Biochips and the Future of Medicine

Nguyen, Anthony; Ro, Jason

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I. Abstract

In the past decade, research in nanotechnology has received a considerable amount of enthusiasm. Not only does nanotechnology have many future applications, from structures to electronics to medical systems, it is seen as a possible solution to various challenges we currently face. One of these valuable applications is biochips. The development of microelectronic technologies allows us to miniaturize biochips so they can function at a molecular level. Biochips can be utilized in numerous fields of study; however we will focus purely on its medical benefits. As an emerging technology, only further research will show just how much biochips can accomplish in the future.

II. Introduction

As of November 2012, the world population has grown beyond 7 billion people [1]. This number, 7×10^{9} is certainly the opposite of nano, 10^{-9}. With more people in the world, innovations in health care are now more important than ever. According to the Molecular Diagnostics Survey Reports, "diagnostics testing influences approximately 70% of health care decisions" [2]. Because of this, the better diagnosis techniques we have available, the better health care we will be able to provide in the future. One way this can be accomplished is through the use biochips. In this paper, we broadly examine the current state of a class of technology referred to as biochips. One definition of a biochip is "a collection of miniaturized test sites (microarrays) arranged on a solid substrate that permits many tests to be performed at the same time in order to achieve higher throughput and speed" [3]. The important aspects of the definition are "many tests" and "high throughput and speed". These are aspects that nanotechnology hopes to improve upon. One important advantage of biochips is that they can

perform those many tests on a very small quantities of sample. Imagine a conventional blood glucose tester that can take the same drop of blood and complete a full blood test like one that would currently require days of laboratory work. A proof of concept device was created by UC Berkeley in 2011 [4]. Hopefully, nanotechnology will allow biochips to conduct new tests, more tests, more quickly, helping doctors diagnose disease even in third world countries and greatly improving world health conditions.

III. Experimental and Results

Biochips usually belong to two classes, array plate biochips and integrated biochips [5]. The distinction between the two is that array plate biochips consist of only the substrate on which the sample(s) are examined, while the detection systems are separate. These biochips are only appropriate for laboratory research [5]. The integrated biochip also includes the sensor chip, which is a micro or smaller sized integrated circuit, which means that these devices are portable and can be used in doctor's offices or in the field [5]. Taking the integrated biochip further results in something often referred to as a Lab-on-a-Chip (LOC) device, which because of its density, can provide a very large amount of information from the sample provided to it [6]. It is microfluidic technology that has allowed LOC devices to be produced [7]. The UC Berkeley device mentioned earlier is an example of one of these LOC devices [4].

Given these working definitions, some current application of biochips will be discussed; these ones are not necessarily nanobased. The HyChip system, a microarray based system for genomics applications like genotyping, was produced by Hytec. Nanogen and Becton Dickinson's genotyping program together "for infectious disease diagnosis and a genotyping program directed at both gene discovery and forensic applications" and are trying to break the 1000 feature barrier [7]. As of right now, we have continuous monitoring technology that allows

us to monitor glucose for up to "8 months in mice… and one year in pigs" [2]. The paper Self-Contained, Fully Integrated Biochip for Sample, published in 2004 talks about a fully integrated biochip meant to prepare samples, chemically react them, amplify them with the polymerase chain reaction, and then provide us with images of them [8]. Different chips that have already been made have had different amounts of the process integrated on them. Some people vie for leaving pumps, valves, and detectors off-chip while others want them in the chips themselves. Right now, there are many applications valuing "portable solutions such as point-of-care diagnostics, in-field environmental testing, and on-site forensic" that are not designed for yet. Some other limitations with biochips today include: not enough signal to noise resolution, and "reproducibility of biochip performance in patient samples" [9].

The paper, Nano-Biotechnology and Sensing Chips, from the Journal *Sensors* focuses on use of nanotechnology for personalized therapy – giving the right doses of drugs to patients directly as determined by the sensors, since people react differently to different drugs. Therefore, sensors for glucose monitoring, DNA detection, drug testing in saliva are some needs that might be solved by nano [10]. New solutions from nano-bio-science were recently demonstrated by using probe surfaces structured with 2D glycol nano-layers and they could pave the way for improved portable device systems in cancer markers detection. Right now, we have chips that can sense in the range 400 μM to 3 mM but the range necessary to use the drug is below 0.3 μM [10]. The sensitivity of these sensors must therefore be improved so that they can sense the level of drugs that would actually be present in the body.

Nanotechnology can also be applied in area of optofluetics. Optofluedics refers to when fluids are used to manipulate light for 2D or 3D imaging [11]. However, neither of these next two devices actually manipulate light with fluid, yet they are still called optofluetic devices. The first

device is the integrated on-chip optofluidic microscope (OFM). It is based on contemporary CMOS image sensors, but using nanomethods of coating with a thin layer of metal, and thin apetures are milled above the CMOS pixels as in the figure 1 [11]. The channel is lit and the specimen passed through, producing line traces which can be made into a single image with resolution comparable to the aperture. As seen in Figure 2, the picture generated by this technique is very good [11]. The Ozcan group, which is a UCLA based group, used nanotechnology to improve a tomographic microscope. This microscope is based off 24 fibers that are lit by LEDs. The sample is moved, and each time a sensor records a hologram, as illustrated in Figure 3.

Some of the most promising current results came from the journal Nanomedicine in 2010, in a paper about programmable nanochips. The concept behind these programmable nanochips is that they are, more than other LOC products, "highly flexible interface[s]" which, with one chip, can examine a "broad portfolio of analytes" allowing "cardiac and cancer health, HIV monitoring, bioterrorism screens and nucleotide point mutation detection" [12]. This is possible because the input is a labcard, and there is a specific labcard for processing proteins and a specific card for processing cells. The labcard uses plastic, stainless steel, and agarose beads to keep costs down [12]. Also, this programmable chip uses 3D beads that concentrate analytes from the biofluid, so that a smaller sample can be used.

IV. Discussion

In this survey of contemporary nanobiochip research, it was clear that current researchers have had very promising results. Biochips, especially fully integrated biochips results have been improving. The addition to new components during fabrication can greatly increase its analyzing rate. One such solution would be to increase the density of arrays (test sites) and the surface or

panel of a biochip. Also, biochips are uniquely made for a specific application. Biochip activation varies for specific tests, meaning that one activation procedure may not be optimal for another. For instance, the direct attachment of a ligand to the surface of a biochip may be optimal for studying low-weight molecular analytes versus studying high-weight molecular analytes [8]. While current biochips do boast great results such as reduction of sample size per test and simultaneously analyzing all analytes, the high costs per test and fabrication are burdensome [8]. Scientists and researchers must overcome challenges at such a small scale, many related to high cost fabrication techniques for components such as pumps and mixers [7]. Possible solutions that are currently being researched include simply utilizing the deficiencies within the system instead of trying to add more components in. For instance, fluid transport and mixing fluids at the nano or micro level is difficult to maintain due to the presence of bubbles. Pure diffusion mixing techniques are inefficient. However, setting the bubbles into vibration using an external piezoelectric transducer reduces mixing times from hours to seconds while simultaneously providing rapid fluid transport. This technique is called cavitation microstreaming and has proven very successful at the micro level [7].

For the biochip comprised of 2-D nanolayers, readings rely on measuring capacitance or impedance variations of the specimen on its sensing surface. Biochips before had utilized VLSI architecture, however, the specificity was not very high due to the chip not being insulated enough. Thus the new solution proposed placing grooves on its surface rather than VLS structures. "Nano-sized grooves crossing the film are related to capacitance time-drift and they provide conducting pathways, which affect the ideality of the electrochemical interface" [9]. Two major drawbacks occur according to the data. First, there is undesired behavior in the resistivity of the layers which in turn affects the capacitance. Second, there is unstable electrochemical behavior

that disrupts capacitance measurements. One suggested solution is using mercaptohexanol or potassium ferrocyanide as a blocking agent placed in between the grooves however the results show that these due not result in insulated surfaces. Thus a new blocking agent must be used or the elements and structures must be altered in order to make more stable capacitance measurements.

Another issue that should be addressed is improvements in the images produced by the biochips. Introduced in the previous section and seen in the data figures, optofluidics shows greater enhancement in imaging, thus a greater method for detection of specimen. The next step would be to produce images in 2-D and 3-D. A method for 3D imaging called Stochastic Optical Reconstruction Microscopy (STORM) exploits the photoswitchable nature of specific fluorophores. By switching the fluorophores on and off using a focused excitation source, an image of any sample less than 60 nm can be captured and reconstructed. However producing these images requires the use of off-chip sensors [11]. While current nanofabrication does not incorporate the sensors on the chip, having it otherwise would simplify the tests by making the biochips more portable and easier to use. Another issue that is currently being researched is the rate at which an image is produced. An image must be constructed from multiple scans from the biochip. Its functionality would be greatly improved if the biochip can rapidly produce more images by either improving the rate at which individual sections are obtained or by improving the rate at which the image is put together. In addition, miniaturization is a primary motivation for research in this area. Using light that moves on the plane, as opposed to out of the plane, would effectively decrease the length in the vertical direction. However, current research is performed using out-of-the plane imaging because it produces interesting results [11].

Improvments to the technology behind the sensors aside, there is one more significant gap in the area of biochips, and that is bringing the biochips out of the lab and into conventional healthcare. Only "approximately one biomarker per year received US FDA approval between 1995 and 2005" [12], and this is not good enough. The Ozcan group's microscope research has been combined with cell phone attachments in order to project holographs of an image onto the cell phone's CMOS sensor, send it over at network for processing, and then send the results back to the cell phone quickly. This takes this nanoimaging technique and allows it to be applied for point of care medicine [11]. This research is unique compared to others because what the Ozcan group has produced "are more than proof-of-concept devices, they are care- fully devised prototypes with comprehensive functionality" [11]. The programmable biochip group also is working on this issue, having "successfully deployed in resource-poor settings (Botswana)" [12]. They "project" that innovations would "Moore's Law type growth in POC diagnostic research," which would be very optimistic.

V. Conclusion

Biochips are an exciting new application of nanotechnology that we hope to see more of in the future. In this paper we have discussed what constitutes a biochip. We also touched upon its various applications along with possible procedures and techniques create biochips for said specific use. We have discussed the many challenges that biochips face, including stability, accuracy, and low-cost production. While many of subjects discussed were performed in laboratory tests, the goal of many of these experiments is to achieve real-world deployment. After reviewing these applications, the ones that stand out the most for solving the most difficult problems are certainly the "lab-on-a-chip" products that fully integrate everything together. The benefits to be gained by producing such chips greatly outweigh the initial costs. A low cost biochip

would effectively decrease the cost of healthcare in an inflating society of the west while offering an affordable option to developing countries. In addition, biochips would allow for treatments and therapies become personalized as biochip would continually send information about that specific patient, not to mention the time it would save since most samples under analysis must go to a lab for testing. One estimate made in early 2012 "expect[s] that in a five-ten year horizon we can anticipate reliable technology for the remote telemetry of the human metabolism" [2]. Hopefully, this estimate is not far off, because as the human population grows, it becomes essential that there be a means to identify and treat the ailments of the 21st century. Biochips will be one means toward this challenging goal.

Works Cited

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VI. Figures and Tables

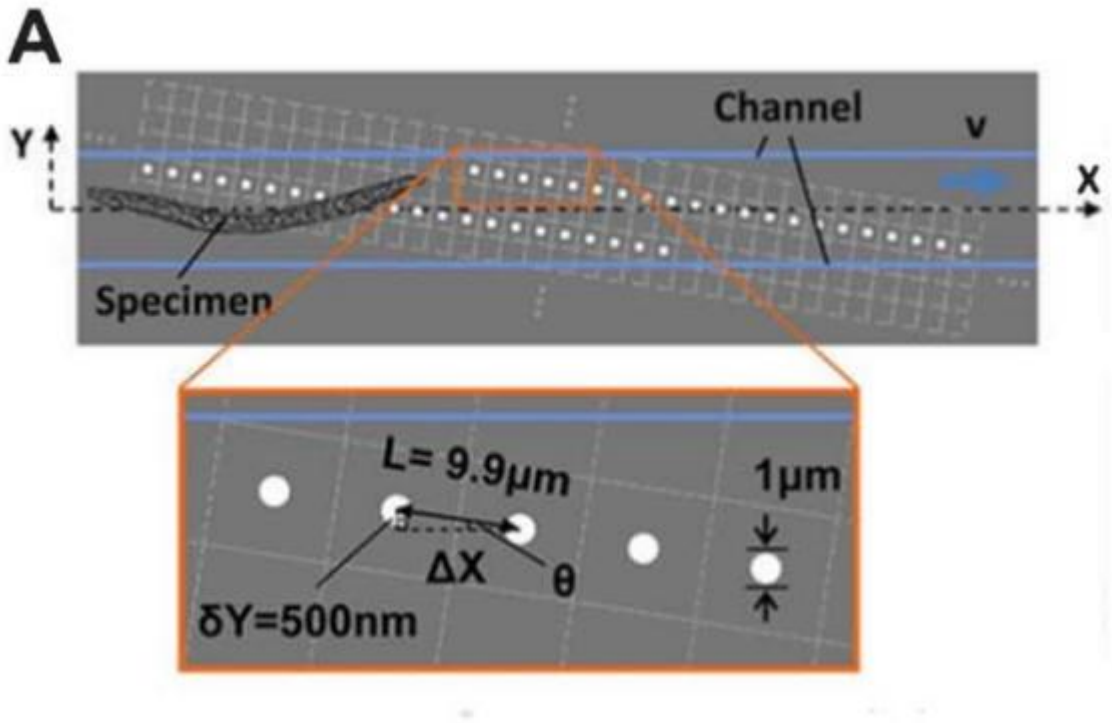

Figure 1 – Schematic of apetures in the metal

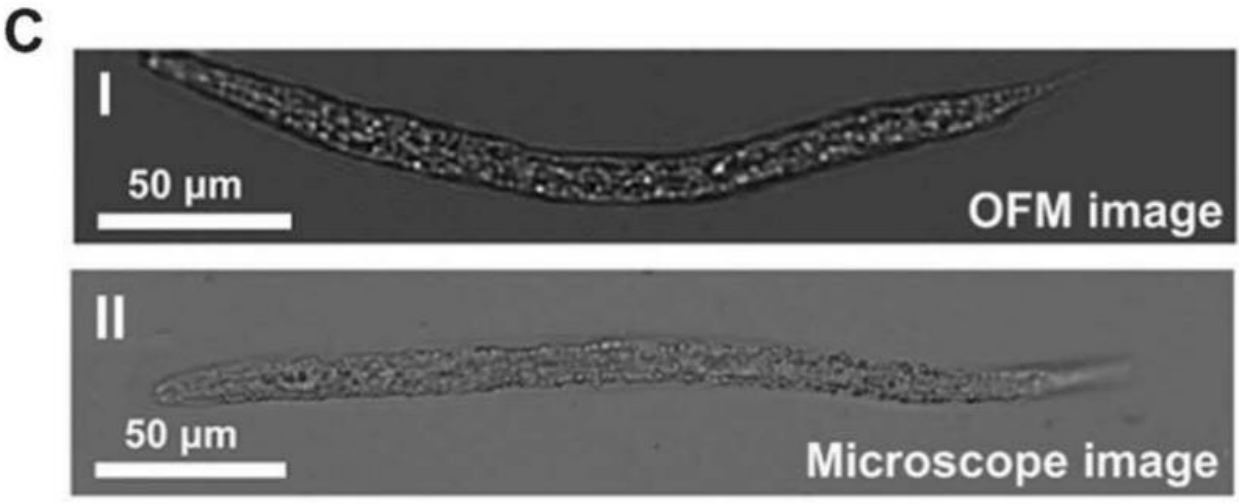

Figure 2 - Comparison between an image of a nematode with one from a conventional microscope

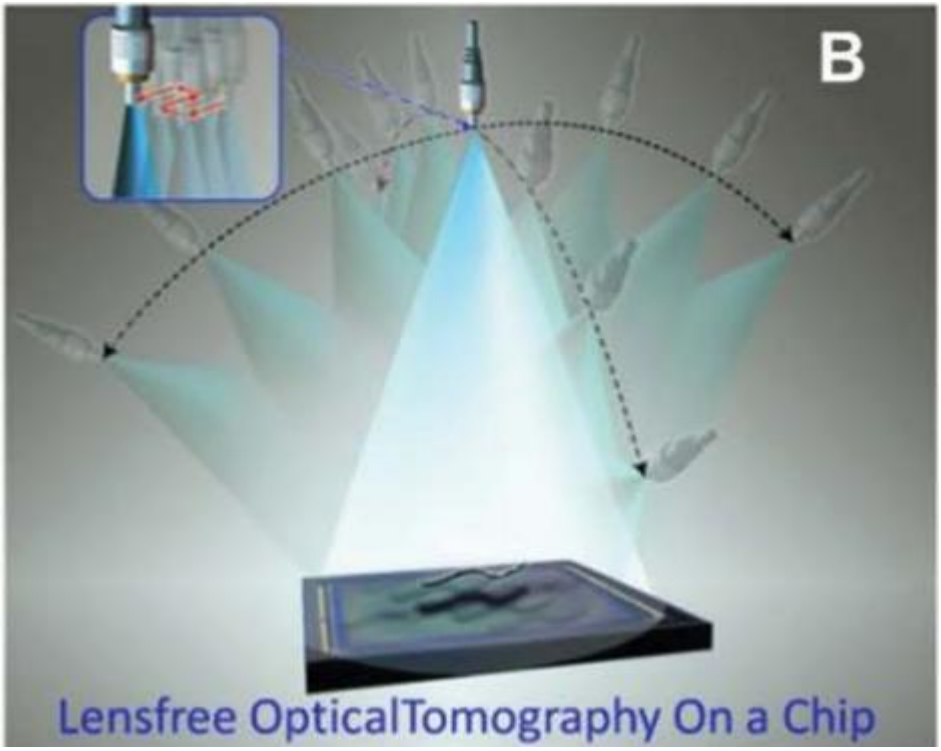

Figure 3 – Illustration of Tomograph Techinque