1

What is bioelectronics?

Sandro Carrara

Although the term was first proposed in 1968, the birth of *bioelectronics* as we know it today is much more recent. In fact, the first meaning of the word bioelectronics was the intermolecular electron transfer found in biological systems [1], while its modern meaning is quite different, as discussed in this chapter.

Tony Turner, founder and Editor-in-Chief of the Elsevier journal *Biosensors and Bioelectronics*, wrote in 2005: "Bioelectronics is a recently coined term for a field of research that works to establish a synergy between electronics and biology" [2]. Over the years, his journal became the main forum in the field of bioelectronics. The journal originally appeared in 1985 with the simple name of *Biosensors*, and the title was expanded to include the term *Bioelectronics* in 1992 [2]. The expressed scope of the journal [3] explains that a key aspect of bioelectronics is the interface between biological materials and electronics.

To better understand the modern state of the field, we can also consider the meaning of "advanced bioelectronics" as mentioned in April 2013 by the National Institute of Standards and Technology (NIST – an agency of the US Department of Commerce) and represented by the example of electronic DNA sequencing, as supported by single-molecule mass spectrometry to develop innovative electronic devices for healthcare [4]. The authors [4] refer to devices in which an electric field drives individual molecules of single-stranded DNA through a nanometer-scale pore (Figure 1.1). That approach is a step toward applications for rapid sequencing of DNA [5] and DNA transcription complexes [6], and could lead to further developments in protein sequencing [7] too. The application is clearly focused on devices for healthcare and, more generally, includes both diagnostic and therapeutic tools.

We could briefly summarize bioelectronics as "the application of electronics in the field of biology", and, in fact, IUPAC accepts the definition of bioelectronics as "the application of biomolecular principles to microelectronics such as in biosensors and biochips" [8]. However, in the literature we actually have much more than that. It is easy to find extensions of bioelectronics into the area of electronic components and circuits that include proteins or other biological macromolecules. For example, it has been outlined that this field might include biotemplated circuitries [9]. To quote the Elsevier journal *Biosensors and Bioelectronics*, already mentioned above as a leader in the field: "The emerging field of bioelectronics seeks to exploit biology in conjunction with electronics in a wider context encompassing, for example, biological fuel cells, bionics and biomaterials for information processing, information storage, electronic components and actuators" [3].

Another historical pioneer of the field, Wolfgang Göpel, wrote in 1998: "Bioelectronics is aimed at the direct coupling of biomolecular function units of high molecular weight and extremely complicated molecular structure with electronic or optical transducer devices" (Figure 1.2) [10]. Two key points are introduced here: the "direct coupling" and the "high molecular weight". The first indicates an intimate integration between biomolecular principles and microelectronics. The second implies large biomolecules such as proteins or complex biological systems such as cells or bacteria. That means we need to integrate biomolecular functions with extremely complicated biological structures. However, "organic bioelectronics" has been introduced, too, by proposing, for example, organic polymers for drug delivery systems [11]. Now, we cannot say that "a polymer" can be seen as "an extremely complicated molecular structure" and, therefore, we need to

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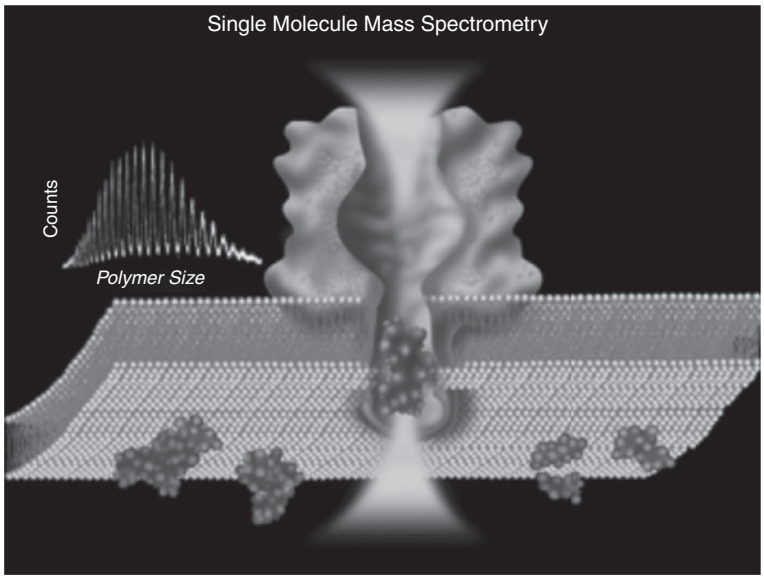

Figure 1.1 Single molecule spectroscopy at nanopores (reprinted from NIST website, courtesy of Jeffrey Aarons [4])

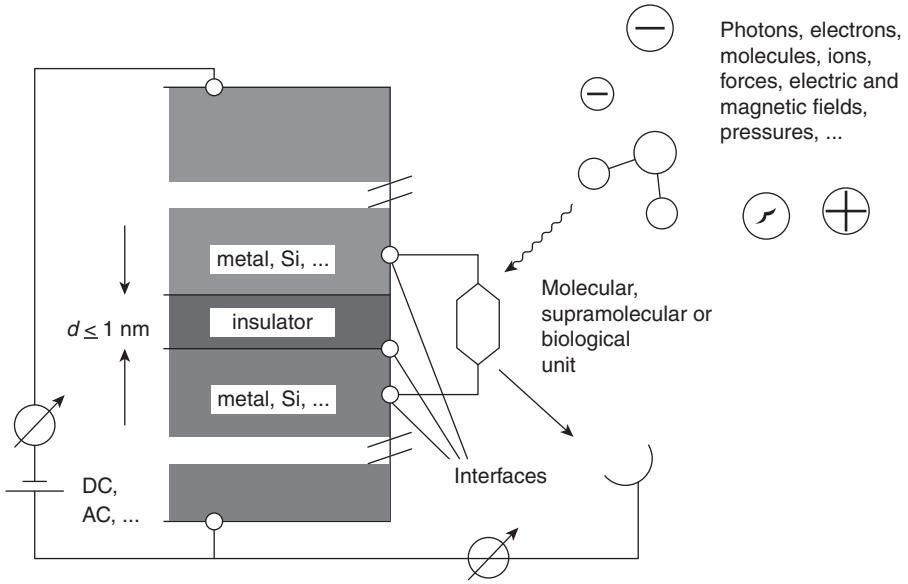

Figure 1.2 Schematic representation of a bioelectronic sensor device (redrawn from [10])

conclude that the field of bioelectronics has further expanded beyond the original definition of its pioneers. In fact, it has also been declared that "the fundamental element of molecular electronics is a molecular device or a supramolecular device, which is an organized molecular system constructed mainly by **organic molecules or biomolecules** that have some specific functions in signal detection, process, storage, and transmission through chemical or physical interactions at molecular or supramolecular levels" [12]. Very recently, this extension of the field toward organic molecules has been certified by a special issue in the journal *Biochimica et Biophysica Acta* dedicated to *organic bioelectronics* [13]. The field was presented there as an interdisciplinary field that "encompasses many different applications, including neural interfaces, tissue engineering, drug delivery, and biosensors" [13].

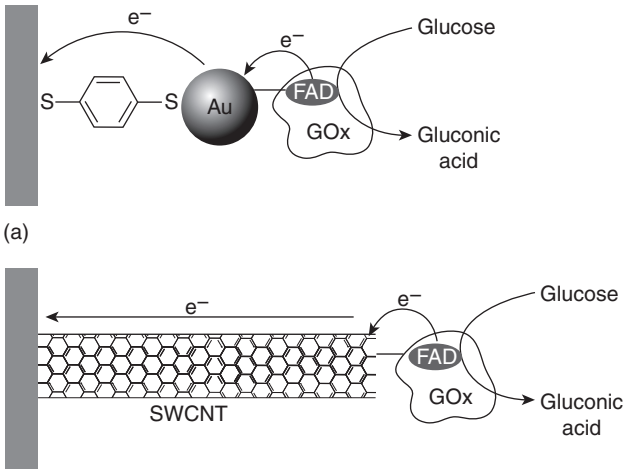

Figure 1.3 Redox enzymes electrically contacted by nanostructures such as gold nanoparticles or carbon nanotubes (redrawn from [9]). SWCNT, single-walled carbon nanotube

Going back to the original definition set in 1998 by W. Göpel, we can then say that the intimate integration with "extremely complicated molecular structure" may also lie in the interface between the realized inorganic device and the more complex biological system once the device has been implanted for use in an application. Göpel also agreed that "with increasing complexity and demands for future information technologies, a trend is to be seen towards the design of *'smart' nanostructures* which will be interfaced to silicon or other substrates. These structures may consist [. . .] of *chemically synthesized* units such as molecules, supramolecules and biologically active (biomimetic) recognition centers" (Figure 1.3) [10]. This prediction made in 1998 has been confirmed by several developments that exploit nanotechnology for sensing [14], and has now reached the stage of a fundamental co-design of the interface between biological macromolecules, organic nanostructures, and CMOS circuitries [15].

Several books have been published over the last 20 years to cover the field of bioelectronics. However, these books usually only partially cover this vast field. For example, we can find books that mainly cover molecular devices [16], devices for sensing and computing [17], neural networks and biosensors [18], artificial retinas [19], interfaces for biosensing [20] [15], smart materials [21], biophysics of electron transfer [22], or low-power design [23]. We might find good introductory books [24] but nothing fully exhaustive. The aim of this book is, then, to address this gap and try to propose a comprehensive overview of the whole field of bioelectronics.

To be sure that we address the whole variety of different aspects of bioelectronics, we can look at the division of the field first made in a session of the main congress *Biosensors*, held in Bangkok in 1996 [10]:

- Biocompatible electronic devices
- *In vivo* sensors; sensors based on biological materials
- Biological materials for electronics and optics
- Materials for electronics synthesized by biological processes, including bacteriorhodopsin
- Concepts and materials inspired by biology and useful for electronics
- Algorithms inspired by biology
- Artificial senses
- Biological–inorganic hybrids
- Imaging and addressing of individual biomolecular function units

The book is organized into the following separate sections in order to address this aim.

- **Bioelectronic components**
- **Biosensors**
- **Fuel cells**
- **Biomimetic systems**
- **Bionics**
- **Brain interfaces**
- **Lab-on-a-chip**

Then the final section is:

- **Future perspectives**

This last section of the book aims to show the trends in bioelectronics emerging at the frontiers of worldwide research in the field of electronics, and to indicate how these might meet our new needs for more advanced healthcare systems.

The book ends with a chapter on *distributed theranostics* as supported by *personal electronics*. In our daily lives,

all of us carry personal electronic devices (such as smartphones, touch-screen tablets, laptops, and satellite navigators). The new frontier of bioelectronics is to integrate, expand, and transform part of these personal devices into new healthcare tools that can provide distributed diagnostics and personalized therapy: *theranostics*.

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Part I

Electronic components

2

Molecular components for electronics

Sandro Carrara

As stated in the previous chapter, Wolfgang Göpel wrote, "Bioelectronics is aimed at the direct coupling of biomolecular function units of high molecular weight and extremely complicated molecular structure with electronic or optical transducer devices" [1]. The statement emphasizes two key points: the "direct coupling" and the "high molecular weight". This leads us now to develop bioelectronic circuitries by moving from building blocks, or molecular components, that involve high-molecular-weight biological molecules (typically proteins) by providing electrical contact at the nanoscale, in order to address direct coupling. The first problem to solve is therefore that of a nanoscale electrical contact.

During the last 15 years, several fabrication methods have been proposed to obtain a nanogap [2], based on the original work of Morpurgo *et al.* [3]. Among the possible solutions, a very effective strategy is to create an extremely tiny disconnection along a conducting wire in order to accommodate a biological molecule in between (Figure 2.1). The idea is to erode the electrical wire laterally in order to reduce its size until one obtains a nanoscale conductor that becomes disconnected at a certain stage of the erosion. Morpurgo *et al.* [3] demonstrated that the wire's conductivity becomes quantized in the moments immediately before the electrical connection breaks because the wavelength of the Schrödinger function associated with electrons becomes comparable to the lateral size of the wire. We can therefore control the breaking of the connection by monitoring this quantum current. Now, we can obtain a nanoscale interruption in the wire by stopping the erosion immediately after the appearance of quantum states. If electrochemical etching provides the erosion, then it is easy to control the process by means of a feedback system driven by the wire conductivity. Experimental results show that gaps can be obtained in the interrupted wire with sizes down to 20 nm [3]. Considering now the typical size of metalloproteins, close to 5 nm [4], or of antibodies, up to 15 nm [5], we can see that gaps of 20 nm are too large for quantum tunneling from the Fermi level in the metal to the LUMO (lowest unoccupied molecular orbital) in the protein [6]. Therefore, the gap needs to be reduced in order to fit the sizes of the molecular structure. Electrodeposition is useful for this purpose [7]. Once the nanogap has reached the desired size by re-deposition of materials, the biological molecule may be successfully located in between the nanometer-distant electrical contacts (Figure 2.1) in order to realize a bioelectronic component. Molecules are typically trapped inside by using different techniques, including drop-casting [8] or electrophoresis [9]. Alternative methods are layer-by-layer deposition [10] (Figure 2.2) and Langmuir–Blodgett films [11], which also allow one to manage the orientation of the film molecules. As we have seen in Chapter 1, "organic bioelectronics" has also been introduced [12] and therefore we can develop molecular components by also considering organic molecules within the gap. For example, nanogap arrays functionalized with thiophenes have been fabricated to realize molecular optoelectronic components [13].

Alternative methods for electrical contacts at the nanoscale have been proposed in which the molecules are just contacted in the z-direction instead of in the plane. Several authors have used piezoelectric movers to locate an electrical contact just on top of a biological protein (Figure 2.3) that was previously deposited on a flat electrode [14]. Piezoelectric movers have also been proposed to obtain polymer-based nanoscale Schottky junctions [15],

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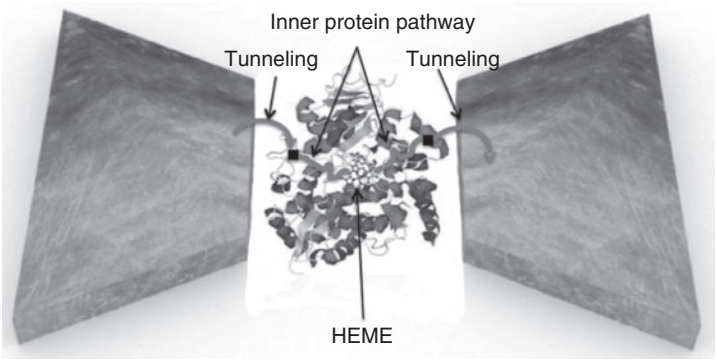

Figure 2.1 A metalloprotein engaged within a nanogap for electron-transfer based devices

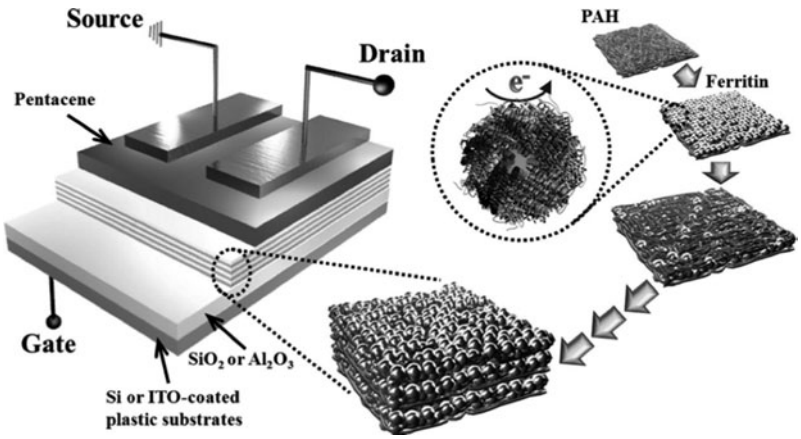

Figure 2.2 Memory device with layer-by-layer assembled multilayers based on ferritin (reprinted from [10])

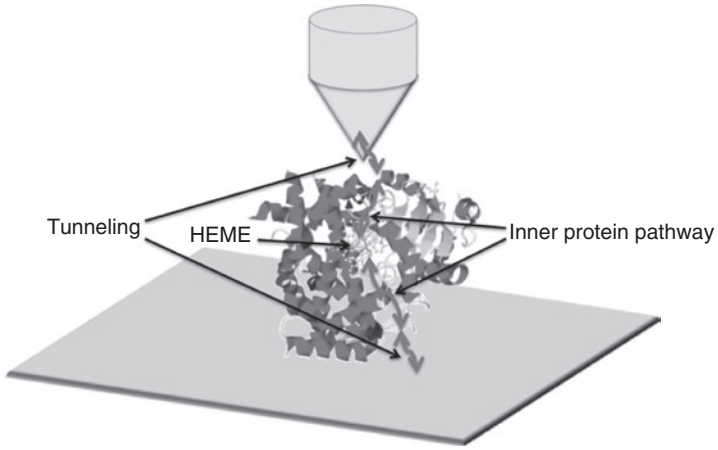

Figure 2.3 A metalloprotein engaged for electron transfer between a piezo-moved tip and a flat electrode

room-temperature single-electron elements [16], quantum devices [17], and devices based on fullerenes [18].

A further alternative method is to create crossing nanoscale bars and to locate the molecules in between: the most famous results obtained with this approach are the molecular memories proposed by Hewlett-Packard [19]. They also proposed to realize molecular switches based on several organic molecules such as benzoperylene, pentacene, tetraphenylene, triphenylene, decacyclene, pyrrole, thiophene, and porphine [20].

We can now see how to develop several bioelectronic devices to address several different applications by considering all the above-mentioned options to fabricate nanoscale electrical contacts and adding techniques to immobilize biological molecules in between the contacts. The biomolecular function is the key feature of the obtained final element. For example, optoelectronic devices have been proposed by using photoactivated proteins, such as reaction centers or bacteriorhodopsin, within a nanogap [21] or contacted by piezoelectric movers [14]. Identity cards have been developed by printing with a bacteriorhodopsin-based ink [22]. Metalloproteins are useful to obtain tunable molecular switches thanks to the control of their redox state with an external voltage [23]. Among metalloproteins, azurin was proposed as a good and robust biomolecule to implement prototypes of protein transistors operating both in air [24] and in aqueous environments [25]. More recent results have shown coherent quantum conductivity in the electrochemical tunneling microscope in general agreement with conductance estimates in air over a large number of measured junctions [26], and demonstrate the possibility to use that protein for multifunctional 4-bit bio-memory chips based on recombinant variants [27]. Iron-storage protein-based nanoparticles deposited in multilayers with pentacene [10] have also been used for memory devices, while single-molecular magnets have been used for spintronics devices [28]. Single amino acid chains have been proposed for building bioelectronic circuits to demonstrate the catalytic activity of lysozymes [29]. The investigation of complex circuitries based on devices operating on the molecular scale was pursued until a programmable automaton was achieved, encoding the information in double-stranded DNA sequences thanks to the biomolecular function of enzymes (nucleases and ligases) in order to autonomously solve computational problems [30].

So it is easy to see how broad the potential is for making molecular components for applications in bioelectronics by combining the power of nanotechnology in building nanoscale electrical networks and contacts with that of biotechnology in providing molecules with improved functions. The aim of this section of the book is to provide a deeper overview of the field of molecular devices for electronics by presenting the details required to understand how to design, fabricate, and test several kinds of such devices.

In Chapter 3, the research group of Danilo Demarchi, based in Politecnico di Torino, presents nanogap-based devices as fundamental building blocks for fabricating nanometer-sized devices and circuits. The chapter considers several possible devices such as rectifiers, switches, and opto-transistors.

In Chapter 4, Giuseppe Scarpa and co-authors start from basic principles to present the state-of-the-art of organic thin-film transistors, either back-gated or electrolyte-gated. The chapter focuses in particular on different functionalization methods, which are presented in order to assure selective responses of the devices. The chapter presents more recently published applications of organic thin-film-transistors dealing with DNA, proteins, and enzymes. The sensing mechanism and the influence of the Debye screening length are also discussed in the chapter.

Chapter 5, written by Paolo Facci and Andrea Alessandrini, is a review of the main results obtained using metalloproteins when used as the biomolecular function in hybrid electronic devices. The chapter considers both piezoelectric movers and electron-beam lithography to realize 5–10 nm gap-electrodes in order to assure electrical contact to azurin and cytochrome c. Several device features are reported, including current values of the order of a few hundred picoamps, rectification, and negative differential resistance.

Chapter 6 is written by the group of Philip G. Collins, working at University of California at Irvine, and it reviews the techniques of fabricating and using a new class of bioelectronic transistors based on carbon nanotubes. The chapter demonstrates and gives details on how a transistor may be used to monitor biomolecular activity. It provides three examples based on different enzymes: lysozyme, cAMP-dependent protein kinase (PKA), and the Klenow fragment of DNA polymerase I (KF). The chapter shows the chemical versatility of these devices and promises tools for single-molecule research investigations. The chapter then concludes with new design rules for creating equally effective nanocircuits using biomolecules of interest.

The final chapter of the section is by Jeong-Woo Choi and co-authors, from Sogang University, Seoul (Korea). His chapter describes the development of protein-based biomemories composed by recombinant proteins organized in thin molecular films, and proposes various readout mechanisms to obtain a memory device. The chapter also summarizes recent outcomes on nanoscale bio-memory devices starting from the Write-Once-Read-Many (WORM) characteristic of the proposed systems. The chapter then closes by considering applications to non-volatile memories thanks to device features such as multi-bit storage, very low voltages, good stability, and excellent reversibility.

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