Time-domain based impedance measurement: strengths and drawbacks

Uwe Pliquett
Institut für Bioprozess- und Analysenmesstechnik, Heilbad Heiligenstadt, Germany

E-mail: uwe.pliquett@iba-heiligenstadt.de

ABSTRACT: While most applications of bio-impedance measurements for characterization of cells or tissue do not have any time requirements, newer developments like real time monitoring of moving cells or membrane recovery after high voltage application depend on fast measurement. This is not compatible with sweeping the frequency through the desired range while assessing magnitude and phase of the material under test (MUT). A high speed is only achievable by using broad-bandwidth excitation signals and monitoring the response in time-domain. Time-domain based methods can be distinguished by the excitation signals as well as by assessing the transmission or reflection behavior of the MUT. Although there is good agreement regarding the advantages of fast measurements, time-domain measurements are often rejected because of low precision and noise sensitivity. This paper points not only the advantages of impedance measurements in time domain but shows also drawbacks together with possible solutions.

1. Introduction
The electrical characterization of biological material is well established but lacks applicability for a variety of potential use. Especially if the MUT is fast changing like after the application of electrical pulses for cell manipulation if the material is fast moving along the electrodes like by monitoring cells in a sample stream in capillaries, established methods like frequency sweep for assessment of the impedance spectrum fail. Using broad bandwidth excitation signals and tracing the electrical response in time will greatly enhance the temporal resolution [1]. Moreover, due to the fast measurement, multichannel arrangements with reasonable time for testing all channels become affordable.

Biological objects composed of cells surrounded by insulating cell membranes show a β-dispersion but also α-dispersion at low frequency and γ-dispersion above the β-dispersion [2]. Depending on the application, narrow bandwidth measurements at one frequency or broad bandwidth measurements spanning over 6 to 10 decades are required. A change in impedance or permittivity magnitude by several orders is likely for the majority of living objects.

Two characteristics of biological material challenge bio-impedance measurement: (1) broad bandwidth and (2) a high dynamic range in measurement amplitude. Although this can be solved in frequency domain as well, fast broad bandwidth measurements are not compatible with this approach.

2. Frequency domain vs. time domain
Although impedance measurement in time domain is well established in many areas, the majority of bio-impedance measurements are done either at a single frequency or by sweeping over the desired frequency range. This was mainly supported by the broad availability of gain-phase and network analyzers. Although time domain spectroscopy (TDS), mostly in reflection mode [3], was used since
the 70’s of last century it was almost not recognized until about 10 years ago. There have been several arguments against it:

- Time domain spectroscopy is not precise and susceptible to noise;
- Using the ‘classical’ square wave approach, the energy at high frequency declines fast;
- Devices which have been developed for bio-impedance measurements are rarely marketed.

The most important advantage over frequency domain based measurements is the speed. However, with only a few exceptions like process instrumentation (i.e. meat classification) or monitoring of fast processes (i.e. recovery of membranes after high voltage manipulation) there was no real demand for fast measurements. For instance, time domain reflectometry [3] (Y. Feldman termed it later time domain dielectric spectroscopy, TDDS) used a sampling approach where in each period only one point was sampled and converted using a high resolution ADC. In this way and together with averaging a single measurement could take as long as getting the same information in frequency domain.

The interest in time domain approach rose during the last ten years with exploring new areas in process measurement and biomedical instrumentation. The intention was now to have fast and robust measurements using simple and therefore economic devices with low energy consumption. Even though specialized integrated circuits for frequency domain approach exist (Analog Devices, Texas Instruments), time domain based instrumentation can be even simpler, for instance consisting of only one microcontroller. However, a front end for matching the electrodes to the digital circuitry but also to the input of the ADC is always advisable for practical approach [4].

TDS in general is the use of a broad bandwidth signal for excitation and monitoring the response in time. While the most prominent excitation signals (Dirac and step function, square wave) are successfully employed since more than 40 years, today more sophisticated excitation signals like multi-sine, pseudo random noise (i.e. maximum length sequences) or chirp are used or under development [5]. Two pronounced development targets are the minimization of the crest factor and the confinement of the energy within the frequency range of interest. Moreover, efficient algorithms aiming in speed increase and pre-compression of high data volumes are under investigation by several groups. Further data processing is either done direct in time domain by fitting the response signal to an biophysical model in order to obtain time constants and amplitude factors or the excitation as well as the response signal are transformed into frequency domain (e.g. by Fourier transformation) for calculation of the impedance as function of the frequency. Other methods like correlation, convolution or other transformations (wavelet, Gabor) are used for several applications but they are not widely distributed. Even though non-uniform sampling for great reduction of the data stream together with discrete Fourier transformation with non-equally spaced time vector is known since decades [6], there are still only a few applications in bio-impedance measurement practice. This raises questions: Are the new techniques not good enough? Are their advantages not understood? OR: Is there no need for new techniques due to the overwhelming quality of existing ones?

The simple answer is: There is the need for new techniques. Their acceptance increases with advancing the knowledge, which can be seen especially in the field of bio-impedance measurement during the last years. However, further success of TDS depends on managing drawbacks of this technique which includes a pragmatic decision for forcing its application only where the advantages make either the measurement or the post-processing better or simpler.

3. Advantages of time domain spectroscopy

The clear advantage of TDS is the speed but also a significantly simpler hardware. Further advantages, especially for use at high frequency, are less known and should be briefly mentioned. Correlated transients form switching events or from reflections along the connection circuitry are simply detected and can be compensated. Using a reflectometry arrangement without directional couplers, the same channel for voltage and current is used, which circumvents the common problem of never perfect match of these both channels. Although reflection methods in frequency domain exist as well, they use direction couplers and separate channels for the incident and reflected wave. Due to the low impedance magnitude above about 100 MHz, similar to this of the wave guide impedance (coaxial
cable, stripe line) time domain reflectometry becomes advantageous over transmission spectroscopy. The available frequency range extends currently up to 200 GHz. The bandwidth of time domain spectroscopy is easily scalable, irrespectively of excitation signal used. The lower cutoff frequency is determined by the time duration of the excitation signal while the upper frequency depends on the fastest change of the signal with respect to time (i.e. rise time of a step function). The critical quantities at the sample side are the speed and the resolution of the ADC.

4. Drawbacks of time domain spectroscopy – what can we do?

Although the robustness of new algorithms has been shown in numerous studies even in noisy environment, some significant drawbacks are well known. However, there are solutions making this approach emerging during the last years.

Random noise, originating from resistors, amplifiers, electrodes or also high frequency noise due to the wiring of the setup is a negligible problem when measuring at a single frequency due to the use of selective amplifiers (i.e. lock-in-principle). For TDS, broad bandwidth amplifiers are used, not enabling any noise reduction in a single acquisition mode. Three prominent principles for noise reduction apply: (1) For slow signals where the amplitude change within one sampling interval is significantly less than the resolution of the ADC, oversampling with averaging around a single point in time decreases not only the noise but increases also the resolution of the analog-digital-conversion. The advantage of oversampling is a high speed, since it still works in single shoot mode. (2) Averaging over several periods does not require extremely fast ADC but comprises time resolution. (3) Using a biophysical model for the biological material enables the meaningful fit of a time function. In case of a step function for excitation, the response will be sum of exponentials which can be easily fitted. It should be noted that even smoothly appearing signals after fitting a noisy curve are not better because the significance of fitted values decreases fast with increasing noise. It is in any case better to obtain good results by optimizing the hardware.

Besides random noise, crosstalk from power lines can greatly distort the impedance signal even though the lower frequency of the excitation signal is above 50 Hz (60 Hz) (e.g. 1 kHz rectangular wave). Besides proper grounding and shielding of the setup, a simple approach is the synchronization of the excitation signal to the frequency of the power line. This can be done by Schmitt-triggering the 50 Hz (60 Hz) in order to obtain a noise free digital signal where the frequency can be multiplied in a PLL (phase lock loop) with proper division of the VCO (voltage controlled oscillator) output. Practically, a suppression of the power line noise of more than 80 dB can be achieved. A further suppression is possible by averaging over a full period of the power line frequency. Although this comprises measurement speed to 50 (60) measurements per second, it pays back by a much higher significance of the single measurement result.

Correlated noise like signal distortion from switching events in the chain of excitation signal generation or arising from reflections at mismatches along the measurements chain do not disappear by averaging. Applying a simple filter, analog or digital, will distort the entire signal, especially parts with fast changing voltage or current and would be therefore an additional error source. Using a step function for excitation results in a sum of exponentials for typical biological materials. Replacing the transient distortion by a fitted exponential does not disturb the spectrum but removes artifacts.

In general, impedance measurements should be performed at linear objects only. However, biological materials especially in contact with metal electrodes show slightly non-linear behavior. The overall rule in bioimpedance measurement, independent of frequency or time domain, is to use excitation signals as small as possible. In frequency domain measurement with sine wave for excitation together with using selective amplifiers the non-linearities create harmonics which are completely suppressed and thus they are not detected. However, by using broad bandwidth amplifiers, such harmonics influence the high frequency behavior. Suppression is possible by employing known behavior of the response signal. In particular, when using symmetric square waves for excitation, averaging of the positive half period with the inverted negative half period suppresses harmonic distortion at least to some extent. This is particularly useful when the time varying dynamic impedance at an operating...
point with dc-offset is assessed (e.g. electrode bias, electrical manipulation, a membrane with resting potential.

An often underestimated characteristic of the measurement system is the transient response of the amplifier used. While this does not matter for sine wave signals, it may considerably disturb the high frequency region of time domain signals, especially if their deviation yields singularities as in case of Dirac or step functions. This requires carefully selected amplifiers (high slew rate, negligible overshoot, fast settling) and a well-designed layout of the printed board.

The resolution of the ADC and the jitter of the sampling system is an important limitation of any system working in time domain [4]. The choice of the sampling system does not only influence the accuracy and speed of the entire measurement setup but determines considerably the prize. While at fast changing parts of the signal the jitter is an important quality factor, the resolution of the ADC becomes increasingly important for slow changing parts.

Low cost but precise systems use the principle of the sampling oscilloscope, where a periodic signal is sampled once in each period at a continuously shifting time point until the entire curve is sampled (stroboscopic under sampling). This requires as many periods as sample points which yields a rather long measurements time. The great advantage of this approach is use of slow ADC with high resolution (16 – 24 bit) but is very sensitive to jitter in the timing of the sampling points.

Better systems use a single shot approach where the jitter is low but this needs much faster ADC which in turn comprises ADC-resolution (usually 8 or 12 bit). High end systems use very fast ADC together with oversampling where each point is the average of several fast samples. This increases the overall resolution without the need of averaging over several periods.

A problem is the high swing of signals in time domain measurements. For confining the signal arising from the MUT, difference or ratio measurements with known equivalent circuits, mimicking for instance the electrode system, are used. Since only changes are amplified, higher amplification factors become possible which in turn increases the sensitivity of the system.

In order to reduce the data volume, adaptive sampling with fast sampling at fast changing parts of the signal and slow sampling when the changes over time are slow [7], is used. This overcomes also problems associated with the low energy of higher harmonics, particularly due to square wave excitation. With adaptive sampling not the energy distribution of the excitation signal but the product of signal/time gradient and sampling interval determines the useful frequency range. Although, this requires sophisticated data processing and is not compatible with the most popular fast Fourier transformation, solution in hard- and software already exist.

5. Conclusion

This paper could only give a brief introduction into the problems associated with impedance measurements in time domain. The practical experience shows that time domain measurements can be made as precise as frequency domain measurements but it needs more sophisticated data processing and more attention in terms of generation of high quality signals and noise suppression.

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