Sandro Carrara

Bio/CMOS Interfaces and Co-Design

Springer

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Do you want to sell sugar water for the rest of your life or come with me and change the world?

Steve Jobs

Sandro Carrara

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To the girls of my life: Chiara, Noemi, and Lorella!

Foreword

The search for efficient means of linking biological to electrical–optical and information systems gravitates around the design and implementation of biosensors and biointerfaces, which are the key links between the living and the computing worlds. Biosensors and chemical sensors are based on a wide variety of techniques. Even a simple classification would require spanning a variety of axes, ranging from the targets to the sensing elements to the transduction mechanisms. Moreover, nanotechnology has greatly improved the performance of biosensors due to both quantum confinement effects and the match in size between engineered nanostructures and biological entities.

Understanding and mastering the key area of biointerfaces requires a plurality of skills going beyond traditional disciplines. Indeed, biosensor design requires knowledge of biology and chemistry, surface and semiconductor technology, and electronics. It is still uncommon to find textbooks that span these fields and provide the necessary background to understand this complex and evolving field.

This book is an excellent introduction to biosensing. It provides the reader with information in the various areas that are fundamental to biosensor and biointerface design. The book will appeal to engineers and scientists who wish to enter this domain and to students seeking an introduction to this fascinating discipline. The book will also serve as a reference point to engineers and scientists in the field; it describes a wide set of technologies and provides a comprehensive and unified scientific platform.

EPFL, Lausanne, 2012 Giovanni De Micheli

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Contents

Chapter 1
Introduction

1.1 Personal Bioelectronics

Electronic provides devices that are ubiquitous features of our lives. We watch television and listen to the radio, connect to the rest of the world using Wi-Fi systems, adjust our home heating systems remotely, and on and on. This control over our world extends to our cars: electronic regulation of air conditioning, stability, antilock brakes, anti-skating systems, and other microprocessors that constitute new electronics control units and that enable complete control over total-vehicle operations, including the engine and transmission. The next step in car evolution will be cars that drive themselves (there are already cars on the market equipped with automatic blocking on obstacles). The same goes for airplanes: nobody wants to use it, but the technology already exists to fly with airplanes without pilot, including takeoff and landing. Electronics is part of our daily lives: we have a mobile phones in our pockets and laptops in handbags. Some of us also carry an iPod® or iPhone® (which is more than just a mobile phone!) in our pockets and an iPad® in a case. It is now easy to see people using e-book readers in airports or airplanes. We have fully integrated electronics into our daily lives in a manner that is totally embedded. We are so comfortable with it that we sometimes aren't even cognizant of electronic devices and consider them an extension of our own bodies. They are what we might also call *personal electronics*.

It seems natural, then, to extend the use of personal electronics to health applications. We can take it a step further to arrive at *personal bioelectronics*. Personal electronics have actually been a reality since *Wilson Greatbatch's* invention of the pacemaker. In 1960, the first *pacemaker* was implanted in a person's heart. This device artificially supplies electrical signals to damaged biological tissue, prolonging human life for decades. With *epilepsy*, electrodes implanted deep in the brain are used to identify the origin of seizure activity and for seizure suppression. Even this is a long story. In 1972, *Irvin Cooper* became the first person to implant a cerebral stimulator in an epileptic patient. The next step in the field of implanted electrodes for functional stimulation will be leg movement

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recovery in patients who had suffered spinal cord injuries. Patient monitoring is also common. A good example of this is the *holter*, a portable device for continuous monitoring of the electrical activity of the cardiovascular system. Human monitoring is also concerned with metabolic states at the molecular level. In 1953, *Leland C. Clark, Jr.*, invented the famous *Clark electrode*, an electrochemical sensor for measuring oxygen content on the surface of a platinum electrode. Its historical importance is related to modern devices for *glucose automonitoring* that enable a diabetic patient to measure *glycemia* (or *glycaemia*) in his blood at home, up to three times a day; the cost: a few dollars.

1.2 Distributed Diagnostics and Personalized Therapy

All these devices, which are already on the market for both electrical and molecular monitoring, actually prove that *distributed health care* is possible and leads to *distributed diagnostics*. Of course, we can measure a wide range of physiological parameters on the surface of our skin, for example, temperature, blood pressure, heart beat, respiration, and swelling. On the other hand, we can also measure relevant molecules in our bloodstream, for example, glucose, cholesterol, and triglycerides. Blood contains millions of different molecules that are involved in the regulation of our metabolism; hence their name – *metabolites*. The extension of personal diagnostic systems to sense a wide class of metabolites contained in the blood may provide frequent diagnostic sampling and address human telemetry. The availability of low-cost and easy-to-use tools for frequent diagnostics is a key requirement if we plan to finally address the new concept of therapy personalization. *Personalized therapy* is a new branch of medicine that tries to address the problem of the low efficacy of current pharmacological treatments. In fact, therapy outcomes vary widely from patient to patient, even when a group of patients is treated with exactly the same drug compound or with exactly the same cocktail of drugs. For same patients, the cure is effective and the supplied compound is nontoxic, while for other patients the drug is toxic and not even beneficial. The framework is so complex that some patients experience toxicity but also treatment efficacy, while others experience neither toxicity nor treatment efficacy (Fig. 1.1). The reason for this has to do with the differences among patients at the individual level. Each patient has his or her own *genetic predisposition*, which is the tendency to suffer from a certain disease as registered in a person's DNA. Patients differ at the *epigenetics* level (epigenetics is the study of heritable changes in gene expression). They differ at the *phenotype* level, which refers to the outcome in an organism resulting from the interaction of its genetic character with the surrounding environment.

People are also different at the level of daily metabolism. This means that one patient's reaction to the same treatment may be different from one day to another. All these differences might explain the low efficacy of so many pharmacological treatments currently used in very common diseases (Fig. 1.2). For example, the

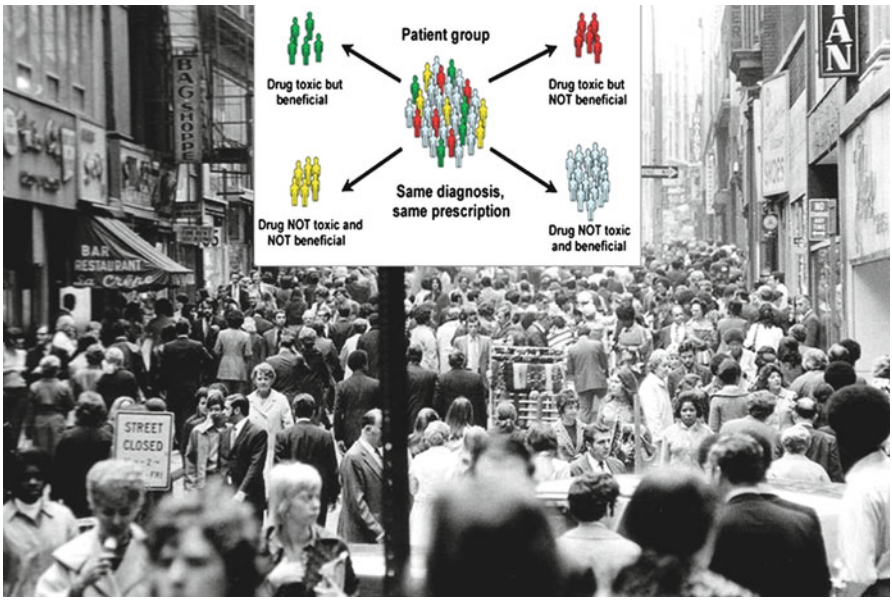

Fig. 1.1 Humans are unique, and this affects cure efficacy

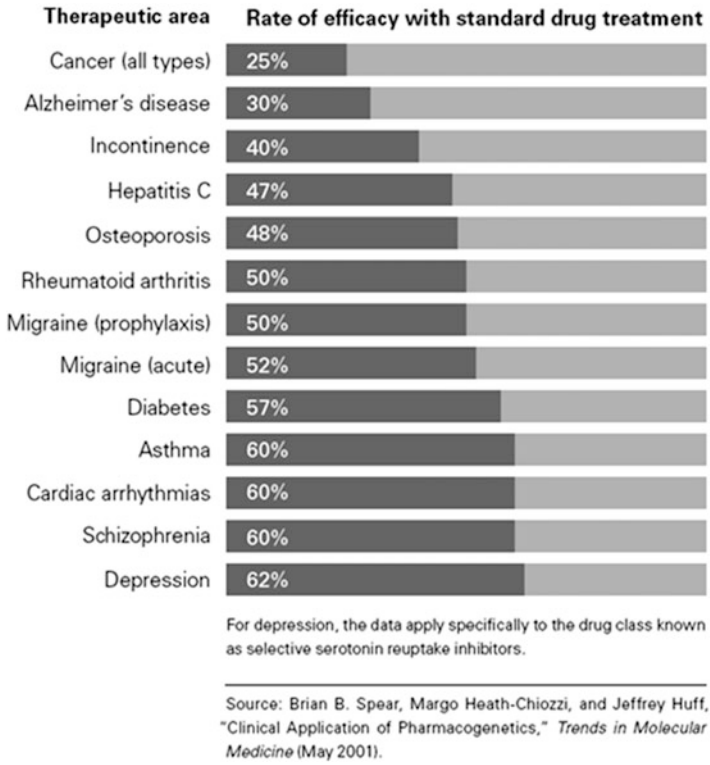

Fig. 1.2 Efficacy rates of drug treatments for most common diseases

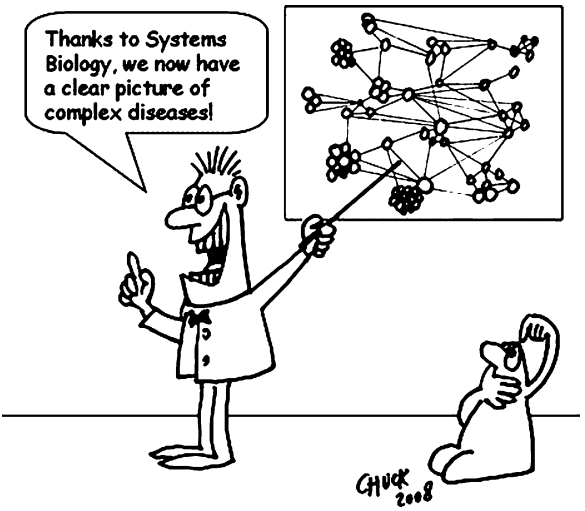

Fig. 1.3 System biology explains complex diseases at molecular level

registered efficacy of anticancer treatments is estimated to be only 25%. Now, if we take into account that all the anticancer drug treatments are highly toxic, then an efficacy rate of only 25% is actually a very poor result in chemotherapy.

Of course, systems biology is a modern branch of medical research that attempts to investigate all the complex interactions in biological systems with the aim of identifying all the complex pathways that are related to particular diseases at the molecular level (Fig. 1.3). However, systems biology is insufficient because it does not provide us with a simple approach to improving treatment. There is actually a need for the personalization of therapy that would take into account, on the one hand, a patient's predisposition and daily metabolism and, on the other hand, the actual efficacy of the prescribed therapy. Only this combination opens up the real possibility of a personalization of treatment based on a patient's actual characteristics. This is the concept behind personalized therapy.

1.3 Impact in Society

To get an idea of the impact on society of personalized therapy, we can consider the huge costs of health care and the enormous potential to improve treatment efficacy and decrease costs by adopting personalized therapies. Worldwide, no country spends more on health care than the United States. Estimates peg the figure at approximately $2 trillion annually. (Note: All costs are given in US dollars unless otherwise stated.) Of these costs, a percentage is related to diagnostics. Costs for molecular and *genetic diagnostics* have been estimated at approximately $8 million in 2010 and $40 million in 2011; they are expected to double in 2012. According to *Molecular Diagnostics* Survey Report done in 2008, by the analysts company G2

Intelligence the cost for per molecular or genetic test (usually ranging from $300 to $3,000) will soon compromise one-third of all diagnostics costs. Moreover, diagnostics testing accounts for 70% health care decisions and therefore is of key importance in treatments. Molecular tests improve diagnostics, improve the reliability, accuracy, and efficacy of treatments, and have the potential to reduce health costs. They also have the potential to reduce the incidence of ineffective treatment and may also impact patient outcomes and improve disease management.

Two examples clearly show the effect of molecular tests on choice of treatment. The first example deals with the chemotherapy drug known as *Herceptin*. Herceptin was introduced in 1998 and widely prescribed in the USA, with annual costs ranging from $50,000 to $100,000. However, it was demonstrated years later that Herceptin only worked in women with tumors that overproduced the protein HER2. This happens only in a maximum 30% of patients. Based on this knowledge, a test on the *HER2 protein* was introduced in 2006 to precheck its overproduction from the neoplastic mass before approving the use of Herceptin. This test has reduced by 70% the number of patients treated with a noneffective drug compound. Another example is related to deleted proteins in our bodies. It was demonstrated that 7% of the German population do not express two *enzymes*: the *cytochromes* P450 2D6 and P450 2C19. The P450 cytochromes are key enzymes of our metabolism that also allow for the transformation of ingested drugs. If patients have deleted these enzymes, the injection of a (supposedly) curing drug results in toxic doses after the third series of chemotherapy. Thus, the treatment kills instead of curing them. Roche introduced in 2006 the AmpliChip CYP450 as a genotyping test for patient classification. Patients are classified a poor, intermediate, extensive, or ultrarapid metabolizers to personalize the chemotherapy treatments based on the patients' genetic predisposition.

These are only two examples from the long list of medical cases that led former Secretary of U.S. Health and Human Services Michael Leavitt to declare in November 2008 that "issues surrounding molecular diagnostics must be a priority, and personalized health care should be an explicit goal of health care reform."

1.4 Need for New Bio/Nano/CMOS Systems

We can control the daily variations of patients' metabolism by frequently measuring all the molecules related to their diseases and to the considered pharmacological treatments. Nowadays, many molecules are detected with high parallelism in systems with millions of different probes on the same passive chip that optically query all spots in the same moment. Examples of such systems are those supplied by *Affymetrix*, a U.S. company that provides systems for large-scale screening of the human genetic code (Fig. 1.4).

These systems are very powerful, but they are suitable only for hospitals or research labs. They are definitely not suitable for personal and distributed diagnostics because they are bulky and costly, and require special sample preparation that requires expert technicians. Moreover, the cost per assay is in the range of

Fig. 1.4 Bulky lab systems versus light automonitoring systems

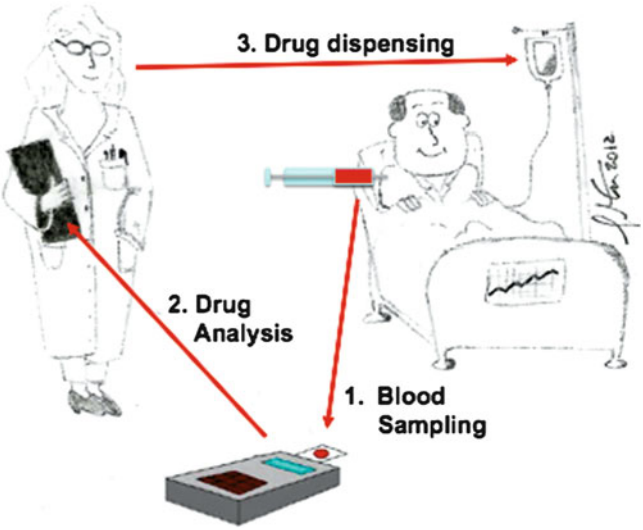

Fig. 1.5 Closed-loop concept in personalized therapy

thousands of dollars, which is unaffordable for daily tests in personalized therapy. Here, the goal is to repeat the widespread success we enjoyed in the past with glucose automonitoring (Fig. 1.4), with equipment costs of close to $50 and costs for fabrication of each assay strip less than few cents. Thus, the aim is to provide new tools to doctors that can present features similar to those of the glucose automonitoring systems and detect all molecules related to both disease and cure. Having such systems is a key factor for checking the amount of all relevant metabolites in patients' blood before deciding on the kind and amount of subsequent drug injections (Fig. 1.5).

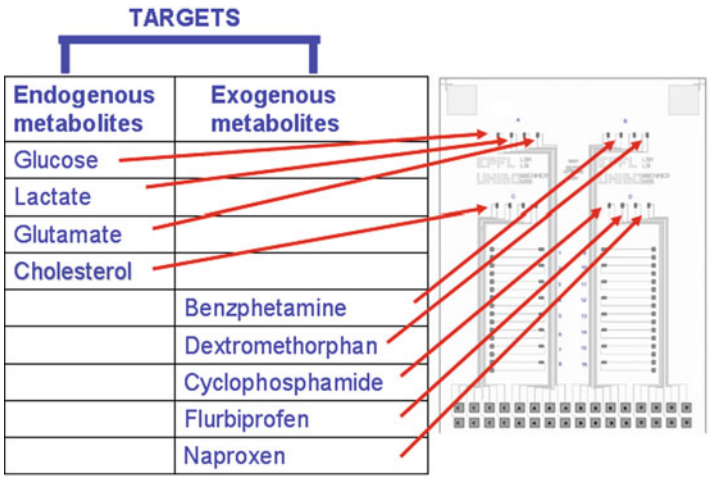

Fig. 1.6 Sketch of monitoring system in personalized therapy

This approach closes the loop between supplied compounds and treatment efficacy, which is mediated by the metabolism of each individual patient, which is presently unchecked and, thus, unknown. In principle, closing the loop between the supplied compounds and the treatment efficacy does not seem so difficult. We simply need innovative systems that can incorporate many diagnostic parameters at the same time and relate them to the supplied treatment to control its efficacy. Figure 1.6 shows how to address such a development with system designs that employ multipanel diagnostics: different endogenous and exogenous metabolites (Chaps. 3, 4, and 10) are detected at different locations on the same chip in a way similar to the well-known Affymetrix systems.

However, molecules are also detectable in a fully electronic manner, avoiding costly and bulky laser sources and optical detectors. The plan here is to obtain fully electronic readers that can address the parallel detection of so many molecules. If we succeed in that, then we just might be able to secure all the low-cost, efficient, and easy-to-use devices we need for personalized therapy (Fig. 1.7). However, measuring physiological parameters on the skin's surface is one thing; measuring molecules below the surface is quite another. In the latter case, we need to breach the skin barrier to reach the underlying tissues. In all likelihood, we would be able to obtain much information from a single, small drop of blood, as we do in the case of glucose automonitoring. However, the nanoscale interactions of molecules on the surfaces of our devices are very complex, which means we will have to deal with very complex interactions taking into account their reflection in the three main features of our systems: specificity, sensitivity, and time reliability. To put it briefly, we need systems that are fully reliable and robust enough to address automatic monitoring of human health.

Fig. 1.7 Quicklab® concept from Siemens

1.5 Aim and Synopsis of this Book

Obtaining fully reliable and robust systems is not trivial because we always acquire both specific and nonspecific signals from the Bio/CMOS interface (Fig. 1.8).

In fact, we are interested in measuring only signals coming from specific interactions that occur at the interface because only these are related to the metabolites we want to deal with. However, the bio interface is embedded in a liquid, water-based medium that usually contains salts. Both water and salt molecules provide conductivity to the liquid medium, which is not related to the specific interactions in which we are interested.

Thus, we need new paradigms to build the interfaces between our CMOS circuits and the bio environment; otherwise, an excellent CMOS technology would be insufficient if molecules were not doing their own job at the Bio/CMOS interface (Fig. 1.9). We may get enough nonspecific signals that would give us wrong measurements resulting in bad quality of our electrical transduction of the biological information we are trying to acquire. This is a general problem we have encountered whenever we have had to deal with the interface between CMOS integrated circuits and biological samples. Biological samples require a water-based environment to keep their biological components alive. We need to have biological components that are alive; otherwise, we cannot interact with them. No interactions, no signals. Thus, we need to find a way to dramatically increase the specific signals and decrease nonspecific ones because these latter may completely hide our biological information (Fig. 1.10).

The aim of this book is to address how nanotechnology may help us in pursuing this new approach and developing new paradigms in the development of Bio/CMOS systems. We will see in this book how both engineered molecular monolayers and carbon nanotubes are used to create the right nanoscale structures to improve the behavior of our biointerface (Fig. 1.11). We will see how special structures with the right biochemical functions may provide specific behaviors on a

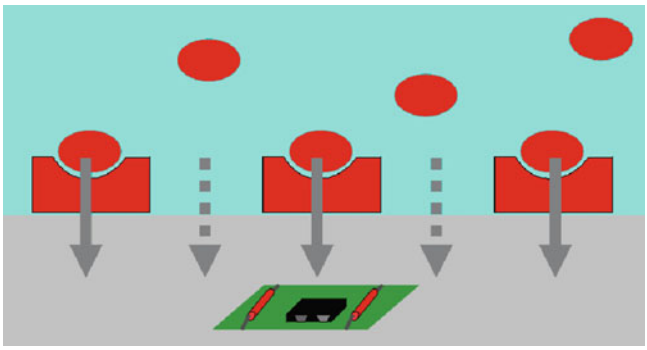

Fig. 1.8 Specific and nonspecific signals from the bio interface

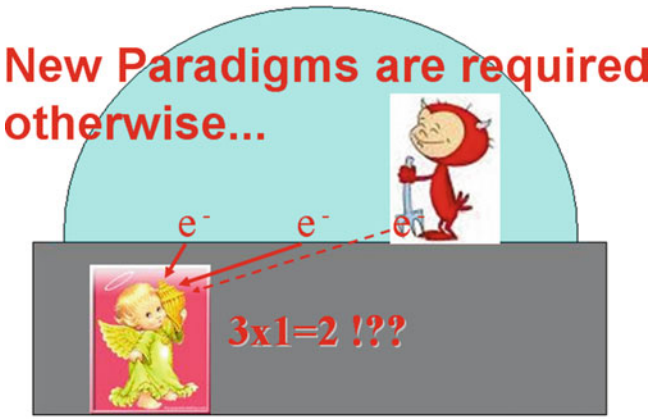

Fig. 1.9 Bad signals from a bad Bio/CMOS interface

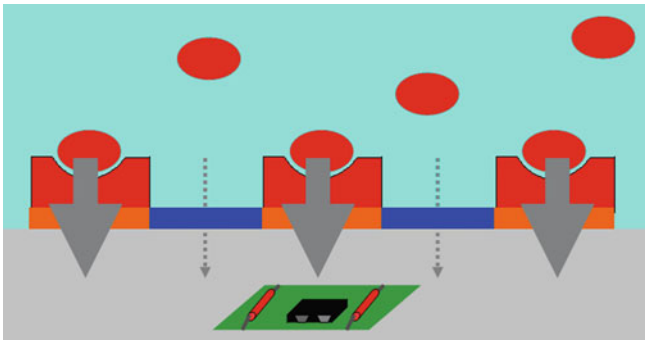

Fig. 1.10 Enlarging specific and blocking nonspecific signals

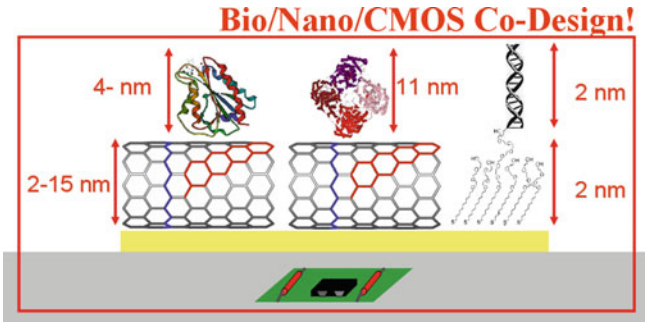

Fig. 1.11 Codesign of bio, nano, and CMOS systems

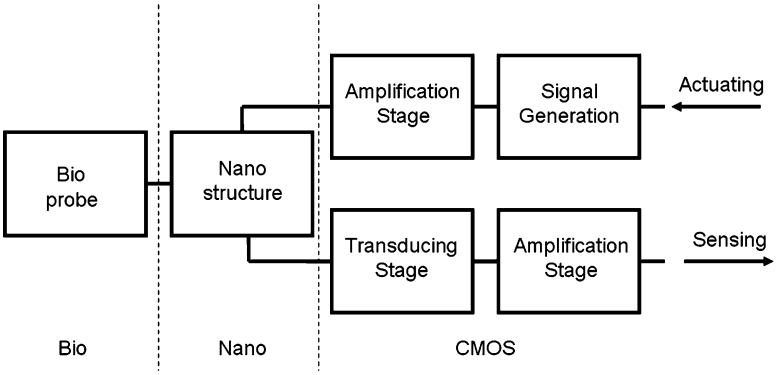

Fig. 1.12 Bio/nano/CMOS interface

surface in the presence of different metabolites in a sample. We will see how a special CMOS design might supply the right query of the interface for obtaining the best possible electrical signals from the interactions between molecules.

We need to develop a new approach to enlarge the concept of CMOS design at the level of nano- and biostructures that we will integrate into our CMOS chip. This means we need to take into account not only the design of our CMOS circuits but also the design of our nano- and biointerface. Furthermore, we cannot separately design the three systems – the CMOS, nano, and bio. Indeed we need a special codesign (Fig. 1.11) that could help us in designing the entire interface in such a way that takes into account the functions of the biological materials we have on top as well as those functions that are changed by the presence of the nanomaterials at the interface. Therefore, we need to define a new integrated interface, the *Bio/Nano/CMOS interface*, and we need to design the three levels (bio, nano, and CMOS) in a way that accounts for an integration of the characteristics of each layer (Fig. 1.12).

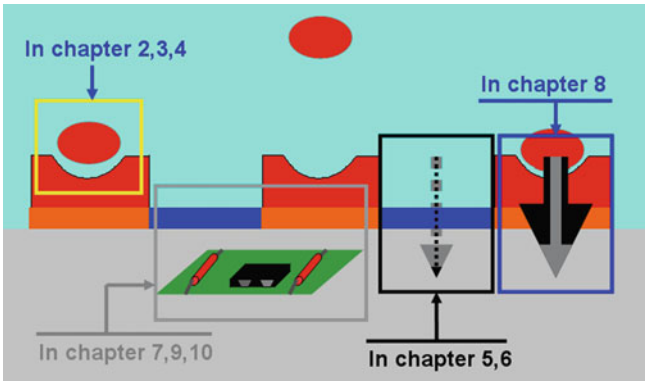

Fig. 1.13 Book synopsis

This Bio/Nano/CMOS interface requires knowledge and skills in fields ranging from chemistry and biology up to analog and digital design, moving through the physics of nanofabrications. This book will consider all of these disciplines trying in depth do as to allow for the emergence of a CMOS design from the requirements of the biological and nanostructured molecules. The book's synopsis (Fig. 1.13) shows that Chaps. 2, 3, and 4 are focused on the chemistry, biochemistry, and electrochemistry related to the molecules we might have in the Bio/Nano/CMOS interface. Chapters 5 and 6 focus on the physics of immobilization and characterization at the nanoscale of molecules at the CMOS interface. Chapter 8 deals with the electrochemical behavior of nanoscale materials. Chapters 7, 9, and 10 show how to design proper CMOS architectures that can address the electrochemical behavior of the new Bio/Nano interfaces.

The book as a whole presents a new approach to deal with complex and structured Bio/Nano/CMOS interfaces with the ultimate goal of developing the right engineering skills to address system design to provide feasible and robust personal bioelectronics for distributed diagnostics.

Further Reading

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