Politecnico di Torino
Department of Electronics and Telecommunications
MASTER'S DEGREE IN ELECTRONIC ENGINEERING

Definition of a system for harvesting in an ultra-scaled CMOS sensing device

Candidate:
Stefano Revello

Supervisors:
Prof. Danilo Demarchi
Prof. Sandro Carrara

Academic Year 2020/2021

I want to dedicate these lines to thank Professor Danilo Demarchi and Professor Sandro Carrara, who gave me the rare opportunity to peek inside the research world with a so challenging project, patiently attending my researches.
I am grateful to Roberto La Rosa, for the precious knowledge and support that placed at the disposal.
I want to thank my mother and Maurizio, to always be present when I need, when I don't, when I don't imagine to.

Author: **Stefano Revello** (s255402)

Supervisors:
Prof. Danilo Demarchi
Prof. Sandro Carrara

Definition of a system for harvesting in an ultra-scaled CMOS sensing device

The future improvements of medicine require personalized drug therapies, a direct consequence of precise health parameters analysis. In order to achieve continuous real-time monitoring, the optimal solution is represented by implantable medical devices (IMD), typically composed by a sensor, a battery and a circuital control module. IMDs present three main issues: the presence of a battery reduces the autonomy of IMDs, requiring periodical maintenance, causing heat dissipation and introducing toxicity risks. A second point, to locate an IMD a surgical operation has to be performed. Furthermore, the presence of two different blocks, for power supplying and sensing, drastically increases the occupation area.
Enzymatic biofuel cells (EBFCs) partially solve problems typical of a lithium-ion battery: an EBFC generates electrical power converting chemical energy obtained from an oxidation-reduction reaction; the reaction involves enzymes present in the human blood, as glutamate, lactate, glucose, with a reduced generation of by-products. EBFCs are used for both, sensing, due their output stability, and harvesting, even though the low output voltage.
The aim of this project is to verify the feasibility of a device that exploits EBFCs properties to perform sensing and harvesting with the same structure, avoiding the presence of a dedicated power unit. The consequent volume reduction allows to obtain a system usable in a CMOS Body Dust (BD) context: a challenging microelectronic emerging diagnostic technology.
BD is based on thousands of miniaturized sensing elements able to mimic the behavior of blood red cells, reaching the gut and be absorbed. In order to reach an understanding of the problem, within Chapter two, possible available power sourcing for BD have been considered, confirming that EBFCs are the optimal solution to create a self-powered device.
Within Chapter 3, the structure of a EBFC has been studied, comparing existent solutions based on possible enzymes. The glucose has been chosen among different fuels accessible in the human body, considering the huge presence in tissues and organs.

Once the glucose reaches the electrodes, the glucose oxidation at the anode produces charges. The electrons reach the cathode by an external path, the ions diffusing through the blood. The charge movement creates a difference between the electrodes potential. The best configuration of the cell's geometry has been pointed out, justifying the removal of the membrane between the

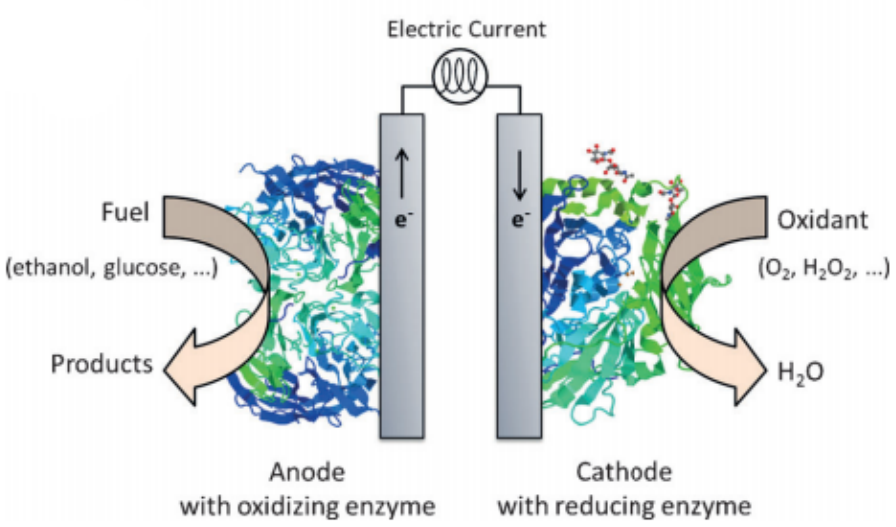
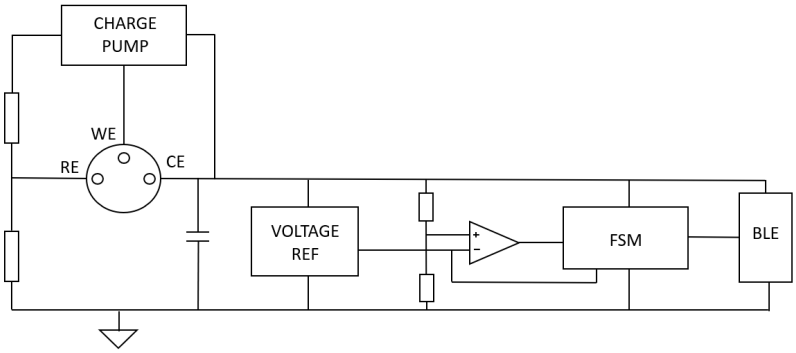


FIGURE 1: Scheme of an enzyme-based BFC [20]

electrodes, typical of an inorganic fuel cell. Direct electron transfer has been the mechanism selected to transfer electrons from the active centre of the reaction to the electrode, motivating the absence of a mediator.

within Chapter 4, a schematic of a readout circuit that controls the cell, collects and transmits data has been proposed, as reported in the figure below. The cell has three electrode pin: the counter electrode is connected to the storage capacitance, that starts to gradually accumulate energy when the BFCbegin to work. The charge and discharge cycle are repeated. The capacitor is connected to the input of a charge pump and to the '+' pin of a comparator. The charge pump controls in output both the working electrode and, through a resistances partitioning, the reference electrode, guaranteeing the stability of the cell. The comparator is a hysteresis comparator, that receives in input the potential drop on the storage element and a voltage reference. Once the drop on the capacitance overcomes the reference value, the output is triggered and the circuit passes into a discharge mode. The output of a comparator can be interpreted as a logic value, and thus treated with a digital circuit. The digital circuit is a basic four-port finite state machine, that bases on the output of the comparator choices the correct reference value, that is transmit at the output,where a Bluetooth low energy transmission system is modeled with a generic load.
The glucose concentration is obtained analyzing the charge-discharge frequency of the capacitance received outside the body.

At the moment, the system has been realized at a theoretical level. Possible further improvements consist in performing simulations of the circuital part passing from an ideal to real components: Thus, aspect as environmental noise or heat dissipation, whose possible consequences have been up to now



only outlined, have to be considered. Moreover, characterization of the BFC has to be performed, to have precise information of the output parameters. Looking forward, a physical realization of the device is desirable, to understand downscaling limits and to collect data with in-vitro simulation.

Contents

List of Figures

List of Tables

History and State of the Art 1

1.1 Medical technology

The relationship between biology and electricity has been reported for the first time by Galvani's experiment (1781) that observed a frog's leg muscular contraction after an electrical pulse. The physiologist started to support the theory that body operations are ruled by a complex net of current stimuli creating the basis of the idea that, with a correct interaction, it is possible to interfere with the human body to adapt its natural behaviour to our purposes.
1958: Ake Senning, Finnish surgeon, concluded with success the first surgical operation to implant an electronic pacemaker in a patient hit by a heart attack. Since that occasion, electronics and medicine started to collaborate with the aim of improving the treatment of either emergency or chronic situations. Useful results have been obtained: cochlear implants, defibrillator, prosthesis, biosensors became a well-established resource and diffused into everyday life to such an extent that is possible to estimate that 6% [31] of people living in wealthy countries entered in contact with some device, resulting from the application of the electromagnetic theory to a physiologic field. Moreover, the same surgical operations have been influenced, with the introduction of automatized techniques that help to obtain a level of precision not reachable with human capabilities only. Several advantages in the medical analysis have been made possible by lab-on-chip systems, that through precise electronic monitoring, allows rapid and high quality diagnostic.
Nowadays, scientific advantages differentiation of purposes occurred on the market to the point that electronics allows not only to treat serious diseases but also to monitor less significant aspects of everyday life through wearable technologies, that are able to keep the hearth beat under control, to inspect the sleep quality, to register burnt calories.
Food and Drug Administration and European Union subdivide medical devices

into three classes [32](with a further two-way splitting of the second classes by European Community based on the using duration), based on risks and consequences due to a failure:

- **Class I**: low risk, do not require electrical currents or voltages and are not fundamental for life-sustaining, e.g. bandages, protection kits, handheld surgical instruments.

- **Class II**: intermediate risk, e.g diagnostic machines, defibrillators, prosthetic heart valves.

- **Class III**: high-risk, monitoring of the final product is required, e.g.pacemakers, aneurysm clips, cardiovascular catheters. To obtain marketing approval, the effectiveness of clinical studies have to be demonstrated, and specific quality inspections have to be sustained.

1.1.1 Implantable devices

Among the various results derived from this synergistic electro-medical cooperation, implantable devices (IDs) play a strategic role in checking and restore body functions, improving the effectiveness of treatments through precise drug delivering or stimulation. Over the past years, IDs have been improved hand in hand with the growth of knowledge about sundry aspects of the human system and with the technological improvements in terms of materials and construction that ensure longer day-by-day durability. The Italian law defines an active ID as any medical device whose operation depends on an electric source different from those originated into the human body intended to be partially or totally implanted with a surgical or medical operation (D.Lgs. 507/92). A further definition distinguishes between passive devices if the aim of the ID is just to support mobility or organs' activities, and active ID if the implant totally substitute prime functions [33]
An ID can continuously keep vital parameters under control: the constant presence in loco allows an immediate ad more effective automatic correction of anomalous behaviours. From a theoretical point of view, the possibility to observe the inner of the body from a closed perspective enhances the knowledge of diseases whose chemical comprehension results hardly derivable just from symptoms.
From an engineering point of view, the general structure of an electronic ID can be schematized with fundamental blocks (figure 1.1). It is possible to recognize four elements that, during a design process, require a specific focus:

- **Sensor**: or more generally the element that performs the aim of IDs. Constituted by biosensors for vital signs or biomolecules detection, electrodes for stimulation, chemical cells for drugs delivery.

- **Powering**: handles the energy supplying of the cell, directly from a battery or received from the transmission module.
- **Analog circuit**: provides data transmission through wireless, infrared or cabled communication, manages interactions between blocks. It includes potentiometer, comparators, antennas, DA and AD converters.
- **Packaging**: encloses the global structure, preventing external contamination and preserving the integrity of the ID.

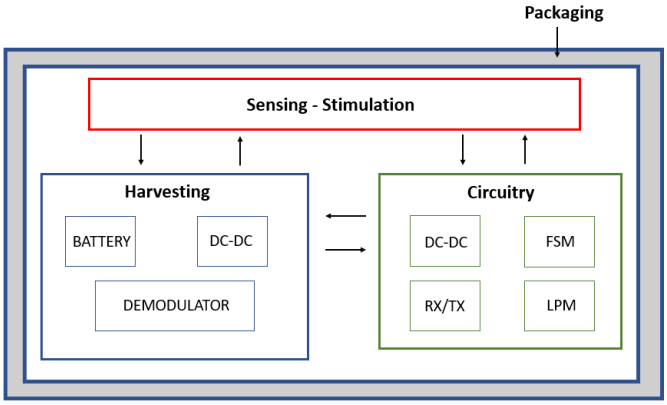


FIGURE 1.1: Block structure schematised common components of ID

Since IDs can belong, basing on the main aim, to Class II or Class III this implies, of course, the presence of current, thus electromagnetic fields are produced and their compatibility with the environment have to be taken into account, to prevent temperature increases and cell's alterations; furthermore e.m. waves produced by IDs can actively interfere with others electrical implanted apparatus, generating malfunctions that could lead to various effect, from measurements inconsistencies to more serious consequences, up to the death of the patient.
In terms of further possible innovations and improvements, some challenges have still to be solved: scalability of sizes and weight is a main requirement to obtain a final performing product that not interferes with daily activities. In spite of design convenience, the choice of internal batteries diminishes the lifetime of the ID, imposing periodical maintenance to recharge, when possible, or to substitute the power source; as a consequence of the increase in complexity and performances of the device, the power demanding grows, requiring larger batteries and counteracting the down-scaling purposes. To limit high power consumption without renouncing to competitive performances Both, scaling and batteries, will be further analysed within the next chapter as critical issues of the ID design.

1.1.2 CMOS Body Dust

A specific application towards which the content of this thesis is to realize a device-oriented to the Smart Dust concept, that expands the standard CMOS structure of ID, moving away from a classical design of micro-electromechanical systems actually used for sensing and wireless communications.
The basic idea is to start from a micro-sensing system and obtain, through an aggressive miniaturization process, a final device with an extremely reduced volume, introduced in [34] as 120 millionths of a meter, small enough to be implanted or suspended in the atmosphere. The dimensions of common industrial sensors are reported in Table 1.1:

Type of sensor	Dimensions (mm)
Speed sensor	33.5 x 36.9 x 8.1
Vibration sensor	15 x 15 x 15
Motion sensor	24 x 32 x 24
Electrochemical sensor	18 x 18
Tilt sensor	4 x 12
Accelerometer	20 x 20
Sound	22 x 23

Table 1.1: Sample of commercialized sensors dimensions, relied from data in [31]

It is evident that, since the dimensions are orders of magnitude higher than the required ones, the massive scaling process takes a lot of effort. However, it is worth the exertion because of promising advantages and possible applications: because of the low power consumption, low production costs and tiny size various fields as temperature prediction, pollution monitoring, agriculture analysis, military improvements, wireless networks can benefit from this highly innovative technology.
In particular, body activities monitoring seems to be a promising case of study. When Smart Dust is applied to solve human issues, it is known as Neural dust if used for brain sensing and stimulation, whereas it is called Body Dust when the target is a tissue or an organ different from the brain. There are two main possibilities to introduce into the body the thousands of particles of which the body dust is composed: by injection or by ingestion. The first one is simpler because it does not need a specific external control system that guides dust to the region target but is less comfortable and requires the presence of medical staff. For example, it has been proposed an injectable miniaturized electrocardiogram platform by Medtronic in [35].
The alternative proposed in [36] concerns the feasibility of a drinkable solution containing hundreds of particles that, once reaching the gut, is absorbed and

independently identifies a specific region to the head, miming the behavior of white and red cells. The figure 1.2 gives a general view of the idea.

FIGURE 1.2: Body Dust particles flowing within blood [37]

While for Smart Dust the dimensions constraints can be a little exceeded, losing something in terms of performances but obtaining something still effective, Body Dust must strictly satisfy size requirements to be correctly absorbed. Thus, it is necessary to provide a volume up to $10\mu m^3$ [38]
Once ingested, Body Dust enters in contact with the gut-associated lymphoid tissue, where the antigene recognition and the mucosal immune response start, to guarantee the biological compatibility of assumed substances. Considering the large size of dust, the cells responsible of the internalization, that allow Body Dust to overcome the gut-wall barrier, are the Microfold cells (M cells). M cells do not are directly employed during digestion; their main role is trans-epithelial transport, thus they move particulates and macromolecules (carbon, ferritin, antivirus antibodies, lectins) from the lumen of the intestine [80]. Trans-epithelial process, which through the dust enters with the organism, can be divided in three stages: endocytosis, transport, exocytosis. To be concluded, the whole process takes from ten minutes on. Even considering the production and release of antimicrobial peptides, this site has been established as one of the most easily reachable access points for pathogens and, as a consequence, for most of the particles that are intentionally introduced in biomedicine.
The choice of coating material, as furtherly discussed in chapter 3, is fundamental to make the transport possible, since the M cells do not have a specific receptor for the Body Dust and thus the packaging characteristics, in terms of pH, residual charge, hydrophobicity, play a fundamental role in the internalisation effectiveness as in DesRieux et al., 2005.
This type of technology has been conceptualized by theoretical models but only a few experimental progress have been built up to now. In [81] a CMOS circuit with an area of 36 mm^2 has been proposed, basing the design on a 130nm CMOS technology; the availment of more complex technological nodes, e.g. with a CMOS technology with a gate length of 5 nm or lower, increases the possibility to satisfy volume requirements.

Even though the extremely reduced volume, BD maintains a structure similar to those typical of ID described in section 1.1.1: focusing on sensing applications of BD, it will be required the presence of sensor and a power unit. Of course, the choice of each component is bound of maintaining a low power consumption and a small occupational area. The power density of Lithium-ion batteries has been improved up to 0.2 Wh/g [40] but their massive structure still significantly influences the final dimensions of the device. From this perspective, the aim of this thesis is to study the feasibility of a self-powering sensor that does not need further power supplying.
The idea is, indeed, to conjugate a harvesting system, able to transform the energy from chemical reactions into usable power, with a sensor by the same solution. The amount of power generated by a sensor may not satisfy the energy necessities of the circuital block; nevertheless, an iterative power scavenging on a capacitance allows the ID to work. While the specific design of the circuital block that handles the data transmission outside of the body will be described in chapter three and the sensor modeling is the goal of chapter two, the aim of the next subsection of this chapter is to review possible strategies used to internally or externally power a MEMS device, to appreciate the elegance of the proposed coincident biosensor-harvesting system and to better understand benefits in terms of costs, area and simplicity.

Powering alternatives 2

First of all, in order to correctly analyse available power alternatives it is necessary to separate devices into two categories: dependent on a direct contact to be powered from those that not need a physical connection and get energy from external sources through a wireless transmission system, as summarizing in figure 2.1. Direct contacts, in turn, can use batteries or environmental power sources (heat, motion, friction).

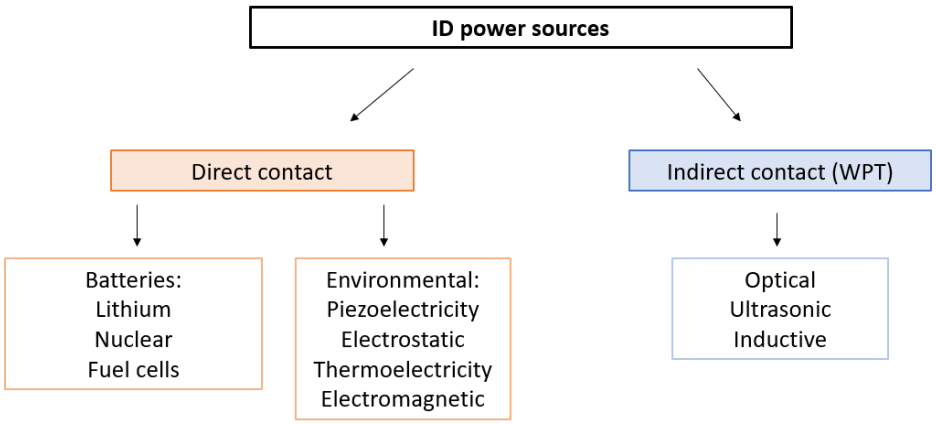


FIGURE 2.1: Powering techniques summarize, adapted from [33]

It is important to notice that not all these solutions can be considered useful for both implanted and wearable devices. Optical and thermal-transfer power sources, for example, cannot be used for something planned to be inserted into the human body, due to the fact that the temperature must be kept constant to preserve vital functions and light has a too low value of penetration depth,

that makes impossible the achievement of organs and tissues not located close to the skin.

2.1 Batteries

Due to the fact that a broad section of the industrial market produces solutions battery-based, it is general habits to adapt existent and mature solutions, originally destined to other duties, to fit MEMS purposes. However, specific researches are required to correctly perform down-scaling, keeping in mind that a battery can increase the weight of a wearable sensor of 200% [42]. Thus, evaluating weight, potential toxicity, slow improvements in [41] is excluded that batteries can represent a valid solution for incoming technologies.
Most diffused batteries are composed of Zn-$Mn0_2$ or Li-ion. The zinc-based alternative is characterized by low production cost, and negligible lost of charge when unused, both qualities that alleviate the impossibility to achieve high power output. Li-ion presents higher voltages by their side, but unfortunately the self-discharge rate must be considered treating remote power nodes, which may be extremely difficult to recharge. The shape of the battery influences performances: comparing a coin battery with a cylindrical one, the second shows a longer total lifetime and a greater capacitance value but it results to be less integrable because of the volume. Lowering the volume is possible but, as a consequence, really small capacitance are obtained: [41] chose a Li-ion solution to realize an implanted ECG sensor, with a generated power of 10 mWh, that required a continuous external recharging, remarkably reducing benefits.

If, in spite of available valid alternatives, the designer persist in implementing a Li-ion battery, several adjustments may be made: the energy dissipated by the transmitter can be reduced acting on the operative frequency, since most of the IDs do not need an intense data transmission rate. In [44] is suggested an intermittent discharge mode, characterized by the battery deactivation except for reduced transmission periods.
A separate mention is deserved for nuclear batteries: whenever the purpose is to guarantee the maximum lifetime and extremely precise stability, as Class III ID requires, a solution based on radio-nuclide has to be taken into account. Medtronic implemented this technology to supply a pacemaker able to overcome 15 years of operability [45]. The working principle is to use a radioactive material, e.g. Plutonium 238, whose radiations heat up a metallic package; the amount of heat is converted into exploitable power through thermocouples. For sure, high costs derived from fuel unavailability, the risk of nuclear radiations leakages and issues related to nuclear waste disposal make nuclear batteries an unfeasible choice except in cases when durability requirements prevail over all

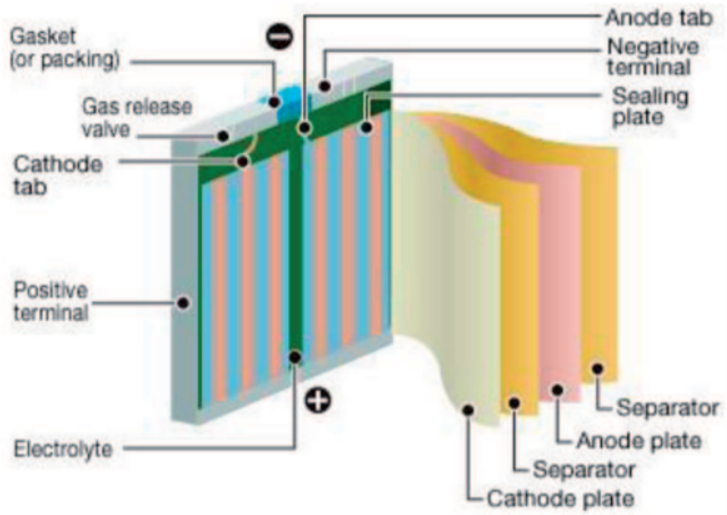


FIGURE 2.2: Li-ion battery physical structure [43]

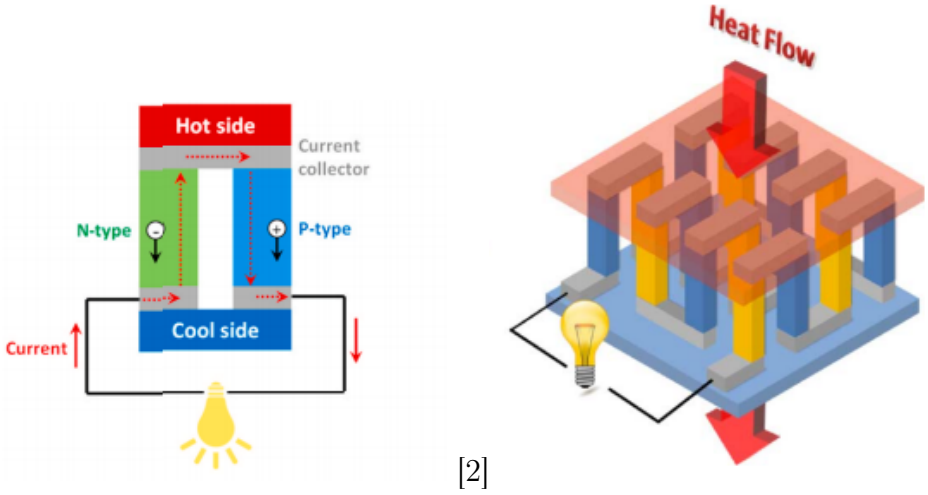
other aspects.
In fact, batteries provide extremely stable output, avoiding the necessity of a voltage regulator, required in most of the following technologies: this saving of area allows to partially compensate the higher volume of batteries. Moreover, when coupled with an external source as in [46] they enhance the conversion efficiency and improve the lifetime of the device. [47]

2.2 Thermoelectricity

Considering that human metabolism provides to keep the body temperature constant between 35.5 °C and 37 °C, it is possible to take advantage of this heat source realizing a device that obtains power directly from the human body. This kind of devices are based on the Seebeck effect: a voltage difference can be generated applying a gradient of temperature on a bar composed of two different metal or semiconductor, that causes a carriers motion from the hot to the cold extreme. The relation among ΔV, the thermal difference and the two Seebeck coefficients is expressed by the formula:

$$V = \int_{T_1}^{T_2} (S_1(T) - S_2(T))dT \tag{2.1}$$

The voltage difference generated by a single thermocouple is generally quite low, on the order of few μW, which is not sufficient for a common implantable or wearable sensor on the market. To improve power capacitance, it is possible to stack thermocouples with a parallel connection, obtaining a thermoelectric generator. Nevertheless, in [48] is noticed that these composed structures have a poor harvesting capability: even though the human body is able to make



[1] [2]

Figure 2.3: 1) Thermocouple behavior principle. [41] 2) Thermocouples stacked in a TEG configuration. [40]

available up to 20 mW cm^{-2}, a thermoelectric generator stores approximately 30 μW^{-2} only. In fact, the Carnot law limits the conversion efficiency η:

$$\eta \leqslant \frac{T_2 - T_1}{T_2} \tag{2.2}$$

As a second temperature source, besides the body's one, the environment temperature, generally lower than 36°C is taken as reference. Supposing a room temperature of 20°C, the conversion efficiency will be limited to 5.5% [49].
Thermocouples can not be considered as a valid alternative for ID, first of all because of difficulty to identify a secondary heat source without using a thermal probe connected to the outside; moreover, BD in mind, such low generated power would require an ultra-low power management module, further increasing the total area.

2.3 Kinetics

The same reasoning done in section 2.2 can be repeated for mechanical sources of power: basing on the fact that the body is continuously subjected to vibrations, caused by movements, walking, external stimuli, it seems reasonable the possibility to convert kinetic energy derived from motion into available energy. Kinetic harvester are general modeled as a spring-mass system, and they can be subdivided into four categories basing on transduction technique:

- **Electrostatic**: an amount of charge is introduced in between of the two parallel plates with a dielectric in between, during a temporary pre-

charge phase. Afterward, due to the plates' misalignment the overlying area changes, causing an increment or diminishment of the capacitance; the same effect is generated when the relative distance between plates is modified. Unfortunately, a manufacturing process compatible with standard CMOS fabrication techniques does not compensate the need of a precharge, and thus the involvement of a further power source.

- **Electromagnetic**: as schematised in figure 2.4.a, it is realized with a magnet and a coil, whose relative movement generates a variable magnetic field and, as a consequence, an electromotive force, as theorized by the Faraday-Neumann-Lenz law. To maximize the energy produced, the frequency should coincide with the fundamental oscillation frequency of the system. For electromagnetic generator, a conversion efficiency up to 30% has been estimated. Due to the fact that that a biological system is subjected to a wide frequency range of stimuli, a system whose performances are subjected to a precise frequency value may not be the optimum choice.

- **Triboelectric**: Tribolectricity is a phenomenon that occurs when two materials are rubbed together, creating a distribution of charges that modifies the local neutrality. It depends on rubbing intensity, surface roughness, contact pressure.

- **Piezoelectric**: A voltage difference is generated when a mechanical strain or compression is applied to a specific class of materials, known as piezoelectric; examples of piezoelectric material are $BaTiO_3$, $LiNbO_3$, ZnO.

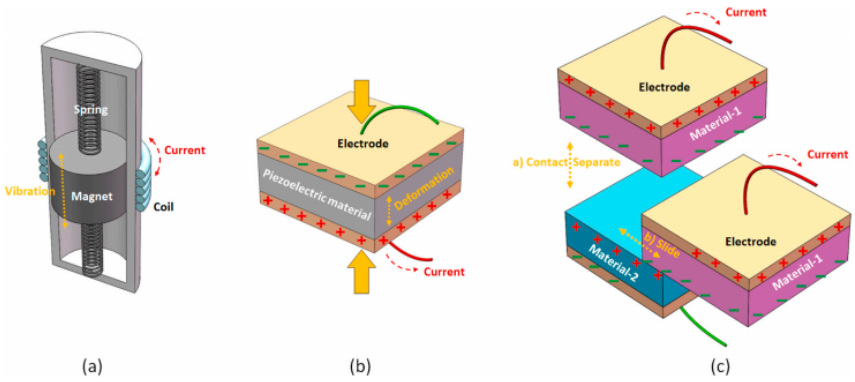


FIGURE 2.4: a) electromagnetic generator b) piezoelectric generator c) triboelectric generator ([41])

In particular, recalling our interest in realizing a micro-dimensions system that performs harvesting and sensing at the same time, the focus is now moved on two specific applications of kinetic harvesters:

Piezoelectric nanogenerator: a piezoelectric nano-generator (PENG) has been built exploiting ZnO nanowires (ZON), extremely safe for what concerns toxicity and biodegradable. When a ZON is deposed on a flexible surface, the combination of the mechanical-electrical coupling induced by mechanical strains and the Schottky contact, where an unbalancing in Fermi level is produced, causes an electron displacement to balance the system and a subsequent current flow.
For a ZON measuring system, fundamental parameters are the total length of the wire and the thickness of the flexible membrane, that influences its deviation from the resting position [51]; these two aspects are inversely proportional. In **??** is described the in-vivo implantation of two self-powered sensors based on PENG that profit by heartbeat and breath to scavenge energy and obtain data on vital parameters. A single ZON has a length of 100-500 μm and a diameter of 500 nm; the open circuit voltage obtained with in vivo implantation resulted lower than 50mV. It is possible to combine ZON on a denser structure chemically growing a ZnO film on a flexible polyester support, increasing the output voltage and current but obviously the volume too.
Considering the small size of BD particles, an energy of 50 mV provided by a ZON coupled with an appropriate power management unit can be suitable for the application. However, as with any device based on a cantilever-model system, the precision of measurements is corrupted by noise interferences:

Triboelectric nanogenerator: Due to the impossibility to attribute the triboelectric effect to a restricted class of materials, it is a phenomenon that has always to be taken into account in industrial applications because it may lead to negative effects as power leakages or electronic damages. Creating physical contact between two materials different in terms of electron affinity and potential, a voltage drop occurs and, as a consequence, a current flows from one electrode to the other. Not only vibrations contribute to the possibility to scavenge energy, but also rotational movements.
In [53] a detailed model of triboelectric nanogenerator is reported, included the description of the behavior at a physical level, possible geometrical configurations and consequent applications. In particular, it is presented a possible implementation of triboelectricity in self-powering sensors for health functionalities monitoring: a combination of Nylon and Polytetrafluoroethylene composes the triboelectric couple deposed one on the other with a circular shape, with a diameter of 2cm. The sensor, implanted in a carotid, exposes an output voltage of $4V_{pp}$, proving the feasibility of measuring arterial pulse without the necessity of an external source of power, with remarkable stability over forty thousand cycles.

2.4 Wireless

Energy harvesters discussed up to now are characterized by a low generated power, often not sufficient for a multipurpose platform that includes more than one sensor and more sophisticated circuitry on the market, implementing an on-chip analysis of collected data and an ADC to transmit at output already converted data. Recalling the fact that to transfer data outside of the body, a wireless transmission module is needed, all the same, it seems reasonable to use the module not only as a transmitter but also as a power source. Extending an existing unit's functions, certain advantages will be reported in terms of saved area and reduced complexity.
A wireless powering system (WPS) is composed of two or more coils mutually coupled that interact following the near field theory [54]. If the number of coils grows, it is lowered the effect of parasitic resistances. A model that described the antenna and possible optimization for the transmission system, including either a Bluetooth low energy system or a single-coil structure, will be detailed in Chapter 3. The widely diffused operating frequency for medical devices is 13.56MHz, a low value that involves, in general, the presence of large antennas and difficulties in maintaining a useful data rate. WPSs used for ID have to satisfy constraints about the specific absorption rate (SAR), a factor that points out the maximum absorbed power that an organism can tolerate in order to avoid dangers caused by tissue heating.

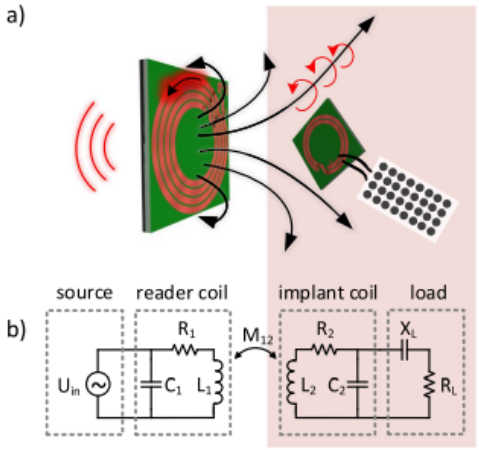


FIGURE 2.5: a) Schematic behaviour of Inductive link generator b) Inductive link equivalent circuit [54]

SAR is a quantity directly proportional to the applied electric field E, the

tissue conductivity σ, while of it decreases when the mass density ρ_m grows.

$$SAR = \frac{\sigma |E|^2}{2\rho_m} \tag{2.3}$$

It is measured over a cube containing a reference mass, European Union specifies two different values: a maximum of 2W/kg over 10g of body tissue, except for parts that do not contain vital organs, for which the limit rises up to 4W/kg.

The efficiency value is remarkable, estimated up to 60% [41] for wearable implementations. However, transcutaneous energy transfer presents some issues: the internal coils and the generator have to be carefully aligned to maximize the efficiency; nevertheless the proximity of the external device, required to avoid power losses, implies the positioning of a device that generates a magnetic field extremely close to the skin, increasing the SAR value.
A possible alternative to common near-field powering is the so called witricity, technology explained in [55], that increases the distance patient-apparatus that allows to obtain electric current through wireless signals. Two resonators exploit an efficient interaction by their resonance frequency instead of entering in contact with a more common radiative field, characterized by higher losses. The coil located on the implanted device is made by a metal covered with a polymer film, thin enough to do not modify the resonance frequency but sufficient to prevent the oxidation, natural consequent into a body environment. Tested with a core of 35mm, the size of this coil is still far from being considered valid for BD purposes.

2.5 Infrared

Another solution to avoid the use of a battery exploiting electromagnetic waves is infrared (IR) transmission, a type of wireless powering that allows energy transfer through a near-infrared light beam. As previously anticipated, not all electromagnetic frequencies are suitable: with light in the visible spectrum the interference probabilities increase, due to the fact that many medical instruments may typically suffer noise, working at the same frequency value. IRs stimulation can be coupled with an internal rechargeable battery, that takes the advantage of be able to store energy without the duty of immediate exploitation, but gets back all issues related to the presence of a battery.
The incident beam, characterized by a wavelength of 810nm[47], illuminates an inner photodiode whose total area is $26\mu m^2$ that stores energy in a Lithium battery: this configuration allows a maximum output voltage of 3.1 V, when the device operates at a typical body temperature. Once the device has been embedded under the rat's skin, conversion efficiency up to 21% has been measured. As announced within wireless considerations, when electromagnetic

waves are applied onto the body, the skin temperature rises: in [47] an increase of 2.2°C with an applied power density of 32 mW/cm^2 is reported, limiting both the maximum incident power, that would speed up the charge time needed to compensate losses, and the exposure time.

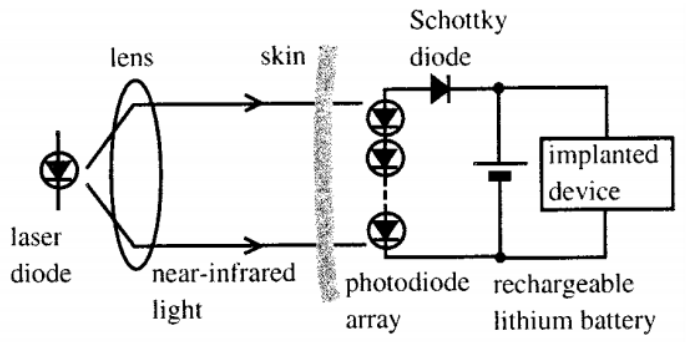


FIGURE 2.6: Near-infrared powering system [40]

2.6 Fuel cells

Even though the existence of the fuel cell (FC) is known since the middle of '50, only from the last decade of the twentieth century the scientific community started to consider as promising this electrochemical power source, hand by hand with the growth of the interest for environmental impact and renewable energies. As proposed above, it is possible to implement different solutions to avoid the presence of a battery, whose components are often difficult to dispose of. With respect to a battery, fuel cells are more sensible devices, that require a well calibrated control system to limit instabilities derived from alterations of temperature, reactant concentrations, electrodes poisoning.
On the pros side, they may guarantee an uninterrupted operation as long as correct boundary conditions are preserved. In fact, fuel fills the cell from outside, without the necessity to handle its storage. In the following subsection, the basic behavior of a hydrogen cell and the working principle of the so called proton exchange membrane will be described. Other types of fuel cell configurations, such as phosphoric acid FC, molten carbonate FC and solid oxide FC, have been intentionally neglected, because typical of the industrial context, characterized by a high operating temperature and a large occupational area, all features that do not feat our main goal. To support this sentence, refer to Table 2.1

Type of Fuel cell	Mobile ion	Operating temperature (°C)
Alkaline	OH^-	50-200
Proton exchange membrane	H^+	50-100
Phosporic acid	H^+	220
Molten carbonite	CO_3^{2-}	650
Solide oxide	O^{2-}	500-1000

Table 2.1: Sample of commercialized sensors dimensions, adapted from [57]

2.6.1 Hydrogen cell

Hydrogen fuel cell (HFC) is, among wide possibilities of choice of fuel, one of the simplest. Let's consider as a starting point a setup composed by two Platinum electrodes merged in a water basin. If a current flows through the Pt electrodes is imposed from outside, connecting a battery, the water molecule is decomposed into hydrogen and oxygen: the chemical reaction of the whole process, known as electrolysis, is reported below:

$$2H_2O \rightarrow 2H_2 + O_2 \tag{2.4}$$

If the battery is replaced with an ammeter, this causes the oxygen-hydrogen recombination, and a small amount of electric current is generated. The geometry of the electrodes is very important, because they have to exhibit the larger surface of contact between the electrode and the fuel to maximize the current, thus they are typically flat. The two electrodes are differently polarised, the cathode is positive and the anode is negative, a convention opposite to the one commonly used in electronics.
Entering in details allows to better understand the electron genesis in a cell as in figure2.7: hydrogen fuel enters in contact with anode, this step ionizes the gas that releases electrons and a small quantity of energy:

$$2H_2 \rightarrow 2H^+ + 4e^- \tag{2.5}$$

The electrons are transferred to the cathode through an external low, whereas hydrogen ions directly reach the other electrode crossing a zone where an electrolyte enhances the transition. Same working principle at the cathode, where Oxygen in gas form enters in touch with the positive electrode, absorbing the electrons and ions coming from hydrogen gas to produce water:

$$O_2 + 4e^- + 4H^+ \rightarrow 2H_2O \tag{2.6}$$

Cells that exploit the presence of an intermediate layer to permit the ions cross are defined as proton exchange membrane (PEM).

Depending on the polarity of the exchange ions, the cell can be acid (H^+) or alkaline (OH^-).

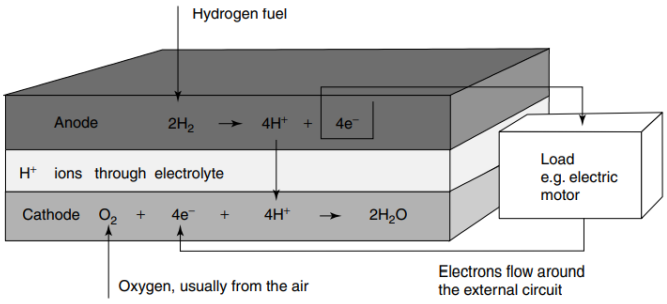


FIGURE 2.7: Three-layer acid proton exchange membrane structure [57]

Of course, HFCs are not an unlimited source of current: first of all it is required a small amount of energy to get the reaction starts, often supplied by a single-purpose battery. Moreover, the reaction rate, which gives information about the speed of the chemical reaction, tends to saturate when the temperature decreases, because the reactants start to have not enough energy to overcome the activation level.
The main reason that, for decades, led to neglect of this technology is the small amount of energy provided at the output, few μW for centimeter square, with respect to a battery that can reach without many problems $1W/cm^2$. Nevertheless, as for batteries, for some configurations and materials it is possible to stack multiple HFC together with a parallel connection, a design tip that increases the output voltage. However, it will be analysed in section 3.6 that not always a multiple combinations of cell generates growth of performances.

2.6.2 Proton Exchange Membrane

The PEM concept has been introduced in the previous section: basically it extends the concept of HFC to whatever cell based on a transfer of positive ions membrane-based. PEMs operate in a range of temperature (20-80) C suitable for human implantation. In the membrane-based, the polymer electrolyte is confined: the polymer contains compounds, e.g. sulphonic acid, strongly hydrophilic, that may lead the absorption of large quantity of water. As a result of hydration of the intermediate layer, hydrogen ions are attracted by the SO_3^- group of sulphonic acid and, as a consequence, they cross over the structure.
The electrode constitutes the higher production cost, due to the huge price of the compounds (gold, platinum). To improve the control on the reaction rate, an electrode is covered with a catalyst: the function of the catalyst layer is moreover to dry the electrode from water product, due to its hydrophobic behavior. In fact, the management of water is one of the most critical aspects of the PEM that has to be considered: theoretically, the flux of fuel on the

cathode side not only provides a correct fueling of Oxygen but also dry out water excesses. It may happen that, due to the extremely reduced size of the electrolyte membrane, water molecules reach the anode. The presence of water at the anode can lead to an electro-osmotic drag: hydrogen ions, moving on the opposite path of water, cause an inversion of water direction. A subsequent dryness of the anode and an unbalance of the electrolyte density occur, thus performances diminish due to the fact that, as further analysed in paragraph 3.6, it is necessary that the density of the electrolyte remains as stable as possible, a requirement in contrast with the electro-osmotic drag. Larminie et al. suggested that the inconvenience can be kept under control through further external humidification of the reactants bubbling them through a temperature controlled water layer, preventing dryness. One of the advantages of biofuel cells is that both reactants are obtained from a liquid substance, blood for our purposes, and thus it seems reasonable to consider the dry issue as negligible.

Recently, membrane-less FCs have been proposed. [58] This type of cell is designed with a Reynolds number less than ten, to exploit a laminar flux phenomenon (a flux is defined laminar when the Reynolds number is lower than 2100) that allows filling the cell with two different solutions that flow in parallel. The presence of a membrane to keep the two fluids separated becomes meaningless. This solves a possible problem of fluid-based PEM FC: even though a strict separation of fuels is maintained, it is possible that contamination through the permeable membrane occurs, especially when FC are stacked in a parallel configuration.

2.7 Conclusions

Within this chapter, possible alternatives to supply power to an ID have been discussed: obviously each presented technique has some pros and some cons:

- **Batteries**: batteries are characterized by an high, stable output power. However, it results difficult to downscale a battery structure to reduce its large occupation area. The toxicity of the compounds and of the chemical reaction product imposes strict requirements on packaging, which can increase the difficulty of a sensor interface between the ID and the inner of the body.
- **Piezoelectricity**: characterized by high output power, piezoelectrical devices present interesting characteristic in terms of sensing-harvesting matching. However, the performances are limited by the intermittent nature of power sources, which may not guarantee constancy over time, and by the frequency dependence. The noise sensitivity is an issue: an ID

designed to take advantage of a precise source of vibrations is influenced by the whole environment without selection possibility.

- **Thermoelectricity**: on the pros side, thermoelectric power sources do not show a decrease of performances over time. The output power is low, and the necessity of a connection to the environment to obtain a gradient of temperature makes them inefficient for ID applications.
- **Inductive link**: they allow high power transmission, the choice of a wireless power module exploit the presence of the transmitter. For IDs, power is limited by SAR.
- **Fuel cells**: FC have a stable output voltage, ease of scaling. The wide choice of manufacturing compound easily satisfies the biocompatibility requirements of IDs. However, the short lifetime due to electrode poisoning and the need of activation energy require precise design choices to be prevented.

Biofuel cell 3

3.1 Classification

The intuition to exploit substances naturally present in the human body to obtain energy derives from the desire to copy a similar process that occurs in plants, the photosynthesis, that starting from adenosine triphosphate and nicotinamide adenine dinucleotide phosphate and carbon dioxide produces glucose. Worldwide studies have been intensified to maximize demonstrations of the effectiveness of the BFC, to obtain not only a technology consolidated at a research-level but also competitive on the global market.
Different from FC, biofuel cells (BFC from now on) do not scavenge energy from inorganic compounds but derive power from enzymes operating under temperature conditions suitable for medical applications, generally lower than 40°C and with a neutral pH. [59] Some hybrid solution, that use different organic and inorganic compounds depending on the electrode, are proposed in literature [21].

A BFC exploits one or more enzymes: enzymes are biologically proteins, characterized by an high molecular weight: the redox reaction occurs in an active center, that can be located on the board of the enzyme or deeply inside the shell. Depending on its different positioning, it varies the way in which the active redox centre behaves.

BFCs are, in general, inferior with respect to FCs because experiments showed off worse power density and stability over long periods. Nevertheless, the advantages in terms of biocompatibility are unquestionable. [20] are in fact subdivided basing on the type of catalyst that enhances the reaction 3.2: the cell can be microbial if the cell profit by the whole bio-entity to obtain a

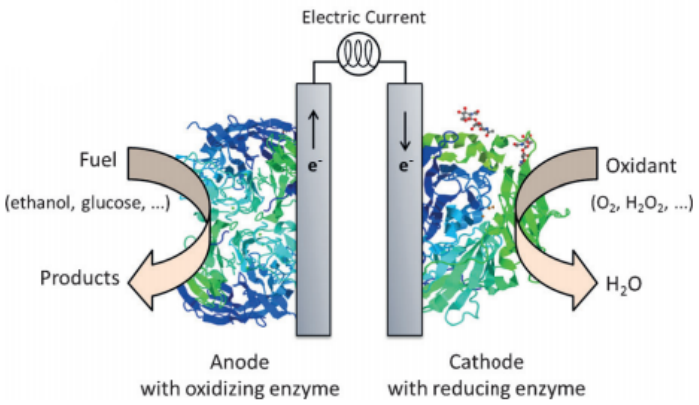


Figure 3.1: Scheme of an enzyme-based BFC [20]

catalyst or enzymatic, when an isolated type of enzyme guides the reaction. A BFC that relies on a whole organic system can rely on a greater number of enzymatic alternatives and, indeed, it is preferable for the realization of multi-purpose sensing. [11]

3.1.1 Active centre

The enzymatic solution, of course, preferable if the aim is to combine selective sensing to scavenging and thus appears as the most suitable solution for BD. Even though an enzymatic system is a less common choice, numerous examples have been reported during the last two decades. It is possible to distinguish three different categories, depending on the type of enzyme and the kind of reaction that occurs with the electrode.
First of all, the focus is moved on redox reaction based on enzymes containing nicotinamide adenine dinucleotide ($NADH/NAD^+$), which works as an electron transfer centre. This molecule is characterized by a weak bonding, that allows a rapid distancing from the enzyme, and thus the NADH can behave as a mediator too. However, some issues must be considered: the hydrolysis velocity must be controlled; moreover, the electrode has to be designed such that the transmission process involves two electrons and does not generate a potential higher than the one of the main reaction, to prevent side effects. To obtain a two-electrons reaction, the electrode can be modified with PQQ or flavin adenine dinucleotide (FAD), a very diffused strategy in glucose cells.
The enzymes of the second group, for example peroxidase, the redox centre is on the board of the protein shell. This location allows peroxides to play the role of a recombination centre, absorbing electrons by contact. Thus, they may be considered anisotropic enzymes, since their absorption properties depend on their orientation. This kind of enzymes represents the best solution to handle

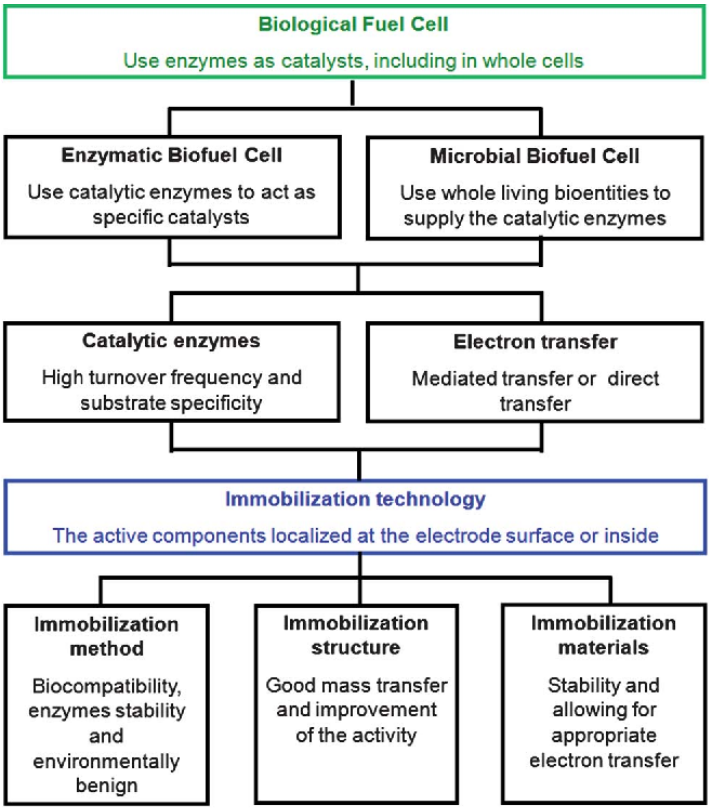


FIGURE 3.2: Diagram of BFCs classification [12]

direct electron transfer, explained below. The active centre of the immobilized enzyme has to be located at a maximum of 1.4nm [20] to the surface of the electrode to maximize electrons transfer.
The third class of enzymes has a redox centre strongly located on the inner part of a protein shell. In this situation, it is extremely difficult that electrons interact directly with the outside of the reaction centre and this makes impossible a direct absorption of electrons by the electrodes: the only way is the destruction of the shell, but the application of such a strong potential makes the contribution of the electrons negligible. The study of this type of reaction is particularly important for the purpose of this thesis, because it is typical of Glucose oxidase (GOx), one of the most frequent enzymes in glucose-based BFC.

The main problem to be solved to create a sensor that is suitable for BD applications is the scaling of the dimensions: even preferring to common Li-ion batteries the use of PEMFC, there are still some elements of the structure that results superfluous, bulky and indeed can be eliminated [71]. BFC without the separation membrane was then created: this is made possible by the immobilization at each electrode of a selective enzyme. A first example test was reported in 2001 by Katz et al. [65], a membrane-less BFC that provided

an output of 60mV only, which is definitely too low to guarantee the correct functioning of a circuit but which plays the role of a pioneer for subsequent improvements.

3.1.2 Membrane

From this point of view, membrane-less glucose BFC, as reported in [70][58], have numerous advantages:

- the presence of glucose in all organs and tissues of the human body avoids the need to dedicate a specific area of the sensor to fuel storage, metabolism provides to continuously replace them within biological fluids.
- Considering that the blood is in constant motion, it do not require a pumping system that delivers the fuel into the cell.
- Oxygen is normally contained in the blood, so the cathode breathing membrane is pointless.
- Neither reactants nor products are toxic, thus requirements on packaging thickness and safeness are less strict.

Removing the membrane and acting on the package is indeed possible to significantly reduce the total occupation area. A separating membrane is still needed for those BFC that employ a catalyst at the electrodes that contains Platinum group metals, because a reduction in the potential output of the cell, due to side effects consequence of platinum electrodes poisoning, is measured [33]. On the cons sides platinum, in addition to having to require the presence of a membrane, is not suitable for large-scale production due to high costs and reusability difficulties. Regarding the electrode poisoning issue, enzyme-based catalyst represent an optimal solution with respect to inorganic compounds, because electroxidation products that interfere with the platinum activity do not affect enzymatic catalyst, thus that allows an effective action of electrodes even if not insulated.

3.1.3 DET - MET

To improve the reaction efficiency, defined in section 3.3, it is fundamental to make the electron transferring as fast as possible. It is not rare that the reaction area does not coincide with the location of the electrode, thus a secondary compound is used to mediate the diffusion of the electrons to the surface of the electrode (mediator electron transfer, MET). The reaction that occurs at the electrodes usually regenerates the mediator. Whenever the presence of a mediator is not necessary, the BFC is characterized by a direct electron transfer

(DET). The mediator may cross the membrane of a PEM, diffusing to transport electrons from one side to other, or simply release electrons close to the membrane. The reaction potential of the mediator has to be similar to the one of the biological components, to avoid an increase of losses. In general, A DET process is preferable because it is easier to control and involves fewer power losses. For what concerns glucose, a mediator, e.g.ferrocene monocarboxylic acid, methylene blue or pyrroloquinoline quinone (PQQ), can be considered the simpler choice

DET	**MET**
Orientation dependent	Efficient electron transfer
Limited to PQQ-FAD	Similar enzyme-mediator potential required
Higher output voltage	Higher current
More complex design	More complex production

Table 3.1: Comparison between DET and MED characteristics

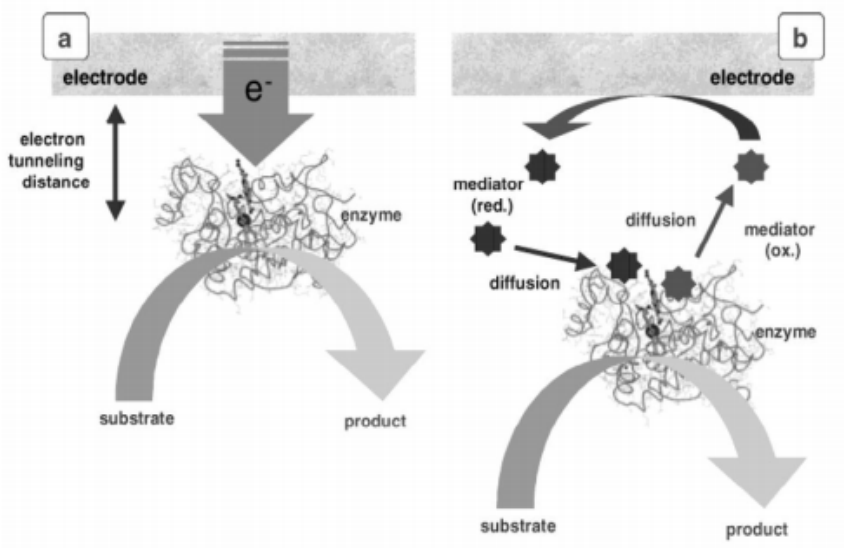


FIGURE 3.3: Possible transfer mechanism: a) DET, direct electron transfer. b) MET, mediator electron transfer [59]

Recently, a third alternative comes out: fixing nanomaterials to the electrode allows to conjugate positive effect of direct and mediated electron transfer. In fact, as demonstrated in [22], despite the presence of an element between the enzyme electrode, indeed a MET by fact, the electron transfer maintains

the characteristics of a direct transmission unaltered.
As observable in figure 3.2, whether it concerns the immobilization of nanomaterials to favor a DET or whether it is needed to anchor a mediator to the surface of the electrode the choice of the correct immobilization technique is the last critical point of the device, after choosing the material of the electrodes and the enzyme to be used: entrapment, physical adsorption, covalent bonding, cross-linking, the selection of the technology depends on the decisions that have been made previously. The immobilization may promote conformational changes, which modifies the chemical-physical characteristic denaturalizing the properties of the deposed materials.
Carbon nanotubes (CNT)or graphene-based materials allow to increase the lifetime of the enzyme, to reduce the criticalities related to electrons transfer kinetics and increase the BFC power density. CNT are characterized by a large aspect ratio. Treating the surface of CNT with aulfuric and nitric acid enhance the dispersibility in solution, favoring the deposition process. In [30] single wall carbon nanotubes SWNT are used to mediate electron transfer in a cell with oxidoreductase as enzyme and FAD as active centre. SWNT are realized with an innovative pulsed laser technique, that allows to obtain a final structure of few μm length and around 1.2 nm of diameter. Multiwall nanotubes are used in sensing of cholesterol [66] or glutamate [67]

3.2 Enzymatic glucose sensors

Updike and Hick for the first time succeeded in GOx immobilization to perform glucose measurements. The history of enzymatic glucose sensor passed through three different approaches. The first one used the Oxygen as mediator to promote electrons transfers from GOx to the electrode. The choice of glucose oxidase with respect to others possible enzymes derives from stability advantages.
The second-generation sensors substituted the Oxygen, limited by low pressure characteristic, with artificial mediators. As described above, it is a common will to reach an optimized DET: it has been reached for some specific enzymes totally removing the mediator and treating the electrode with chemical compounds that favor the electrons release, e.g. PQQ. Actually, a common BFC configuration for glucose-based membrane-less material, with GOx as catalytic enzyme for the anode and an oxygen at cathode. The chemical reactions that occurs at the anode, when PQQ-GDH is utilized, is the following:

$$C_6H_{12}O_6 \rightarrow C_6H_{10}O_6 + 2H^+ + 2e^- \tag{3.1}$$

The oxidation of glucose results in the production of an electrons couple, ionized hydrogen and gluconolactone $C_6H_{10}O_6$. At the cathode, cations and

electrons, reacting with oxygen that has an higher redox potential [62], generate a current flow:

$$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O \tag{3.2}$$

Thus, the global reversible reaction can be written as:

$$2C_6H_{12}O_6 + O_2 \longleftrightarrow 2C_6H_{10}O_6 + H_2O \tag{3.3}$$

The oxygen is often used at the cathode for the enormous availability in the organic systems, however is characterized by sluggish kinetics, that diminishes the rate of reaction.

3.2.1 Self-powered sensors

In order to satisfy strict BD's requirements in terms of dimensions that, as described in chapter 1, imposing a maximum size of (10x10x10)μm, it is important to try to understand how may be possible to downscale the total volume of the existent technology, widely tested and validated, without interfering with physical properties and working principle; the impact of dimension reduction is often unknown. [62]
without certainty about downscaling, a great alternative are a self-powered sensor. A so reduced structure, as BD theoretically is, may benefit of the absence of a specific harvesting module, that have no role except power supplying. Considering that no voltage is externally applied on a self-powered cell, noise and measurement interference are strongly reduced.
Different solutions to self-power a BFC have been studied over the years, three, in particular, are noteworthy:

- Gymama et al. [63] proposed a glucose sensor with PQQ-GDH as anodic catalyst and laccase as a cathodic catalyst, both immobilized on the electrodes. Multi-walled carbon nanotubes have been used to build the bulk of the electrode, with an areo of (1x0.2)cm. The BFC provides at the output 15.98μW/cm^2 only, with an open circuit voltage of 0.3V, average performances for what concerns a BFC at physiological conditions, that rarely overcomes 0.6V, as observable in data reported in figure 3.4. The low voltage is the reason why the cell has been linked to a charge pump: a charge pump, as explained in section 4.2, it is the easiest implementation to increase the available energy and let the circuit work.

- In [65] is reported a self-powered glucose/lactate sensor, based on two gold electrodes (0.19cm^2). Cathode is realized for both, glucose and lactate sensors, with a monolayer of glutaric dialdehyde-cross-linked

Cyt c/COx. For the glucose one the anode is made with amino/FAD-PQQ. The lactate dehydrogenase interacts, instead, with a PQQ-NAD^+ catalyst. A combination of both electrodes guarantees at the output an open circuit voltage of about 30mV. The results got possible to declare that it is generated a sufficient amount of energy to supply to sensing without external power sources.

- Within [68] paper a glucose-biosensor has been developed, basing on MWCNTs for the electrodes, PQQ-GDH at the anode and Bilirubin oxidase at the cathode. The output voltage measured over a range of (1-20)mM reached 0.25V as maximum. This research will be further discussed in Chapter 4 because of the particular readout circuit.

Anode	Mediator	Cathode	Implantation Place	Power Density	OCV (V)
Graphite discs containing glucose oxidase, ubiquinone and catalase	Ubiquinone	Graphite modified with polyphenol oxidase and quinone, surrounded by a cellulose dialysis membrane	Retroperitoneal space in rats	6.5 μW	0.275
Buckypaper modified with PBSE and glucose dehydrogenase	PQQ	Buckypaper modified with PBSE and laccase	Snail hemocoel	30 $\mu W \cdot cm^{-2}$	n/a
FCF microelectrodes modified with neutral red and glucose oxidase crosslinked with glutaraldehyde	Neutral red	FCF modified with PAMAM-G4 dendrimer and PtNPs	Intravenous in a rat	95 $\mu W \cdot cm^{-2}$	0.125
Buckypaper modified with PBSE and glucose dehydrogenase	PQQ	Buckypaper modified with PBSE and laccase	Clams visceral mass	40 $\mu W \cdot cm^{-2}$	0.3–0.4
Carbon rod modified with osmium polymers and glucose oxidase crosslinked with PEGDGE	Osmium polymers	Bilirubin oxidase crosslinked with osmium polymers using PEGDGE and grafted onto carbon rods	Cockroachabdomen	55 $\mu W \cdot cm^{-2}$	n/a
Buckypaper modified with PBSE and glucose dehydrogenase	PQQ	Buckypaper modified with PBSE and laccase	Cremaster tissue in a rat	0.175 $\mu W \cdot cm^{-2}$	0.140
Carbon fibre modified with glucose dehydrogenase crosslinked with osmium polymers	Osmium polymers	Carbon fibre modified with bilirubin oxidase crosslinked with osmium polymers	In vitro with human blood	68.1 μW cm^{-2}	0.65
Cellobiose dehydrogenase adsorbed onto graphite electrode	DET	Bilirubin oxidase adsorbed onto graphite electrode	Ex vivo with human blood	0.74 μW	0.31

Figure 3.4: Summary of implantable BFC open circuit voltages and output powers. [64]

3.2.2 Glucose properties

It is important, now, to specify reasons that lead to base the first approach to self-powering sensors on glucose instead of glutamate, insulin, cholesterol or any other type of enzymes that may play the role of fuel for the bio-cell.
It occurs spontaneously to think of glucose when powering is the aim, since that molecule represents the main source of energy for every cell functions in

vertebrates. Glucose, also known as dextrose, belongs to the class of monosaccharides, carbohydrates that can not be decomposed in a simpler structure by hydrolysis but that may be joined to obtain more complex molecules as oligosaccharides and polysaccharides. [61]
Considering that the goal of this work is based on sensing, it is necessary to specify normal and anomalous ranges of glucose values: the blood of a healthy human is characterized by a typical glucose level between 3.5mM and 5.5mM; in vitro simulations are commonly performed with a 5mM setup. Levels higher than 7.8mM (after 75g dose ingestion) are a wake-up call to suspect diabetic pathologies. Liver and muscles absorb and store dextrose, around 7g per kilogram body weight, in form of glycogen, blood contains 0.08%-0.1%. Daily introduced into the human body with a balanced diet, in forms of fructose, lactose and maltose, if a deficiency occurs the metabolism is able to synthesize glucose through a process called glucogenesis that transforms non-saccharide precursors (glycerol, lactate, pyruvate).
From a chemical point of view, glucose can be considered as both, polyalcohol and aldehyde, because of the presence of both functional groups; as is possible to observe from the open-chain structure reported in figure 3.5 the molecule ($C_6H_{12}O_6$) is composed by four chiral atoms of carbon: Often a D- in front of the substantive is specified, to recall the presence of a hydroxyl group bounded with the fifth carbon atom.

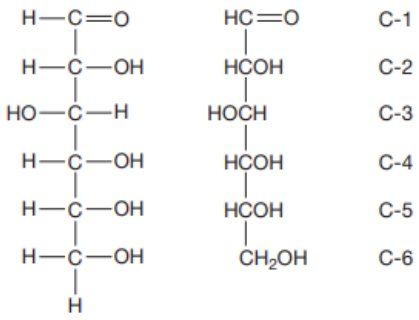


FIGURE 3.5: Glucose molecule open chain, explicit and compact representation [61]

Main physical properties are reported in table 3.2. In particular, the importance of water solubility is remarkable, considering the fact that the blood is water-based and indeed the presence of glucose is related to the water content percentage [60]. During sensors comparison special attention has been paid to test environments: if tests are performed in whole blood, red cells only or plasma strongly influences the final result, because of the different water/volume ratio, as analysed by Brunkhorst et. all.

The viscosity is strictly dependent to metabolism processes: acid or en-

Properties	Characteristic
Appearance	White, crystalline
Molecular weight	180.16 g mol $^{-1}$
Melting point	150° (α-D)
Density	1.5620 g cm $^{-3}$
pH	5.9
Water solubility (100ml) @25°C @50°C @90°C	 91 244 556
Ethyl solubility	Insoluble

Table 3.2: Glucose physical properties, adapted from [61]

zymatic hydrolysis can cause a decrease of molecular weight and, indirectly proportioned to the viscosity value that increases.

3.2.3 Non enzymatic glucose sensors

In order to perform a field analysis as complete as possible, it is important to report the existence of non enzymatic glucose sensors too. The absence of an enzyme solve numerous issues [29]:

- Due to high temperatures and extreme pH conditions, GOx suffers manufacturing processes, that can strongly modified chemical properties.
- The absence of enzymes simplifies the fabrication, which for BFC requires a tricky immobilization procedure.
- They are not strictly related to the environment pressure conditions.

Of course, without employing organic enzymes that are naturally linked with glucose reaction, it is necessary to improve glucose sensitivity of elements such as noble metals: Platinum-based electrodes exhibit a current density of $0.14\mu Acm^{-2}$. The doping of Platinum with some heavier metals (Bi, Pb, Tl) has been proved to increase catalytic activity, even though in basic or acid solutions only. However, heavy metals are toxic, thus they have to be excluded from all those applications, as BD, that take advantage of a permeable membrane, to prevent a compromising of organic tissues. Moreover, it has already been considered that platinum can be poisoned by aminoacids, creatinine, UA in blood.
Recently, it has been suggested the use of nanoporous platinum film to increase the platinum electrodes performances: from a macroscopical point of view nothing changes during a rapid reaction, the faradaic current of the FC seems

to remain proportional to the original area without seeming to notice the presence of the nanoporous layer. When the dynamic of the reaction is kept under control, instead, the current is proportional to the nanoscopic area, and the glucose selectivity increases drastically.
Weighting pros and cons, due to the numerous incompatibilities with the body environment and the low glucose selectivity, unless the surface is modified at a nanoscopic level, non-enzymatic glucose sensors can not be considered a valid alternative for our purpose.

3.3 Physical model

The main aim of a correct physical model is to build an instrument that allows to obtain predictions on the voltage and power at the output basing on the physical behavior. An electrochemical reaction is guided by the enthalpy variation ΔH, that can be obtained from the Gibbs free energy by:

$$\Delta H = \Delta G - T\Delta S \tag{3.4}$$

with ΔS variation of entropy, T is the temperature and ΔG the Gibbs free energy mentioned above. Only this last term is transformed in available power during the reaction, the other one is the amount of heat dissipated. As for the fuel cell, BFC chemical reaction release electrons that pass from one electrode to the other, creating electrical work (w) and a voltage drop between the electrodes (ΔE). It is possible to relate the two quantities by:

$$w = -Q\Delta E = \Delta G \tag{3.5}$$

Through the ratio between the Gibbs energy and the enthalpy, it is found the efficiency η of the cell: $\eta = \frac{\Delta G}{\Delta H}$. Notice that, computing the efficiency by the previous formula, losses are neglecting indeed a lower real value is theorized. All the terms that contribute to the efficiency diminishment will be analyzed below.
The cell voltage V_c is the result of a combination of the E_{cell}, which is the theoretical voltage if the reaction were perfectly reversible, and terms that represents losses. Supposing steady-state conditions and uniform distribution of reactants, basing on [14] it is possible to define the cell potential as:

$$V_c = E_{cell} - j\sum_i(\rho_i l_i) - \eta_{act} - \eta_{conc} \tag{3.6}$$

where the summation stands for ohmic dispersion, computed through the resistivity ρ and the thickness of the resistive element l; η_{act} is the activation

overpotential and the η_{conc} is the concentration overpotential. In electrochemistry, the overpotential (OP) is defined as the difference between the measured potential and the reversible one. The activation OP is the amount of energy necessary to start the reaction, and it depends on reactants and electrode compounds, on the presence of a mediator, on the density of current. η_{act} can be derived inverting the Butler-Volmer formula, which defines the electric current in a BFC:

$$I = i_0 \left[e^{\left(\frac{\alpha F \eta_{act}}{RT}\right)} - e^{\left(\frac{-(1-\alpha)F\eta_{act}}{RT}\right)} \right] \tag{3.7}$$

where α is the charge transfer coefficient that gives information on the velocity of the electron transfer from an electrolyte to the correspondent electrode. i_0, is the exchange current density. The concentration OP is, instead, a potential difference that results from resistance to mass transport:

$$\eta_{conc} = \frac{RTln\left(\frac{I_L - I}{I_L}\right)}{nF} \tag{3.8}$$

I_L is the so-called limiting current density. Finally, the ohmic OP can be described as all the resistive terms, as interconnections, electrodes, electronic resistance of the enzyme, that in specific condition satisfy Ohm's law. In [13] is pointed out how the Ohm's law could be useful to determine the limiting current density: at that limit, in fact, the inverse of electric resistance tends to zero, and thus it may be possible to derive the limiting current from experimental I-V curve calculating the stationary points.
It is possible to compute the reversible potential by the Nernst equation:

$$E = E^0 - \frac{RT}{nF} lnQ \tag{3.9}$$

where Q is the activity quotient, n the number of involved electrons, E^0 is the standard reduction potential, F the Faraday constant. The output power can be expressed as:

$$P_c = V_c \int Idt \tag{3.10}$$

V_c can be externally controlled, by cyclic voltammetry, so that the voltage at the initial instant does not generate a faradaic current , remaining close to the open circuit voltage. In figure 3.6 it is possible to observe the BFC's behavior of output voltage and output power with respect to the current density: the left side of the graph is dominated by losses, mainly due to the energy barrier between the enzyme and the electrode, previously indicated with η_{act}. Notice that the maximum voltage drop is obtained when the current density tends to zero. The activation losses depend on temperature, electrode surface, pH and mediators. When the current starts to increase, the same

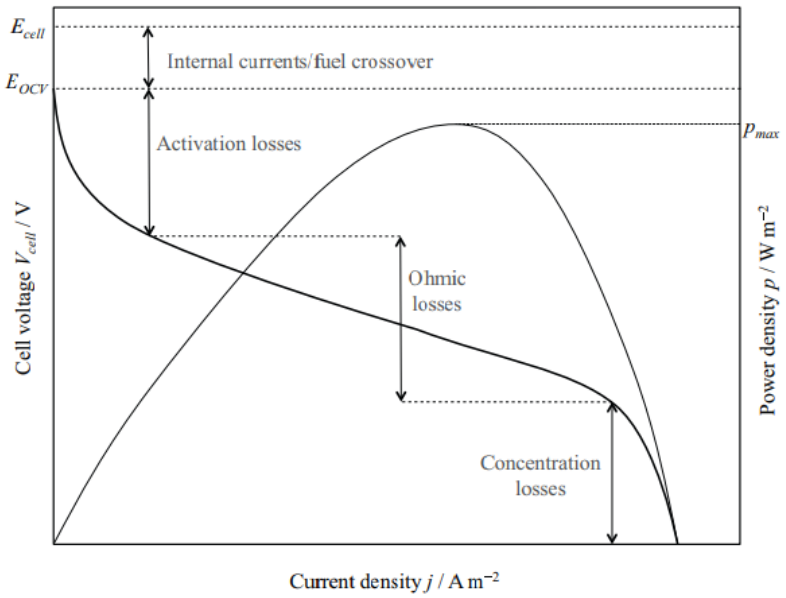


FIGURE 3.6: Behavior of a fuel cell with current density [15]

power, entering in the ohmic region, where current and voltage are theoretically related by the ohmic resistance only. The main elements that contribute to increasing the electrical resistance are the wire resistivity of the path that the electrons must traverse to reach the other electrode, the membrane, if present, all contacts between areas of different materials, as the electrode-mediator or the electrode-enzymes interface.
The reduction of the ohmic resistance is a trade-off between design variations, as the reduction of the external electrons path or the material of the electrode, and the will to keep performance unchanged.
Last of all, it is possible to observe a diminishment of output power when the concentration losses start to dominate: the fuel refilling is not sufficient to keep the concentration of the reactants close to the electrode constant. When the voltage difference between the electrodes goes to zero, recalling equation 3.2 is evident that no electrical work is done and a short circuit condition is reached. Considering the voltage curve over the three region, it may be noticed that the decrease is not constant: in regions where activation and concentration losses prevail, the function diminishes rapidly. As figure 3.6 demonstrates, the maximum power is limited and the main reason has to be research into the redox potential difference of the active centre at the anode and the cathode.

3.4 Equivalent circuit

As it has been analyzed in section 1.1.1, the BFC, be that exploiting as harvester or sensor, has to be inserted in a circuital environment to be polarized and controlled. In order to correctly perform electrical simulations of the entire device, an equivalent circuital model that mimics the behavior of the cell in terms of voltage and current is needed. Parameters have to take into account not only the electrochemical field, but also physical aspects as the heat dissipation or the noise of the vibrations introduced by the day-life activities of the body. An equivalent circuit allows a correct understanding of the cell and consequent prevention of issues.
To perform a complete analysis both operating conditions, steady-state and dynamic, have to be considered; expected results are an evaluation of the open circuit voltage and modeling of losses through resistances and capacitance. Some preliminary assumption are required [69]:

- Uniform distribution of reactants
- Homogeneous fuel flux
- Constant temperature of the environment

One of the most diffused equivalent circuit, described by the Larminie model, is reported in figure 3.7. it describes the electrical behavior of a membrane-based FC, In order to make a comparison with the elements of the physical model

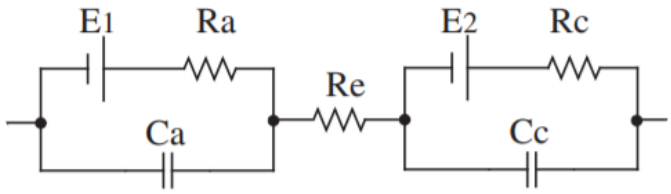


Figure 3.7: Larminie equivalent circuit of BFC [16]

that has just been made, the role of each component is briefly resumed: the resistances R_a and R_c represent respectively the activation and concentration losses, the capacitors C_a and C_c describe the double layer capacity, a direct effect of the double-layer charging effect. A potential drop is generated due to the charges gathering at the interface between electrode and electrolyte. The two voltage generators, E_1 and E_2 model the potential gradient between the electrodes.

However, this model is not the most accurate: in [19] is proposed an equivalent circuit whitin Nerst factor, activation and concentration OP are represented by nonlinear current control voltage sources (figure 3.8), trying to fit the complex dynamic behavior of the cell. On the other side it may result too complex for basic simulations. In [16], in fact, it is suggested a model that does not involve the concentration resistance and capacitance, with only a single generator that plays the role of Nernst potential. A similar solution was presented by Dicks-Larminie et al.
A more precised circuit, able to explain the current ripples of a cell, has been proposed in [27]. A frequency response analyzer has been used in order to determine an impedance model. Although it has been shown that current ripples reduce the power available at the output, this reduction only corresponds at 0.5-1%.

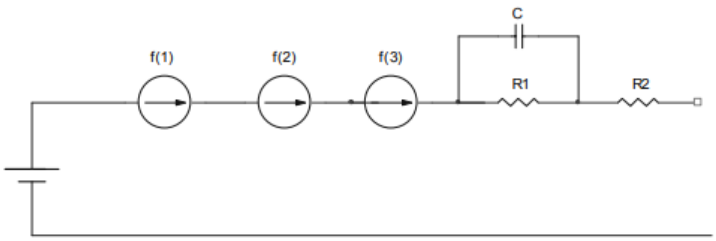


FIGURE 3.8: Choi's equivalent circuit of a BFC [19]

A possible alternative is the Randle's model, reported in figure 3.9: it combines in the same resistance and capacitance the effects of both charge double layer and activation energy. Moreover, a further element is added: the component w is called Warburg element, it is frequency dependent and it is used to take into account losses related to the diffusion of cations and anions through the electrolyte, and the fuel movements to the environment. Thus, it represents an improvement to describe the dynamic behavior of the cell [17].

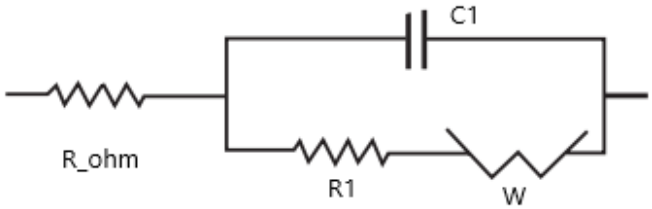


FIGURE 3.9: Randle's equivalent circuit of a BFC [18]

In figure 3.10 the Nyquist plot of a BFC modeled with the Randle's equivalent circuit, also membrane losses are considered by the resistance in the middle. For high frequencies the complex impedance tends to become completely real at value R_ω. The first part of the graph maintains the shape of two semicircles, typical of a resistance and a capacitance connected in parallel, before the Warburg element prevails. It is fundamental to notice that the

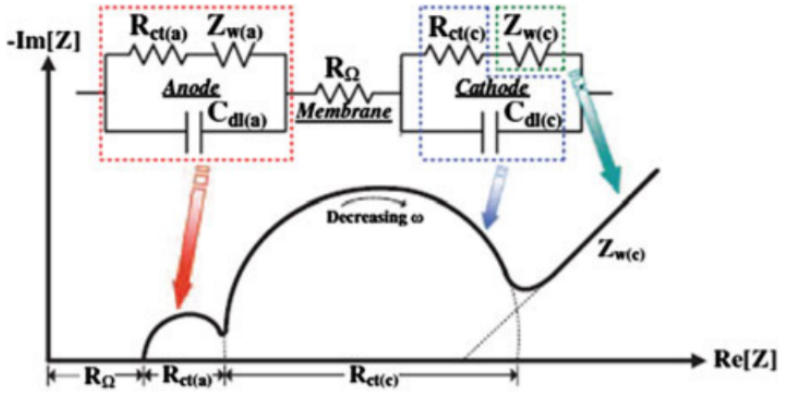


Figure 3.10: Nyquist plot of a double-electrode equivalent circuit [26]

Warburg-Randles model does not fit perfectly the whole general transient analysis; a single order approximation of the double layer capacitance is not precise and the dynamic of fuel refill is not described [10].

3.5 Biocompatible packaging

The main goal of an ID is certainly not only to obtain a fast and precise response but also to achieve a worktime as long as possible. Indeed, it is not always feasible to perform the positioning process into patients through non-invasive techniques, even though the dimensions of devices have been remarkably scaled during past decades. As a consequence of a massive surgical operation, a great amount of stress is produced, increasing the risk of ruinous results.
After the implantation, the human immune system reacts to the unknown presence releasing antibiotic substances. Due to this response, if the packaging materials are not compatible with the human environment, the probability that the ID is rejected is extremely high, causing the development of infections, and stimulating the fibrocellular shields to stave off the extraneous element. Thus, it is evident that all the compounds that enter in contact with organic tissues have to be well matched in terms of compatibility with surrounding cells, guaranteeing durability. A further grade of complexity is that a material, that does not provide biocompatibility issues if used in a specific application, can be adverse if the implant changes [2].
Moreover, a meticulous sterilization procedure has to be performed, to remove microorganisms potentially dangerous. Among different types of usable materials, that do not elicit significant local rejection phenomena, it is useful to recall the titanium, noble metals, silicon, alumina, quartz and polymers specifically created. The heat dissipation has to be controlled as well, the electronic circuits temperature can become high especially when a dense component distribution is required by strict specifications on the total occupation area. A local increase of temperature causes tissues and organs to damage and alters the basic life function. All the ID must satisfy the ISO 10993 standard, which clarifies tests that have to be performed to exclude possible toxicity of the device.
A wrong design of the boundaries materials is one of the most significant failure points: even considering theoretically hermetic material a partial degree of permeability to gases has to be considered [24]. In the case of water or ion migration, moisture starts to permeate to the substrates, causing an impairment of the metallic structure and, as a consequence, open circuits or electrical leakages. The choice of materials depends not only on the physical characteristic of the environment, but also upon the encapsulated technology. For a CMOS building process, it should be recommendable to choose a packaging technique that maintains low temperatures, such as a polymeric encapsulation. Nevertheless, it has to be taken into account that mostly diffused polymers do not guarantee hermeticity, as demonstrated in [25] even if some promising technology based on liquid crystals are under analysis [23], this lack significantly reduces the life expectation of the device.
Moreover, moisture alters not only the correct behaviour of sensors and stimulators but also the correct data transmission outside the body: humidity

modifies the inductance of the transmission module, lowering the quality factor of the antenna. A good compromise between biocompatibility requirements, cited above, and insulation from liquid and gases are metals, ceramic and glasses packaging.
A further selection can be made considering the type of connection required: input and output data can be transmitted to the ID through a wireless communication protocol, requiring an antenna. In case of metal packaging, to prevent power losses the RX-TX (receiving-transmitting) coil must be placed outside the hermetic device and connected utilizing wires passing in feedthroughs pins. The risk is that the electromagnetic field generated by the coil is absorbed by the metal cover and, as a consequence, Eddy currents increase the local temperature of the bulk, damaging neighbor tissues.
With this issue in mind, biograde glasses are preferable because they provide radio-frequency transparency allowing the presence of the coil inside the device without energy dissipation. Handling external contamination is not sufficient to prevent possible fails of the implant, many ID in fact are based on chemical reactions that produces gases and vapor as secondary effects. The outgassing can condensate on the internal surface of the device causing a diminishment of performances and heavily influencing the long-term behaviour. Avoiding the presence of moisture inner the device started to be complex in parallel with the extreme miniaturization of the device, since vapor and liquid easily cross the thinner package.
A diffused solution is based on polycarbonate or epoxy-resin, which are perfectly compatible with sensing processes as they allow enzymes to penetrate inside the device.

3.6 Losses minimizing

As stated above, one of the main problems of the BFC is the low output voltage: therefore, it becomes fundamental with a technology that guarantees only a small output power to try to minimize losses. Within paragraph 3.3 activation and concentration OP and Ohmic resistance have been individuated as the main causes of potential losses. Moreover, it is necessary to add to the list coulombic losses too: coulombic efficiency is defined as the percentage of charges that are correctly collected beyond the electrode with respect to the total amount of coulombs released by the donor [6].
Considering an efficiency always lower than zero, there is a part of the reaction that not produces active current. This is a problem that could affect both, membrane-less and membrane-based FC. When a membrane is present, if a large quantity of oxygen enters in contact with the anode generate an aerobic conversion of the substrate and the efficiency decreases.
to reduce the ohmic losses the first solution is to act on the conductivity of the electrode, improving transport properties. In this case metals, whose

resistivity is two order of magnitude lower than carbon-based materials, have to be preferred. An other possibilities is to modify the electrolyte but for BDs glucose BFC operating in blood, this is certainly not an option, because altering the blood properties with fluidifying substances would invalid the sensing measurements. The absence of a membrane lowers the losses of (9-45)$m\Omega cm^2$, in neutral pH conditions.
The pH is a further reason to not adopt a membrane, because the membrane tends to create a gradient of pH from one side to the other creating a potential drop. A spontaneous solution during an engineering design process is to compensate a low open circuit voltage of a single cell connecting two or more of them in series or in parallel [7]. However Katz et. al [8] demonstrated that this type of solution requires caution: they proved with an in vivo implanting that when two FC are connected in series into a tissue characterized by a low internal resistance, a coupling between anode and cathode creates a low impedance path that minimize the benefits of a double implanting, with a huge increase of area as only result.
To conclude, it has to be taken into account the strong dependence of current losses with respect to the active area of the electrode. the enzyme fails to exploit the entire area of the electrode where it may react, therefore the concept of effective area is defined as the only portion of the available electrode surface in which the reaction takes place, a larger area imply a higher current.
In [28] CAD simulations of a glucose based BFC have been performed with different electrodes shape, in order to find the perfect geometry that maximizes the exposed surface. It is notice that a uniform glucose diffusion has to be enhanced, since it naturally tends to concentrate around the corners; the concentration gradient create an inhomogeneity of the potential. Thus it is proposed a round-corners cylindrical geometry to overcome the difference in diffusivity and, as a consequence, a concentration gradient that produces concurrent voltage drops.

3.7 Conclusions

Within Chapter 3, enzymatic BFCs has been treated, describing the biochemical behavior and underlying the advantages that make them preferable with respect to inorganic FCs and mircobial FC, with a particular focus on the self-powering aspect. The choice of glucose as the most effectiveness fuel for BDs has been explained, basing on chemical and physical properties.
The choice of a membrane less BFC has been motivated and compared with membrane based solution. The direct electron transfer, assisted by carbon nanotubes technology, has been identified as the most effective way of interaction between the enzyme and the electrode for out purposes. Main critical points

in terms of biocompatibility and losses have been pointed out, suggesting alternatives and possible solutions.

Circuital Design 4

4.1 Third electrode

Within Chapter 3 the internal structure of a biofuel cell has been analyzed, specifying material and structure choices to maximize the output voltage, allowing easier power management. From a circuital point of view, the worst case of a cell that guarantees in output only a few tens of millivolts has to be considered. Thus, within the following sections existent solutions will be pointed out, in order to retrace the reasoning made to choose the best components that allow handling the low available output power and transmitting data outside of the body.
As specified within the last section of chapter 3, a critical step of the design procedure is to understand how to model the cell and, to be precise, the required number of electrodes. The following descriptions are based on a three electrodes assumption that, as seen, represents the best choice in terms of stability. However, an alternative with only two electrodes, find in the literature, will be discussed below.
There are two possible configurations of a BFC read out circuit: potentiometric, amperometric.

- **Potentiometric configuration**: it measures an electrochemical potential variation and involves two electrodes: one used as reference and one, ion-selective, whose potential changes during the reaction. Above the detection limit, the configuration linearly depends on the analyte concentration logarithm.

- **Amperometric configuration**: three-electrodes configuration that measures a current variation with respect to a constant potential. It is considered most of all in cells that involve a redox reaction. The redox

process that governs the current that comes out from the cell has been described in detail within section 3.3.

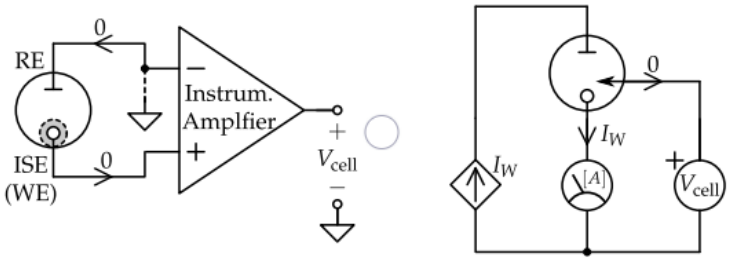


Figure 4.1: Left) potentiometric setup. Right) amperometric setup [4]

4.2 Third electrode

Within chapter two, structures using only two electrodes have been predominantly discussed. In electrochemistry, however, it is very frequent the use of cells based on three electrodes instead of two, because it allows to have greater control over the chemical reaction and guarantees higher accuracy of the measurement results.
A three-electrodes cell configuration is composed by working, counter and the reference electrode. The presence of the reference electrode (RE) does not actively interfere with the chemical reaction, but it keeps the working electrode (WE) potential under control: since a current variation through the CE may cause a potential variation too, RE compensates the excess of current in the BFC introducing a current itself. It is fundamental to build the electrode with a compound whose potential does not change over time, when only a small current is present, to preserve the reference effectiveness. In [73] it has been demonstrated, through impedance tests on a Li-ion cells, that measurement performed with only two electrodes may be not correct. Moreover, the presence of the third electrode allows to obtain information regarding the anode or cathode single behavior; with only two electrodes, instead, is easy to measure potential drop over the entire cell but not to correctly understand how the single electrode change in term of impedance and potential.

In figure 4.3 is reported a schematic of a single-walled CNT biofuel cell, in a three-electrode configuration. The RE is realized with Ag/AgCl: the material requirements are less strict, since the electrode is not supposed to enter in contact with biofluids. Also this paper confirmed that the third electrode is

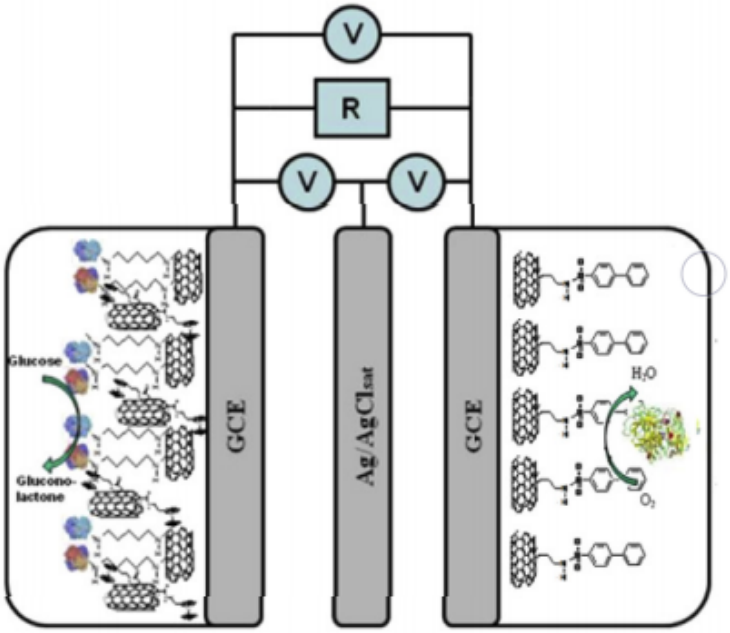


FIGURE 4.2: Three electrode biofuel cell [72]

essential to monitor changes in working potential.
To improve the stability of a three-electrode cell, some precautions can be taken into account: the first point is to decrease the RE impedance, changing material or increasing the active section where the current flows. Therefore, it is possible to add a resistance to the CE, decreasing the bandwidth of the effective gain of the control amplifier. Generally, adding a small capacitance between the wires of CE and RE cuts the high frequency noise.
In [68] has been realized a circuit with only two electrodes to perform instant-sensing, connecting the output of the cell to a capacitor and measuring the voltage drop. The main problem of the absence of the third electrode, as specified above, is the stability of the cell. Measuring the charge-discharge variation over a capacitor, considering that a BFC charge rate is strongly influenced by the electrical noise due to the small size. The relation between glucose concentration and output frequency has been related through the formula:

$$Frequency = 1.5062[glucose](mM) + 18.302 \tag{4.1}$$

Without the stabilization feedback of the RE, it is not possible to establish if small changes in the polarization curve occurs, and thus if the measurement data are obtained with the same cell conditions of the previous results. The output frequency results strongly temperature and pH-dependent, with a

maximum variation of around 10 %. Moreover, it seems anomalous the value of integrated resistances, that do not have standard value, so customization should be required to practically simulate the circuit.
Unless design differences, it constitutes tangible proof that the idea investigated within this thesis is promising and feasible.

4.3 Final circuit

The basic idea of the circuit is to measure a frequency outside of the body to sense the glucose concentration. As a first approximation, the glucose BFC can be modeled by a basic electrochemical equivalent circuit. As analyzed in Chapter 2, the validity of the model is not absolute, because of neglecting of secondary effects and frequency dependence, but it is a good starting point to verify the circuital behavior. the relation that occurs between frequency and concentration can be obtained by interpolation techniques: comparing data from in-vitro experiment, where the concentration of glucose is known, with data received by the sensor allow a correct calibration.
The cell has three electrode pin: the counter electrode is connected to the storage capacitance, that starts to gradually accumulate energy when the BFC begin to work. Charge and discharge cycle are repeated. The capacitor is connected to the input of a charge pump and to the '+' pin of a comparator. The charge pump controls in output both the working electrode and, through a resistances partitioning, the reference electrode, guaranteeing the stability of the cell.
The comparator is a hysteresis comparator, that receives in input the potential drop on the storage element and a voltage reference. Once the drop on the capacitance overcomes the reference value, the output is triggered and the circuit passes into a discharge mode. The output of a comparator can be interpreted as a logic value, and thus treated with a digital circuit. The digital circuit is a basic four-port finite state machine, that bases on the output of the comparator choices the correct reference value, that is transmit at the output, where a Bluetooth low energy transmission system is modeled with a generic load.
Possible alternatives:

- **AD-DC**: the presence of an analog to digital converter may be required in case of in-loco data analysis. Some devices implemented the possibility, whenever the stability of the sensing system is not so high, to handle and store data before transmission, to prevent errors due to analog samples instability. However, since a stable output is typical of BFC, it is possible to avoid it.

- **Oscillator**: the presence of an oscillator (ring, pulse) it may be useful to allow a more complex finite state machine work, to control switches

and latches.

- **Memory elements**: In some cases it could insert a memory block, mostly in multiple-purpose cells, to store and elaborate data without instant transmission.

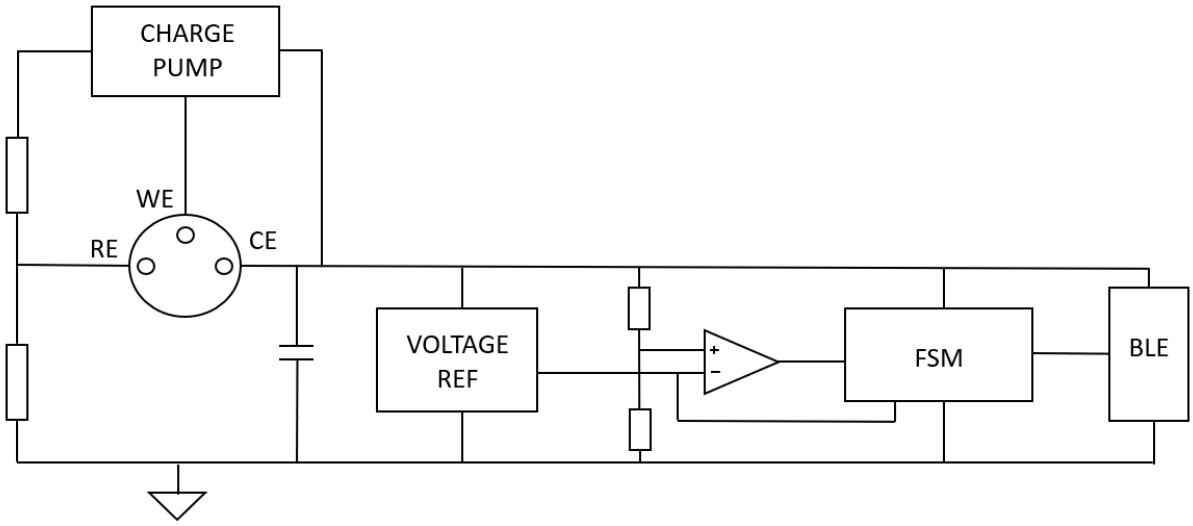


Figure 4.3: Schematic of the BFC readout circuit

4.3.1 Voltage reference

In order to let properly work the comparator, a voltage that plays the role of reference to be compared to the potential stored in the capacitance has to be implemented. When a voltage reference is designed, it is necessary to pay attention to some issues: a fixed voltage reference is commonly obtained by a partitioning of the supply voltage.
The correct behavior of a voltage reference may be corrupted by insufficient headroom, due to the high heat dissipated, or by an incorrect choice of load. Moreover, it has to be taken into account also the reversed current coming from the output. For what concerns the circuit above, the voltage reference is connected to the negative pin of an hysteresis comparator, from which the flowing current can be considered negligible. The circuit power supplying is not constant, because it is generated by the voltage coming out from the BFC and stored in the capacitor, constantly charging and discharging depending on the storage or transmission phase. Thus, it is necessary to project a device that gives at the output a constant voltage even when the input source changes.
For these solutions, a strong dependency on temperature is often reported: however, on the pros side of working in a human-body environment there is

the constancy of temperature, whose variations are not so huge and not so fast to be a reason of worrying.
A typical choice to realize a voltage reference is a bandgap reference. A frequent design problem is that a bandgap reference requires a voltage at the input higher with respect to the one provided at the output [74]. This aspect surely has to be evaluated, considering that during the discharge phase of the capacitance, the available voltage may not be so high. This problem can be solved with a resistive subdivision. [75]

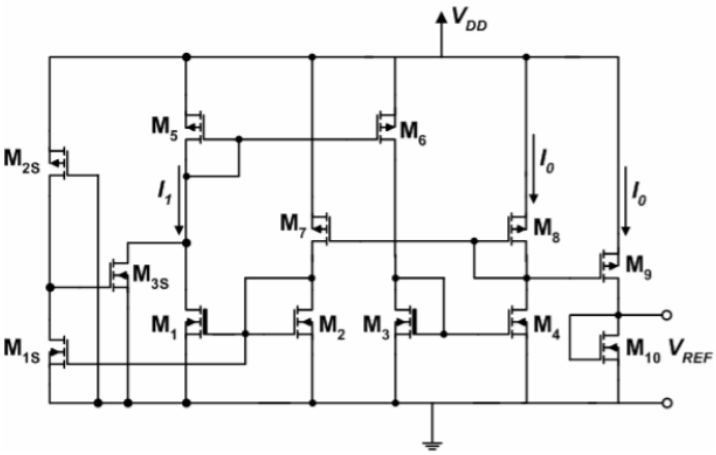


Figure 4.4: Schematic of a bandgap reference in CMOS technology [74]

The bandgap can be realized with in CMOS technology, exploiting the MOS regions of saturation and subthreshold. The occupied area can be reduced down to 0.045mm^2, with a sub-μW power consumption [74].
The drain current of a NMOS is subthreshold region is:

$$I_d = \frac{\mu C_{ox}}{2}\frac{W}{L}(V_{GS} - V_{th})^2(1 + \lambda V_{DS}) \tag{4.2}$$

And for saturation region:

$$I_d = \mu t_T^2 \frac{W}{L} exp\left(\frac{V_{GS} - V_{th}}{mV_T}\right)\left[1 - exp\left(-\frac{V_{DS}}{V_T}\right)\right] \tag{4.3}$$

V_{th} is the threshold voltage, V_T is the thermal voltage. W is the channel width, L is the channel length, these are the key design parameters to can obtain the desired voltage at the output. In fact, the reference voltage is derived as a function of W, L and N, where $N = \sqrt{(W_4/L_4)/(W_2/L_2)}$:

$$V_{ref} = V_{th10} + \frac{mV_T}{N-1}\sqrt{\frac{W_4/L_4}{W_{10}/L_{10}}} ln\left(\frac{W_3/L_3}{W_1/L_1}\right) \tag{4.4}$$

Notice that the circuit reported in figure 4.4 does not comport the use of resistances, and this can be considered an advantage: the final circuit will work with a current of tens of nano-Ampére, such small current wold require, if used, very large resistances. This increases the occupation area and the power dissipation.
The other alternative, not based on bandgap reference, has been proposed in [76], to further downscale the value of the dissipated power from nW to pW order. Ultra low power technology is commonly characterized by a low output voltage too, which makes their use unfeasible with some analog components, as comparators, whose dynamic can be restricted. The issue was solved, reaching an output of 1.2V in 0.18μm technology. At the worse side, the 55μA current makes its integration challenging in a BD system.

4.3.2 Output transmitter

Bluetooth low energy systems (BLE) allow interfacing the device implanted or injected into the body with a simple smartphone at the outside, without the need of a specific external transmission system, and contributing to develop a possible solution for the internet of things (IoT), where a patient can directly tracing the glucose level itself. If bluetooth standard protocol is used, the data transfer frequency guarantees a lower tissue absorption, a necessary requirement to satisfy SAR limitation described in section 2.4. The variations of glucose are not so rapid, indeed, a low sampling time is not required and a low duty cycle may be handled. In order to satisfy Nyquist criterium, it seems reasonable to perform a data sampling every 10 minutes [77].
BLE are, moreover, characterized by extremely low power consumption. A suitable transfer frequency is 13.56MHz, because it represents a standard value for data transmission, thus the related technology has been well developed and consolidated. At 13.56MHz the attenuation constant is lower (1/10 with respect to 2.4GHz), reducing the power losses during propagation through the human body. BLE use Gaussian frequency shift keying (GFSK) modulation, which combines frequency modulation and pulse shaping, obtained by a Gaussian filter.
However, In [78] a low power data transmitted is proposed: a ree-running oscillator enables to communicate with the outside of the body basing on OOK, a simple modulation protocol that turns on the oscillator only to transmit a logic one; the absence of signal is instead interpreted as a zero. This solution, reported in figure 4.5 belongs to those ID that requires the installation of the transmission module, or at least of the coil, outside of the packaging.

The efficiency percentage of the antenna is computed by the formula:

$$\eta_{ant} = \frac{R_{rad}}{R_{loss} + R_{rad}} \tag{4.5}$$

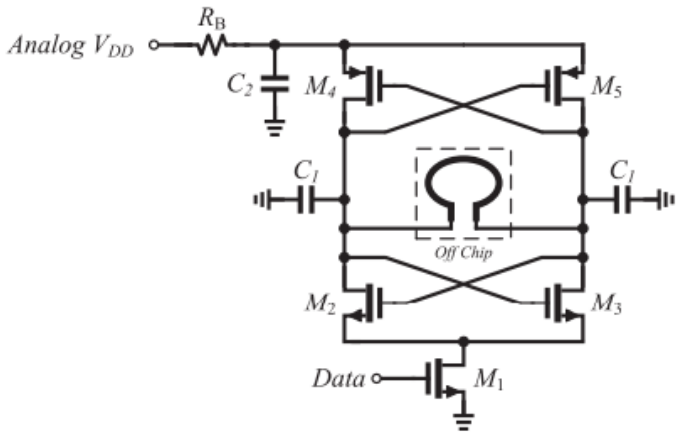


Figure 4.5: Single coil data transmitter circuit [78]

that contains the ratio between the radiating power and the total power, losses included. The radiating power, considering a single turn coil:

$$R_{rad} = 20\pi^2(\frac{2\pi r}{\lambda})^4 \tag{4.6}$$

The power radiation increases if the radius of the coil r becomes larger or if the wavelength λ diminishes.
To guarantee the absence of interferences among the sensing operation, the read out circuit activity and the transmitting phase, it is suggested to time-interleaved data transfer and the other functions.

Conclusions 5

The aim of this work was to investigate the feasibility of a CMOS system that performs sensing and harvesting with the same technology. More generally, a possible application of this type of sensor has been proposed: integrated to Body Dust CMOS technology to exploit drinkable electronics. In order to fully understand the device characteristics, available harvesting techniques, commonly used in implantable device technology, have been taken into account. Fuel cells resulted in the most promising technology to adapt a power scavenger to perform sensing. In particular, biofuel cells, fuel cells based on enzymes, have been selected, due to their ease of finding fuel into the human body.
Among possible enzymes, the glucose-based technology came out as the most advanced and widespread in literature, with a lot of available alternatives in terms of geometries and materials. The physical and chemical properties of glucose biofuel cells have been described, to provide a theoretical basis that allows to enhance the technology. Self-powered glucose sensors present in literature, deriving common characteristics and highlighting critical issues. Finally, a block schematic of the readout circuit has been proposed. Each element that composes the device has been investigated: the voltage reference, the electrodes configuration, the comparator, the transmitter, the charge pump, pointing out possible alternatives to reduce power consumption and occupation area, critical issues for a biofuel cell. At the moment, the system has been realized at a theoretical level. Possible further improvements consist in performing simulations of the circuital part passing from an ideal to real components: Thus, aspect as environmental noise or heat dissipation, whose possible consequences have been up to now only outlined, have to be considered. Moreover, characterization of the BFC has to be performed, to have precise information of the output parameters. Looking forward, a physical realization of the device is desirable, to understand downscaling limits and to collect data with in-vitro simulation.

Bibliography 5

[1] Carrara, Sandro, and Pantelis Georgiou. "Body Dust: Miniaturized Highly-integrated Low Power Sensing for Remotely Powered Drinkable CMOS Bioelectronics." arXiv preprint arXiv:1805.05840 (2018).

[2] Onuki, Yoshinori, et al. "A review of the biocompatibility of implantable devices: current challenges to overcome foreign body response." (2008): 1003-1015.

[3] Shendurse, A. M., and C. D. Khedkar. "Glucose: properties and analysis." Encyclopedia of Food and Health 3 (2016): 239-247.

[4] Dei, Michele, et al. "CMOS interfaces for Internet-of-Wearables electrochemical sensors: Trends and challenges." Electronics 8.2 (2019): 150.

[5] Carrara, Sandro. "Integrated Bio/Nano/CMOS interfaces for electrochemical molecular sensing." IEEJ Transactions on Electrical and Electronic Engineering 13.11 (2018): 1534-1539.

[6] Clauwaert, Peter, et al. "Minimizing losses in bio-electrochemical systems: the road to applications." Applied microbiology and biotechnology 79.6 (2008): 901-913.

[7] Aelterman, Peter, et al. "Continuous electricity generation at high voltages and currents using stacked microbial fuel cells." Environmental science technology 40.10 (2006): 3388-3394.

[8] Katz, Evgeny. "Implantable biofuel cells operating in vivo: Providing sustainable power for bioelectronic devices: From biofuel cells to cyborgs." 2015 6th International Workshop on Advances in Sensors and Interfaces (IWASI). IEEE, 2015.

[9] Stolarczyk, Krzysztof, et al. "Biobatteries and biofuel cells with biphenylated carbon nanotubes." Journal of Power Sources 249 (2014): 263-269.

[10] Wey, Todd A., et al. "Electrical circuit model and dynamic analysis of implantable enzymatic biofuel cells operating in vivo." Proceedings of the IEEE 102.11 (2014): 1795-1810.

[11] Kilinc, Enver G., Franco Maloberti, and Catherine Dehollain. "Short-range remote powering for long-term implanted sensor systems in freely moving small animals." SENSORS, 2013 IEEE. IEEE, 2013.

[12] Yang, X., Ge Tian, N. Jiang and Bao-Lian Su. "Immobilization technology: a sustainable solution for biofuel cell design." Energy and Environmental Science 5 (2012): 5540-5563.

[13] Káňavová, Natália, Lubomír Machuča, and David Tvrzník. "Determination of limiting current density for different electrodialysis modules." Chemical Papers 68.3 (2014): 324-329.

[14] Annepu, Jyothsna Jagannath. "Mathematical Simulation of Direct Glucose Fuel Cell." (2015).

[15] Osman, Mohamad Hussein. Mathematical modelling and simulation of biofuel cells. Diss. University of Southampton, 2013.

[16] Chang, Wen-Yeau. "Estimating equivalent circuit parameters of proton exchange membrane fuel cell using the current change method." International Journal of Electrical Power Energy Systems 53 (2013): 584-591.

[17] Page, Shannon C., et al. "Test method and equivalent circuit modeling of a PEM fuel cell in a passive state." IEEE Transactions on Energy Conversion 22.3 (2007): 764-773.

[18] Shervedani, Reza Karimi, Abdolhamid Hatefi Mehrjardi, and Najmehsadat Zamiri. "A novel method for glucose determination based on electrochemical impedance spectroscopy using glucose oxidase self-assembled biosensor." Bioelectrochemistry 69.2 (2006): 201-208.

[19] Famouri, Parviz, and Randall S. Gemmen. "Electrochemical circuit model of a PEM fuel cell." 2003 IEEE Power Engineering Society General Meeting (IEEE Cat. No. 03CH37491). Vol. 3. IEEE, 2003.

[20] Luz, Roberto AS, et al. "Enzyme biofuel cells: thermodynamics, kinetics and challenges in applicability." ChemElectroChem 1.11 (2014): 1751-1777.

[21] De Souza, Flavio Leandro, and Edson Roberto Leite. Nanotechnology Applied for Energy Production. Springer-Verlag Berlin Heidelberg: Switzerland, 2013.

[22] Teymourian, Hazhir, Abbas Barfidokht, and Joseph Wang. "Electrochemical glucose sensors in diabetes management: an updated review (2010–2020)." Chemical Society Reviews (2020).

[23] FARRELL, Brian, et al. "The liquid crystal polymer packaging solution." SPIE proceedings series. 2003.

[24] Jiang, Guangqiang, and David D. Zhou. "Technology advances and challenges in hermetic packaging for implantable medical devices." Implantable Neural Prostheses 2. Springer, New York, NY, 2009. 27-61.

[25] Nichols M F (1994) The challenges for hermetic encapsulation of implanted devices- A review, Biomed. Eng. 22(1): 39–67

[26] Nabag, M., et al. "Review of Dynamic Electric Circuit Models for PEM Fuel Cells." ICREGA'14-Renewable Energy: Generation and Applications. Springer, Cham, 2014. 59-71.

[27] Choi, Woojin, Prasad N. Enjeti, and Jo W. Howze. "Development of an equivalent circuit model of a fuel cell to evaluate the effects of inverter ripple current." Nineteenth Annual IEEE Applied Power Electronics Conference and Exposition, 2004. APEC'04.. Vol. 1. IEEE, 2004.

[28] Parikh, Yamini S., et al. "Simulation of C-MEMS based enzymatic biofuel cell." Proceedings of the COMSOL Conference Boston. 2008.

[29] Park, Sejin, Hankil Boo, and Taek Dong Chung. "Electrochemical non-enzymatic glucose sensors." Analytica chimica acta 556.1 (2006): 46-57.

[30] Guiseppi-Elie, Anthony, Chenghong Lei, and Ray H. Baughman. "Direct electron transfer of glucose oxidase on carbon nanotubes." Nanotechnology 13.5 (2002): 559.

[31] Joung, Yeun-Ho. "Development of implantable medical devices: from an engineering perspective." International neurourology journal 17.3 (2013): 98.

[32] Jin, Jill. "FDA authorization of medical devices." JAMA 311.4 (2014): 435-435.

[33] Fadhel, Y. Ben, et al. "Used methods to wirelessly powered implantable medical devices." 2016 17th International Conference on Sciences and Techniques of Automatic Control and Computer Engineering (STA). IEEE, 2016.

[34] Sathyan, Shreya, and Sini Raj Pulari. "A deeper insight on developments and real-time applications of smart dust particle sensor technology." Computational Vision and Bio Inspired Computing. Springer, Cham, 2018. 193-204.

[35] Sanders, Prashanthan, et al. "Performance of a new atrial fibrillation detection algorithm in a miniaturized insertable cardiac monitor: Results from the Reveal LINQ Usability Study." Heart Rhythm 13.7 (2016): 1425-1430.

[36] Snoeijs, Jan, Pantelis Georgiou, and Sandro Carrara. "CMOS body dust—Towards drinkable diagnostics." 2017 IEEE Biomedical Circuits and Systems Conference (BioCAS). IEEE, 2017.

[37] Carrara, Sandro. "Body Dust: Well Beyond Wearable and Implantable Sensors." IEEE Sensors Journal (2020).

[38] Carrara, Sandro, and Pantelis Georgiou. "Body Dust: Miniaturized Highly-integrated Low Power Sensing for Remotely Powered Drinkable CMOS Bioelectronics." arXiv preprint arXiv:1805.05840 (2018).

[39] S. S. Ghoreishizadeh, C. Baj-Rossi, A. Cavallini, S. Carrara, and G. De Micheli, "An integrated control and readout circuit for implantable multi-target electrochemical biosensing," IEEE Transactions on Biomedical Circuits and Systems, vol. 8, no. 6, pp. 891-898, 2014.

[40] Olivo, Jacopo, Sandro Carrara, and Giovanni De Micheli. "Energy harvesting and remote powering for implantable biosensors." IEEE Sensors Journal 11.7 (2010): 1573-1586.

[41] Wang, Yifei, et al. "Powering future body sensor network systems: A review of power sources." Biosensors and Bioelectronics (2020): 112410.

[42] Ko, JeongGil, et al. "Wireless sensor networks for healthcare." Proceedings of the IEEE 98.11 (2010): 1947-1960.

[43] Shin, S. M., et al. "Recovery of electrodic powder from spent lithium ion batteries (LIBs)." Archives of Metallurgy and Materials 60.2B (2015): 1145-1149.

[44] Khan, Jamil Yusuf, et al. "Wireless body area network (WBAN) design techniques and performance evaluation." Journal of medical systems 36.3 (2012): 1441-1457.

[45] Parsonnet, Victor, Alan D. Berstein, and Gershon Y. Perry. "The nuclear pacemaker: Is renewed interest warranted?." The American journal of cardiology 66.10 (1990): 837-842.

[46] Murakawa, Koji, et al. "A wireless near-infrared energy system for medical implants." IEEE Engineering in Medicine and Biology Magazine 18.6 (1999): 70-72.

[47] Goto, Kazuya, et al. "An implantable power supply with an optically rechargeable lithium battery." IEEE Transactions on Biomedical Engineering 48.7 (2001): 830-833.

[48] Vullers, R. J. M., et al. "Micropower energy harvesting." Solid-State Electronics 53.7 (2009): 684-693.

[49] Gilbert, James M., and Farooq Balouchi. "Comparison of energy harvesting systems for wireless sensor networks." International Journal of automation and computing 5.4 (2008): 334-347.

[50] Wang, Zhong Lin, and Jinhui Song. "Piezoelectric nanogenerators based on zinc oxide nanowire arrays." Science 312.5771 (2006): 242-246.

[51] Hu, Youfan, et al. "Self-powered system with wireless data transmission." Nano letters 11.6 (2011): 2572-2577.

[52] Li, Zhou, et al. "Muscle-driven in vivo nanogenerator." Advanced materials 22.23 (2010): 2534-2537.

[53] Wang, Zhong Lin. "Triboelectric nanogenerators as new energy technology and self-powered sensors–Principles, problems and perspectives." Faraday discussions 176 (2015): 447-458.

[54] Stoecklin, Sebastian, et al. "Efficient wireless powering of biomedical sensor systems for multichannel brain implants." IEEE Transactions on Instrumentation and Measurement 65.4 (2015): 754-764.

[55] Zhang, Fei, et al. "In vitro and in vivo studies on wireless powering of medical sensors and implantable devices." 2009 IEEE/NIH Life Science Systems and Applications Workshop. IEEE, 2009.

[56] Bullen, Richard Andrew, et al. "Biofuel cells and their development." Biosensors and Bioelectronics 21.11 (2006): 2015-2045.

[57] Larminie, James, Andrew Dicks, and Maurice S. McDonald. Fuel cell systems explained. Vol. 2. Chichester, UK: J. Wiley, 2003.

[58] Choban, Eric R., et al. "Microfluidic fuel cell based on laminar flow." Journal of Power Sources 128.1 (2004): 54-60.

[59] Slaughter, Gymama, and Tanmay Kulkarni. "Enzymatic glucose biofuel cell and its application." Journal of Biochips Tissue Chips 5.1 (2015): 1.

[60] Brunkhorst, Frank M., and Hans G. Wahl. "Blood glucose measurements in the critically ill: more than just a blood draw." Critical Care 10.6 (2006): 178.

[61] Shendurse, A. M., and C. D. Khedkar. "Glucose: properties and analysis." Encyclopedia of Food and Health 3 (2016): 239-247.

[62] Walter, Xavier Alexis, et al. "Scalability of self-stratifying microbial fuel cell: Towards height miniaturisation." Bioelectrochemistry 127 (2019): 68-75.

[63] Slaughter, Gymama, and Tanmay Kulkarni. "A self-powered glucose biosensing system." Biosensors and Bioelectronics 78 (2016): 45-50.

[64] Gonzalez-Solino, Carla, and Mirella Di Lorenzo. "Enzymatic fuel cells: Towards self-powered implantable and wearable diagnostics." Biosensors 8.1 (2018): 11.

[65] Katz, Eugenii, Andreas F. Bückmann, and Itamar Willner. "Self-powered enzyme-based biosensors." Journal of the American Chemical Society 123.43 (2001): 10752-10753.

[66] Tan, Xuecai, et al. "An amperometric cholesterol biosensor based on multiwalled carbon nanotubes and organically modified sol-gel/chitosan hybrid composite film." Analytical Biochemistry 337.1 (2005): 111-120.

[67] Batra, Bhawna, and C. S. Pundir. "An amperometric glutamate biosensor based on immobilization of glutamate oxidase onto carboxylated multiwalled carbon nanotubes/gold nanoparticles/chitosan composite film modified Au electrode." Biosensors and Bioelectronics 47 (2013): 496-501.

[68] Slaughter, Gymama, and Tanmay Kulkarni. "Highly selective and sensitive self-powered glucose sensor based on capacitor circuit." Scientific reports 7.1 (2017): 1-9.

[69] Chavan, Sudarshan L., and Dhananjay B. Talange. "Electrical equivalent circuit modeling and parameter estimation for PEM fuel cell." 2017 Innovations in Power and Advanced Computing Technologies (i-PACT). IEEE, 2017.

[70] Korani, Aazam, and Abdollah Salimi. "Fabrication of High performance bioanode based on fruitful association of dendrimer and carbon nanotube used for design O2/glucose membrane-less biofuel cell with improved bilirubine oxidase biocathode." Biosensors and Bioelectronics 50 (2013): 186-193.

[71] Heller, Adam. "Miniature biofuel cells." Physical Chemistry Chemical Physics 6.2 (2004): 209-216.

[72] Stolarczyk, Krzysztof, et al. "Biobatteries and biofuel cells with biphenylated carbon nanotubes." Journal of Power Sources 249 (2014): 263-269.

[73] Nagasubramanian, Ganesan. "Two-and three-electrode impedance studies on 18650 Li-ion cells." Journal of power sources 87.1-2 (2000): 226-229.

[74] De Vita, Giuseppe, and Giuseppe Iannaccone. "A Sub-1 V, 10 ppm/° C, Nanopower Voltage Reference Generator." 2006 Proceedings of the 32nd European Solid-State Circuits Conference. IEEE, 2006.

[75] Leung, Ka Nang, and Philip KT Mok. "A sub-1-V 15-ppm//spl deg/C CMOS bandgap voltage reference without requiring low threshold voltage device." IEEE Journal of Solid-State Circuits 37.4 (2002): 526-530.

[76] Lee, Inhee, Dennis Sylvester, and David Blaauw. "A subthreshold voltage reference with scalable output voltage for low-power IoT systems." IEEE Journal of Solid-State Circuits 52.5 (2017): 1443-1449.

[77] Ali, Mai, Lutfi Albasha, and Hasan Al-Nashash. "A Bluetooth low energy implantable glucose monitoring system." 2011 8th European Radar Conference. IEEE, 2011.

[78] Ghanad, Mehrdad A., Michael M. Green, and Catherine Dehollain. "A 30μW Remotely Powered Local Temperature Monitoring Implantable System." IEEE transactions on biomedical circuits and systems 11.1 (2016): 54-63.

[79] Li, Zhou, et al. "Muscle-driven in vivo nanogenerator." Advanced materials 22.23 (2010): 2534-2537.

[80] Corr, Sinead C., Cormac CGM Gahan, and Colin Hill. "M-cells: origin, morphology and role in mucosal immunity and microbial pathogenesis." FEMS Immunology Medical Microbiology 52.1 (2008): 2-12.

[81] Barbruni, Gian Luca, et al. "Body Dust: Ultra-Low Power OOK Modulation Circuit for Wireless Data Transmission in Drinkable sub-100 μ m-sized Biochips." arXiv preprint arXiv:1912.02670 (2019).

[82] Sode, Koji, et al. "BioCapacitor: A novel principle for biosensors." Biosensors and Bioelectronics 76 (2016): 20-28.

Colophon

This document was typeset using the pdfLaTeX typesetting system and the memoir class created by Peter Wilson. The body text is set 12pt with Adobe Caslon Pro. Other fonts include Envy Code R and Optima Regular.