Skin Impedance Analysis Aids Active and Passive Transdermal Delivery

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Drug delivery is one of the fastest growing areas in the pharmaceutical industry, with leading firms actively developing alternatives to injections. Options such as oral, topical, pulmonary (inhaler type), nanotechnology enabled, and transdermal drug delivery systems are all current research areas. Transdermal methods, which feature noninvasive delivery of medication through the patient's skin, overcome the skin's protective barrier in one of two ways: passive absorption and active penetration.

The transdermal patch is one of the most common methods of passive drug delivery. Applied to a patient's skin, it safely and comfortably delivers a defined dose of medication over a controlled period of time. The drug is absorbed through the skin into the bloodstream. The nicotine patch is a prime example, but other common uses include motion sickness, hormone replacement therapy and birth control. Passive delivery has two major disadvantages: the speed of drug absorption is dependent on the skin impedance, and only a limited number of drugs are capable of diffusing through the skin's protective barrier at acceptable rates. As a result, major investment has been undertaken on active methods of transdermal drug delivery. Active methods of transdermal drug delivery include: using ultrasonic energy to speed up drug diffusion, using RF energy to create microchannels through the stratum corneum (outer layer of the epidermis), and iontophoresis.

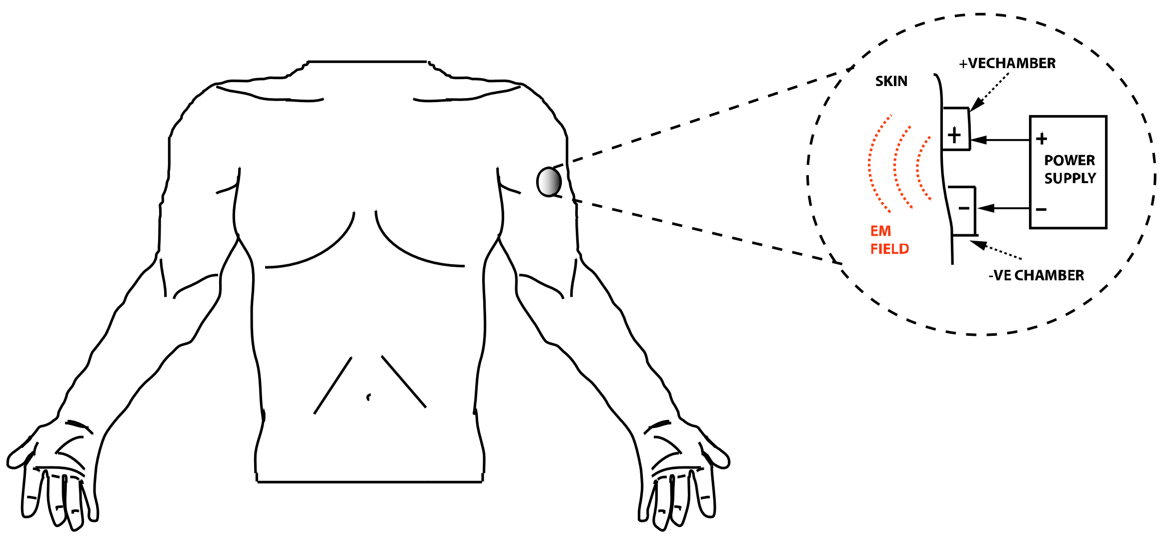

Figure 1. Iontophoresis.

Iontophoresis uses electrical charge to actively transport a drug through the skin into the bloodstream. The device consists of two chambers that contain charged drug molecules. The positively charged anode will repel a positively charged chemical, while the negatively charged cathode will repel a negatively charged chemical. The electromagnetic field developed between the two chambers actively propagates the medicine through the skin in a controlled manner.

Skin impedance is a key variable for transdermal delivery. The complex impedance, which depends on age, race, weight, activity level, and other factors, is frequency dependent and difficult to model. Dynamic measurement of skin impedance offers an accurate and practical solution for optimal drug delivery.

Impedance spectroscopy facilitates accurate analysis of complex impedances such as human skin, leveraging the fact that resistor, capacitor, and inductor impedances vary differently with frequency. As frequency increases, a resistor's impedance remains constant; a capacitor's impedance decreases; and an inductor's impedance increases. Exciting a test impedance with a known ac waveform makes it possible to determine the resistive, inductive, and capacitive components of the unknown impedance. Direct digital synthesizers (DDS) have flexible phase frequency, and amplitudes, sweep capability, and programmability, making them ideal for exciting unknown impedances. Embedded digital processing and enhanced frequency control allow the devices to generate synthesized analog or digital frequency-stepped waveforms. Figure 2 shows a block diagram of a simple impedance analyzer. The ac waveform generated by the AD9834 complete, low-power, 75-MHz DDS is filtered, buffered, and scaled by the AD8091 high-speed, rail-to-rail op-amp. Another AD8091 buffers the response signal and scales it to match the input range of the AD7476A 12-bit, 1-Msps, successive-approximation ADC.

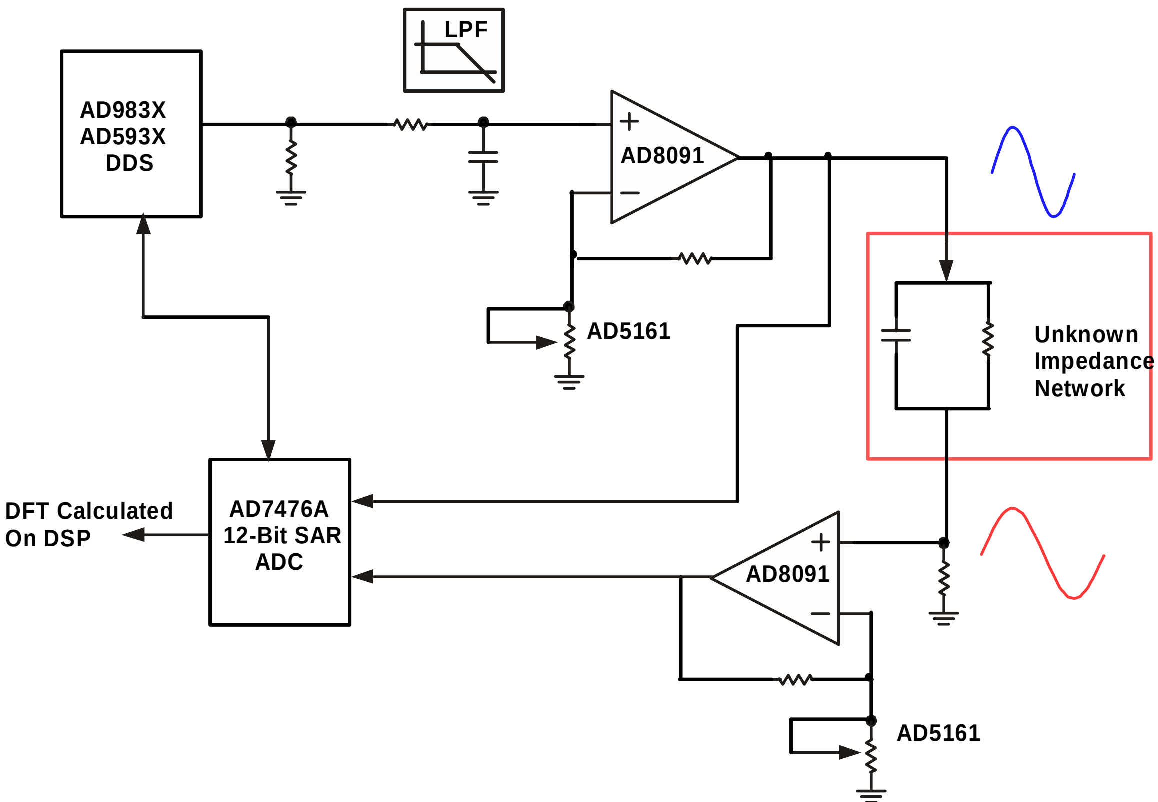

Figure 2. Simple impedance analyzer.

This simple signal chain masks some underlying challenges, however. First, the ADC must synchronously sample the excitation and response waveforms over frequency so that phase information can be maintained. Optimizing this process is key to overall performance. In addition, numerous discrete components are involved, so varying tolerances, temperature drift, and noise will degrade measurement accuracy, particularly when working with small signals.

The AD5933 12-bit, 1-Msps integrated impedance converter network analyzer overcomes these limitations by combining the DDS waveform generator and the SAR ADC into a single-chip, as shown in Figure 3.

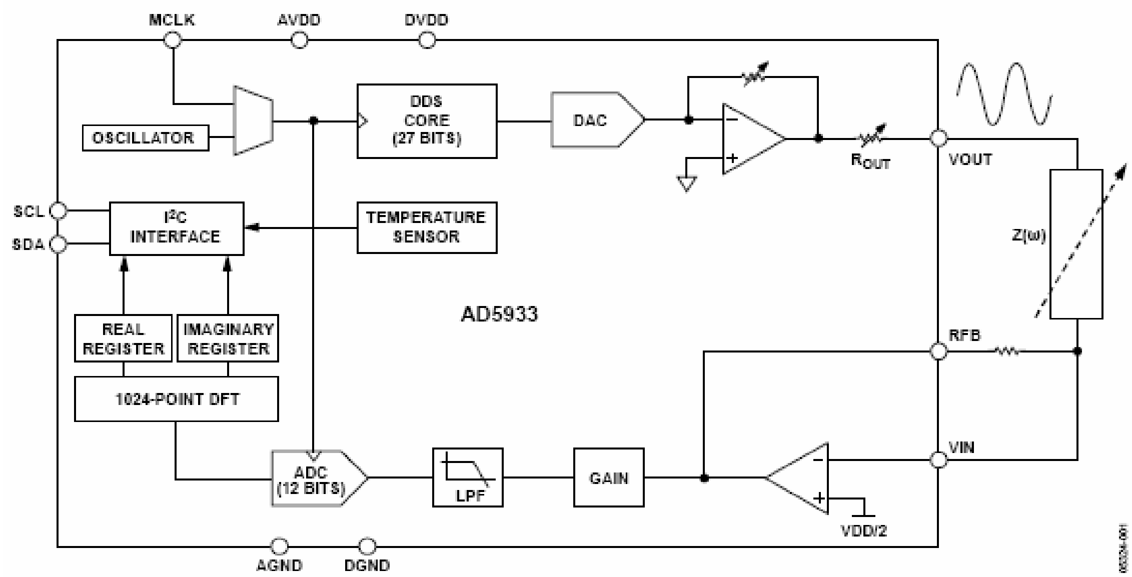

Figure 3. AD5933 functional block diagram

The AD5933 has an output impedance of a few hundred ohms depending on the output range. This impedance could swamp the unknown impedance, so an AD8531 op-amp buffers the signal, as shown in Figure 4. Note that the receive side of the AD5933 is internally biased to $V_{DD}/2$, so this same voltage must be applied to the non-inverting terminal of the external amplifier in order to prevent saturation. For safety reasons, all excitation voltages and currents need to be signal conditioned, attenuated and filtered before they are applied to human tissue.

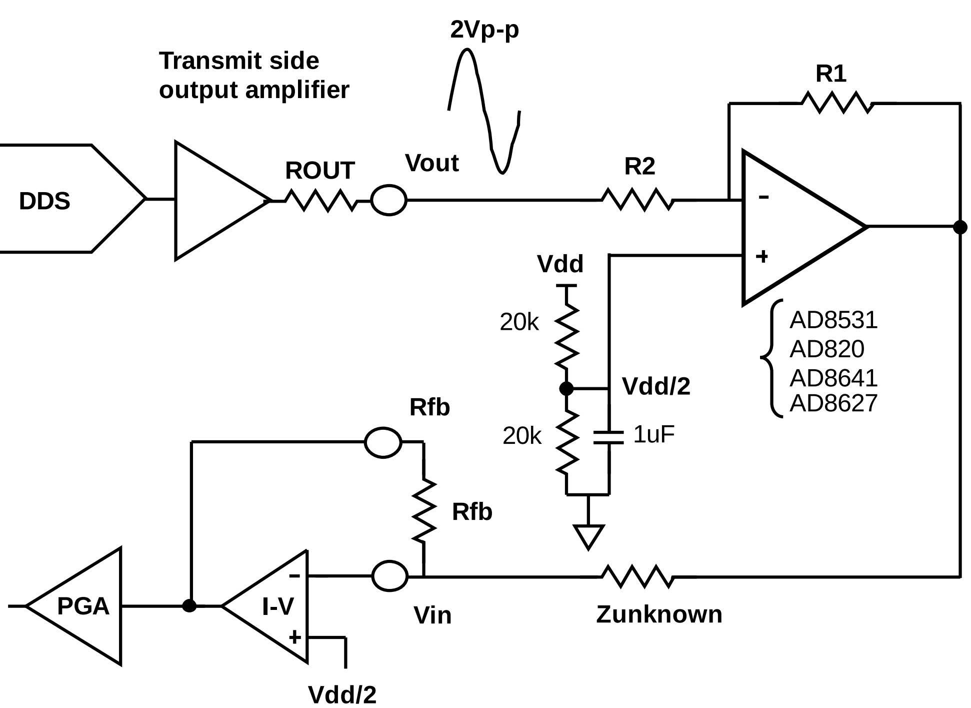

Figure 4. Low-impedance measurement configuration