Bio-Microelectromechanical Systems

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Lecture No. # 01

Introduction to BioMEMS and Microsystems

Good afternoon. I am Shantanu Bhattacharya and I will be your instructor for this course on the introduction to BioMEMS and Microsystems. Let me introduce a little bit of what BioMEMS really is. BioMEMS is also in other words called Bio-Microelectromechanical systems. It is really about things which do very useful and important things; at a scale which is micro or sub micro in the regime. I would like to discuss today a few basics or few introductory concepts which are important for understanding this course more properly. Let us have a look at what by definition, Micro/Nano-systems can do.

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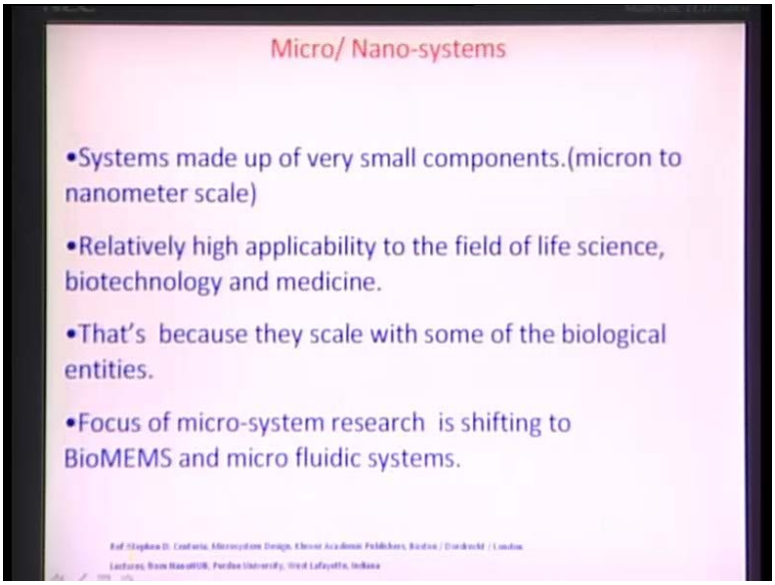

They are really systems made up of very small components microns or nanometer in scale (Refer Slide Time: 01:00). They have a relative high applicability to the field of life sciences, biotechnology and medicine which has really started more with you know the advent of things

called lab on chip technology as I will be describing later throughout the course and essentially, one of the reasons why these components rhyme so well with life sciences based detection and diagnostics, or biotechnology and medicine applications is because, they really size with, similarly to some of the biological entities and as of late, the focus of such micro system research is gradually shifting to micro fluidic systems.

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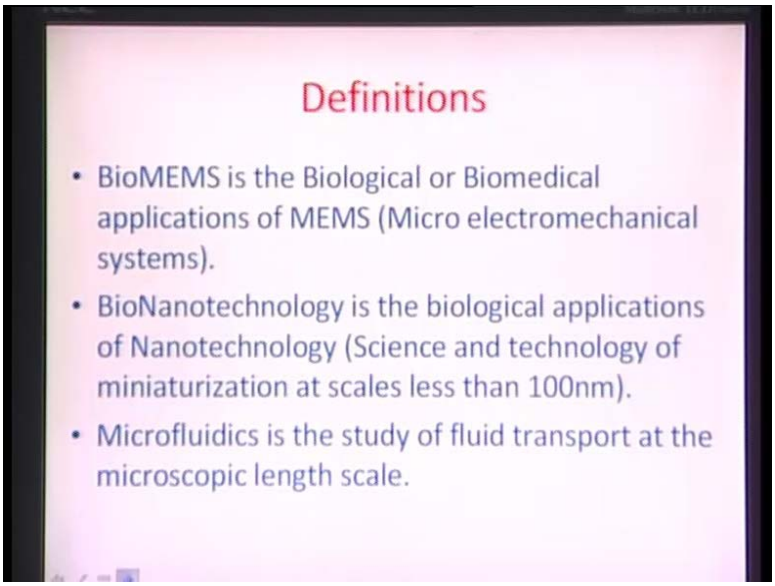

Let us understand little more of what by definition BioMEMS can be laid out as. BioMEMS really is the biological or biomedical application of MEMS technology and there are few more important terms that I would like to discuss (Refer Slide Time: 02:00) before starting. One is BioNanotechnology which is the biological application of nanotechnology, science and technology at the scale less than 100 nanometers is really what nanotechnology is and if we combine that to biological concepts, then it is also known as BioNanotechnology. Micro fluidics as we will be seeing later on throughout our module is the study of fluid transport at microscopic length scale. These concepts are really all very integrated, important to understand the utility or the essence of BioMEMS.

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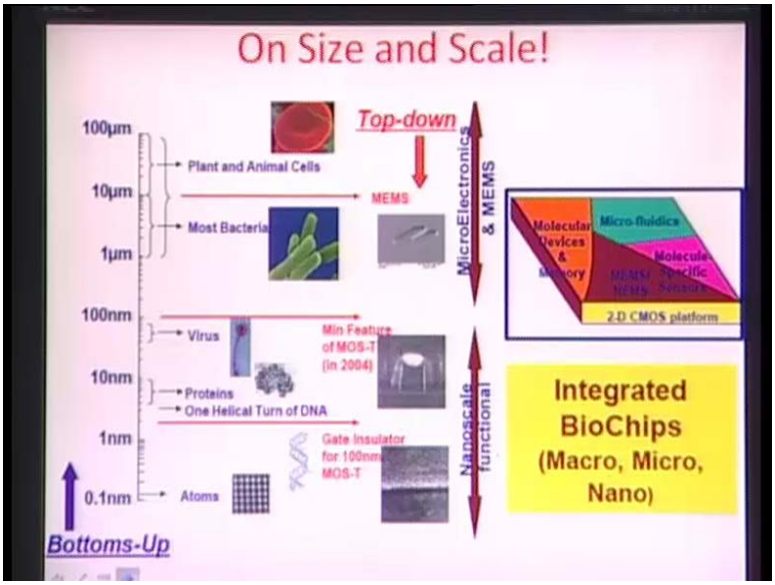

Let us have a little more diagrammatic representation on what are the sizes and scales that I have been talking about. So if you really look at this scale here, the scale here (Refer Slide Time: 02:45) on the left, on your left starts from 0 point 1 nanometers all the way to about 100 microns and let me be a little more specific on what 100 microns would really look like. Human hair diameter typically (Refer Slide Time: 03:00) is that of about 100 micrometers. So that is how small it is and point 1 nanometers is several thousands of that dimension actually. So you are dividing that or splitting that into almost about 10,000 times in order to achieve something like point 1 nanometers.

Now, if you look at some of these entities here as can be represented just very next to the scale, most of the plant and animal cells and this right here (Refer Slide Time: 03:31) is actually red blood cell. There are millions of such cells within the human body; this is shaped something like a button and they rhyme in the range of about 100 to 10 microns. In fact, the red blood cell, the same image of which is represented here, is about of 20 microns or so.

If you go a little bit down this cell for example, this here is E. coli, the assumed image of E. coli bacteria.(Refer Slide Time: 04:00) Most bacterial cells rhyme in the range of about 1 to 10 microns; so they are at least a tenth smaller than the millions as the plant and animal cells. Let us go a little bit down further here, this right here, (Refer Slide Time: 04:15) is actually a virus

which is essentially nothing but a coat of a capsid made up of proteins and enclosing some genomic information. Typically the sizes of these viruses are of the order of a few 100 nanometers. If you go a little bit further down we have molecules like let us say proteins or DNA and here, something very interesting; DNA is nothing but a twisted ladder. So you take a ladder and kind of twist it, and one helical turn of a DNA is something like about 2 to 3 nanometers; about 20-30 armstrongs and if you go a little bit down further, you have atoms and molecules and this really is an approach which is also known as the Bottoms-up approach or bottom up means of manufacturing. Somehow, we can illustrate this as if mother nature has been making these higher forms from these lower ones which are principally atoms, by using concepts of self assembly and energy driven mechanics and so on so forth.

If you look at the figures from the right here (Refer Slide Time: 05:17) really they are things which are actually made using the top-down approach which means you have a much bigger size wafer or platform and you are trying to reduce it through micro machining or technologies which we together know as micro technology. I am trying to make smaller and smaller sizes in the way. So, if you look at this figure here, this illustrates actually nothing but a micro cantilever. I call it something like diving board in a swimming pool. As if there is a pool and there is a kind of you know board which is sticking out and the only difference here is that this board is about 200 to 300 nanometers thick and they are projected about 10 to 50 microns ahead and so the scale is simply too very small.

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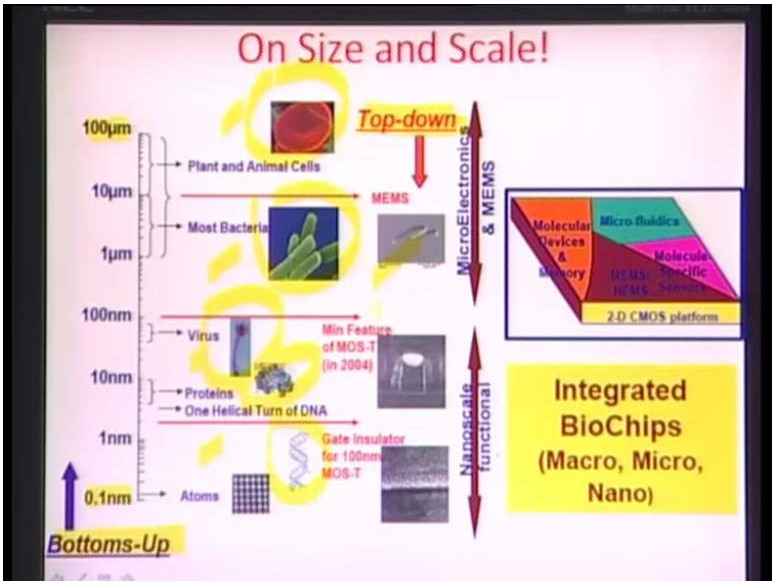

I go down a bit further; this right here (Refer Slide Time: 06:09) is a very interesting example. It is a polysilicon gate with nitride spacing. In fact, it is a commercially available device and so, if we look at the ITRS road map, the International Semiconductor Technology Road map, it mentions that by the year 2004 actually which was about three to four years back, the transistor the minimum feature size on a transistor was close to about 100 nanometers and it has even reduced now further. For such a device, the gate insulator which is actually something like you know a packing between the…, it is like the dielectric material between the metal contact and the actual device; that insulator is about 2 to 3 nanometers.

So, why I am showing you all this is that if you really compare these features and objects on a size scale, (Refer Slide Time: 07:00) they very well rhyme with each other. Like for an example, as I told you virus is about few 100 nanometers and you can really with micro and nanotechnology produce features like a polysilicon gate which is of the same range. Molecules are even little bit further down and that rhymes very well with this gate insulator. So, this size comparison kind of allows us the luxury of bringing these two worlds close together so that, there can be accurate sensing detection diagnostics, so on and so forth. So, that is why BioMEMS and if you look at some of these kind of modules or you know figures here (Refer Slide Time: 07:43), this represents the basic schematic of how this MEMS can be laid out on a simple let us say 2 DC MOS platform so it is combination of different concepts like molecular

devices and memory, MEMS and NEMS technology, micro fluidics systems (Refer Slide Time: 08:00) and then the microelectronics. You combine everything together to form something which can sense or diagnose these life size entities very sensitively and accurately in this area of BioMEMS and so because of that, you can develop these kind of approaches and call them integrated biochips at the micro, macro and nano scale and this could be very useful as we will see throughout the lectures later how there can be various applications of such architectures or such technologies. So, one thing very important to mention here is that because these life type of entities tend to be happy within fluidic environments, therefore, for their accurate diagnostic or detection it is very important for the entities to be in actual fluids.

We should prepare fluidics in a manner which can again rhyme very well with their sizes so that we can have concepts like you know, single cell by single cell transfer or trying to isolate you know, molecules on a plate or a surface. Therefore, the concept of micro nano fluidics emerges from there; so these are all really integrated together and it is very important for understanding. It is simple intuitive engineering design I would say, for doing something with more precision, rapidity, accuracy, so on and so forth.

I really put this whole field as it is a synergistic learning experience between the area of micro nanotechnology and systems and biology and biomedicine and you know really, these technologies or these systems are bio inspired in the sense that there is a to and fro learning between biology and this technique.

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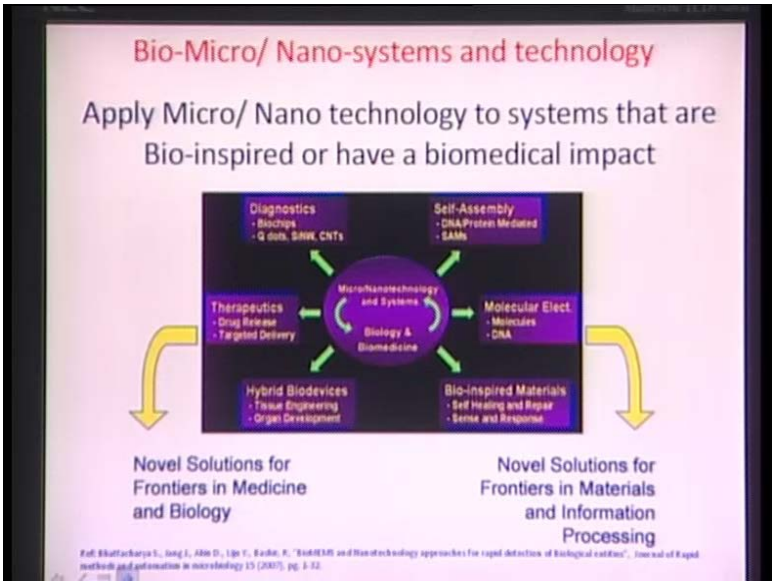

If you look at this figure here, it more clearly illustrates this idea. So here (Refer Slide Time: 09:52) if you see, the circle in the centre here represents these two areas of micro nanotechnology and systems and biology and bio medicine and if you see there are these two arrows (Refer Slide Time: 10:02) on both sides where they are showing what can be learnt from what. So, if you look at the boxes on the left like diagnostics, biochips, quantum dots, silicon nano wires, carbon nano tubes, these are really some of the technologies that we can apply to biology and bio medicine and we can learn from the micro nanotechnology and systems.

Similarly, you have areas like therapeutics, drug release targeted deliveries. Now a days, there is a huge impetus of how microscopic quantities or miniscule quantities of drugs can be injected. How do you do that? You have a very good learning experience from micro nanotechnology and systems and try to realize dimensions and features in a manner that this is doable; the miniaturized fluid delivery is doable. Another very interesting area is this hybrid bio device. Now a days, there are these whole initiatives of tissue engineering. You can develop something like an artificial heart or artificial kidney or an artificial liver (Refer Slide Time: 10:59). So, essentially this is nothing but an approach where you try to utilize some of the learning experiences from micro nanotechnology and system and apply it directly to make artificial organs. The boxes here on the right (Refer Slide Time: 11:15) are actually reverse process of learning. That means, they are based on concepts where learning is borrowed from biology and

biomedicine and applied on to micro nanotechnology and systems and you can see some of the examples as this self assembly; DNA or protein mediator. I will be describing little bit details later what the DNA structure looks like or how it actually self assembles.

The DNA is a unique kind of entity which is able to kind of pack together in a certain shape or feature or pattern. It really gives us a lot of inspiration or lot of learning. So, from the zeal or vigor with which the two strands of the DNA which are complimentary (Refer Slide Time: 12:00) to each other and self assemble and stitch on each other's base pairs, we could have a lot of learning which we can apply to really micro and nanotechnology. So, self assembled mono layers as a matter of fact, are another area where you know from just basic elemental chemistry we could make micro nano patterns or features or heaps of these molecules over the different parts of the surface and that could realize micro nano domain or micro nano features from learning borrowed from biology and bio medicine

Similarly, now the very fascinating area is this molecular electronics (Refer Slide Time: 12:37) where we talk about a single molecule being able to conduct current between two posts which are placed one molecular apart or may be, a single DNA and there is lot of interesting work in this area. We say, if you have DNA as a wire which is connecting between two posts and just simply use it as just a you know, (Refer Slide Time: 13:00) the resistive circuit, it just follows V equal to IR relationship. However, in this case, you know as the GC content or the guanine-cytosine content of the DNA is increased, you see that there is a change in conductivity, so on and so forth.

So, there is a huge effort of using some of these entities towards transferring charges very sensitively at a very small scale and this could be immensely contributing to the field of micro nanotechnology. Similarly, human skin: it is a very interesting example. I mean, we call it bio inspired material. Just think about how important the human skin is. What kind of properties does it have? it can self feel, it can respond, it can do all sorts of self repairing kind of things automatically and if we really want to replicate something like human skin that would be a fascinating essay of micro nanotechnology where probably, millions of sensors are packed on to the surface (Refer Slide Time: 14:00) and each of these sensors does a different job.

So, I really call these areas that the inspirational learning from micro nanotechnology to biology and biomedicine would be able to develop novel solutions for some of the frontiers and medicine in biology and similarly, the learning experience that we have from biology and bio medicine would be able to develop some novel solutions for frontiers and material information processing. So, it is really a synergism which exists between these two areas and therefore, it is also in the best interest to integrate the area of bio with this micro nano systems. Thus, these terminologies that we have been describing like BioMEMS, bio nanotechnologies etcetera, automatically self emerge because of these mechanisms.

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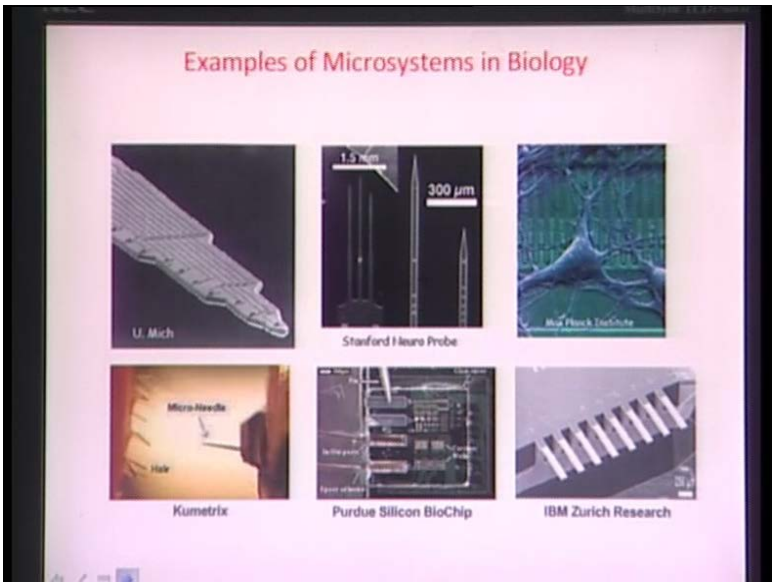

Let us see what can this kind of micro systems really do in biology and this is a slide (Refer Slide Time: 14:51) which I really keep on illustrating time and again. It gives an essence of what kind of applications are really available and some of them (Refer Slide Time: 15:00) mind you, are really commercially available applications as I will be illustrating. So, this here as you see is nothing but a neuro probe (Refer Slide Time: 15:08). It is developed by Dr. Weiss's group at the University of the Michigan and Arbor. Essentially, if you see, this is again a very fine example of micro nanotechnology wherein, this particular feature is probably the size of just a few microns and there are as you see here, small wires which are printed by lithographic processes on to such a probe. This probe is used for monitoring the electrical activity of brain cells or brain tissues.

Now, why micro technology is required is that, if you think about a neuro surgeon who is actually just operating on somebody's cranium portion and he wants to inject a big tool which can do electrical response monitoring. It is not a very feasible option, you know. The patient would suffer a lot of pain. There would be general tendency of unnecessary damage which may have a long consequence in terms of patient's post surgical health and lot of other issues are considered. Now, if instead of that you replace the whole electrical sensing tip with a very small micro-needle which can just go into a very small area of the cranium and do the same job as a big tip would be doing. Then, that gives really the utility or essence of such a technology.

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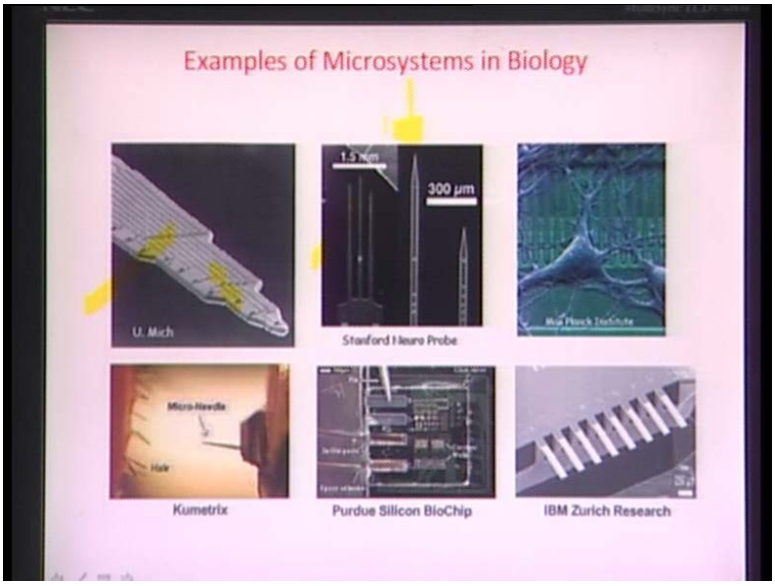

This again is a very fine example. It is basically a very long, slender like probe, neuro probe developed at Stanford and is used for giving deep electrical stimulation especially to patients suffering from Parkinson disease. This area again is a very fascinating area and I call it probably the future in the area of BioMEMS or biotechnology. This is essentially a set of neuron cells which are growing on an array of MOSFETs. You can see these here (Refer Slide Time: 17:13) are the cells and they are growing on a set of MOS transistors. This area is also known as nanobiology. Now, think about the signaling between these cells and I would go into a little bit of details of the biology later as we go along this area. Essentially, these cells grow in a very unique manner; there is lot of signaling path way between the two, which would certify or signify the behavior of such cells. So, if we can study uniquely on a single cell basis, what are

those signaling path ways in terms of may be exchange of ions or chemicals between these two cells. This is of immense utility in general, understanding life processes as such. So, there is a huge initiative now on how to study these cells on a single cell basis and try to illustrate what kind of chemical reactions on the surface or within the cells is going on and what kind of communication is going on between such cells which would relate to their behavior in general. Again, this is a very good example that you know I almost always keep on mentioning. This is a Micro-Needle (Refer Slide Time: 18:27) and this comes from very common life experience. The needle of a mosquito, essentially when a mosquito bites you do not really feel the pain. What happens is that as the needle goes into the skin, the needle of mosquito goes into your skin, there is a post injection swelling which comes up. That swelling is not because of any you know pain effects or any effects because of the needle pricking. That is essentially because, when the mosquito actually tries to draw blood it releases some enzymes which kind of tries to thin the blood sample and so it becomes very easy for it to withdraw the blood sample in this manner. But, again the fact is when the needle goes into the skin, it hardly makes any difference to the skin. You do not feel any pain and the reason why the pain is really felt in the human skin is because, there are, if you look at the skin really beyond you know about let us say, 100 microns of a layer of dead cells which we also know as the epithelium, there is a set of receptors called pain receptors which are nerve endings essentially and the mosquito's needle is so thin that it goes into this 100 micron and goes very close to that region of pain receptors; but, it is hardly able to deflect or damage some of these receptors. So, there is no pain sensation and the mosquito does its job; it goes into one of the vasculatures, picks up blood samples and then it kind of feeds itself on that basis (Refer Slide Time: 20:10).

The same principle has been used, borrowing this inspiration from the biology and bio medicine to make what you call micro-needles. This right here, (Refer Slide Time: 20:20) is an illustration of what a micro-needle really means. If you look at this needle, it is something close in dimension to that of mosquito and there is in fact a commercial company called Kumetrix which sells thousands of these needles on something like a patch which you really wind around the patient's hands and it can do things like you know parallel processing including monitoring of analytes inside the blood sample, drawing of samples from time to time etcetera. So it is a fascinating example of what micro nanotechnology can do by replicating biology or getting bio inspired and do something useful and important.

This again is a very interesting and fascinating example of what we call biochip or lab on chips (Refer Slide Time: 21:00). I am going to come to it in just about a minute with more details about what bio chips really are. Essentially, these are protocols where whatever is possible within a laboratory is all miniaturized down to single chip scale. In terms of handling very small droplets or micro liters of fluidic volumes, you quickly and rapidly do whatever a laboratory does on a much bigger scale. So, this is also known as lab on a chip or bio chip and a lot of research where in integration of electronics optics lot of different transaction techniques are taking place into densely integrated platform which is also known as biochip or you know, lab on a chip kind of mechanism.

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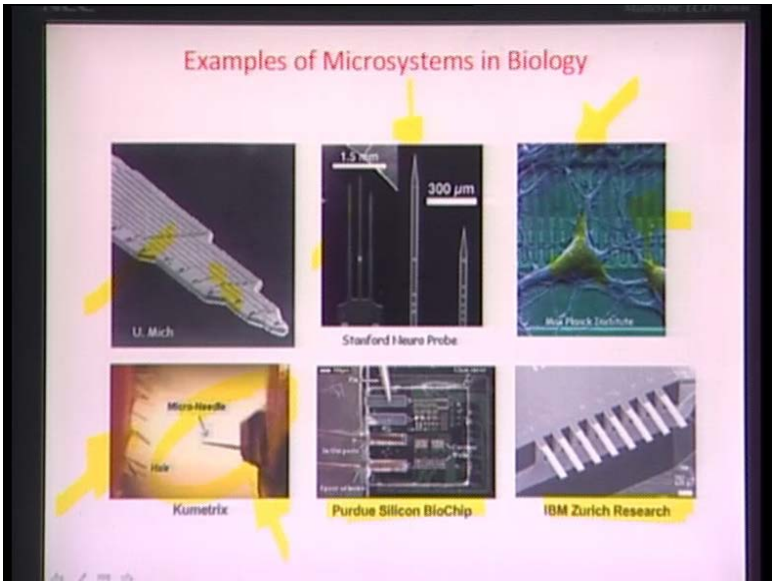

This again is a very fantastic example of what micro nanotechnology can do in biology. These here are those diving-board-in-a-swimming-pool kind of structures as these are micro cantilevers (Refer Slide Time: 22:12). The scale here if you see is only 250 microns which means that they are projected about let us say about three times that size, about 750 microns but if you look at their thicknesses really, they are about a tenth which is about let us say about 300 nanometers or so. Interestingly, there are several of these uniquely positioned and spaced small cantilever devices available to this edge of this particular let us say, piece of material which can be silicon (Refer Slide Time: 22:43).

What it essentially does is, it is nothing but a mass detector. So, if you are able to somehow immobilize some cells or some molecules on the top of this particular structure (Refer Slide Time: 23:00) of cantilevers, due to the weight that is somehow immobilized on to the top, there is a deflection and bending. From the deflection and bending, you could back calculate by using an equation called the Stoney's equation. I will be doing details of these a little bit later, the mass of the particular entity. However, the advantage here is that, because of the small size of these cantilevers, the resolution up to which you can really pick up masses go up to the order of about femto grams - pico to femto grams and that is what gives the uniqueness of applications of micro systems in biology.

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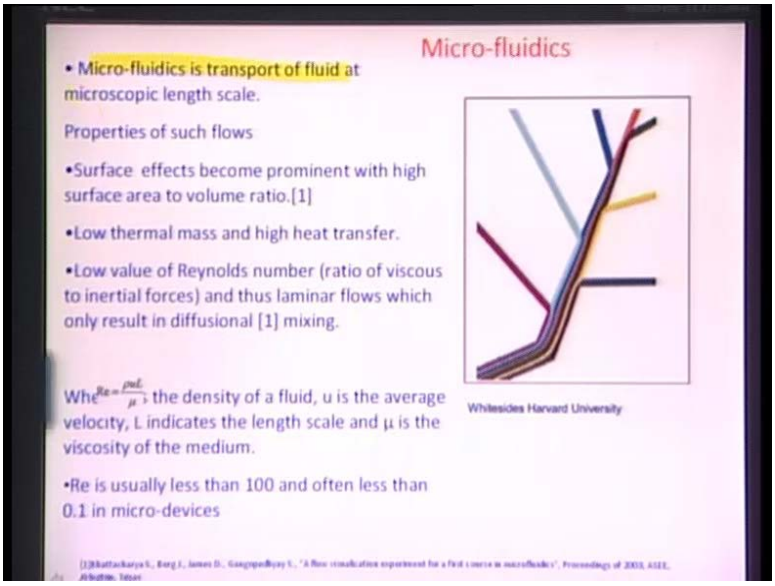

So, we have been discussing earlier about micro fluidics and we have been really learning it as important because we are talking about biological entities and typically all biological entities are happy when they are in fluidic environments. But, it is very interesting that you know the behavior of fluidics at this particular scale, the microns scale, really is very counter intuitive to any person who is trained in the macroscopic fluid behavior in any engineering curriculum. As I earlier indicated, that the definition of micro fluidics really is a transport of fluid at the microscopic length scale and there are some unique properties and changes which happen because of the scale change (Refer Slide Time: 24:20).

One of the properties which is very important to mention is, that the surface effects become prominent with high surface area to volume ratio and if you look at, dimensionally if you just compare the surface area to the volume, it can be represented as L square by L cube, right? which is about l0 to the power of minus 1. So, if this L is going to the micron level micro meter level which is nothing but about 10 to the power of minus 6 meters you can just think about that.

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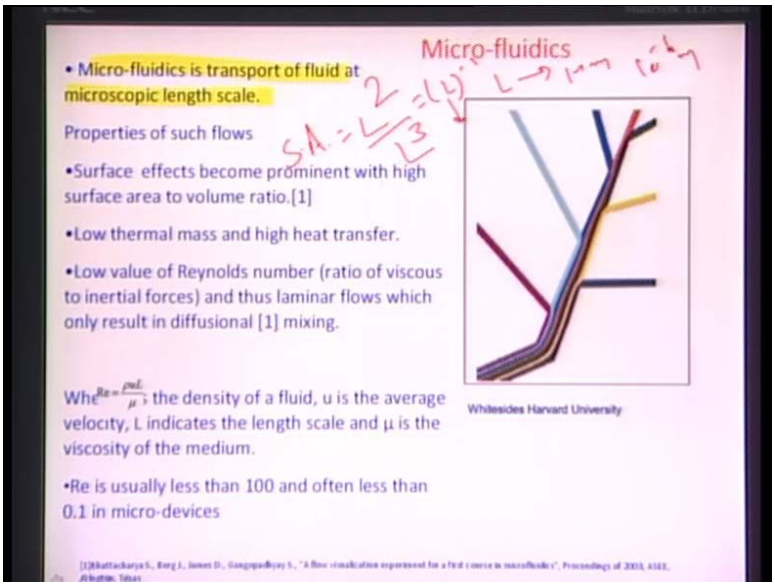

You know the surface area becomes so much more prominent with respect to the volume. It becomes about 10 to the power of 6 times more prominent with respect to the volume. So, you have some forces or some effects which are related more toward the surface; they gain much more in prominence in comparison to the volume forces. In case of fluid volume forces, it could be something like, you know inertia. It could be something like just acceleration due to gravity of a small fluid mass and these are also packed together as inertial effects essentially. You know the pressure driven aspect of flow which is concerned with the mass of the fluid flow. Surface area on the other hand, is something where there could be forces of surface tension which is just related to what is the length you know of interface of fluid with respect to some other particular boundary or may be viscous forces where surface area becomes more prominent. So, as the surface area related activities or events become prominent in this case therefore, the viscous forces or surface tension related forces are much more into question and these are critical

parameters for designing such devices over the general macroscopic idea or designing devices on the basis of volume based flows.

Another very interesting effect here is, because of the lower thermal mass and high heat transfer, we are talking about a miniaturized droplet size in terms of few micro liters of volume and therefore, it is very easy to probably conclude that it has a very low thermal mass that is number one (Refer Slide Time: 26:40). Essentially, because of this low thermal mass, there would be a high heat transfer. There are initiatives inside micro fluidic devices wherein, some of these fluids are tried to make into a thin layer on the surface. If you look at that, instead of making a thick layer more volume based, you are making more surface based and thinner layer. How you make that is again what BioMEMS tells you; BioMEMS technology, BioMEMS fabrication technology tells you. Essentially, you are taking the whole fluid over a huge surface and therefore, trying to increase the heat transfer value.

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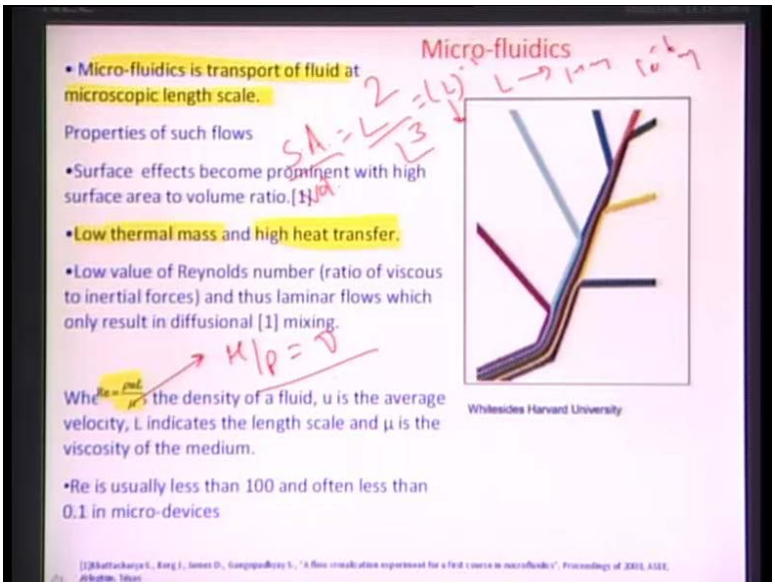

Another very interesting factor is the low Reynolds number. Reynolds number as we all know, is the ratio of viscous and inertial forces and essentially, you can also represent it as rho u l by mu as you can see here (Refer Slide Time: 27:31). rho is the density of the fluid which is flowing, u is the velocity, l is the corresponding length scale and mu is essentially the viscosity of the

medium. Also, you can actually make this into mu by rho and make this dynamic viscosity of the material.

Now, low Reynolds number really, is typically, at certain domain of micro fluidics you know, there are lot of changes because of this low Reynolds number value. The number one change which happens is, we can consider this as let us say, a pack of cars. You have about hundreds of cars which are moving in a very small street which is you know may be in peak traffic hour in our city here. What would happen? What do you think could happen if such a situation happens? The cars would try to move in an aligned manner; in more like streamlined fashion, without really much crisscross because, you are packing a lot of cars together. Number one, the velocity of the car would also go down and then even if we assume that there is a high velocity, there is always a tendency of cars to move one beneath or one behind another. There would be hardly any people who are trying to or who will be trying to act smart and change their lanes because, that essentially means a collision or a chaos or an accident. Therefore, if we just can compare a similar analogy in terms of molecules which we are compressing to a very small street or a very thin area. These molecules also tend to move in something called streamlines where in, they would move parallel to each other without many of them really venturing to go into each other's tracks and colliding with each other.

Therefore, the very unfortunate or may be in some situations fortunate, I will be illustrating later these with examples. The fact is that these molecules tend to remain in their own paths without really going across parallel tracks or paths. A situation where mixing becomes hardly; I mean, it becomes next to impossible until and unless as we see later, there are diffusive forces which let these molecules criss cross on the basis of concentration radiance between the two flows.

Just to illustrate this fact, I have, kind of borrowed an example from Whitesides group here (Refer Slide Time: 30:10) as you see and this is the simulation which talks about… there are a set of these 1, 2, 3, 4, 5, 6, around 6 dyes of different colors which are flowing or which are being flowed in a microscopic dimension and they go in this manner. There are several of these tracks which are emanating from different areas and as you see these fluids kind of go by together. There is a unique tendency of the color to get separated without getting mixed.

This red color which was injected here (Refer Slide Time: 30:42) is as it is retrieved after a while; this blue color is as it is retrieved after some while; similarly, this dark blue color is again retrieved after some while and the colors seldom mix. This is really a real time simulation and this is what happens in a micro scale also where you can see the fluids although flowing in parallel (Refer Slide Time:31:00) hardly tend to mix because of the low Reynolds number volume. So, just for illustration Re in BioMEMS devices Reynolds number in BioMEMS devices is usually less than about 100 and often or actually most often, they are less than about 0 point 1 or so.

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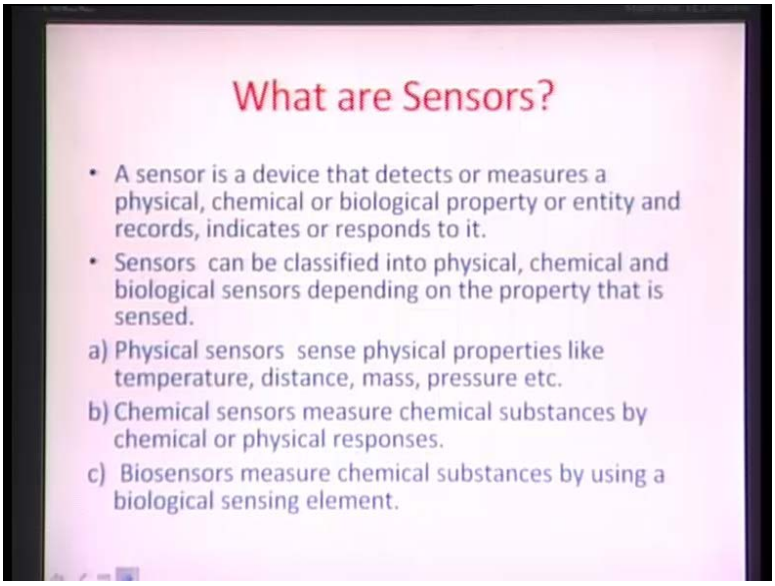

We will talk a little bit of sensors now because, this would be important for understanding sake. Essentially, the purpose of the BioMEMS device is to really sense something; sense or detect something with some degree of accuracy. So, by definition if we look at what sensors is, sensor really is a device that detects or measures a physical chemical or biological property or entity and records or indicates or responds to it. Essentially, it would be used for some kind of measurement.

Measurement could be of a physical property; something like temperature, distance, mass of an object, or pressure in a particular channel. These are all physical properties and therefore a sensor can be something which detects a physical property and those sensors are known as

physical sensors as is illustrated here (Refer Slide Time: 32:43). It could detect chemical properties and chemical substances where in things like may be the chemical nature of an analyte or you know the chemical or physical responses of a substance to an environment are recorded. These type of sensors also known as chemical sensors. Finally, we have biological sensors which monitor or measure the chemical substances using biological sensing elements. So, essentially there is always integration between what chemistry has to offer and what biology has to do. But, the idea is that you can classify some of those chemical sensors as biosensors if the detection elements are actually more like biological sensing elements. So, that is what biosensors would do (Refer Slide Time: 33:21).

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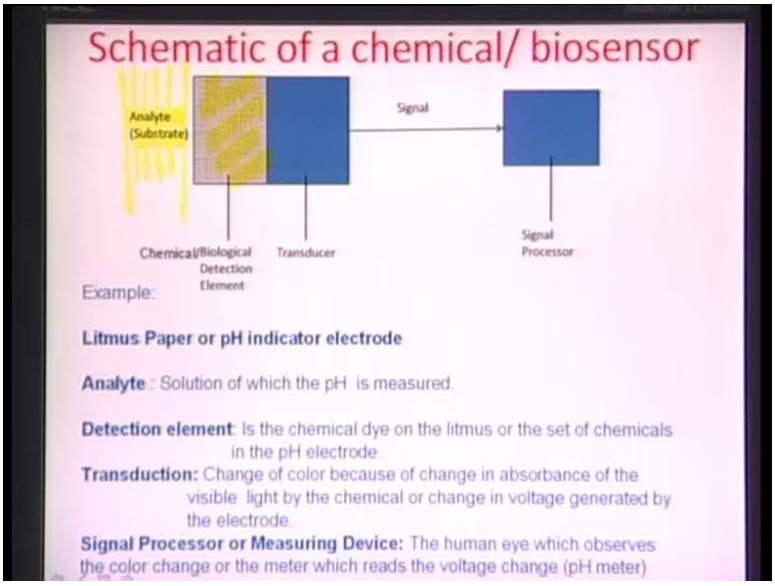

Schematically, we can really in a very organized manner represent a sensor as something which is going to detect this analyte or substrate which is present in this region and for detecting it you have something called a detection element which can be either chemical in nature or biological in nature and then the detection element has a change in property (Refer Slide Time: 33:45). It may be a change in chemical property; it may be change in optical property; it may be change in electrical property. Essentially, this element which is there for the detection purpose has a change in property in the presence of the analyte or the substrate of interest. It generates something called as signal and the signal can be further transduced by this particular element here (Refer Slide Time: 34:14) which is also an integral part of the sensor. What does transduction really

mean? Transduction is nothing but a change of signal from one form to another. If you have a chemical agent there it is going to change into a electric signal or an optical signal; this is called transduction.

Transduction is a change in signal of one kind to another. You have an element here on the biosensors as you see here (Refer Slide Time: 34:38) which does this transduction. Whatever signal is generated from the biological detection element or the chemical detection in the presence of the analyte or substrate, is transduced into a signal of some form. The signal is essentially fed into a processor which would be trying to read, analyze, interpret the signal and trying to conclude whether (Refer Slide Time: 34:58) there is an analyte of interest present or absent or in what quantities these analyte of interests are present. Together this thing can be defined as an organized schematic of what a chemical or a biosensor would do.

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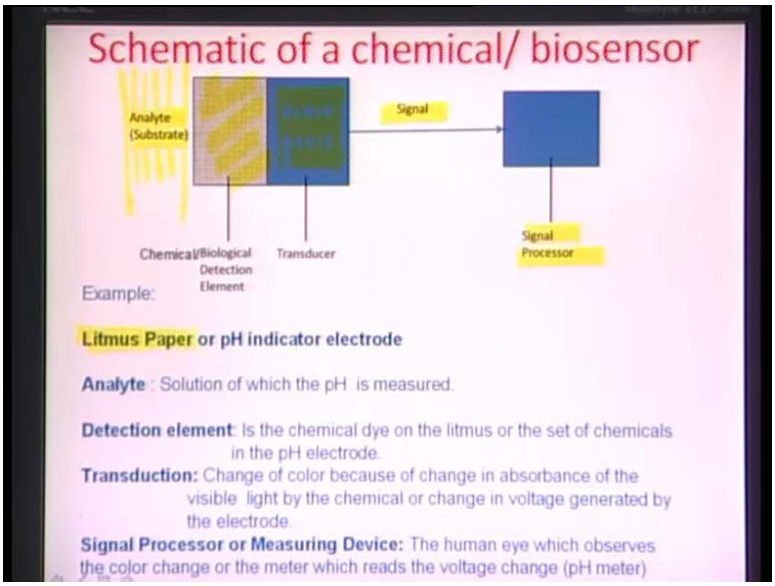

Let me give you an example. The laboratory level litmus paper is something that probably all of you have used in your school days and what essentially happens is that if you expose this paper to variety of phs that means, a variety of acidic or basic fluids, it changes its coloration. There is a change in the absorption wave length of light because of which you can find different colors appearing based on different phs. There are now commercially available litmus papers where there are range of colorations which are illustrated for even having a resolution of 1 point 0 ph

change. So, you can at all different phs get a different absorption spectrum and the color. This is the finest example of a sensor or may be something like a ph indicator electrode where you dip an electrode in a material and the electrode has a change in electrical property which is signifying what does the hydrogen ion concentration of a particular medium.

So, these are examples of sensors - chemical sensors. Let us try to illustrate this simple litmus paper or ph indicator electrode as a sensor model. You have an analyte which is a solution right in which the ph is to be measured. It can be a basic or acidic ph. You have a detection element and in case of a litmus paper it is a chemical dye and in case of ph electrode, there is a set of chemicals of course. This chemical dye what it does is, it does the transduction that means when it is exposed to an acid or a ph of certain you know kind it rapidly changes its absorption spectrum (Refer Slide Time: 36:55). Therefore, as we know as the absorption spectrum is changed there is change in coloration of a particular material; so it changes color.

The change in color is because of the chemical dye getting exposed to a certain level of hydrogen ions and have been calibrated in a manner that if you have x concentration you will have a different color; if you have y concentration, you have a different color and so there is a certain scale on which this can be mentioned in terms of a color scale. That is what the transduction element is and in case of the litmus paper, the human eye which observes this coloration changes is nothing but the signal processor (Refer Slide Time: 37:26).

It is the measuring device which tells you what color correspond to what ph by looking at a calibrated scale; which has been done before by somebody and which is mentioned in all these packs of litmus papers and you just compare the color through your eye to the color that is on the scale. That is essentially the signal processor. Similarly, if you look at the ph electrode, the set of chemicals inside the ph electrode is the detection element and the change in voltage which is generated by the electrode is essentially the ways and means of chemical to electrical transduction. So, what solution you are trying to gage, that solution is essentially measured by putting the electrode inside and there is a change in voltage or potential because of that. The transduction is from chemical that means, generated by the hydrogen ions in the particular solution of a particular ph to a voltage; so it is essentially a potentiometric sensor as we will study in little bit detail later on. The signal processor in this device is really a meter which can read what the change in the voltage is. That can be an electronic meter which can do that reading

and therefore you can also illustrate the electrode as an analyte which is the acid or the chemical of whose ph is to be measured; set of chemicals inside the ph electrode as the detection element and then the chemical to voltage change is the transduction process and the measuring device has the meter which eventually reads the voltage change (Refer Slide Time: 39:11).

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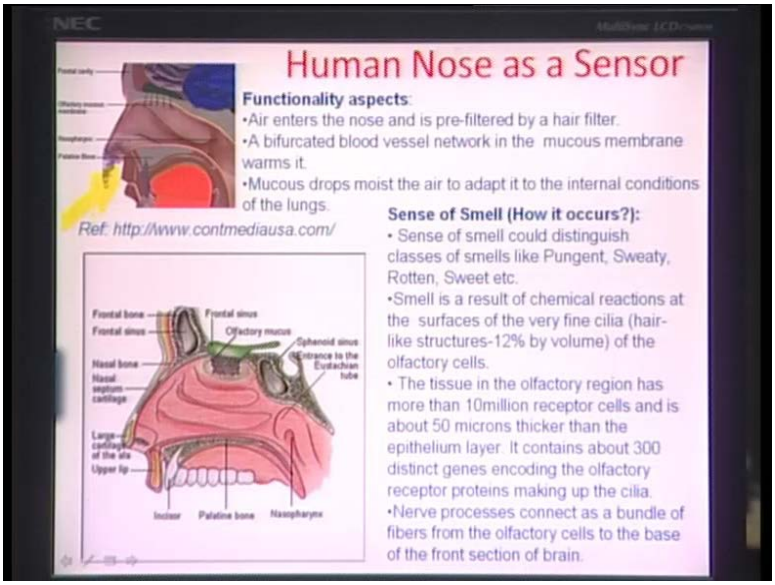

As we have been talking about sensors, let us actually look at some of the interesting senses that human body has. Human nose, as a matter of fact, is one of the most important sensors the human body has. In fact, our eyes can be illustrated as a sensor model. I would like to look at little bit into how a human nose functions; specially because it is a you know BioMEMS area and there is substantial amount of life sciences aspect in it one should know really how our body can be adjusted or how different senses of our body can be laid out as sensors. This is what the internal view of the nasal track look like in a human body (Refer Slide Time: 40:00) and let us first illustrate the functionality aspect; what do we really need the nose for? There is air which has oxygen which is an oxygen rich component and we have to intake this air for our survival. The first thing that this air has to do is to get pre-filtered. So, as it enters the nasal track here, there are set of these as you see here, in this region there are these hair like entities (Refer Slide Time: 40:39) which are able to kind of pre-filter whatever particulates the air has if for just cleaning it before entering the human body.

Once the air goes inside it actually touches set of bifurcated blood vessel network in this region also known as olfactory mucous region where there is a membrane which does two fold objectives (Refer Slide Time: 41:00). One is that it warms up the air which you have taken in and then it makes it little bit moistened so that it adjusts to the internal conditions of the lungs into which the air is directly sent in after passing through it. So it becomes warm and it becomes a little moist; that is how the nose operates. Now, the very interesting factor in the nose is what we know as the sense of smell. How does really the sense of smell occur? If you look at it, it is nothing but a signal transduction process and as we know that we can really classify something called smell into different classes: like pungent, sweaty, rotten, sweet, so on and so forth depending on whatever the ambient is and really if you look at what is going on smell is a result of thousands or actually millions of chemical reactions which take place at surfaces of very fine hair like moieties called cilia in this olfactory cells which are in this particular area or in this area as a matter of fact (Refer Slide Time: 42:12). There are these fine hair like cilia kind of moieties of the cell surface where thousands of chemical reactions are taking place by the input air that comes in which classifies the smell as pungent, sweaty, rotten, sweet, so on and so forth so essentially this hair like structure is about 12 percent by volume of the whole olfactory membrane. That is how small it is and this is kind of illustration, the smaller it is the better; it is the driving lesson from micro nanotechnology. Just to give you some fraction figures, the tissue in the olfactory region has more than 10 million receptor cells. Each have this hair like moieties and it is about 50 microns thick than the normal epithelium layer. The epithelium layer that we have in our body is about 100 microns; so the total thickness of this particular olfactory region is about 150 microns or so. It contains about 300 distinct genes which encode the olfactory receptor proteins which make up the cilia. The cilia that we are talking about where these thousands of chemical reactions are going on are made of some protein molecules and they are coded by about 300 different genes inside these olfactory cells and this is a self emerging process.

As there is some transduction of let us say some kind of reaction, a chemical reaction into an electronic impulse which goes through your bundle of nerves which are connected at the back end of olfactory cells like this (Refer Slide Time: 43:55) to your brain. It is an electronic impulse which is going because of this electro chemical process which is happening on the surface of the cilia and so basically, the protein that is changing its classification is continuously being updated or typed by the distinct genes which are available inside the cells. So, it is a continuous process.

There are new moieties every time where new reactions would take place and because of that new electrons would be generated and the electrons flow is the continuous process which goes to the brain and that classifies again based on the response that you get something as too pungent or too sweet or some rotten or sweaty kind of sensations; so there are some categories.

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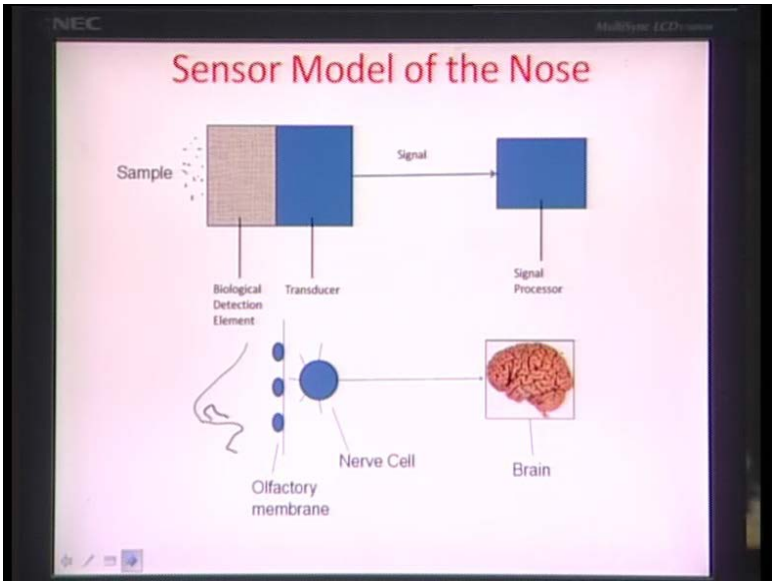

Therefore, if I really like to look at the human nose as a sensor model, it is containing a biological detection element which is working on a sample of interest here, which is nothing but the air sample. The biological detection element in our case is this olfactory membrane; this uniquely made or crafted tissue which gives you a transduction from chemical to electrical and electrical impulses taken by the nerve cell in forms of an electrical signal all the way to the microprocessor that we have in our body; the signal processor which is the brain in this case. Really, human nose can be categorized as an artificial sensor (Refer Slide Time: 45:28).

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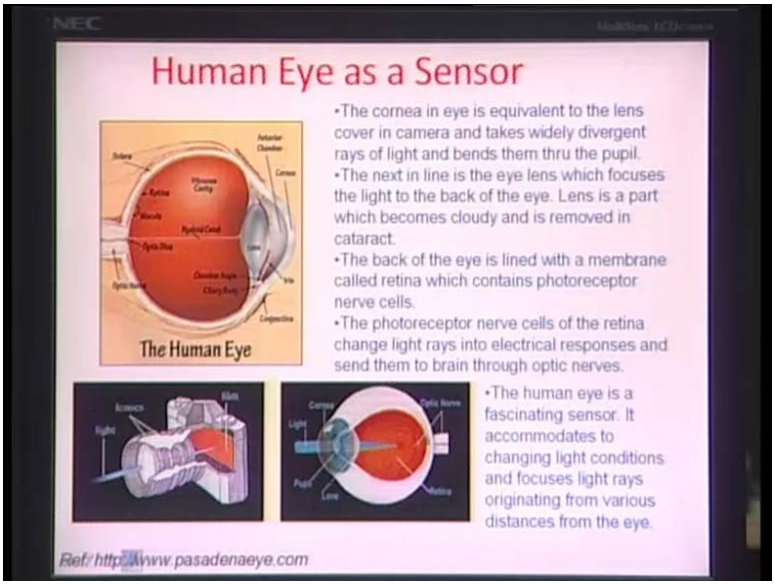

Let us look at eyes. Eyes are typically very important constituents of the human body which takes up light that is able to distinguish or identify between objects and this is how it works. The cornea in the eye can be illustrated in this particular figure here, is the equivalent to the lens cover of a camera (Refer Slide Time: 45:46). Let us try to provide an analogy between the cornea or the lens of the whole eye structure and a simple camera, an optical device.

The lens cover here (Refer Slide Time: 46:07) in this region is equivalent to something which we call the cornea and rays which come and strike the cornea kind of get bent through this region called the pupil region which is just immediately behind the cornea and the focus is on to the lens. The eye lens further focuses these rays into the back end of the eye which is this particular membrane here also known as the retina (Refer Slide Time: 46:33).

It is pretty much same as you have these lenses here as you see in the camera; you have a lens cover which is the cornea and these lenses focus the light ray into something called the film into which the response is recorded in terms of an optical signal. The back end of the eye is really the centre where the responses can be converted from optical into electrical and we will learn in little bit how that happens.

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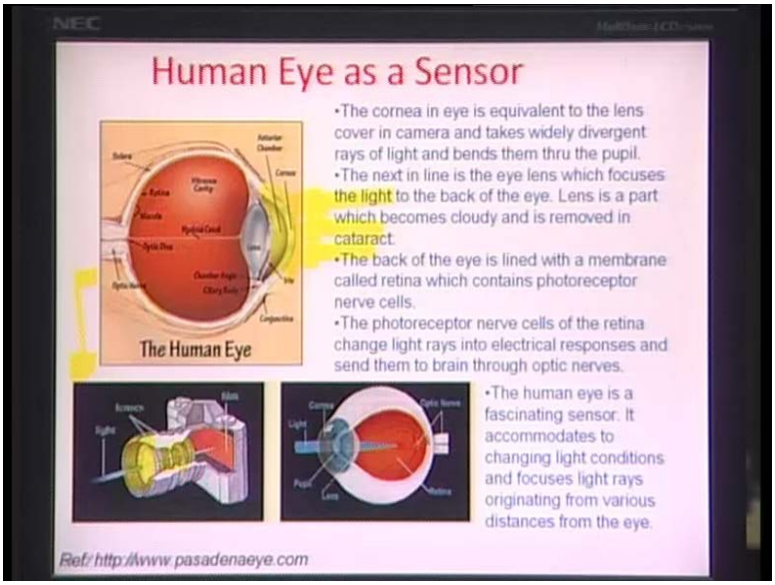

The photoreceptor nerve cells of the retina change light rays into electrical responses and send them to the brain through the optic nerves and there is an electro chemical transaction process which happens; there is a compound called cis-retinol which changes into its transform, giving an electron which goes into the brain and causes the sensation because of that. So, the human eye in a nutshell, is a fascinating sensor it accommodates to changing light conditions automatically there is a contraction or expansion in this receiving part of the eye due to which the light can be focused on to the retina. For light emanating from various distances placed close or far away from the eye, you have a different focusing aspect of the lens which can accurately focus it every time on to the retina irrespective of how far or how near the object is. It is again, an interesting sensor model.

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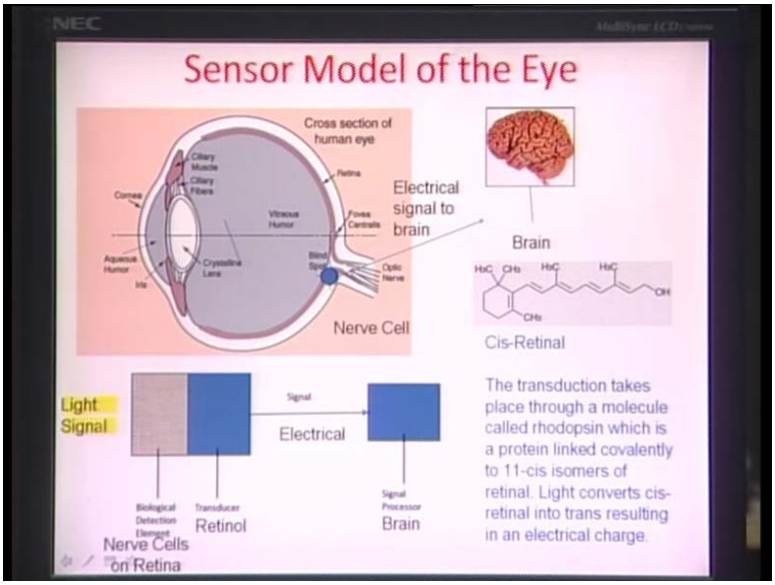

If we put this whole thing together as a sensor device, the analyte of interest here really is the light signal which we are trying to detect; the biological detection element here are the nerve cells on the retina as we have been talking about and the transducer here is the retinol which we are just coming to in a little bit. There is a conversion of the light really passing through this biological detection element into an electrical signal which goes through these optic nerves into the brain and thus the brain here is the signal processor and it detects and changes according to the response that it gets. What happens essentially in the transducer? Let us look at this molecular structure here called cis-retinol (Refer Slide Time: 49:00) illustrated here.

The transduction takes place again through a molecule called Rhodopsin which is an opsin protein and this is covalently linked to this compound called 11-cis isomer of retinal. Whenever light falls on it, the cis-retinal is converted into its transform. The cis converts into a trans retinal form which is a slight change in orientation; there is a changeover of a part of the molecule and what it generates is an extra electron. The electron is what causes sensation.

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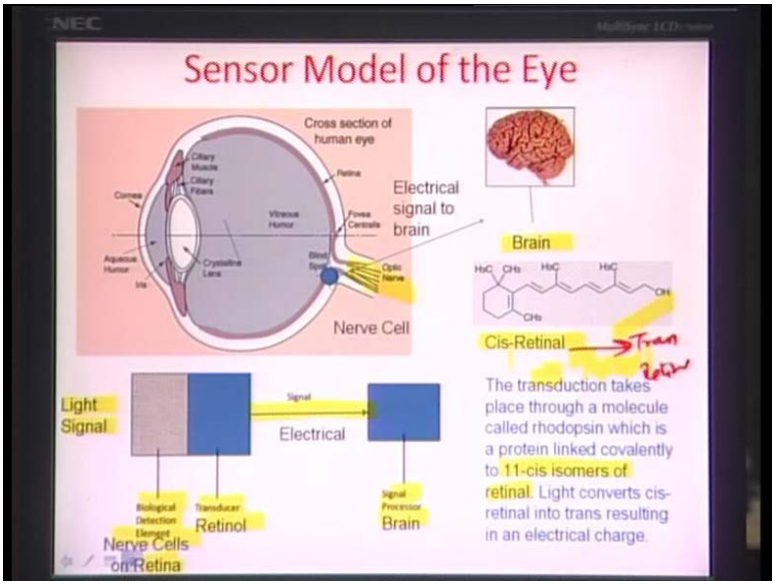

The whole retina is split up into millions of cells; each of which is essentially a work centre. There is a change in these compound retinal from cis to transform and that generates an impulse or a signal which is also known as light. Now, this light can be of various intensities based on how many electrons are really generated and goes into the optic nerve. So, human eye again is a fascinating sensor one can really think of.

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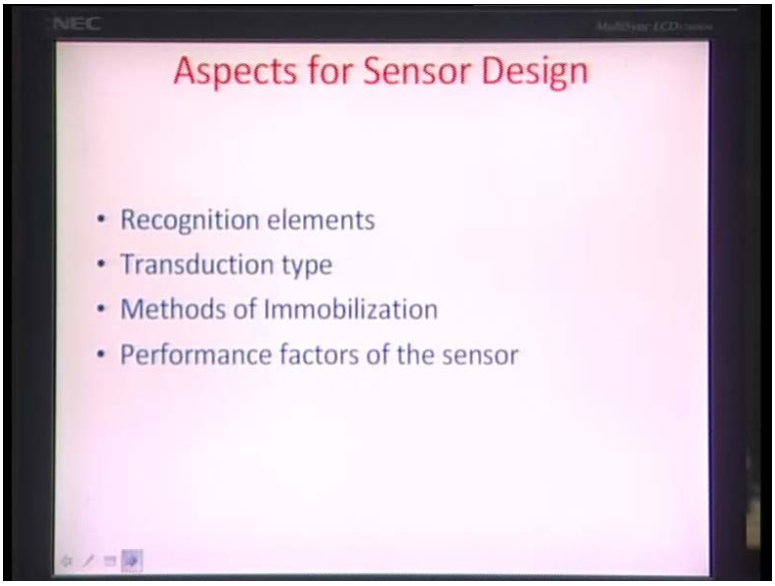

We look at the various aspects for sensor design and I would like to first illustrate this point very well because, again the purpose of the BioMEMS devices is really sensing or diagnosing some of the things or the analytes of interest. What all aspects go into sensor design? There are four different broad areas into which it can be categorized: One is, what is the recognition element really? Is it a biological element? Is it a physical element? What exactly is recognizing the analyte of interest or the object of interest which has to be sensed?

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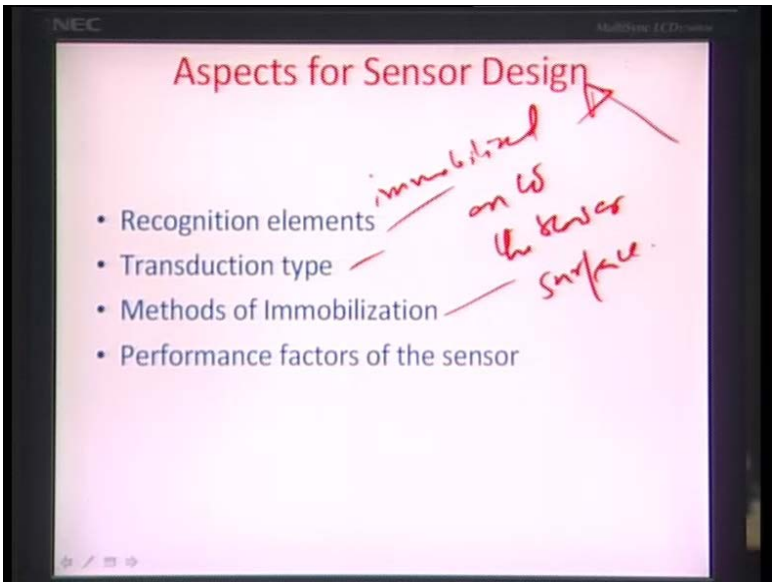

What exactly is the transduction type? Is it a chemical to electrical, is it a chemical to optical is it an electrochemical process? and then we have (Refer Slide Time:51:00) very important issue called methods of immobilization, which means that this recognition element has to be immobilized on to the sensor surface. There are different ways and means of doing that. That is another aspect when we consider sensor design and then finally we are left with this performance factors of the sensor wherein we gage how effective the sensor would be and is it really doing its job in the manner that it is supposed to or it is designed to do for.

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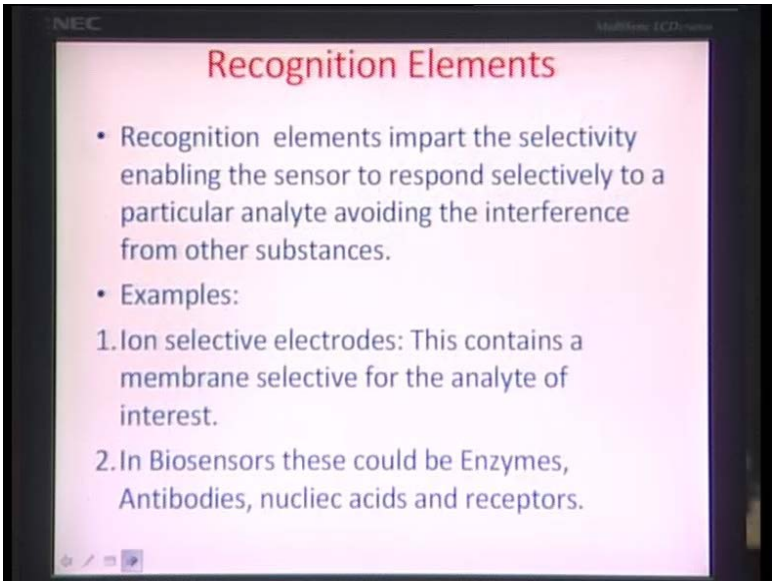

We will study these aspects one by one and go a little bit more into recognition elements. What really recognition elements are? Recognition elements as I told you as before, are elements which would impart the selectivity enabling the sensor to respond selectively to a particular analyte avoiding the interference from other substances (Refer Slide Time: 52:06).

If there are more than one analytes in a solution and you want to investigate a certain analyte over the others, the recognition element is something which would give the selectivity of measuring what you want to measure as opposed to the other 5 components, may be 6 components which are just present there. Therefore, some examples of this recognition element could be things like let us say, in ion selective electrode you have a membrane which is selective for the analyte of interest. So, there is a membrane which would pick and choose the particular ion of interest into the picture. That is what the recognition element would be or probably in biosensors these could be biological moieties like enzymes, antibodies, nucleic acids receptors etcetera. We will be studying this off and on in detail later.

Let us say for example, if it is glucose biosensor. There is an enzyme called glucose oxidase. In short form we call it GOD which converts glucose into gluconic acid and H_2O_2. So, here having a ph base sensor to monitor the increase in the hydrogen ion concentration, you will see that there is a steep increase because of the formation of H_2O_2 as the GOD catalyses the process and

converts gluconic acid. But, the recognition element there is nothing but that enzyme and so there is a very important aspect, what that element would be which can select a specific chemical of interest over the others. Therefore you know this as I was telling the recognition element is very important for any sensor. Let me give you an illustration of what some of these elements would look like.

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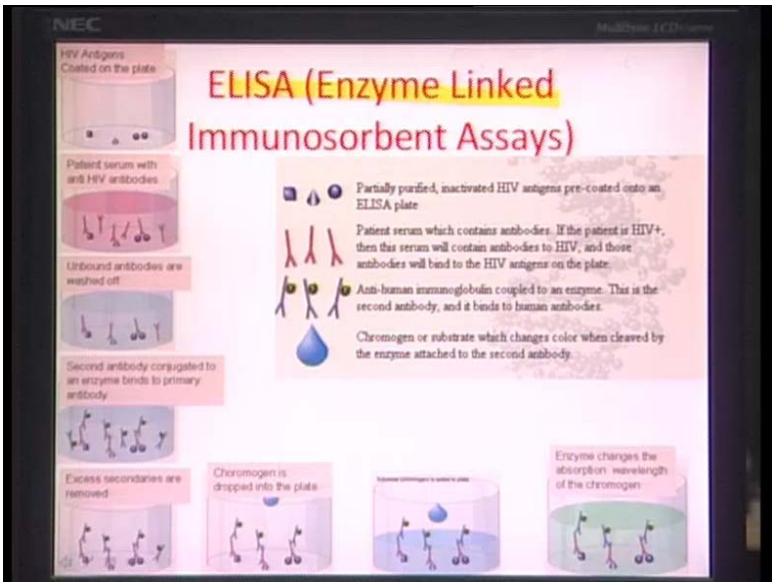

This is a diagnostics or a detection process known as ELISA which you also know as Enzyme Linked Immunosorbent Assays. Let us look at step by step what happens in such a mechanism or such a diagnostic protocol.

Here, it is essentially the play of an enzyme which cause a change in color or change in the absorption spectrum of the particular media which lets you know whether there is presence or absence of the antigen of interest inside or the analyte of interest inside the blood of the particular patient. If you look at the various steps here, you take something called a plate in which antigens and I will in a minute come to what antigens are. HIV antigens are immobilized. you see these particular you know these moieties which are present here (Refer Slide Time: 54:50), they are HIV antigens. So, antigens are a set of chemicals which come as a response of a pathogenic attack within the human body.

The first line of chemical generated inside the body is nothing but these antigens which show or signify the presence or absence of a particular attacking species which may be detrimental to the health or overall physiological setup of a particular being. There are these antigens which are coated on these particular plate here (Refer Slide Time: 55:27). We take the serum of the patient who is probably going to be diagnosed for HIV, as positive or negative and as we know that the first line of defense within the human body is our human immune system. Whenever there is some kind of antigenic attack, the first line of defense generates chemicals or moieties called antibodies which would try to go and bind and cleave or block some of these attacking species and they do very well with the antigens; they bond very well with the antigens. We drop the blood into this particular coated antigens and assuming that the patient is positive and there is a immune response which has happened, there is a tendency of some of these antibodies to get bonded on to these immobilized antigens. The unbonded ones are washed away later on and so have only these bonded ones to the antigens. The antigens are immobilized; that means, they are chemically somehow attached to the surface of interest; in this case, which is actually a Petri dish. Here, the antigens as you are seeing is getting bonded. So the unbounded ones are typically washed off this surface. Then we add a secondary antibody which would bind to this primary antibody but, the only difference in this particular secondary antibody is that you have an enzyme of a certain kind conjugated on to the secondary.

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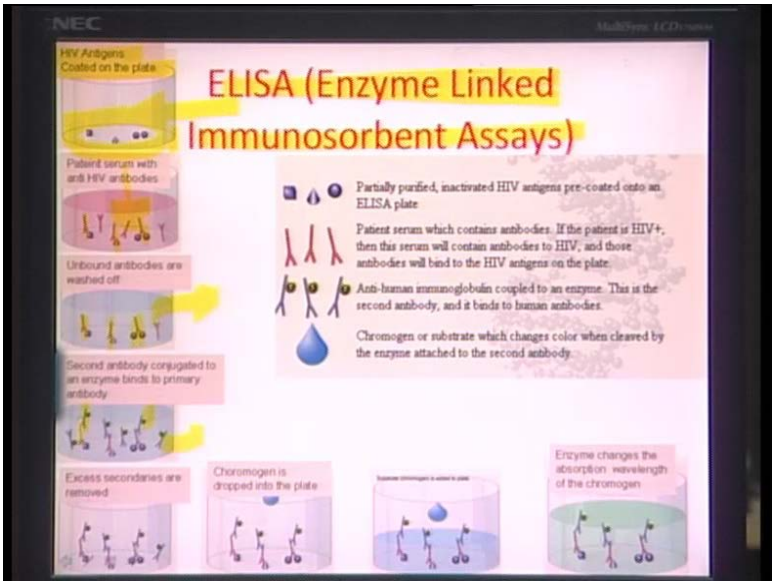

These two chemicals as you are seeing here by the blue arrow (Refer Slide Time: 57:06) or by this blue feature or this red feature, they are conjugates of each other, so they can bind very well. So this is the secondary antibody; this is the primary antibody which is bonded already to these immobilized antigens and the secondary antibody has something called an enzyme which is actually conjugated to the secondary antibody.

Now, with this kind of an orientation again, you wash off those secondary antibodies which are not bound and you have only the bound specimens on the surface of the plate and then you put something which can change color on coming in contact with this enzyme of interest. This is called a chromogen. In this case you are dropping a material a chromogen into this plate where as soon as this chromogen comes in contact with the enzyme here the colour of the chromogen changes you can see there is a change in coloration from blue to green (Refer Slide Time: 57:57).

Assuming that there were no antibodies in the patient serum at the very beginning here, there would be hardly any bound antibodies on the surface due to which the enzymes will not bind in turn to the immobilized antigens. Because, the secondary antibody can only bind to the primary antibody the red antibody. The absence of the red would mean that these would be all free and they would be washed off and there would be hardly anything which can change the colour of the chromogen. If there is a change in the chromogen, it kind of reflects the concentration of the secondary antibody in the patient's blood and sorry, the primary antibody in the patient's blood which is also an indication of how badly or you know how worse the patient has been afflicted or affected or inflicted.

With this, I would like to round up the first lecture and in the next session we would discuss little more details on how the other aspects of sensor design can be illustrated or studied in detail.

Thank You.

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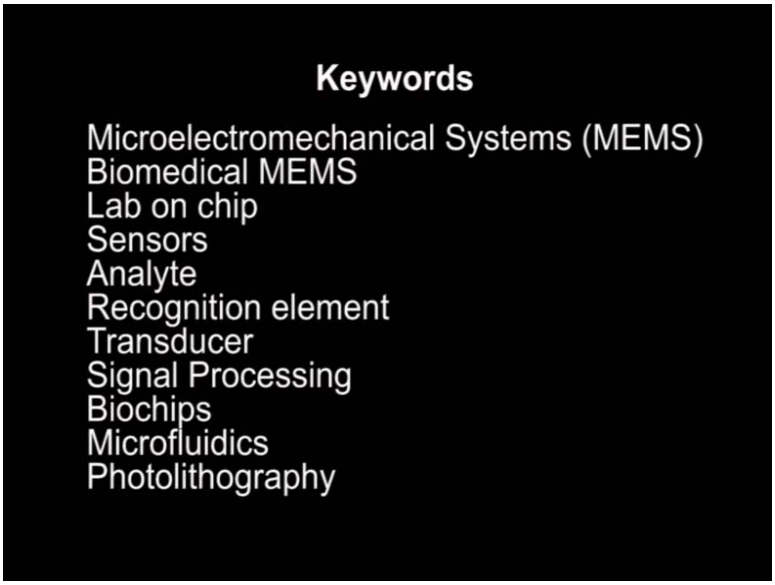

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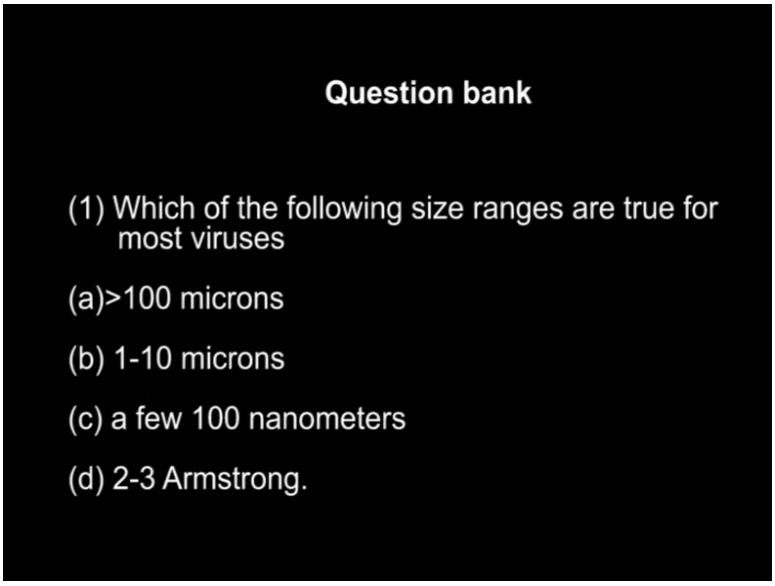

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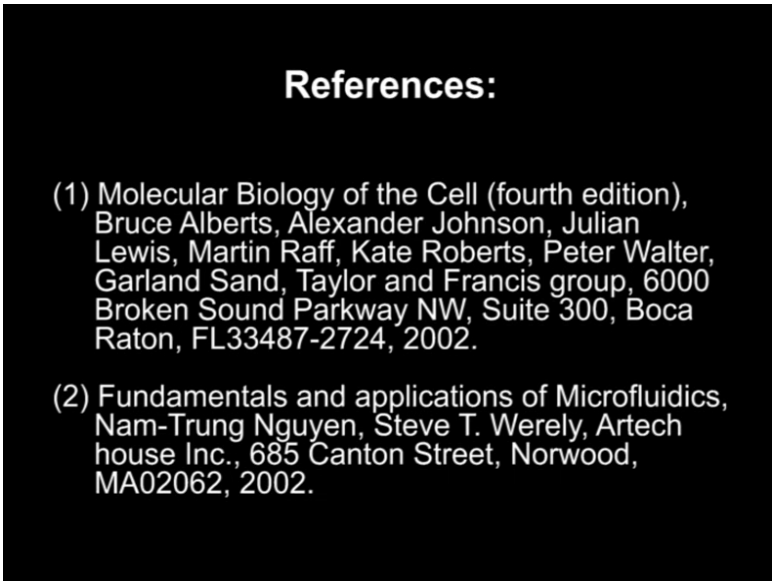

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