Charge and Current Measuring Electronics for Bio-Medical Applications

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The motion of electric charge is involved in several processes such as an electrochemical reaction taking place at a metal/electrolyte interface, the measurement of electrical impedance of a sample between a couple of electrodes or the absorption of a photon in a semiconductor and its conversion into an electron/hole pair (Fig. 1). Consequently, the quantification of the amount of charge collected at a sensing electrode is relevant in a broad variety of applications. This brief tutorial focuses on the challenges and techniques of measuring charge, primarily at the micro-scale, with application in the bio-medical field.

Measurement Challenges

The quality of a charge measurement is assessed mostly in terms of accuracy and resolution. Accuracy is the most relevant feature from the metrological point of view, and it is typically addressed by means of calibrations and control of polarizing

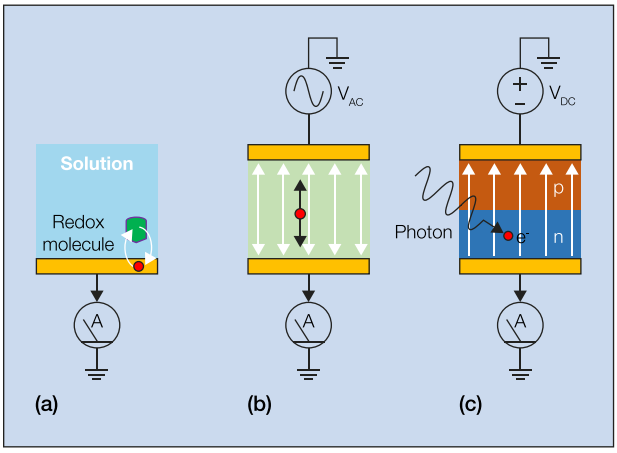

Fig. 1. Common mechanisms involving the measurement of charge. (a) Electrochemical detection of redox molecules; (b) Impedance sensing; and (c) Electron-hole generation upon absorption of a photon in a depleted region of a semiconductor.

effects and drifts, such as those due to temperature sensitivity. For example, gain and offset non-idealities of the acquisition chain (converting the input charge into a digital number and thus, being composed of both analog and digital blocks) are commonly corrected by simple linear equations. Non-linear errors can be corrected through extensive calibration and by using look-up tables or higher order polynomial functions. Furthermore, in the presence of multiple acquisition channels, cross-talk among them has to be assessed and minimized.

On the other hand, resolution represents the most important feature from the sensing point of view. It is defined as the minimum change of the measurand that can be detected, and it is set by the level of fluctuations affecting the measurement. Fluctuations hampering the measurement of an electrical quantity can have multiple origins. For the sake of clarity, in this context we will define *interferences* those undesired signals produced by external origins that couple with the measurement system such as RF electromagnetic interferences (EMI) picked-up by the conductors in the system acting as antennas. Interferences can be reduced by using grounded Faraday cages to shield the system from irradiated EMI or filters. Instead, we call *noise* the random fluctuations superimposed to the electrical quantities inside the measuring circuit due to intrinsic internal sources, such as the statistical behavior of electrons inside the electronic components of the system. Noise is unavoidable in electronic circuits, and its impact can be minimized, often made negligible with respect to other sources of uncertainty, by proper design techniques. Noise should not be analyzed in absolute terms but always in comparison with the signal level. Thus, the primary figure of merit in the design of such measuring systems is the signal-to-noise ratio (SNR), and its maximization is one of the major design criteria, especially of the first analog stages of the chain. In fact, the total noise present at the end of the acquisition chain is the combination of each individual source of noise. However, since the noise introduced at the beginning of the chain will experience the same

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amplification of the input signal, the most relevant part of the chain is the front-end, and noise is conveniently referred to the input of the chain to be directly comparable with the input signal. Noise is treated as a statistical quantity with zero mean and it is frequency dependent. It is described by its spectral density, whose integral across the measurement bandwidth sets the RMS level of the fluctuations. This relationship highlights the first message: the wider the measurement bandwidth, the higher the noise. Thus, filtering and signal shaping, both in analog and digital domains, are pivotal in reducing the bandwidth to the minimum required to track the signal dynamics. Filtering strategies are different for current sensing (continuous signals) and charge pulses (discrete packets). In either scenario, maximization of the SNR is pursued both by looking for solutions to increase the numerator and adopting counter measurements to decrease the denominator.

Applications

High-resolution current measurements find several applications in the bio-medical field, especially in the area of biosensors (Fig. 2). In most cases, the current flows through an electrochemical interface between an electrode and an electrolytic (saline) solution that hosts a biological entity. Charge can be hopping between molecules in solution and a properly biased metal in the case of redox reactions (Faradic interface) or simply induced in the case of a non-Faradaic interface (i.e., with ions in solution being attracted in the double-layer region of the interface). Thanks to the advancements in microfabrication of planar electrodes and microfluidics, it is possible to fabricate structures in the micrometer size range, matching with the dimensions of individual biological entities such as biological cells [1]. Focusing only on the bottom end of the size range, i.e., on the sub-micrometric scale, we can mention the amperometric detection of molecules, in particular of neurotransmitters and glucose, patch-clamp and nanopores techniques, and affinity biosensors.

Electrochemical detection of molecules is a label-free approach opposed to marker-based techniques, such as optical fluorescence, that require the chemical linking of a marker (the fluorophore) to the molecule for its detection and quantification. Clearly, the avoidance of the labeling step represents an advantage in terms of the sample preparation process. From

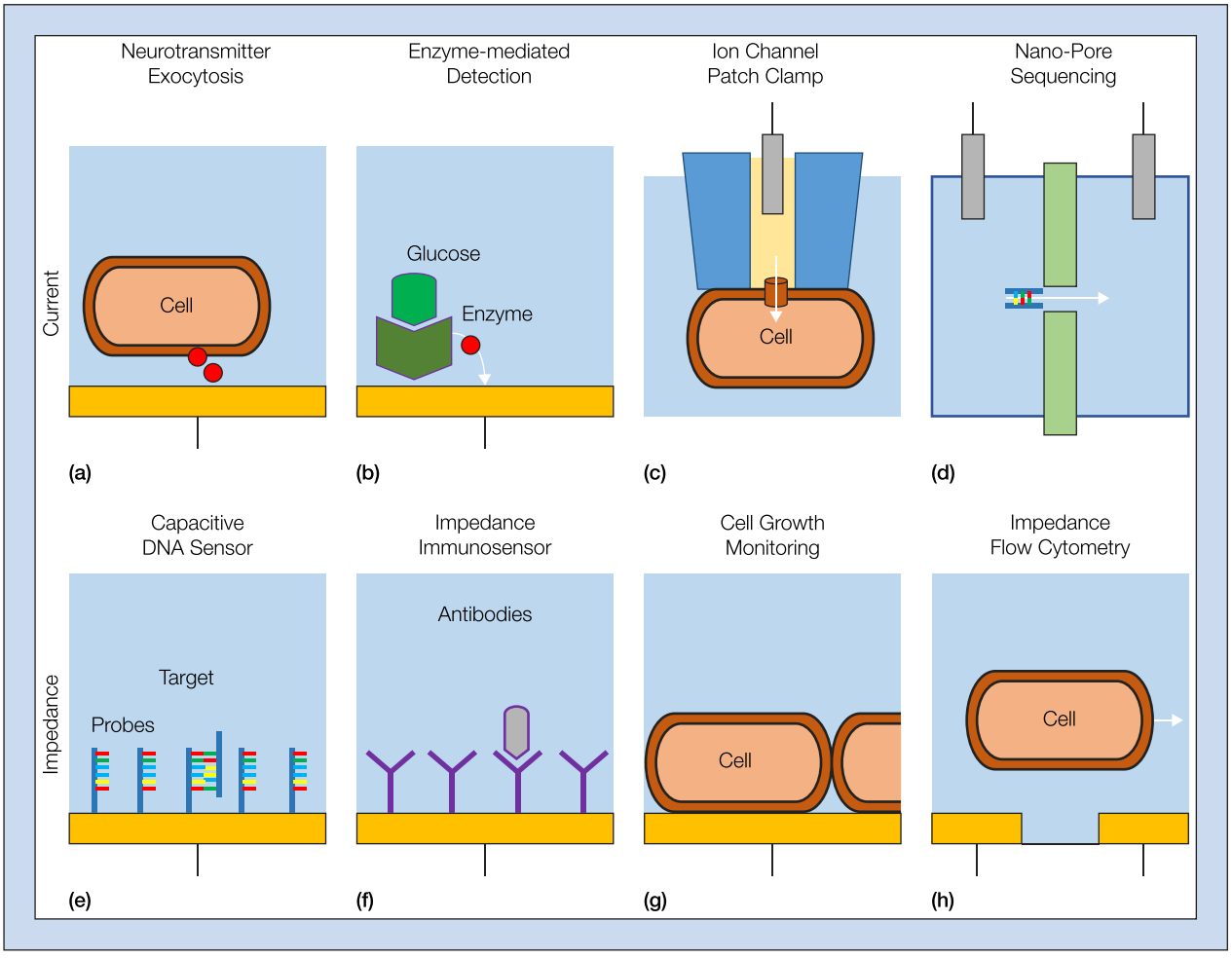

Fig. 2. Examples of current measuring applications in bio-medicine. (a) Direct detection of redox molecules and indirect detection; (b) mediated by an enzyme; (c) tracking current flowing through an ion channel in patch clamp; or (d) nano-pore. Impedance detection of: (e) DNA strands; (f) antigens binding to antibodies; (g) cells growing on planar electrodes; and (h) flowing in a micro-channel.

the system point of view, electrical detection is largely preferred with respect to the optical one requiring light sources, filters and optical components. However, labeling provides the highest (molecular) selectivity, whereas amperometry can be adopted only when there is no risk of interference (in the electrochemical sense) in the detection.

The majority of neurotransmitters (such as dopamine, adrenaline and other catecholamines) are redox detectable. Thus, their concentration can be directly measured by simply collecting the electrochemical current by means of a small electrode biased at the potential corresponding to the reduction or oxidation potential of that redox reaction and placed in close proximity to the release point of the molecules. In the synapse, the junction between two neurons, these chemical messengers are released from the transmitting cell through exocytosis, a mechanism in which a vesicle containing about $5{\cdot}10^4$ molecules fuses with the cell membrane, thus expelling them in the synaptic cleft. This process lasts about 1 ms, producing a current pulse of about 10 fC / 1 ms = 10 pA. The detailed shape of this current pulse provides relevant information about neuro-pathologies [1]. However, measuring a current with picoampere resolution and kilohertz bandwidth is challenging from the electronics point of view, since it is at the limit of standard topologies [2].

Even if the molecule does not support a redox, in some cases it is possible to detect its concentration by an indirect amperometric technique, thanks to the action of a catalyst. The most popular example, due to the relevance of diabetes, is the case of glucose, whose concentration in blood has to be measured several times per day by diabetic patients. Glucose is not redox active, but when it binds with an enzyme (*glucose oxidase*) that catalyzes a transformation of glucose and oxygen into gluconic acid, hydrogen peroxide is also produced. The latter byproduct of the reaction is in turn redox detectable and allows a quantification of glucose concentration from the area of the current pulse (tens of µA for a few seconds for typical concentrations of glucose of a few g/L). Interestingly, the enzyme survives on the shelf in dried state immobilized on the electrode in the disposable cartridge and it is activated when a droplet of blood is placed on the electrode for a test.

Picoampere current resolution with kilohertz bandwidth is also required in *patch clamp*. This is a technique developed in the late 1970s in the field of electrophysiology, for which the Nobel prize was awarded in 1991 to Neher and Sakmann. It allows the electrical activity of an individual ion channel to be investigated. An ion channel is a trans-membranic protein crucial for the operation of neural cells: when open, it allows the flow of a specific ion (Ca, Na, K, Cl) through the cell membrane depending on the concentration gradient, producing a current pulse and, thus, the propagation of the action potential along the cell. This technique consists in isolating a single channel by capturing a fragment of a cell membrane inside the tip of a glass pipette whose position is manually controlled by a human operator with a microscope. The pipette is filled with an electrolyte acting as liquid electrode contacting the external side of the channel, while the inner side is contacted through the saline medium hosting the cell (since several channels are simultaneously open). The response of the pore to voltage and chemical stimulation can be studied in detail by means of current recording.

In the last decades, solid-state devices analogous to ion channels and called nano-pores have emerged as tools to dynamically investigate molecules, among which DNA is the most relevant one. The presence in solution of a molecule of nanometric dimensions can be electrically detected with a nano-pore structure: a nanometric orifice is opened in a membrane separating two reservoirs filled with an electrolyte. An artificial nanometric pore can be drilled with good repeatability in micrometer-thick silicon-based membranes with clean-room instrumentation such as focused electron or ion beams. Pores of natural origin, such as α-hemolysin (a trans-membranic macro-molecule with 1.5 nm inner diameter) can be also used. Each reservoir is contacted with an Ohmic electrode (such as Ag/AgCl) in such a way to measure an ionic current, whose value is set by the liquid conductivity and the geometry of the pore. When the pore is temporarily blocked by the translocation of the molecule (driven, for instance, by an electric field in the case of charged molecules), the measured current drops down, close to zero. This represents a nano-scale version of the Coulter counter, where a micro-scale orifice is leveraged to count and size biological cells at high-throughput. From the amplitude and duration of the current pulse, it is possible to infer the size of the molecules. This tool is perfectly suited for DNA analysis: a macromolecule with a negative charge (about one electron every three bases) and the diameter of the double-strand chain of 2.5 nm. Beyond measuring the chain length, high-resolution current sensing can enable sequencing of the DNA molecules, i.e., identification of the sequence of individual bases that represent the genetic information coded in the chain. Different from the application discussed above and requiring picoampere resolution with kilohertz bandwidth, DNA sequencing would require megahertz bandwidth, not compatible with picoampere noise floor and thus demanding for alternative approaches spanning from slowing down the translocation to adding additional sensing mechanisms such as tunneling electrodes.

Single-molecule specificity can be achieved by leveraging the bio-chemical affinity of natural macromolecules such as enzymes, antibodies and nucleic acids, which bind very selectively with matching molecules. The receptor is chemically immobilized on a substrate on which the sample flows and the target molecule can be captured. A transduction mechanism with nano-scale sensitivity is then employed to convert the conformational change of the molecular complex, after binding, into an electrical signal. The most promising approaches are magnetic, optical (using for instance, micro-ring resonators functionalized with probes), and electrochemical ones, all requiring a current-sensing readout.

The detection scenarios discussed so far refer to a condition where the analytes to be identified are present in physiological samples, typically extracted from the body (such as blood, urine, saliva) and analyzed *in-vitro* or by the application

of electrodes *in-vivo*. If the marker of the pathology is not accessible in external samples, a radioactive tracer, whose concentration in the body can be imaged from outside by means of emission tomography techniques (PET and SPECT) thanks to the penetration of gamma rays, can be molecularly attached to the probe molecule and injected in the patient.

Circuits

As the majority of modern instruments are based on a digital processing device (such as a microcontroller or FPGA [3]), the acquisition chain of a charge measuring system is composed of an analog front-end stage and an analog-to-digital converter (ADC). I will follow the signal path along this chain and will discuss highlights and relevant applicative examples for each block (Fig. 3). Let us start from the input. Since the ADC typically operates in voltage mode, the purpose of the input stage is to convert the input charge into a voltage. This could be easily performed by storing the charge on a capacitor C_D, often associated with the structure of the device collecting the charge. The smaller is the capacitance, the larger is the conversion factor. Analogously, to convert the input current into a voltage, a resistor R_C could be used. However, the main limitation of this approach is due to the sensor parasitic impedances in both cases. The optimal solution to these issues is the adoption of negative feedback. A classical active scheme based on an operational amplifier and a passive feedback branch, so called transimpedance amplifier, provides a very low input impedance at the input (virtual ground) that is suitable to read the input current and a very linear conversion factor from current/charge to output voltage. The feedback impedance can be resistive or capacitive. When analyzing the noise performance of the transimpedance stage (see [2] for details), it becomes apparent that the dominant noise sources are the thermal noise of the feedback resistance and the input equivalent noise of the operational amplifier which is differentiated across the input capacitance and thus dominates at high frequency. In order to reduce noise, the value of the feedback resistor can be increased. This results in a decrease of the amplifier bandwidth that can be compensated, for instance, with zero-pole cancellation stages. The feedback resistor can be avoided by adopting a purely capacitive feedback. This is the typical configuration to read charge packets that are integrated in the feedback capacitance, thus producing steps at the voltage output. In order to avoid the saturation of the stage due to input dc currents, such as unavoidable leakage currents, a reset mechanism is needed. Discrete-time (periodic reset) or continuous-time (with additional feedback branches) can be implemented, depending on the constraints of the application [2]. Continuous reset is more suitable for current sensing, avoiding dead-time during the periodic reset, which instead is suitable for charge sensing.

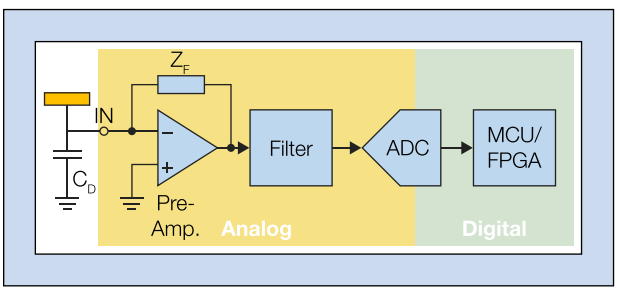

Fig. 3. Typical architecture of a current readout chain composed of an input transimpedance amplifier, an optional shaping filter and an ADC allowing data sampling and processing by a digital embedded device.

Once the impact of the feedback resistor is addressed, it is crucial to minimize the value of the total capacitance connected at the input node: it includes the amplifier input capacitance, the feedback capacitor and the parasitic capacitance associated with the sensing electrode and its connection to the preamplifier. There are three strategies for the reduction of the input capacitance. The first is the reduction of size of the charge-collecting electrode, whose capacitance typically scales with the area. Unfortunately, the collected current signal also often scales with electrode area, especially in electrochemical applications. Two actions can be implemented to mitigate the decrease of the signal: (1) an active mechanism drives the molecules to be detected towards a small sensing electrode (analogous to the case of the electric drift used in Silicon Drift Detector to drive, in a depleted semiconductor, the charge generated by the absorption of a photon or by an electron towards a small collecting anode [4], thus combining large detection area with small sensor capacitance); and (2) splitting the sensor area into small pixels readout by parallel channels, whose outputs are then summed to reconstruct the signal [5]. The latter approach provides a SNR improvement at the expense of increased area and power dissipation, proportional to the square root of the number of parallel circuits since the signals combine linearly, while the noise of the individual channels, being uncorrelated, sum in power. Splitting a large sensor into subpixels can be also beneficial when the rate of incoming charge packets is large (e.g., millions of photons per second in x-ray and gamma-ray detection), again at the price of parallelizing the whole acquisition chain up to the digital processing stages. In this context, it can be highlighted how analog processing, especially when leveraging microelectronic integrated circuits, though less versatile, is typically more compact and thus, scalable compared with the digital one, often offering comparable performance [6].

The second method is the reactive canceling of the capacitance by means of an inductor [7]. This is a simple and effective solution, though limited by the properties of the resonance: the noise improvement is limited to about one order of magnitude due to the quality factor of the inductor and is suitable only for narrow-bandwidth single-frequency (the resonance frequency) measurements such as impedance time tracking at a single frequency.

The third approach consists in the reduction of the distance between the electrode and the input node of the amplifier. This is mandatory when the stray capacitance of this interconnection is the dominant source of noise. Miniaturization of electronic components and boards enables more compact realizations that can be placed very close to the sensing electrodes. Such miniaturization trend is aligned with similar ones

in microfluidics and microfabrication of electrodes. The ultimate level of compactness is the combination on the same chip of the sensing electrode with the integrated circuits of the preamplifier. Although sometimes a semiconductor substrate is not ideal for hosting electrodes due its parasitics [8], on-chip electrodes are optimal in terms of shortening connections, and thus in terms of achievable resolution (as in the case of capacitive detection of dust particles with zeptofarad resolution [9]). Furthermore, monolithic integration and on-chip sensing enable cost reduction, thanks to mass production, ultra-compact devices and integration of smart functionalities, pivotal in several paradigms that span from wearable/ingestible devices up to Internet of Things wireless environment sensing nodes. Some open challenges in this area concern packaging, lack of standardization and the combination of design toolboxes and materials employed during the chip fabrication, as usually materials used in bio-electrochemical detection (gold, platinum, silver) are different from those used in microelectronics (copper, aluminum, tungsten).

In parallel to the important efforts for minimizing the noise illustrated above, sometimes it is also possible to improve the SNR by acting on the signal. One example in bio-chemical detection of molecules, in particular neurotransmitters, is redox cycling. With this technique, the molecule to be identified undergoes a series of alternate oxidation and reduction reactions in contact with two combs of interdigitated planar electrodes, spaced with sub-micron distance to cope with the diffusion length of the molecule and properly biased so that more than a single electron is exchanged per molecule. In this way, for every detected molecule, the current pulse is increased by a factor ~10. Another example concerns the widespread diffusion of Silicon PhotoMultipliers (SiPM). These are the solid-state equivalent of PhotoMultiplier Tubes (PMT) and consists of large arrays of individual single-avalanche photo diodes put in parallel in order to combine single-photon sensitivity with a current signal whose peak amplitude is related (non-linearly) with the amount of photons impinging on the detector, thus granting good dynamic range. The avalanche mechanism provides a multiplication of the charge that allows the the signal to be amplified. Unfortunately, from the noise point of view, spurious dark counts due to thermally generated electrons triggering the avalanche need to be considered as well. Another important advantage of SiPMs with respect to PMTs is insensitivity to the magnetic field that has fostered the realization of gamma cameras for nuclear imaging (PET and SPECT) compatible with magnetic resonance for multi-modal imaging [10], simultaneously combining anatomic details with molecular specificity of the radiotracer bond to an affinity molecule and enabling intrinsic alignment and attenuation correction.

The readout of SiPMs represents a very critical case for negative feedback. In fact, the combination of large device capacitance (up to a few nanofarad for pixels with a size of a few millimeters) with stringent requirements in terms of bandwidth (above 10 MHz), low input impedance (below 10 Ω) and large dynamic range (current up to milliampere) would require extremely high gain-bandwidth products to grant stability. An interesting solution proposed to address these challenges is the adoption of positive feedback: a current conveyor based on a positive loop gain (slightly below 1) de-multiplies the input current to be integrated in a gated integrator with a time window matched with the duration of the current pulse [11].

Impedance

Impedance detection represents a specific case of current sensing, with vast application in industry and, in our context, for instance, in monitoring of biological cells from eukaryotic ones [12] to bacteria [13], from organs and tissues down to single-cells at the micro-scale level, in static and dynamic conditions. From the metrological point of view, in addition to the current sensing chain, which remain unaltered, two more blocks must be considered: the stimulation generator and the demodulation stage (Fig. 4). The voltage source applies a time-varying excitation potential V_{force} to the unknown impedance Z_S to correspondingly measure the current whose flow is forced in the sensor. If impedance is measured at a single frequency, the stimulation is commonly a sinusoidal one (generated by an oscillator or a DDS), while, if multiple frequencies are probed simultaneously, a more complex stimulation is applied, typically produced by an arbitrary waveform generator (i.e., a DAC fed with the digital samples of the waveform). The electronic components in the source introduce additional noise. The source voltage noise is converted into a current noise at the input of the transimpedance stage divided by the magnitude of the measurand. Thus, its impact depends on the sensor and is negligible for large values of its impedance. In either case, a very effective way to get rid of this noise contribution is to leverage a differential sensing scheme [14]. In a differential configuration, any non-ideal behavior of the source (noise and drifts) becomes a common-mode signal and it is canceled by the difference operation. A differential configuration can be realized by an intrinsic symmetry of the device or by adding a dummy impedance branch, properly driven. The difference can be taken in current mode (Fig. 4b) or in voltage mode (Fig. 4c). The better the matching between the twin branches, the better the mitigation of this noise. A recent example of the potential of this approach consists in the impedimetric counting with 3 μm micro-electrodes of single beads of 800 nm diameter functionalized with antibodies for Dengue virus detection below 100 pg/mL [15].

The extraction of the complex impedance values from the sinusoidal signal can be realized in different ways. From the SNR point of view, the use of synchronous demodulation is the optimal choice. This technique, very common in sensing with the name of *lock-in* for shifting the sensor signal in a region of the spectrum where the noise of amplification chain is minimal, is based on the multiplication of the detected signal by a reference sinusoid in phase or quadrature with the stimulation one. Such multiplication can be performed either in analog or digital domain. The replica of the spectrum at twice the sensing frequency is then removed by a low-pass filter that

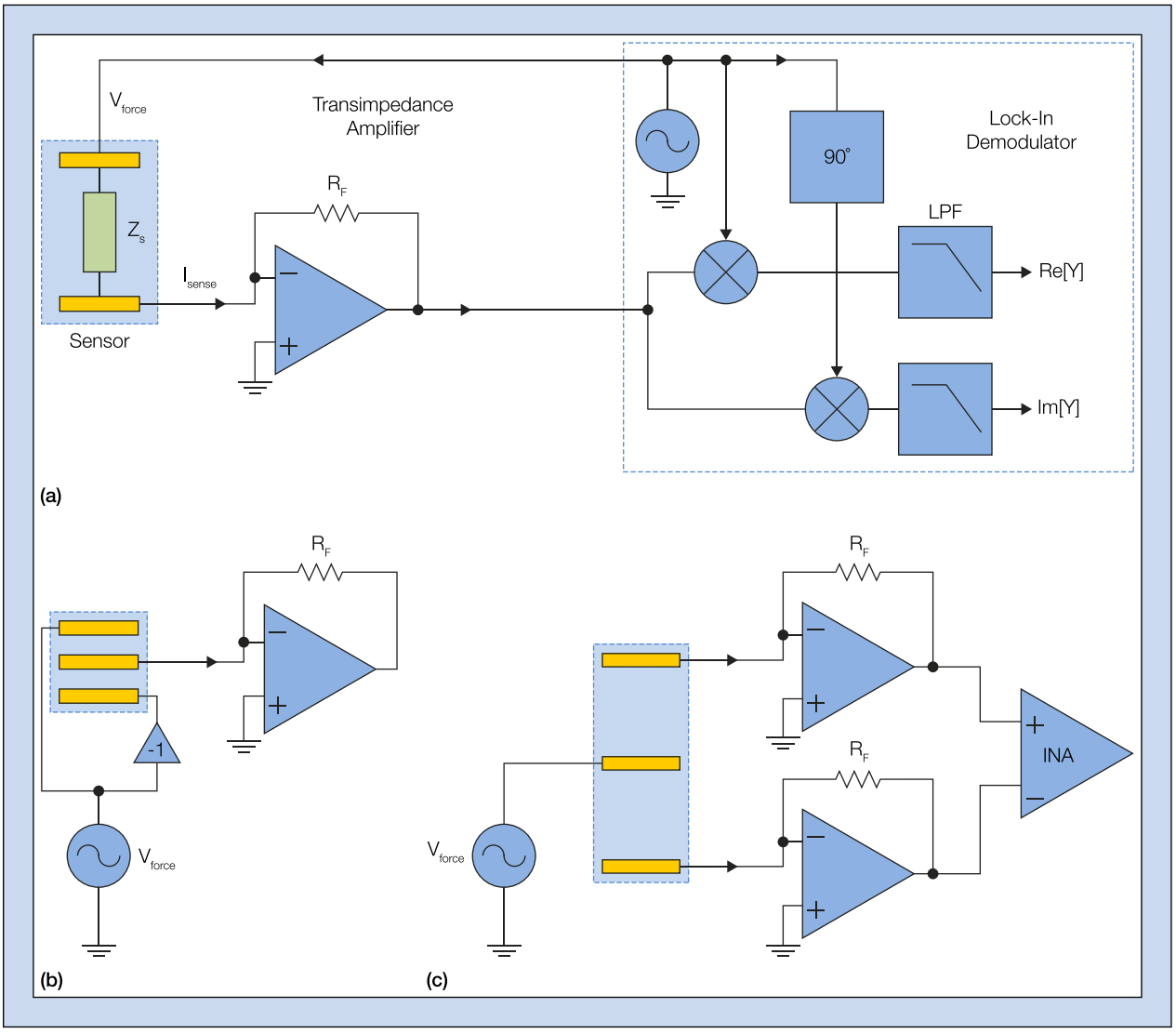

Fig. 4. Configurations for impedance measurement with a current-sensing input. (a) Lock-in synchronous demodulation; Differential schemes with (b) current or (c) voltage difference.

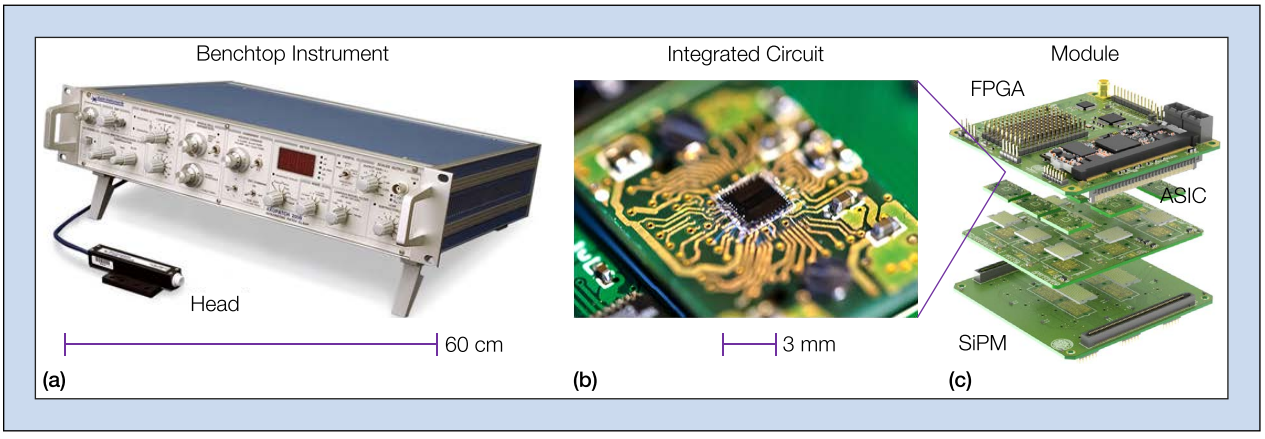

Fig. 5. Examples of miniaturization of current-sensing instrumentation. (a) Bench-top state-of-the-art Axopatch 200B (Molecular Devices) with capacitive feedback preamplifier head for patch clamp; (b) 16-channel GAMMA ASIC for analog processing of SiPM currents for gamma-ray imaging and spectroscopy [11], featuring (c) 144 independent readout channels in a compact module.

acts a self-tuned narrow band-pass filter and allows the optimization of the SNR under the classical trade-off between resolution and speed.

Finally, it must be highlighted that, so far, we have considered additive noise. However, in some cases multiplicative noise has to be considered as well. This is the case of the low-frequency fluctuations of the voltage references of ADCs and DACs used in digital lock-in amplifiers. A ratiometric architecture based on high-frequency switching between two parallel independent channels has been proposed to address this effect, improving the ultimate noise performance in impedance detection of more than an order of magnitude [16].

Conclusions

Current and charge measuring circuits are ubiquitous in bio-medical applications and are pivotal in the readout of electrochemical, optical and nuclear instrumentation. Noise reduction represents one of the main analog design guidelines, and co-design of the device (electrodes), interconnections and front-end circuit is needed for optimization of the performance. Microelectronics can offer valuable advantages in terms of miniaturization, as shown in Fig. 5. In addition to miniaturization and multi-disciplinarity, another relevant trend that has been consolidating in research and industry is the combination of multiple sensors and the fusion of heterogeneous data with the purpose of addressing complex diagnostic challenges. The renewed popularity of artificial intelligence is further pushing this trend, offering efficient mathematical tools and hardware/software techniques to automatically process large amounts of data, such as those generated by the ongoing pervasive sensorization of environmental and health care monitoring systems.

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