

EIS White paper 03/20/09
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EIS system Features and Background

EIS Measurements and ESG graph

A DC, very low frequency (0.02-1Hz) and then a low frequency (1 KHz) are applied between six tactile electrodes placed symmetrically on the forehead, hands, and feet of the subject. Each electrode is alternatively cathode and anode (bipolar mode), which permits the recording of 22 segments from the human body (measurement sequence according to the figure 1). The intensity is transmitted with a numeric form for each segment to an informative program.

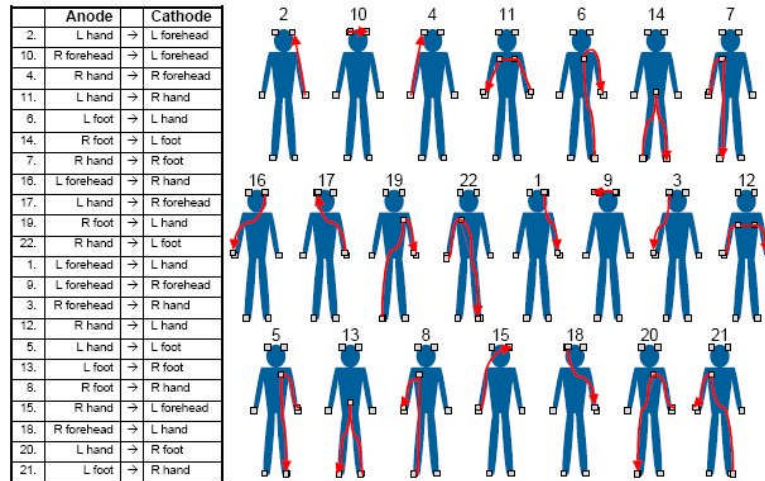


Figure 1

The intensity value is converting to conductivity by application of the Law of Ohm⁽³¹⁾
 $U = RI$ then $C = 1/R$, incorporated in a Graph. The graph of the conductivity of the 22 segments is called an Electro Scan Gram (E.S.G) (Figure 2).

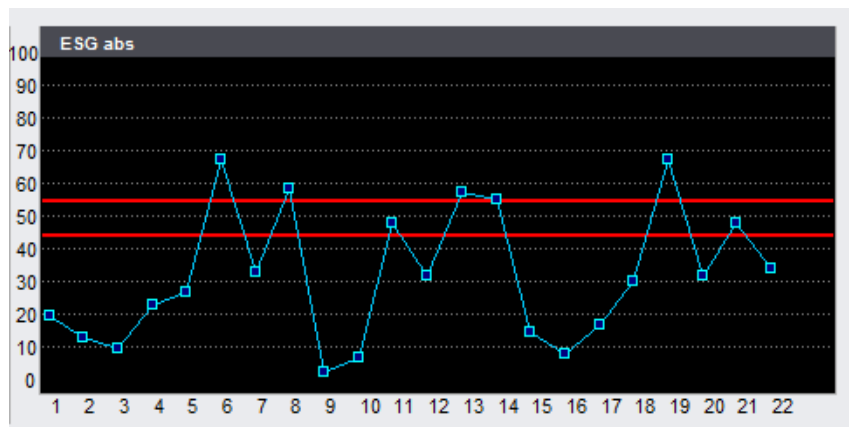


Figure 2

Normal range of ESG conductivity

The normal ranges of conductivity of the ESG graph (Figure 3) were estimated by the formula of the TWB volume using in BIA (Body Impedance Analysis) and a coefficient p related to the age, height, weight, and the gender of the subject.

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Formula of the calculation of TWB (total body water) $v = \rho Ht^2/R \Rightarrow R = \rho v / Ht^2 \Rightarrow C = \rho Ht^2/v$

R is the measured resistance from the right hands and the right feet.

The estimated coefficient ρ had been determined with the statistical analysis raw data of healthy control groups of the pre-studies, clinical investigations and users' databases.

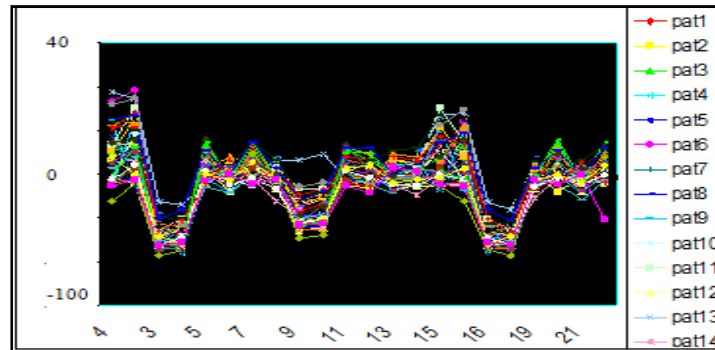


Figure 3

Background of the used technique

Techniques:

The used techniques are:

- ✓ The Electrode Polarization Impedance (EPI)⁽¹⁾,
- ✓ The galvanic skin responses⁽⁷⁾
- ✓ The electrical Bio Impedance Analysis (BIA)⁽³²⁾
- ✓ The bio Impedance Spectrometry (BIS)⁽³³⁾

The BIA is used in many applications like the estimated of the body composition and water balance^{(5), (14)} but also in cardiology^{(3) (13)}, Ischemia (O₂ and pCo₂ delivery)⁽²⁾ and imaging⁽¹⁹⁾. The BIS is used for estimated the body composition and water balance^{(5), (14)}, but also for estimated the neurotransmitters^{(23) (24)} The galvanic skin responses is used for the stress evaluation⁽⁷⁾ and the EPI is used for Na/Cl concentration⁽¹⁾

Electrode Polarization Impedance (EPI)⁽¹⁾

The polarization ratio is a ratio of polarization impedance and bulk resistance of the electrolyte. The polarization ratio diminishes as a function of concentration in diluted Na/Cl solutions regardless of electrode material. The data for the medical stainless steel behaved concentration independent and it had high electrode polarization impedance compared to other electrodes.

Bio Impedance Analysis (BIA)

The specificity of the technique is the utilization of a very low frequency that cannot cross the cellular membranes and therefore can only reach the interstitial fluid (Interstitial tissue)⁽³⁴⁾, whose intensity, resistance, and conductivity can then be measured

These facts were confirmed by the research of Kanai and Meijer^{(11), (18)}, i.e., that the cellular membrane and capillaries behave as one capacity because of dielectric properties, so a direct

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current cannot penetrate its membranes and circulate solely in the interstitial fluid. The tissues constitute an electrolytic environment; conduction of electric current is assured by the ionic porters⁽³⁵⁾, under the effect of a tension applied between two electrodes.⁽¹⁴⁾ The conductivity is also related to the volume (water content) of the space traversed⁽¹⁴⁾ (Interstitial Fluid)

The electric current is sending from anode to cathode and therefore the sodium (higher extracellular concentration in positive charges) represents the main ionic porters. Figure 5 and 6 are showing the correlation of the traversed compartment intensity and the Na⁺ concentration.⁽⁵⁾. The figure 7 is showing the correlation between **the volume** (water content) and the traversed compartment conductivity.⁽¹⁴⁾.

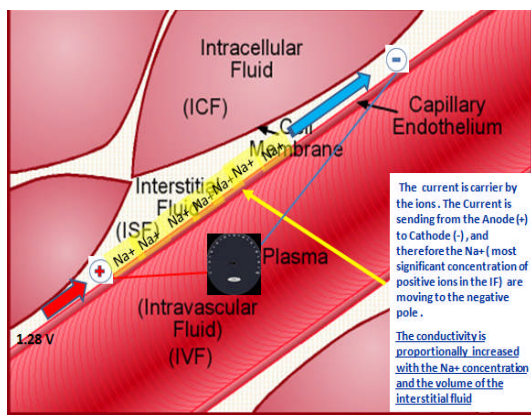


Figure 5

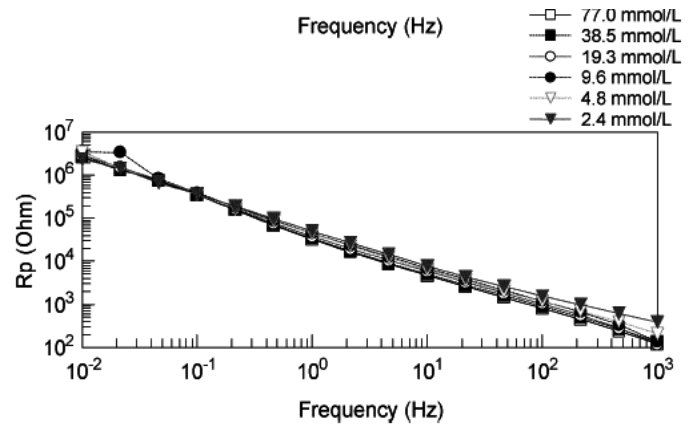


Fig. 6. Polarization impedance for one medical stainless-steel electrode surface (0.07 cm²) in 2–77 mmol/L NaCl solutions.

Figure 6

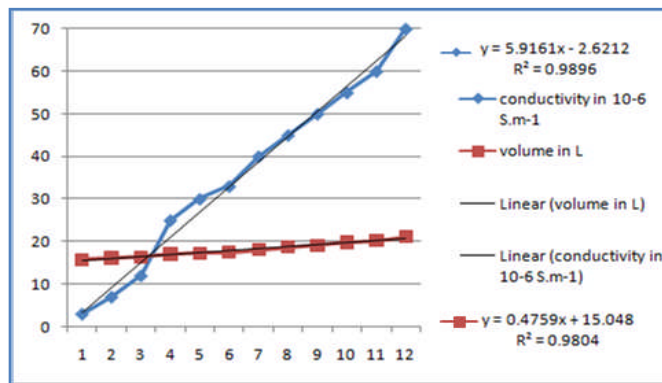


Figure 7

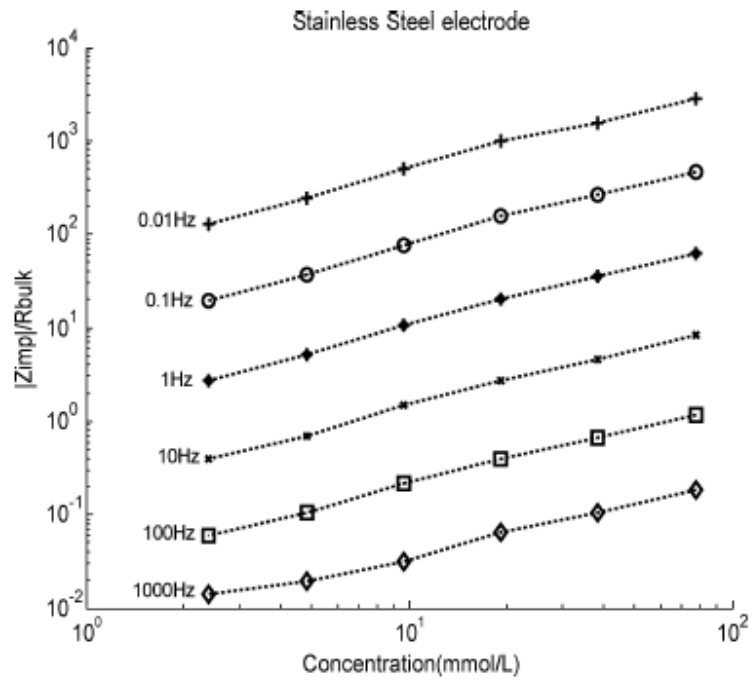


Fig. 9. Ratio of impedance $|Z_{imp}|$ and R_{bulk} as a function of concentration, two stainless-steel electrode surfaces.

Normal range in volume of the interstitial fluid

The volume of interstitial fluid is related with

The total weight: normal range 16% +/- 3 of the total weight

The size of this space (inter capillary distance): 80 +/- 5 μm

Estimated Tissue Oxygen delivery

- I. Estimated of oxygen delivery related to the inter-capillary distance ⁽³⁶⁾.

The figure 10 is showing the effect of inter capillary distance variations (interstitial fluid volume) in relation with the tissue oxygen delivery. In case of increased of interstitial volume, the oxygen delivery is reduced.

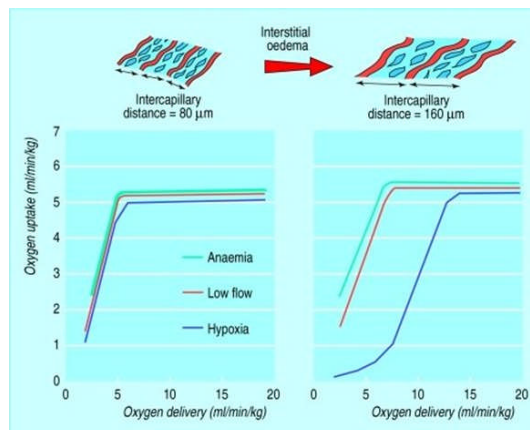


Figure 10

2. Estimated of oxygen delivery related to the resistance ⁽³²⁾

Low frequencies Bio impedance measurement and Ischemia

The electrical impedance of a living tissue can be continuously measured in order to determine its patho-physiological evolution. Some pathology like ischemia, infarct or necrosis implies cellular alterations that are reflected as impedance changes. The bio impedance monitoring has been proposed for ischemia detection. 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 bio impedance measurements. During the normoxic condition, a significant amount of low frequency current is able to flow through 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 bio impedance measurement at low frequencies is an indicator of the tissue ischemia.

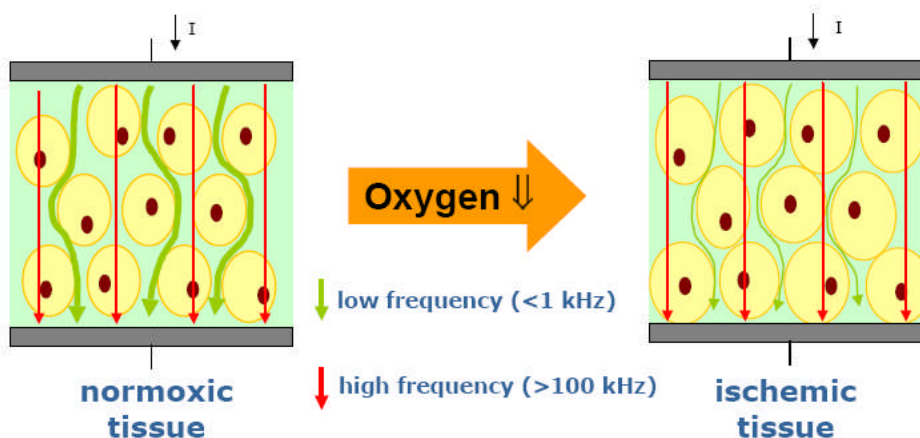


Figure 11

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.

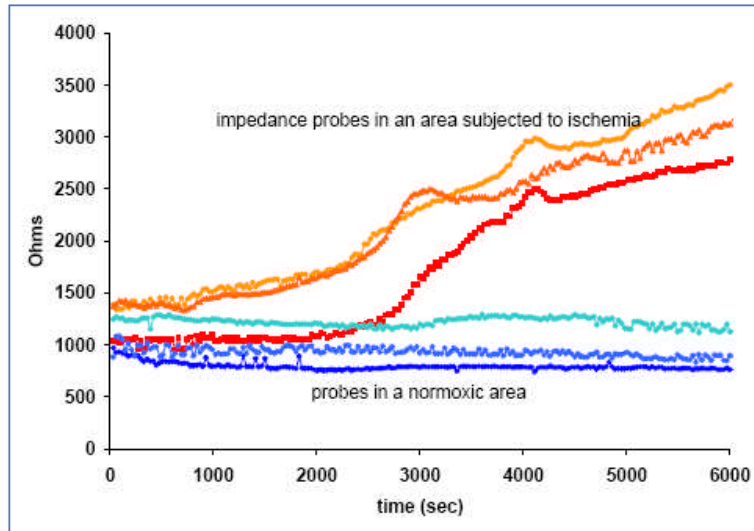


Figure 12

The necrosis process that follows a long ischemia period can also be detected because the loss of membrane integrity allows continuity between the extra and intra-cellular media and, consequently, the impedance magnitude at low frequencies decreases (Haemmerich et al., 2002). Single-frequency measurements are relatively easy performed and provide the necessary Information to follow the ischemia processes. Therefore, some researchers have promoted them as the basis for a clinical parameter to monitor the tissue condition.

Bio Impedance Spectrometry (BIS)

By Using the Spectrometry technique and in particular the EPI⁽¹⁾, The EIS system makes the calculation and estimated the interstitial fluid Na⁺ concentration

Result of BIS: Applications of the measurement of the estimated interstitial fluid Na⁺ concentration:

The interstitial fluid Na⁺ concentration gives access to the estimated activity of:
 Na⁺/K⁺ ATPase⁽³⁸⁾ (Fig.12)

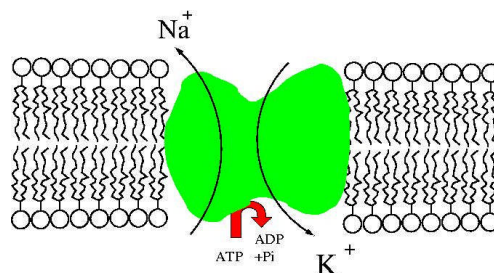


Figure 13

- Na⁺/H⁺ exchanger⁽³⁹⁾
- Na⁺/Ca²⁺ exchanger⁽⁴⁰⁾
- Na⁺/Cl⁻ symporter⁽⁴¹⁾

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Effect of the interstitial fluid pH in human body ^{(27), (28) (29), (30)}

The interstitial fluid or tissue pH (normal range 7.31-7.35) has action on the enzyme activities and therefore in the function of the liver and the pancreas ^{(28) (29), (30)}

The cerebral interstitial fluid or tissue pH (normal range 7.28-7.32) has action in the brain blood flow and neuronal excitability. ⁽²⁷⁾

Hydrostatic and Osmotic pressure: The Starling equilibrium ⁽⁴²⁾

Physiology of the interstitial fluid ^{(25) (26)}

No direct methods for sampling interstitial fluid are currently available. The composition of interstitial fluid, which constitutes the environment of the cells and is regulated by the cells activity and ionic distribution, has previously been measured by the suction blister or liquid paraffin techniques or by implantation of a perforated capsule or wick. The results have varied, depending on the sampling technique and animal species investigated.

In one study, the ionic distribution between vascular and interstitial compartments agreed with the Donnan equilibrium ^{(25) (26)}; in others, the concentrations of sodium and potassium were higher in interstitial fluid than in plasma ^{(25) (26)}. However, the publications ^{(25) (26)} could establish the following elements:

1. Interstitial fluid differs from whole blood by the absence of red blood cells, and it differs from blood plasma because the far fewer proteins. The absence of haemoglobin and poor level of proteins which are the main buffers of the blood system explains a more acid interstitial pH and more importantly, the acid base balance and gases variations in interstitial fluid.
 2. Any substance passing between cells and the bloodstream must traverse the interstitial space. These substances include oxygen, carbon dioxide, glucose, as well as thousands of other compounds.
 3. Unlike the bloodstream the interstitial fluid is stagnant
 4. The volume of the interstitial fluid is closely related to the containing sodium pool
- The exchanges between the vascular sector and the interstitial fluid are complex. The distribution of the electrolytes on each side of the membrane is regulated by “the Donnan equilibrium” which explains why the sodium concentration is more important in the plasmatic sector.

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Correspondence of the interstitial electrolytes/H⁺ and blood electrolytes/H⁺: ⁽²⁵⁾ ⁽²⁶⁾

Reference Studies: Niels Fogh-Andersen, Burton M. Altura, Bella T. Altura, and Ole Siggaard-Andersen CLIN. CHEM. 41/10, 1522-1525 (1995)

Gilanyi M, Ikrenyi C, Fekete J, Ikrenyi K, Kovach AGB. Ion concentrations in subcutaneous interstitial fluid: measured versus expected values. Am J Physiol 1988; 255:F513-9

The results of interstitial electrolytes and blood electrolytes can be completely different for 4 reasons:

- ✓ *The interstitial fluid is stagnant*
- ✓ *Each compartment of the human body presents different concentrations of biochemical values. These differences come from the Donnan equilibrium*
- ✓ *The interstitial Na⁺ and K⁺ have not the same interpretation as the natremia of kalemia, and only reflect the Na⁺/K⁺ ATPase activity*
- ✓ *The measurement of the interstitial electrolytes represent the pool of the substance because the interstitial fluid is at least 4 times higher in volume than the vascular system and therefore less sensible to the water variation*

Interstitial Acid base balance and blood acid base balance

- ✓ *Interstitial fluid acid base balance differs from whole blood by the absence of red blood cells, and it differs from blood plasma because the far fewer proteins. The absence of haemoglobin and poor level of proteins which are the main buffers of the blood system explains a more acid interstitial pH and more importantly, the acid base and gases variations in interstitial fluid.*

Analysis of the ESG graph Statistical domain analysis

EIS Modeling ⁽⁴³⁾

What is a modeling?

The modeling is not the same imagery conventionally used in medicine. The approach is more like that of a physicist's approach. We reduce the diversity and complexity of the bodily functions by an appropriate choice of assumptions and measurements.

We are only keeping the physical properties of the bodily system which relate to the posed problem. In short, we approach reality through a model. Abstraction is the conceptual base of a model: a real object, a phenomenon is analyzed in order to save only the essential characteristics, those that have an influence on that which we wish to study.

We must break up complex problems into simpler problems. This method was expressed by René Descartes (France) in his *Discourse on the Method*: "...divide each of the difficulties for me to examine into tiny fragments and that will be necessary to solve them all..."

The medical modeling is a control tool and helpful in therapeutic decisions. Modeling is not intended to reproduce reality exactly; only a model identical to the system could be regarded as an exact representation of reality. Simulation provides comprehension, it makes it possible to formulate theories and to test them and sometimes it leads to the understanding of that which is incomprehensible without it, by functioning according to a logic centred on the computer.

EIS modeling process

Direct evaluation

- Scale conversion : EIS conversion from the scale 0-100 to -100/+100 (step1)
- Venn diagram (step2)
- Maxwell equation (step3)

A first localization of organs by direct problems came out through application of the mathematical calculation of Venn diagrams ⁽⁴⁴⁾ and application of the Maxwell equation ⁽⁴⁵⁾ for the value of intensity of the different zone of the human body modeling

Chromatology (step 4)

The modeling of the EIS system is made according to a chromatology from blue to red related to the conductivity (from 0 to 110 10⁻⁶ S.m⁻¹) of the zone.

Diagram of the process of EIS modeling:

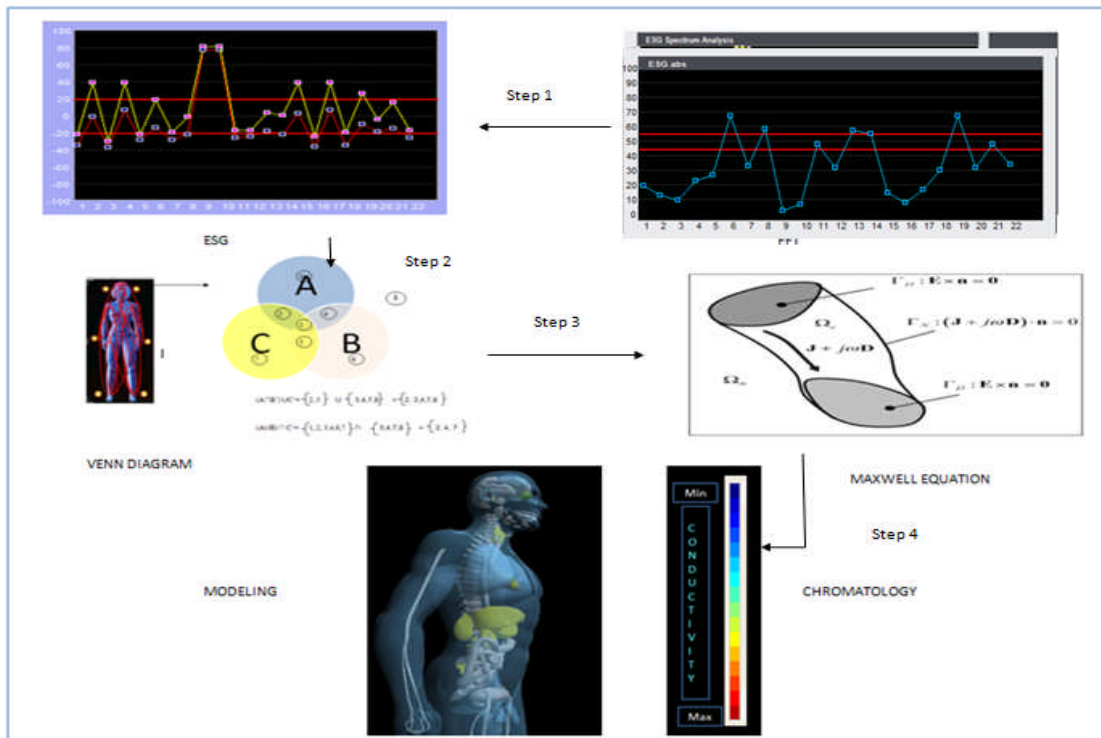


Figure 14

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EIS Estimated indicators of the localized body system on the modeling presentation:

Electrical indicators

- Interstitial Intensity
- Interstitial Conductivity
- Interstitial Resistance

Physiological indicators

- Interstitial pH
- Oxygen delivery
- Na⁺/K⁺APTase pump activity

Micro circulation indicators

- Hydrostatic pressure
- Osmotic pressure

Frequency domain or Spectrum analysis of the ESG graph:

Fast Fourier Transform (FFT)⁽⁴⁶⁾

As shown above, the conductivity of the interstitial fluid is related to the Na⁺/K⁺APTase pump activity.

The Na⁺/K⁺APTase pump activity is related to the ANS (Autonomic Nervous System) activity or inflammatory process.

The mathematical application of the FFT to the ESG graph (Fig.14) , as same application to the Heart Rate variability (HRV is also related to the ANS activity) , and the analysis of the Frequencies graph of the FFT (HF, High Frequency, LF, Low Frequency, VLF, Very Low Frequency) can provide indicators of the ANS activity (Sympathetic and Parasympathetic activities)

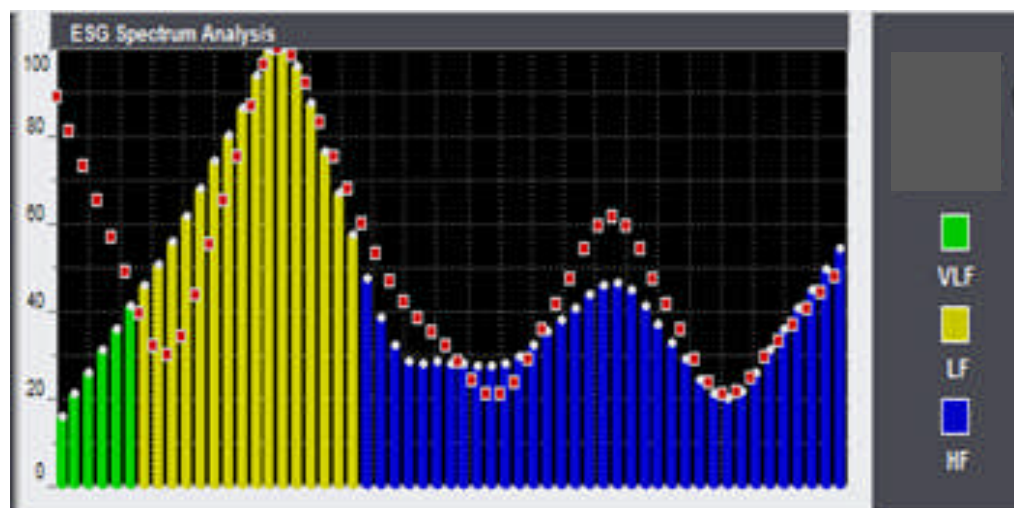


Figure 15

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