

# How Advances in Bioimpedance Spectroscopy Drive Innovation in Portable Devices

Fulvio Bagarelli, Technical Leader

## Abstract

By leveraging bioimpedance spectroscopy, scientists and doctors can now monitor the effectiveness and pharmacokinetics of drug delivery via transdermal applications. This article looks at how this technology works in detail—from its basic principles to the characteristics of human dermal tissue, as well as the technologies available for implementing portable monitoring devices.

## What Is Bioimpedance Spectroscopy?

Impedance spectroscopy is a measurement technique used to characterize the electrical properties of a generic medium. It measures the impedance, or resistance to alternating current flow, as it varies with frequency—providing fast and cost-effective insight into material characteristics that are otherwise difficult to assess. The impedance measurement is based on a ratio of two measurable quantities, voltage, and current. To measure the impedance, it is necessary to perturb the system by applying an electrical potential. Two options are possible for this perturbation: (a) Use an AC excitation voltage and measure AC current response; (b) use an AC excitation current and measure AC voltage response. If the applied voltage or current is a small signal, the system can be considered linear. There's no frequency shift in the response signal. This means that all the alternating quantities can be linearly related and described just by their amplitude (that is, magnitude) and phase, then they are well represented by complex numbers in the frequency domain.

Several physical systems can be characterized by their impedance pattern and the measurement method is generically defined as electrochemical impedance spectroscopy (EIS). EIS is applied in a variety of use cases including in the measurement of electrochemical cells (batteries), in gas or liquid sensing, and in the analysis of biological tissues. The latter is also known as bioimpedance spectrometry and describes the response of a living organism, or part of it, to an externally applied electric current.

In the past decade, bioimpedance spectroscopy has become popular in some traditional applications such as human body composition analysis, hydration measurement, galvanic skin response (GSR), or electrodermal activity (EDA). In addition to this, there is a new set of innovative emerging techniques that apply bioimpedance concepts to pharmacodynamics. One promising line of research in this latest topic is related to medicine delivery analysis.

One notable use for bioimpedance spectroscopy in the field of pharmacodynamics is the noninvasive real-time monitoring of drug bioavailability after transdermal delivery.<sup>1</sup>

## What Is TMD?

Transdermal medicine delivery (TMD) is a method of delivering drugs by applying a medicine mix through intact skin. This method has many advantages over other conventional routes of medicine delivery. It is noninvasive, painless, and systemic, avoiding all the issues related to needle pricks or more invasive biopsies that require local anesthesia. The TMD applies a partial negative pressure to a large and healthy portion of the skin surface disrupting the epidermal-dermal junction, and forming a blister filled progressively with interstitial fluid and serum. The medicine penetrates the various layers of the epidermis passing through the corneum stratum, the outermost layer of the skin, and reaching the inner tissues without accumulating into any of the intermediated layers. Systemic absorption happens once the medicine reaches the inner dermal layer, making it available via dermal microcirculation through the blood vessels. Topical and TMD methods have some advantages over systemic administration routes. These methods offer more uniform and smoother drug delivery profiles, which reduce the risk of toxic side effects by avoiding medicine concentration peaks. Finally, this technique minimizes systemic uptake and concentrates the action at the site of delivery.

There are many different physical principles used to enable skin permeation and facilitate the transport of the pharmacological compound across the skin in TMD: chemical enhancers, diffusion, absorption, thermal energy, vibrational energy (ultrasound), electrostatic force (electrophoresis) or electric field (iontophoresis), and even radiofrequency energy. Sonophoresis uses ultrasounds to transport topical treatments from the stratum corneum to the epidermis and dermis. On the other hand, Iontophoresis and electroporation make the skin permeable to medicines by creating pulsed electrical fields that open pores in cell membranes using low and high voltage respectively.

All these techniques enable the delivery of various medicines without any incision of biological tissues. Some of these methods have been standardized in daily clinical applications with treatments like patches and ultrasonic delivery systems for hormone therapy, contraception, or opioid analgesia, while others have demonstrated their effectiveness only in laboratory test studies. Today more than ever, medical research is experiencing a hype focused on the development of simple needle-free systems for vaccination purposes.

Since impedance measurement is a minimally invasive method to detect the amount of medicine delivered, it represents a perfect match with the noninvasive TMD technique. This is in contrast with traditional methods that require needles or more invasive analysis techniques.

Bioimpedance analysis applied to TMD offers medical researchers a wide range of investigation strategies, including the monitoring of insulin delivery in diabetic patients.

### Impedances Involved in the EIS Measurement

The proper interpretation of the electrical measurement applied to the human body must pass through electrical modeling of its various sections. Going down to the very basic element of each model, the resistance of a biological tissue must be defined. Biological tissue can be considered in first approximation as a layered electrolyte containing densely packed cells that can be characterized by ionic conductivity and dielectric relaxation phenomena. This is because the mechanism of electric conductivity in the body involves ions as charge carriers. Several characterizations show that applying a DC to the human body will flow through the extracellular fluids (ECF). If the spectral content of the current is enriched with high frequency components, then the current will flow through both ECF and intracellular fluid (ICF) as well.

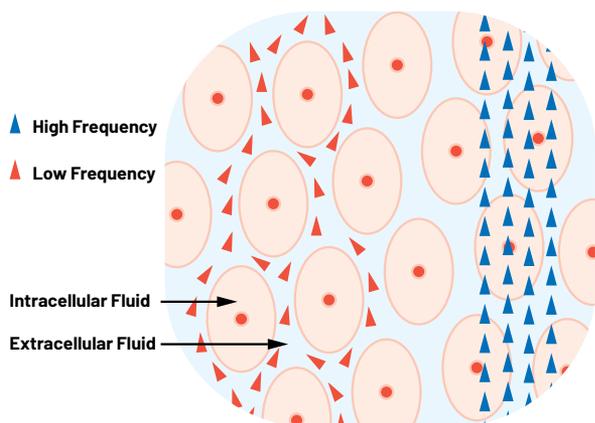


Figure 1. Electric conductivity of human body tissues.

Thus, as a first approximation, the electronic circuit that emulates the behavior of the human body can be modeled as a resistor  $R_i$  (intracellular resistance) in series with a capacitor (cell membrane capacitance), all in parallel with another resistor  $R_e$  (extracellular resistance) as shown in Figure 2.<sup>2</sup> The impedance range of the human body goes from 10 k $\Omega$  to 1 M $\Omega$  at low frequencies (around 1 kHz) and from 1 k $\Omega$  to 100  $\Omega$  at high frequencies (around 1 MHz).

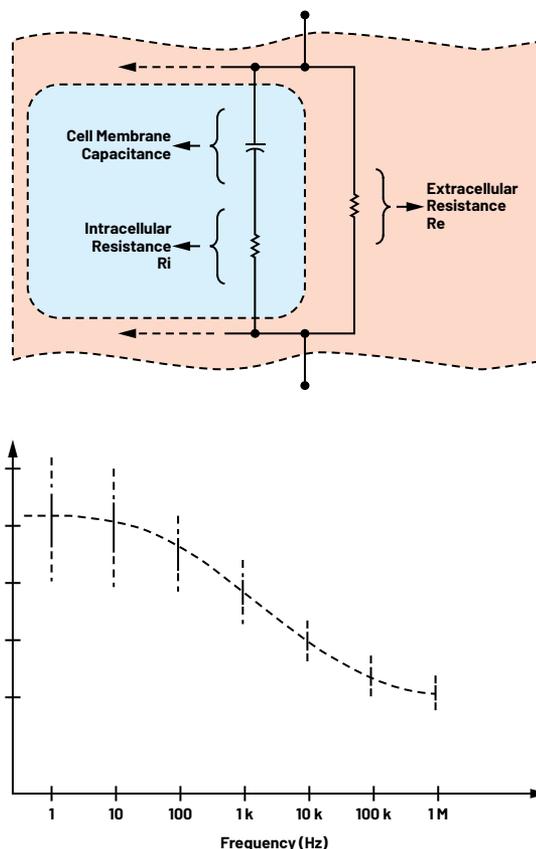


Figure 2. An equivalent model of biological tissue at a cellular scale.

Going from the basic biological tissue up to macroscopic structures of the body, the portion of interest of the impedance spectrum may change; thus, the excitation frequency of the EIS measurement will change accordingly on the medical application and the body section to be investigated.

The human skin can be structured in three main layers: epidermis, dermis, and hypodermis. The epidermis is the external layer exposed to the external environment through the stratum corneum. Each layer has its equivalent electric model whose impedance reflects the specific changes from one to another. Modeling human skin is indeed a very difficult and complex operation due to the extreme variability both over individuals and over time in the same individual (age, hydration, season, etc.). Then many different skin impedance models have been proposed by various researchers. The three most popular, designed considering the hierarchical structure of the skin and classified as RC layered models, are the Montague, Tregear,<sup>3</sup> and Lykken models (see Figure 3). Among these, the three-element model proposed by Montague is the most widely used, since it's simple, intuitive, and easy to simulate. Its popularity comes from its ease of simulation, intuitive nature, and allows lumped parameter analysis.

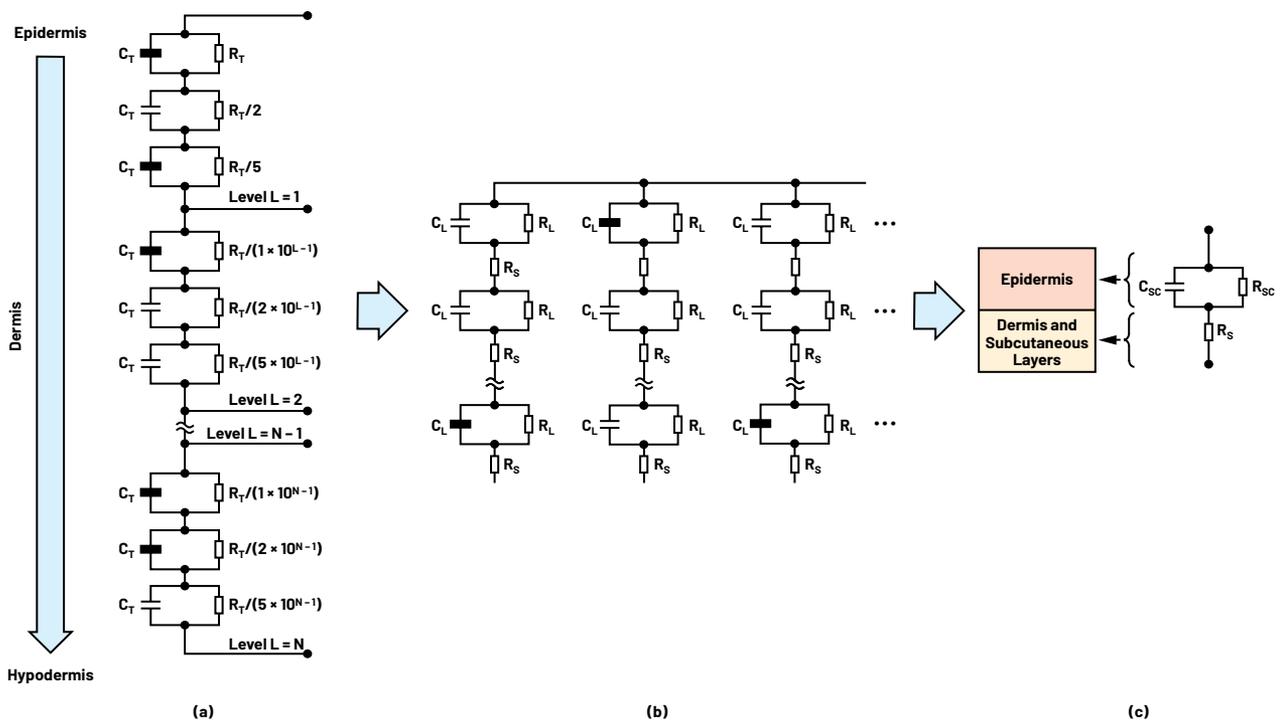


Figure 3. Three main RC layered models for human skin: (a) Tregear, (b) Lykken, and (c) Montague.

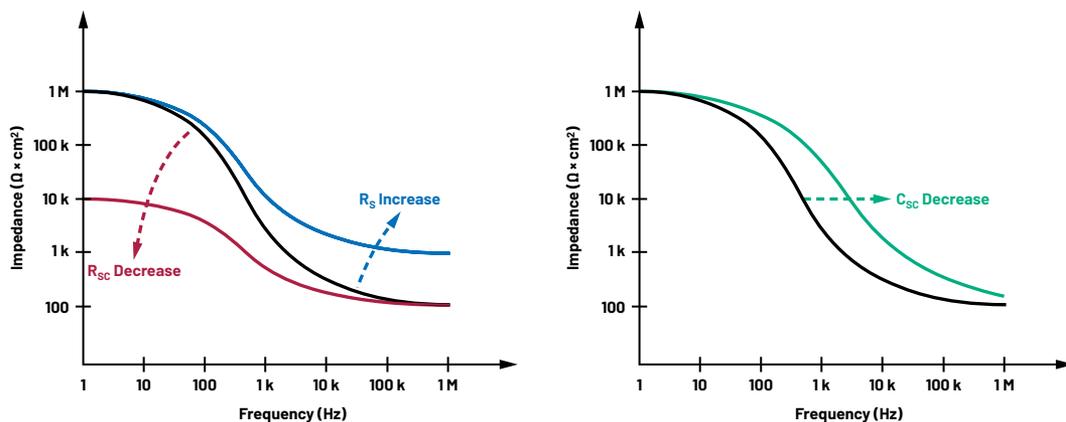


Figure 4. Impedance of a simplified Montague model and its dependence on electrical parameters variance.

Typical ranges are:  $R_{SC} = 104 \div 106 \Omega \text{ cm}^2$ ,  $R_S = 100 \div 200 \Omega \text{ cm}^2$ , and  $C_{SC} = 1 \div 50 \text{ nF/cm}^2$ .

The key aspect of the application of impedance analysis to the TMD is that the injection of a substance in the living material changes the impedance of the tissue itself as a function of the amount of conductive substance delivered. The impedance, or more precisely its variation over time and space, is then the key parameter that must be measured and correlated to the amount of delivered medicine to assess the proper penetration of the moisture into the tissue after transdermal delivery injection in medical applications.

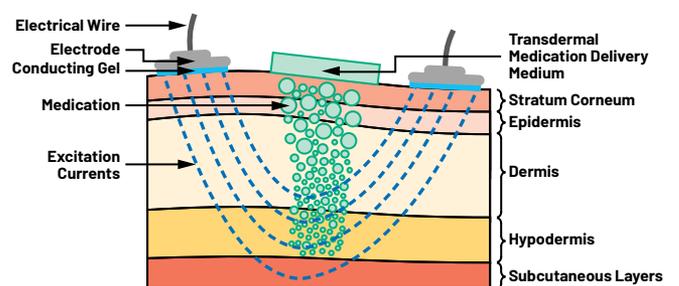


Figure 5. Human skin layers in cross-section with TMD and bioimpedance measurement.

Considering the noninvasive nature of the bioimpedance analysis, two metal electrodes represent the electrical transducers interfacing the electrical circuitry of the analog front end (AFE) and the patient's skin. This metal-to-nonmetal point of contact represents an additional critical section composing the overall electrical circuitry, which connects the AFE and the human body electrical model. The interaction between charge carriers (electrons in the electrodes and ions in the body) can have a significant impact on the performance of these sensors and requires making specific considerations for every kind of application. First, the interaction between a metal in contact with an ionic solution produces a local change in the concentration of the ions in the solution near the metal surface. This phenomenon causes a change of the charge neutrality in the area beneath the electrode, causing the electrolyte surrounding the metal to be at a different electrical potential from the rest of the solution, thus establishing a potential difference known as the half-cell potential between the metal and the bulk of the electrolyte. Second, the DC component of the injected current produces the electrode's polarization.

**Table 1. Various Electrode Types and Correspondent Half-Cell Potential**

Metal and Reaction	Half-Cell Potential (V)
$Al \rightarrow Al^{3+} + 3e^-$	-1.706
$Ni \rightarrow Ni^{2+} + 2e^-$	-0.230
$H_2 \rightarrow 2H^+ + 2e^-$	0.000 (by definition)
$Ag + Cl^- \rightarrow AgCl + e^-$	+0.223
$Ag \rightarrow Ag^+ + e^-$	+0.799
$Au \rightarrow Au^+ + e^-$	+1.680

This additional undesired phenomenon tends to decrease the electrode's performance. These considerations suggest that also the electrodes require to define an appropriate electrical model (see Figure 6). We can represent a dry electrode as a circuit with three elements in series: one DC source emulating the half-cell potential (EHC), an RC parallel cell ( $R_D || C_D$ ), modeling the contact between the metal and the nonmetal (the human body) and a resistor  $R_S$ , modeling the resistance of the electrode's metal.

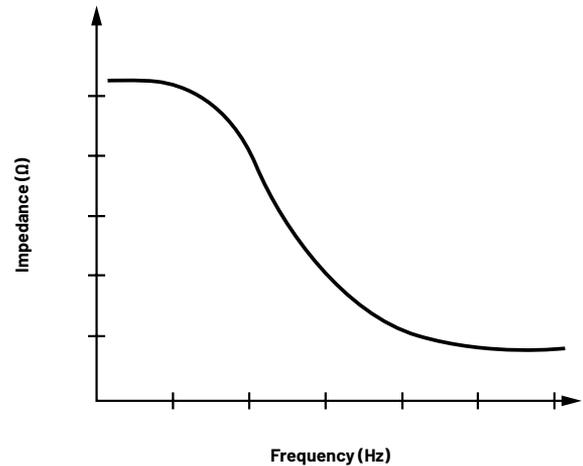
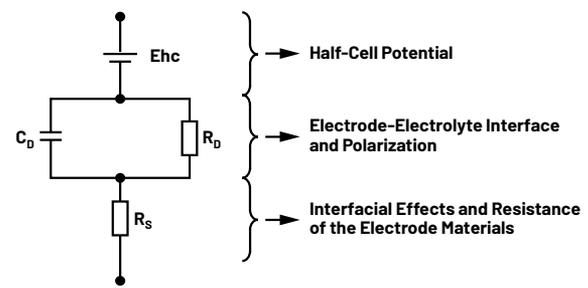


Figure 6. An equivalent circuit of a generic dry electrode.

Other types of electrodes will have different electrical models.<sup>4</sup> For example, wet electrodes require an additional RC parallel cell representing the gel conductivity impedance, a parameter that can be critical, as it tends to progressively penetrate the skin of the patient, determining a gradual decrease in the impedance over time, thus producing a drift in the measurement. This is not an issue with insulated electrodes (for pure AC measurements) where the half-cell potential is substituted with a capacitance modeling the capacitive gap ( $C_{gap}$ ) between the electrode and the skin. A variation of insulated electrodes can be found in noncontact electrodes, using an additional cotton layer on the electrode surface, which can be represented as an additional RC parallel cell (see Figure 7).

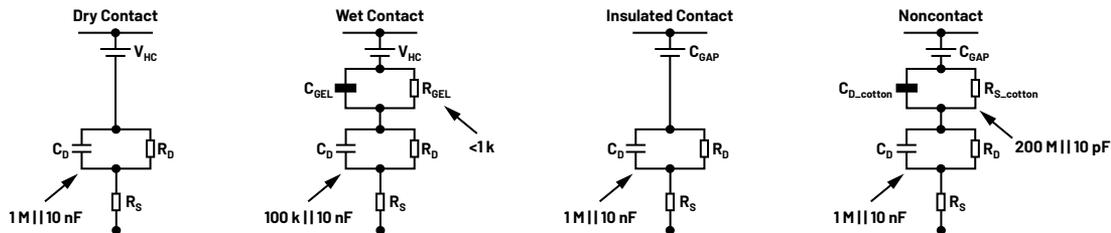


Figure 7. An equivalent circuit of different electrode types.

Combining the appropriate electrode model and the biological tissue electrical model, the overall circuit interfacing with the AFE can be represented as follows:

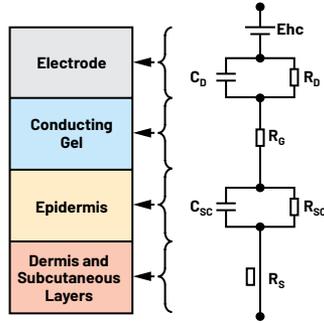


Figure 8. A wet electrode and a human skin equivalent circuit.

## EIS in TMD

The equivalent circuit resulting from the modeling presents a complex impedance spectrum that can be measured through an accurate EIS meter, an electronic device that till a few years ago consisted of a medium-sized sophisticated laboratory instrument and today can be integrated into a compact meter-on-chip solution. This is the case of the EIS AFE [AD5940](#), or [MAX30009](#), both from Analog Devices.

These devices allow an extreme integration of the bioimpedance EIS system in a portable device that can capture the impedance spectrum of the biological tissue under the skin of the patient, assessing the volume of medicine conveyed through the skin before and after the administration through the TMD.

Such EIS systems can evaluate both the magnitude and the phase of the impedance over the whole spectrum, but laboratory studies<sup>4</sup> demonstrated that the magnitude is the most significant parameter as the phase is affected by low linearity and monotonicity as a function of the amount of drug. On the other hand, the amount of medicine delivered is related by a linear relationship to the impedance variation before and after the delivery. Typically, the linear relationship can be obtained by previous proper calibration.

Since the biological tissues significantly change their electrical conductivity properties depending on some characteristics like the skin thickness or the state of the hydration of the stratum corneum, it is crucial to make bioimpedance analysis reproducible to characterize the tissue under examination before each TMD treatment, even on the same individual patient. Moreover, the characterization is important to prevent errors due to the drift caused by gel penetration in wet electrodes over time. As mentioned before, in fact, the high concentration of ions in the electrolyte gel significantly affects the tissue conductivity, producing a short-term instability of the measurement that can be prevented through a continuous monitoring of the impedance itself.

## Bioimpedance AFE Solutions: AD5940 and MAX30009

ADI can provide multiple solutions to design a bioimpedance meter device targeting TMD portable applications. In principle, two main methods are possible to measure bioimpedance: voltage excitation and current excitation. In the first method, a variable voltage is applied to the tissue under test and the resulting current is measured, while the second does the opposite by applying a current and measuring the resulting voltage. The voltage method can easily be implemented with the AD5940, while the current method system can be designed using the MAX30009.

The AD5940 is a high precision, low power AFE designed for EIS portable applications consisting of two excitation loops and one common measurement channel. Each of the two loops has 12-bit DACs aimed to generate excitation signals, one from DC to 200 Hz and the second up to 200 kHz. Each DAC has an excitation buffer with dual output controlling the noninverting input of the related potentiostat and the noninverting input of the transimpedance amplifiers (TIA), which measures the current by converting the current flow in a voltage. A digital waveform generator can generate sinusoid, trapezoid, and square waveforms. Both the excitation voltage and the resulting current (converted in a voltage by the TIAs) can be measured through the input channels feeding an input analog multiplexer (mux) connected to a successive approximation register (SAR) ADC, featured by a resolution of 16-bit, 800 kSPS. The data stream coming from the ADC can be postprocessed in a variety of ways including integrated programmable digital filters (sinc2, sinc3), 50 Hz/60 Hz for power supply rejection, programmable statistics for calculating minimum, maximum, mean, and variance automatically, or more important a complex impedance engine, a discrete Fourier transform (DFT) embedded DSP accelerator that can provide both the real and imaginary components of the measured impedance, reducing the processing workload required to the host microcontroller.

The MAX30009 is a complete, integrated data acquisition system for bioimpedance analysis and spectroscopy (BioZ) specifically designed for portable medical applications and wearable devices. The BioZ system shown in Figure 10 primarily consists of a transmit (Tx) channel, a receive (Rx) channel, and an input/output mux. Differently from the AD5940, the transmit channels of the MAX30009 inject body currents directly through an independent stimulus current generation circuit. The current injecting electrodes can be configured both as bipolar (two electrodes) or tetrapolar (four electrodes). The stimulus transmit channel is driven by an internal sinusoidal current generator that is programmable and can inject AC currents into the body skin over a wide range of frequencies (16 Hz to 806 kHz) and current magnitudes (16 nA rms, up to 1.28 mA rms maximum), allowing the device to be used over a various range of BioZ applications in addition to the dermal impedance measurements, such as the impedance cardiography (ICG) monitoring cardiac output and stroke volume, or impedance plethysmography (IPG) and automated external defibrillator (AED) body impedance.

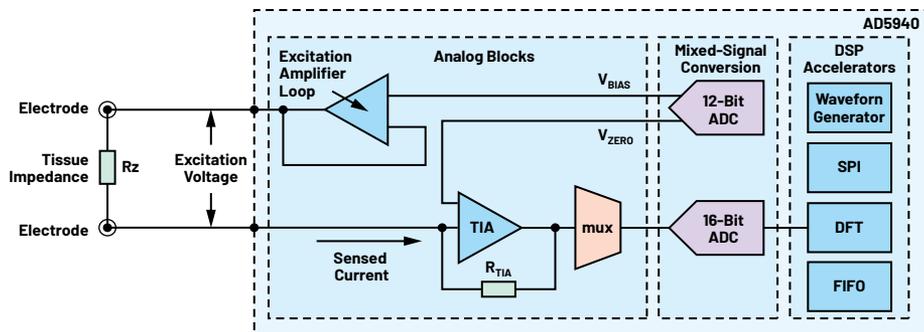


Figure 9. An AD5940 bioimpedance measurement simplified diagram—voltage excitation method.

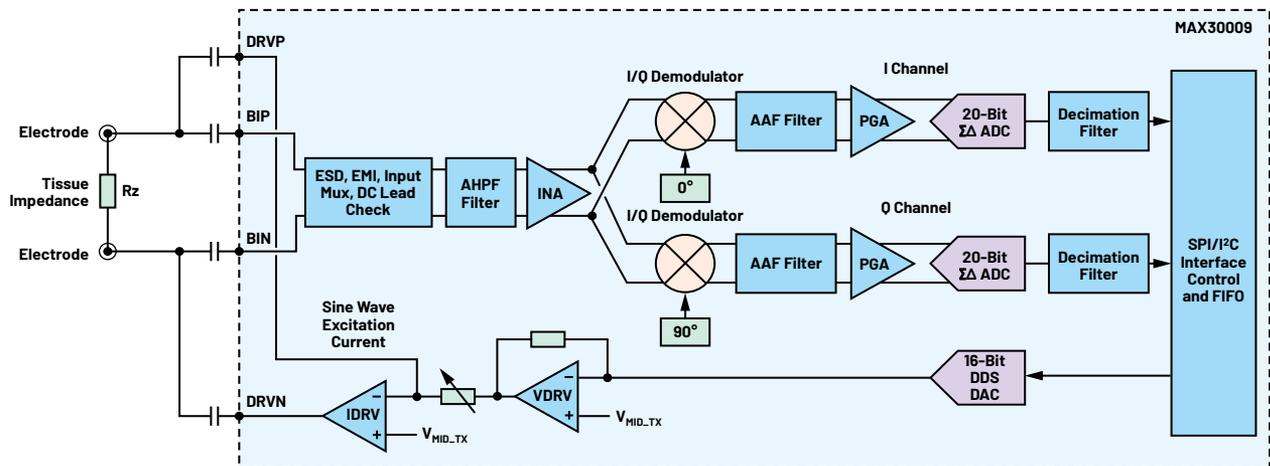


Figure 10. The MAX30009—bioimpedance measurement simplified diagram—current excitation method.

The receive channel measures the corresponding voltage with high precision thanks to the high input impedance, high common-mode rejection ratio (CMRR), and low noise. While the AD5940 integrates a DFT hardware accelerator to calculate the real and imaginary parts of the impedance from the digital data output of the ADC, the MAX30009 uses an I/Q demodulator to split the received analog signal in its I/Q components (in-phase and quadrature-phase with the stimulus signal) offering resistance and reactance measurements capability with an 0.1% accuracy. The two resulting signals are then fed into a programmable gain amplifier, various optional low-pass and high-pass filters, and finally are converted to digital through two high resolution 20-bit  $\Sigma\Delta$  ADCs. Advanced diagnostic and calibration features allow the user to check the proper lead connections and offer various sets of self-tests.

Large transients injected into the electrodes are prevented thanks to soft power-up sequencing.

## Conclusion

Both in diagnostic medicine and in therapeutic applications, it is crucial to be able to monitor the quantity of medicine administered to the patient. One of the most inexpensive and least invasive techniques for administering a particular medicine is TMD and it is currently being used for a wide variety of therapeutic compounds. Electrochemical spectroscopy techniques allow for the measurement of the quantity of medicine transferred through the skin before and after administration, allowing for the monitoring of both drug bioavailability and pharmacodynamics. Thanks to a new generation of meter-on-chip devices now available on the market such as the AD5940 and the MAX30009 from ADI, bioimpedance measurement is no longer limited to the clinical laboratory setting but can be made available as a low cost portable solution for any diagnostic and therapeutic setting.

## References

- <sup>1</sup> Pasquale Arpaia, Umberto Cesaro, and Nicola Moccaldi. "Noninvasive Measurement of Transdermal Drug Delivery by Impedance Spectroscopy." *Scientific Reports*, Vol. 7, 2017.
- <sup>2</sup> Dhruva Jyoti Bora and Rajdeep Dasgupta. "Various Skin Impedance Models Based on Physiological Stratification." *IET System Biology*, Vol. 14, No. 3, 2020.
- <sup>3</sup> R.T. Tregear. *Physical Functions of Skin*, Vol. 5. Academic Press, 1966.
- <sup>4</sup> Yu Mike Chi, Tzzy-Ping Jung, and Gert Cauwenberghs. "Dry-Contact and Noncontact Biopotential Electrodes: Methodological Review." *IEEE Reviews in Biomedical Engineering*, Vol. 3, No. 1, 2010.

## About the Author

Fulvio Bagarelli joined Analog Devices in 2017 as a senior field applications engineer and currently holds the position of a field technical leader. Previously, Fulvio worked for Linear Technology (now part of ADI), Arrow Electronics, and STMicroelectronics. He has a master's degree in electronics engineering from Politecnico di Milano in Italy and holds an executive M.B.A. from SDA Bocconi School of Management in Italy.

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