Bio-Microelectromechanical systems

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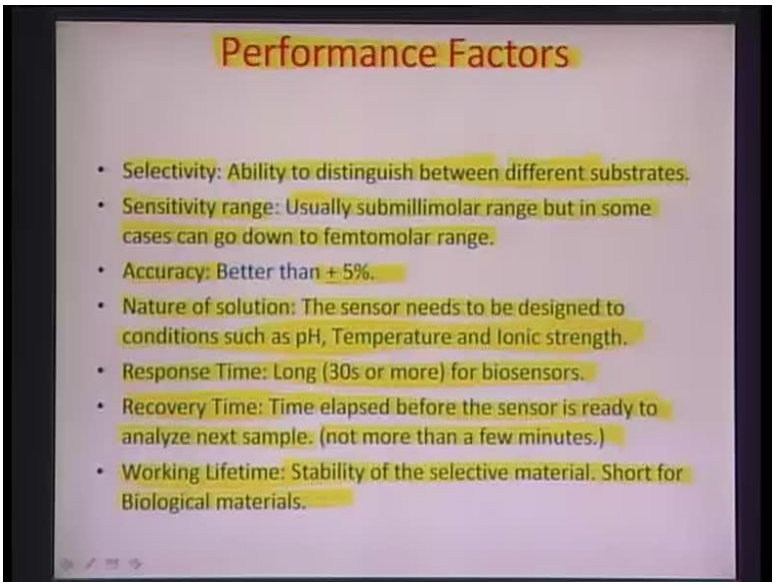

After the sensitivity range in the performance factors, another very important aspect is the accuracy. The sensor accuracy, has to be in most of the cases, better than plus minus 5 percent. So, accuracy also reflects the repeatability or kind of parity between the measurements; that the sensor makes with time, if you have multiple readings. Another very important aspect of performance which has to be kept in mind – it is a kind of intangible aspect, is the nature of solution or the variety of solution that the sensor can scan. So, when designing the sensor very important aspect to take care of is - whether the sensor can with stand various conditions of pH, temperature and Ionic strength, etcetera. So, essentially the sensor - when you talk about designing the sensor, it has to be designed for its ability to get operated in varied conditions or different pH, temperature and Ionic strength, etcetera. That is another aspect, a performance factor aspect of a particular sensor.

Another very important aspect, which makes the sensor really give a commercial angle, is its performance time or response time. For biosensors typically, the response time has been found out to be a little longer, it takes about 30 seconds or more. In this context, I would also like to say that - in electro-chemical sensing operation, this sensor time becomes very high because of the fact that you have to re-condition the sensing electrodes and that is a very time consuming process. . Although it is not a part of the actual response time, it comes in the overall time of sensing of such an electrode.

If you are having a real time process, where there is a continuous monitoring of the analyte of interest with time, it is a very critical aspect that what is the response time of the sensor? How soon can it process a chemical information into an electrical or otherwise optically readable signal? Another, very important aspect which also a part to the performance factor is the recovery time of a particular sensor. I would like to define this as the time elapsed, before the sensor is ready to analyze next sample.

So, essentially it is the time between the readouts. So, if you have two or more certain readings that you want to take with the same sensor, how much amount of reconditioning time is needed; so that you can get the sensor have initio, so that the sensing can start on very accurate basis.

So that is an important aspect of the performance factor of the sensor. If you have a recovery time of more than a few minutes, then really it does not make sense in real time operations anymore. Another very important aspect is a working life time of a sensor - things likes stability of the selective material. It defines these kinds of issues. In case of, glucose sensors, as I was illustrating in my last lecture - this enzyme glucose oxidize, is a very finicky enzyme. It can only have defined shelf life.

If with these kinds of moieties, which are essentially recognition elements, they change their behavior with time. What good it is, to the sensing aspect? So, the working life time is a very important factor that needs to be considered, if you want to design good sensors.

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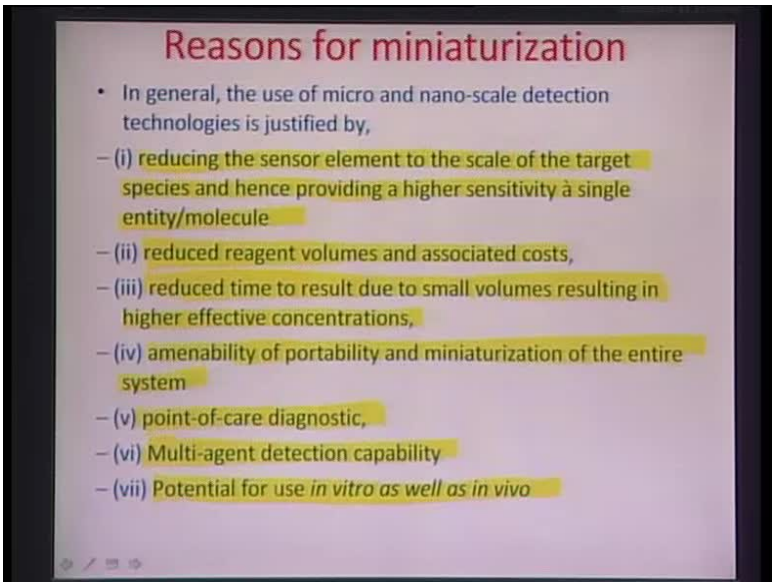

Let us actually, now go to the next level and try to find out that this whole kind of race to miniaturize, starting from the microchips. Why really it is important? What are some of the reasons for miniaturizing? Let say sensors.

The justification can be provided by looking at several aspects. One aspect could be that as we had talked in the scales and sizes, the reduction of sensor element to the scale of the target species would actually give a higher sensitivity for detecting a single entity or a molecule, it is a very important aspect. So, you are talking about the particular detecting element, to be of the size of a single molecule or a single moiety of interest. So, when the size comparison is there, there is automatically higher sensitivity of detection of such a process.

Another very interesting aspect is reduced reagent volumes and cost of operations. Some time back, I was mentioning about this process of polymerized chain reaction, where you artificially trying to amplify small segment of DNA; it is a fascinating process. But unfortunately it is a very expensive process too, because it uses some of these chemically isolated base pairs, some enzymes, some ironing buffers, etcetera, which gives the whole reaction cost a difference dimension all together. Therefore, more number of PCR runs essentially, as the cost is at more money spending issue.

Therefore, it is important that if we can design sensor in a manner which can do a micro PCR, that means you take small volume - where let us say - the overall volume is about 1

micro liters nature and, then you have these different components, which going to the reaction probably of the order of Pico liters. In that case, overall associated cost reduces. So, one of the reasons is why miniaturization is important? The regent volume used for chemical analysis automatically reduce because of the size factor. Reduce time to results, due to small volumes is a very important aspect. As we know, that when we talk about concentrations of different moieties within a solution, there is an aspect of diffusion which comes into picture automatically. If you have a gradient of concentration, there is always a tendency of molecules to diffuse and homogenize the particular medium.

So, if this overall volume over which we are talking is very small, then the diffusion mechanics is much much more rapidly taking place. As a result of which, the homogenization from which the sensing activity would start really, is much quicker. This has its effects in terms of response time of the sensor also. Miniaturizing a sensor or miniaturizing the volume of fluid which is to be sensed, essentially reduces the time to homogenize. So that you can have an accurate read out, much faster.

Of course, portability is a major issue. These days, there is a concept of bedside monitoring of patient wherein, we also know this whole area as point of KR diagnostics, where we take a small sensor, to where a patient is and really the sensor does its job on a real time bases, just by continuously monitoring the patient's health. Such sensors have to miniaturize, because otherwise if you move the whole laboratory, how is it possible really?

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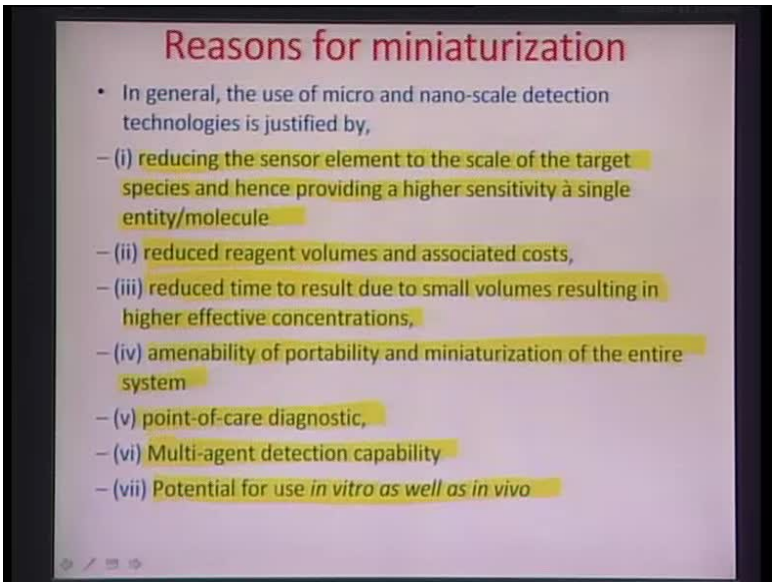

The concept of Lab-on-chip really emerged because of the need to make things more portable. So, that they can be delivered at the point, where it is needed essentially. Amenability of portability is very important aspect, why the sensors should be miniaturized? So, point of care diagnostic essentially which we talked about. I would just like to share with you that now a days in advanced health care schemes, there are small ring like sensors, which they would just put around your finger and they can monitor your things like blood, glucose level very easily on an optical bases. So, any patient who goes into emergency care essentially, is given such a ring to wear. The ring has perfectly wirelessly communicating system, which would give information about the glucose content of the patient from time to time. This is point of care, this comes very close to where the patient is placed actually and does it is job on a continuous basis.

Miniaturization is also helpful for multi-agent detection capabilities. What essentially it means is that, if you have more than one agent that you want detect and if you really want to detect each agent on a very small basis, you could densely integrate such detection protocols, on small particular chip. That is the essence of microchip technology, essentially that you can on a very dense networked basis do multi-agent detection on a very small area. The very important, last but not the least - why miniaturization is needed? At least in some of the reasons which appear to be the most prominent once, is potential for use invitro as well as invivo.

For those of you - who are new in this area - invitro essentially means, outside the human body. So, the sensor can do its job outside the human body. Invivo on the other hand, is inside the human body. So, all these real time sensors, that we have been illustrating from time to time are essentially invivo sensors. You implant sensor on to the human body and it keeps on monitoring the health rapidly and it keeps on giving data rapidly. So, that is invivo sensor. So, miniaturization is very helpful for invitro as well as invivo sensing.

One of the reasons is that, if you are talking about an implantable sensor and the sensor is of the size of pen, can you imagine the amount of pain that the patient is inflicted upon ,if you want to locate the sensor somewhere within this body? So, the smaller the sensor is the better in that case, because it can cause a pain less delivery of the sensor to the target, where it can detect or it can start detecting.

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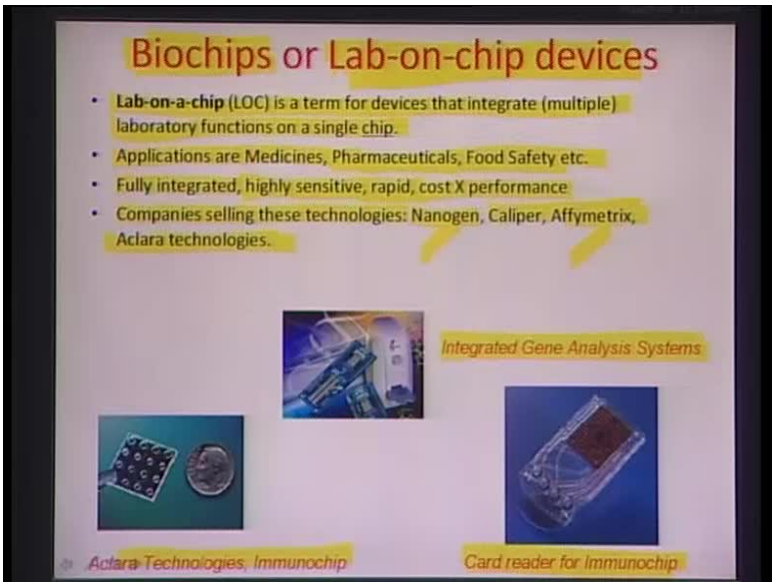

Again, you have been talking about Lab-on-chip devices. I guess you have a fairly good idea about what biochips are? So, let me just definitionelly kind of outlay what this technologies is all about. Lab-on-chip is a term for devices that integrate multiple laboratory functions on a single chip.

So, very obvious definition that we have, several functions in a laboratory which are kind of integrated together to do some detection. So, Lab-on-chip is something that brings all this functions to very small single chip. There are enormous applications of Lab-on-chip

as on date several commercially available protocols to their applications in medicines, pharmacology, pharmaceuticals, for food safety, so on so forth. Some of the advantages that such devices offer on a commercial basis is that, they are fully integrated and essentially without or may be with very less, I should say human intervention. It is a very clean process; you do not have chances of contamination just because of multiple handling as happens very often in the laboratory. They are highly sensitive in nature because of the miniaturized form of these chips, as we have been often on talking about before - were extremely rapid. So, the time of response is very less, because of all those homogenization aspects of the analyte and being small volume the diffusion restrictions are automatically minimized so on so forth.

Then this other aspect of cost performance product - so essentially, these are low cost high performance devices. So, that is why the Lab-on-chips are really high utility kind of devices. Some of the companies selling these technologies across the globe and to name a few: Nanogen, Caliper technologies, Affymetrix, Clara technologies, so on. Essentially these two companies: Nanogen and Affymetrix, they are selling auto catering to the whole diagnostics industry by selling gene identification platforms. We will be discussing in details about these as we go along our lectures as to. Some of the strategies and mechanisms that this manufactures use to identify this chemical, this sequence of base pairs on single DNA molecule.

In general, this is known fact that if we look at all the commercial applications of all these Lab-on-chip systems more or less, majority I would say almost 80, 90 percent of the products, which are currently available are in this integrated gene analysis area. There are some products which have been developed in the immunology like Aclara has a product or this Caliper technologies has product, where in Immuno Chemistry is used for identification of a cells or biologically moieties.

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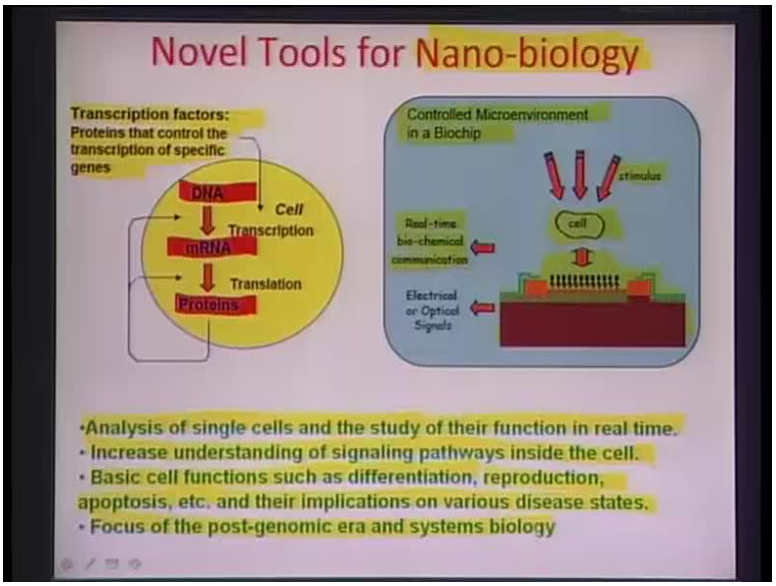

That is in nut shell, what the states of Lab-on-chip techniques are? I would now like to illustrate very important area which has come of late, because of the developments of these tools this is also known as Nano-biology. The MEMS technology in fact the miniaturization technology is very useful for studying certain aspects of single cells. Here, in this particular case as you are seeing, this is a controlled micro environment in a biochip, where you have kind of, it is something like, a let us say a Nano wire between two posts. You have a silicon platform here; it is like a MOSFET device.

So, essentially, whatever is going on in terms of Chemical changes in top of this region gets converted in terms of a surface potential. If there is charge transfer process, which is happening in this particular region, the surface potential change would result in a variation in the drain source current in the MOSFET device. So, therefore, it can be a very good identification basis for what is going on in a single cell, which is immobilized into this area. So, you give stimulus to the cell and see the how cell performs. Now, how is it important? This is very very interesting that actually, there is an increased requirement of understanding of the Physiology of a single cell in the presence or absence of its identical other cells. There is a lot of signaling mechanism between, let us say more than one cells growing on certain area, which results in totally different behaviorally change of cell of interest.

So, cell Physiology essentially, nowadays focuses on to these molecular events which take place in the presence or absence of a group of other cells. One more interesting factor is the way that proteins are produced, and I am going to actually introduce this topic a little bit doing basic Biology that what happens in a cell.

There is certain programing aspect of particular cell, which we have to really read if we come to such a mechanism. So, as we know that there is molecular information stored with in the DNA of a particular cell. This information is a basis of giving what kind of proteins the cell produces. This area, nowadays increasingly growing, because protein essentially are very important bases of the state of health of a certain cell.

There is a process called transcription and translation within single cells and it is huge Nano machinery which is at work. There is a tendency of this messenger RNA, which is a compressed code essentially encoding a certain area region of the gene that we are talking about. This RNA actually comes all the way from the nucleus into the cytoplasm and through the cytoplasm it goes to something called endoplasmic reticulum, which is also the protein warehouse of a cell where there is a coding which happens on this MRNA. The base payers of MRNA are converged rapidly into a sequence of amino acids, which is essentially the protein which is being produced.

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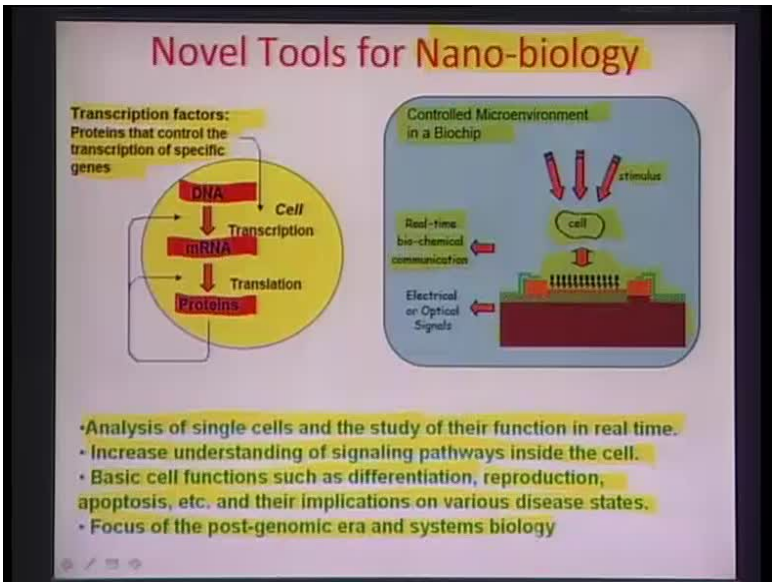

So, this fantastic process which is going on. So, Nano-biology again studies very closely these signaling effects within the cells, which ask the cell to code a certain region of the

gene based on the impulse of the response that it has from an environment. Such studies can only be possible when you make the sensing system. Doing so, these studies on very highly miniaturized basis. So, in a nut shell, what I would like to say, the increase in this concepts of miniaturization has resulted into this fantastic field of Nano-biology to developed; where analysis of single cells and the study of their function in real time can be accomplished. There can be an increased understanding of the signaling pathways inside the cell, some of them we have been mentioning off and on.

Basic cell functions such as, how the cells differentiate in the presence or absence of its own types around it, the way they reproduce, the way they apoptosis or die. After certain time and their implications on various disease states, they can be understood on a very molecular level. Essentially focus of the post genomic era and systems biology, some of these newly emerging fields are in this area more often. So, Nano-Biology definitely is probably one of the areas of interest, which automatically gets cropped up because of this micro systems technology. So, this pretty much brings us to the end of this lecture. Next time we will be seeing, how micro fabrication tools can be used to realize things which are small and miniaturized, which could do some of these jobs that I have been mentioning over the last two lectures.

So, probably we will discuss a little bit of micro fabrication related processes in our next lecture. Thank you.