Bioimpedance Monitoring for physicians: an overview

Antoni Ivorra

July, 2002
(revised and expanded July, 2003)

Sometimes I have had to explain the basics of electrical Bioimpedance Monitoring (BM) to physicians, biologists or veterinarians, all of them from the biomedical community and familiarized with the cell biology. In general, these professionals are **not skilled in circuit theory** or **electromagnetics** and I found difficulties to explain concepts such as impedance phase, real part of the impedance, complex numbers... In these cases, I would have liked to provide them some written material to clarify those concepts. Unfortunately, the literature about bioimpedance is mostly written by physicists for physicists and a background in electromagnetic theory is assumed. On the other hand, the basic circuit theory texts are too much dense and remote from the bioImpedance field. Therefore, I thought that a short paper trying to fill this gap could be profitable.

I have not tried to write a scientific review about BM. My objective has been to be didactic and I have specially focussed the electrical concepts.

0. INTRODUCTION

Electrical Bioimpedance Monitoring is an emerging tool for biomedical research and for medical practice. It constitutes one of the diagnostic methods based on the study of the passive electrical properties[1] of the biological tissues. These properties have been object of study since Luigi Galvani (1737-1789) discovered that while an assistant was touching the sciatic nerve of a frog with a metal scalpel, the frog's muscle moved when he drew electric arcs on a nearby electrostatic machine. However, it was not until the end of XIX (McAdams et Jossinet, 1995) that these properties started to be measured thanks to the development of new instrumentation and the set up of the electromagnetic field theory by James Clerk Maxwell (1831-1879).

The practical use of the electrical passive properties started in the middle of the XX century. Different properties and techniques resulted in a collection of methods that are now used for multiple applications. Usually, these methods have three advantages in common:

- require low-cost instrumentation.
- are easily applicable in practice.
- enable on-line monitoring.

Excellent reviews about the applications of BioImpedance (BI) methods can be found in (Grimnes et Martinsen, 2000), (Bourne, 1996) and (Scharfetter, 1999). Here some of these applications are listed in order to show the BI potentiality.

Cellular Measurements

Coulter counter. This method is the best known application of impedance methods in the cellular field. It is used to count the amount of cells in a suspension. The measuring principle is quite simple: cells are forced, or enabled, to pass trough a capillary (~100 μm) that changes its electrical impedance at each cell passage. Then, the concentration of cells is estimated from the rate of impedance fluctuations and, in some cases, it is even possible to extract information about the cell sizes from the impedance peak values at each cell passage.

Measurement of the hematocrit. The concentration of dielectric particles in a conductive solution can be estimated if the shape and size of the particles is known. This fact has been used in commercial blood analyzers to determine the hematocrit.

[1] The passive electrical properties are determined by the observation of the tissue electrical response to the injection of external electrical energy. That is, the tissue is characterized as it was an electrical circuit composed by resistors, capacitors, inductors...
Some biological tissues also show active electrical properties since they are capable of generating currents and voltages (e.g. the nerves).

Monitoring of cell cultures. BI can be used to quantify the biomass in industrial bioreactors (Bragos et al., 1999) or to study the response of cellular cultures to external agents (toxins, drugs, high-voltage shocks and electroporation) (Giaever et Keese, 1993) (Borkholder, 1998).

Volume Changes

As it will be explained later, the bioimpedance is not only related with the tissue properties but it also depends on the geometrical dimensions. Therefore, it is possible to measure sizes or volumes when some data about the tissue electrical conductive properties is known a priori. Moreover, if tissue electrical properties remain constant, it is possible to obtain information about volume or size changes from the detected impedance fluctuations (Geddes et Baker, 1989).

Impedance plethysmography. In this method BI is used to estimate the blood volume in the extremities. One of its applications is the detection of venous thromboses and stenoses in the extremities by measuring the blood filling time when an occlusion of the veins in the limb is removed.

Impedance cardiography. The stroke volume of the heart can be estimated by measuring impedance via an invasive mutielectrode catheter or with skin electrodes (transthoracic impedance cardiography.)

Impedance pneumography. The same principles of the impedance cardiography can be also applied for monitoring the respiration air volumes.

Body composition

As the BI depends on the tissue properties and its geometry, it is possible to estimate the relative volumes of different tissues or fluids in the body.

Fluid compartments. For the determination of the total body water, the relative volumes of extra and intracellular spaces is estimated by measuring BI. Two procedures are in use: bioimpedance analysis (BIA) and bioimpedance spectroscopy (BIS). BIA measures impedance at a single frequency and assumes that the measured value corresponds to the extracellular fluid volume. However, the broad variety of persons and pathologies causes important disturbances. Those disturbances are reduced when BIS (measurement at several frequencies) is applied.

Fat compartments. With important restrictions, the same techniques of the hydration monitoring can be applied to calculate the fat/fat-free mass.

Tissue classification

Since different tissue types exhibit different conductivity parameters, it is easy to conceive that BI can be applied to characterize the tissues. Obviously, the most interesting application would be the **cancer detection**. Unfortunately, although this idea was born long ago (Fricke and Morse, 1926) few significant achievements have been obtained up to now and the field is still under research (Walker et al., 2000), (Jossinet et Schmitt, 1999).

Nevertheless, it must be said that one multichannel-BIS device is now commercially available for breast cancer screening (TransScan Medical, 2002)(Malich et al., 2003). The probe consists of an array of electrodes that is pressed onto the breast. The system displays a map of the impedance which yields typical patterns for healthy and cancerous breast. Its usefulness has been positively demonstrated against the competing methods.

Tissue Monitoring

Cellular edema, interstitial edema and gap junctions closure are some events that induce variations of the BI parameters. These events are related to the metabolism of the tissue cells and their on-line monitoring could be of great relevance. Nowadays, this field of application is at the research level. However, the results are very promising and a future clinical usage seems reasonable.

Ischemia monitoring. In some cardiac surgical procedures the heart is artificially arrested. In these cases, the medical team does not have any information about the myocardium condition and the unique controllable parameter is the time before circulation is restored (ischemia period). Thus, a system able to indicate the evolution of the damage caused to the heart by the ischemia is interesting (Benvenuto et al., 2000). Several papers show that ischemia in the heart, and in other organs or tissues, imply the alteration of some BI parameters (Schwartzman et al. 1999), (Tsai et al., 2002), (Songer, 2001), (Warren, 1999), (Cinca et al., 1997) , (Bragós et al., 1996), (Jenderka et Gersing, 1996), (Linhart et al., 1995), (Gersing et al., 1995), (Osypka et Gersing, 1995), (Fallert et al., 1993), (Kléber et al., 1987), (Ellenby et al., 1987).

Graft viability assessment. BI monitoring of organs to be transplanted has been proposed to determine which organs are suitable for transplantation. The idea is to quantify the damage caused by ischemia before, during and after the transplantation (MicroTrans, 2002), (Sola et al., 2003), (Yamada et al., 2002), (Haemmerich et al., 2002), (Raicu et al., 2000), (Gersing, 1998), (Ishikawa et al., 1996), (Fourcade et al., 1973), (Harms et al., 2001), (Konishi at al., 1995), (Gebhard et al., 1987), (Garrido et al., 1983).

Graft rejection monitoring. The rejection processes in transplanted organs cause inflammatory processes that could be detected by BI measurements (Pfitzmann et al, 2000), (Grauhan et al., 1996). An implanted electrode probe with telemetry has been proposed for this application (Harms et al., 2001). A noninvasive approach has also been suggested but it implies some important practical problems (Ollmar, 1997).

Electrical Impedance Tomography (EIT) expands the usefulness of all this methods by adding spatial resolution. EIT provides a mapping of the impedance distribution in a tissue layer or volume. Multiple electrodes are used to inject and record the voltages and currents and computer reconstruction algorithms process the resulting data to generate an image. The resolution is very poor compared to other imaging methods (echography, X-ray tomography or Magnetic Nuclear Resonance) but it is sometimes justified in terms of cost, acquisition speed and information provided by the quantitative results. However, although some clinical studies have been carried out, EIT is not applied now as a standardized method. For more information about EIT read (Bourne et al., 1996)

1. CIRCUIT THEORY

Impedance is a common word in electronics. It denotes the relation between the voltage and the current in a component or system. Usually, it is simply described as the **opposition** to the flow of an alternating electric current through a conductor. However, impedance is a broader concept that includes the **phase shift** between the voltage and the current. We will see it later, but first it is necessary to review some basic concepts about electricity.

Voltage (or potential) in a point A indicates the energy of an unitary charge located in this point compared to the energy of an unitary charge in a point B. If an electric path exists, this energy difference forces the electronic charges to move from the high energy position to the low energy position. In other words, voltage is the electrical force that causes current to flow in a circuit.
Voltage is measures in Volts (V).
Traditionally, an analogy with water pressure has been set up in order to explain the voltage concept.

The **electrical current** denotes the flow of electrical charge (Q) through a cross-section in a second. It is measured in Amperes (A) (= Coulombs/s.m^2).
Following the same hydraulic analogy, current is viewed as the water flow (amount of liters/second) through a pipe.

Charge can exist in nature with either positive or negative polarity. Forces of attraction exist between opposite charges and forces of repulsion exist between like charges.
In the materials that conduct electricity, some particles exist that are able to move. These particles are called **charge carriers** and they are usually **electrons** or **ions**. There are many materials, called insulators or dielectrics, that do not conduct electricity. All the charges in these materials are fixed (**fixed charges**).

1.1 RESISTIVE NETWORKS

In an element able to conduct electricity, the **resistance** (R) denotes the relation between the applied voltage difference and the flowing current. It is measured in Ohms (Ω).
The resistance of an ideal conductor (superconductor) is 0 Ω while the resistance of an ideal dielectric is infinite.

The **Ohm's law** says that there exist a linear relation between voltage and current:

$$v=i.R$$

This law is valid for most materials but there are some exceptions. For example, biological tissues do not obey Ohm's law if the current density (current/cross-section area) is beyond a threshold[2].

Resistance implies energy loss. The amount of energy lost by a conductor in a second (Power) is:

[2] When a system obeys the Ohm's law it is said to be a linear system because all the voltages and currents are related trough linear expressions.

$$P = v.I \quad [W = V.A]$$

The resistance is compared to the opposition of water flow in a pipe.

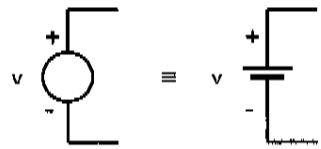
The resistance depends on different parameters and physical facts:

- Amount of charge carriers in the conductor: the resistance is inversely related to the concentration of charge carriers. For example, in an ionic solution the **conductance** (1/**R**) is directly related to the ion concentration[3].
- Mobility of the charge carriers. Charges are freer to move in some circumstances and that determines the resistance. For example, in ionic solution the 'viscosity' of the solvent decreases as the temperature rises, increasing the ion mobility and, consequently, decreasing the resistance. On the contrary, in metals, electronic conductors, the temperature causes electrons to collide more frequently and that causes a mobility decrease.
- Geometrical constraints. The resistance is inversely related to the conductor section and it is directly related to the conductor length. For a given material and temperature, the **resistivity** (ρ, units [Ω.cm]) is defined as:

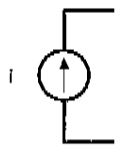
$$R = \rho \times (\text{Length/Section})$$

In a circuit, the elements able to provide energy are:

Voltage source. An element that maintains a fixed voltage difference between its two terminals no matter the current that is flowing through it. This element would be analogous to a waterfall. The most known examples are batteries.

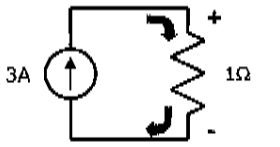


Current source. An element that maintains a fixed current through it no matter the voltage difference between its terminals. This element would be analogous to a peristaltic pump.

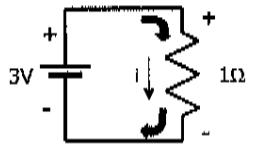


An electric circuit containing multiple connected resistors[4] can be modeled as a single resistance. That is, the circuit behaves as a single resistance. The following examples show how this simplification is performed.

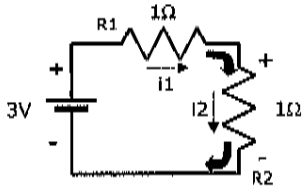
[3] This is true while the concentration is not too much high.
[4] A resistor is an electric component with a fixed resistance.



$\Rightarrow \quad v = I \times R = 3A \times 1\Omega = 3V$



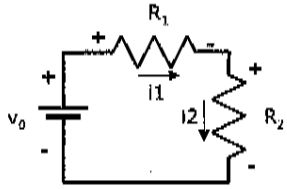
$\Rightarrow \quad I = v/R = 3V/1\Omega = 3A$



$$\boxed{I = I1 = I2 = v/R2}$$

$I = I1 = I2 = v/(R1+R2) \Rightarrow v2 = I.R2 = 1.5V$

Resistors in series:

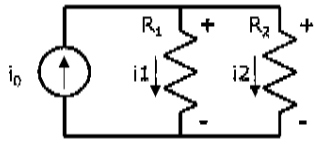


$$V_0 = V_1 + V_2 = i_1.R_1 + i_2.R_2 = i.(R_1+R_2)$$

$$i = V_0 / (R_1+R_2)$$

$$\boxed{R_{eq} = R_1+R_2}$$

Resistors in parallel:



$$I_0 = i_1 + I_2 = v/R_1 + v/R_2 = v.(R_1+R_2)/(R_1.R_2)$$

$$v = i_0.(R_1.R_2)/(R_1+R_2)$$

$$\boxed{R_{eq} = \frac{R_1 \cdot R_2}{R_1 + R_2}}$$

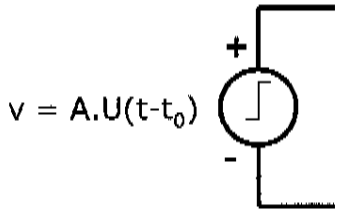
$R_1 || R_2$

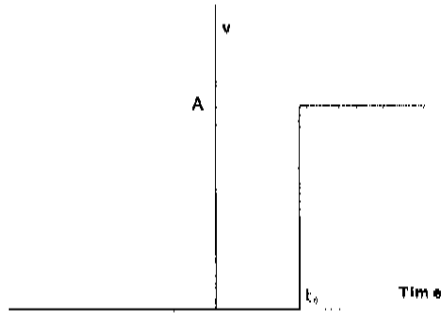
In a biological tissue, each slab of extra-cellular space can be modeled as a resistance. Thus, as we have seen, the behavior of the whole extra-cellular space will be equivalent to a single resistance. Unfortunately, biological tissues are more complex than that, they include dielectrics and consequently they show time dependent responses.

1.2 TIME AND FREQUENCY RESPONSE IN LINEAR SYSTEMS

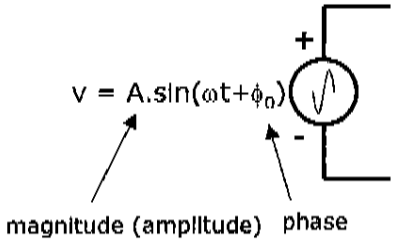
Apart from fixed value voltage and current sources, it is also possible to find, or to implement, sources with a time dependent output. Here, two examples are presented.

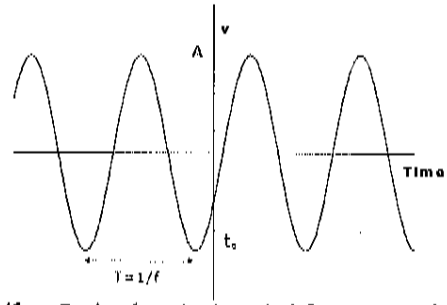
Step voltage source:
The output voltage is 0 V until time equals t_0. Then, the voltage is A.





Sinusoidal voltage source:
The output voltage is a time dependent sinusoid. The shape of the sinusoid is determined by the frequency (number of cycles/second), by the amplitude (maximum voltage value) and by the angle or phase (expressed in degrees).





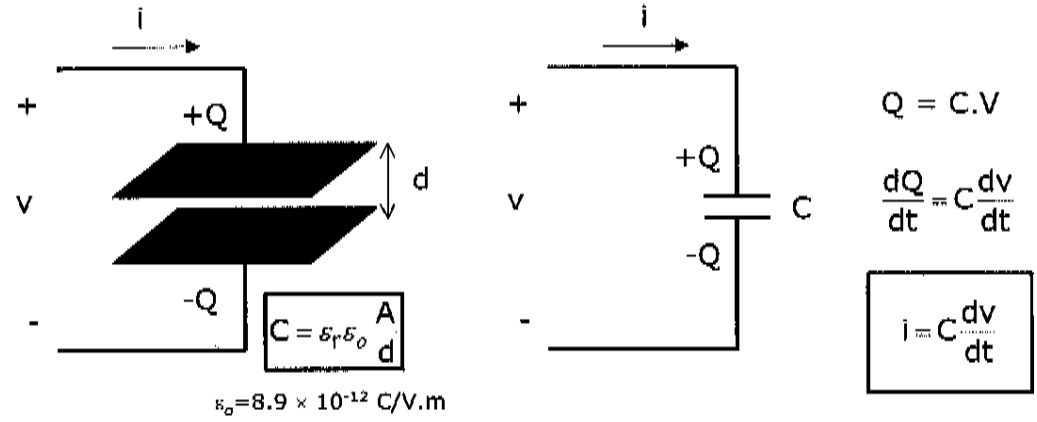
$T = 1/f = 2\pi/\omega$ (period = 1 / frequency)
$t_0 = -\phi_0/\omega$

The phase determines when the sinusoid starts. It can be understood as a delay (t_0) and its value can be either positive or negative.
This signals are also referred as **AC signals** (AC = alternating current).

As it has been said, the biological tissues include dielectrics. Apart from the fact that the resistance of these materials is ideally infinite, they imply another electrical phenomenon: **capacitance**.

Dielectrics are not capable to conduct charge but they are capable to store it. The basic charge accumulator is the **parallel-plate structure**. This element consists of two conductive plates separated by a dielectric. The amount of charge that it is capable to store (Q) is determined by

Its dimensions and by a dielectric parameter: **permittivity** ($\varepsilon = \varepsilon_r.\varepsilon_o$). The **capacitance** (C) relates the voltage with the accumulated charge and it is measured in Farads [F]

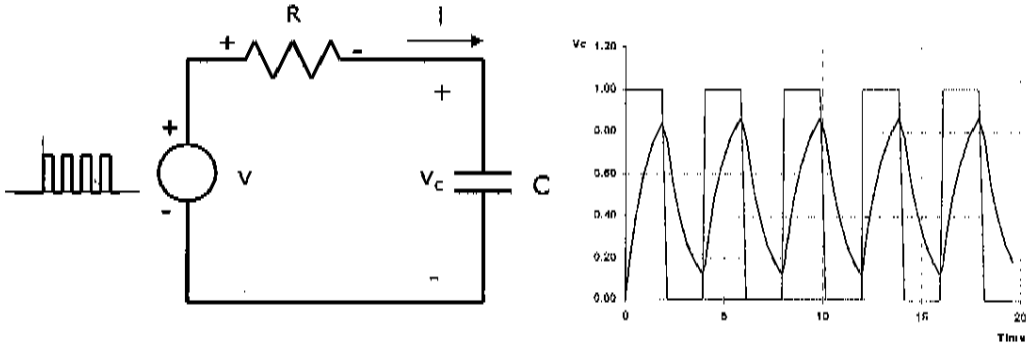


$\varepsilon_o = 8.9 \times 10^{-12}$ C/V.m

The relative permittivity (ε_r) depends on the material between the two plates. If this material is vacuum or air, the permittivity equals ε_o ($\varepsilon_r = 1$).

From the equations it can be easily observed that the relation between voltage and current depends on time. If the capacitance voltage is kept constant, no current enters or leaves the capacitance. However, if this voltage changes with time, a certain quantity of current (proportional to the time derivative of the voltage) will enter and leave the capacitance to charge or to discharge it. That does not mean that charge carriers can physically flow through the dielectric but, from the voltage source point of view that is what happens when the voltage is not constant with time. That is, if a time varying voltage is applied to the capacitance, some current is able to flow through the source.

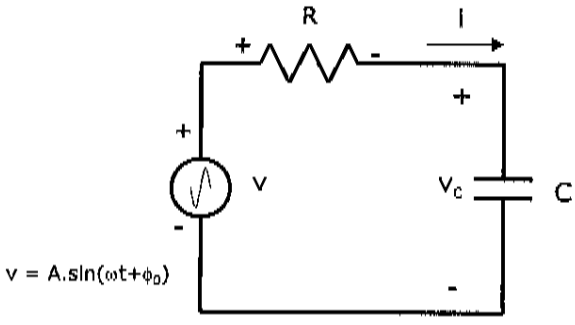
The following example shows what happens when a pulse-train voltage source is connected to a circuit composed by a resistance and a capacitance (RC circuit).

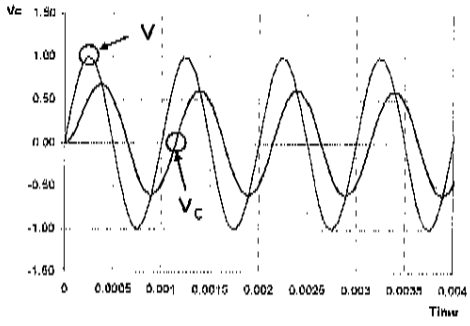


C=1F; R=1Ω

At the beginning the capacitance is discharged (Q=0 Coulombs) and, consequently, the voltage difference between its terminals is 0 V. The first input voltage pulse (plotted in red) causes some current to flow trough the resistance and starts to charge the capacitance. However, since the capacitance increases its voltage (plotted in blue), the current decreases and the voltage evolution is flattened.
When the voltage source comes back to 0 V, the capacitance is charged and it starts to return the accumulated charge through the resistance. The evolution is also flattened because the capacitance voltage decreases as it losses charge.

As it can be observed, for this kind of input signal, the voltages and currents in the circuit can show a different shape (input: rectangular pulse train → output: saw shape). However, there is a special kind of signal that maintains its shape: the sinusoidal signal.





$f = \omega/2\pi$ = 1kHz; ϕ_0 =0

C=200nF; R=1kΩ

The voltage at the capacitor is a sinusoidal with the same frequency as the voltage source. The only differences are the amplitude and the phase. The same can be said about all the voltages and currents around the circuit. This is a fundamental property of linear circuits (for instance, any combination of resistors, capacitors and inductors):

> In a linear circuit, when the excitatory signal is a sinusoidal current or voltage source, all voltages and currents are sinusoidal signals with the same frequency of the excitatory signal.

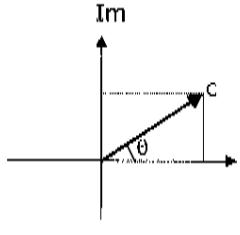
This fact, combined with the fact that any signal can be expressed as a combination of sinusoids (Fourier Series) is of great relevance in electronics and communications. Once that the circuit has been characterized for each frequency (two parameters for each frequency: amplitude and delay) it is possible to compute the output signal for any kind of input signal.

The **impedance** of an element at a certain frequency is defined as the relation between the input voltage and the input current for that frequency. Thus, it should be clear that for a linear element two relations will exist between voltage and current: 1-relation of amplitudes (or modulus or magnitudes) and 2- relation phases ('delay' between current and voltage).

AC signals are usually represented as **complex numbers**. This special kind of numbers contains information of the modulus and the phase. Below there are some figures and equations trying to explain this concept. However, the only thing that must be clearly understood is that complex numbers are a proper way to represent modulus and phase simultaneously. The reason to use this nomenclature is for calculus.

Complex number: **c=a+j.b**

- real part of c: Re{c}=a
- imaginary part of c: Im{c}=b



Complex plane

$$\begin{cases} module: |c| = \sqrt{(Re\{c\})^2 + (Im\{c\})^2} \\ phase: \angle c = arctan\left(\dfrac{Im\{c\}}{Re\{c\}}\right) \end{cases}$$

In electronics, the letter **j** ($\sqrt{(-1)} = (-1)^{1/2}$) is used instead of **i** to avoid confusions with the current symbol.

1.3 ELECTRICAL IMPEDANCE

For a given frequency, if **V** and **I** are the complex numbers representing the input voltage and current (magnitude and phase): The **electrical impedance**, **Z**, is a complex number with magnitude equal to the relation of magnitudes and phase equal to the difference of phases.

$$\mathbf{Z} = \mathbf{V} / \mathbf{I} \Rightarrow \begin{cases} |\mathbf{Z}| = |\mathbf{V}| / |\mathbf{I}| \\ \angle \mathbf{Z} = \angle \mathbf{V} - \angle \mathbf{I} \end{cases}$$

The real part of the impedance is called **resistance** while the imaginary part is called **reactance**. The resistive part causes the power loss (the impedance of a resistor is purely resistive, without reactance term, $\mathbf{Z} = \mathrm{Re}\{\mathbf{Z}\}$) while the reactance causes the delay between voltage and current (the impedance of a capacitor is purely reactive $\mathbf{Z} = j.\mathrm{Im}\{\mathbf{Z}\}$)

Although it is not strictly accurate, the impedance concept is also applied when voltage and currents are injected or measured at different points. In those cases it would be more correct to use the term **transimpedance**.

Impedance of a resistance:

As it has been shown before, a resistance obeys the Ohm's law by definition. Thus, the only relation between voltage and current can be a relation of magnitudes.

$$\mathbf{Z} = \mathrm{Re}\{Z\} = R = V/I$$

The same expression is valid for any combination of resistances that can be grouped as a single equivalent resistance.

Impedance of a capacitance:

For a capacitance, the current is proportional to the time derivative of voltage. This means that the Ohm's law as we expressed before is no longer valid.

The impedance of a capacitance is[5]:

$$\mathbf{Z} = -j.(1/(2.\pi.f.C))$$

Thus, the capacitance impedance depends on frequency (f) and is purely reactive (phase = -90º).

It is sometimes said that a capacitance behaves as a resistance with value $1/2\pi fC$: an open-circuit (no conductance) for very low frequencies and a short-circuit for high frequencies. Another way to say the same:

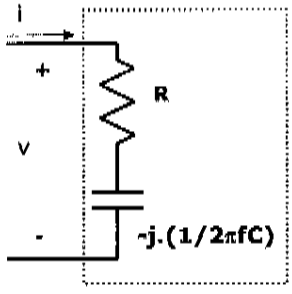
> In a capacitance, high frequency currents are free to flow and low frequency currents are blocked.

This rule is especially useful to understand intuitively the behavior of simple RC circuits.

[5] The demonstration of this expression is beyond the scope of this paper.

Extended Ohm's law:

The Ohm's law, and the parallel and series equivalents, can be applied to any linear circuit using the impedance complex values. For instance, the following figure shows how to calculate the impedance of a circuit formed by a resistance and a capacitance in series.

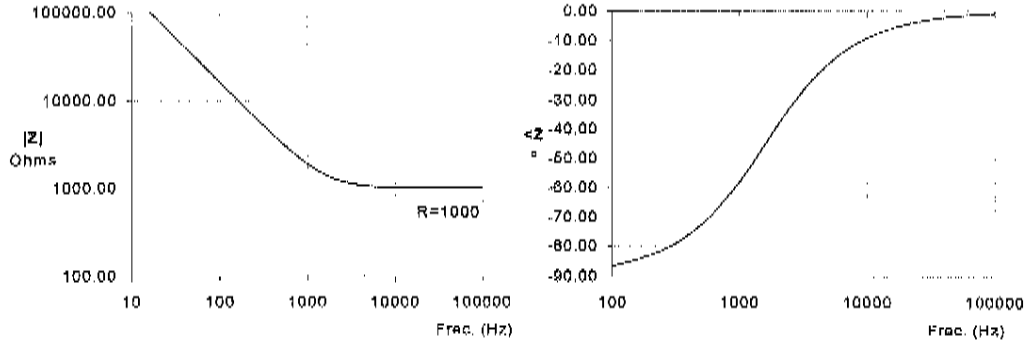


$$Z = R + \frac{-j}{2\pi fC} \Rightarrow \begin{cases} Re\{Z\} = R \\ Im\{Z\} = \frac{-1}{2\pi fC} \end{cases}$$

$$|Z| = \sqrt{R^2 + \frac{1}{(2\pi fC)^2}}$$

$$\angle Z = \arctan\left(\frac{\frac{-1}{2\pi fC}}{R}\right)$$

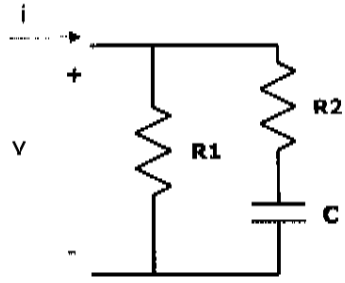
For R = 1 kΩ and C = 100 nF (10^{-9} F) the following graphs are obtained:

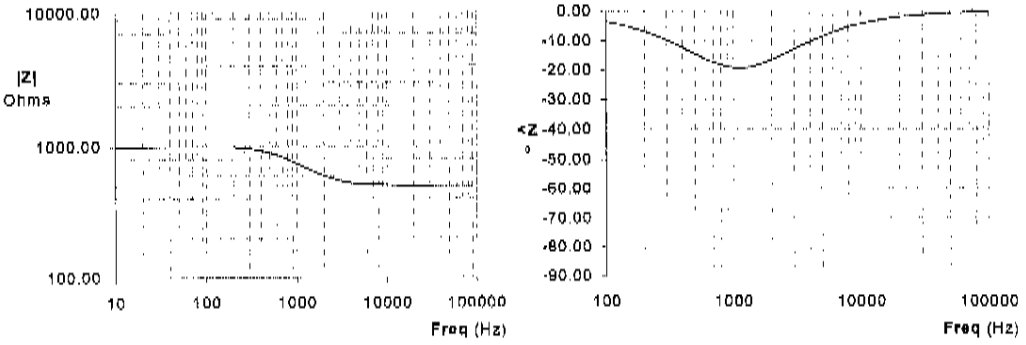


These graphs are the **Bode plots** of the impedance. On the left, the magnitude, or modulus, of the impedance is displayed for each frequency (f). Both axes, horizontal and vertical, are expressed in logarithm base 10. The graph on the right shows the phase value for each frequency. In this case, only the frequency is expressed in the logarithm form.

It is possible to describe intuitively such behavior. At low frequencies, f < 10 Hz, the capacitance blocks the current and, therefore, the impedance modulus must be very high. Because of that, the 'most important' impedance is the impedance of the capacitance and the phase is imposed by it. Thus, the impedance phase gets closer to -90° as the frequency is reduced. On the other side, at high frequencies, the current is free to flow trough the capacitance and the limiting element is the resistance.

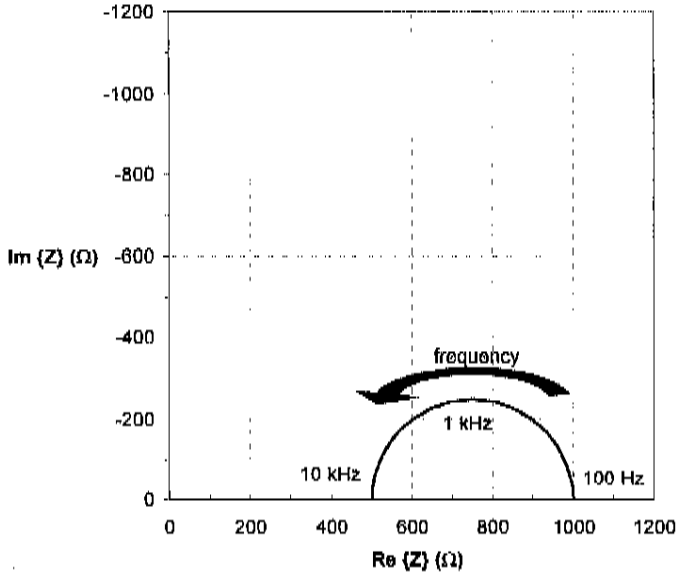
In the following example, try to describe the Bode graphs by yourself (C=100nF, R1=1kΩ and R2=1kΩ):





At low frequencies the current is blocked by the capacitance and the current is only capable to flow trough R1. Therefore, the impedance is imposed by R1 and that means that the modulus is $|R1| = R1 = 1\ k\Omega$ and the phase is $\angle R1 = 0\ °$. At high frequencies the capacitance behaves as a short-circuit and the impedance is R1 in parallel with R2 = R1||R2 = (R1*R2)/(R1+RR2) = 500 Ω. In this case it will be said that a single **dispersion** exists, that is, a single transition from a constant impedance value (|Z| at low frequencies) to another constant value (|Z| at high frequencies) is detected. In general, the number of observable dispersions (or transitions) will depend on the number of RC branches provided that their values are quite dissimilar (different frequency regions).

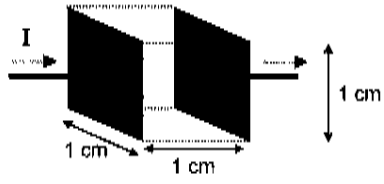
The same information can be displayed using another kind of representation: the **Wessel diagram** (also called **Cole** diagram or **Nyquist** plot).



The imaginary part (with negative sign) of the impedance is plotted versus the real part of the impedance for each frequency. This representation is particularly used in electrochemistry and has been adopted by many researchers in the bioimpedance field. Its main advantage is that each dispersion is easily identified because it is displayed as an arc.

1.4 ELECTRICAL CHARACTERIZATION OF THE MATERIALS

As it has been noted, the impedance values are not only determined by the electrical properties of the materials (conductivity and permittivity) but also by the geometrical constraints. In general, the values of interest will be the electrical properties of the materials since they will be not dependent on the geometry used in each study. The values displayed by the instrumentation setup will be expressed as impedance or conductance values but they are easily transformed into material electrical properties by applying a scaling factor that depends on the geometry, the **cell constant**. The reference geometry is a cubic slab of the material in which the impedance is measured trough two ideally conducting plates at opposite sides. In the bioimpedance field, the size of this cube is usually 1 cm × 1 cm × 1 cm.



$$\mathbf{Y} = G + jB = G + j\omega C = K(\sigma + j\omega\varepsilon) = K(\sigma + j\omega\varepsilon_r\varepsilon_0)$$

Where:

Y is the admittance (=1/**Z**, inverse of the impedance)

G is the real part of the admittance and it is called conductance (expressed in Siemens (S) = 1/ Ohm (1/Ω))

B is the imaginary part of the admittance and it is called susceptance (expressed in Siemens (S) = 1/ Ohm (1/Ω))

C is the capacitance (expressed in Farads (F))

K is the scaling factor of the measurement cell = area/length (expressed in $cm^2/cm=cm$)

σ is the conductivity of the material (expressed in S/cm)

ε is the permittivity of the material (expressed in F/cm)

ε_r is the relative permittivity of the material and is the permittivity of the material/permittivity of the vacuum (8.8×10^{-14} F/cm)

Unfortunately, there is no general agreement on how to express the dielectric properties of the materials and different parameters and symbols will be found the literature. The following list summarizes the most commonly used parameters and their relationships. It must be noticed

that the proper characterization of a dielectric material requires two parameters for each frequency.

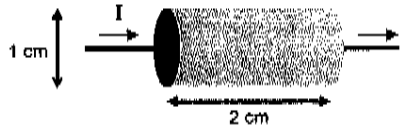
Parameter	Symbols	Units	Equations
conductivity	σ, κ	S/cm	$\mathbf{Y} = G + jB = K(\sigma + j\omega\varepsilon)$; $\sigma = G/K$
permittivity	ε	F/cm	$\mathbf{Y} = G + jB = K(\sigma + j\omega\varepsilon)$; $\varepsilon = B/(\omega K)$
relative permittivity	ε_r	no units	$\varepsilon_r = \varepsilon/\varepsilon_0$
resistivity	ρ	Ω.cm	$\mathbf{Z} = 1/\mathbf{Y} = (R + jX)$; $R=(1/K).\rho$; $\rho \neq 1/\sigma$

Notes:

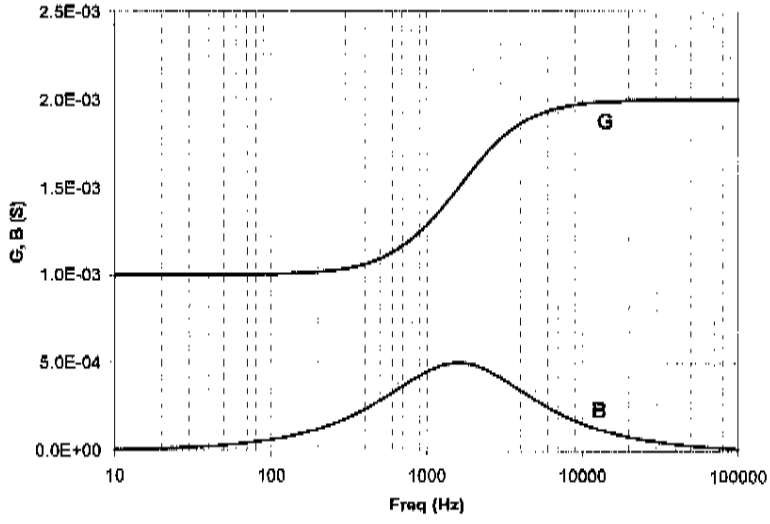
1. In some studies, specially those working at a single frequency, the conductivity and resistivity values are not strictly treated. In those cases, it is assumed that the imaginary part is not relevant (an assumption that is quite well-founded in BM field) and, consequently, the following equations are adopted: $Y = |Y| = K.\sigma$; $\mathbf{Z} = |Z| = (1/K).\rho$; $\rho = 1/\sigma$

2. the "complex conductivity" and "complex permittivity" parameters have also been defined and are being used by some authors (see Grimnes and Martinsen, 2000)

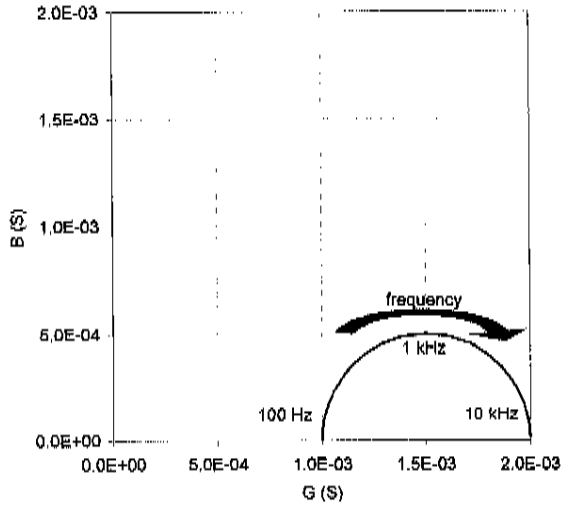
As a didactical example now it will be shown how the conductivity (expressed in Siemens/centimeter, S/cm) and the relative permittivity ($\varepsilon_r=\varepsilon/\varepsilon_0$, no units) can be obtained from the measured impedance values:
Imagine that the impedance values of the previous circuit (R1 in parallel with R2 and C in series) have been obtained by measuring the following piece of material.



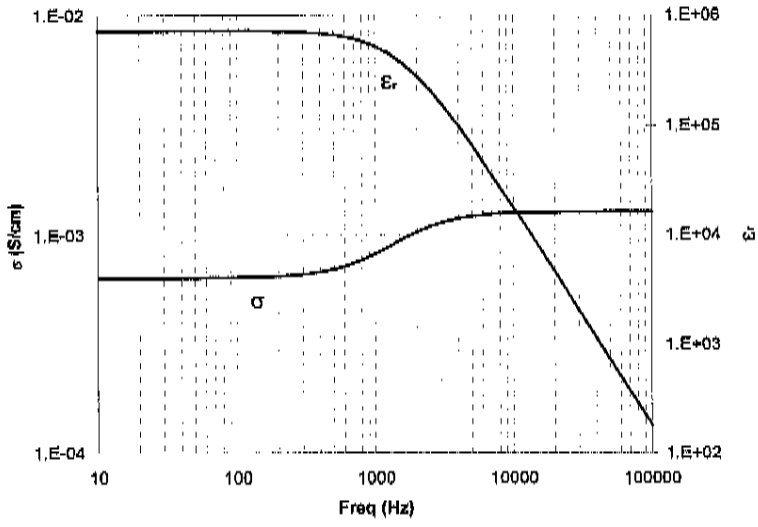
Since the admittance ($\mathbf{Y}= G+jB = G+j\omega C = K(\sigma+j\omega\varepsilon)$ = (section/length)$(\sigma+j\omega\varepsilon)$) is directly related with the parameters of interest, the first step is to obtain it by inverting the impedance ($\mathbf{Y}=1/\mathbf{Z}$). Then, the real part (G) and the imaginary part (B) of **Y** can be isolated. The following plot shows the conductance (G) and the susceptance (B) expressed in Siemens(S). Observe that this is not a Bode plot (the Y axis is expressed in linear units).



A Wessel diagram can also be plot with the conductance and susceptance values.



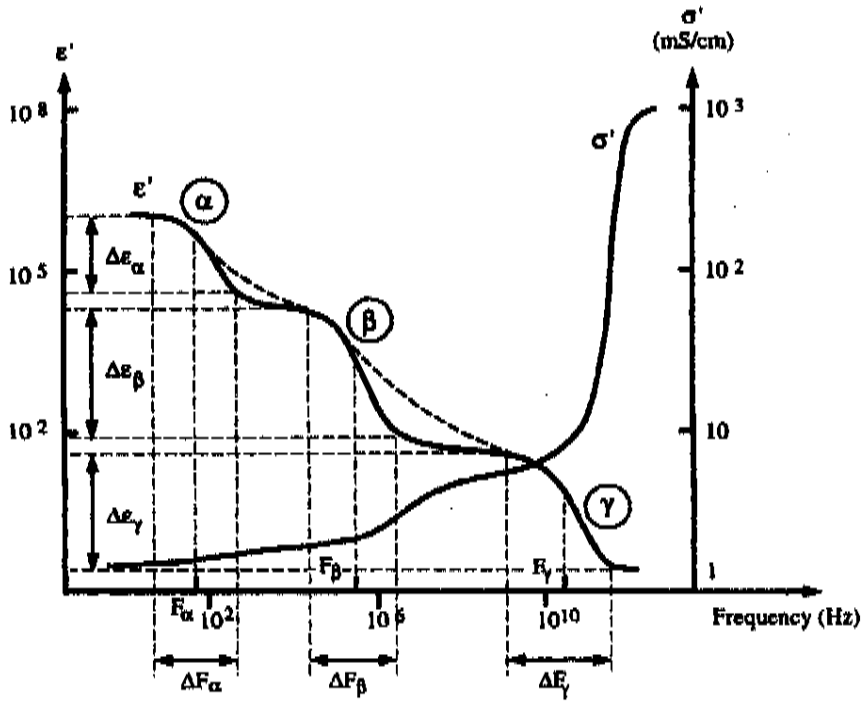
The scaling factor (K) is ($\pi \times 1$ cm^2)/(2 cm) = 1.57 cm. Then, the conductivity ($\sigma = G/K$) and the relative permittivity ($\varepsilon_r = \varepsilon/\varepsilon_0$, $\varepsilon_0 = 8.8\times10^{-14}$ F/cm; $\varepsilon = B/(\omega K) = B/(2\pi f K)$) can be obtained from the conductance (G) and susceptance (B) values:



2. ELECTRICAL BIOIMPEDANCE

Electrical bioimpedance is defined as the measurement of the electrical impedance of a biological sample. This parameter per se is of minor importance. However, it can reflect some interesting physiological conditions and events.

Schawn (Schawn, 1957) defined three frequency regions for the dielectric properties of biological materials from the observed main dispersions of the conductivity and the permittivity (see the plot below).



(reproduced from Bourne et al, 1996)

The large dielectric dispersions appearing between 10 Hz and tens of MHz (α and β dispersion regions) are generally considered to be associated with the diffusion processes of the ionic species (α dispersion) and the dielectric properties of the cell membranes and their interactions with the extra and intra-cellular electrolytes (β dispersion). The dielectric properties at the γ region are mostly attributed by the aqueous content of the biological species and the presence of small molecules (Foster et Schawn, 1989). Some authors also reference a fourth main dispersion called δ between the β and γ the dispersions, around 100 MHz, (Pethig, 1984) that would be caused by the dipolar moments of big molecules such as proteins.

The reader just needs to keep in mind that the purpose of this paper is to describe the tissue impedance changes observed between 100 Hz and 10MHz and, therefore, we will be dealing with the so called β **dispersion**.

2.1 ORIGIN OF THE β DISPERSION

The cell is the basic unit of living tissues. Its basic structure (a phospholipid bilayer membrane that separates the intracellular medium from the extracellular medium) determines the tissue electrical impedance from some Hz to several tens of MHz.

Extracellular medium

From the electrical point of view, the extracellular medium can be considered as a liquid electrolyte (ionic solution). By far, the most important ions are Na^+ (~ 140 mM) and Cl^- (~100 mM). Thus, the electrical properties depend on all physical or chemical parameters that determine their concentration or mobility.

The **temperature** plays an important role in ionic conductance. As it has been said, the viscosity of the solvent decreases as the temperature rises, increasing the ion mobility and, consequently, decreasing the resistance. Specifically, there exist a linear relation between temperature and ionic conductance (1/resistance) that lies around 2%/ºC. However, this temperature coefficient is not fixed and should be determined for each kind of tissue (Gersing, 1999).

For small **ion concentrations** or small concentration changes, a linear relationship between conductance and concentration can be assumed. Of course, other ions than Na^+ and Cl^- or charged molecules (proteins) will contribute to the overall conductivity (see the table below).

In most tissues, the **pH** is in the range 6-8. Hence the concentration of H_3O^+ ions is very low (~μM) and does not contribute significantly.

Intracellular medium

The ionic concentration of the intracellular medium is similar to the concentration of the extracellular medium (180 meq/L against 153 meq/L). In this case, the important charge carriers are K^+, protein- and HPO_4^{2-} + SO_4^{2-} + organic acids.

Besides the ions and other charged molecules, inside the cell it is possible to find numerous membrane structures with a completely different electrical response. These membranes are formed by dielectric materials and their conductivity is very low. Thus, the impedance of the intracellular medium must be a mixture of conductive and capacitive properties. However, for simplification, it is generally accepted that the intracellular medium behaves as a pure ionic conductor.

	cations (meq/L)			anions (meq/L)	
	extracellular	intracellular		extracellular	intracellular
Na^+	142	10	Cl^-	103	4
K^+	4	140	HCO_3^-	24	10
Ca^{2+}	5	10^{-4}	protein-	16	36
Mg^{2+}	2	30	HPO_4^{2-} + SO_4^{2-} + organic acids	10	130
H^+	4×10^{-5}	4×10^{-5}			
Sum	153	180	Sum	153	180

Concentration of electrolytes in body liquids. From (Grimnes et Martinsen, 2000).

Cell membrane

The cell membrane has a passive role (to separate the extra and the intracellular media) and an active role (to control the exchange of different chemical species).

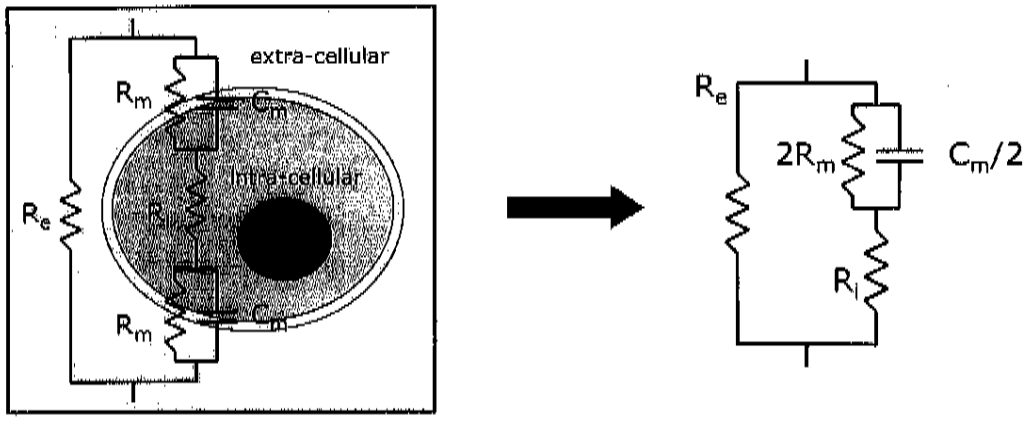
The passive part of the cell membrane is the bilayer lipid membrane (BLM). This film (~7nm thick) allows lipids and water molecules to pass trough it but, in principle, it is completely closed for ions. Its intrinsic electrical conductance is very low and it can be considered a dielectric. Therefore, the structure formed by the extracellular medium, the BLM and the intracellular medium is a conductor-dielectric-conductor structure and it behaves as a capacitance (~1 $\mu F/cm^2$).

In parallel with the BLM there are embedded proteins, transport organelles, ionic channels and ionic pumps. These structures are the basic elements of the membrane active role. Of particular interest to us are the ionic channels and the ionic pumps.

The **ionic channels** are porous structures that allow some ions to flow from the outside to inside of the cell or vice versa or to flow from one cell to another one (**gap junctions**). These structures are selective to ions and can be opened or closed by some electrical or chemical signals.

The **ion pumps** are energy-consuming structures that force some ions to flow trough the membrane. Apart from creating a DC voltage difference across the membrane, they are responsible of maintaining the hydrostatic cellular pressure and their failure yields to cellular edema.

It is desirable to depict **equivalent circuit models** of the tissue bioimpedance because they are useful to attribute a physical meaning to the impedance parameters. Now, from what has been said about the main constituents of the cell, a simple electrical model for the cell can be induced (see the figure below). The current injected into the extracellular medium can flow trough the cell across the BLM (Cm) or across the ionic channels (Rm) or can circulate around the cell (Re). Once the current is into the cell it 'travels' trough the intracellular medium (Ri) and leaves the cell across the membrane (Rm || Cm)



The circuit on the right is equivalent to the left model after performing some simplifications (resistances in series and capacitances in parallel). The same simplifications can be applied to reduce a tissue composed by many cells to a single cell equivalent circuit.

Usually, the membrane conductance is very low and Rm is ignored. In this case, the equivalent circuit is very simple and a single dispersion exists (see the last circuit example). This model has been adopted by many authors and is used to explain the impedance measurements from DC to some tens of MHz. At low frequencies (<1 kHz) most of the current flows around the cell without being able to penetrate into the cell. At high frequencies (> 1 MHz) the membrane capacitance is no impediment to the current and it flows indiscriminately trough the extra and intracellular media.

The previous model works reasonably well for dilute cell suspensions. However, the tissue bioImpedance tends to be more complex than that and it is not unusual two observe two superimposed dispersions in the frequency band from 10 Hz to some MHz[6]. An example is the myocardial muscle (Casas, 1998) (Casas et al., 1999). This fact means that another resistance-capacitance couple should be added to mimic the bioimpedance results. In the case of the myocardium, this second dispersion is attributed to the significant presence of gap junctions (Gersing E., 1998).

Furthermore, it is necessary to substitute the capacitance in the previous dispersion models by a part called **Constant Phase Element (CPE)** in order to fit accurately the modeled impedance values to the actual bioimpedance measurements. The CPE is not physically realizable with ordinary lumped electric components but it is usually described as a capacitance that is frequency dependent. The impedance of the CPE is:

$$Z_{CPE} = \frac{1}{(j \cdot 2\pi \cdot f \cdot C)^{\alpha}}$$

The α parameter usually is between 0.5 and 1. When it is 1 the behavior of the CPE is exactly the same of an ideal capacitance.

The physical meaning of the CPE is not clearly understood. Some authors suggest that α can be regarded as a measure of a distribution of resistance-capacitance combinations. That is, the tissue is not homogeneous and the sizes of the cells are randomly distributed, thus, the combination of the equivalent circuits can differ from the simple RC model.

When the CPE is included in the simple bioimpedance equivalent circuit (a resistance-capacitance series combination in parallel with a resistance), the expression of the impedance is:

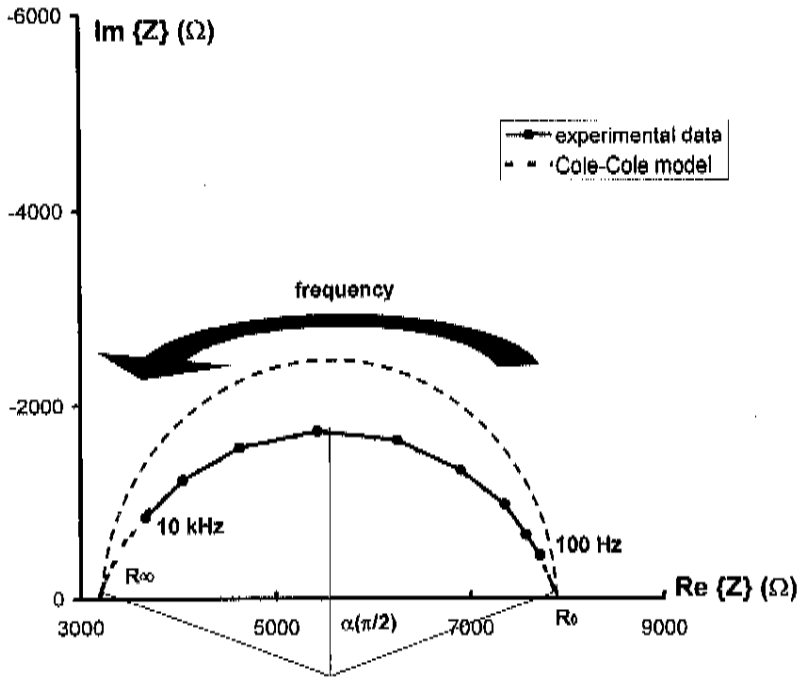
$$Z = R_{\infty} + \frac{\Delta R}{1 + (j \cdot 2\pi \cdot f \cdot \tau)^{\alpha}}$$

This expression, called **Cole-Cole equation**, was found by the Cole brothers in 1941 and is used by most authors in the bioimpedance field to describe their experimental results. Hence the tissue bioimpedance is characterized with four parameters: R_{∞}, ΔR, α and τ. The parameter R_{∞} represents the impedance at infinite frequency (only resistive part), Ro (= R_{∞} + ΔR) is the impedance at frequency 0 Hz, τ is the time constant ($\Delta R.C$) and α is the α parameter of the CPE.
The resistive values (R_{∞}, ΔR, Ro) are usually scaled to resistivity values by using the by the cell constant. The α and τ are not dependent on the cell dimensions and, therefore, do not need to be scaled.

In the representation of the Cole-Cole equation on the Wessel diagram, the arc is no longer a semicircle centered in the real axis. Instead of that, the semicircle center is above the real axis and the arc is apparently flattened. That displacement depends on the value of α ($\alpha = 1 \Rightarrow$ semicircle centered on the real axis).

The following Wessel diagram shows an actual bioimpedance multi-frequency measurement (**bioimpedance spectrometry**) from a rat kidney. Observe that the Cole-Cole model fits the actual data and that it is equivalent to a semicircle centered below the real axis (take into account that the imaginary axis has been inverted)

[6] In this situation, two arcs will be observed on the Wessel diagram.



In the case that two or more dispersions are observed (e.g. in the myocardium), the above equation is expanded to include the model of each dispersion.

$$Z = R_{\infty} + \frac{\Delta R_1}{1 + (j \cdot 2\pi \cdot f \cdot \tau_1)^{\alpha_1}} + \frac{\Delta R_2}{1 + (j \cdot 2\pi \cdot f \cdot \tau_2)^{\alpha_2}} + \ldots$$

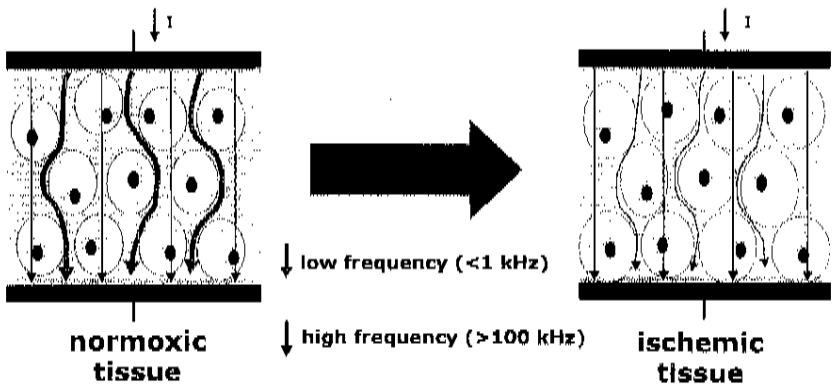
Hence the characterization parameters are: R_{∞}, ΔR_1, α_1, τ_1, ΔR_2, α_2, τ_2 ...

It must be said that some authors renounce to depict equivalent circuits of the bioimpedance because they consider them a dangerous practice that can produce erroneous interpretations (McAdams et al., 1995). The same impedance measurements can be interpreted as completely different circuits with different topologies and values. Thus, these authors chose a mathematical model (Cole-Cole equation) to describe their results without trying to interpret them.

3. BIOIMPEDANCE MONITORING

The electrical impedance of a living tissue can be continuously measured in order to determine its patho-physiological evolution. Some pathologies like ischemia, infarct or necrosis imply cellular alterations that are reflected as impedance changes. As it was described in the introduction, the bioimpedance monitoring has been proposed for myocardium ischemia detection, for graft viability assessment and for graft rejection monitoring. In most of the cases, the event is detected or monitored because an alteration of the extra-intracellular volumes occurs.

The following figure illustrates how Ischemia is monitored by biomedance measurements. During the normoxic condition, a significant amount of low frequency current is able to flow trough the extracellular spaces. When ischemia and the following lack of oxygen (hypoxia) is caused by any means, the cells are not able to generate enough energy to feed the ion pumps and extracellular water penetrates into the cell. As a consequence, the cells grow and invade the extracellular space. This causes a reduction of the low frequency current that yields an impedance modulus increase at this low frequency. Thus, the bioimpedance measurement at low frequencies is an indicator of the tissue ischemia.



This simplistic description of the ischemia-impedance relationship could be not correct for cells containing gap junctions. In those cases (e.g. myocardium) the observed impedance increase at low frequencies is mostly attributed to the closure of the gap junctions (Gersing, 1998) (Groot, 2001).

As an example, the following graph shows the evolution of the impedance modulus at 1 kHz for six impedance probes inserted in a beating pig heart subjected to regional ischemia (see the method in Groot, 2001). Three of them are within a normoxic area and the other three are within the area influenced by the ischemia.