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School of Medicine - Department of Pharmacy

NANOCHIPS AND MEDICAL APPLICATIONS

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Thesis Subject: Semiconductor Devices and Integrated Circuit Systems

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1. Abbreviations

AAM All-area modification

AFM Atomic force microscopy

AI Artificial intelligence

AIa Avian influenza virus antigen

anti-AI Anti avian influenza antibody

APTES 3-Aminopropyl-triethoxysilane

ASR Artificial silicon retinas

AuNP Au (gold) nanoparticles

BCI Brain-computer interface

BMI Brain-machine interface

CAD Computer-aided design

CEA Carcinoembryonic antigen

Chem-SAM Chemical self-assembled monolayer

circNFIX Circular RNA nuclear factor I X

circRNA Circular RNA

CK-MB Creatine Kinase MB

CK-MM Creatine Kinase MM

CNS Central nervous system

CNT Carbon nanotubes

COVID-19 Coronavirus disease 2019

CRC Colorectal cancer

CRP C-reactive protein

CTC Circulating tumor cell

CVD Chemical vapor deposition

CZ Czochralski (Author name)

DFA Discriminant factor analysis

DNA Deoxynucleic acid

ECD Electrochemical deposition

ECG Electrocardiogram

EEG Electroencephalogram

EES Epidermal electronic system

ELISA Enzyme-linked immunosorbent assay

EMG Electromyogram

FET Field-effect transistor

F-FET Flexible field-effect transistor

GET Graphene electronic tattoo

GTPES Glycidyloxy-propyl-trimethoxy-silane

IC Integrated Circuit

IgG Immunoglobulin type G

IgM Immunoglobulin type M

IMNS Integrated micro nano systems

IoT Internet-of-things

ISF Interstitial Fluid

JLFETs Junctionless Field-effect Transistors

LED Light-emitting diode

LOC Lab-on-a-chip

LoD Limit of Detection

mAbs Monoclonal antibodies

MDMA	Methylenedioxy methamphetamine
MEA	Micro electrode array
MERS-CoV	Middle East respiratory syndrome coronavirus
miRNA	microRNA
ML	Machine learning
MOSFET	Metal oxide FET
ncRNA	Non-coding RNA
OECT	Organic electrochemical transistor
OOSI	Organic optical sensing inverter
p-BNC	programmable-BioNanoChip
PCR	Polymerase chain reaction
PNA	Peptide nucleic acid
POC	Point-of-care
POSFET	Piezoelectric oxide semiconductor field-effect transistor
ppb	Parts per billion
PSA	Prostate-specific antigen
PtNW	Platinum nanowires
PVD	Physical vapor deposition
QCMs	Quartz-crystal microbalances
RBC	Red blood cells
RNA	Ribonucleic acid
SARS-CoV	Severe acute respiratory syndrome coronavirus 2
SBA-AIa	Silica-binding proteins avian influenza virus antigen
SBP	Silica-binding proteins
sDNA	synthetic DNA
SEM	Scanning electron microscope
SiNR	Silicon nanoribbon
SiNW FET	Silicon nanowire field-effect transistor
SiNW	Silicon nanowire
SOI	Silicon-on-Insulator
SSM	Selective surface modification
TENS	Transcutaneous electrical nerve stimulation
THC	Tetrahydrocannabinol
UTC	Ultrathin chip
UV	Ultraviolet
VOC	Volatile organic compound
WBC	White blood cells
ΔI_{ON}	Change in on-current values
µTAS	Micro total analysis system

2. Abstract

Background: The term “nanochip” pertains to an integrated circuit (chip) with nanomaterials and components in the nano-dimension (1-100nm). An integrated circuit is essentially a collection of electronic components, like transistors, diodes, capacitors, and resistors. Current transistors are in the nanoscale but can also be modified with nanostructures like nanoribbons and nanowires to manufacture biosensors that can perform label-free, ultrasensitive detection of biomolecules like ions, DNA molecules, antibodies and antigens.

Materials and Methods: A systematic literature search was conducted using the electronic databases PubMed, Google Scholar and Scopus for the development and use of nanochips in medical applications. For the identification of relevant papers, the inclusion criteria referred to articles not prior to 1999, English language, review and/or research articles. The exclusion criteria were newspaper articles, conference abstracts and letters.

Results: In-vivo and In-vitro techniques have been used for detection of DNA molecules, ions, antibodies, important proteins, and tumor markers, not only from blood samples but also from sweat, saliva and other biological fluids. Another diagnostic application of nanochips is detection of volatile organic compounds via a breath test. There are also several therapeutic applications of these semiconductor devices like brain-computer interface chips for paralytic or epileptic conditions, manufacture of “bionic” organs like artificial retinas, artificial skin and robotic prostheses for amputees or robotic surgery.

Conclusion: The use of nanochips in medicine is an emerging field with several therapeutic applications like diagnostics, health and fitness monitoring, and manufacture of “bionic” organs.

3. Introduction

3.1. What Is a Nanochip?

"Nano" is a prefix denoting 10^{-9}, meaning that 1 nanometer is equal to a billionth of a meter. That's about the size of 2 silicon atoms. In recent decades, the study of things nano has erupted with various emerging fields like nanotechnology and nanomedicine, since materials behave differently in the nanoscale than they do as bulk materials in the macro-world (1). "Chip" or microchip (as in a fragment of something) is more of an urban term that has evolved to be a synonym of the 'Integrated Circuit' (IC).

3.2. Integrated Circuits

An Integrated Circuit is essentially a collection of electronic components, like transistors, diodes, capacitors, and resistors, built into a circuit on a semiconductor material, usually silicon. The transistor was invented in 1947, by William B. Shockley, and has since revolutionized the field of electronics. Some argue that the transistor is the single most important discovery of humankind after fire. It is the functional component of the IC. Without it, there would be no integrated circuit. Every component in the IC is positioned to allow optimal operation of the transistor. (2) Shockley and his team discovered that under specific conditions, electrons can form a barrier at the surface of certain crystals, and that if one can control this barrier one can control the flow of electricity through that crystal. Appropriately, they named it the transistor as a combination of the words 'transfer' and 'resistor', since it could do both. They managed to manufacture a device that could perform electrical functions that were until then performed by vacuum tubes, and hence emerged the study of solid-state electronics. Solid electronic devices are vastly superior to vacuum tubes since they are more dependable and resilient, use less power, and can be manufactured in much smaller sizes, with greatly reduced costs. (2) Transistors are the main reason computers evolved from occupying a whole room to fitting in our pockets.

After miniaturization of the transistor, the bulkiest part was now the wires interconnecting components of the circuit. In 1958, Jack Kilby and Robert Noyce came up with the next most important advancement for circuit miniaturization. Instead of using

wires, they deposited ultrathin metal paths on the device itself to connect the individual components. This meant that there was a conductor path on top of the semiconductor plate to propagate current through the circuit, thus acting as microscopic wiring. (2) Semiconductor manufacturers are able to produce large quantities of integrated circuits with high reproducibility to satisfy commercial needs. Each circuit contains more than 100,000 components of micrometer scale, with delicate 3D interconnections lying on and even within the silicon plate. (3)

Integrated circuits can be analog or digital. Analog circuits process analog signals in interaction with the environment, whereas digital circuits process specific voltages in a binary manner. Using Boolean algebra, they register the presence of voltage (of a specific value) as “on”/ ”true”/ ”1” and the absence of current as “off”/ ”false”/ ”0”. This binary system is used by our computers to perform functions and arithmetics. (2) The most complex integrated circuits are the Microprocessor Circuits. These contain billions of transistors that have been specially arranged to form thousands of digital circuits. Each circuit performs a logic function and a microprocessor is made up of logic circuits interconnected with each other. (2) A logic function, put simply, is a type of calculation of incoming voltages “ones” or lack thereof “zeros” to produce an outcome: one or zero.

A simple example of a logic gate function is the following:

$$0 + 0 = 0 \qquad 0 + 1 = 0 \qquad 1 + 0 = 0 \qquad 1 + 1 = 1$$

If the two inputs are 0 OR 1 the output is 0, meaning if there is no or only one incoming voltage the outcome is no voltage. The outcome is only 1 (outgoing voltage) when BOTH inputs are also 1 (two incoming voltages). Microprocessors perform billions of these calculations per second and are found in almost all electronic devices used today. To conclude, chips or integrated circuits are an accumulation of interconnected transistors (or FETs: field-effect transistors) on a semiconductor plate, the silicon wafer.

3.3. Semiconductors and the n-p junction

All materials can be categorized as either insulators, conductors, or semiconductors depending on how they conduct electricity, in other words how freely electrons can move within the material. For example, metals are conductors since they have a high number of

freely moving electrons and can thus easily conduct electricity. An insulator, on the other hand, has few or no free electrons and thus cannot conduct electricity. A semiconductor (e.g., silicon or gallium) is somewhere in between, they can conduct more electricity than insulators but less than conductors. (2) This property is ideal when the objective is "controlled" movement of free electrons, which is exactly what is necessary in the case of integrated circuits.

The band gap between valence and conduction bands in an insulator is large, so it doesn't conduct current. In a conductor, there is no band gap, the valence conduction bands overlap, so all valence band electrons are available for conducting electricity. A material is considered a semiconductor if the band gap is smaller than that of an insulator and allows valence electrons to jump into the conduction band if it receives external energy. At room temperature, pure silicon has few electrons in the conduction band, not as many as a conductor, so there is resistance to current. However, with a technique called "doping", impurities are introduced into the silicon lattice, adding free electrons, thus allowing it to conduct electricity. In this way, we can design "impurity paths" along the silicon plate where we want to conduct electricity and leave the surrounding silicon in a more resistive state. Thus, we obtain special control over the movement of free electrons within the crystal. (2)

Silicon doping results in an n-type semiconductor or a p-type semiconductor depending on the atom used as the impurity. The silicon atom has 4 valence electrons, which form covalent bonds with the electrons of neighboring silicon atoms, forming a tetrahedral crystal lattice. In pure silicon, all these electrons are held tightly in their bonds and few get enough energy to travel through the lattice, hence, the semiconductor. (2,3)

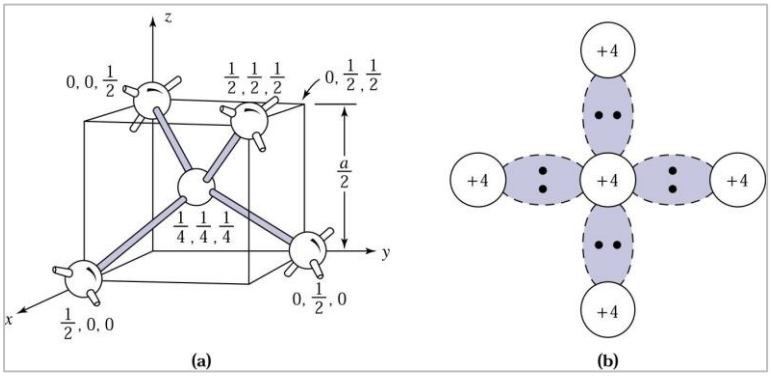


Figure 1. Tetrahedral structure of the silicon atom, 4 valence electrons forming covalent bonds with valence electrons of neighboring silicon atoms. (4)

To create an **n-type** semiconductor, the dopant element used must have 5 valence electrons (one more than silicon), like phosphorus or arsenic. The structure of phosphorus is similar to that of silicon, which means it fits perfectly into the lattice structure but carries with it one extra freely moving electron. After doping with phosphorus atoms, the end result is many freely moving negative charges (n-type, for negative) in the lattice and thus better conduction of electricity. (2,3)

In **p-type** doping, an element with 3 valence electrons, e.g., boron, is injected into the lattice, leaving an electron-hole, where silicon's 4th electron would be. Even though no extra electrons are added this still increases the conductivity, because it allows electrons to move into and out of it, easing the movement of current. Even though it is still the electrons that are moving, we refer to this as moving of the holes since there are fewer of them and they appear further down the lattice in the opposite direction each time an electron moves. (2,3)

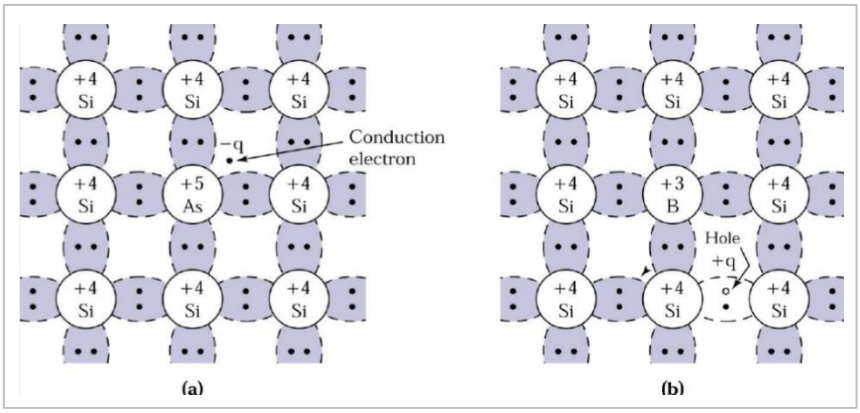


Figure 2. (a) Arsenic and (b) Boron atoms fitting into the silicon crystal lattice providing a conduction electron or a hole, respectively. (5)

The terms negative-type (n-type) and positive-type (p-type) do not mean that the semiconductors are negatively or positively charged. They are both neutral since the number of electrons is equal to the number of protons in the atomic nuclei of the lattice. The terms denote the type of charge that is moving, i.e., a negatively charged electron is moving in the n-type and a positively charged hole is moving in the p-type semiconductor. An **n-p junction** is formed when an n-type semiconductor is placed directly adjacent to a p-type semiconductor. The electrons from the n-type are attracted to the holes in the p-type, however, they lack sufficient energy to cross over, forming a type of barrier. Electrons can

only surpass this barrier if additional external energy is applied, but the movement is only permitted in one direction and not in the opposite. This unidirectional permission of current conduction makes the n-p junction a type of diode, which is essential in constructing semiconductor switches. (2)

3.4. Field-effect transistors (FETs)

A crucial physical property of semiconductor devices is the Field-Effect. The Field-Effect is defined as, the modulation of conductivity of an underlying semiconductor layer by the application of an electric field to a gate electrode on a surface. (Brennan K. et al., 2012) (6) In other words, applying a negative voltage to an n-type semiconductor repels the electrons on the surface of the material, thus creating holes. This means that the area under the applied voltage is now behaving like a p-type semiconductor. Thus, we observe a change in polarity due to the application of an electric field. This phenomenon can be exploited to manufacture a switch of electric current, a transistor, which is why it was named the field-effect transistor (FET). (2) The field-effect transistor is a remarkable device since it allows us to switch current on and off, without mechanical work, merely by applying a small voltage. Instead of a mechanical switch, we use a voltage, and the electrical contact that applies this voltage is called a Gate. A common FET configuration is as follows:

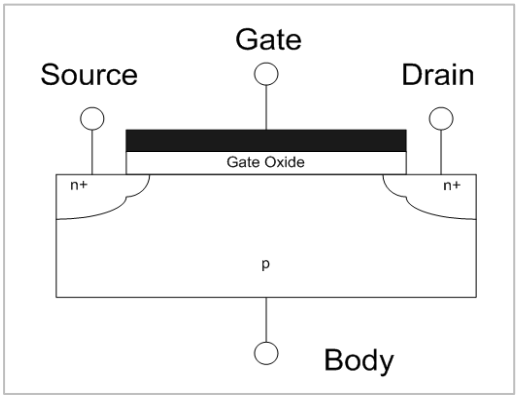


Figure 3. Schematic representation of a FET with p-type semiconductor in the middle and two n-type semiconductors on each side. The source and drain are in contact with the n-types, the gate overlies the p-type with a slight overlap of the n-types on both sides. (7)

Each FET is composed of two n-type semiconductors on each side of a middle p-type semiconductor material. The incoming current is applied by the source and the outgoing current flows through the drain. The source and the drain are the electrical contacts over the n-type semiconductors. A thin insulating layer separates the gate from

the transistor to prevent short-circuiting the current from the source to the drain. (2,8) In a transistor, when the semiconductor is doped to have n- and p-type material next to each other, the electrons from the n-type (where they are in excess) diffuse into the p-type to fill the holes, but only along the n-p junction. So, the added electrons on the p-side make the surface of the p-type negative. This is called the Depletion layer because there is a depletion of free-moving electrons since they have occupied the holes. This layer is depleted of moving charges. The negativity in the p-type, created in the depletion layer will repel any other electrons crossing from the n-type, creating a barrier against the flow of current. In the absence of applied voltage by the gate, two depletion layers form at the n-p junctions of the transistor, acting as a barrier to the free electrons in n-type, thus blocking the flow of current (the "switch" is off, in the 0 state). The electrical circuit is open. Upon application of a positive voltage by the Gate, the repulsion from the depletion layer is overcome and the electrons from the n-type are now attracted to the positive voltage. This creates a conducting channel for current to flow. In this state, the transistor switch is on (in the 1 state), and the electrical circuit is closed. (2,8)

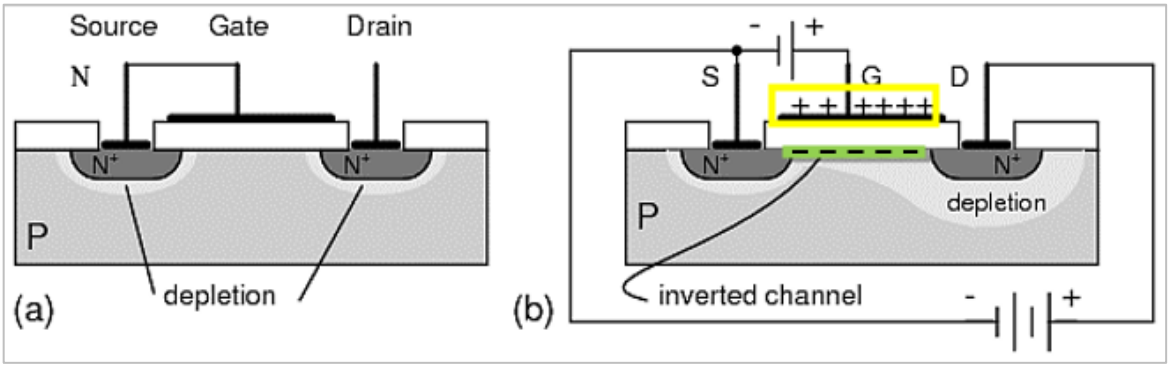


Figure 4. (a) Depletion layers between n- and p-type materials in the absence of applied voltage by the gate. Formation of n-channel (green) though p-type region via application of positive voltage (yellow) by the gate. (8)

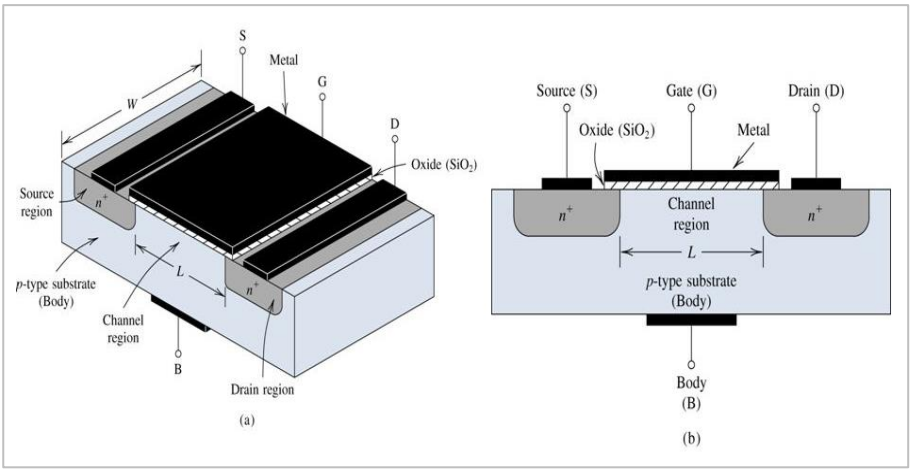


Figure 5. Side and frontal view of a FET showing the region of channel formation, upon application of positive voltage by the gate. (9)

The revolution of the transistor has allowed us to turn switches on and off without any change in their physical configuration. Additionally, transistors can be made extremely small making them even cheaper to manufacture, less power-consuming, and more practical for incorporation into commercial devices. In fact, since its invention, the size of the transistor has been steadily decreasing, which brings us to Moore's Law. (10)

3.5. Moore's Law

In 1965, Gordon E. Moore observed that the number of transistors in Integrated Circuits doubled approximately every 2 years, due to miniaturization of the transistor and thus increase in their density per chip. He also predicted that this trend will continue for many years to come, and he was, in fact, right. The problem is that as transistors become smaller, constituents get closer to each other, and quantum effects start being relevant, meaning that eventually, electrons might be able to tunnel through the transistor and the barrier will no longer stop them. From 1965 to around 2010 his prediction was proven true, however, since then the trend has somewhat decelerated with the number of transistors in a chip doubling every 3 years, instead of every 2. Nevertheless, transistor sizes keep getting smaller and density keeps increasing to this day. As transistor densities increase, the capabilities/operating speed of integrated circuits become faster, and the relative cost of each chip keeps decreasing, which explains the industry's strive to keep going smaller. Moore's correct observation and prediction have since been termed Moore's law. It isn't actually a physical law. (10)

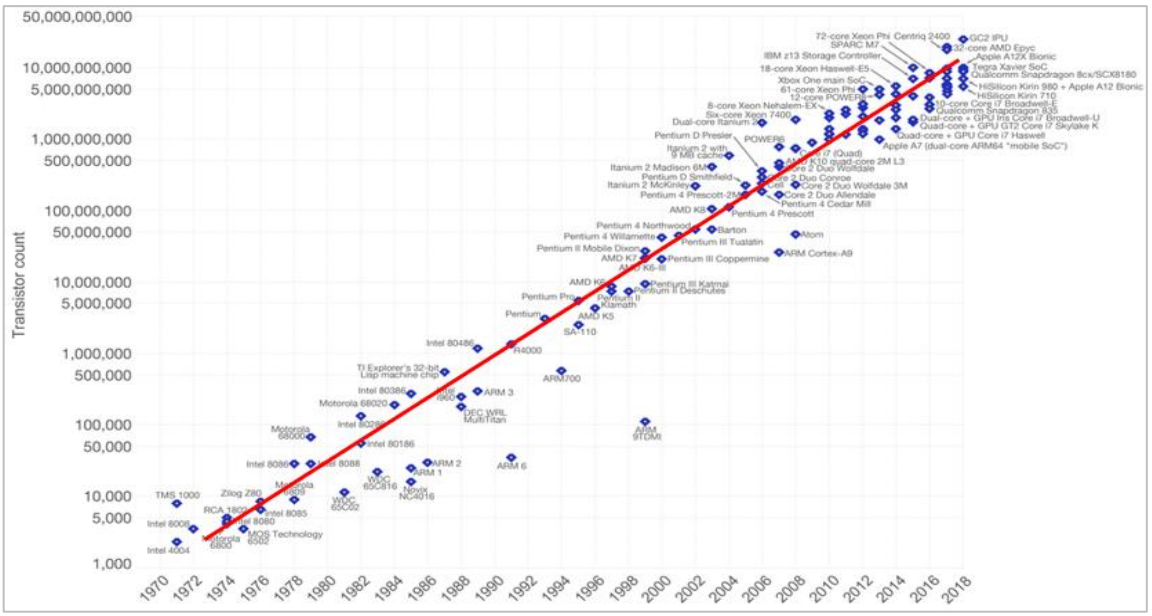


Figure 6. Moore's Law: number of transistors on integrated circuit chips between 1971-2018. (11)

However, Moore's law is slowly becoming irrelevant since the next generation of transistors will not depend on decreasing size to improve speed. Currently, computing data is stored on bits (0s and 1s) that are defined by the state of the transistor. However, with components getting smaller, quantum physics enters the equation. Today's typical transistors (blocking or allowing electron currents) are around 10-20 nm. As transistors are shrinking to the atomic scale, electrons will eventually be able to cross/bypass the transistor gate via quantum tunnelling, rendering the transistor useless. (12,13)

Thus, we are approaching the era of the **quantum** computer, where the quantum properties will be used toward the advantage of computing, and where immensely faster speeds can be achieved. This will no longer depend on further miniaturization of the transistor, but rather on employing qubits (quantum bits) as our new binary digits. As with normal computing bits, qubits can also be set to one of two values. These values represent the possible states of any two-level quantum system (e.g., horizontal or vertical photon polarization). Qubits, however, are in superposition, thus when unobserved they can be in any proportion of both states at the same time. Only upon observation, a qubit collapses into one of the two definite states. This exponentially increases computing speeds and data storing capabilities. Qubit entanglement and qubit manipulation allow for quantum gates

to manipulate an input of superpositions, meaning that all possible probabilities are calculated instantaneously. This is relevant for scientific research since database searching and simulation experiments can be performed much faster and more accurately. (14,15)

3.6. Back to the Nanochip

Thus, a chip is an integrated circuit made up of billions of field-effect transistors along with other parts interconnected on a semiconductor surface. (2) A nanochip is an integrated circuit (IC) having components of nanometre scale, that is 1-100 nm, thus individual particles of matter play major roles. Nanochips may also involve nanomaterials and nanotechnologies for functional applications. In fact, IC components have been made in this dimension since the year 2000. (16) This is significant not only for the purpose of further miniaturization but arguably more so, because of the novel properties of nanomaterials and nanostructures. These properties open a whole new realm of applications for nanochips. This dissertation is a review of the applications of nanochips in the medical field, including diagnostic, therapeutic, and other biomedical applications.

3.7. Medical applications

In recent decades the scientific community has found a way to exploit the unique properties of nanochips to create biosensors for ultrasensitive, real-time detection of biomolecules. In-vivo and In-vitro techniques have been utilized for detection of DNA molecules, ions, antibodies, (17) important proteins, and tumor markers not only from blood samples but from the skin, breath, sweat, and more (18). These methods seem to be faster (real-time), less invasive, with increased accuracy and are label-free diagnostic procedures, thus do not necessitate laboratory expertise and could completely transform the rather time-consuming diagnostic field as we know it today. Additionally, therapeutic applications of semiconductor devices include, manufacture of “bionic” organs like artificial retinas, artificial skin, “robotic” prosthetic limbs, and possibly even brain-machine/computer interfaces for restoration of motor and sensory ability in paralysis and communication abilities in “locked-in-syndrome” patients. (122,124)

4. Theory

4.1. IC Manufacturing Process – Lithography, Etching, Doping and Metallization

Silicon Dioxide (SiO_2) is the second most abundant element on the crust of the earth and the main constituent of sand. Silica sand is used to make pure silicon by heating in combination with carbon to remove oxygen. The result is pure monocrystalline silicon which is then fabricated into a silicon ingot ('Boule'). This is done by melting silicon in a crucible and keeping it just above melting temperature. (Doping of the pure silicon can be performed at this stage). A seed crystal is submerged into the raw material and then slowly pulled back out while in rotation. The crucible (container) is also rotated in the opposite direction allowing the crystal to grow. This is known as the Czochralski (CZ) crystallization method. (3,19)

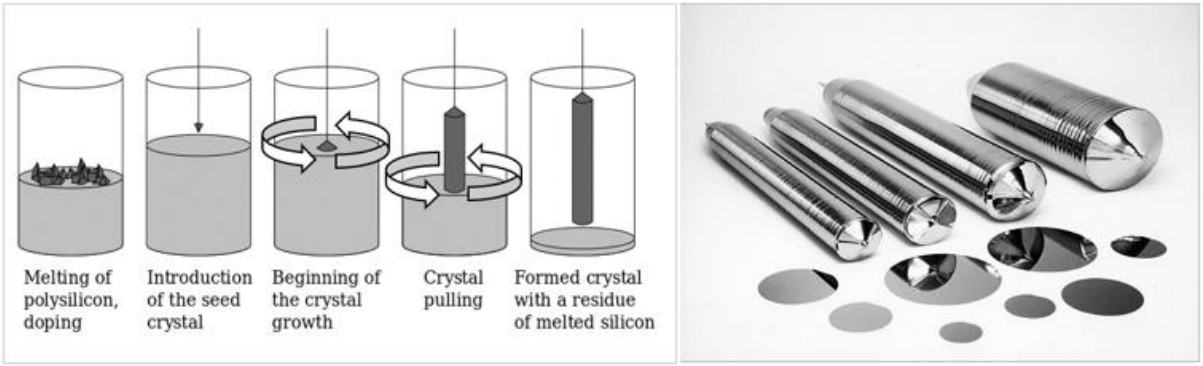


Figure 7. (a) Illustration of Czochralski (CZ) crystallization process, to create a pure monocrystalline silicon ingot (boule), (19) (b) Picture of silicon boules of several sizes and respective sliced wafers. (20)

Once the ingot is made, it is refined to remove any uneven surfaces and to adjust the cylinder to the desired diameter. It is then sliced into thin silicon wafers. Depending on their size, hundreds to thousands of chips can be made on each wafer. To ensure purity of the wafer and high-quality manufacture, IC production is carried out in a Cleanroom with steady temperature and humidity as well as strict staff protocols, to ensure that dust particles do not compromise the product. (3,19)

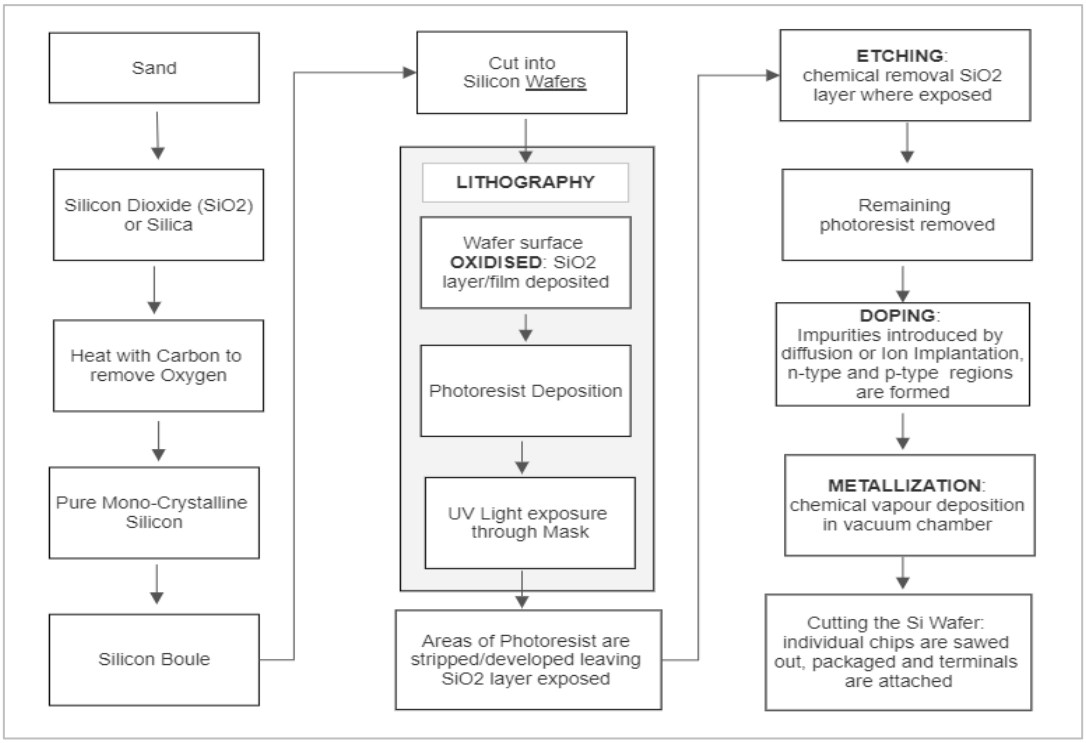


Figure 8. Main steps in fabrication of an integrated circuit 'chip' from raw materials. (3)

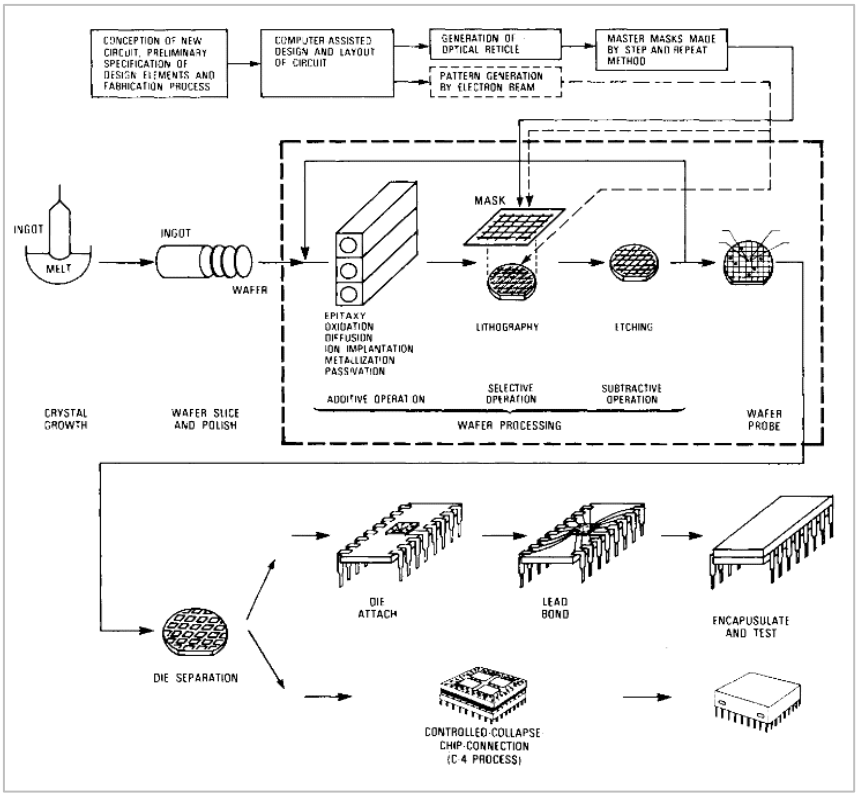


Figure 9. Illustration of chip manufacturing process, from silicon ingot to packaged IC. (3)

4.2. Mask Design

To manufacture an integrated circuit, its architecture and interconnections must first be accurately designed on a computer program. With the help of CAD (computer-aided design) systems, trained professionals design a blueprint of the circuit, according to the desired function. This blueprint is then used to create a lithography mask that will transfer the designed pattern onto the silicon wafers. This mask can be used repeatedly, without affecting its shape, meaning that all the resulting chips will be exactly identical, making it ideal for large-scale commercial manufacturing. (21)

4.3. Lithography

The wafer is placed in a high-temperature furnace, and the surface of the wafer is **oxidized**, creating a non-conductive/insulating silicon dioxide surface layer. Then a **photoresist** is deposited on top of the SiO_2 layer. A photoresist is a light-sensitive material that can either be degraded by exposure to light in developer solution, a positive photoresist, or may become insoluble in the presence of light, aka a negative photoresist. Either can be used, but for the purposes of this description, the positive photoresist method will be discussed. After the photoresist is applied, it is exposed to **UV light** through the lithography mask. The photoresist is stripped away in the areas exposed to light and the designed pattern is thus transferred onto the photoresist. Strips of the underlying silicon oxide layer are now exposed in the areas where the photoresist was removed. (3,22–24)

4.4. Etching

Etching removes the silicon oxide layer revealed after the development of the photoresist. The oxide layer under the intact photoresist remains protected from the etching process. (This is exactly the purpose of the photoresist.) **Wet etching** is performed by submerging the silicon wafers into a chemical solution, which comes into contact with the silicon oxide layer and etches it out. **Dry etching** utilizes chemically reactive gasses or physical bombardment with argon atoms. At the end of this process, the conducting silicon layer is now exposed again in certain locations. The remaining photoresist can now also be removed. (23)

4.5. Doping

Once the etching process is complete, the underlying exposed silicon can now be selectively doped (doping occurs only in the exposed windows). Ion Implantation and Diffusion are methods used in the IC industry for semiconductor doping. **Ion Implantation** involves accelerating dopant boron or phosphorus atoms in a powerful electrical field to bombard the unmasked wafer surfaces. The dopant elements are implanted in various depths of the crustal. **Diffusion,** on the other hand, uses a furnace and usually dopants in the gaseous state, that pass into the semiconductor via the pressure of a concentration gradient, again only in the exposed areas of the wafer. This means that we can create n-type doping tracks on a p-type semiconductor and vice versa, to thus increase conductivity, and build transistors over the n- and p- layers. (3,22–24)

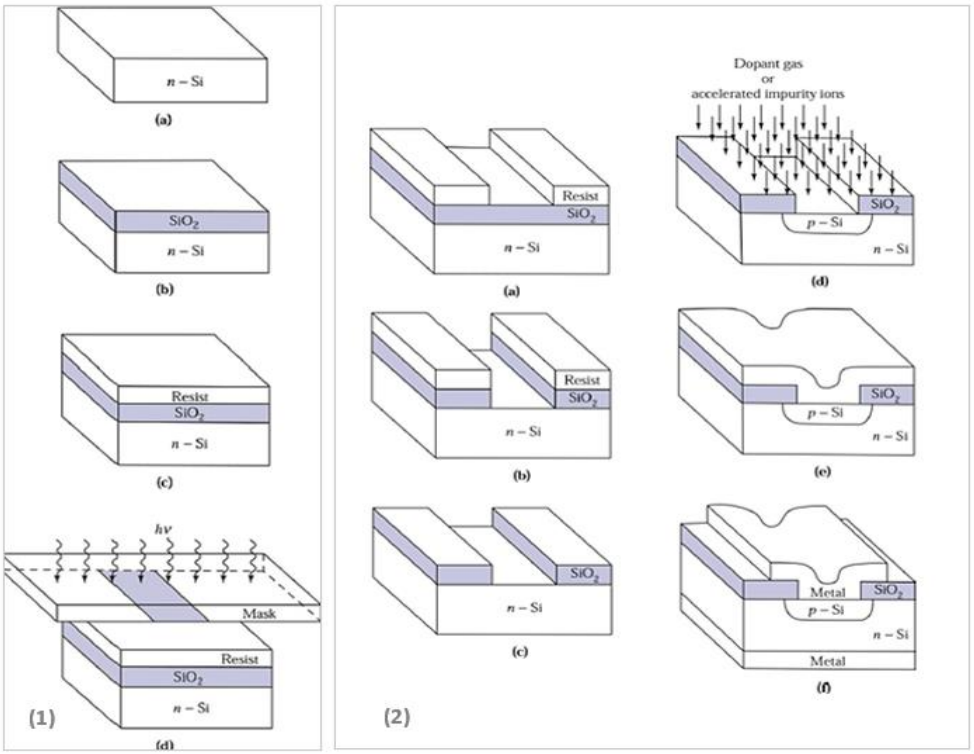


Figure 10. Chip processing steps (1) (a) pure silicon wafer, (b) Oxidation: addition of silicon dioxide layer, (c) Photoresist deposition, (d) UV light exposure through the lithography mask, (2) (a) photoresist dissolution in areas exposed to UV light, (b) Etching: exposed SiO2 layer removed (etched-off), (c) remaining photoresist stripped, (d) Doping (e, f) Metallization (25).

4.6. Metallization

After doping, the individual components of the circuit (transistors, capacitors, etc.) are added to the wafer. These components must then be interconnected with each other with ultrathin 'wiring' to allow the flow of current through the circuit. This is accomplished by metallization. In the past, aluminium was used, however, in the 90s the industry switched to copper for its superior conductivity and because it can be deposited in thinner lines, thus apt for the miniaturization of transistors and chips. (3,22–24)

Metallization begins with deposition of another silicon dioxide layer, a dielectric material. This acts as an insulating layer between individual deposited copper wires. The dielectric SiO2 layer is then etched according to the wiring design. The channels are subsequently filled with a layer of copper to create the first level of wires. **Physical vapor deposition** (PVD), **evaporation**, **chemical vapor deposition** (CVD), and **electrochemical deposition** (ECD) are frequently used for metal thin film deposition. Each with its own intricacies, the main concept behind these techniques is to induce movement of metal vapor ions through a medium (vacuum or electrolyte solution), which will then settle on the wafer surface thereby depositing a uniform metallic layer, a 'wire'. (3,22–24)

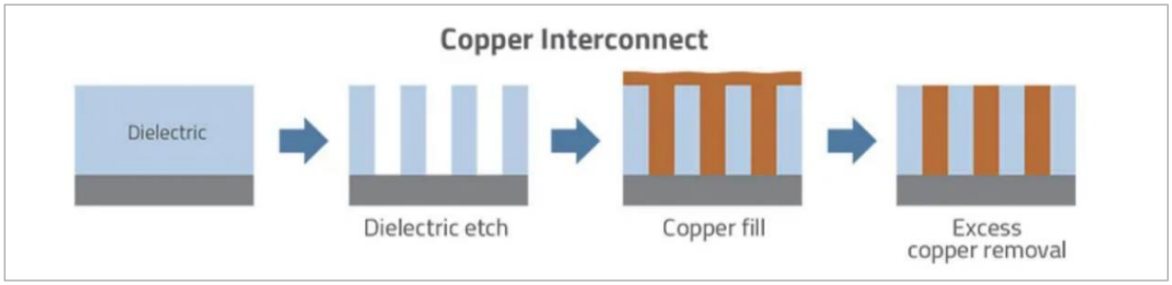


Figure 11. Metallization: steps of copper interconnect (wire) deposition. Dielectric (insulating) layer deposited and etched-out according to wiring design, copper is then deposited to fill etched wells, and excess copper deposited over the dielectric surface is removed. (26)

The cycle of oxide layer deposition, photolithography, and etching are repeated several times to create several layers of wiring. Instead of doping between these cycles,

metallization is performed. Due to the small size of these chips, in order to connect all elements and regions of the chip, several vertical layers of interconnecting wires are manufactured. Lower-level wiring connecting neighbouring components are called 'Local Interconnects' – whereas higher up, 'Global Interconnects' join different areas of the chip. (3,22–24)

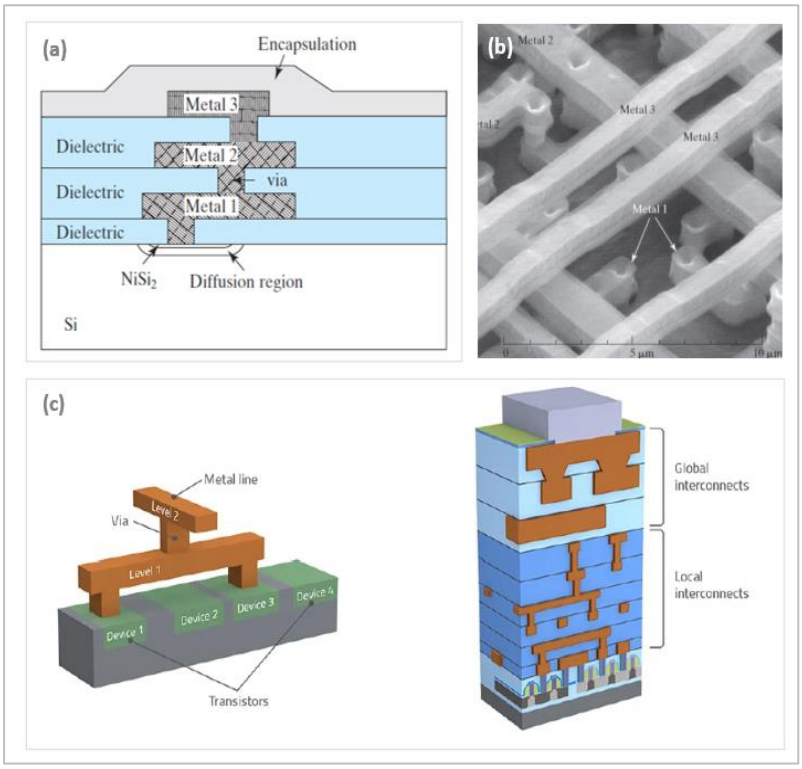


Figure 12. (a) 3-layered interconnects surrounded by insulating dielectric over a silicon wafer, (b) (SEM) Multi-layered interconnect after removal of the dielectric (27), (c) (Left) Level 1 interconnect bridging devices 1 and 3 and level 2 interconnect joining level 1 with other areas of the chip through a 'Via': metal connections between each layer of interconnects, (Right) multi-layered local and global interconnects overlying part of a silicon wafer. (28)

4.7. Dicing and Assembly

After metallization, each wafer contains hundreds to thousands of identical integrated circuit chips in series. Dicing is performed, to saw out the individual chips from the wafers. Dicing can be performed with a blade, laser or plasma dicing. Each individual fragment containing a chip, after dicing, is also called a 'silicon die'. Terminals are attached to the die and they are packaged (for protection from the physical and chemical environment) into semiconductor devices that can be mounted into circuit boards, thus completing the manufacturing process.

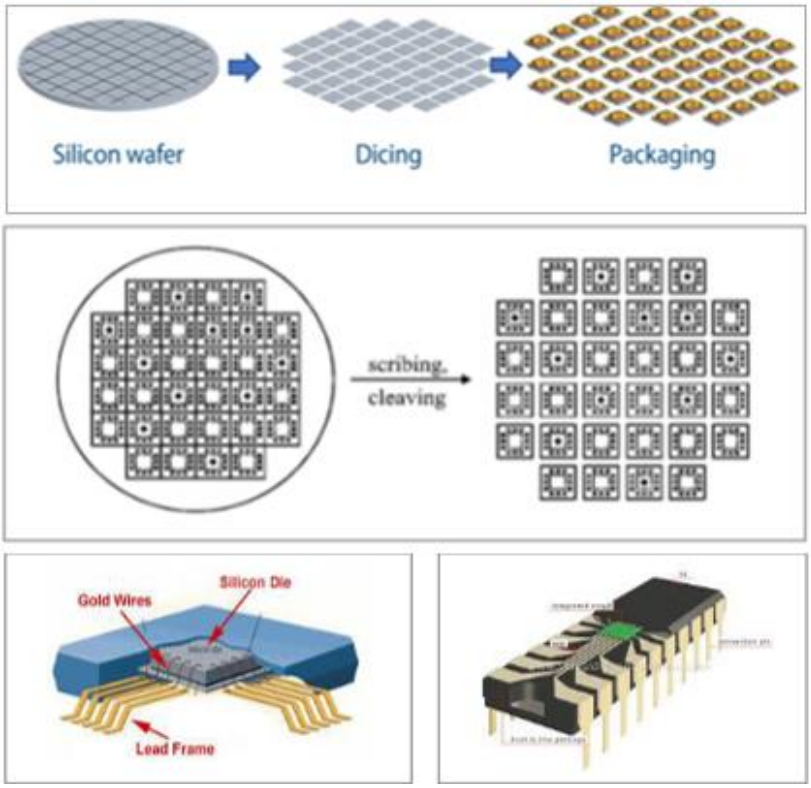


Figure 13. (Top) silicon wafer diced into individual chips which are then packaged, (Middle) silicon wafer cleaved into IC chips, (Bottom) Final product: Packaged chips with attached terminals (gold wires, lead frame). (29–31)

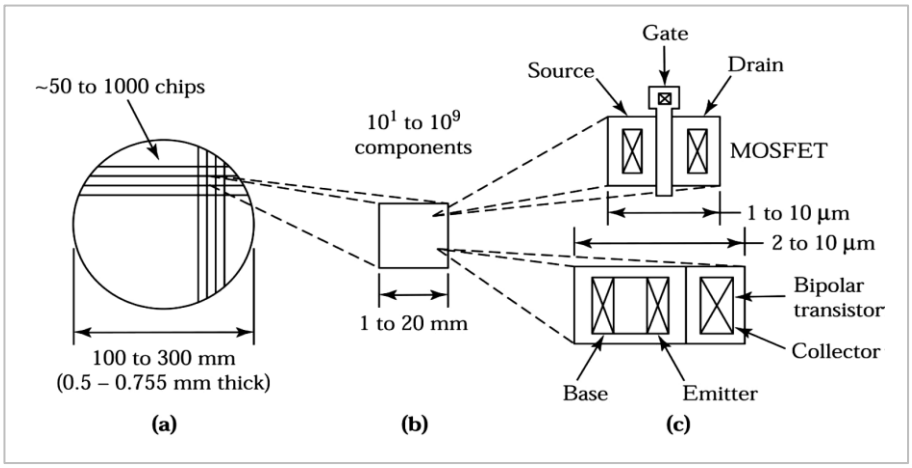


Figure 14. Schematic Illustration showing the scale of (b) IC chip to (a) silicon wafer, and that of the (c) field-effect transistor (FET/MOSFET: metal-oxide-semiconductor field-effect transistor) to the IC chip. (32)

4.8. From FET to Biosensor

As nanochips contain billions of transistors (their functional unit), we can modify field-effect transistors, to form biosensors on a chip. Since we have events of electrical conductance within the transistor, we can use the properties of electrical current, like conductivity and resistance, to gather information about the presence of biological molecules. If a transistor gate is modified with capture probes (receptors), binding of a biomolecule to that probe will change the conductance through the circuit, since we will have somewhat altered an element of the circuit. This translates as a change in conductivity which can then be recorded and documented as an event of biomolecular detection, i.e., proof of target molecule detection.

The desired outcome is that since transistors are such sensitive devices, even the binding of a few molecules in a large sample can be recorded as an electrical event, thus achieving extremely high sensitivity in diagnostics. The conductance can be changed either by the molecule adding resistance to the circuit (decreasing conductivity) or by forming a conductive bridge between two electrodes (allowing the flow of current). (33) The changes in conductivity depend on the type of semiconductor (p or n) and the type of charge (positive or negative) on the surface creating the field effect. (34) In this way, biological molecules can be used as components of an electric circuit, i.e., either as a resistor or a switch. Researchers have manufactured and are investigating field-effect transistors that could enable this process. Each reported biosensor may have its intricacies, but this chapter is an attempt to explain the general concept of FET-biosensing.

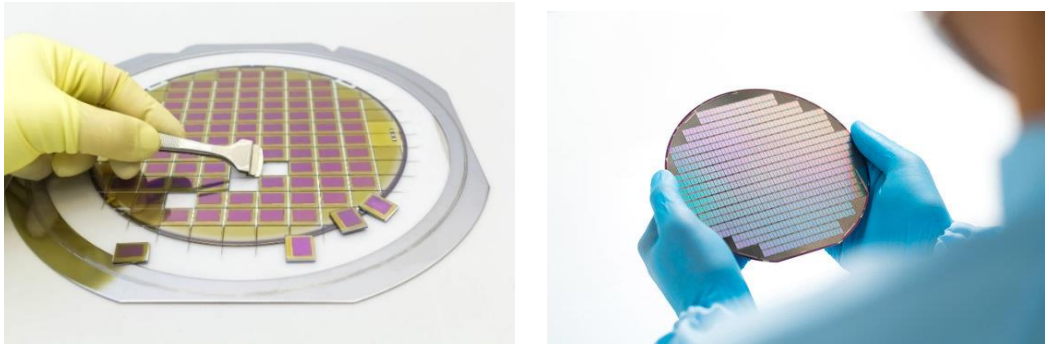


Figure 15. Photographic image of a silicon wafer containing manufactured integrated circuit chips on the surface in series, showing scale to the human hand. (35)

Silicon nanowire FETs (SiNW-FETs) seem to be promising candidates for biosensing chips for their capacity to perform label-free sensing of biomolecules, metal ions, and gas molecules with ultra-low limit-of-detection (LoD). Additionally, if modified with ion-specific aptamers, the concentration of ions like potassium can be measured, and thus neuron and cardiomyocyte action potentials can be studied. Label-free biosensors are analytical devices that transduce the binding of target molecules to their biologically sensitive layer into an electrical signal (Tintelott et al). The biologically sensitive layer is receptor-modified for selective binding. This concept is implemented to create label-free biosensing SiNW-FETs. Biosensing SiNW-FETs are similar to traditional FETs; however, a receptor layer is bound to the gate dielectric via surface chemistry. When in contact with a biological sample, the gate dielectric is submerged within this liquid, and target molecules, if present, bind to the receptor layer. This results in an electrical response in the SiNW-FET. (The source and drain are protected with a passivation layer to disable short-circuiting via the liquid.) (17)

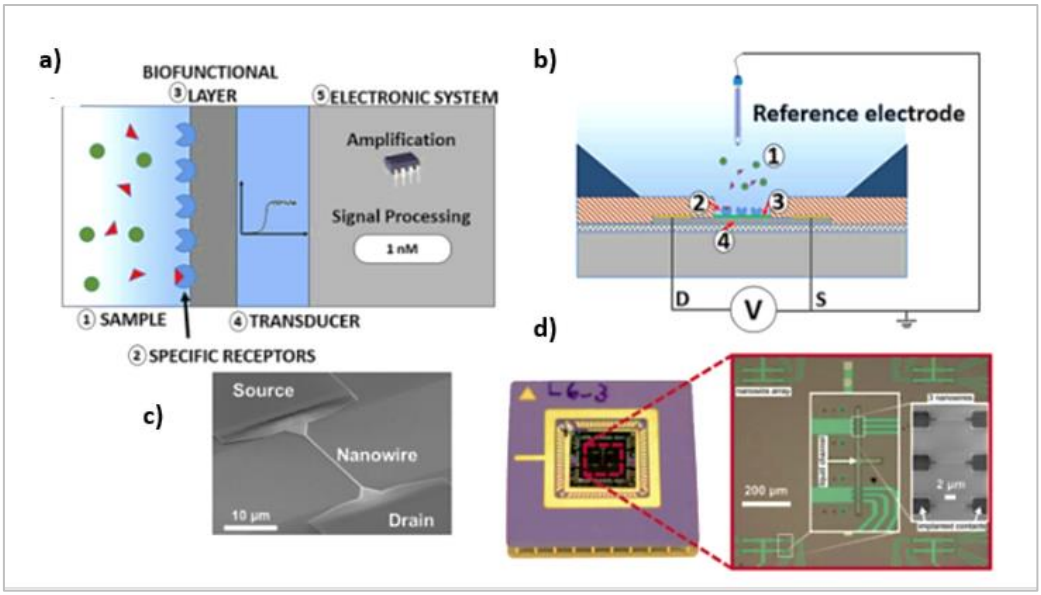


Figure 16. (a) Illustration of an electrical biosensor: The target molecule is detected by receptors on the biosensitive layer, alters its electrical characteristics, which are recorded by the electronic system. (b) Illustration of a biosensor based on SiNW-FETs in liquid sample. (c) (SEM) scanning electron microscopy image of a SiNW bridging source and drain. (d) SiNW-FET chip with microfluidic structures. (17)

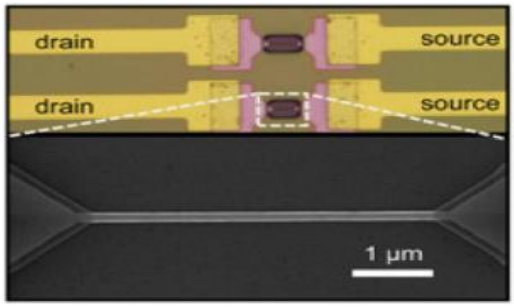


Figure 17. Silicon nanowire gated transistor with connecting circuit drain and source and silicon nanowire in high magnification. (17)

Impedance is the total resistance of electrical equipment to alternating current (36). Each SiNW-FET is set at a reference point and a sinusoidal signal is added to the gate electrode. When target molecules bind to the receptors of the biolayer they alter the effective gate capacitance and resistance of the transistor, resulting in a change in the frequency response and the impedimetric readout of the device.

The nano-dimensions of these SiNW are crucial since they affect their surface-to-volume (S/V) ratio and thus their detection sensitivity. The electrical properties of the nanowires in turn determine the LoD and signal-to-noise ratio of the biosensor. The sensitivity of such nanowires is expressed by the change in conductance occurring, as binding events occur on the surface. Additionally, their sensitivity has been shown to decrease with a reduction in cross-section and doping concentration. Optical or electron beam lithography can both be used to manufacture such silicon nanowire FETs for biosensors. (17)

The interface between the biological world and electronics (i.e., the sample and the biosensor) is accomplished in this receptor-ligand interaction. Physiologically, in living organisms, billions of very specific receptor-ligand interactions happen all the time and are the basis of functioning cells and organ systems. In other words, there is an abundance of different types of molecules in the human body but each receptor only binds its own respective ligand. This very selective intermolecular interaction is true for all sorts of biomolecules. Antigens and antibodies, complementary DNA strands, ligands and receptors attach to each other very selectively, therefore, there is no binding event if the two are not analogous. We can exploit this naturally occurring phenomenon to make highly specific biosensors in which a change in conductivity will only occur if there is precise complementary binding, making the sensor an accurate device to measure the presence of a biomolecule. (17)

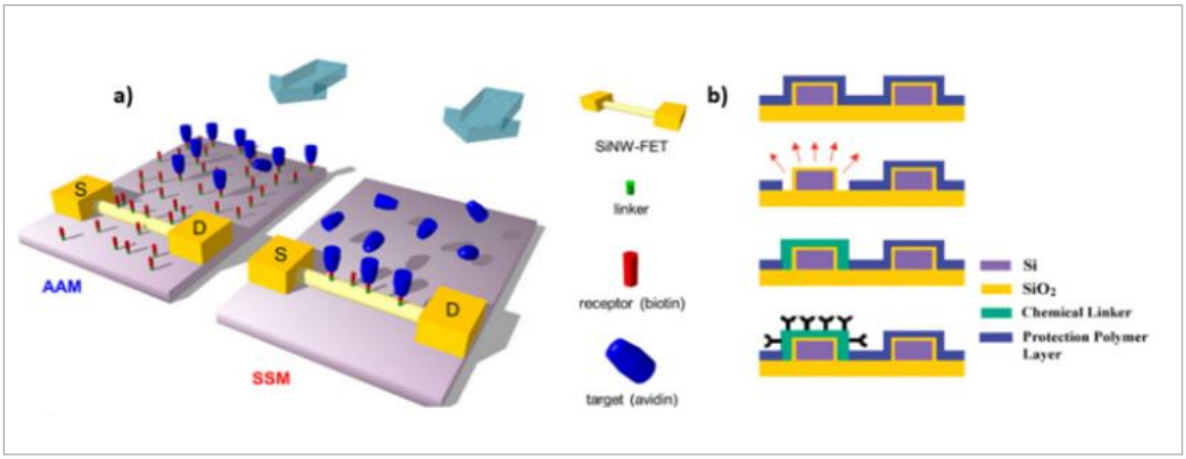


Figure 18. (a) Illustration of (AAM) all-area modification and (SSM) selective surface modification of the silicon nanowire FET surface with receptors (red) to bind the target biomolecule (blue) (b) Single nanowire receptor modification with the use of a protective layer. (17)

Surface functionalization of the nanowires with high-affinity receptors can be accomplished by Silanization with (APTES) 3-Amino-propyl-triethoxy-silane or (GPTES) Glycidyloxy-propyl-trimethoxy-silane. In this way, the target molecule receptors can be covalently bound to the gate oxide surface. Two approaches exist, namely, all-area modification (AAM) and selective-surface modification (SSM). All-area non-uniform receptor binding may induce surface charges and influence the threshold voltage of the sensor whereas the SSM decreases the LoD compared to AAM. (17) Finally, SiNW can reportedly be manufactured in both top-down and bottom-up fabrication approaches. (34)

Nanoribbons may also be used in biosensor FETs. They are made of graphene and are compatible with semiconductor devices. (37) They too can be incorporated into a transistor and surface functionalized with probes for detection of target molecules. They are capable of real-time, label-free detection of biomolecules in sub-femtomolar concentrations. Nanoribbon biosensing is likewise based on the principle that binding of biomolecules to the FET's probe (receptor) results in a change in the conductance of electrical current. (38)

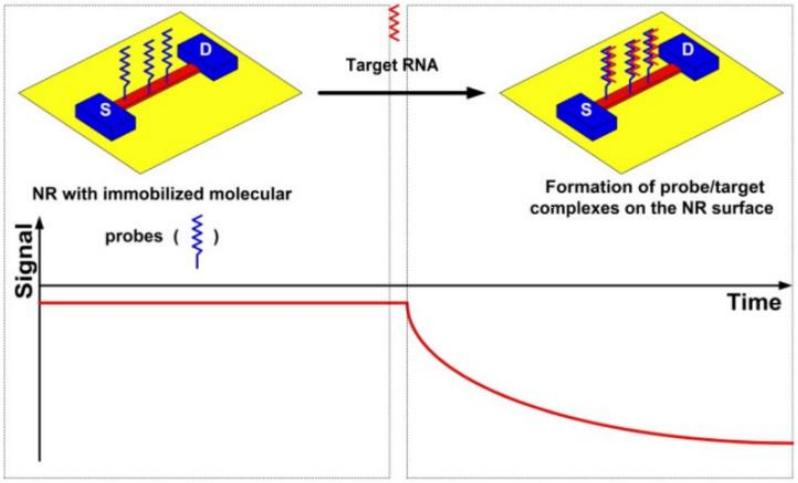


Figure 19. Illustration of the concept and mechanism of real-time biomolecular detection using nanoribbons. The first image shows a baseline signal from the biosensor when the probes (blue) are unbound/free. In the second image, the sample is introduced and the target biomolecules (red, target RNA) selectively interact with the probes. This interaction causes a change in the conductance of the NRs and consequently a drop in the biosensor signal. (38)

4.9. Rethinking Current Diagnostics

In summary, field-effect transistors can be receptor-modified to produce real-time ultra-sensitive bioelectrical sensors. This is significant because it addresses some of the major problems the medical field faces today. Diagnostic procedures with a latency period to results often lead to decreased compliance in patients. A second patient-physician consultation is necessary, to discuss the diagnostic result, which can further decrease compliance and adds to the workload of both the medical staff and the patients. Patients often delay or even entirely dismiss diagnostic tests or medical care, because of their time-consuming nature. Especially in the case of chronic conditions, real-time diagnostics can half the number of visits and significantly improve quality of life and possibly even the quality of medical care. Furthermore, label-free automated electronic tests free up/liberate time and funding from diagnostic laboratories and could even render them unnecessary in the future.

Relieving these barriers can potentially mean that patients will be less hesitant to seek medical attention and therefore lead to diagnosing diseases before progression. To

add to this, FET biosensors are immensely more sensitive than conventional tests used today, so biomarkers of disease can be detected even in the very early stages of the disease. The stage of a disease at the time of diagnosis is one of the most important factors affecting prognosis. Detecting tumor markers in a blood sample when a tumor is still in-situ, versus identifying a tumor after the appearance of symptoms can quite literally mean the difference between life and death. Therefore, ultrasensitive real-time FET biosensors have the potential to save thousands of lives in the future.

5. Methods

5.1. Research Strategy

An extensive search of the published literature was conducted using the electronic databases PubMed, Google Scholar and Scopus to collect information concerning the nature of nanochips and how their properties can be applied in the medical field. The objective was to analyze the available literature to obtain a complete and all-inclusive understanding of diagnostic and therapeutic applications of nanochips, as well as their potential to help advancement of the academic and clinical biomedical field. Additionally, an assessment of their advantages over conventional methods used today, along with their limitations is presented in this review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed when conducting this review.

5.2. Selection Criteria

For identification of relevant papers, specific inclusion and exclusion criteria were applied.

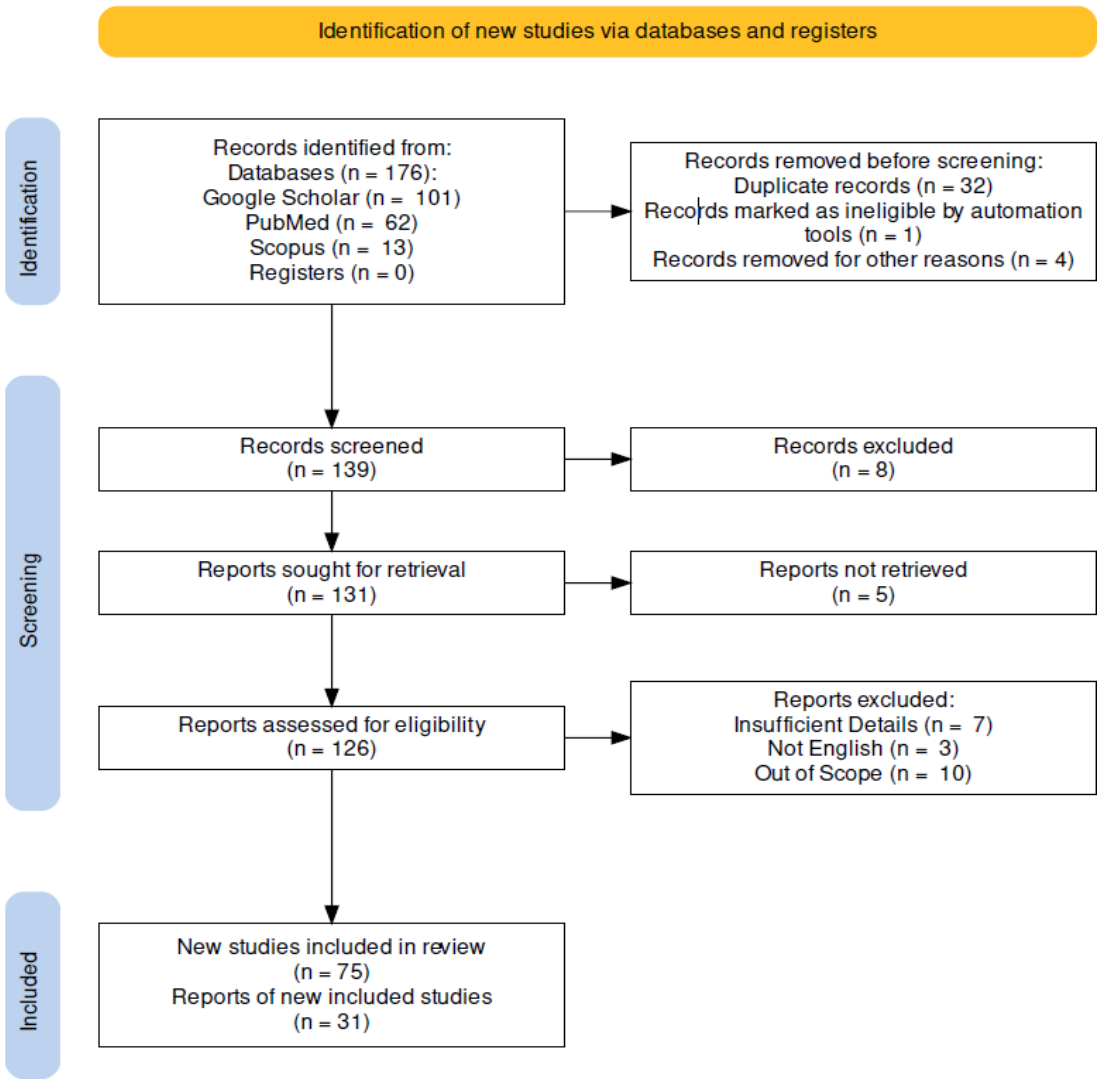
Inclusion Criteria:

- Textbooks, Research articles: Experimental Studies, Literature Reviews, Case studies
- Papers related to integrated circuits, FETs or semiconductor devices in some form
- OR Paper had to relate to nanotechnology, medicine or nanomedicine in some form
- Published not prior to 1999
- English language

Exclusion Criteria:

- Newspaper articles
- Conference abstracts and letters
- Papers concerning operating computer systems and programming of integrated circuit systems

5.3. PRISMA Flow Diagram



Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–12.

6. Results

6.1. Diagnostic Applications: Molecular and Cytological Detection

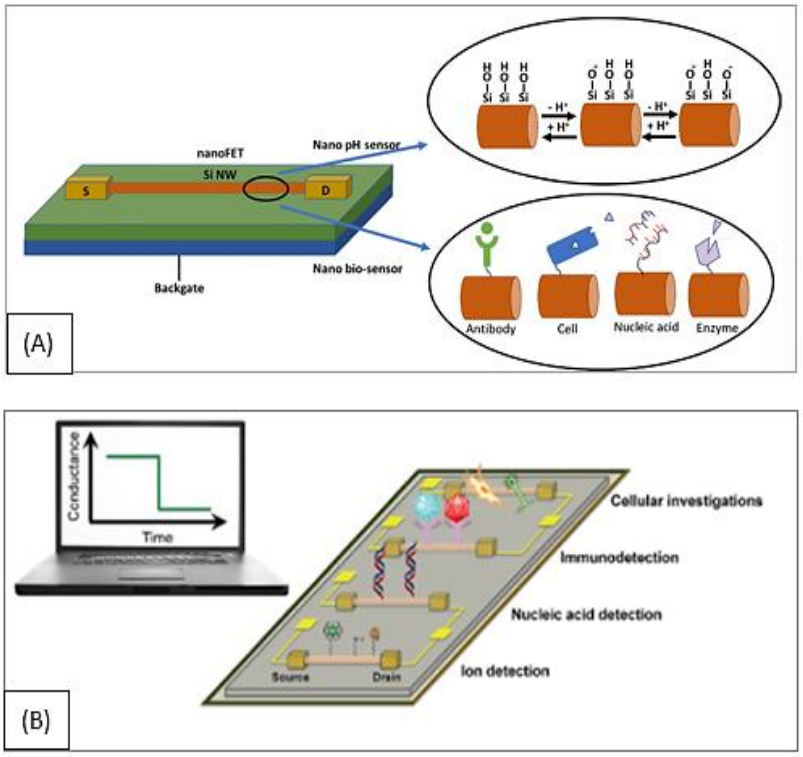


Figure 20. (A) Nanowire-FET-based biosensor for detection of pH, antibodies, cells, nucleic acids and enzyme-based detection via NW functionalization, (39) (B) Simplified illustration of chip with modified FETs for biomolecular detection on the basis of conductance changes due to hybridization. (40)

6.1.1. DNA and Gene Detection

Zhiqiang et al. and colleagues demonstrated successful DNA detection with transistor-compatible silicon nanowire arrays. The SiNW were surface-functionalized with -complementary to the target DNA- (PNA) peptide nucleic acid capture probes, that exhibit a change in resistance proportionate to the concentration of hybridized molecules. PNA molecules were used instead of DNA probes due to their greater affinity, stability and discriminating ability for complementary molecules. Upon binding, the DNA molecules cause a change in negative charge density in the SiNW, increasing the electrostatic gating effect (i.e., the field-effect) resulting in increased resistance, sensed between the source and the drain. This is the basis of their sensing mechanism. The sensor was tested at several concentrations of DNA and against a control (non-complementary DNA). Non-

complementary DNA molecules were excluded by the probes to an acceptable degree, and for complementary molecules a detection limit as low as 10fM was achieved. 60 minutes were enough for most samples to achieve hybridization. As a result, they managed to create an ultrasensitive, real-time, label-free and non-radioactive biosensor, to detect existing DNA molecules in samples and thus monitor gene expression. (41)

This principle of DNA detection based on the field effect has also been reported by other studies on semiconductor nanowire devices (42–44) including silicon nanowires (41,45). Even though a PCR can also perform genotyping, its capability and reliability are limited when it comes to detection of scarce genes. Additionally, in comparison with fluorescent techniques, electrical sensing platforms are simpler, faster and portable. They eliminate biological and/or chemical ligation steps and the need for heavy optical readout machinery. This could allow the transition to simple bed-side or point-of-care genotyping, which is currently an expensive, 2nd line diagnostic step. Thus, we can achieve earlier diagnosis of evermore present genetic diseases and take anticipatory measures before the appearance of symptoms. (41)

Silane coupling agents are used for surface functionalization of SiNW-FETs for label-free detection of nucleic acids. DNA and RNA molecules possess negatively charged sugar-phosphate backbones, which enable their detection in the femtomolar range. (46–48) Additionally, reported is the use of electrostatically neutral PNA probes and alkyl-phosphonate oligonucleotides to improve signal-to-noise ratio upon DNA or RNA hybridization. (49,50) PNA molecule hybridization with DNA seems to be more stable compared to DNA-DNA hybridization for FET biosensing purposes. (51) PNA probes have been used for the detection of the CFTR gene genotyping for diagnosis of cystic fibrosis (46), detection of single nucleotide polymorphisms (52), as well as the detection of microRNA (miRNA) which can be associated with signalling processes in cancer development (50,53).

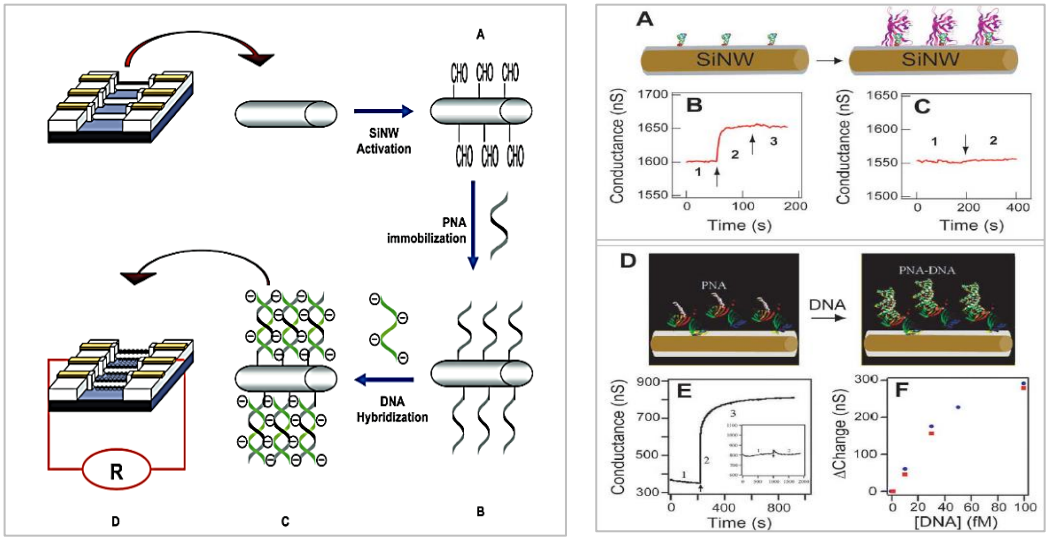


Figure 21. (Left) Biosensing concept: SiNW array functionalized with PNA for DNA detection. (41) (Right) (A, B, C) Change in conductance as a result of molecular hybridization (D, E) DNA hybridization to PNA probes and associated conductance change (F) change in conductance as DNA concentration increases, measured from 2 different devices (red and blue dots) (45).

6.1.2. Electrolyte and pH Sensing

Cui et al., report APTES and underlying silanol-modified p-type SiNW for operation of a pH nanosensor. The APTES film deposition introduces primary amine functional groups to the SiNW surface. At low pH, the high concentration of H+ protonates the NH_2 functional groups (into NH_3+), depleting the (holes) charge carriers of the p-type SiNW, thus decreasing conductance. At high pH, the silanol groups are deprotonated, and the number of holes increases and thus so does the conductance of current. (54)

Additionally, Cui et al. also demonstrated the successful selective detection of calcium ions by surface modification of silicon nanowires with Calmodulin (CaM - calcium modulated protein). (54) Luo et al., demonstrated the applications of SiNW-FETs as metal ion sensors. Through modification of the SiNW oxide layer with MPTES (3-Mercaptopropyl-trimethoxysilane), detection of cadmium (Cd^{+2}) and mercury ions (Hg^{+2}) was achieved. The detection limits were 10^{-4} and 10^{-7} molar, respectively. (55)

6.1.3. Detection Cardiac Biomarkers

In a study conducted by Elnathan et.al., antibodies and antibody fragments were used as probes on SiNW-FETs for the detection of Troponin T and Troponin I, two cardiac biomarkers for the diagnosis and evaluation of the extent of myocardial infarction. The sensitivity of the FET sensor was compared to that of an ELISA assay in Troponin detection. The SiNW-FET biosensor proved vastly more sensitive with an LoD proved 6 times lower than that of ELISA. (56)

Multiplexed detection (simultaneous detection of several molecules) of cardiac biomarkers was also performed by Zhang et al., using an integrated FET chip. In this study, Troponin T, Creatine MB (CK-MB), and Creatine Kinase MM (CK-MM) were sampled from fingerpick blood drops using a SiNW-FET. The detection cycle of the SiNW-FET chip lasted 45 minutes which included mechanical filtration of plasma from whole blood. Multiplexed detection was achieved by the SiNW-FET sensor, which was functionalized with different monoclonal antibodies (mAbs) in different areas, achieving an LoD of 1 pg/mL. (57) In a second study by Zhang et al., 100 fg/mL LoD was achieved without necessitating filtration and sample processing prior to detection by the SiNW-FET biosensor. (58)

Li et al. studied the use of SiNW-FETs for detection of C-reactive protein (CRP) and Troponin I. CRP is a general marker of inflammation in the body (59) and Troponins are proteins of cardiac muscles cells, which when detected in blood signify cardiomyocyte injury (and leakage of this protein into the bloodstream). Simultaneous elevation of CRP and Troponin I have been associated with increased cardiovascular risk (60). In this study, biosensing SiNW chip technology was used to detect these two proteins. APTES silanization was used to link anti-CRP and anti-troponin-I antibodies to the silicon nanowires. Atomic force microscopy (AFM) was used to confirm the formation of antibody-antigen complexes on the nanowire surfaces. Even though the LoD reached is impressively low, when it comes to low concentrations, adequate detection time can be a challenge. This is because biomolecular detection is a dynamic process by which, depending on their concentration, the molecules settle on and bind to the receptors. The higher the concentration the faster the settling and detection time, which means that detecting low concentrations takes longer and can pose an obstacle in electronic biosensing. (61)

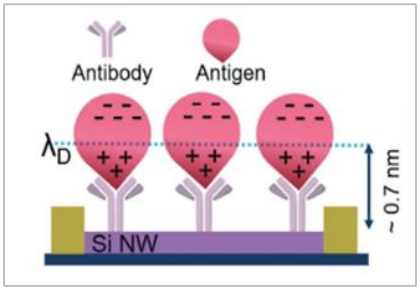


Figure 22. Illustration of a SiNW-FET functionalized with anti-CRP and anti-Troponin-I antibodies for their detection in the sample. (61)

An alternative strategy is thus proposed, that involves utilizing the kinetics of biomolecular settling to estimate the concentration. Since the settling time of the target molecules depends on their concentration in the sample, instead of allowing for settling of all biomolecules to obtain the reading (which could take hours/days), the signal response rate (k) can be used. Since the biomolecular concentration and settling rate are in direct correlation, rate curves can be drawn, to quickly deduce the concentration. (61)

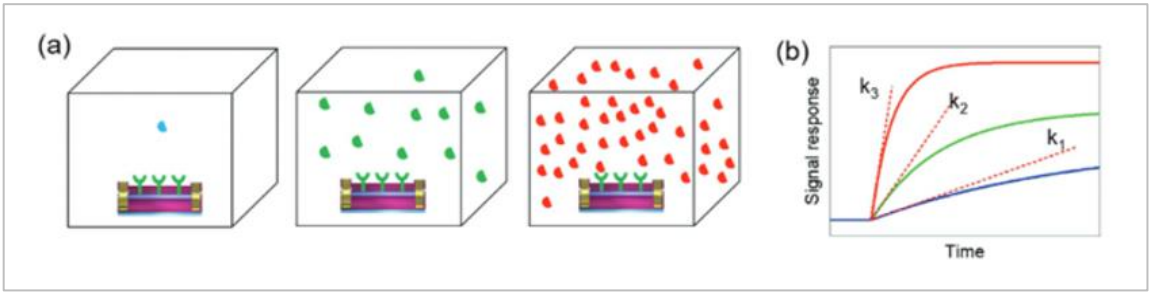


Figure 23. Schematics showing (b) signal response curves (solid lines) and their respective response rates (k_1, k_2, k_3) for different molecular concentrations. These rates (k_n) can be used to deduct the concentration of a sample. (61)

6.1.4. Detection of Tumor Markers

Multiplexed detection is also valuable in the case of cancer screening and diagnosis as more than one tumor marker must be screened for. Zhang et al., achieved real-time label-free detection of tumor markers PSA-α1-ACT, CEA and Mucin-1 by attaching monoclonal antibodies to separate nanowires of the SiNW array chip. Sensing of femtomolar concentration was achieved from undiluted serum samples. The conductance change evoked upon PSA binding was proportional to its concentration. For multiplexed detection, nanowires 1, 2, and 3 were modified with anti-PSA mAb, anti-CEA mAb and anti-

Mucin-1 mAb, respectively. The conductance changed only in response to the presence of each corresponding tumor marker only in the respective nanowire. Femtomolar range LoDs were achieved for tumor marker detection. (62)

Gliomas are aggressive tumors of the central nervous system and represent a major cause of neoplastic mortality in the human population. Early diagnosis is vital for improving prognosis and survival rates, however, there is a lack of a standard screening strategy or a means of early diagnosis. (38) Non-coding ribonucleic acids (ncRNA) are molecules that regulate gene expression during processes like carcinogenesis (63). Circular RNA (circRNA) molecules are involved in neoplastic development and are thus acknowledged as a form of tumor marker for several types of cancer including prostate, gastric colorectal cancer and gliomas. (64–66) Specifically, circNFIX-RNA has been associated with proliferation of glioma cells and is an acceptable tumor marker for glioma. Ivanov et al., successfully developed nanoribbon-based sensor chips for the detection of circNFIX. Functionalized with oligonucleotides, it attained real-time label-free detection of circNFIX with LoD of 3.3×10^{-17} M. They report detecting higher levels of circNFIX in the plasma of glioma patients compared to a control group of healthy volunteers. (38)

In 2020, colorectal cancer (CRC) was the third most common form of neoplastic disease worldwide and the second most common cause of cancer-related mortality, with predictions showing an increasing trend in the future (67). An essential part of reducing these statistics is screening and early diagnosis. The current screening strategy for colorectal cancer involves a regular colonoscopy and fecal occult blood test starting at the age of 50 (68,69), both of which are unpleasant and their avoidance is likely correlated to late-stage diagnosis and thus a worse prognosis. Detection of tumor markers for CRC via a biosensor could potentially have a role in the screening procedure given that they offer high sensitivity and specificity. Currently, the best available options for CRC tumor markers are carcinoembryonic-antigen (CEA), carbohydrate-antigen 19-9 (CA-19-9) and cancer-antigen 242 (CA-242) (70,71), however, they are not suitable for screening purposes and are only used as follow-up surveillance of cancer progression.

Recently, the association of miRNA-17-3p has been studied as a CRC tumor marker and Ivanov et al. have developed a silicon-on-insulator (SOI) nanochip for detection of its synthetic DNA analogue. This nanoribbon-based biosensor was modified via covalent

immobilization of an o-DNA probe complementary to the sDNA (synthetic DNA, analogous to miRNA-17-3p). Control (unmodified) nanoribbons were used to detect and normalize for the signal of non-specific molecular binding to the nanowires. Blood samples from prostate cancer patients and healthy patients (as controls) were analyzed by the sensor which produced no significant difference in the nanochip signal. Conversely, a signal was registered in response to a CRC blood sample and a subfemtomolar detection limit was achieved, LoD: 1.1×10^{-17}M. The study concluded that their nanoribbon sensor chip is suitable for real-time ultrasensitive detection of synthetic DNA as well as miRNA-17-3p from blood samples. (72) Such technologies are expected to have higher compliance and could be used for CRC screening.

6.1.5. Lab-on-a-chip (LOC) and Antibody Detection

It is important to mention the novel lab-on-a-chip technology, not only because it entails a form of circuit integrated onto a silicon surface, but also because FETs have been used as detectors in LOCs of diagnostic purposes (73,74). Some definitions are important here: **Micro total analysis system (μTAS)** is the miniaturization of an overall analytical process from sample preparation through reaction and separation to detection. **Microfabricated devices** are microstructures fabricated by methods typically applied in microelectronics, such as microlithography, etc. **Microfluidics** involves transporting and manipulating minute amounts of fluid through microchannels on micro/nano chips. **Lab-on-a-chip** is a microfabricated device, integrating several laboratory processes on a single chip. (Lee et al.) (75) The LOC can be described as an integrated circuit of microfluidics and electronics on its surface. With the ability to control micro amounts of fluids this novel technology has several applications including assays on fluid bodily samples, PCR tests, cell culture, drug discovery, and drug testing simulations (73,76). Furthermore, FETs can be incorporated into LOCs for detection of biomolecules upon hybridization (73). Microfluidic LOCs have several components to execute complex biochemical processes in the correct order including Injector, Preparator, Transporter, Mixer, Reactor, Separator, Detector, Controller, and Power Supply. (74)

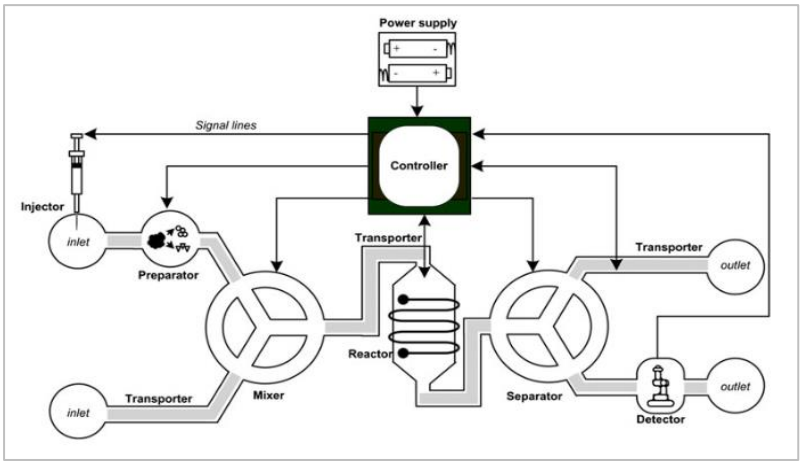


Figure 24. Schematic of a LOC and its components depicting: an Injector, Transporters, Preparator, Mixer, Reactor, Separator, Detector, Controller and Power Supply. (74)

The injector ensures precise delivery of a sample or reagent into the inlet with nanoliter precision. Transporters ensure the microfluidic movement from one component to the next. Preparators isolate the analyte of interest from the sample or pre-treat the sample for further analysis. This may include filtration, pre-concentration, cell lysis or derivatization. Mixers may combine samples with reagents from several fluid streams in microchannels at several steps of the LOC. The reactor maintains a controlled environment while monitoring the biochemical reactions occurring and usually include heaters, actuators and sensors. Detectors are transducers that translate physical measurements into electrical signals and typically use optical or electrochemical methods, mass spectrometry, capacitance or magnetic techniques. Capacitance changes in detectors can be converted into a frequency signal via an electrical circuit. Controllers which can be on-chip or off-chip manage data and signal-processing operations. They issue control signals to the components of the LOC in order to perform their function. They typically consist of a communication interface, microcontroller, control circuitry, programmable memory, signal preconditioning circuitry and power interface circuitry. Finally, a power supply is needed for the chip's transducers, actuators and electronic circuits. Batteries or programmable power supplies are often used. The goal is to achieve automated sample analysis without necessitating trained personnel while decreasing the possibility of contamination during consecutive steps. Lower reagent volume requirements decrease costs and ultimately provide a more accessible sample analysis tool, allowing remote usage and real-time results. Real-time, bedside diagnostic tools are in high demand by the diagnostic field. However, the lack of standardized designs for Lab-on-a-chip models is a

major obstacle towards their commercialized mass production and use. Nevertheless, nanotechnology has contributed significantly to evolving the detector component of LOCs. (74) Integration of nanotubes and nanowires into biomolecular detectors has increased their sensitivity and enables label-free detection (77).

Although LOCs are not considered conventional integrated electrical circuits, they can harbor field-effect transistors for diagnostic purposes as sensors and integrated into their controllers. Choi et al., report integration of FET-based biosensors into a digital microfluidic LOC device for the detection of (anti-AI) anti-avian influenza antibodies. Their device achieved real-time, label-free detection of anti-AI via detection of drain current with an LoC equal to 0.5pg/mL. A reduction in drain current was observed upon specific binding of the antibody on the sensor-bound SBP-AIa antigen. The device worked as a LOC with the ability to electrically control the microfluidic droplets and perform label-free detection with its FET, all on the same chip within seconds. Although this device is still not portable, its monolithic integration enables further integration of a readout circuit and self-power supply for a future all-inclusive diagnostic chip. Furthermore, the technology used for its fabrication is suitable for mass production and multiplexed detection. (73)

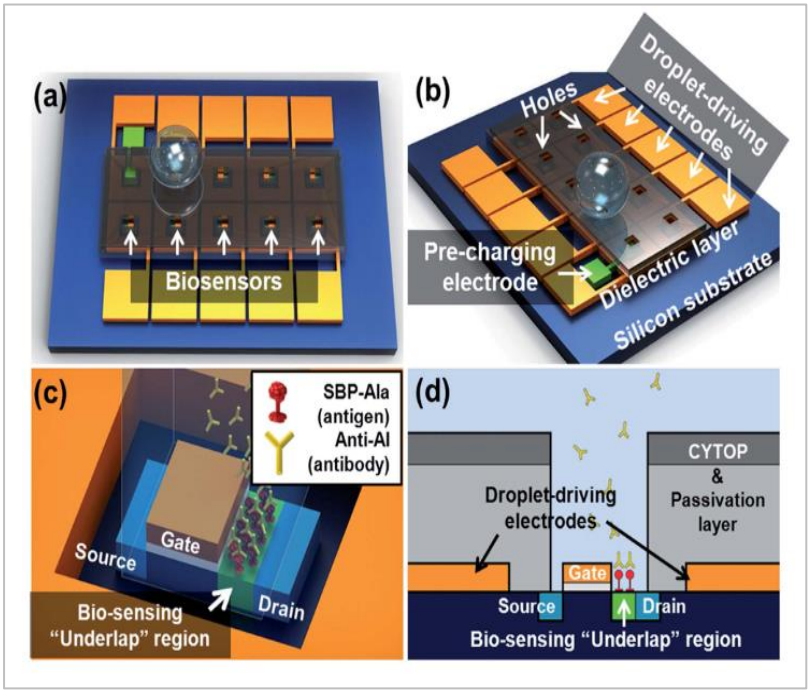


Figure 25. Schematic of the proposed digital microfluidic device with embedded FET-biosensor, (a) top-view, (b) side-view, (c) magnification of the incorporated FET biosensor (d) cross-sectional view of the FET-biosensor showing FET-bound antigen and incoming antibodies from the microfluidic droplet. (73)

6.1.6. Detection of Illicit Drugs

Current laboratory tests for the detection of illicit drug intoxication are invasive (blood or urine sample necessary), laborious and time-consuming. Christodoulides et al., have developed a LOC-type (p-BNC) programmable BioNanoChip device for the detection of drugs of abuse (including cocaine, methamphetamine, THC, MDMA and benzodiazepines) from oral fluids as well as provide a time-course profile of the metabolites. This technology could be immensely beneficial for treatment of drug addiction. Emergency rooms and first responders would have accurate information of one's intoxication profile to provide the appropriate often lifesaving treatment. Furthermore, rehabilitation centers could have real-time information about adherence to abstinence. (78)

6.1.7. Detection of Cancer Cells

In metastatic neoplastic diseases, early detection and follow-up examinations are key for a favorable outcome. This is achieved by surveillance of tumor markers and circulating tumor cells (CTCs). CTCs are metastatic tumor cells that have been liberated from the main tumor mass and circulate in the body's blood vessels until they invade other tissues, leading to propagation of the disease, thus vastly worsening the prognosis. Once a malignant tumor has metastasized the chances of curative treatment and survival are minimized. Early diagnosis of cancer means detection of such markers when they are still in low concentrations. (79) Importantly, CTCs can be detected in blood samples even before biopsies can prove the presence of a tumor. (80) Additionally, detection of CTCs is an important indicator of treatment progress or lack thereof, in which case, adjustments to the treatment plan are made. Therefore, optimal CTC detection techniques are of vital importance. Existing methods of CTC detection are labor-intensive, time-consuming and require trained personnel. Furthermore, the methods used today require enrichment steps for CTC detection since they are present at such low concentrations, thus there is a need for tools of higher sensitivity. (79) Microfluidic systems have proven useful in a number of medical applications, including CTC enrichment. (81,82) Additionally, FETs have demonstrated cell-detecting biosensor capacity and have proven sensitive, compact and label-free, as well as able to count cells individually.

Chen et al., propose for the first time an all-inclusive microfluidic LOC-like platform with integrated FETs for automated CTC detection. Their microfluidic chip includes microchannels and chambers for hydrodynamic cell trapping. Each cell trapping chamber can isolate 3 CTC over a FET sensor for detection and quantification. Furthermore, they demonstrate that after detection the cells can be retrieved by applying backward flow for further analysis, such as cell culturing or cytological examination. The microfluidic channels include a cell flow inlet and outlet, a cell retrieval buffer inlet and outlet, trapping chambers, a FET sensing area, and conducting wiring. CTCs are hydrodynamically directed through the microchannels in the fluid stream and are trapped in the narrowest channel segment. This segment is precisely where the surface-modified FETs are placed so the presence and number of cells can be electronically detected and recorded. (79)

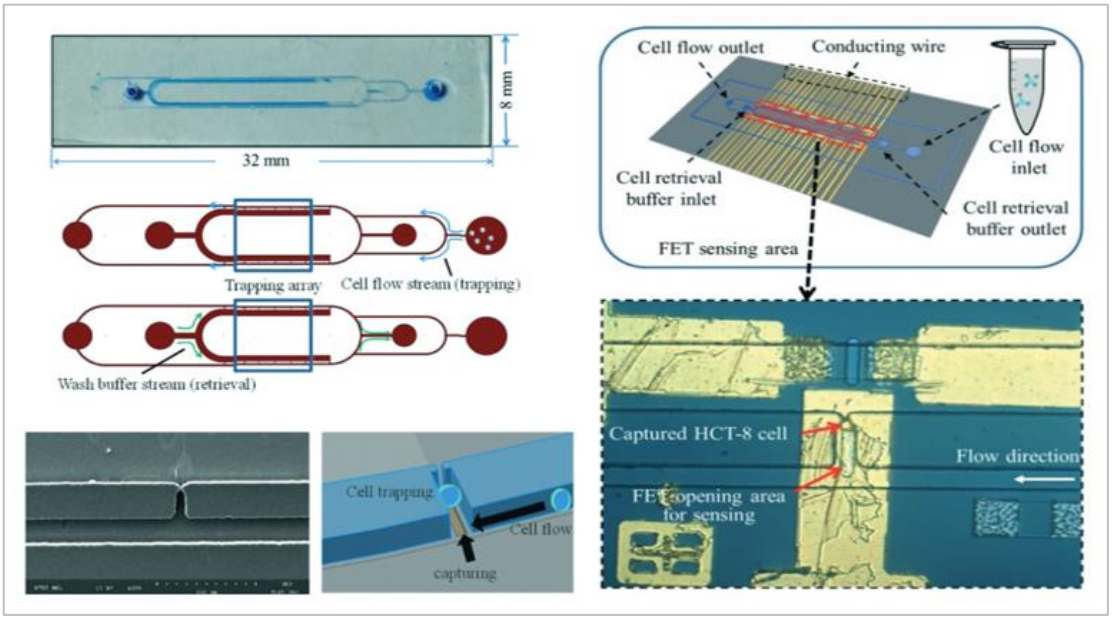


Figure 26. (Upper left) microfluidic chip design, picture and schematic illustration showing the cell flow stream direction and the opposite buffer stream direction, (Lower left) SEM image and illustration of cell trapping chamber showing the cell flow and capture. (Right) Illustration of the microfluidic chip with integrated FET sensors with close-up image of the captured cancer cell (HCT-8) over the FET's gate. (79)

Depending on the CTC type of interest, the FET gates are functionalized with aptamers specific to that neoplastic cell type. These aptamers bind the cell receptors and

an electrical signal is detected via the change in current gain between source and drain. A direct correlation was observed between the number of cells captured and the current gain, meaning quantification of the CTCs is possible. Non-specific cells did not evoke an electric signal, suggesting that the signal was a result of the high-affinity electrostatic interaction between the CTC and its respective aptamer. The chip was designed to detect up to 42 CTCs. This highly sensitive microfluidic chip requires a mere 5 min of incubation time to provide an automated, label-free, and accurate result. Furthermore, detection and enumeration of CTCs were achieved in a sample of physiological concentration, without pre-treatment processing, suggesting a very promising future for point-of-care diagnostic tools. (79)

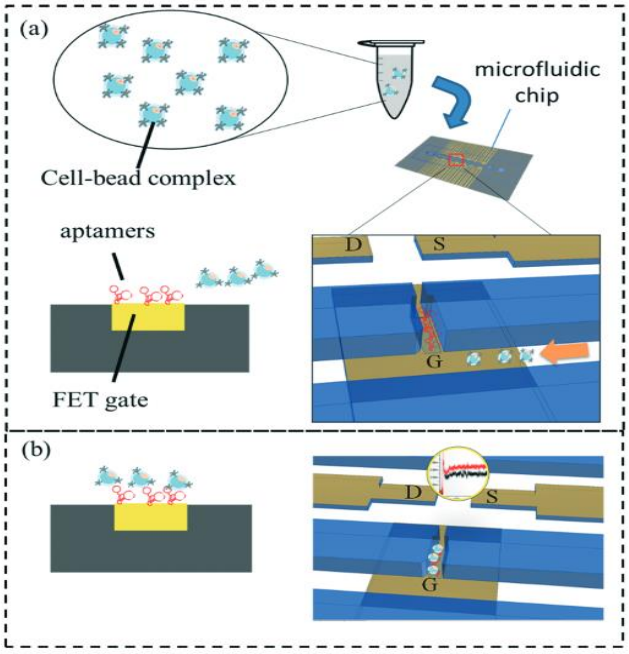


Figure 27. Illustration of microfluidic chip used for CTC-bead complex sample analysis. The field-effect transistor gate is conjugated with the CTC-specific aptamers for CTC detection after immobilization. Capturing process above the FET gate illustrated evoking an electric signal. (79)

6.1.8. Detection of Pathogens: Viruses

The recent pandemic has highlighted the need for and accelerated the production of automated biosensors for the detection of pathogens. Additionally, serological assays and detection of inflammatory markers can be performed by novel sensor technologies for surveillance of the immune response. The current gold standard for viral detection is the (PCR) polymerase chain reaction, a laboratory test of immense value to the medical field. However, the workload that arose in the last 2 years for diagnosis of COVID-19, and the anticipation by the scientific community of another pandemic made obvious the need for

cheaper and real-time diagnostic techniques. (83) Biosensors seem to be a promising candidate since they offer continuous, rapid and multiplexed detection, lower costs, high specificity, selectivity and adaptability, and can be integrated into wearable devices. Finally, they are compatible with IC devices for simultaneous data transfer and integration with existing databases, for remote or telemedicine applications. Biosensors are made up of 4 essential components, namely bioreceptors (for target molecule binding), transducers (of measurable signal), electronic circuitry (for processing the generated signals, and data transfer) and an integrated display as a user interface. The integration of nanomaterials as bioreceptors have allowed even detection of single molecules. (83)

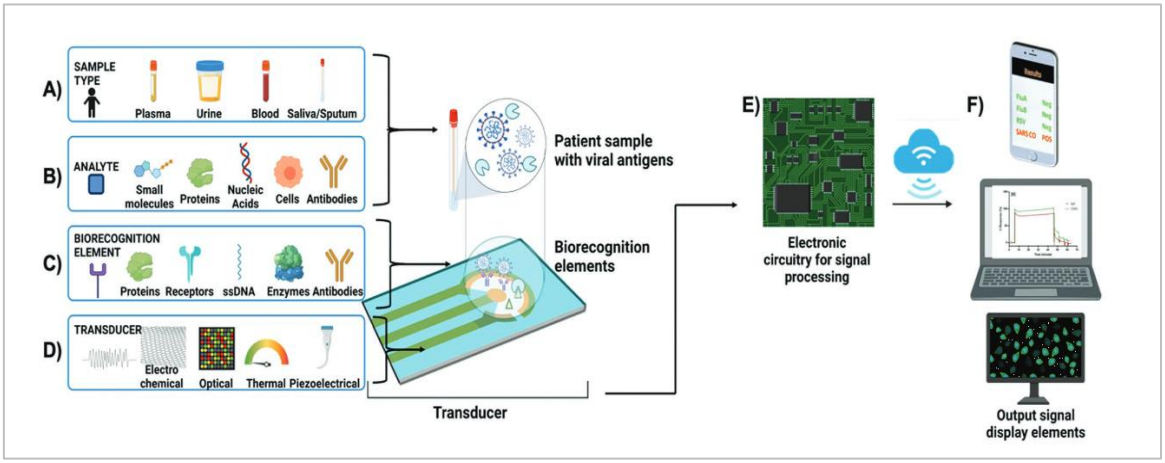


Figure 28. Biosensor components including: biorecognition element (for detection of analyte in patient sample) on the transducer, which converts and sends the detected signal to the electronic circuit, to be processed and displayed on the interface for analysis by the user. (83)

Apart from the biosensing FET nanochips, conventional nanochips (as in nano-integrated circuits), would also be ideal as electronic circuitry of such devices as they facilitate miniaturization and lower energy consumption and thus costs. They can be designed to disregard certain frequencies and thus improve signal-to-noise ratios. Thus, we can see that nanochips and FETs have both sensing and signal processing applications. Furthermore, integration of such point-of-care biosensors with smart electronics already in use today, and the IoT could allow wireless data transfer between patients, medical staff,

and even researchers, and eliminate costly and time-consuming visits to intermediaries (e.g., laboratories, clinics, institutions). (83)

Field-effect transistors make excellent transducers for viral detection. Seo et al., report a FET-based biosensor for direct detection of SARS-CoV-2 spike proteins via functionalization of the transistor gate (sensing area) with antibody-conjugated graphene sheets (Figure 29). They achieved ELISA equivalent detection standard, from nasopharyngeal swab samples without the need for pretreatment. No cross-reactivity was detected with the antigen of MERS-CoV. Furthermore, this technology can be adjusted for detection of other viruses. (84,85) Patolsky et al., report an antibody-modified nanowire FET for detection of Influenza-A (Figure 30). They achieved real-time electrical detection of even single, isolated viruses and suggest that such devices can be used for simultaneous detection of several viruses in parallel. (86)

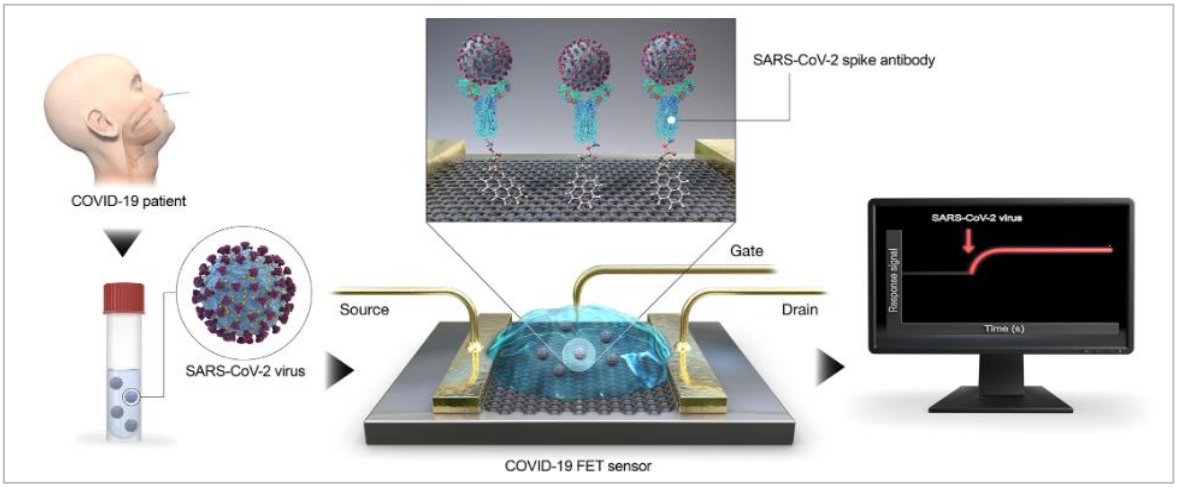


Figure 29. Diagram of FET-based biosensor for SARS-CoV-2 detection. The transistor gate was functionalized with a graphene sheet, conjugated with anti-spike-protein antibodies for interfacing with the viral protein antigen. Upon linkage, the response signal ($\Delta I/I_0$ - change in the real-time detected current over the initial current) is displayed on the interface screen. (84,85)

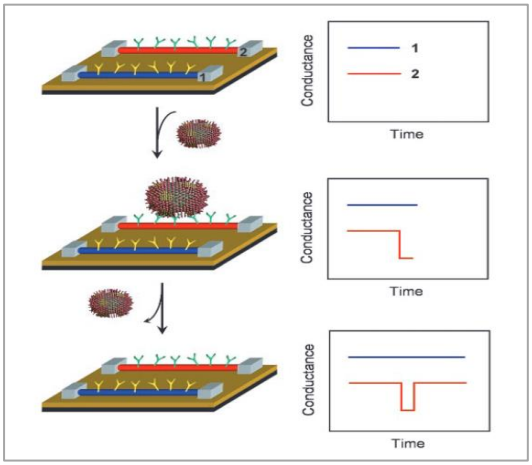


Figure 30. Antibody-conjugated nanowire-FET for detection of Influenza A. The 2 nanowires (red and blue) are modified with different antibodies. Specific binding is illustrated by a conductance change (only in red nanowire) as a result of the viral surface charges on the NW surface. Conductance is seen to return to the baseline value upon release of the virus. (86)

Guo et. at., report an (OECT) organic electrochemical transistor for the detection of SARS-CoV-2 and MERS-CoV-2 spike proteins from untreated nasopharyngeal and saliva samples of microliter scale. Their sensor achieved single molecule sensitivity results after 10 minutes. This OECT involved a gate electrode functionalized nanobodies (receptor unit made from antigen-binding domain) against the target virus. (87)

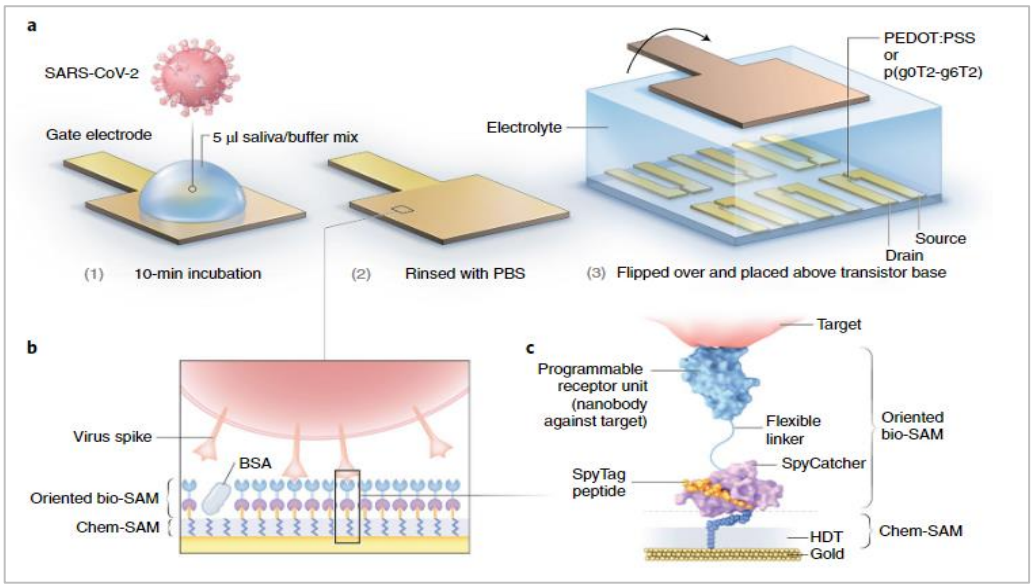


Figure 31. Nanobody-modified OECT biosensor, (a) Gate electrode in contact with the clinical sample in buffer, rinsed then placed over the transistor base where drain and source are, (b) (c) magnified illustration of Chem-SAM (chemical self-assembled monolayer) and Oriented bio-SAM layers linking gold gate layer to nanobody which binds the viral spike proteins. (87)

6.1.9. Detection of Proteins and Viral Infection

A graphene-based biosensing chip platform is reported by Torrentre-Rodriguez et al., for diagnosis of COVID-19 as well as for following the immune response. They present a wireless, portable device for rapid, simultaneous detection of viral antigens SARS-CoV-2 nucleocapsid protein (NP), anti-spike-protein immunoglobulins S1-IgM, S1-IgG and CRP. Their device achieved highly sensitive, electrochemical detection in physiologically relevant ranges from blood and saliva samples. Multiplexed detection allows for differentiating between positive and negative cases, but also, by surveillance of immunoglobulins and CRP, we can distinguish between healthy, infectious (pre/asymptomatic/symptomatic), recently or formerly recovered patients as well as individuals who present inflammation unrelated to COVID-19 (Table 1). Additionally, these parameters can evaluate which individuals already possess some immunity to the virus and which are vulnerable to a more severe course of the disease. (88)

Viral Antigen (NP)	IgM	IgG	CRP	Expected Condition
–	–	–	–	Healthy
+	+ / –	–	–	Infectious, presymptomatic
+	+	+	–	Infectious, asymptomatic
+	+	+	+	Infectious, symptomatic
–	+	+ / –	+ / –	Recovered (recently)
–	–	+	–	Recovered (past)
–	–	–	+	Inflammation unrelated to COVID-19

Table 1. Expected patient condition based on the presence or absence of viral antigen, IgM, IgG and CRP. (88) IgM levels rise earlier and decline earlier so high IgM with low IgG denote early stages of the infection, high IgM with high IgG denote a current infection. IgG rise later and stay elevated for longer, thus, high levels with low IgM denote a recovered infection. (89)

This biosensor platform utilizes capture antibodies and antigens conjugated to graphene on polyimide (PI) substrate sheets for target molecule detection on electrode surfaces. These sheets contain working electrodes (WEs), reference electrodes (RE) and a

counter electrode (CE), which are low-cost, mass-producible and ultrasensitive sensor platforms. (88) The properties of graphene include high surface area and high charge mobility making it ideal for use in sensitive biosensors. The device was able to detect a significant difference between the presence or absence of the respective target molecule after a mere 60 seconds. The graphene electrodes engraved on the polyimide sheet together form a sensor array unit. This easily mass-producible and disposable sensor unit is connected to a printed circuit board with a microcontroller and a Bluetooth module for signal analysis and wireless communication. Together they form the SARS-CoV-2 RapidPlex integrated circuit system which achieved real-time, PCR-confirmed, accurate, multiplexed data for assessment of COVID-19 from blood and saliva samples. This device shows great potential for POC or remote diagnostics and triage classification of patients. (88)

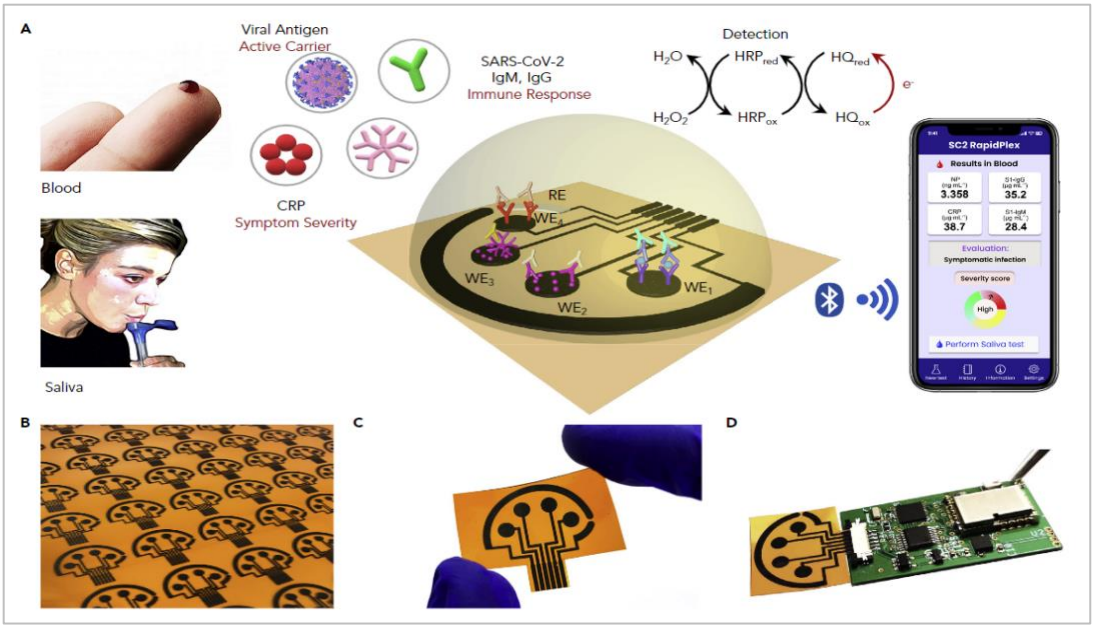


Figure 32. SARS-CoV-2 RapidPlex telemedicine chip platform. (A) (Left) blood and saliva sample collection, the target biomolecules: virus with surface antigens, SARS-CoV-2 IgM, IgG and CRP, (Middle) sensor array with functionalized electrodes and immobilized target molecule, reactions leading to electrons (e-) which can be detected as current. (Right) illustration of a smartphone interface for wireless presentation and analysis of the collected data. (B) Mass-produced graphene sensor arrays on PI sheet (C) Flexible graphene sensor array to scale, (D) SARS-CoV-2 RapidPlex system including graphene sensor array and the integrated circuit board for signal processing and wireless connectivity. (88)

6.1.10. Detection Pathogens: Bacteria

Bacterial pathogens cause rapidly transmittable disease, food poisoning, public health and even bioterrorism crises worldwide, therefore, rapid detection and identification of bacterial species is of vital importance. Nanomaterial-enhanced FET-based sensors have proven effective candidates for LOC and point-of-care sensor devices. (90) Nikkhoo et al., report a CMOS (complementary metal-oxide-semiconductor)-integrated, on-chip platform, for detection of *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* species with bacteriocins as receptor elements in under 10 minutes (91). Similarly, Lerner et al., used single-walled CNT-FETs with antibody functionalization to detect *Borrelia burgdorferi* spirochete antigen (Lyme disease) with LOD at 1ng/ml. (92)

6.1.11. Detection Pathogens: Parasites

Malaria is amongst the most serious often fatal parasitic diseases affecting millions of people. Responsible for the disease is the Plasmodium genus (commonly the *Plasmodium falciparum* species) which is slowly acquiring resistance to existing antimalarial drugs, urgently necessitating a means of accurate POC diagnosis before the appearance of symptoms, to limit spreading of the disease. (90) Lab-on-a-chip systems using ion-sensitive FETs have established successful detection of malarial DNA, even for drug-resistant strains. (90,93) Such POC diagnostics could be of significant benefit in tropical and subtropical geographical regions most affected by the disease.

6.1.12. Volatomics and Artificial E-noses

Humans have evolved over millions of years to have sophisticated olfactory systems that allow us to detect molecules in the air, and to evaluate things such as the difference between fresh and spoiled food since it was essential to our survival. (94) In 2015, Joy Milne's name made headlines, when she accidentally discovered that she could smell her husband's Parkinson's disease 10-12 years before he got symptoms or a diagnosis. (95) What Joy was smelling was Parkinson's VOC profile secreted from her husband's skin, and

has since spent countless hours with scientists to further investigate how this can be achieved with automated technology (95,96). They also discovered that she could distinguish between the olfactory profile of Alzheimer's which had a vanilla-like smell and cancer which had more earthy-vegetable tones. It is hypothesized that her hyperosmic capabilities may be related to her synesthesia diagnosis (a neurological condition where smells can be visualized or experienced as sensations). Of course, Joy is the exception and since not all people have this ability or training to deduce a diagnosis from smell, reliable and automated VOC detectors could save many lives owing to earlier diagnoses and thus earlier treatment, which is proven to improve disease outcomes. (95)

However, digitalizing olfaction is not a simple task. The biological nose has around 400 olfactory receptors but can identify many more smells than that. Consequently, this sensory mechanism is not a "lock and key" model. The brain undergoes sophisticated computations to identify the source of the VOC profile. Accordingly, artificial neural networks, artificial intelligence (AI) and machine learning (ML) are vital for e-nose technologies to be applicable to the real world. (94) It is clear that artificial/e-noses are a highly desired technology. Today, many artificial noses have been developed and are in use for commercial purposes like agriculture, food and drug safety, to detect bacterial contamination. Furthermore, apart from individual health applications, e-noses can be immensely beneficial for public health purposes in detecting pollutants in landfills or water streams. However, at this time, their widespread integration into the medical field is to be expected. The idea is that miniaturized, non-invasive devices will continuously screen for conditions such as cancer, kidney disease, infections, neurodegenerative and even mental diseases. Healthy individuals secrete more than 2000 VOCs, so a lot of research is going into distinguishing healthy vs pathological VOC profiles, as well as identifying VOC patterns that are linked to each disease. Nakhleh et al., successfully classified VOC patterns and detected 17 different diseases including multiple sclerosis many cancer types, Parkinson's and more, by analyzing VOCs in exhaled breath samples using GC-MS (gas chromatography linked with mass spectrometry) (97). Additionally, it seems that VOC sensors will be an integral part of portable and wearable accessories for continual monitoring of the physiological parameters to ultimately detect any abnormality as soon as it arises.

Furthermore, these systems can be connected to the IoT (internet of things) to notify the patient and the physician and even generate ML-enabled feedback. (94)

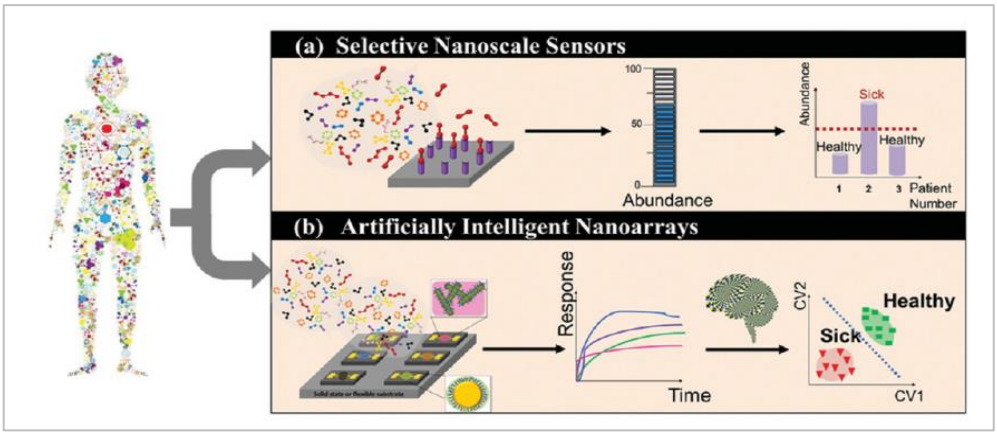


Figure 33. Schematic representing the a) selective (lock and key) sensing approach and b) the cross-reactive sensing approach for detection of volatile organic compounds and disease. (94)

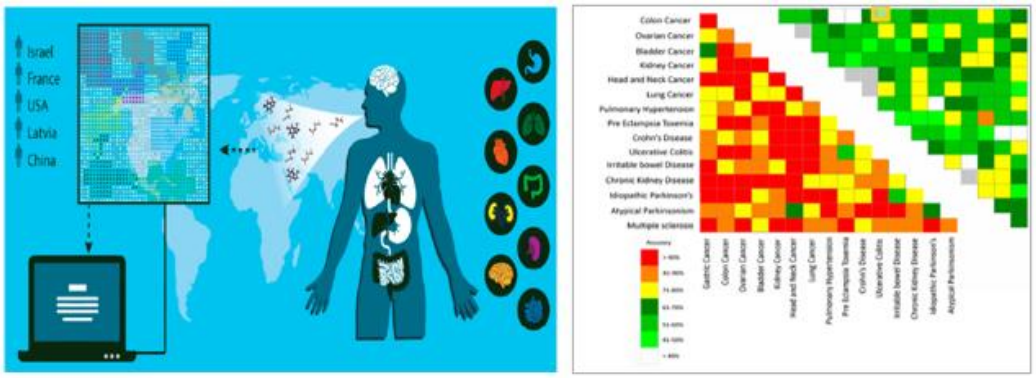


Figure 34. (Left) Schematic of the concept of diagnosing diseases via breath sample, with VOC detection by GC-MS. 1404 patients from Israel, France, USA, Latvia and China were analyzed and detection of 17 diseases was achieved. (Right) Heat graph depicting the accuracy of disease classifiers with binary DFA classifiers in blind validation. (97)

6.1.13. Volatomics – Detection of Volatile Organic Compounds

Volatomics refers to the study and detection of VOCs (Volatile Organic Compounds) in gaseous state. VOCs can be found in the environment but are also emitted from bodily excretions. Examples of VOC categories include, but are not limited to, alcohol, hydrocarbons, ketones, aldehydes, aromatic and nitrile VOCs. These compounds have relatively high vapor pressure at room temperature and atmospheric pressure, thus vaporize and can be detected in the air (94,98). Excreted VOCs are byproducts of metabolic reactions occurring in the body and can thus relay information about physiological or pathological processes occurring at the cellular level. Thus, they offer a method of disease screening and early diagnosis. VOCs are released from their cell of origin into the circulation, and make their way to be excreted from the urine, feces, sweat, exhaled breath as well as breast milk. Consequently, VOCs can be detected in all the aforementioned as well as in blood and the headspace of cells (air above cells in a sealed container). Therefore, they can be used for diagnostic purposes in a non-invasive manner. (98)

Several methods of VOC detection have been identified, including colorimetric sensors, surface acoustic waves, quartz-crystal microbalances (QCMs), electrochemical sensors as well as field-effect transistors. In the case of FET-based sensors, exposure to a VOC sample is reflected by a change in electrical characteristics, thus facilitating detection and quantification. Progress in nanotechnology has greatly facilitated the manufacture of FET-based VOC sensors. Nanomaterials such as carbon nanotubes (CNTs), graphene and silicon nanowires have extensively been used to generate FET-based VOC sensors with enhanced and tunable performance. Additionally, nanotubes and nanoparticles (e.g., AuNPs) have been utilized as synthetic receptors in VOC sensors. (94) Additionally, nanomaterial-FETs have several advantages over other sensing technologies owing to their small size, low energy consumption, the ability to control their gate voltages and thus tune the sensing signal. (98)

SiNW FETs seem to have a significant role to play in VOC detectors, which have applications in medical diagnostics, homeland security (detection of explosives) (94), as well as in industrial and environmental safety. (99) Ermanok et al., report chemically sensitive SiNW FETs with discriminative abilities for detected VOCs. They used a variety of

molecular modifications to functionalize the SiNW FETs and detect VOCs in atmospheric relative background humidity of 40%. The sensing measurements were obtained by 3 FET parameters, namely changes in threshold voltage, carrier mobility and on-current, compared to the reference values under vacuum. In this study, the detection abilities of SiNW FETs toward both polar and nonpolar VOCs were analyzed and the results were significantly superior for polar VOCs. (100) This obstacle was addressed by Yair et al., who showed that modification of the SiNW FETs with silane monolayer containing fewer Si-O-Si bonds between neighboring molecules, significantly improves detection sensitivity for non-polar VOCs. (99) Polar VOCs were detected by a change in the dipole moment of the molecular layer (used for functionalization of the SiNW) or by the electrostatic effect on the SiNW, whereas non-polar VOCs were detected via indirect interactions with the SiNW molecular modifications. The type of molecular modifications and the length of their backbones were varied in this experiment which was significant for VOC detection. The modifications of the SiNW FETs significantly improved the discrimination power of the sensor array, whereas bare (unmodified) sensors produced non-specific outcomes. (100)

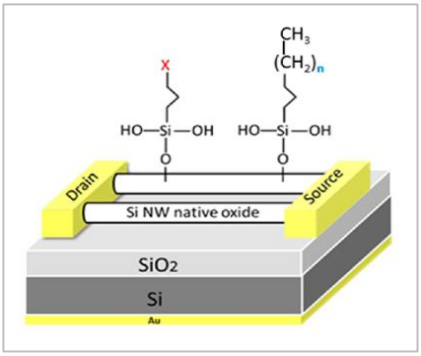


Figure 35. Molecularly modified SiNW FET for detection of volatile organic compounds, (red X): functionalization with molecules having different end groups, (blue n): or different backbone lengths on alkyl chains. SiNW is found between source and drain of the FET. (100)

Sensor arrays were used since variability was observed in terms of sensing signals depending on the surface modification. Each sensor responded differently to each VOC used, and none of them showed adequate selectivity to enable VOC detection based on one sensor alone. Nevertheless, their moderate selectivity was enough to allow combinations of different sensors to create a self-learning platform for accurate VOC identification and quantification. Different sensor combinations were studied. Discriminant function analysis (DFA) was used as a predictive model to evaluate their discriminative power and deduce the optimal combination for the sensor array. The resulting sensor arrays exhibited excellent discrimination between VOCs based on their polarity as well as

between different subgroups (e.g., alcohols). They conclude that SiNW FET arrays can be tailored to detect molecules of interest and produce non-invasive, cost and power-effective automated detectors for medical diagnostics from exhaled breath or even skin. (100)

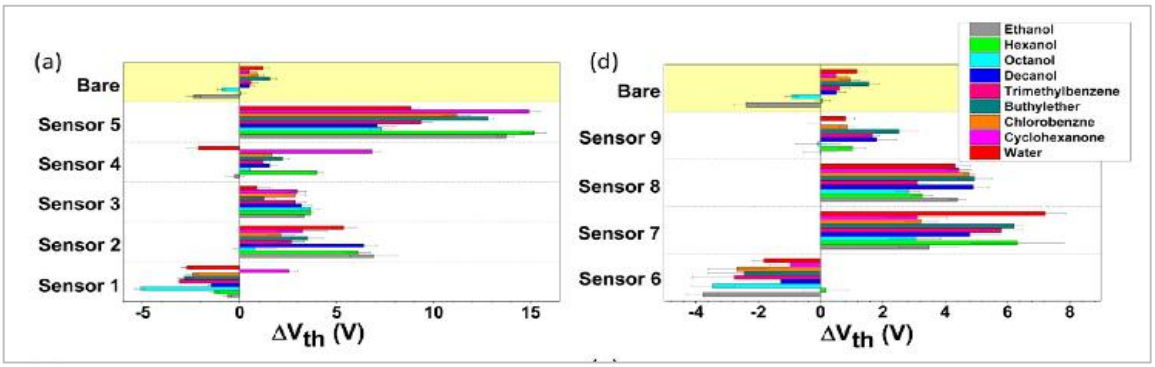


Figure 36. The charts depict the variability in sensing signals (ΔV_{th} - change in threshold voltage) using bare and molecularly modified sensors (sensors 1-9) for the detection of VOCs: ethanol, hexanol, octanol, decanol, trimethylbenzene, buthylether, chlorobenzene, cyclohexanone and water. (100)

6.1.14. Volatomics and Detection of Cancer

Indeed, Shehada et al., report an ultrasensitive trichloro(phenethyl)silane-modified SiNW FET-based sensor for detection of cancer from the exhaled volatome. This molecularly modified sensor detects gastric-cancer-related VOC profiles and distinguishes them from the environmental and non-cancer-related exhaled VOCs. They used actual gastric cancer patients and healthy volunteers as controls and achieved >85% accurate discrimination between the two groups based on the breath volatome sample, validated by blind analysis.

It is important to note, that VOCs, characteristic of cancer, can also be found in the breath of healthy people; however, it is their distinctive combinations that enable statistical determination of whether cancer is present or not. Two approaches exist for VOC sensing with SiNW FETs. The lock-and-key type involves selective detection of 1 specific compound with high sensitivity and low LoD. However, this method alone is unsuitable since the

diagnosis is not based on the presence or absence of the compound but rather the composition of the entire volatomic profile. Cross-reactive sensor arrays, on the other hand, convey varying affinity profiles from different mixtures of volatile species. The selectivity of these sensor arrays is realized by pattern recognition algorithms. Shehada et al., proposed and used a combined approach. This SiNW FET sensor achieved an impressive detection limit of 5 ppb while not being affected by significant variables such as gender and tobacco smoking. Even though a larger-scale clinical trial is necessary for assessing the applicability of this technology, it is still an innovative step toward, real-time, bedside, non-invasive diagnostics. (101)

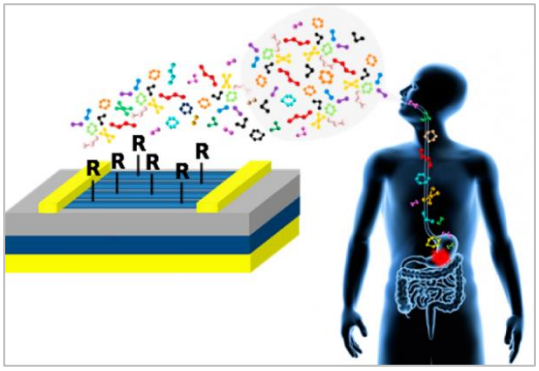


Figure 37. Illustration of the concept of VOC sensing for detection of gastric cancer. We can see the exhaled breath as a mixture of different vaporized compounds which bind to the surface modified SiNW FET to be analyzed by the algorithm. (101)

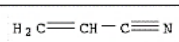
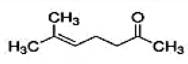
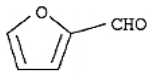
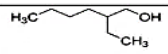
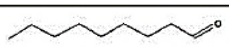
Name	Compound	Concentrations in experiment (ppb)	Concentrations in breath (ppb)	Structure
VOC1	2-Propenenitrile	50– 150	1.9 – 16.7	
VOC2	6-Methyl-5-Hepten-2-one	5 – 150	16.3 – 37.6	
VOC3	Furfural (Furfuraldehyde)	5 – 500	2.5 – 10.3	
VOC4	2-Ethyl-1-hexanol	5 – 500	105.0 – 462.6	
VOC5	Nonanal	5 – 500	57.2 – 179.1	

Table 2. VOC 1,2,3: Volatile Organic Compounds associated with gastric cancer, VOC 4-5: Volatile Organic Compounds associated with environmental confounding factors. (101)

Jaeschke et al., have developed a handheld compact and portable device, the SNIFFPHONE, for non-invasive detection of gastric cancer from exhaled breath. The platform is to be wirelessly connected to a smartphone for data transfer and analysis. Even though a clinical trial is still ongoing, it seems to be an innovative concept for remote diagnostics. (102)

Figure 38. SNIFFPHONE (a) concept of operation, patient exhales into the device's port containing the sensors, (b) data is transferred to a smartphone for analysis (c) open and closed view of the device. (102)

6.2. Diagnostic Applications: Wearable Sensors and Electronics, Telemedicine

In recent years, the Internet of Things has been attracting the attention of the scientific community as well as the general population. This term refers to network connectivity and computing capabilities of sensors and everyday objects that are not generally considered computers, allowing these devices to exchange and consume data with minimal human intervention. (Rose et al.) (103) The popularity of this concept has initiated an effort to integrate medical and health devices into the IoT. Wearable, as well as stationary molecular sensors connected to the IoT, could change the face of medical diagnostics, disease screening and surveillance. Furthermore, electronic actuators providing a therapeutic response to sensor-detected signals are a very attractive prospect that may give way to the next industrial revolution and incidentally transform healthcare and disease management. (104)

Field-effect transistors are a potential candidate as the operating unit of sensor devices, owing to their flexibility in material utilization for surface functionalization, compatibility with existing circuit boards and electronics, and excellent amplification of electronic signals. FETs seem to have a central role in wearable diagnostic sensors, not only as conventional transistors in logic circuits for signal amplification and processing but also

as sensing platforms for detection of physical and electrophysiological parameters as well as biochemical compounds. They have demonstrated sensitivity for detection and continuous monitoring of external stimuli such as temperature, pressure, biological molecules and chemical compounds on both wearable and non-wearable sensors. Such wearable sensors should be characterized by functional adaptability, mechanical flexibility, portability and negligible mass and volume, for effortless integration into platforms such as electronic skin and implantable micro/nano-chips, etc. Thus, fabrication of flexible field-effect transistors (F-FETs) is quickly becoming a field of interest. (104)

Although FET-based sensors for diagnostic purposes have demonstrated undeniable success in laboratory settings, implementation for clinical and personal use is somewhat more complex. They require a miniaturized or self-renewable power source, wireless connection with data processing software for user interfacing, while also being biocompatible, reversible but simultaneously unaffected by daily use. Even though their commercialization is still to be expected, significant developments in the field indicate a promising future for electrical, wearable sensors. In the next chapter, a summary of recent efforts and achievements is presented, indicating potential applications through which wearable sensors and electronics may become integrated into our lives and the medical field. (104)

Optoelectronic materials can also be used to modify the gate of F-FETs. Upon exposure to electromagnetic waves, the photogenerated charges flow through the conductive channel which can thus be detected and measured. F-FET-based sensors can detect pressure changes via means of piezoelectricity, piezoresistivity and capacitance. Mechanical deformation can be detected by changes in the F-FET's dielectric layer to be used as pressure sensors. F-FET modified with piezoelectric materials can also be used as pressure sensors of environmental conditions owing to the voltage generated within them. Such pressure sensors can be used in sensors of tactile sensation for prosthetic limbs, robotics as well as remote tactile evaluation in robotic or tele-surgeries. (104) CNT and graphene composites have been investigated. (105) Similar (PTNW) Platinum nanowire and graphene-based flexible-FETs have also been explored for implantation into blood vessels as continuous blood pressure monitors. A pressure sensor with dual functionality has also been reported with humidity-sensing modalities. (104)

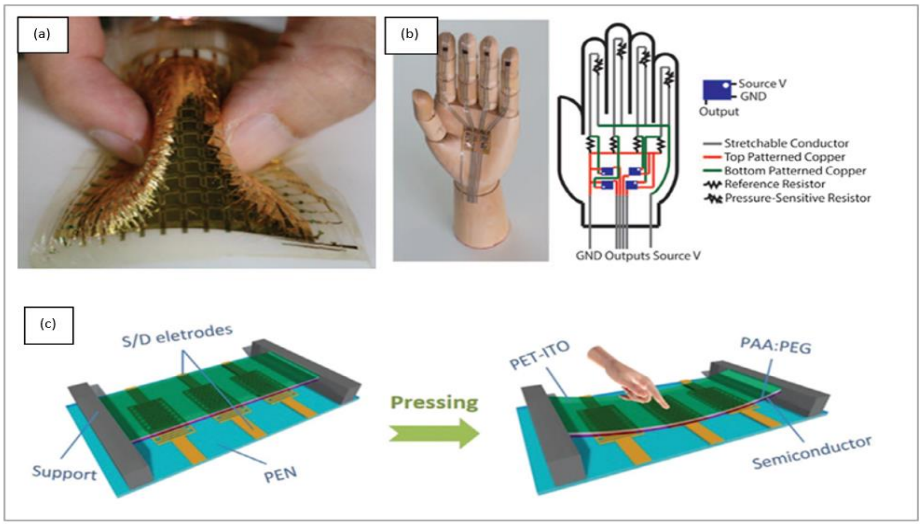


Figure 39. (a) Piezoresistive F-FET - pressure sensor matrix under mechanical deformation, (b) picture and circuit schematic of hand model with flexible tactile sensors, (c) illustration of flexible FET and reversible deformation under mechanical stress. (104)

Flexible FETs can additionally be utilized for sensing body temperature for health monitoring purposes, the environmental temperature and for restoring temperature sensation to users of prosthetic limbs. The drain and source of such flexible FETs are connected to thermistors, and Ag nanoparticles in the conductive channel permit the electrical conductivity to vary according to temperature. Additionally, electrolyte-gated transistors can also be used for temperature sensation, as Na+ were demonstrated to diffuse toward colder areas, and fewer mobile anions were retained in warmer areas between 2 electrodes. (104)

As described, FETs are excellent sensors for biochemical compounds and molecules. Contact with their surface active semiconductive or dielectric layers alters the charge carrier density and thus the current output of the FET. Enzymatic reactions on active layers can also have similar effects and can thus be used for functionalization of FETs. Integrating biochemical FET sensors into wearable devices can be used for continuous monitoring of emitted VOCs and electrophysiological parameters of the user, as well as assess the safety of the environmental conditions via detection of pollutants or dangerous chemical compounds. Surveillance of environmental conditions is an important possible application of such sensors, both for individual use as well as for institutions and governments as a

public health safety measure. Furthermore, athletic performance and relevant parameters can be documented for improved fitness, performance and overall health. (104)

It seems that flexible, wearable or implantable wireless FET sensors are an attractive prospect, to move away from invasive blood tests with static information toward non-invasive, dynamic continuous health monitoring. Sweat, tears, saliva and exhaled breath seem to be the popular alternatives as clinical samples for wearable sensors. Nanomaterials and nanochips (circuits) seem to have a significant role in the generation of appropriate active layers and surface modifications for such F-FETs, as well as in generating self-powered energy sources and wireless connectivity embedded in said sensors. (104) Currently, electrolyte and metabolite detection are performed by invasive blood tests, which for many can be psychologically distressing, especially for children and people with chronic conditions who need regular follow-ups. Tear, breath, saliva and sweat-based sensors could offer an alternative, less invasive method of data collection for continuous health monitoring. (106)

6.2.1. Tear-based Wearable Biosensors

Tears contain water, electrolytes, proteins and metabolites, which can reflect the physiological or pathological state of the body and thus offer valuable diagnostic information for wearables. Although there are currently no commercialized tear-based sensors in use, important successes have been reported in laboratory settings. A contact lens sensor was first engineered in 2009 by Parviz et al., and tested on an anesthetized rabbit. Glucose and lactate detection was shown to be possible via a contact lens sensor. Furthermore, a contact lens sensor was developed for multifunctional detection of glucose as well as intraocular pressure. Graphene and nanowires ensure sufficient transparency and comfortable use without obstruction of vision. Biofuel cells can be used for wireless powering using glucose and other tear contents as biofuels. A drawback of the tear-based approach remains that the metabolite levels don't perfectly correlate to the concurrent levels in the blood. (106)

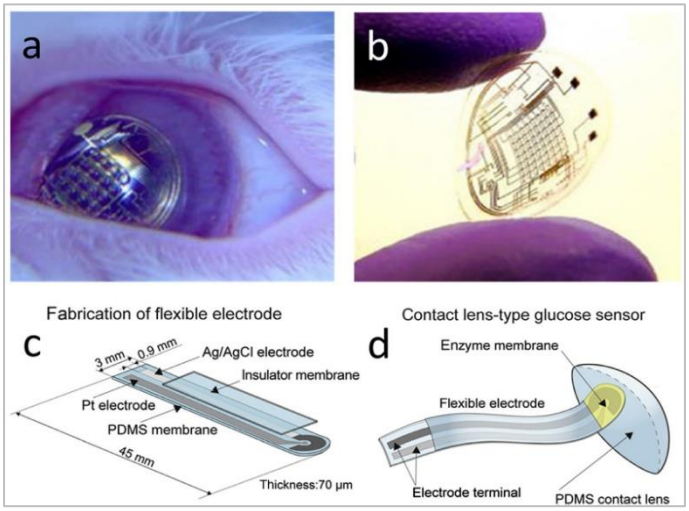


Figure 40. Tear-based contact lens wearable sensor prototype (a) metal circuitry visible in rabbit eye, (b) contact lens sensor, (c) electrode bound to contact lens, (d) schematic of wearable sensor with integrated glucose and intraocular pressure sensor. (106)

6.2.2. Saliva-based sensors

Apart from recent advances in in-vitro salivary diagnostics, wearable options seem promising alternatives for detection and measurement of important metabolites. A **mouthguard** was developed with wireless Bluetooth communication for continuous surveillance of uric acid and lactate in saliva. Additionally, a graphene tattoo-like biosensor was fabricated to be worn on dental surfaces, for detection of pathogenic bacteria on tooth enamel with a low detection limit. Despite recent and impressive progress, there are still technical issues that need to be overcome for commercialization to become a possibility, such as contamination of analytes by consumables, and little correlation between salivary and blood concentrations for some metabolites. (106)

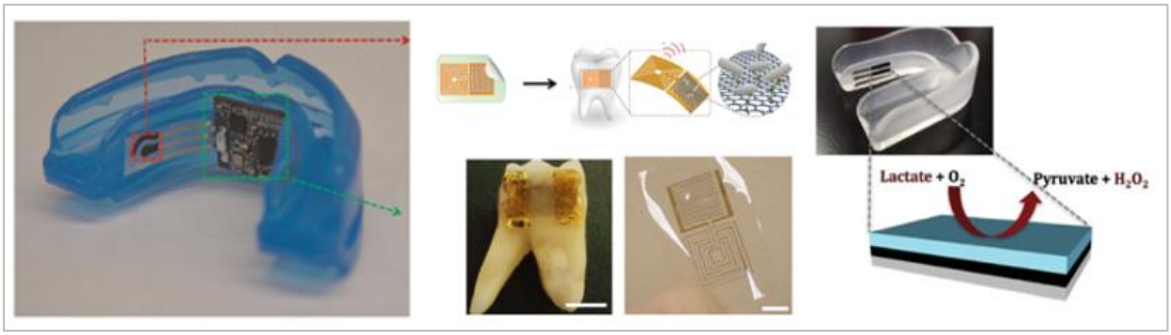


Figure 41. Uric and lactic acid mouthguard sensor, Graphene dental tattoo sensor for detection of bacteria. (106)

Electrolyte concentrations are a critical parameter for retaining homeostasis of physiological functions, even more so in vulnerable preterm and neonates in NICU (neonatal intensive care unit) departments. Currently, their electrolyte levels are monitored by blood draws which are painful, invasive and furthermore only offer static data. Lim et al., propose an electronic microfluidic **pacifier** sensor for continuous real-time measurement of Na^+ and K^+ levels from oral fluids, confirmed efficacy by a NICU clinical trial. This flexible miniaturized and wireless platform allows continuous surveillance of neonatal health without inducing distress with needle pricks or bulky instrumentation, rather with a soothing pacifier platform, especially since contact with the parents is limited in the NICU. The data can be easily transferred via Bluetooth to smartphones for analysis and adjusting the treatment plan accordingly. Furthermore, the group will focus their future efforts on integration of additional sensors to eventually have a complete profile of important electrolytes from one pacifier platform. (107)

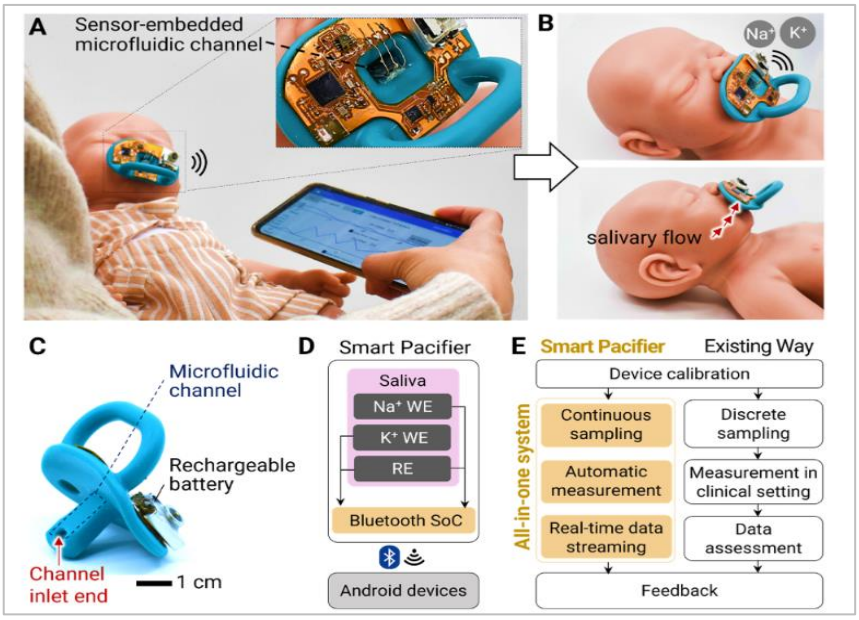


Figure 42. Smart electrolyte-sensing pacifier (A, B) Pacifier with embedded microfluidic sensor on a baby model, (C) Image of pacifier with microfluidic channel, rechargeable battery and oral fluid inlet channel, (D) Components of the pacifier system, WE: working electrode for Na+ and K+ detection, RE: reference electrode, Bluetooth SoC (System-on-Chip) for connection to android devices, (E) Comparison of existing vs pacifier measurement protocol. (107)

6.2.3. Subcutaneous and Implantable sensors

Interstitial fluid (ISF) has a key role in regulating physiological processes within the body and thus contains important ions, metabolites, glucose, lactate and more, in direct correlation with blood analyte levels. Wearable subcutaneous and implantable sensors can therefore deduce important data from the ISF. Subcutaneous glucose monitors are currently commercially available for controlling diabetes mellitus and protecting patients from hyper- or hypoglycemic states. Continuous glycemic control has become a primary focus in the field of wearable electronics. The ultimate objective would be to integrate both a glucose sensor and an actuator for drug delivery (pharmaceuticals for glycemic control) in a theranostic electronic system and eliminate the constant needle burden (blood sampling and insulin injections) that weighs on these patients. (106) This can be achieved by subcutaneous microneedles, simultaneously sensing and performing drug delivery, ideally automatically in response to the glucose levels, but this is currently under investigation. (108) Considerable commercial success has been achieved with the FreeStyle-Libre glucose sensor by Abbott launched in 2016. It utilizes a plastic patch with a subcutaneously implantable sensor placed on the upper arm. It can be worn for up to 14 days, automatically measures glucose every minute, and wirelessly transfers the data to a reader with an on-screen report for user interface. (106) Additionally, Rodrigo et al., report an intravenously implantable carbon fiber biochip, tested in the jugular veins of rats, that successfully distinguished between blood glucose levels, and seems a promising future for implantable bioelectronics. (109)

Figure 43. FreeStyle-Libre glucose sensor, illustration of patient use, internal circuitry of the sensor, sensor applicator, sensor pack, assembled sensor and reader with on-screen interface for presentation of blood glucose levels. (110–112)

6.2.4. Epidermal Interstitial Fluid (ISF) Sensor

Bandodkar et al., have published a proof-of-concept study of an e-skin-like epidermal glycemic sensor. The device used reverse iontophoretic extraction of interstitial fluid glucose and enzyme-based amperometric sensing. ISF glucose correlates to blood glucose and thus this technique seems a promising tool for diabetic control. The on-body tattoo platform can detect the postprandial micromolar rise in glucose levels. While there are still challenges for this technology to advance, and to be usable for long-term continuous monitoring, the group suggests it as a promising approach that could potentially be adapted for transcutaneous drug delivery. (113)

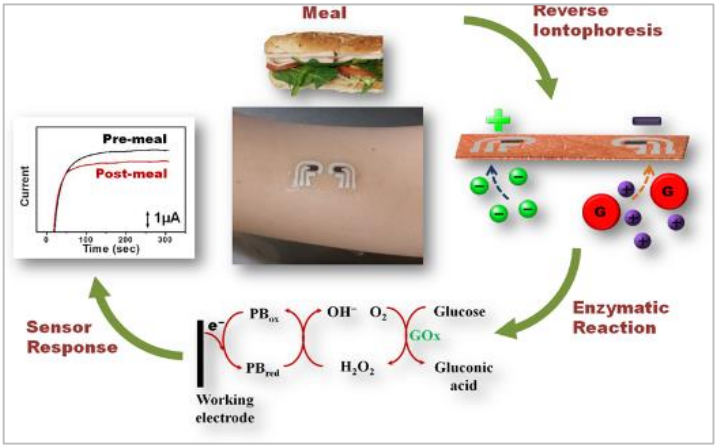


Figure 44. Schematic of temporary tattoo-like epidermal sensor for glucose monitoring. (113)

6.2.5. Sweat-based sensors

Sweat also contains compounds and metabolites at levels that allow for disease screening, diagnosis and monitoring, as well as detection of intoxication and environmental pollutants on the skin. Parameters for fitness monitors can easily be provided in real-time by sweat-based sensors. Two subcategories of such sensors exist, namely, epidermal-based (tattoo-like) systems and plastic (or textile)-based systems. The former offers improved contact with the epidermis, whereas the latter has a longer life span. Wireless wearable patches have been proposed with electronic circuitry and a radiofrequency identification chip for the sweat analysis, which is compatible with Android smartphones for data presentation and interfacing. Electrophysiological parameters (e.g., ECG signals) and sweat-lactate levels have also been successfully monitored with an epidermal patch.

Furthermore, lactate present in sweat is being considered for biofuel, for wearable sensors via the integration of biofuel cells and in-situ power generation during exercise. (106)

6.2.6. Artificial Skin and Epidermal Electronics

Electronic skin has recently generated significant interest in the scientific community mainly for 2 important applications, replacing bulky wired devices used as clinical health monitors with wearable ultra-thin patch-like sensors, as well as restoring tactile sensation to people with prosthetic limbs. E-skin for tactile sensation was originally designed to add this feature to robotics, which remains an attractive prospect and important application, especially for surgical robots. Tactile sensation is an important intraoperative diagnostic tool currently missing from robotic surgery. (114)

Integrated electrical circuits are the functional basis of these technologies. However, construction of such a device has proven challenging since to operate on, or like skin, they must be flexible and maintain the same quality of function upon mechanical deformation. Conventional transistors and semiconductor devices used in today's computer chips are manufactured on silicon wafers that do not possess these properties. Amongst several options of conducting materials, thin single-crystal silicon has demonstrated superior flexibility and similar charge mobility compared to silicon used in rigid semiconductor devices. Kim et al., report the use of a thin, single-crystal silicon layer cut into "chiplets" for electronic skin. The circuitry entails electronics, sensors, and a power supply of serpentine shape to produce a net allowing for mechanical deformation. The electronic circuit layer lies between 2 protective layers, all of which are mounted onto a polyester film engineered to have similar mechanical properties as skin. In other words, it is designed to be thin and soft enough to allow for comfortable usage and can be easily placed on or removed from the skin, much like a bandage tape. Thus, they report an adhesive electronic skin model for collection of physiological data in a cost-effective transfer-printing approach and suggest that the nature of silicon circuitry in electronic skin is suitable for integration of wireless data transfer. (114)

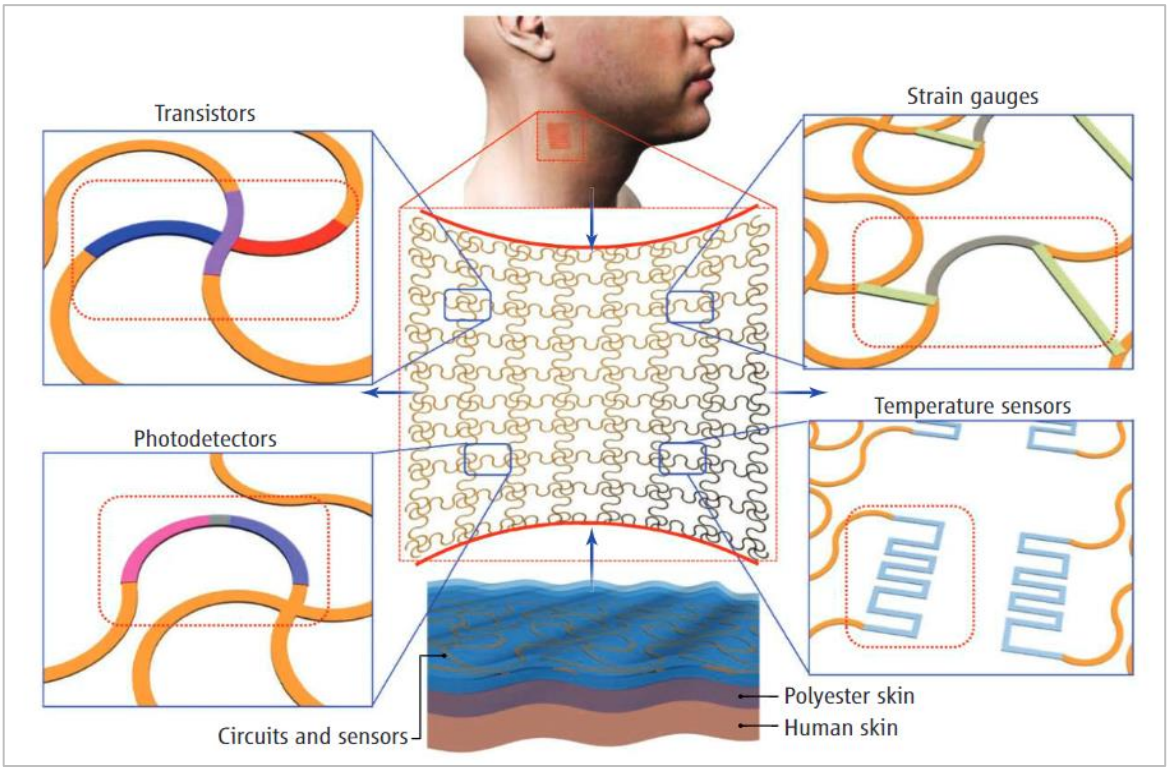


Figure 45. Flexible e-skin, with serpentine circuitry including transistors, temperature sensors, photodetectors, and strain gauges, between 2 protective layers laying on a polyester layer. (114)

Today, the methods of pathophysiological data collection from skin with sensor devices, (like the ECG, EEG, and EMG) use bulk devices and electrodes with long wires, meaning they are uncomfortable and can easily detach. Additionally, such devices are usually stationary, complicating the diagnostic process when long-term monitoring is needed. E-skin patches could solve this problem, especially for people with challenging diseases that need year-round monitoring. Such technologies could detect pathological events e.g., arrhythmias, and notify ambulance units, physicians as well as family members in the event of an emergency. These membrane-like e-skin patches can be manufactured to adhere to the skin exclusively by van der Waals forces, and allow for free, unrestricted movement without constraints on the user's skin, much like a temporary transfer tattoo that recovers in shape after stretching or compression. (115)

6.2.7. E-Skin, Wearable ECG, EEG, EMG and Temperature Sensors

Kim et al., present an epidermal electronic system (EES), as a wearable sensor better suited for remote telemedicine applications. They can be worn for 24 hours or more without irritating the skin, due to a selection of biocompatible Au, polyimides and polyester materials. The EES comprises an electrical circuit of silicon metal oxide semiconductor FETs (MOSFETs), in filamentary serpentine shape crucial to ensure flexibility. The gate connects to an FS (filamentary serpentine) electrode, for coupling with the body's electrical potential, via contact with the epidermal layer. Via this coupling, the EES mounted onto the chest, legs and forehead could be used as electrodes for ECG, EMG and EEG without the need for conductive gels, bulky electrodes and wires or invasive instrumentation. (115)

They introduce an ultra-thin, flexible, stretchable and gas-permeable integrated circuit platform of negligible mass, integrating multiple sensors including electrophysiological sensors, temperature sensors, strain sensors along with light-emitting diodes, transistors, resistors, wireless power coils and radiofrequency communication components. The electrical elements of the platform are filamentary serpentine nanoribbons and nanomembranes made up of silicon and gallium arsenide. (115)

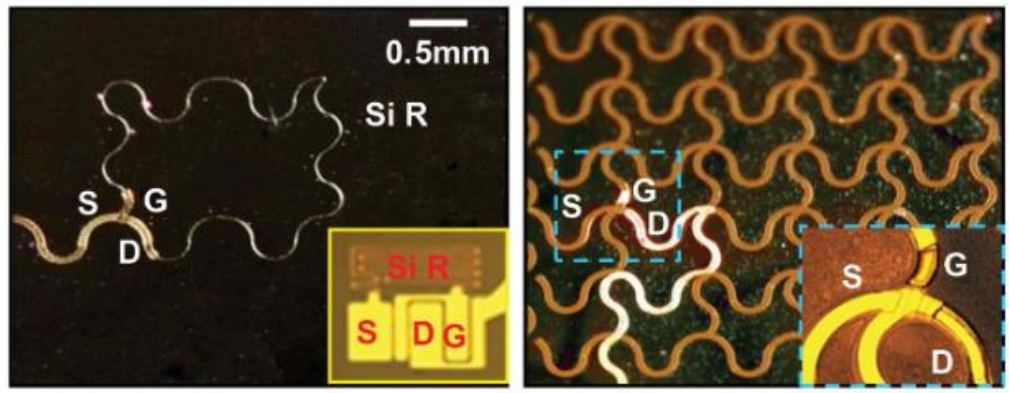


Figure 46. Image of electrophysiological sensor part of FS-EEs, (Left) S: source, D: drain and G: gate of silicon metal-oxide field-effect transistor (MOSFET) with silicon feedback resistor, (Right) MOSFETs in series, metallization of interconnects and sensor electrodes. (115)

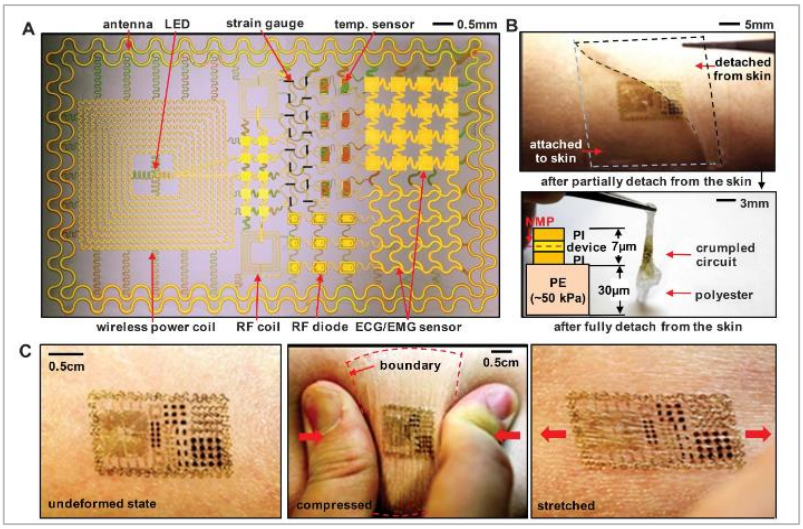


Figure 47. (A) Image of a multifunctional epidermal electronic system (EES) including ECG and EMG sensor, temperature sensor and strain gauge as well as wireless power coil, radiofrequency (RF) coil, RF diode, light-emitting diode (LED) and antennae. (B) Image of EES semi-attached to the skin, lying flat where attached, and its collapsed state upon detachment, (C) Images of EES attached to the skin when undeformed, compressed and stretched. (115)

The EES mounted onto the chest detected cardiac depolarization waves and QRS complexes. The one placed on the leg detected EMG signals upon muscle contraction comparable to the signals of the conventional EMG, and finally, after adhesion to the forehead, alpha waves were recorded upon closure of the individual's eyes. Furthermore, EES can perform an EMG recording of vocal muscles during speech when placed on the neck which together with EEG data is a prospect for human-machine interfacing. (115) A similar but alternative approach was proposed by Ameri et al., who used graphene instead of metal wiring to design filamentary serpentines for an electronic tattoo sensor. Graphene is the thinnest to-date electrically conductive material and makes for a biocompatible, semi-transparent, flexible and compressible electrophysiological sensor. Graphene has also been used to construct a tooth-attached wireless sensor of bacterial cells as well as an array for electrocorticography. This graphene electronic tattoo (GET) successfully detected ECG, EMG and EEG signals as well as skin temperature and hydration measurements. Due to its nanoscale thickness, it can fully conform to the microscopically uneven surface of the skin, allowing for increased surface area of contact, thus lowering contact impedance and

increasing signal-to-noise ratio. Therefore, the GET signal is less susceptible to motion and more suitable for long-term usage and continuous health monitoring. (116)

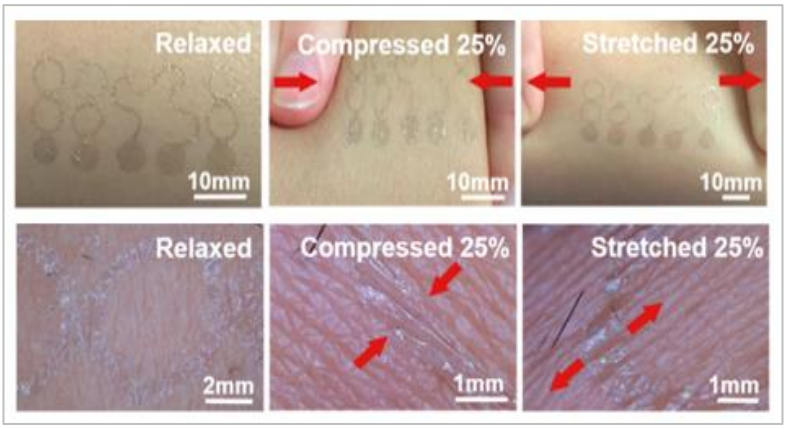


Figure 48. Semi-transparent graphene electronic tattoo (GET) sensor on human skin, in relaxed, compressed and stretched state. (116)

6.3. Preventative Applications

It seems that the future of medical electronics is flexible, wearable and wireless. Smartphone-connected patches may have a key role in epidermal drug delivery and detection of health parameters e.g., heart rate, blood pressure, core body temperature, respiratory rate, blood glucose, urea, inflammatory and tumor markers. Flexible electronics is expected to be a 300-billion-dollar industry before 2030 with applications in diagnostics, therapeutics, screening and prevention of disease as well as rehabilitation. (39)

6.3.1. Wearable UV Dosimeter

Nunez et al., report a preventative application of e-skin type sensors, as they demonstrated a wearable UV dosimeter, to detect and notify users when their UV exposure is approaching harmful levels of radiation, which is well-known to lead to skin malignancies. Thus, users can take advantage of the benefits of sun exposure without increasing their risk for cancer. (117)

6.3.2. Pressure Sensing Insoles – Prevention of Diabetic Foot

Additionally, e-skin could have applications in diabetic neuropathy. This is a common complication of Diabetes Mellitus in which patients lose the ability to detect

pressure points on their soles as well as involuntary pain reflexes. This pressure, in addition to diabetic vasculopathy and associated poor wound healing, can lead to diabetic foot ulcers which can get infected and necessitate amputation. Thus, discreet e-skin type pressure sensing insoles have been described in the literature to allow assessment of plantar pressure points and risk of diabetic foot complications, to ensure the appropriate preventative care. Furthermore, this platform could provide health care practitioners with relevant data on plantar pressure for an optimal treatment plan and feedback. (39) A similar insole platform can also be used to detect toe gestures in order to control elements of a prosthetic limb (e.g., upper limb prosthesis), or even a computer. (118)

6.4. Therapeutic Applications

6.4.1. Electrical Nerve Stimulators

Chronic neuropathic pain is a significant burden for patients and health care providers. Neuropathic pain is due to irritated nerve tissue instead of an extractable or easily eliminable cause. Existing pharmacological treatment options fall short of the desired pain management effect thus electrical nerve stimulation is often used for alleviation. Spinal cord stimulators send signals up the spine that essentially mask the sensation of pain. Current (TENS) transcutaneous electrical nerve stimulation devices are bulky with long wires and a hand-held device. E-skin type flexible electronics could be exploited to generate seamless next-generation TENS for improved electrode contact and control of nociceptive stimuli in neurological conditions and even phantom limb pain. (39)

6.4.2. E-Skin – A Tactile Organ for Prosthesis and Robotics

The applications of e-skin seem to extend further than just surface sensors with implantable applications as well as in prosthetics and surgical robotics. Namely, their applications have been categorized into (39): Topical e-skin (sensors for health monitoring), Implantable e-skin (for cardiac and cerebral interfacing), and Inanimate e-skin (for prosthetics and robotics). (Navaraj et al.) (39) Of course, to take advantage of the full potential of these technologies they would have to be wireless for communication with the

IoT and for actualization of mHealth (mobile health). Nanostructures like (UTCs) ultrathin chips, nanoribbons and nanowires are an already advanced field, offering superior charge mobilities and can thus be the gateway towards realizing these concepts. The possibility to print silicon and semiconductor nanostructures on flexible substrates is key and silicon-based nanoribbons and FETs seem to be the superior candidates for the task. A range of sensors can be manufactured and integrated into flexible electronics including tactile, pressure, stain, magnetic, acoustic, optical, thermal, UV and chemical sensors for multifunctional applications. (39)

Tactile sensors such as flexible touch screens can detect a change in resistance and capacitance of the materials being touched, which would enable an interactive topical e-skin platform. Tactile, thermal and nociceptive sensors are main requirements if e-skin is to be integrated with prosthetic limbs. CNT, graphene and silicon have been used for e-skin developments; however, advancements are still lacking for implementation in prosthetics. Integrated Micro and Nano System (IMNS)-based electronics and POSFETs (piezoelectric oxide semiconductor FETs) are flexible, can conform to fingertips and could help overcome current challenges regarding e-skin sensing. Printed nanowires can be incorporated into POSFETs, which should increase their sensitivity compared to silicon chip POSFETs. Both dynamic and static sensors are necessary in the appropriate density distribution, according to body part, in order to manufacture human-like tactile robotics. (39) FET-based sensors, and especially ion sensitive-FETs and chemoresistors, seem to be the optimal choice for e-skin fabrication due to their small size, compatibility with existing electronics and neural networks, as well as the ease of large-scale manufacture. Furthermore, nanomaterials, like nanowires, are ideal for their composition since they offer superior S/V ratio and thus unmatched sensitivity. (39)

Robotic prostheses are currently capable of executing upper and lower limb functions. However, the lack of sensory feedback prevents intuitive use. Restoration of sensory feedback could alleviate phantom pain and prevent injuries due to improved proprioception. A main focus of artificial skin developers is to restore all types of sensation by studying the various skin receptors, to enable differentiation of gliding sensation, textures, proprioception, wetness, hardness, hand grip, etc. A means of handling such data and decoding user intentions in real-time is necessary and complicated. There are 4 aspects

of neuroprosthetics, namely: 1.) Distributed flexible tactile data-sensing system, 2.) Distributed data acquisition and processing system, 3.) Interface between the residual limb and the prosthetics, 4.) Control of motorized prosthesis output as seen in Figure 49. (39)

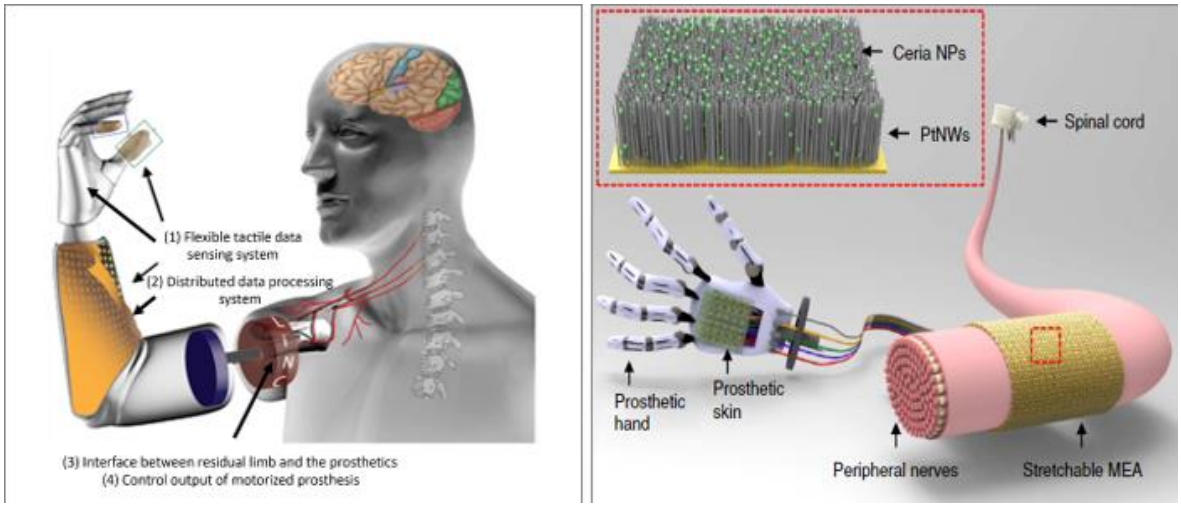


Figure 49. (Left) Key elements of neuroprosthetics with e-skin sensory feedback. (39) (Right) Approach for establishing connection between electronic prostheses and peripheral nervous system with stretchable (MEA) micro-electrode array wrapped around the peripheral nerve fiber. (PtNW) Platinum nanowires are attached to gold electrodes with ceria nanoparticles to suppress ROS neurotoxicity. (119)

Each of these 4 components could benefit from IMNS-based field-effect transistors for improved functionality. Nanowire-FETs and UTCs can be implemented for data processing within neural networks for intuitive prosthesis control as well as for decoding neural signals. Additionally, optogenetic neural interfacing can be used to control neural signaling with specific light wavelengths to avoid electrode-nerve contact. This could be a potential solution to foreign body responses to electrodes, nerve irritation and thus implant failure. Ultrathin silicon JLFETs and UTC can be used as optogenetic µLED drivers. UTCs can act as interfacing chips between implantables and e-skin to enable efficient control of prostheses. (39)

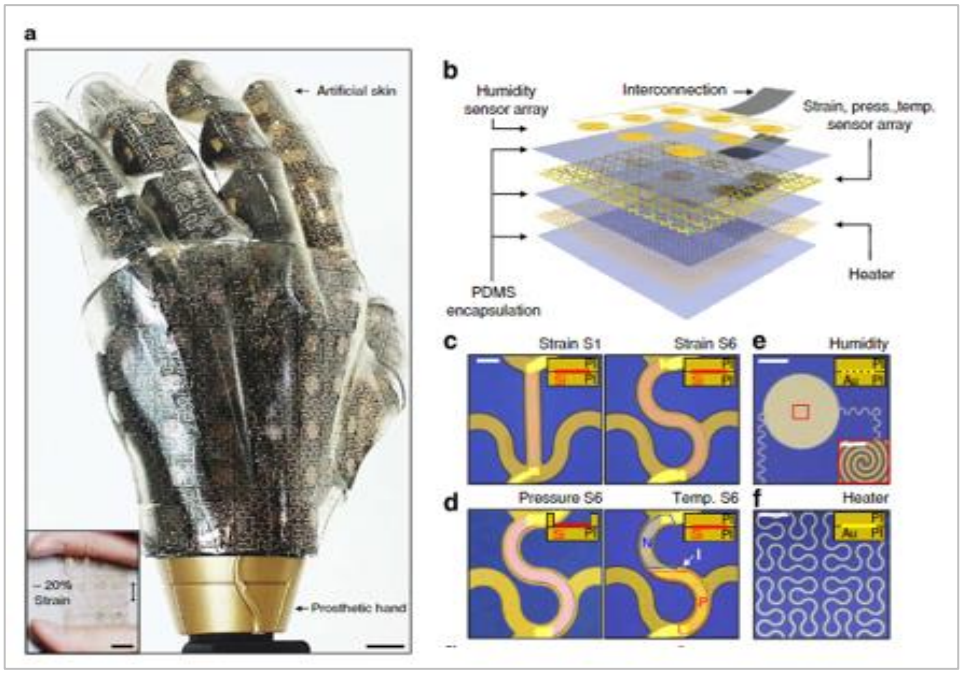


Figure 50. (a) Electronic prosthetic skin on prosthetic hand designed with SiNR electronics, with stretchable sensors, (b) magnified view schematic of the 6 layers of artificial skin including pressure, strain, humidity and temperature arrays, heater and their interconnections with external instrumentation. (c) strain sensors (d) pressure and temperature sensors (e) humidity sensor (f) heater – accomplishing a human-like warm feeling of the prosthesis upon contact with real skin. (119)

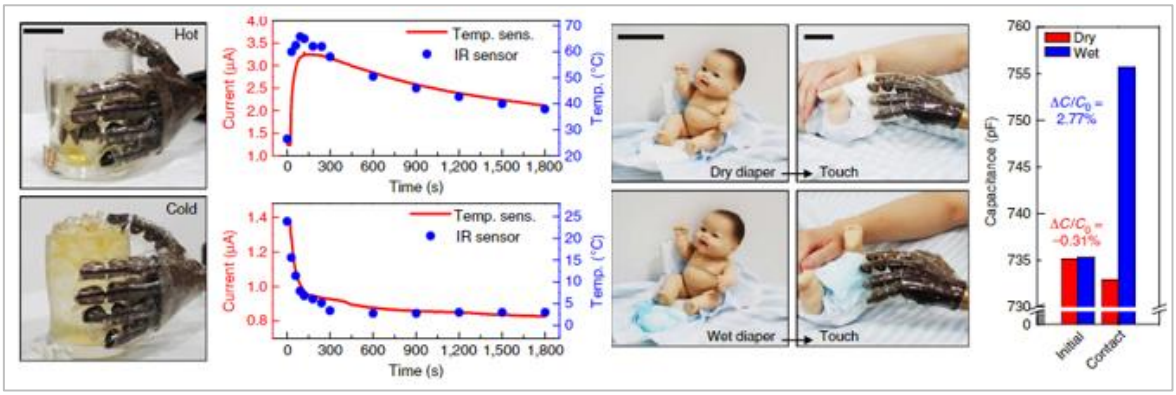


Figure 51. SiNR prosthetic skin on prosthetic hand responding to temperature and humidity changes, (Left) Graph representing temporal current (μA) changes of SiNR temperature sensor in response to contact with hot and cold objects over time, (Right) Bar plot of capacitance (pF) values in response to SiRN in contact with wet vs dry object. (119)

6.4.3. Robotic Surgery

The flexibility of e-skin allows for it to conform to surgical instruments and convey tactile information about the surgical field. This is especially useful in microsurgery or remote surgery settings. Telesurgery has been envisioned for providing high quality medical care from a distance. Additionally, robotics has improved surgical precision to delicate or difficult to access anatomical locations. E-skin can provide haptic feedback, like surface texture, compliance, stiffness and shape of the operating field to surgeons using robotic instrumentation and transform surgical specialties. (39)

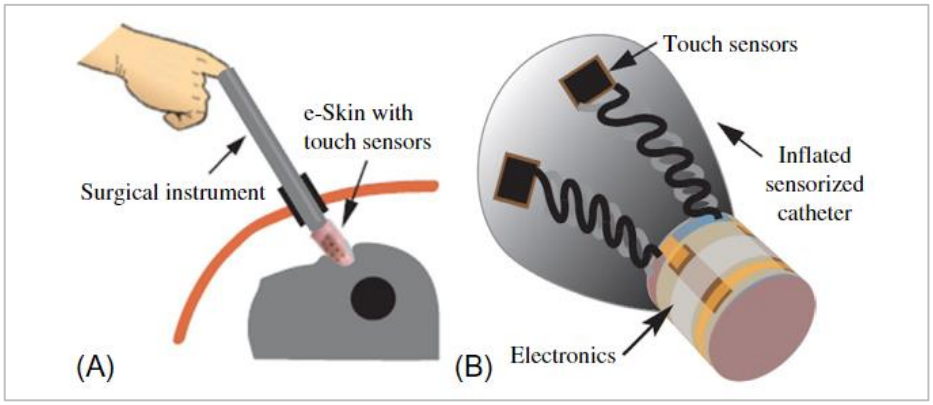


Figure 52. E-skin-covered surgical instrumentation allowing for remote tactile feedback. (39)

6.4.4. Retinal prosthetic systems

Restoration of vision through retinal prosthetic systems seems to be attainable via nanowire FET switches. Their integration into proposed novel microelectrode arrays vastly simplifies wiring complexity and thus allows for their integration into a miniaturized flexible retinal prosthetic system, suitable for intraocular use. (120) Studies on artificial silicon retinas (ASR) using light-activated micro-photodiode array chips have been shown to improve and prolong vision in retinitis pigmentosa patients. 18-month-long subretinal implantation resulted in neurotrophic rescue of color perception, visual acuity and contrast in six subjects, while no structural or functional disruption was observed after 5-year long implantation. (121) Hung et al., report a smart artificial retina system utilizing an (OOSI)

organic optical sensing inverter device. This device consists of n- and p-type MOSFET (metal oxide semiconductor FETs) configurations and can contribute to bionic organ system designs. Furthermore, it is integrated with ocular health monitoring components to avoid the development of retinopathy. (122)

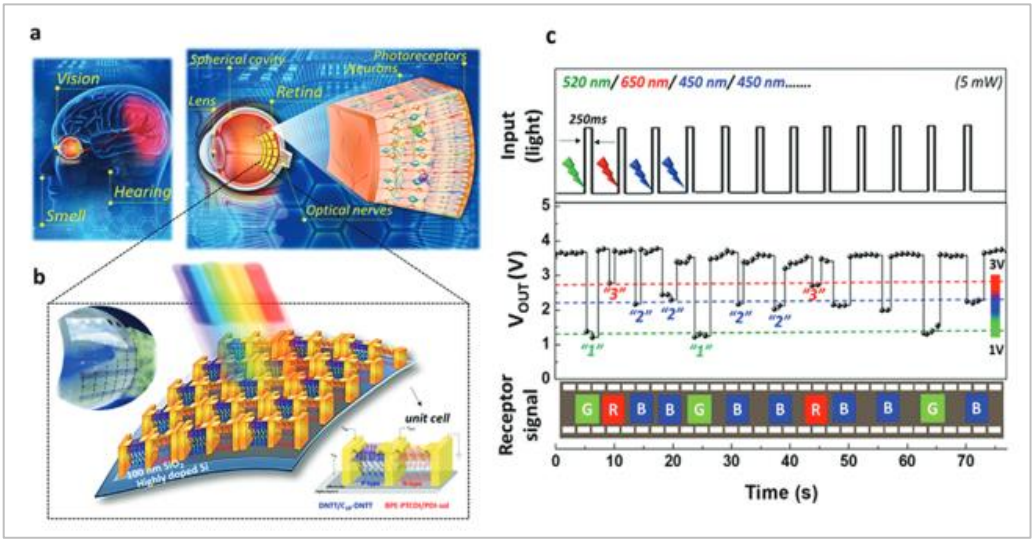


Figure 53. Organic optical sensing inverter smart retina system, (a) human optic system (b) array configuration of inverter acting as retina-like photoreceptors, (c) real-time light-induced receptor signals. (122)

6.4.5. Brain-Computer Interface chips and Neuroelectronics

Neurotechnology is an emerging field of research in which wearable electronics can be utilized to interface with the central and peripheral nervous system. Wearable electronics can measure and monitor electrical signals of the nervous system, block pathological signals and restore motile functionality to paralyzed muscles or future prosthetic devices. A lot of research is dedicated to finding a means of electrode implantation into the CNS or peripheral nerves for this purpose. Foreign body inflammatory response is currently a challenge to be overcome before this can become a reality, so ultrasoft biocompatible nanomaterials could be a potential solution. (39)

Additionally, cerebro-implantable electrode array chips are under investigation as brain-machine interfaces (BMIs). They have the potential to treat neurological disorders and restore sensory and motor function. (123) Tremendous efforts are being made to establish communication with patients of Locked-in-Syndrome via (BCIs) brain-computer interfaces. Control over computer cursors and robotics has been demonstrated via BMI, and even speech composition suggesting the capability for complex information transfer between the nervous system and electronics. (124)

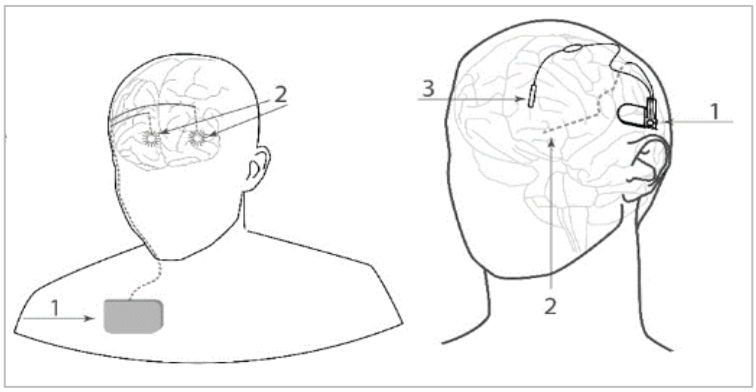


Figure 54. Illustration of implantable BMI prototypes for suppression of epileptic seizures. (124)

7. Discussion

The objective of this literature review has been to investigate the structure, function and abilities of nanochips, as well as whether and how they could be useful in the medical field. Operating systems and programming of nanochip integrated circuits were beyond the scope of this review. Nanochips can be defined as integrated circuits of nano-dimension in which individual atoms and charges are of significance and/or ICs with integrated nanomaterials for enhanced or modified function. The invention of the transistor, its miniaturization and incorporation into ICs have allowed for one industrial revolution and we may possibly be witnesses of a second. Continually shrinking transistors enabled the manufacture of tabletop personal computers and previously unimaginable operating speeds. Despite transistors carrying out a rather simple task of a current switch, their applications seem to be endless.

With the development and advancement of nanotechnology, it is possible to alter and surface-modify transistors, specifically FETs, with nanomaterials and nanoparticles for

interaction with the biochemical and physical world, and create a means of quantifying parameters as a function of electrical current. Electrical current has become the universal language of communication in the last decades via 0s and 1s in computers and smart devices. Furthermore, with the imminent rise of the Internet of Things, integrating our biophysical world with the silicon world can allow for easy and fast data collection about our environment and even our own health.

Nanotechnology has allowed for transistor modification, which can therefore act as biochemical receptors and physical sensors. Silicon nanowires, nanoribbons, carbon nanotubes and graphene have all been used as transistor gates or gate modifications. DNA probes, antibodies and aptamers conjugated to transistor gate surfaces act as molecular receptors and have been successful in the detection of nucleic acids, electrolytes, cardiac markers, tumor markers, neoplastic and pathogenic cells, proteins, antibodies, metabolites, intoxicant drugs and volatile organic compounds (VOCs). Device operation is in real-time, label-free, requires less personnel expertise and does not emit radiation. Furthermore, they can monitor physical parameters like body temperature, pressure and electrophysiological signals (e.g., ECG, EMG, EEG). These platforms have low power and reagent needs and thus can run with lower costs. Their ability to detect the aforementioned biochemical and volatile compounds provides a real-time health profile to assist physicians for diagnostic purposes. Current diagnostic protocols are often invasive, radiation-emitting, time-consuming and with inadequate sensitivity. Integrating nanochips and receptor-modified transistors into the diagnostic field has the potential to alleviate a significant load from healthcare providers and completely change the face of medicine.

Apart from sensor capabilities, transistors are also protagonists in conventional electronics, allowing for smart personal devices, their complex functions and their wireless connectivity. Next-generation diagnostics may involve seamless wearable sensors, for continuous surveillance of health parameters, and immediate communication with the user and physician simultaneously via smart devices and wireless communication. A smartphone notification about a pathological cell or parameter detected in real-time no longer seems like science fiction. Patients and doctors may be informed about pathological processes prior to the appearance of symptoms and therapeutic measures can be taken at the earliest stages thus improving survival and quality of life. Furthermore, continuous

surveillance can also screen for risk factors present to prevent the appearance of certain diseases entirely.

Apart from diagnostics, wearable electronics (with ICs and transistors) can also have therapeutic applications. Drug delivery actuators can be connected with FET sensors for immediate automated response to pathological parameters. Additionally, ICs can operate surgical robots and robotic prosthetic limbs connected to the human nervous system for intuitive motor function and artificial skin for sensation via prosthetic limbs. Furthermore, nanochips can be used to construct artificial retinal prosthetic systems for treatment of impaired vision, brain-machine interfaces for treatment of epilepsy, loss of motor and sensory function in partially paralyzed patients, and even enable communication in complete paralysis. Therefore, nanochips may have a major role in prevention and early diagnosis of diseases, treatment of conditions previously rendered incurable, and integration of all the above in miniaturized wearable electronic sensors and actuators.

As with all technological advancements, challenges and limitations exist here too. Large-scale production of such sensors is hindered by sensor-to-sensor variations and the need for calibration for output data to be universally communicable. There is a need for standardization of manufacturing criteria for these platforms to be used worldwide and for sensor software that is universally compatible. Furthermore, standardized industrial fabrication enables large-scale cheaper production, delegates work hours out of the research lab and allows focus on implementation into clinical settings. Despite remarkable results, nanochip sensors are still at the level of laboratory research, and although there are clinical trials involving patients and real biological samples, they have yet to be fully integrated into clinical practice.

Further advancement of the field seems inevitable, especially with improving nanotechnologies. It seems the two will co-evolve and redefine health monitoring and disease management. Existing literature is in agreement regarding the fact that nanochip FETs can be used for diagnostic purposes directly from biological samples. Moving forward, it seems that additional scientific research is necessary to identify challenges of nanochip integration into wearable biocompatible systems and define hardware limitations to be addressed. Large-scale clinical trials must be conducted with diverse subjects to test the applicability or calibration needs of these technologies depending on gender, body type,

ethnicity and age group. Furthermore, when sensing methods are improved, further investigation is necessary for manufacture of long-lasting, wearable material beds for prolonged use in different environmental settings. Only then would commercialization and large-scale production be worthwhile, profitable and sustainable for manufacturers. Furthermore, due to the interdisciplinary nature of such technologies, time, funding and collaborative efforts are necessary for medical professionals, engineers as well as software developers and programmers, to co-develop the future of the field according to the needs of the real world.

8. Conclusion

Undoubtedly, nanochips have numerous medical applications for real-time, sensitive, safe and accurate, point-of-care or remote diagnostic tests and wearable sensors for continuous health surveillance. The majority of currently demonstrable applications are of diagnostic nature. Most therapeutic applications are still under investigation or immature for commercial markets and clinical indications. A rise is expected in research for therapeutic indications and their integration with diagnostic platforms to construct wearable theranostic systems, via sensors and actuators in the same system with wireless communication. The extensive volume of relative literature allowed for a comprehensive study of nanochips and their integration for diagnostic and sensor applications. Questions that arise are how far we are from therapeutic modalities and clinical integration. Overall, nanochips and FET systems appear to be especially promising candidates for assimilation of electronics into the medical field, and fascinating prospects are to be expected, including smart medical devices, telemedicine and hybrid silicon biosystems.

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