Novel Front-End Circuit Architectures for Integrated Bio-Electronic Interfaces

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Abstract

The prospective use of upcoming nanometer CMOS technology nodes (65nm, 45nm, and beyond) in bio-electronic interfaces is raising a number of important issues concerning circuit architectures and design. In particular, the advantages of scaling and higher density integration must be balanced against the requirements of low noise design, uniform power density and surface temperature distribution, better component matching, and immunity to parameter variations. Dealing with these constraints also requires more innovative approaches towards hybrid integration technologies. In this paper, we discuss the key design issues with specific examples from DNA detection, protein detection, and neuro-electronic interfaces.

1. Introduction

The interface between man-made electronic circuits and living organisms will be one of the focal points of future integrated system design. The "More-than-Moore" paradigm that advocates obtaining advantages beyond those offered by technological scaling has already become an established term for pioneering research in bio-electronic interfaces. Coupling the processing and memory capability of state-of-the-art electronic systems directly with biological systems will enable a whole range of new services and products to be developed.

Initially driven mainly by the same scaling trends as the conventional silicon-based technologies, bio-interfaces have evolved tremendously during the last two decades by integrating new technologies for sensing and fabrication, by exploiting MEMS-based and more recently nanotechnology-based implementations. Still at present we are far away from a complete system where a seamless two-way interface exists between the electronic world and the biological system. Such an interface will be instrumental in "closing the loop" and allow novel systems to be designed. Figure 1 provides a concept view of one such integrated bio-electronic system which includes on-chip microfluidics, sensing elements, analog front-end, as well as digital back-end signal processing and off-chip communication interfaces. While many of the individual building blocks exist today, the seamless integration of such complex bio-electronic systems will depend on choosing the right components.

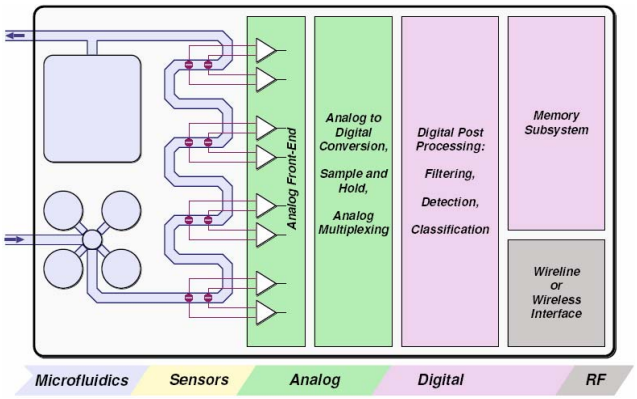

Figure 1 - Typical block diagram for an integrated biosensor system.

The scaling of fabrication technologies is dictated by the market demands in the near future. In this paper we discuss how the bio-interface research can benefit from the continued miniaturization. We present a simple classification based on the main components and application field of present bio-interface solutions in Section 2. Both the advantages and disadvantages of aggressively scaled integrated circuit manufacturing technologies will be explained in Section 3 and some future trends will be outlined in Section 4. Finally Section 5 will provide conclusions.

2. State-of-the-Art for Biosensor Systems

Formally, a biosensor is defined as a sensor that employs biological material as its sensing element [1], which means that the "bio" nature of the analytes is not implicit. Nevertheless, the term biosensor is at present widely used for a number of devices, systems, laboratory equipment and chips that interface with biological matter. While not entirely correct, this definition is still meaningful, as these systems share the same integration, compatibility and stability issues. At the end of the

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nineties, when the miniaturization of sensing elements and introduction of new sensing technologies started to be heavily exploited, the community converged on a definition which was based on an "added-value" characteristic: in a biosensor the biological sensing element is intimately integrated or associated with a transducer. This definition addresses systems based on active substrates or, more generally, in which the substrate material has transducing properties.

Typically, the substrate is a solid-state material that hosts the regions (sites) where the biological sensing elements are deposited to be accessible to the analyte. The substrate can integrate transducers such as diodes, transistors, capacitors, electrodes, piezoelectric elements, cantilevers, resistive membranes and thin metal layers meant to sense a variation of physical or chemical properties, such as light intensity, charge, electrochemical current, mass, surface stress, or refractive index.

Silicon substrate is a natural choice to integrate the transducers mentioned above. It not only allows the sensor to be integrated but also allows the analog front end to condition the signal for each sensing site (channel) and the digital post-processing to be integrated on the same substrate as well.

The sensor is usually equipped with structures for fluid handling that helps to control the conditions of the sample solution (concentration, temperature, ionic force, pH) and the efficient delivery of the analytes on the sensor surface. More complex fluid handling structures may be used to carry out more functions for sample preparation. These can range from simple systems intended for dilution, to systems that can handle complex processes to multiply the number of analyte molecules.

2.1. Classification of Biosensors

Biosensors can be classified according to multiple characteristics which are dictated on one hand by the application purpose of the device and on the other hand by the specific integration and miniaturization limits of the transducer technology.

The electrical properties of a biosensor are mainly determined by three factors: (i) the number (and physical dimensions) of parallel channels used for sensing, (ii) the shape and magnitude of the signals acquired by the biosensor and finally (iii) the rate at which the biosignals are sampled.

The number of channels is one of the most important factors that determine the key parameters of the biosensor. In some systems, each channel may require dedicated electronics to function properly, further increasing the area. The number of channels also sets the I/O requirements of the system. The signal amplitude at each sensor channel dictates the specifications of the analog front-end. Typical biological signals seldom exceed one hundred mV, and can carry very small currents, usually in the range of few μA. Finally, the signal acquisition rate determines the dynamic properties of the system such as I/O bandwidth and clock rate.

Biosensors also differ greatly depending on the application area. We have identified three main classes of application: the first class of applications covers specialized laboratory equipment. Integrated biosensors are used to increase sensitivity, reduce the sample size and increase the sensing density. Such sensors typically employ a large number of channels, and have high demands on the analog front-end. Cost, however, is usually not an issue.

Biosensors for small handheld and/or disposable systems constitute the second class of biosensors. In this category, cost and reliability are the determining factors, which determine the overall feasibility of the overall system. The third class of biosensors includes devices designed to be included within implantable systems. These sensors need to have a small form factor, need to be manufactured using biocompatible materials and have to be operated with minimum power dissipation.

The electrical signal level and type depend on the technique and transducer involved in the detection. Arrays of photodiodes employed in optical detection of fluorescent markers are usually generating down to few pA currents for one single site [2]. Electrochemical detection can produce peaks of 1 nA current through each electrode/site built on a silicon CMOS chip [3].

Mass changes on the surface site can also be utilized to sense the presence of captured molecules. For this purpose, signals with a frequency range of hundreds of kHz have been measured after deposition of biomolecules [4].

More recently, label-free techniques based on electrode interfaces changes implemented on CMOS chips were able to detect the DNA molecules by changes of hundreds of pF in interface capacitance [5].

The scope of interest of this paper is extended to neuro-electronic interface and microelectronic systems, where the microelectronic circuits interact with living matter, in readout or stimulation modes. Implantable micro-electronic systems, as well as systems enabling the behavioral analysis of cultures of brain cells have developed significantly in the recent years. The electrodes have progressed with the evolution of silicon fabrication and micromachining. Specific microelectronic systems are developed to support the electrical characteristics of the electrodes, and living matter. The hybrid nature of the systems to be developed demands new fabrication and packaging technologies, as well as novel microelectronic circuits adapted for this purpose.

Electronic interfacing with living neural cells has emerged as a new filed of advanced research where interdisciplinary competences are demanded, such as

biochemistry of sensor interfaces, biology and neurophysiology, as well as microelectronics [6]. The major goals of this research relate to fundamental research on brain operation and activity, as well as to the development of implants, such as retinal implants for restoring the vision of the blind, or cortical implants systems that are enabling voluntary control of electromechanical prostheses for functional restoration of amputees [7].

Accordingly, two types of systems have been developed, pertaining to their respective target application. *In-vitro* systems, also named *ex-vivo*, rely on the analysis of the electrical activity of cultures of neurons, or acute brain slices placed inside of culture chamber and incubator, i.e. outside of the body. Implants are also referred to as *in-vivo* systems, and are placed inside the body of a living, in direct connection with neurons, or central nervous system cells, to record the activity, or provide external electrical stimulation.

2.2. State-of-the-Art for Biosensors

Ultra dense arrays for gene-based analysis have undergone significant development in recent years. They are now able test the genetic variation on a whole genome by employing millions of sites. Smaller arrays can be utilized for diagnostic applications limited to certain markers or to viral detection [8]. These arrays are generally passive substrates that are measured by optical instrumentation through fluorescence labels. In order to develop high density biosensors for gene tests, arrays of solid state optical devices that are able to detect the emitted light of the fluorescent labels on-site have been implemented and tested. These photodiode arrays are meant both to be coupled with glass structures [2] and to become active sensing substrates for the molecular spotted arrays [9]. Signals in the range of pA can be measured by these photodiodes in a single measurement after DNA recognition on each site. Nevertheless, non trivial design issues, such as the need for integrated filters to screen the excitation light, have to be addressed. Electrical detection based on the measurement of the electrode/solution interface impedance could overcome the issues of optical techniques and labelling drawbacks. Recently, a 128 channel CMOS chip has been developed based on this technique [5]. Measurement circuits were integrated under each channel which consists of a couple of inter-digitated electrodes. The circuits perform a capacitance-to-frequency conversion which evaluates charging and discharging time. Capacitances in the order of 1 nF were measured for 200µm diameter sites and the signal is converted to a 2 kHz square wave.

Significant research effort has been devoted to the development of implanted biosensors for continuous monitoring of chronic diseases as well. Glucose meters have pioneered this trend and presently there are solutions that employ sensors which are implanted under the skin and are monitored by wireless communication. They are based on electrochemical enzymatic reaction that produces current flow through metal electrodes in presence of glucose [10].

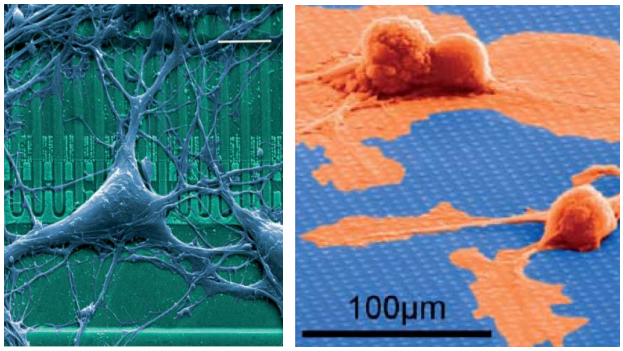

Figure 2 – Neuro biosensors, from [6], [16].

Coupling of micro-delivery systems with sensing devices and processing will be crucial for pre-programmed or remote-stimulated controlled therapeutic treatment. The possibility to release drugs from in-body controlled microsystems could have a tremendous impact on medical procedures, eliminating the injection pain and infections due to frequent injections and offering a mean to reduce side effects and drug volumes by allowing a more precise and efficient delivery [11].

The use of conventional micromachined devices, equipped with wells, microfluidics and circuitry has been tested. Santini et al. presented a multi-well silicon chip in which the release of drugs from the compartments is controlled by an electrochemical stimulus that selectively dissolves covering gold membranes with polarizations of 1V. This signal could be pre-programmed or controlled real-time by sensors coupled with the device [12]. Due to the slow diffusion of drugs (several minutes) these systems work at a very low rate.

Patch clamping techniques have been applied for *in-vitro* studies, where micropipettes connect and penetrate the surface of neuron cells. More recently, multiple electrode arrays (MEAs) have offered an alternate sensing system, where cells are lying on the surface of numerous capacitive electrodes, each connected to an acquisition channel. In order to increase system compactness, and to improve the acquisition and driving capabilities, electrodes are post-fabricated on the surface of CMOS integrated circuits in charge of signal amplification, using standard silicon fabrication techniques.

Several retinal, cochlear and cortical implants systems have been presented in the past few years. Retinal and cochlear implants are using proprietary electrodes. Two systems of electrodes have emerged as the most

prominently used for cortical implants, namely the Michigan and Utah multi-electrode arrays. Cortical implantable systems using these electrodes have been presented, and are still under research [13], [14]. The need to embed radio-frequency (RF) electronics on-system has emerged, thereby enabling wireless transmission of power and data between the implant and a base station located outside the body [15].

The main analog blocks in the acquisition and processing of neural signals include low-noise amplifiers which typically provide exploitable signals in the mV range, filters which limit the range of the in-band signals, optional spike detection circuits, and the analog-to-digital converter(s). Neuron stimulation electronics consists of amplifiers which provide biphasic signals. Typical inter-electrode pitches in the range of 50-100µm in most systems presented so far, has enabled most analog blocks to be embedded in each acquisition/stimulation channel. The densification of the electrode array to a pitch of 1-5µm will dictate analog and time multiplexing to be considered. Analog service blocks include voltage and power regulation modules. Most realizations of these analog blocks have faced 1/f noise issues, and fabrication technologies with feature size larger than 180nm are used to circumvent this issue; moreover, the input stage of the first amplifier in the chain needs to use fairly large MOS transistors, or bipolar transistors.

The digital blocks are related to system control, hardware implementation of spike detection algorithms, and data formatting for further transmission. Memory units must also be included on-chip to temporarily store and to sort large amounts of collected data. The amount of digital processing usually depends on the available silicon area, as well as the power dissipation. Finally, RF blocks enabling bidirectional data transmission are becoming standard for implants, where wireless transcutaneous communication enables preventing infections. RF transmission of power follows the same concern. Generally, RF transmission takes advantage of inductive coupling, and antennas are developed, possibly on-chip.

The main challenges related to bio-electronic neural interfaces include:

- low-noise amplification of signals which have a very low amplitude, typically in the range of several tens of micro-volts; proper handling of 1/f noise, since bio-signals are typically below 3kHz
- extreme low-power electronics, possibly enabling system autonomy;
- energy scavenging, enabling harvesting power from human activity or metabolism;
- strict control over the thermal dissipation into surrounding cortical or body tissues; advances in fabrication technologies, circuit design, as well as system-level control are required;
- increasing spatial resolution of the sensors, and solving consequent issues related to sensor addressing, high data rates to be routed, stored and transmitted;
- high-reliability electronics for implants, possibly including self-healing capability;
- the cost and disposability of *in-vitro* systems must be considered.

3. Effects of Aggressive CMOS Technology Scaling on Biosensors

The analog blocks in charge of signal amplification, filtering and analog-to-digital conversion must be integrated in the close vicinity of the biosensor, due to the weak nature of the signals which is generally observed. Moreover, the development of portable biosensor equipments, implantable systems demands the presence of digital electronics performing signal processing, data formatting and system control. Thus, biosensors are quickly evolving towards embedded systems consisting of hybrid modules.

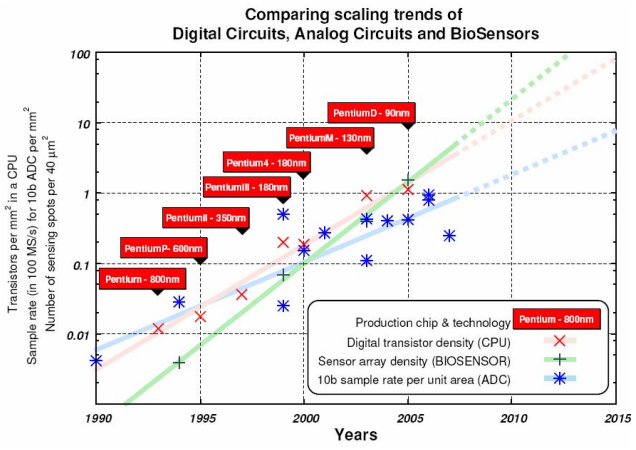

Figure 3 – Recent scaling trends for digital circuits, analog circuits and biosensors.

Downscaled CMOS technologies exhibit specific characteristics in terms of integration density, power supply, noise figure, power dissipation figure. The impact of these characteristics on the various blocks is analyzed in the following.

3.1. Analog Front-End Circuits

Analog blocks need to be redesigned and resized for each new technology, and rarely take benefit of very deep submicron technology features. Indeed, the size of the transistors constituting an analog block is determined by

the performance specifications of the block, which rarely enables using transistors of minimal feature size.

Low voltage supplies affect the SNR adversely. Input amplifiers designed in modern technologies are more sensitive to 1/f noise. Eventually, the use of large transistors is prescribed to circumvent issues related to short-channel effects, and noise, thereby canceling the benefit of a small minimal feature size.

The impact of fabrication and electrical parameter variability is increased in very-deep submicron technologies where SNR is reduced. The variation of transistor threshold voltage is the most prominent parameter which affects analog circuits operating points. The design of analog circuit and systems becomes an intricate task, where increased component sizes may be a reasonable solution, however contradicting the use of very-deep submicron technologies.

The circuit architecture plays a predominant role in relaxing the specifications of some analog blocks, where analog multiplexing of several channels into the ADC unit is considered.

3.2. Digital Post Processing and Storage

The amount of digital processing done on-chip and the complexity of the units dedicated to DSP largely depend on the application. While some applications require a minimum of digital post-processing at relatively low sampling speed, other applications may dictate the use of heavy-duty signal processing such as sorting and auto-correlation functions in order to produce the diagnosis. Clearly, digital post-processing and the associated memory units benefit the most from CMOS technology scaling, which allows very high density integration using nanometer-scale CMOS cell libraries as well as custom logic components. One of the key issues that have to be taken into account in this case is the self-heating of digital blocks due to very high integration density and the high clock frequencies employed in digital operations. On-chip temperature increases can effectively limit the usability of elaborate DSP schemes on the same silicon substrate as the sensor elements and the analog front-end, both of which are usually very sensitive to temperature gradients.

One possible approach to limit the self-heating of digital blocks is to employ aggressive power management schemes such as clock gating and sleep transistors, or utilizing sub-threshold logic to limit the power dissipation. While digital units operating in sub-threshold regime may dramatically reduce the dissipation, the clock speed also drops accordingly, thereby limiting the data throughput. For these reasons, monolithic integration of digital and analog functions on the same substrate may impose some undue limitations for the realization of complex bio-electronic systems.

4. Technology Trends and Future Directions

The scaling trends for pure digital circuits, analog circuits, and bio-sensors over the last years are shown in Fig. 3. Here, two important observations can be made: First, it can be argued that the scaling trends mainly governed by Moore's Law do apply to all specialization areas – in all cases we can see an exponential growth that leads to higher circuit density, and to more processing capability per unit area, over time. The second observation is that the growth rate of analog processing capability (measured as sampling rate for 10-bit ADC) is not following the same steep slope as the growth rate of transistor / device density in conventional digital processing units, or the sensor units. Although the ADC units are among the most scaling-friendly analog circuits due to their highly regular architecture and the high proportion of digital components contained as part of their structure, it can be seen that the scaling trend indicates a clear divergence from the pure digital circuits. This divergence is expected to be even more pronounced in the near future, and emphasized by other constraints such as parameter variations and noise limits.

This key observation leads to the conclusion that the monolithic integration of all units on the same silicon substrate may not be the most efficient solution for future bio-electronic systems. More effective solutions such as heterogeneous integrated systems may be preferred in many cases.

4.1. 3D Integration

Some of the newly developing 3D integration and chip stacking technologies offer very promising opportunities for the realization of heterogeneous bio-electronic systems that consist of several layers, staked vertically and interconnected with thru-silicon-vias. This approach has the advantage of choosing the most appropriate fabrication technology for each particular function (such as special surface treatment and micromachining for the sensor layer, low-noise technology for the analog layer, and very high density electronics for the digital / memory layer. Also, the 3D integrated solution can be combined with the possibility of manufacturing a disposable top layer for the bio-sensor components, which can be attached to the lower layers via chip carrier technology. In monolithically integrated bio-sensor systems, the sensor surface has to be cleaned after each use with special treatment (such as oxygen plasma), which also damages the sensitive electronics that resides on the same substrate. The other alternative is to dispose of the chip completely after one use, increasing the overall cost of the system. Replacing only the top layer in a 3D integrated stack largely eliminates these issues and offers a cost effective solution.

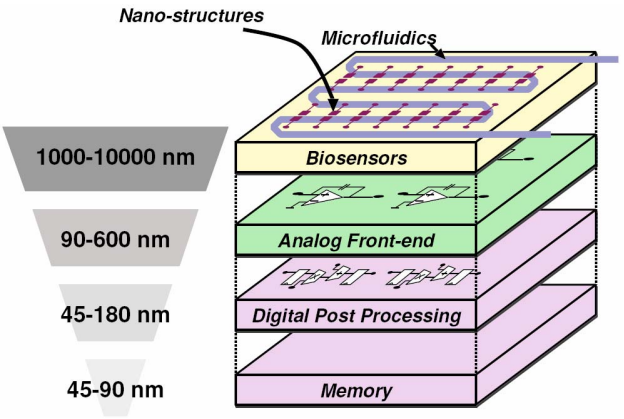

Figure 4 – 3D integration of heterogeneous bio-sensor systems on chip.

4.2. Nano-Bio Integration

Nanotechnologies and nanometer-scale bio-sensor structures are recently emerging to provide applicable solutions in the domain of bio-medical engineering. Physical phenomena which occur in the nanometer range, or related to quantum transports are exploited to create novel transistor and sensor devices. Protein, enzyme and DNA sensors, as well as neural cell sensors have already been reported. If nanotechnologies can be perceived as the ultimate integration goal, interfacing nano-devices with standard microelectronics which is used to drive display and transmission systems remains an open issue. The most obvious application area of nanotechnologies and nanometer-scale structures can be found in the field of specialized / functionalized sensor surfaces and surface coatings.

5. Summary and Conclusions

In this paper, we have reviewed number of important issues concerning bio-electronic systems and interfaces, their design and fabrication. In particular, the advantages of scaling and higher density integration have been discussed, and the potential advantages have been balanced against requirements of low noise design, uniform power density and surface temperature distribution, better component matching, and immunity to parameter variations. It was shown that dealing with these constraints also requires more innovative approaches towards hybrid integration technologies.

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