Interfacing to Living Cells

Rudy Lauwereins
Imec and KU Leuven
Leuven, Belgium
Rudy.Lauwereins@imec.be

***Abstract*—Recent advances in More than Moore technology enable close inspection of and even direct interfacing to living cells. This paper illustrates this through three use cases. In the first use case, the type or quality of billions of cells is quickly inspected in a fluidic medium. Secondly, the effect of potential drugs is monitored in neural cell cultures. In the third use case, neural brain activity is recorded in vivo using implantable electrodes to understand how the brain functions.**

Keywords—interfacing, cells, circulating tumor cells, stem cell cultures, lens free imaging, micro-fluidics, neuroprobes

I. Introduction

Forty years of More Moore scaling brought us supercomputers in our pockets, with an unbelievable compute power, storage capacity and communication throughput. Interfacing to those devices however has hardly changed over time: a human instructs the computer what to do via keyboard entry and the computer feeds back information via a screen. This interfacing method limits the use of computers to human-in-the-loop applications, typically for infotainment purposes.

More than Moore allows us to use the same production tools and methods as we use for electronic integrated circuits, to build non-electronic structures like mechanical devices, chemical interfaces, optical structures etc. at very low cost, integrated on top of electronic circuits. These sensors and actuators enable the computing systems to autonomously interact with the environment, without requiring a human in the loop. Autonomous operation pushes the applicability of electronic devices beyond infotainment to a point where they can help solving the grand challenges we face. In this paper, we focus on their deployment for life sciences.

II. Fast Inspection of Life Cells

Multiple use cases exist where billions of cells need to be inspected individually.

A first use case is the detection of Circulating Tumor Cells (CTC) to improve cancer treatment. Most people diagnosed with cancer do not die from the primary tumor but from metastasis, i.e. the spreading of tumor cells via the blood stream causing the development of multiple secondary tumors (Fig. 1). The threshold for increased risk of secondary tumors is one CTC per 5 billion blood cells. An inspection technique is hence needed that can find this single errant cell in the billions of other cells. This technique should be fast, cheap and easy to use.

A second use case is the inspection of the quality of Induced Pluripotent Stem Cells (iPSC). The medical community hopes to be able to develop spare organs like kidneys or the liver, by reprogramming adult cells (e.g. skin cells) of an individual back into stem cells and directing the differentiation of these stem cells into the right type needed for the spare organ. That way, transplantation of organs coming from a foreign donor can be avoided. Bioreactors are used to reprogram the adult differentiated cells back into stem cells. The quality of each and every individual stem cell has to be inspected.

Using advanced process technology, cheap and fast cell inspection devices can be constructed (Fig. 2). In such devices, the fluidic sample containing the cells is split over thousands of microfluidic channels that have a cross section slightly bigger than the largest cell. Cells hence pass through these channels one by one. An interference based optical imager takes a holographic image of each cell. In software, a three dimensional reconstruction of the cell is created and fed to a classifier. The result of the classifier instructs a microfluidic valve downstream to push the cell into one of multiple bins. In the CTC case, red blood cells, white blood cells, blood platelets and CTCs could each be pushed into separate bins. Further analysis of the cells in the CTC bin could then be performed to determine the type of tumor cell, using for example DNA analysis. This allows for a directed mild chemical treatment, bringing the concentration of CTCs back under the threshold.

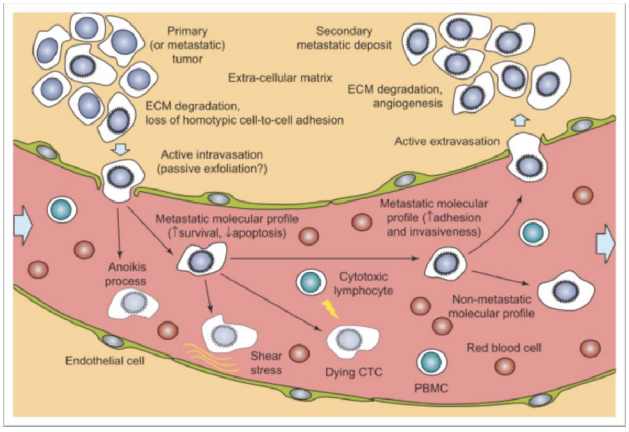

Fig. 1. Circulating Tumor Cells in the blood stream [1]

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In the iPSC case, high quality stem cells could be separated from cells that need further reprogramming.

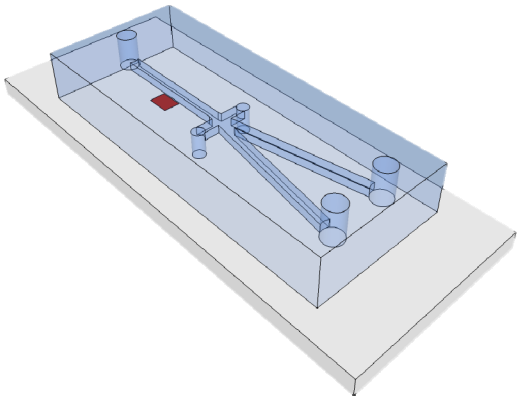

Fig. 2. Microfluidic channel for inspection and sorting of cells

III. Monitoring Neural Cell Cultures

Modern drug development consists of screening millions of candidate chemical compounds to select the single one that combines a positive effect on the disease it has been designed for with an acceptable amount of side effects. Early steps of screening involve growing cell and tissue cultures in multiple 96-well plates. In each of the wells, a different potential drug is administered and its effect on the cell culture is monitored. The main challenge is in detecting the impact of the potential drug on the living tissue in the cell or tissue culture. For neural cells, for example, the impact on the electrical and chemical communication between the individual cells needs to be analyzed. Today, this is done using a patch clamp. This is a glass pipette inserted under a microscope through the cell membrane of a neural cell, a very time consuming process that requires highly trained lab technicians. Typically, at most 4 patch clamps per sample can be used, hence the behavior of at most 4 cells can be monitored. Since inserting a patch clamp through the cell membrane is a brutal technology, the cells typically die in thirty minutes. Analyzing the effect of a potential drug on at most 4 quickly dying cells does not reveal much information. This is why drug screening quickly has to resort to animal models. Ideally, we would like to track the effect of the potential drug on thousands of cells in the culture over a period of at least several weeks.

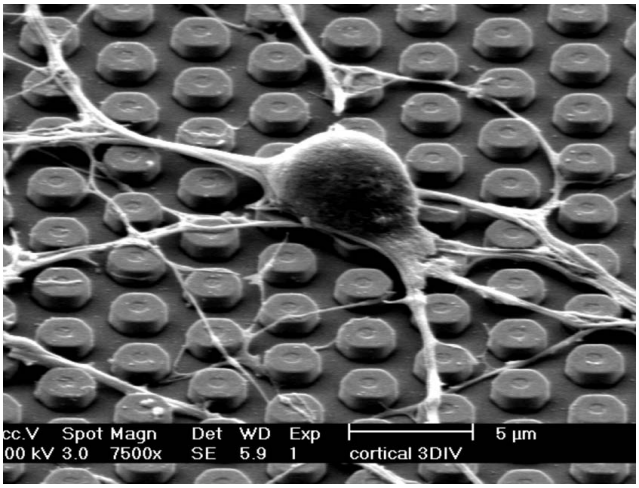

Fig. 3. Neural cell growing on top of a silicon needle bed coated with biocompatible material.

This is exactly what can be achieved through the use of semiconductor technology. On top of a passivated chip containing signal conditioning circuitry, a bed of needles can be constructed (Fig. 3). Those needles are coated with a bio-compatible layer. They contain an electrode at the top, to make electrical contact with the cells. Some of the needles can be made hollow, to allow them to inject fluid to the cell body or to extract fluid from it for analysis in the microfluidic chip underneath. When placed at the bottom of each well in the 96-well plate, cell and tissue cultures grow on top of the bed of needles. Thanks to the coating, a cell engulfs one or more needles, enabling an excellent low impedance contact. This way, thousands of cells can be monitored individually. Experiments have shown that cells survive in this setting for more than a month. The long term effect of the drug can hence easily be monitored.

IV. Recording Neural Brain Activity

Although humankind has proven capable of travelling to the moon and back, and of putting billions of tiny switches on chips the size of a thumb nail to build reliably operating computers, and so on, the mechanism of our own brain is still a mystery. Over time, cortical and deep brain implants have been developed that allow for the in vivo recording of neural cell activity in the brain. There is however an important mismatch between the number of cells in the brain (over 50.000 neurons per mm^3) and the number of electrodes used to capture the neural cell activity which evolved from 4 electrodes in the seventies to 64 electrodes today.

Using advanced processing technology, it is possible to put close to 500 electrodes with integrated analog buffer amplifiers on a thinned down flexible silicon shaft of 10mm length, 100µm width and 50µm thickness. This shaft is monolithically connected to an integrated circuit containing further amplification, filtering and analog-to-digital conversion, replacing the functionality of a 100kg rack of equipment on a silicon surface of $3x3mm^2$ consuming just under 1mW of power (Fig. 4). The silicon scaling roadmap will allow us to exponentially increase the number of electrodes on a single shaft.

Using the abovementioned devices, implanted in the brain of a rat, allowed us to get better insight into how a rat keeps track of where it is in its environment, i.e. how it encodes its position in space. We observed that different neurons fire depending on where a rat is in a maze it visited before. Just looking at which neurons fire, allowed us to know where the rat is in the maze. We also observed that rats, when halted at some point in the maze, plan their next trajectory at 10x the speed. This kind of analysis is still in its infancy, but will quickly lead to deeper insight into the functioning of the brain.

V. CONCLUSION

We described three use cases in the field of life sciences where advanced nano technology, combining More Moore and More than Moore, offer a breakthrough in monitoring and understanding. Visual inspection of individual cells in fluidic media enables the detection of a single circulating tumor cell in 5 billions of blood cells, or allows for high throughput quality inspection of induced pluripotent stem cells. Growing cells and tissue cultures on a silicon bed of needles enhances drug screening capabilities substantially by proving concurrent monitoring capabilities of thousands of cells for prolonged periods of time. High density electrodes on tiny silicon shafts improves in vivo recording capabilities improving our understanding of the brain functions. Today we are experiencing only the tip of the iceberg of life science monitoring and diagnostic capabilities. Further scaling of silicon structures will enable an exponentially growing insight into life.

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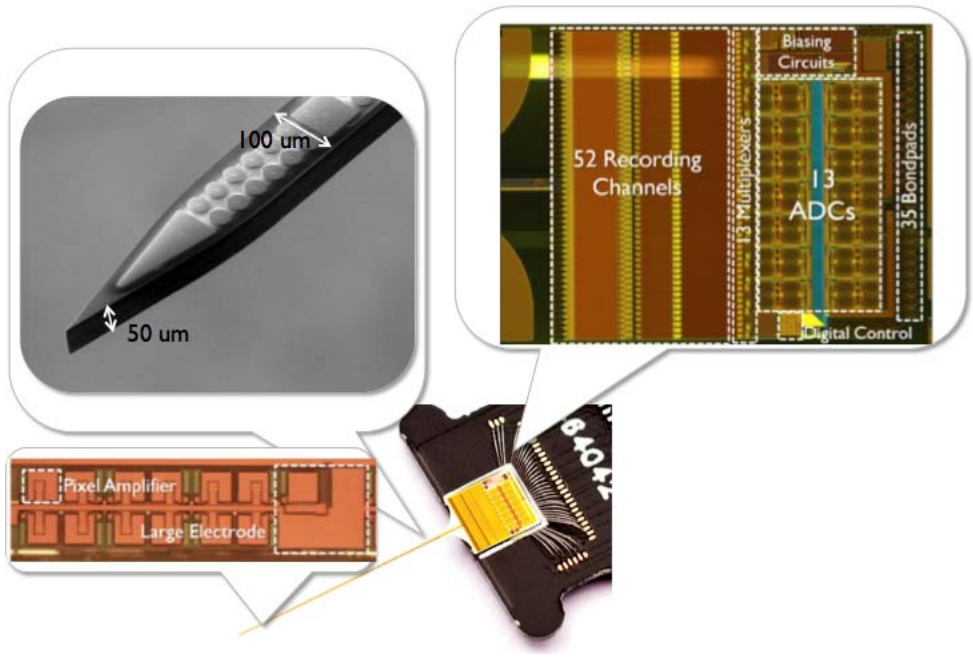

Fig. 4. Silicon neuroprobed with 455 TiN electrodes with integrated amplifier per electrode integrated on the shaft and with 52 parallel recording channels and 13 analog-to-digital converters integrated on the monolithically attached microchip [3]