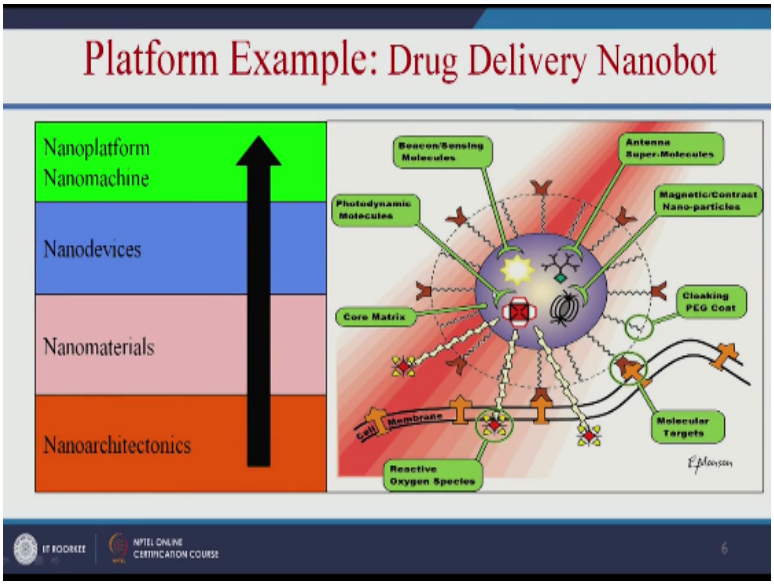

So we can make a drug delivery nano broad that is nano robots so which can precisely reach the tumor location and it can realize the anti constrain drug so here you can see here it is specifically binding to the cancer cells and also it is also realizing the drug and we can make such kind of small size nano machines not only for drug dealing applications and also for various other applications.

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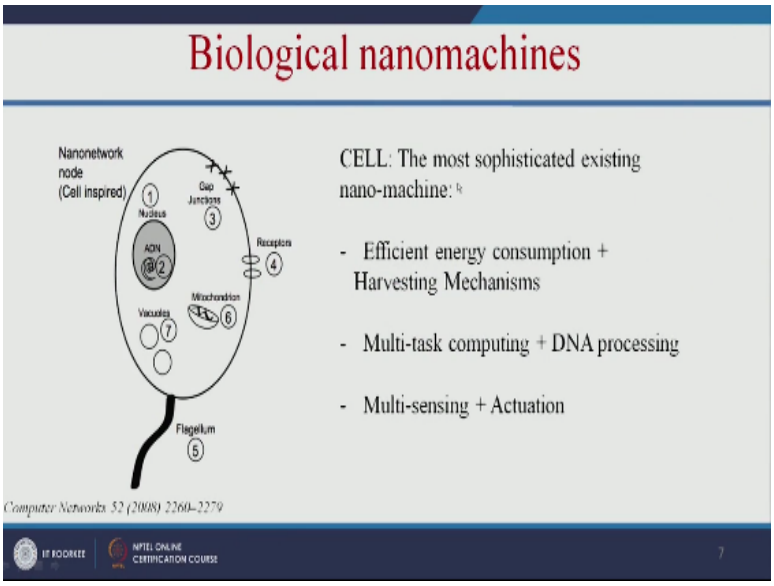

So we can take the idea form the cell okay because the cell is the most sophisticated existing nano machine and it as a efficient energy consumption and it as also multi task computing and multi sensing capacity so when the cell we can easily take the idea and we can micas such kind of nano scale machines or nano scale Robots.

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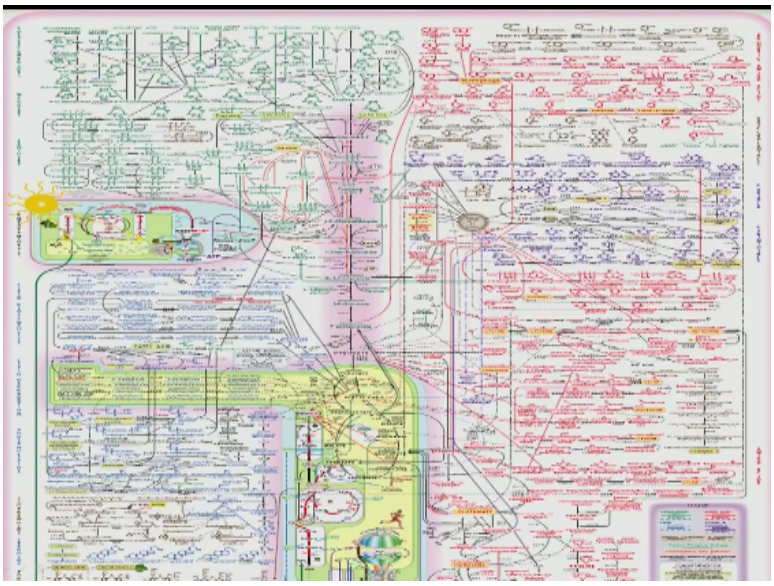

So you can see this slide it is a complex metabolism so this kind of metabolism is going on in your cell every milliseconds or nano seconds and without any disturbs or without any traffic inside this cell so how is it possible and when we understand this kind of complex things and we can make very small nano scale machine which can do the job precisely and which have wide applications so that is why we are idea from the nature.

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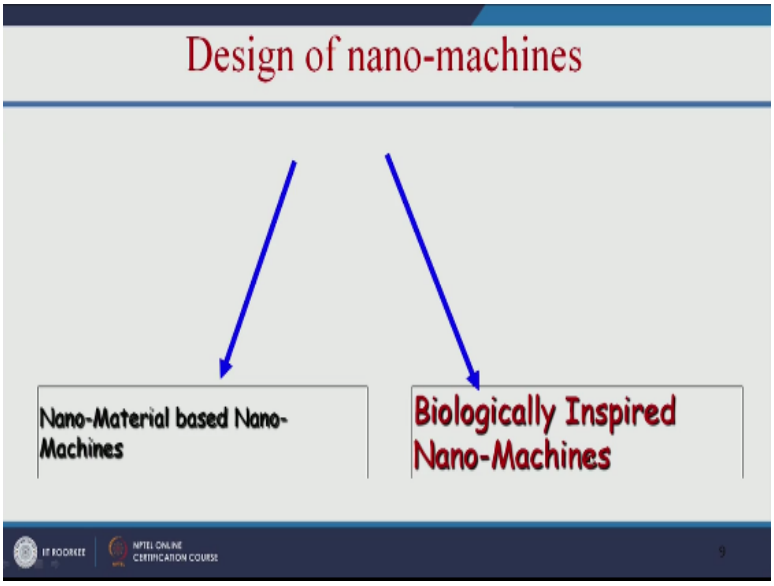

So we can make the biologically in spite nano machines.

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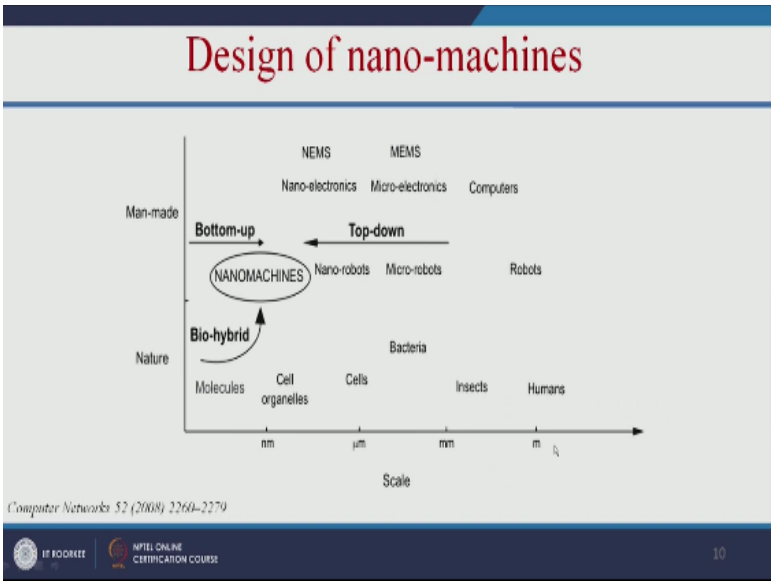

So how to make the nano machines what are the approaches so there are again two approaches bottom up and top down approach so man made nano machines are top down so we started with robots and we are trying make nano robots and but nature they started with bottom up approach, so it assembles DNA and protein and makes the nano scale machines.

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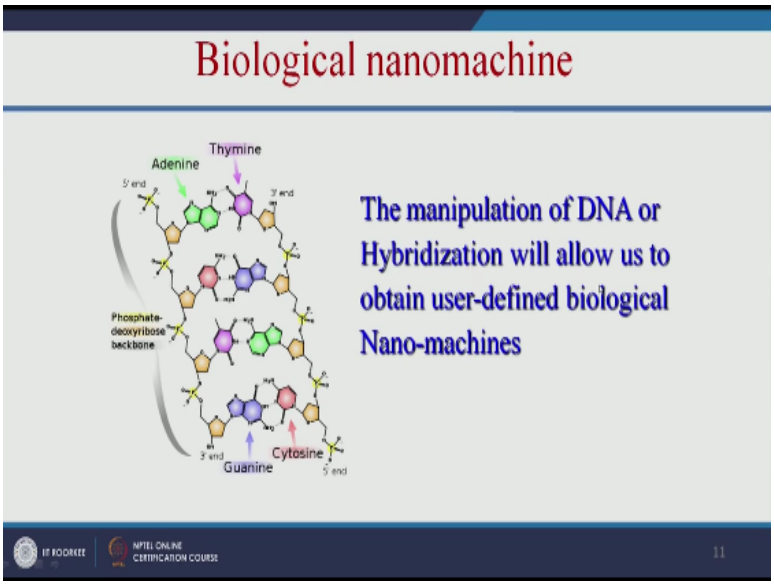

And especially in case of nano machine the DNA and protein plays a major role because the manipulation of DNA or hybridization will allow us to obtain user defined biological nano machine that means like we can easily manipulate or we can easily modify the DNA and we can make such kind of small nano machines and also we can a make user defined biological nano machine so that is the advantage of DNA and protein based nano machine.

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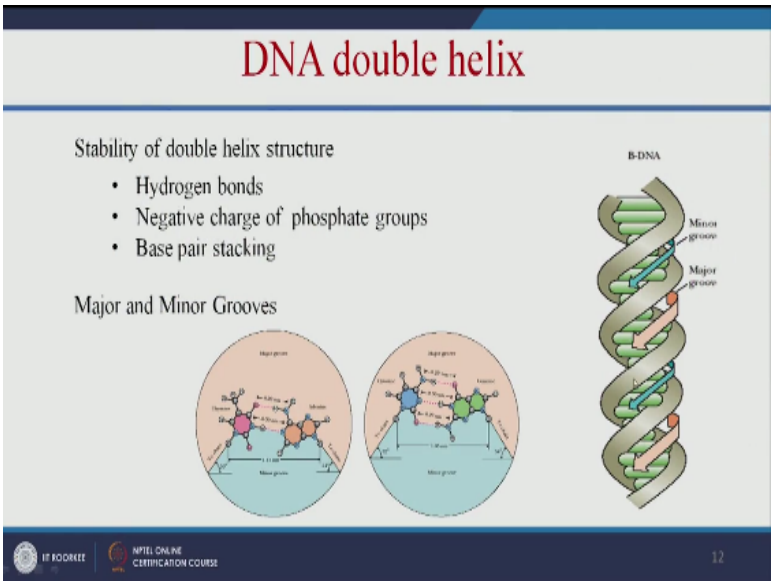

So in the previous lecture I already told you that A always from bind with T and G always from bond with C that is cytosine okay and also already explain why the DNA is helically nature what is the reason for the helical structure of DNA.

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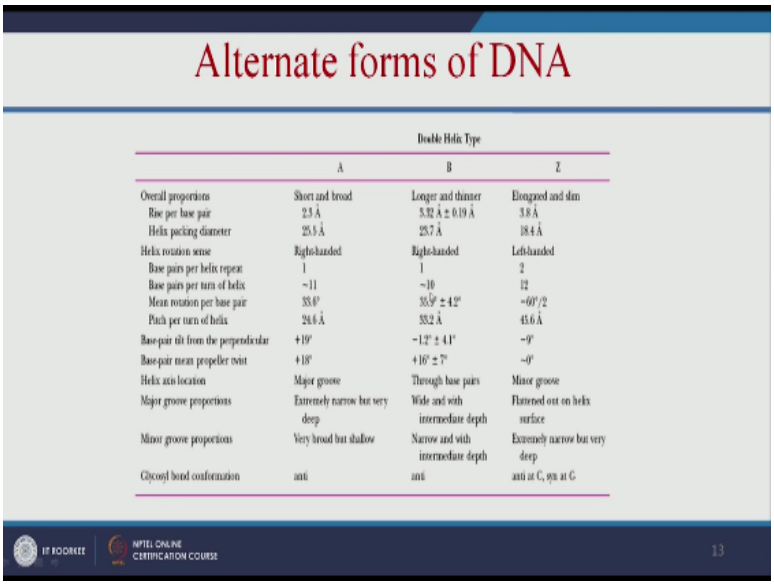

So let us see the various forms of DNA so here we have 3 forms of DNA that is A DNA, B DNA and Z DNA so the main difference if we see that A DNA who 11 base passed per return of helices and B DNA have base passes per helices and Z DNA have 12 base passed per helices.

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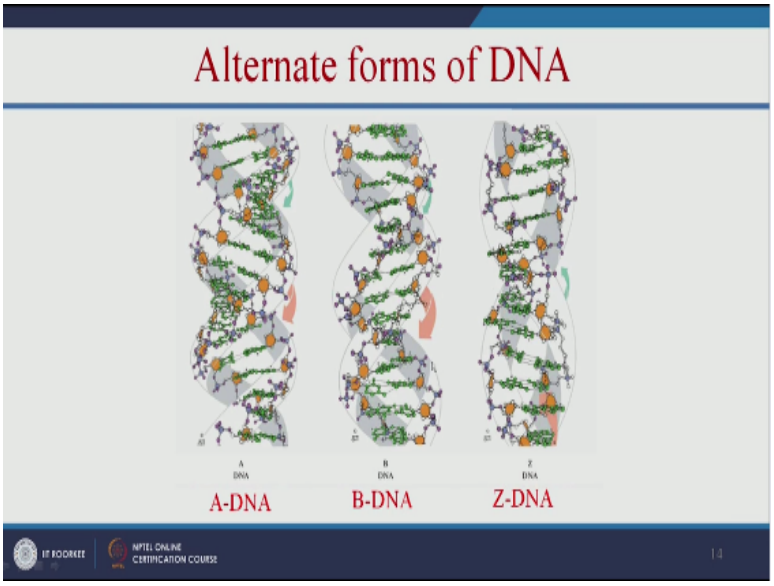

So these are the various forms of DNA A DNA, B DNA and Z DNA so using this how to make nano machines and nano motors we will see in the following slides.

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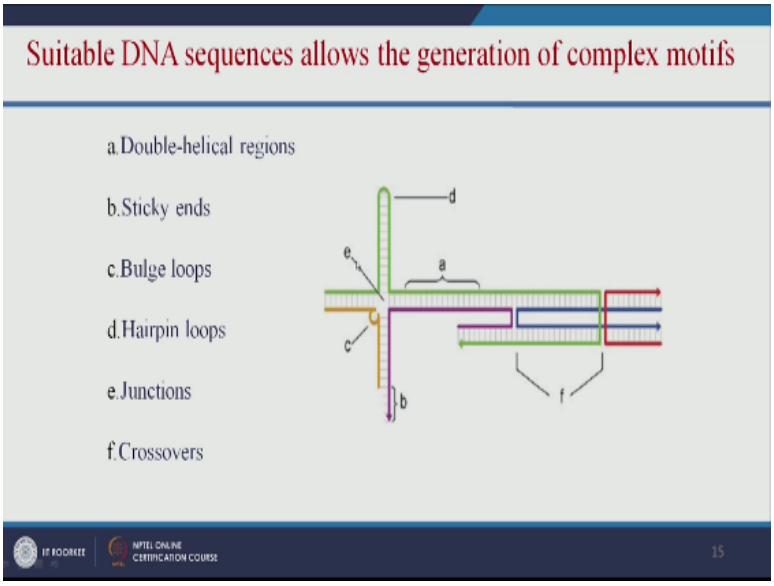

So before we see who to make nano machines let us get idea about some of the terminologies so here you can see here these are double helical region and this b is a strike ends that means over hangs and c is your bulge loop and d is a hairpin loop if you this kind of DNA sequence that is called as hairpin loop and this e is a junction and this f is a cross over.

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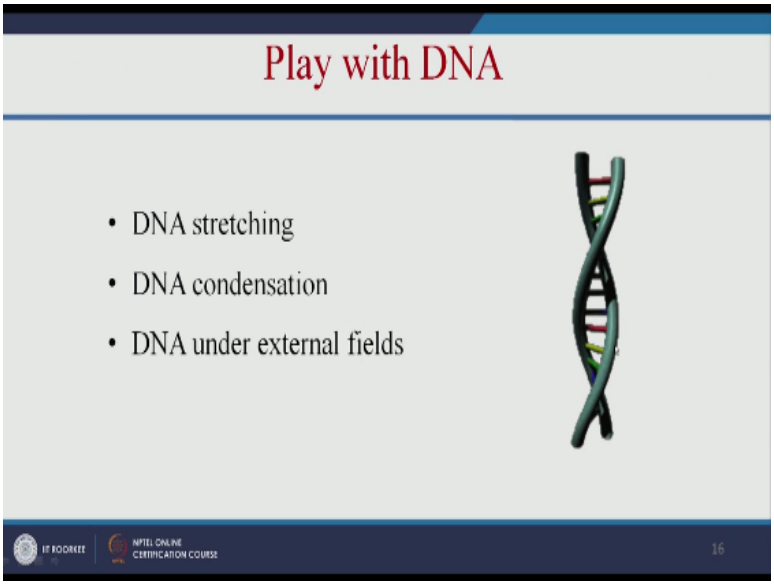

And using this DNA we can stretch the DNA we can condense the DNA and also we can play with the DNA by using external fields.

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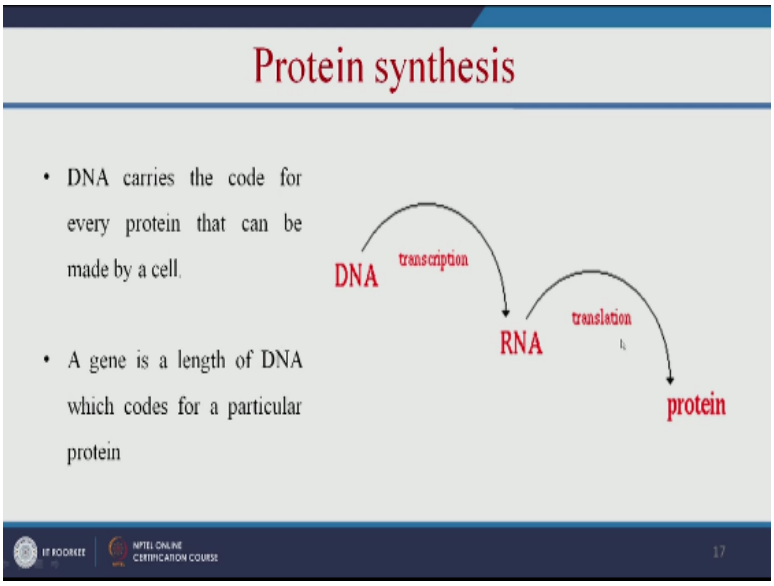

So before we will learn what is DNA based nano machine so let us learn what is protein synthesis so we will get the RNA from the DNA by the process transcription and from RNA you will get the protein by translation process, so we can take the example of transcription and translation we can make such kind of small nano machine.

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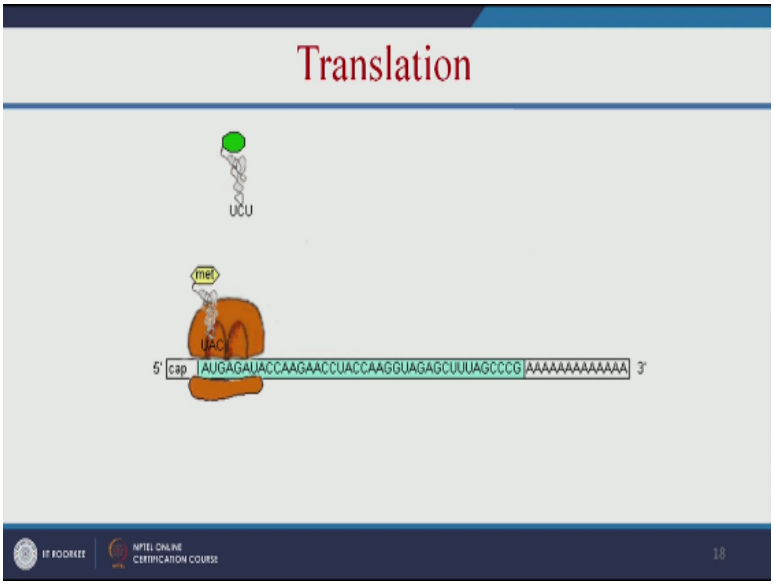

So let see translation so we can see here this your MRNA and this is your TRNA and this orange color is your RRNA so the TRNA is coming here and binding with MRNA and other TRNA is coming if it is not matching it will be removed so this TRNA is matching with the sequence so it is forming a testate bond so similarly one by one amino acids will come and join and form the protein so we can see here how precisely it is moving so it is also a kind of nano machine and at the end of the reaction we can see her this MRNA is getting degraded so this poly A title is very important.

If the length of poly a title is more that means your MRNA half play will be more okay so assume this is as a kind of nano machine and we can take the idea from this and we can make such kind of nano machine.

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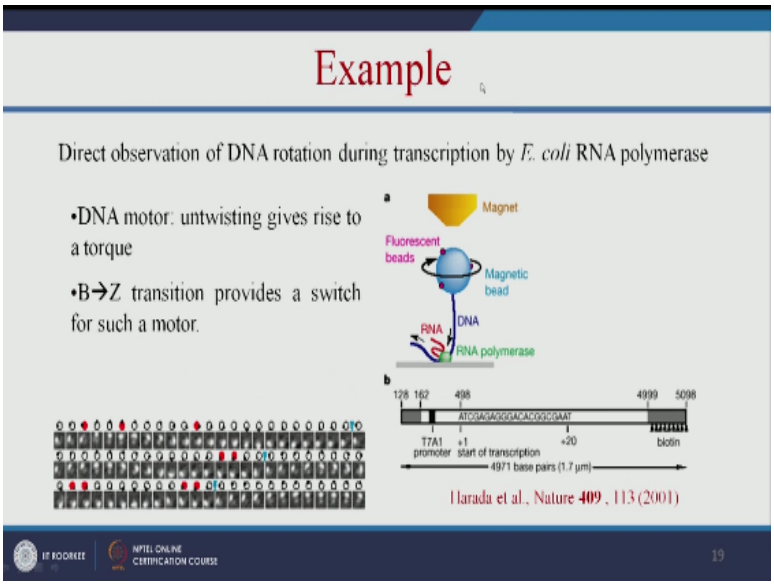

So let us see the another example how to make DNA based rotor or motor, okay. So here we can use the DNA and we can use that RNA polymerase enzyme so what happens is like when it synthesize RNA the DNA will start rotating in this direction, so that we can easily measure by tagging the DNA with this magnetic weed and the top of the magnetic bead we can also add the florescence basic and this magnetic bead will be hold by extend magnetic field.

So when we add this earlier polymerization enzyme so this will make the RNA when it makes the RNA the DNA will rotate in this direction, so this rotator motion can be easily monitored using the microscope.

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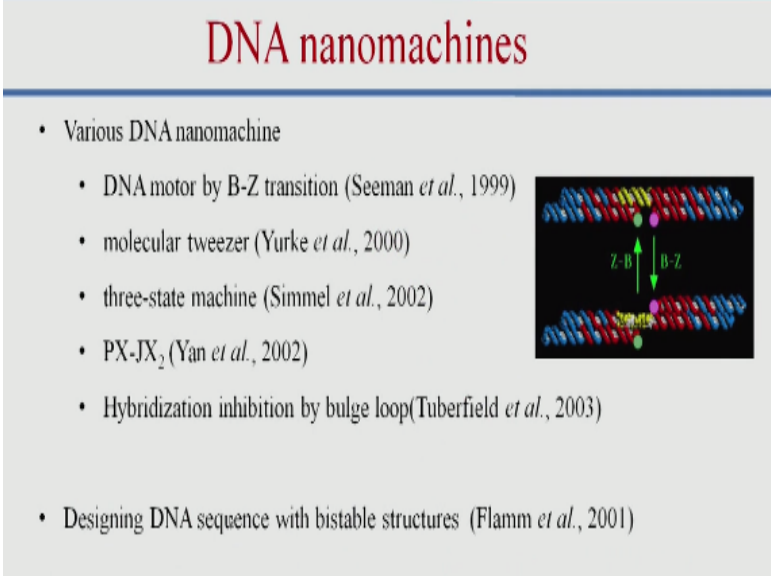

So the next example is, DNA based nano machines and in this we can see like a various machines are available like B the transition, molecular tweezers and also PX and JX_2 so these are the various types of DNA machines available so we will see one by one.

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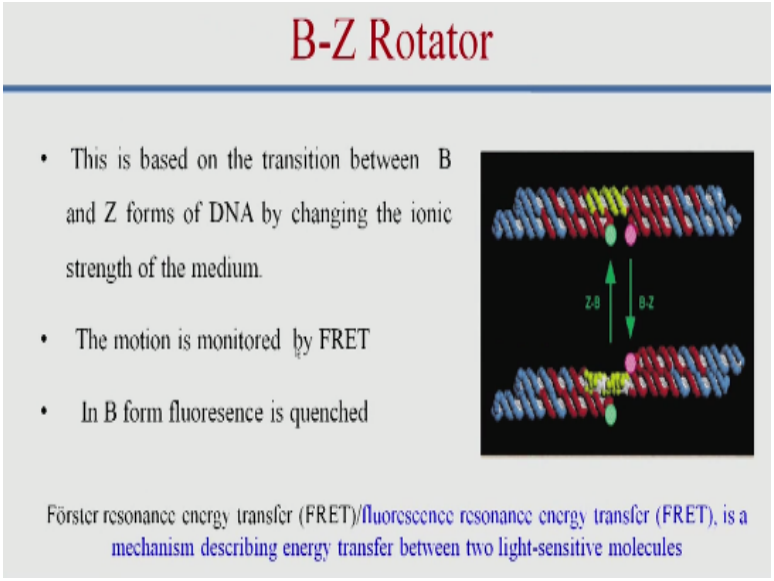

The first one is B is that rotor, so this machine is based on transition between B-DNA and Z-DNA by changing the ionic strength of the medium, okay. So this motion can be easily monitored by FRET, so what is FRET? It is a mechanism describing the energy transfer between two light sensitive molecules, so here we can simply changing the ionic condition of the medium.

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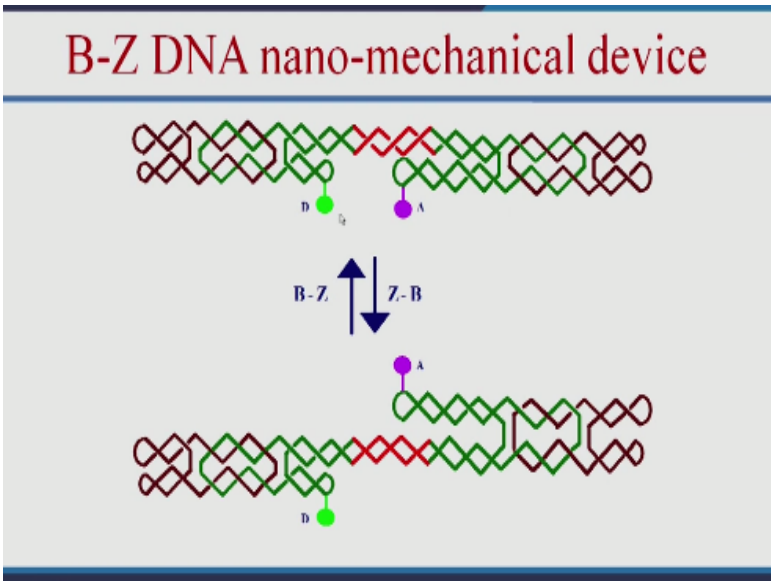

So we can convert the B-DNA into Z-DNA so this is your florescent molecule and this is your quencher, so when in then when it is in the B-DNA form it would not show any florescence when you change the ionic condition, ionic medium so it will become a Z-DNA so where your florescent molecules as well as quencher will be separated and will give the fluorescents.

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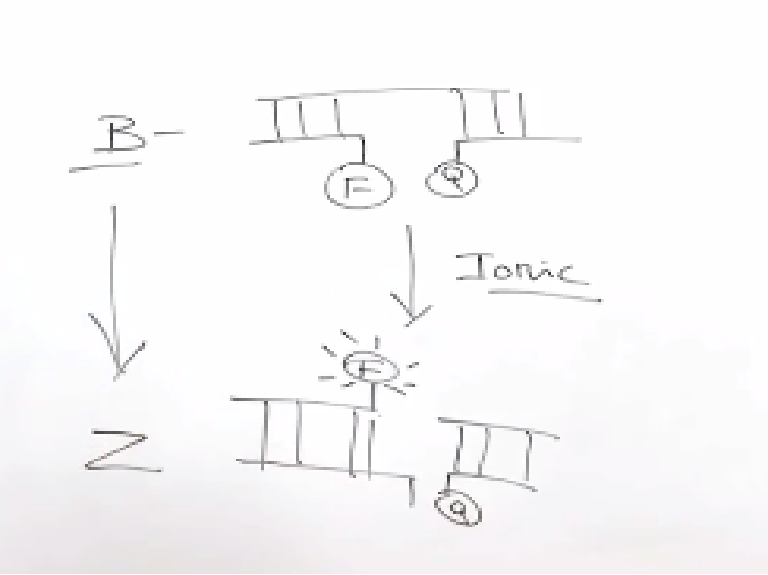

So here you can see here when it is in the B-DNA from both the florescence and quencher will be together, so when you change the ionic condition so this B-DNA will become Z-DNA and your fluorescents and quencher will be separated, so when it gives then it gives fluorescents okay, so this is called as B is that transition. So by simply changing the ionic condition from B-DNA we can make the Z-DNA.

Is the B-DNA is the fluorescents and quenchers are together so it would not show any fluorescents signal so when it becomes Z-DNA what happens its, that fluorescents and quencher will be released and it will give the fluorescents signal.

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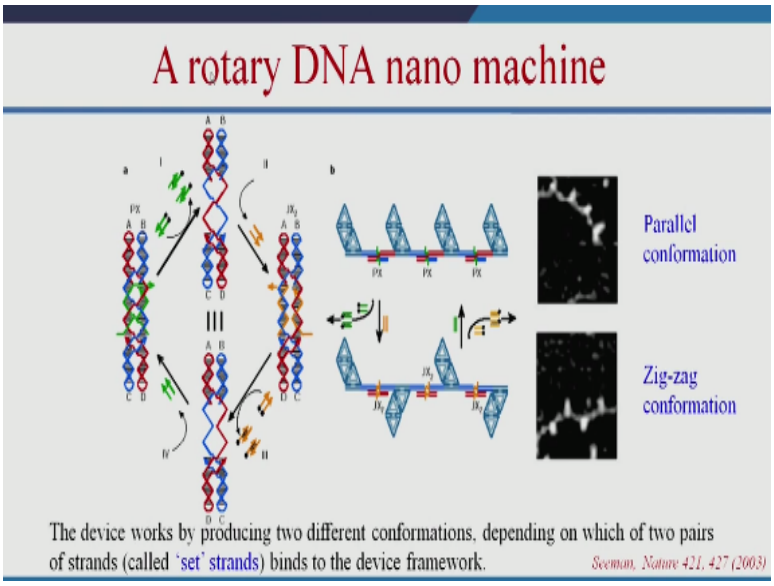

So next example is rotary DNA nano machine, so here this device works by producing two different confirmation parallel confirmation and zigzag confirmation by using a two pairs of strands that is called as, sets strands, okay. So that will binds to the this DNA single stranded and it will make this kind of parallel or zigzag confirmation. So here you can see the example so this double stranded DNA it is holding this single stranded.

And when we add this kind of sets strands and it will form this kind of parallel confirmation and zigzag confirmation, depends on the size of your set strands, if the set strands matching with this size of your single stranded DNA it will produce parallel confirmation if it is slightly bigger than the your single stranded DNA it will form zigzag confirmation, so here your DNA's acting like your fuel. Based on the DNA it will have a rotary motion.

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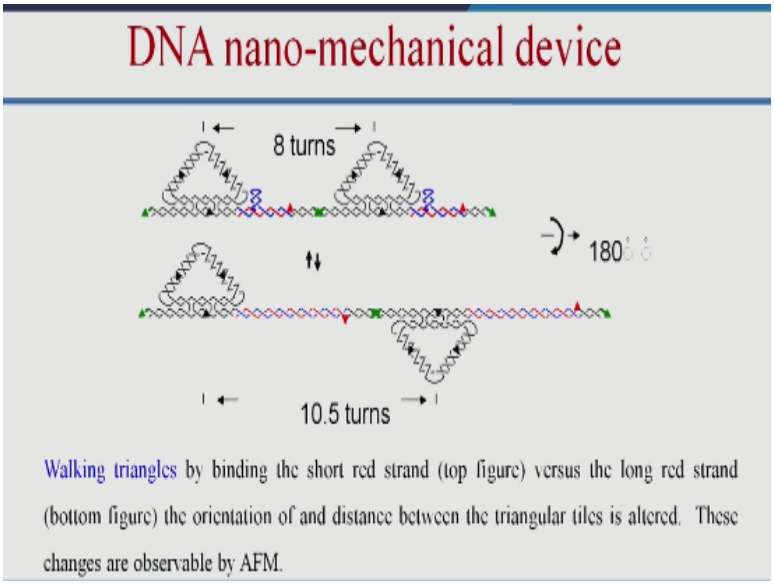

Next example is walking triangle you can have this kind of DNA sequence and when you add short fragment of DNA single stranded DNA the red color one it is binding to this single stranded DNA in-between this two triangles and there are also some unbound the DNA so that DNA will form like a loop like structure, so in this case both the triangles should be on the top and when we add the red color strand DNA which is matching with the single stranded strand that is the blue color DNA.

So when it forms a hybridization what happens is, this triangle will rotate it will have 180^0 rotation and it will move to the bottom, so this is also another example for DNA based nano mechanical device.

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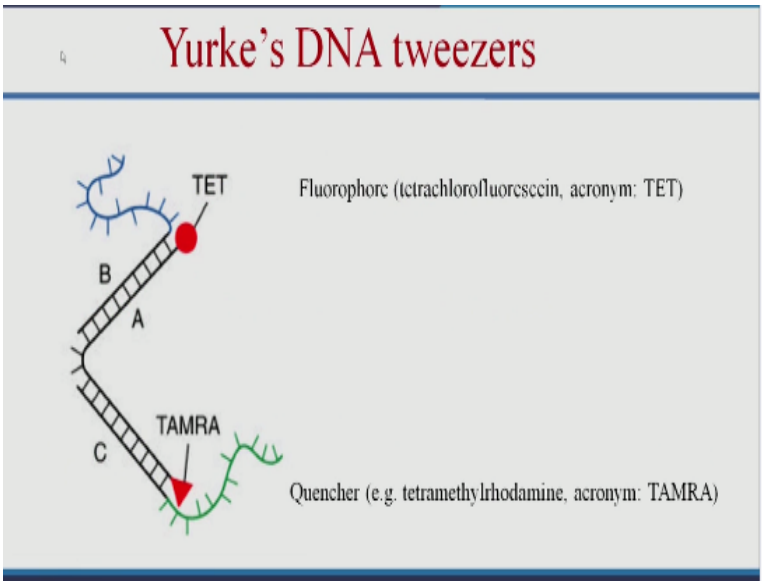

So another example is DNA tweezers, okay. So this is your DNA tweezers here you can have fluorophore that is your tetrachlorofluorescein in short it is TET and another one is quencher that is TAMRA this is called as tetramethylrhodamine and short it is called as TAMRA.

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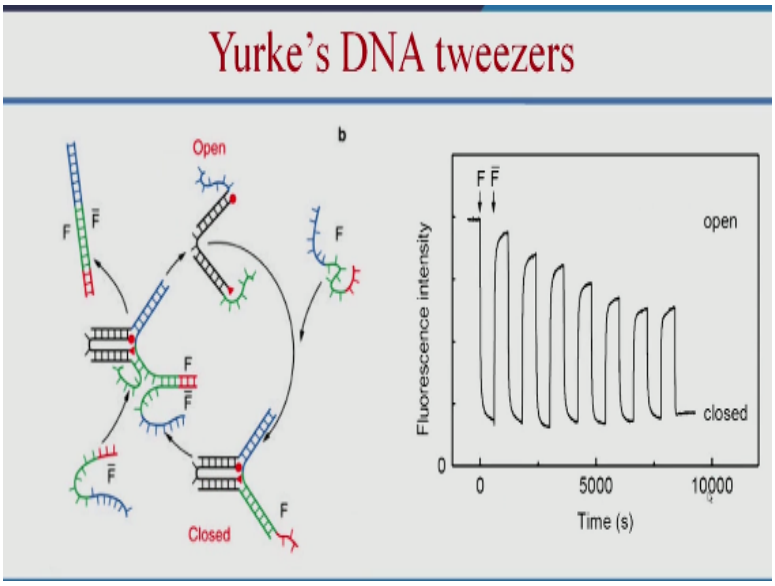

So using this we can make the DNA tweezers we can open the tweezers and we can close the tweezers so what we can do is, you can add a single stranded DNA so this blue color will bind here and this green color will bind here and it form this kind of structure, when it form this kind of structure this fluorescence and quencher are closed together so when it is closed together the fluorescents signal will be off.

And when we add another sequence which is highly specific for this the blue color and green color strand say it will combine and this strand will be removed, so when it is removed this will be in a open state, so here you will get the fluorescent because the fluorescents and quenchers are separated so it will give a fluorescents signal, so in this picture you can see here the fluorescent intensity is more when it is open state. And the fluorescent intensity is down when it is in the closed state.

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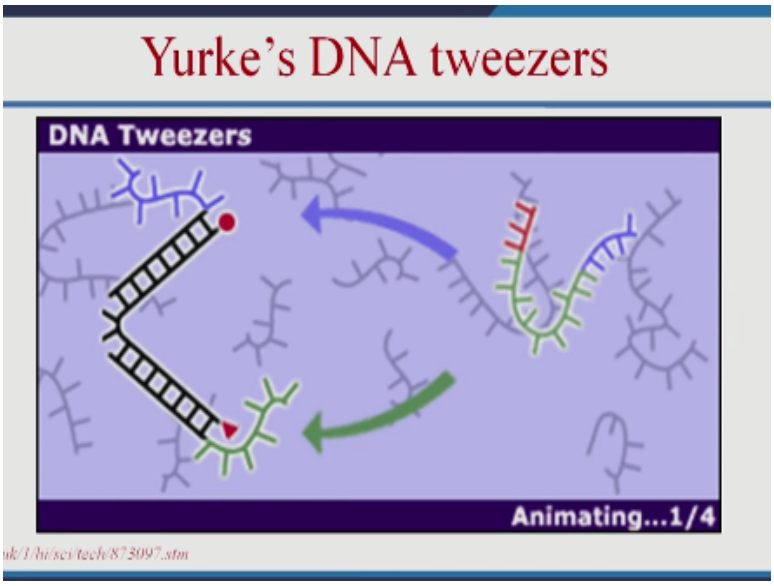

So same DNA tweezers in animation we can see here in this strand binds it become closed state and when the strands get removed again it become the open state.

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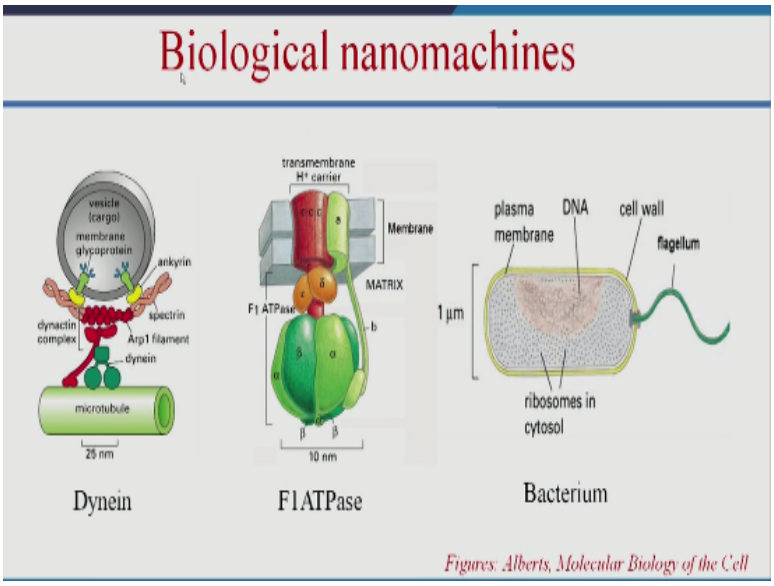

So let us see another example that is a protein based nano machines so that is Dynein, F1ATPase and Bacteria Flagella, okay.

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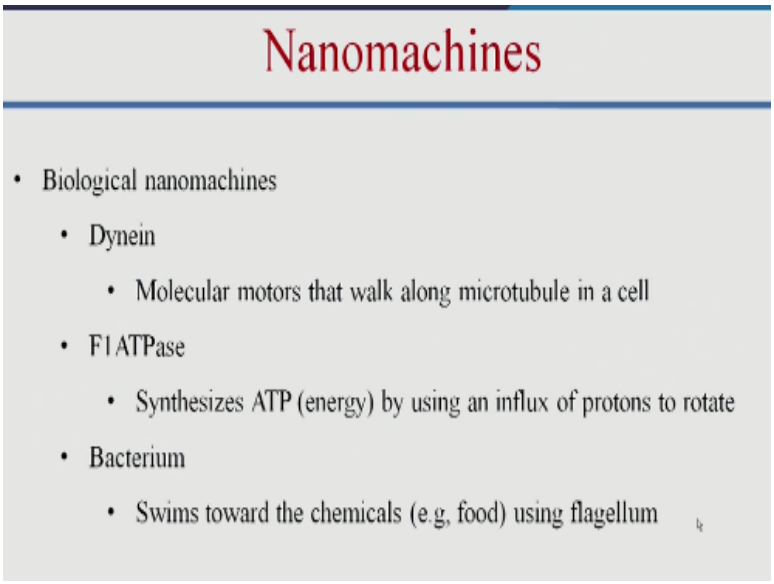

So here this Dynein is a molecular motor that walk along the microtubule in a cell and ATP energy synthesis ATP by using an influx of protons to rotate and bacterium it use a flagella to move from one location to other location towards the chemical that is food.

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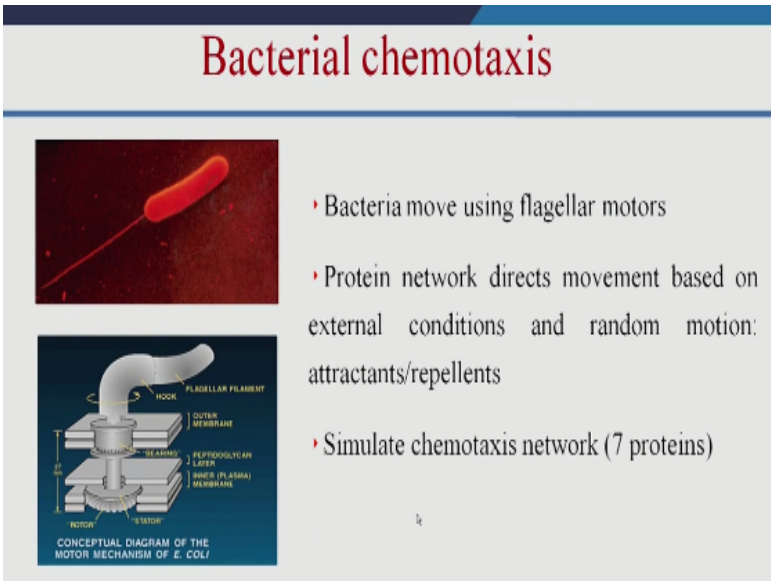

So first we will see bacterial chemo taxis so this bacteria move from one location to another location using the flagella that means it move towards the food okay. And it get the signal from the food and it move toward that food that is called as Chemo taxis it get the chemical signal and the bacteria move towards the food that is called as chemo taxis, so here the bacteria move using flagella motors.

And this protein network directs movement based on the external conditions, if you have food that is attractant or we have some other material that is repellent okay and this will stimulate chemo taxis network it will similar more than 7 proteins than only this flagella will be in accent to move to other food.

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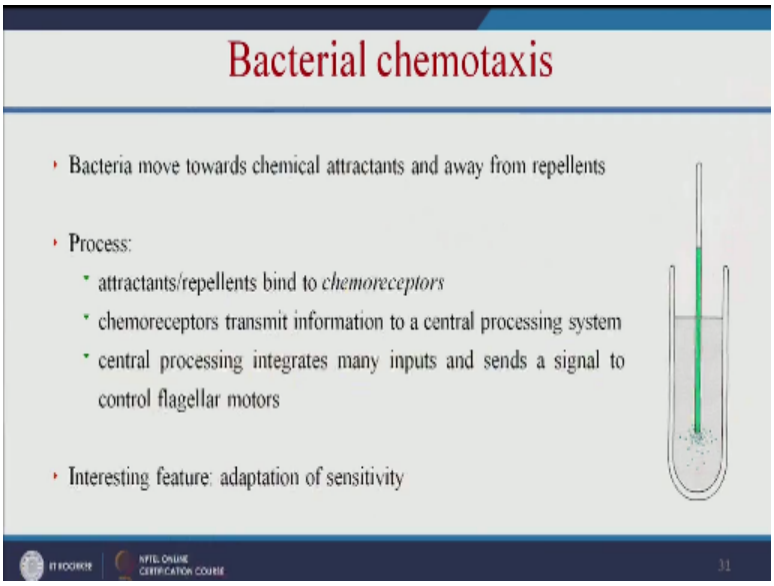

So here the bacteria move towards chemical attractants so the process is the attractants bind t0o the chemoreceptors and the chemoreceptors transmit information to a central processing system, and the central processing system integrates many inputs and send the signal to control the flagella motors, so the bacterial mortality will be look like very simple but you can see that how much reactions are going on to make the bacterial to move from one location other locations so what we can take form these bacteria we can take the sensitivity so if we have any food materials it is sensing and moving towards that.

So we can take the idea of sensitivity and we can develop such kind of nano machines and nano robot which can sense that cancer cell in our body and it can reach the cancer location and it take deliver the anticay center, here you can see here so we have trigger solution all the bacterial moving towards the trigger solution.

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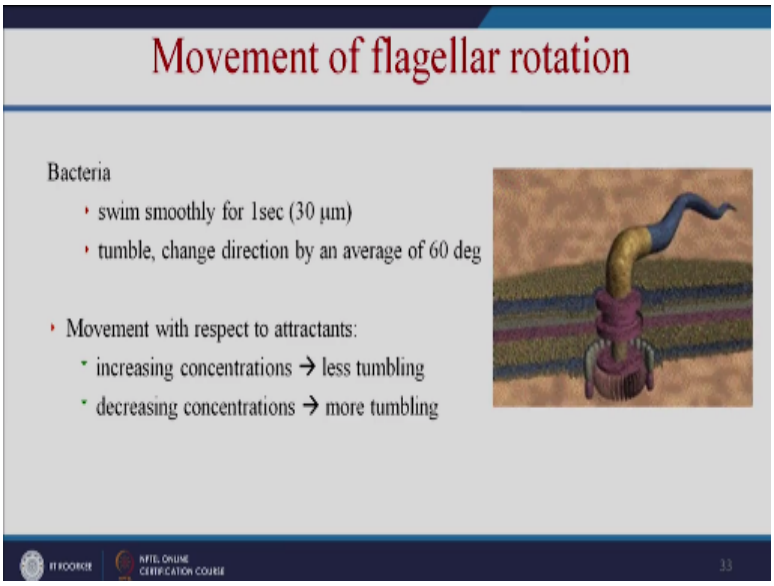

So and bacteria is swim by rotating the flagella and motor located at junction of the flagella and this motor can rotate clock wise or counter clockwise so this bacteria swims smoothly for 1 second and it change the direction by an average of 600, so movement is respect to the attractants if we have increasing concentrations it will be less tumbling and if we have decreasing concentration it will have more tumbling you can see here the bacteria flagella it is like a kind of nano machine or nano motor so now I will demonstrate a simple experiment to steady the mortality of bacteria.

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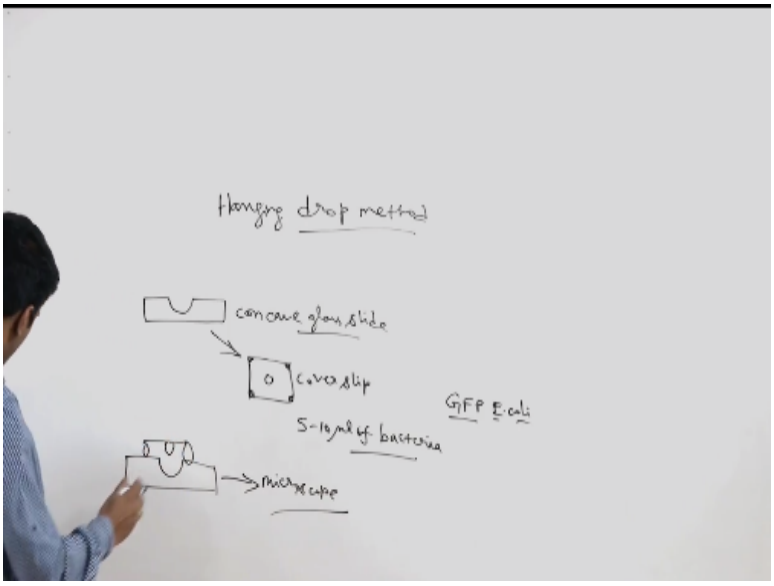

By using hanging drop method we can study the mortality of bacteria for this we need a concave glass light, so this glass light will be having concavity and we also need a covers slip so on the four sides will be adding a Vaseline okay, so keep a simple dot of Vaseline on the four edges then in the middle of the cover slip add 5 to 10 micro troff bacteria, so here we are going to add GFP E- coli, so GFP is green force protein expressing equally so by using this bacteria we can easily monitor the mortality of bacteria.

So once we add these bacteria to this cover slip then gently keep this glass light on the top of this and invert the slide, so we invert slide so the cover slip will be on the tope pf this concaves light and your bacterial solution will be hanging there so it is called hanging drop method, and under the microscope we can study the mortality of bacteria. So let me explain the hanging drop method study the mortality of bacteria so for this we need a concave light and covers it and also the heat grown bacteria.

But in this case I am not going to use a bacteria and going to use a simple water okay, so thi8s is your concaves light and this is a cover slip so on the four edges of cover slip I am going to put the Vaseline just put one dot on all the four corners so all the four edges I will added the Vaseline okay, so I hope it is visible and in middle of the cover slip I will be adding the sample okay. So where to use a bacteria which is in the lock face so that you can see the bacterial mortality nicely, but in this case I am adding water just to demonstrate you just for bacterial sample here to use the lamina group and we have to prepare the sample laser thickly, so then I will take this concave

glass light and put it on the top of this cover slip the gently edges the cover slip. So you can see here so the cover slip is in the middle of the concave glass light and your sample is hanging in the middle of the cover slip.

Slide I will keep it under these microscope and you can focus the mortality of bacteria in this slide.

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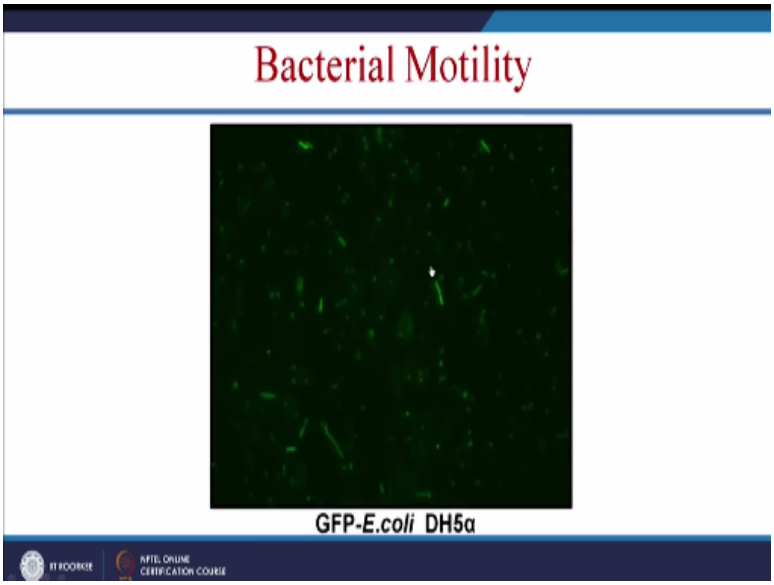

You can see here we have recorded the GFP E.coli bacteria mortality so we can from this slide we can understand the bacterial mortality.

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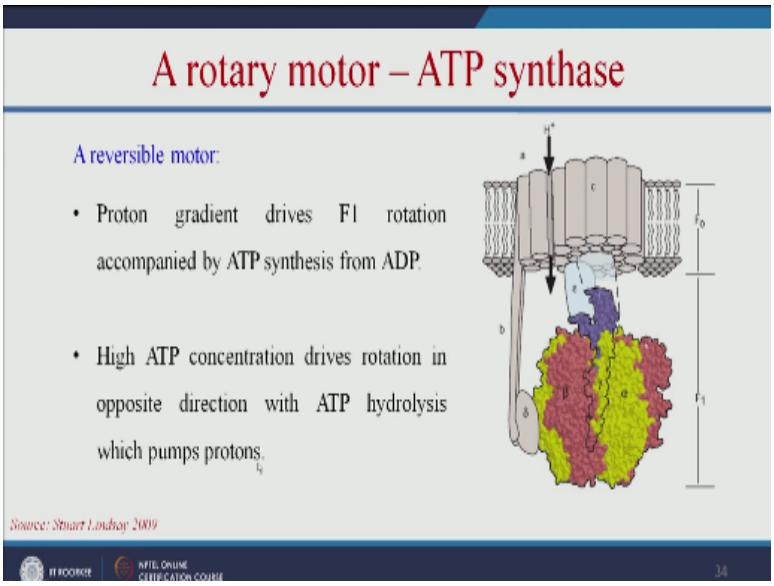

So let us see the another example ATP syntheses okay, so here the proton gradient drives F1 rotation accompanied by ATP synthesis from ADP, so if you high ATP concentration that drives rotation in opposite direction with ATP hydrolysis which pumps protons.

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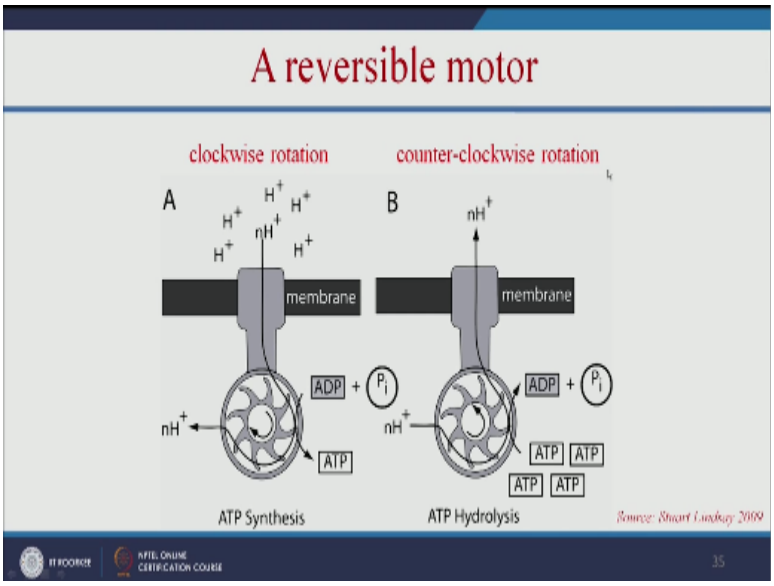

So here you can see here during ATP synthesis it will rotate in the clockwise rotation and during ATP hydrolysis it will rotate in the counter clockwise rotation, so it is the kind of reversible motor.

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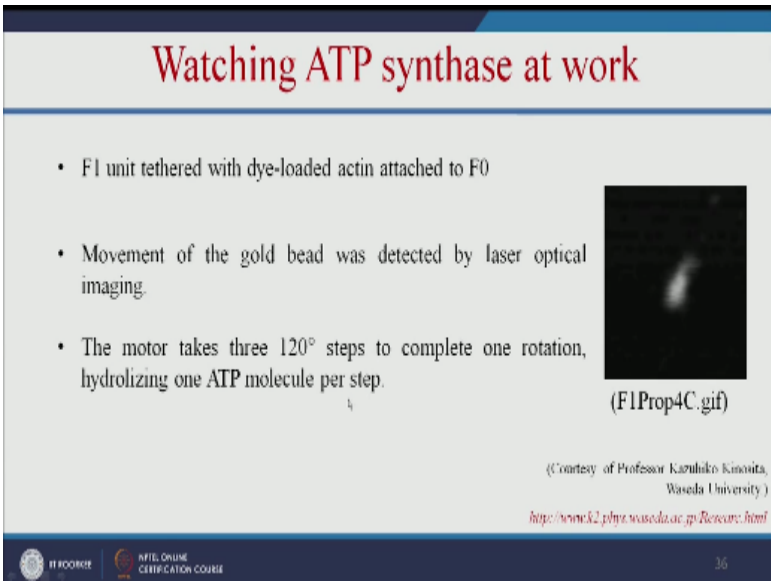

And here the F1 units attached with the dye-loaded action and attached to F0 and we can easily see the movement of gold beat by laser optical imaging this is the goal bit like I can see here rotator motion and here the motor takes 31 200 steps to complete one rotation that means it takes 31 200 steps to complete one rotation and also hydrolyzing one ATP molecule per step okay.

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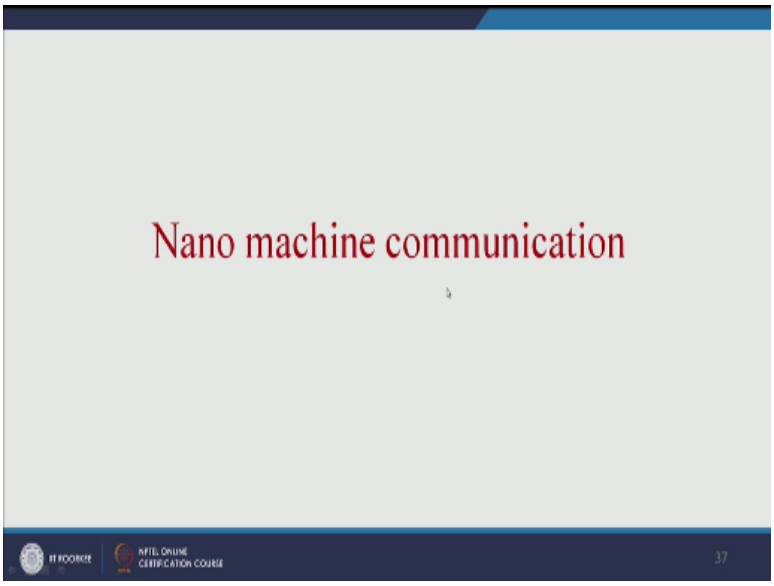

So now let us see a nano machine communication.

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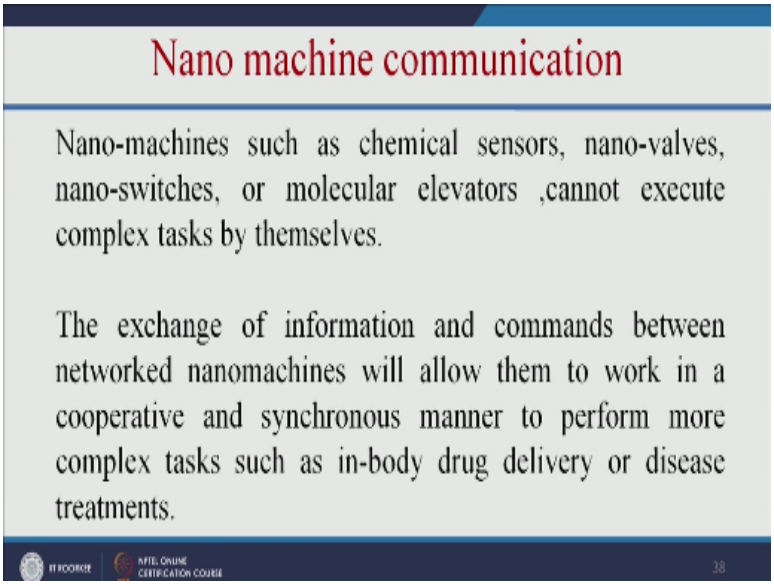

So why this nano machine communication is important, so the nano machines such as chemical sensors nano- valves and nano switches this cannot execute the complete that by themselves so the exchange of information and commands between network nanomachnies will allow them to work in a cooperative and synchronous manner to perform more complex starts such as in the body drug delivery as well as and disease treatment applications okay so the nanomachine communication is very, very important if you want to make a successful nano device or nano motor for drug delivery applications.

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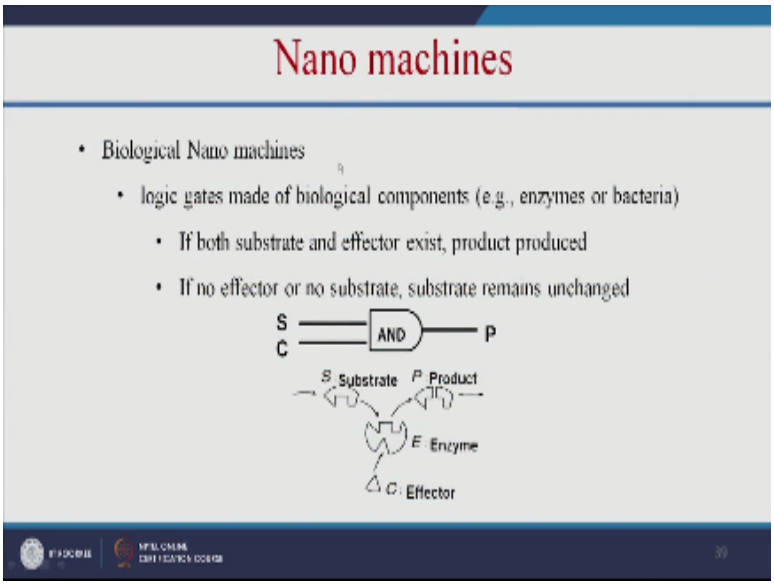

So let us see in case of biological nano machines we can make this kind of logic gates suppose if both substrate and effector is present then only it will make the product. There is no effector or no substrate in the substrate remains and change, so we can make such kind of logical gates for example if your cancer cell is expressing two of receptors or two kind of markers so then only this nano particle will bind, the nano machine will bind and it will release the drug, okay. So it would not release that drug to any healthy cells, so we can target it for various drug delivery applications.

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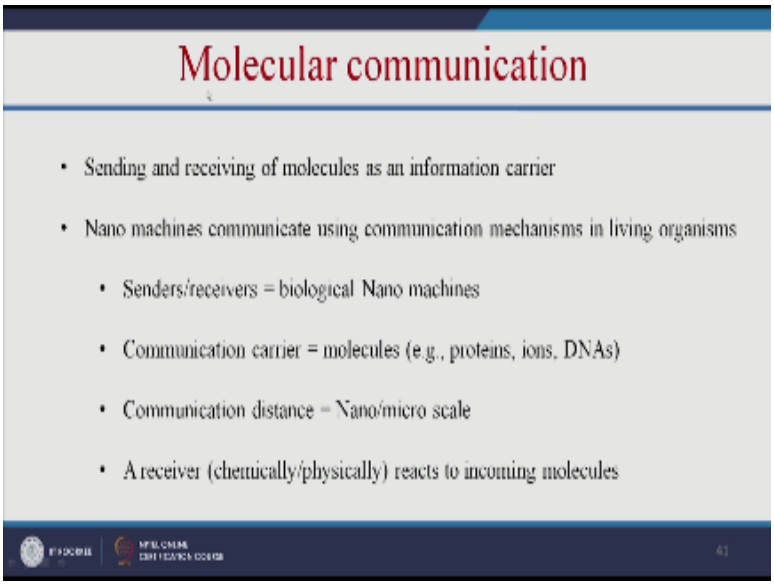

So in this molecular communication here the sender and receiver both are biological nano machine and the communication carrier the molecule that is also in the range of nano scale proteins, ions and DNA these are in the range of nano scale, and the communication distance it will become nano or micro scale and the receiver which receives the signal that is also in the range of nano scale.

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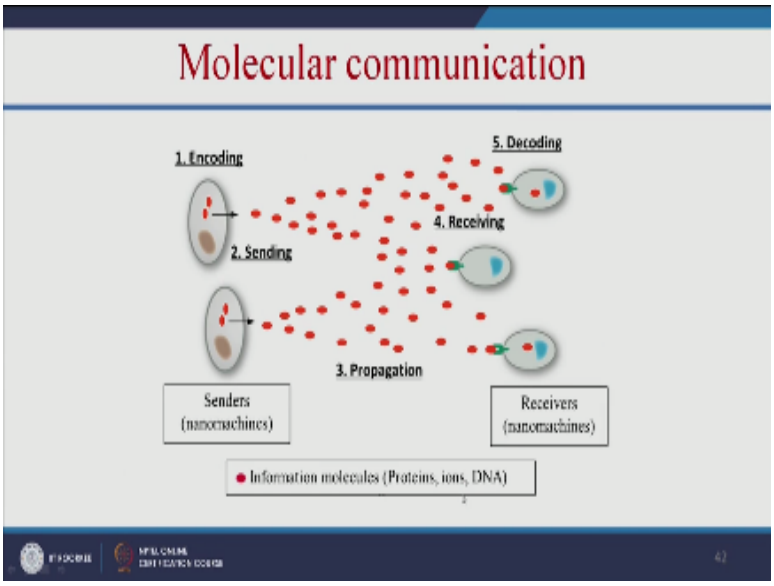

You can see here the sender is the nano machine and also the receiver is also nano machine and the information which is going from sender to receiver that is also nano scale that is protein or ions or DNA.

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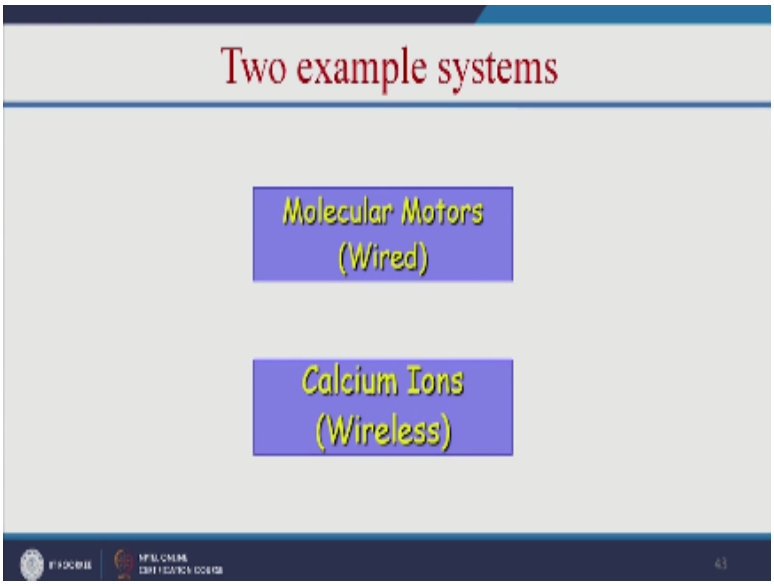

So here the molecular communication is divided into two types that is molecular motors that is a wired and another one is calcium ions based that is wireless. You can simply assume that this molecular motor is similar to your telephone connection, landline connection and this calcium ions based wireless is your similar to your cellular phone, okay.

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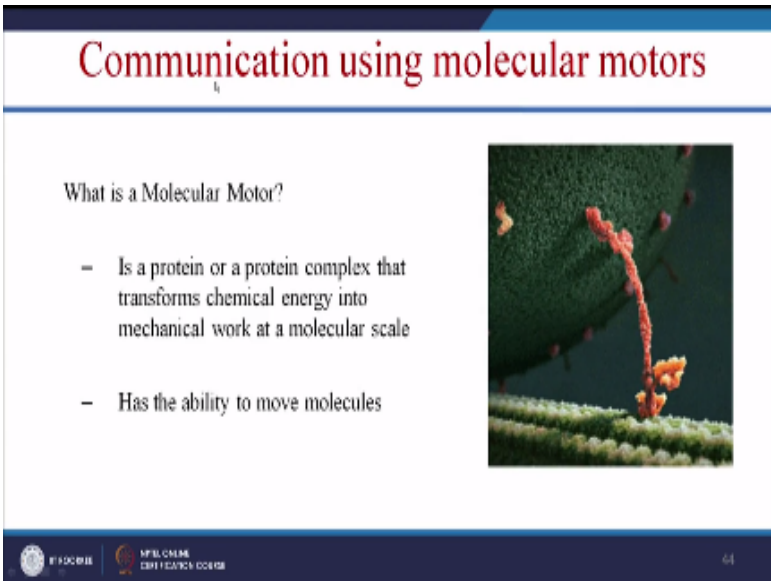

So let us see the communication using a molecular motors, so first we see what is a molecular motor, so it is a protein or protein complex that transforms chemical energy into mechanical work at a molecular scale, and it has ability to move the molecules here this is your microtubules and this is a molecular motor okay, and it is a information so this molecular motor is carrying the information from one location to other location through the microtubules.

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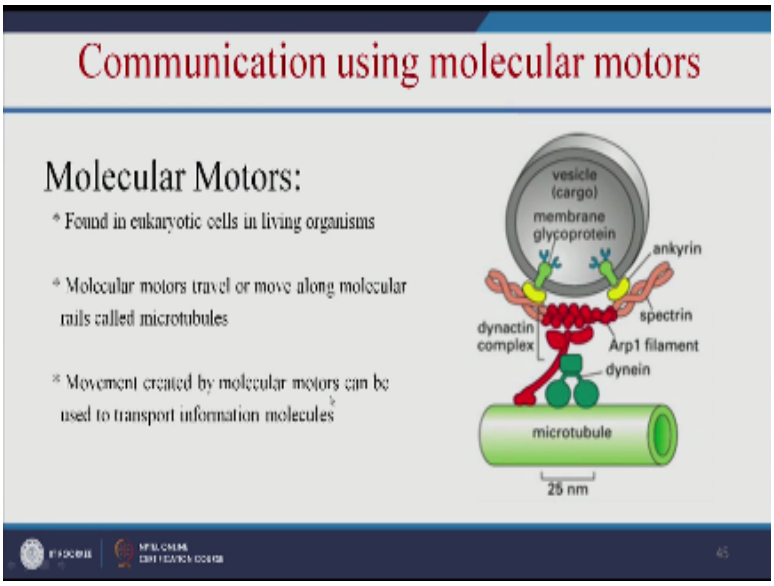

So it is mainly found in the eukaryotic cells okay, so it can carry the message and it can walk on the microtubule, so the molecular motors travel move along the molecular rails call microtubules and the movement created by molecular motors can be used to transport information molecules.

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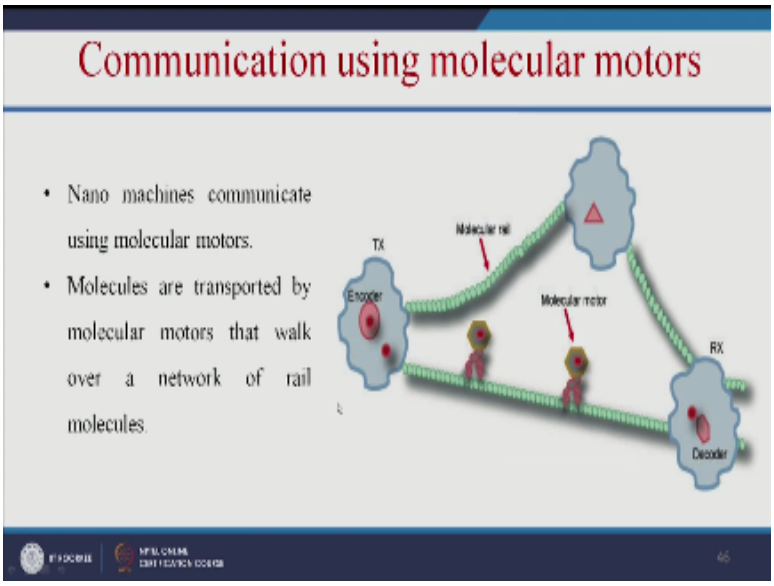

So here you can see here this nano machine communicate using this molecular motors and this molecules are transported from encoder to decoder using this network of rail okay, it is this molecular motor will walk on this network of rail and it reach from encoder to decoder and it will carry the information.

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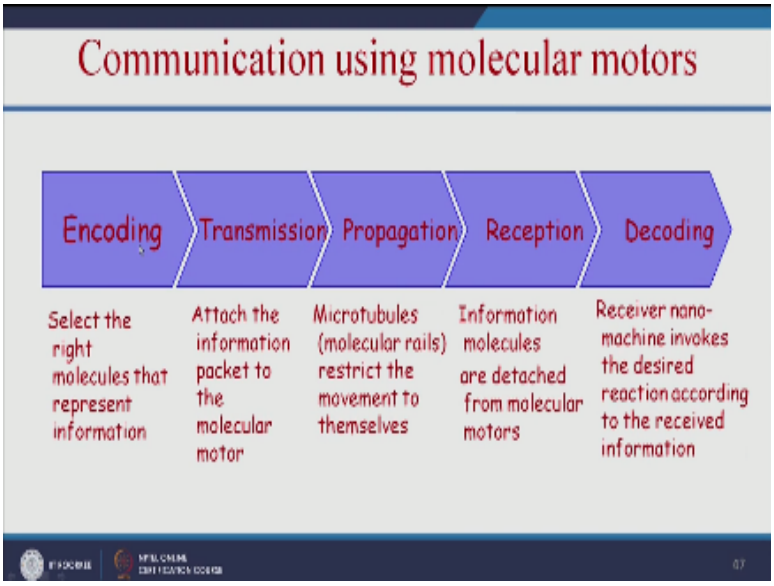

So here how the communication happen in this molecular motors because it select the right molecules that represent the right information and it will carry the information and through the microtubules it will move and it reach the receptor okay, and there your molecule will be detached and it will release the molecule okay, so once the receiver is receive that information it will perform the work according to the information.

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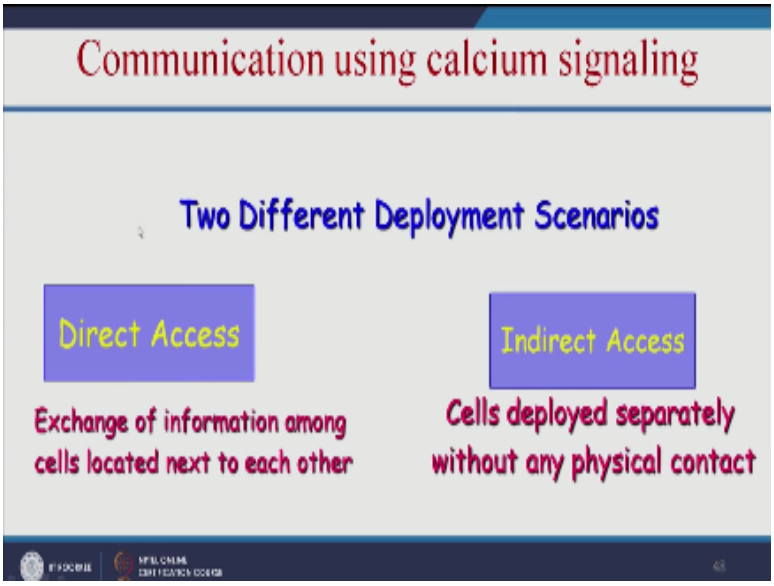

So the next example is communication using calcium signaling okay, so here two different deployment scenarios are available. The first one is direct access and another one is indirect access, so here the exchange of information among cells located next to each other and in indirect access cells it can be separate without any physical contact and the information can reach the receiver.

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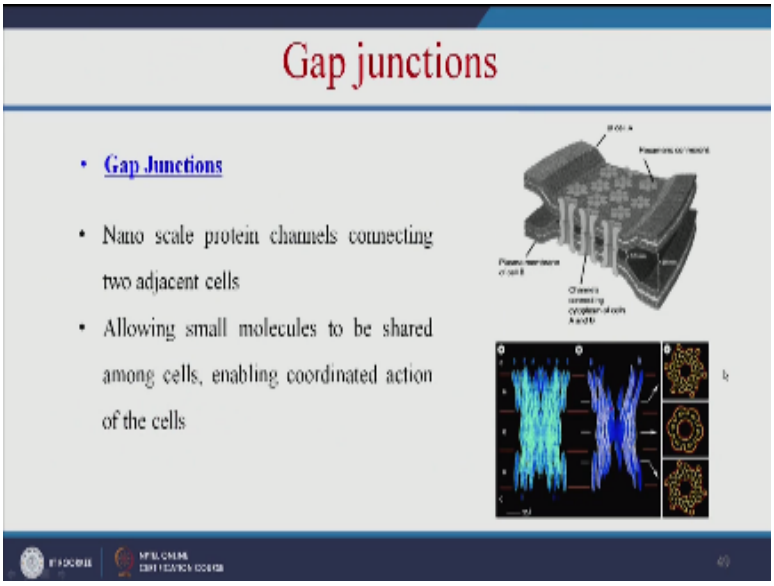

So let us see the direct access that is your gap junctions so all the cells are connected and there is a nano scale protein channels between the two adjacent cells, so it will allow the small molecules to be shared among the cells and it will make the coordinated action of the cells, okay.

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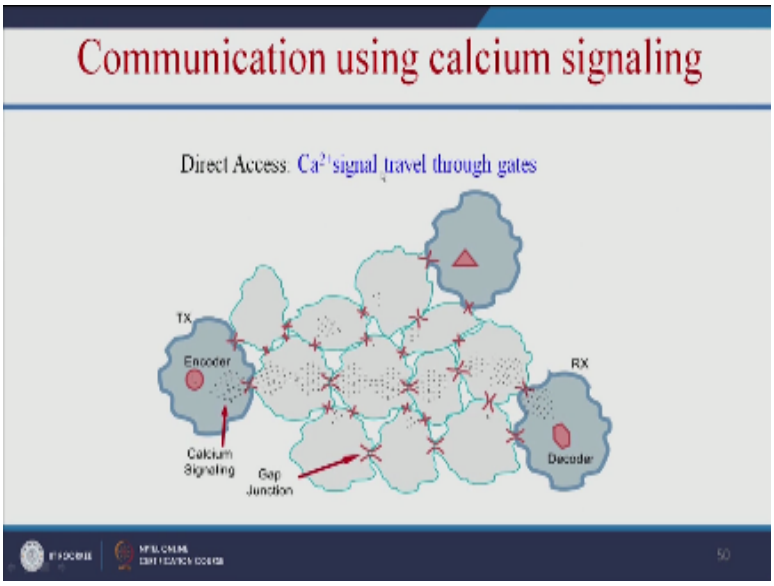

So in direct access the calcium signal travel through the gates that is your gap junction from here then information it will go to the decoder receiver through the gap junction of the cells, okay this is the direct access example.

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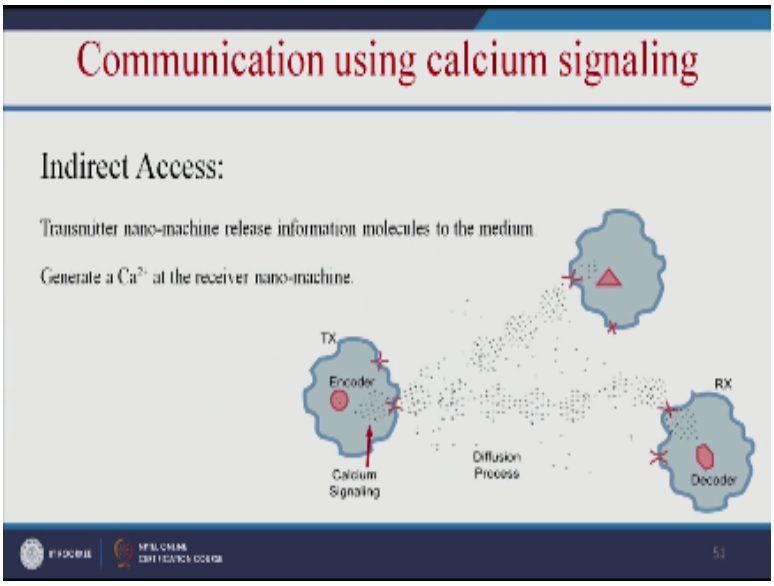

Next one is indirect access here the nano machine release the information molecules to the medium so the calcium molecules can go to the receiver which is little far away okay, and the receiver will receive the information and it will perform the task according to the information.

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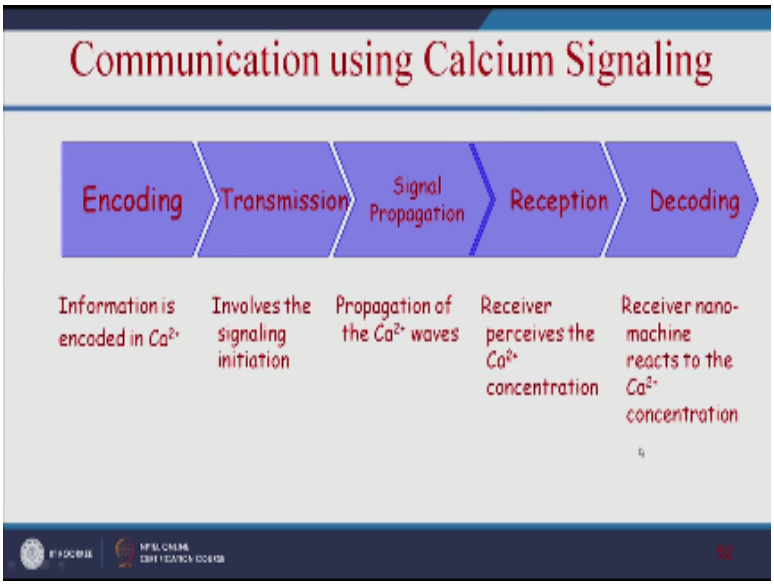

So here the information is encoded in calcium, and it involves the signaling initiation and also it propagate the calcium waves and receiver receive the calcium concentration so according to the calcium concentration the receiver perform the task.

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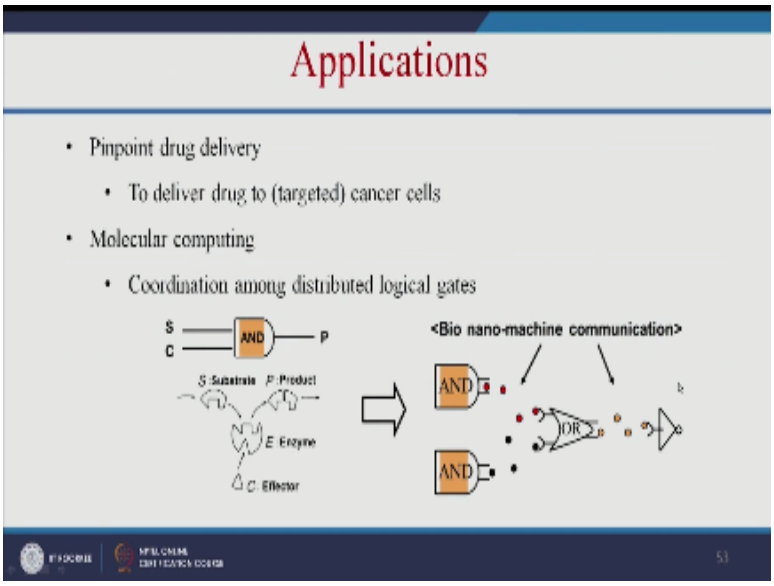

So what is the main application of this we can have the pin point drug delivery we can deliver the drug to the targeted cancer cells very specifically so as I told you earlier if both substrate and effectors is the then only it will form the product.

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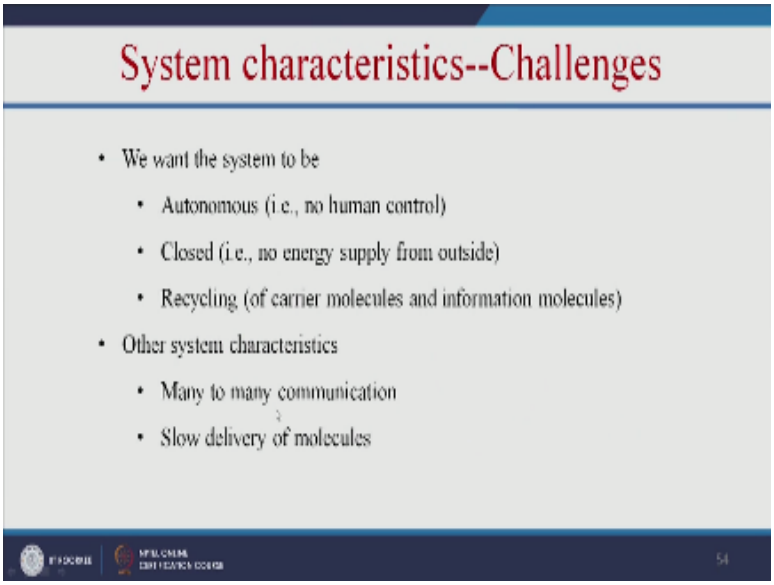

But still lot of challenges needs to be addressed because we want the system to be autonomous we do not want any human control and we want the system to be close that means no energy supply from outside and we also want the recycling of the carrier in molecules and again we want slow and sustain delivery of drug molecules, so as a summary of this lecture we have learnt what is DNA based nano machine and protein based nano machine and we have also learnt nano scale communication and this field need a lot of research to explore the potential application of nano machines in various fields, okay.

So I will end my lecture here thank you all for listening this lecture I will see you in another interesting lecture.

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