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Low-Power Architecture for Integrated CMOS Bio-Sensing

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***Abstract*—Integrated CMOS bio-sensing aims to design and to develop complete lab-on-chip systems. Distributed wireless sensors, at the micrometer scale, can be directly interfaced with the surrounding biological environment. In this scenario, the major challenges to be faced are devices size, power consumption, and an effective communication/system overall architecture.**

We propose therefore a complete and effective sensors/system architecture (data acquisition, encoding, and transmission), along with examples and results from preliminary works. The system leverages on an event-based (quasi-digital) paradigm, where analog information is mapped onto the timings of digital address-events, so to improve the communication robustness while retaining the full information content.

I. Introduction and State of the Art

The alliance between microelectronic integrated circuits (ICs) and living biology leads the way into the design and development of cutting-edge bio-sensing devices and smart lab-on-chips [1]–[4]. ICs can directly interact and interface with the biological world, thus the final spatial resolution can be strongly enhanced [5]. The overall sensitivity is also increased as a consequence of the noise reduction. In fact, such devices allows to create read-out circuits directly underneath the sensing electrodes with no need of cables connection to an external instrumentation [1]. Fig. 1 shows the concept design of our proposal: *in vivo* fully integrated CMOS sensors with a biological sensing interface.

A new terminology was recently introduced, LoCMOS — Lab on CMOS, for highlighting the use of CMOS chips for the fabrication of integrated Lab on Chips [6], embedding and coordinating different sensors in parallel on a single device, using low-cost and standard fabrication processes like CMOS technology [3], [7].

The versatility of this approach makes it possible to be efficiently employed in a wide range of different biomedical applications, e.g., infectious diseased detection [2], cell culture monitoring [8], and implantable devices [9]. For example, Nabovati *et al.* developed a hybrid multi-parameter CMOS biosensors capable of monitoring both pH and cell proliferation on the same chip [10].

Several types of circuits and different transduction mechanisms have been reported in literature such as amperometric [11], magnetic [3], or multi-electrodes array sensing and actuating platforms for electro-physiological studies [12]. In addition, capacitive and impedimetric circuits are also a powerful resource for these applications and numerous examples can be found in the literature [7], [8], [10], [13]. It is also worth mentioning that the capacitance of a layer of cells seeded on-chip can provide important data about the physiological and morphological properties of the cells in culture [5]. For instance, Prakash *et al.* were able to monitor the cell viability of bovine aortic smooth muscle cells (BAOSMC), through a capacitive measurement.

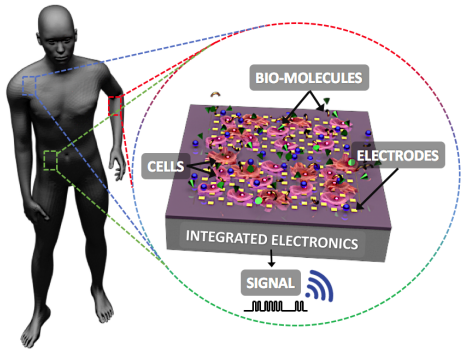

Fig. 1. Concept design of the proposed biosensing solution: a highly integrated CMOS electronics directly interfaced with the biological environment, at the micrometric scale. The potentiality of the system is the ability to generate digital events related to biological phenomena and to transmit them wirelessly for data collection and analysis.

As previously mentioned, the potentiality of this approach allows it to be used also for *in vivo* applications. For example, Guha *et al.* used a capacitive frequency-shift sensor to identify different fat and calcium concentrations in blood, i.e., to characterize artherosclerotic plaques formation in arteries [9]. Following a similar research path and targeting *in vivo* CMOS-based bio-sensors, we believe that it is finally possible to design integrated CMOS bio-sensors at the sub-micrometer or nanometer scale, thanks to the standard CMOS technology consolidating on a nanometer scale, new system architectures inherently minimizing size and power consumption, and CMOS post-processing to directly integrate the bio-interface on top of the CMOS device.

The first point is already an everyday reality. Regarding the second point, about the use for in *in vivo* applications,

standard CMOS materials are not the best choice both because of native oxide formation (e.g., Al, Cu) and intrinsic medium/long term toxicity (e.g., Cu). For these reasons some additional post processing (such as electro- or electroless deposition) could be required to make the CMOS more biocompatible [14], [15]. The third point, i.e., new architectures, is what we want to propose and motivate here. Rather than pushing current conventional architectures to their limits by optimizing constraints and performance, new solutions are available, combining the best of the analog world (continuous information) with the digital one (robustness, minimal power consumption and size). The focus here is on design concepts (Sec. II) and system design (Sec. III) in order to lay down the foundations of a sound and complete framework for wireless networks of *in vivo* bio-sensors (in particular devoted to capacitance and resistance measurements). For each subsystem (including the acquisition, encoding, and wireless transmission), implementation examples and references will be provided and discussed.

II. Event-Based Design Concepts

From a system design engineering standpoint, there are three major challenges in this kind of applications: device size, power consumption, and overall system architecture. These points are not independent, but rather interrelated, making the final system a trade-off among these constraints. As an example, in [16] major constraint is on the device size, so that a common ADC-based architecture is not feasible. The result is a very compact electronic device comprising just one FET [17], with an overall device size of on the order of $\sim$100 µm. The compromise has been mainly on the whole system architecture, with particular regard to the communication aspects. The nature of the involved analog modulation and the absence of the possibility to uniquely identify each node, calls for a beam-forming approach on the interrogator side [18].

In [19] the Compressed Sensing (CS) approach has been applied to bio-sensor applications. In this case the major aim has been power reduction (down to 28 nW per channel), at the expense of the size (estimated to be 93750 µm^2 per channel) and a lossy compression. This means that Percentage Root-mean-squared Difference (PRD) [20], or similar parameters, should be defined and measured/computed to assess the quality of the reconstructed signal. Otherwise it would be tempting to greatly increase the "lossyness" just to further reduce power consumption.

Differently from the cited examples, our aim is to start designing the architecture of the overall system taking into consideration the most important application-specific requirements/desiderata, leveraging on particular information processing/communication paradigms. Ideally, we would like to acquire and transmit analog information in a digital way, at the same time minimizing circuit/device complexity (and therefore physical size) and power consumption.

In this regard, an event-based approach provides an effective and complete framework to support our aim. In this context, we define the Event-Based (EB) paradigm as the acquisition, processing and communication of analog (continuous) information by means of time-distributed digital (discrete) events. With common analog and digital approaches the information is carried by the specific representation of the transmitted signal itself. Here, instead, the information is provided by timings of the signals, and the transmitted signals "mark" the events over time. In this field there are mainly two options, depending on how the events are interpreted: in the first case they are emitted only upon a change in the carried information (neuromorphic approach); in the second one they are part of a periodic signal continuously carrying the related information (quasi-digital approach) [21].

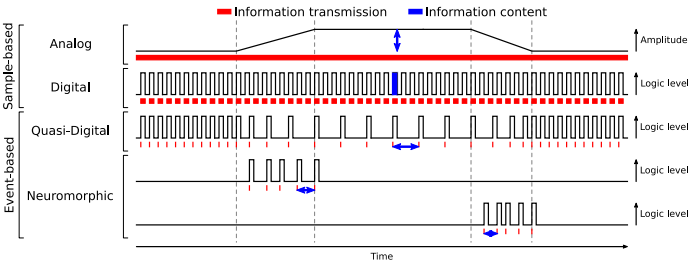

Fig. 2. Asynchronous event-based approach respect to common sample-based systems: it is possible to achieve a significant saving on the transmitted/processed data by mapping the information content on the timings of the transmitted signal (and not onto its representation).

Fig. 2 shows the impact of this paradigm shift, from a sample-based to an event-based, in relation to the information content and the transmitted data. Only by switching to an EB architecture we could potentially have a significant transmission cost saving [22]–[24]. The key difference is on where the information is "mapped". With a traditional approach, the "amplitude" (in a broad sense, being either an analog signal or a discrete numeric, digital, one) represents the information content. With the proposed approach, instead, "time" (again, in a broad sense including the timings of the signals) is the meaningful feature.

As already mentioned, the event based approach can be further split into two sub-categories, the neuromorphic (NM) one and the quasi-digital (QD) one. Although similar, they both have pros and cons [21]. They can be summed up as a huge reduction in transmitted/processed data in the NM case (often at the expense of some information loss mostly due to the non idealities of the implemented circuits). At the same time, they allow to accurately monitor/reconstruct the original signal in the QD case (given that there is no information loss because the information is continuously carried by a stream of events). The other important difference is in the implementation of the corresponding read-out circuits. In the NM case they usually are analog (and often sub-threshold) CMOS circuits, requiring an analog memory element to detect changes. In the QD case they are mostly mixed analog/digital or even fully-digital designs, allowing for more compact/smaller (and simplified) circuits.

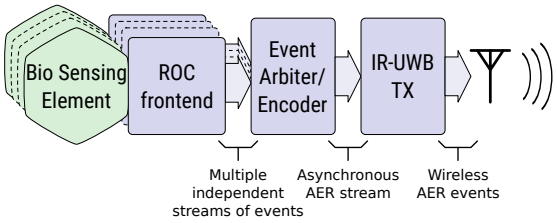

Fig. 3. Architecture overview of a complete quasi-digital system, comprising a front-end directly connected to the bio-sensing element and generating digital events, which are then encoded into address-events and wirelessly transmitted.

III. Event-Based Sensing Architecture

Fig. 3 shows an example of a complete QD sensing system [25]. In this case it comprises multiple read-out-circuits, in order to show how different sensing abilities could be combined together. Each of those Read-Out Circuits (ROCs) generates a stream of digital events as a periodic signal whose timings (e.g., period, duty-cycle) represents the information content. Each event could be marked by a rising/falling edge (or both, depending on the specific system). All the ROCs are independent and asynchronous, and the resulting streams of events are merged and "serialized" by the arbiter. The associated encoder tags each event with a very short data packet, just made of the identifier/address of the event source, then sent to the wireless transmitter (or a wired connection, if allowable).

The idea of using just the identifier or, better, the address of the event source as the representation of the event itself (Address-Event Representation, AER) has already been proven to be an effective way for inter/intra-ICs interconnections [26] or inter/intra-systems communications. It could be implemented in both wired [27] and wireless [25] systems. The overall communication architecture has a push approach, different from a more conventional pull approach where each sensor is interrogated upon need (thereby requiring a more complex protocol). At the same time, being inherently asynchronous (no assumption is made on who, when, and why has to transmit), automatically solves the problems of dealing with sensing systems having different time constants. On the contrary, in sample-based systems everything should be designed according to worst case of the Nyquist-Shannon sampling theorem. Different policies, in case of two colliding events, could be implemented, mainly either dropping one event or slightly delaying one event before sending it [25].

Combining these features of quasi-digital systems with an AER communication, eventually avoiding events misunderstandings by properly designing the wireless protocol [25], allows to solve the complex task of gathering the data from multiple source by implementing, for example, beam-forming for sensors alignment [18]. In particular, the Impulse-Radio Ultra-Wide-Band (IR-UWB) technology is well suited for wireless EB communication, due to the strong similarity between its radio pulses distributed over time and the quasi-digital approach [22], thereby making it an effective solution for transmitting bio-signals [24] or AER events [25].

Considering the design of the ROC, different solutions are possible, depending on the specific application, for example trading off flexibility for complexity or power consumption. As an example, it is possible to combine an operational amplifier with digital inverters so to convert resistance into frequency [28]. This greatly improves the measurement range (50 kΩ–3 GΩ), targeting nanosensing applications, and accuracy (0.8 %), without sacrificing area (0.005 mm^2) and power consumption (142 µW). It is also possible to design miniaturized and effective all-digital ROCs made out of Commercial Off-The-Shelf (COTS) components: in [29] a capacitive to frequency converter was designed around a ring oscillator comprising just six inverters (including an output buffer). Consuming 370 µW, it is also a good example of a transducer/ROC co-design in order to better suit the target application, suggesting that further narrowing and integrating the design of both the biological interface and microelectronics could greatly improve the performance. The same idea has been adopted in [30], where the integrated design allowed to add, on top of the proper ROC, a digital circuit to both control the data acquisition and to provide numerical results (for an easier interfacing with SPI-like systems) while still maintaining a very low power consumption (1.84 µW). It is a good candidate for embedded bio-sensing applications: it has a very small size (few digital gates just for the ROC itself, 17459 μm^2 the whole implemented circuit), fully digital nature (higher noise immunity), robustness to both temperature and power supply variations (process voltage temperature, PVT, robustness in general). It is also possible to combine measurements of both resistance and capacitance into the same ROC, hence providing a complete impedimetric sensor, for example by means of an integrated resistance/capacitance-to-time converter. The sensor interface in [31] provides at the same time, for each cycle of the output QD signal, both the information on the measured resistance (T_{ON}) and capacitance (T_{OFF}). The design is not fully-digital, but still the analog part is minimal, showing good performance overall, both in terms of measurement dynamic ranges (three orders of resistance magnitude, seven orders of capacitance magnitude) and average (experimental) error (0.79 %). Furthermore, it allows the parasitics estimation, and has very small area (0.003 mm^2) and power consumption (14.82 µW).

IV. Conclusion

The need for bio-sensors co-designed integrated with standard CMOS microelectronics is an emerging opportunity for understanding and monitoring biological phenomena. Moreover, it can potentially make *in-vivo* applications portable, hence unlocking them from the need of bulky laboratory equipments. A key aspect is the design of full-fledged sensor platforms integrated with multiple sensors that meet at the same time the requirements of miniaturization, low power consumption, and effective/efficient overall system/communication architecture. With respect to similar solutions (e.g., [9]), the aim is to decrease the device size and power consumption of three orders of magnitude, towards sub-

μm (nm) and μW (or nW) scales, respectively. With respect to alternative architectures (e.g., [16], [19]), the goal is to allow accurate and precise (not lossy) measurements and the deployment of effective and scalable networks of sensors.

We propose therefore a sound and complete event-based approach and system architecture to read-out, encode, and transmit resistance and capacitance measurements. It is based on the quasi-digital paradigm, where analog information is represented by the timings of digital events. This approach allows for precise and accurate measurements while minimizing device size, power consumption, amount of exchanged data; furthermore, mixed analog/digital or fully digital read-out circuits have proven to be effective solutions. The ease of portability on new microelectronics technologies, leveraging on future CMOS nodes, is what makes all-digital sensors promising to further minimize both device size and power consumption, perhaps the two most demanding constraints in bio-sensing applications.

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