BACKGROUD OF THE EIS SYSTEM

EIS system design based upon:

- Bioelectrical impedance and physiology of the interstitial Fluid
- Modeling of the human body according to the mathematical formula of direct and inverse problem
- The chronoamperometry according to the Cottrell's equation (electro chemical formula)
- Clinical investigations
- Statistical analysis

1. Bioelectrical impedance

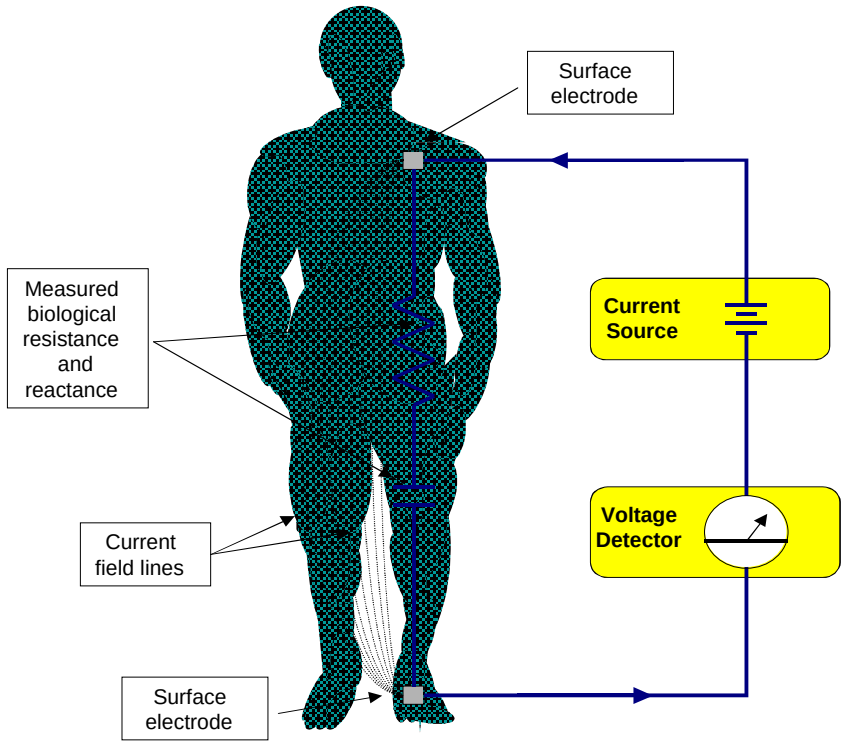
Bioelectric impedance measurements (BIM) represents a wide range of old and new non-invasive technologies and methods where a very small electric current is applied to the body via one or more surface electrode and the resultant electricity pulse passing through the body is detected at other surface electrodes placed elsewhere on the body (see Fig. 1, below). A drop in voltage occurs as the current encounters impedance or resistance inherent in the fluids and tissues it passes through as it courses through the various physiological "compartments" of the body. (1) (3). These compartments include the bloodstream, the intracellular space, the lymphatic system, the interstitial space, and others. (4) (5) this drop in voltage provides indirect information about the physical and chemical properties of the compartment(s) that the current passed through.
Technically, the term "impedance" refers to A.C. forms of electricity and the term "resistance" refers to D.C.

Alternating Current Bioelectric Impedance Methods:
Indication 1 of the EIS system (see the folder: SPECIFICATIONS)

The most familiar form of BIM uses alternating current (A.C.). There are dozens of readily available commercial and custom-built A.C. BIM systems differing widely in design and complexity.(6) Most systems are used to indirectly estimate the fat content of the body by measuring total body water.*(7) (8) These systems typically employ A.C. electricity with a wide range of currents, frequencies, and voltages. The amount of electricity delivered to the body is usually imperceptible and far below the level that would cause cellular or tissue damage.(9) (10) Studies of A.C. BIM systems operating at 50 MHz or higher, have revealed that these high frequency A.C. electric currents flow *non-selectively* through both intracellular and extra cellular spaces (11) (see Fig. 2, below), and thus provide relatively non-specific information regarding the physical properties and chemical composition of body compartments.

*The software calculates total body water (TBW) with the impedance Z issue of sending 200KHz and the formula $v = \rho Ht2 / Z$, (Ht is the high of the subject) , then the extra-cellular water with the impedance Z issue of sending 50KHz and the same formula.
The calculation of fat mass (FM) is described by the formula:
Lean mass = TBW in Kg/0.732
FM in Kg = Total weight – lean mass

Fig. 1: Schematic of the Principles of Bioelectric Impedance Scanning

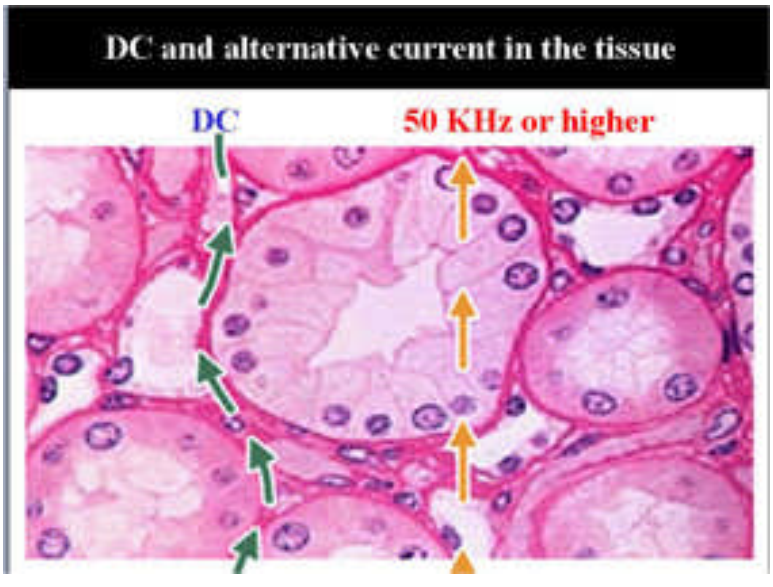


Low-Intensity Direct Current Bioelectric Impedance Methods:
Indications 2,3,4 of the EIS system (see Folder SPECIFICATIONS)

Unlike A.C. bioelectric impedance, the electric current produced by D.C. bioelectric impedance methods specifically passes through the interstitial fluid compartment (23) (see Fig. 2, below). The interstitial fluid compartment represents approximately 16% of the body's total water.(24) (26) **and the DC bioelectric impedance by the same mathematical formula will be measuring the volume of Interstitial fluid .**

Interstitial fluid is *extra cellular* water and solutes surrounding cells, but *outside* of the bloodstream and lymphatic system. Interstitial fluid forms the microscopic interface between cells and capillaries.

Fig.2. Differing routes of DC and AC Electric currents Flowing through the body



Physiology of interstitial fluid

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. (52)

In one study, the ionic distribution between vascular and interstitial compartments agreed with the Donnan equilibrium (51); in others, the concentrations of sodium and potassium were higher in interstitial fluid than in plasma *(51).* However, the publications (51) (52) 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 in that there are far fewer proteins** (51). 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 variations in interstitial fluid gases and blood gases (52).
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 (27) (28).
3. Unlike the bloodstream **the interstitial fluid is stagnant**
4. **The volume of the interstitial fluid is closely related to the containing sodium pool** (52)

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. (51)

By used D.C and the same formula of the measurement of the TBW (see p.2), we can calculate the volume of the interstitial fluid and therefore the estimation of the containing Sodium pool.

Hydrostatic Pressure at the Capillary:

The capillary wall acts as a filtration "barrier". Most of the fluid within the capillaries is retained, but some filters through pores between the cells, pushed by the pressure difference between the capillary blood and the ISF.

Water and small solutes can pass freely through these pores. The net effect of the hydrostatic pressure alone is a net loss of water and solute from plasma to the ISF.

The capillary wall (both cells and pores) are, however, impermeable to the plasma proteins and lipids. Under normal conditions, these stay within the plasma. Note that following injury, the capillaries can also leak protein.

The hydrostatic pressure in the capillaries is lower than that of the arteries, and decreases along the length of the capillary as blood flows through. At the arteriolar end of the capillary, the pressure is usually about **35 mm Hg** (due to the pressure drop caused by the resistance arterioles). On the venule end of the capillary, the pressure is in the range of **15 mm Hg**. The mid-capillary pressure profile can be assumed to be linear.

Osmotic forces in the capillaries:

Because the capillary wall is permeable to water, but essentially impermeant to the plasma proteins, these molecules generate an osmotic pressure. Furthermore, since these proteins are negatively charged, they tend to hold additional cations in the plasma (the Gibbs-Donnan effect), further enhancing an osmotic gradient between the plasma and the interstitial fluid.

The combined effect (osmotic and Gibbs-Donnan) results in a pressure that draws water out of the interstitium and into the plasma. This pressure is known as the **Colloid Oncotic Pressure** (often shortened to the Oncotic Pressure).

This pressure is proportional to the difference in protein concentration between the plasma and the ISF. Compared to pure saline, the plasma exerts about 28 mm Hg Oncotic pressure, whereas the ISF has only about 3 mm Hg. The net Oncotic Pressure is thus about 25 mm Hg. This value remains roughly constant over the length of most capillary beds.

Starling's Relationship

The British physiologist Starling first identified the interrelationship between the hydrostatic pressure and the oncotic forces within the capillary.

Hydrostatic pressure tends to cause fluid to leave the plasma, and oncotic pressure pulls it back. These two forces tend to balance each other.

The hydrostatic forces, however, are gradually decreasing over the length of the capillary, while the oncotic pressure remains constant. If these pressures were graphed, they would look approximately like the following figure:

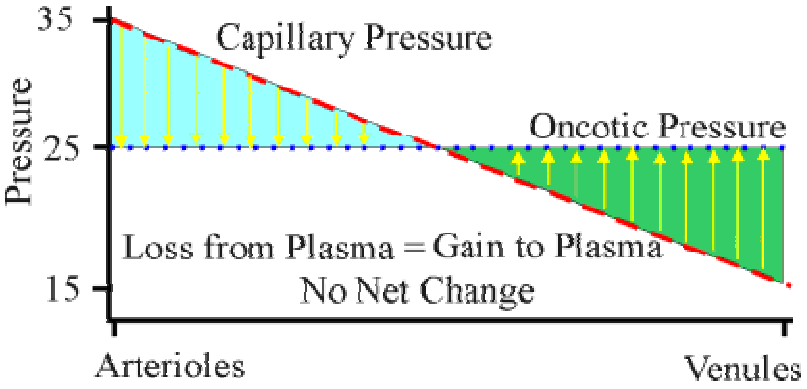


Fig.3 Oncotic and hydrostatic equilibrium

On the arteriole end, the hydrostatic pressure is higher than the oncotic, so there is fluid movement from plasma to interstitial fluid. The magnitude of this water flow is indicated by the light blue area on the left (downward arrows). On the venule end, the hydrostatic pressure has dropped **below** the oncotic. Fluid moves back from the interstitial fluid to the plasma. The magnitude of this reverse flow is indicated by the green area on the right (upward arrows).

In a normal capillary bed, fluid gain and loss from the plasma are closely balanced, so there is little or no net change in plasma and ISF volumes.

Understanding how changing resistance changes capillary pressures:

The vascular system is a highly branched set of tubes that carry the blood to all parts of the body. Blood pressure results from the pumping of the heart, and affects the movement of fluids throughout the vascular system. Many other systems depend how the blood pressure is "felt" in the capillaries as a function of arterial resistance.

Fluids move through blood vessels (as with any kind of pipe) when there is a pressure difference between the start and end of the pipe. Just as water moves continuously downhill as a river flows, the pressure drops continuously from the start to the end of a vessel.

Since the capillaries are (in a sense) midway between arteries and veins, their pressure will be lower than the central arterial pressure and higher than the central venous pressure. Also, within the capillaries themselves, the pressure will gradually drop from their arteriolar side to their venule side.

When a much bigger resistance to flow is introduced in the middle of this pipe (like a damn built on a river, or a "squeeze" on a tube), the pressure upstream from that resistance will be closer to that near the beginning of the pipe, and the pressure downstream will be closer to that near the end.
Arterioles squeeze the blood vessels, giving a relatively large resistance to flow. Upstream, the pressure is much closer to central arteriolar pressure, while downstream at the start of the capillaries the pressure is about 35 mm Hg.
When the arterioles dilate (and make less resistance), the pressure in the capillaries rises (closer to arterial pressure). When the arterioles constrict (more resistance), then the pressure upstream will rise even more, while it will fall at the capillaries.

Oxygen and interstitial Fluid volume

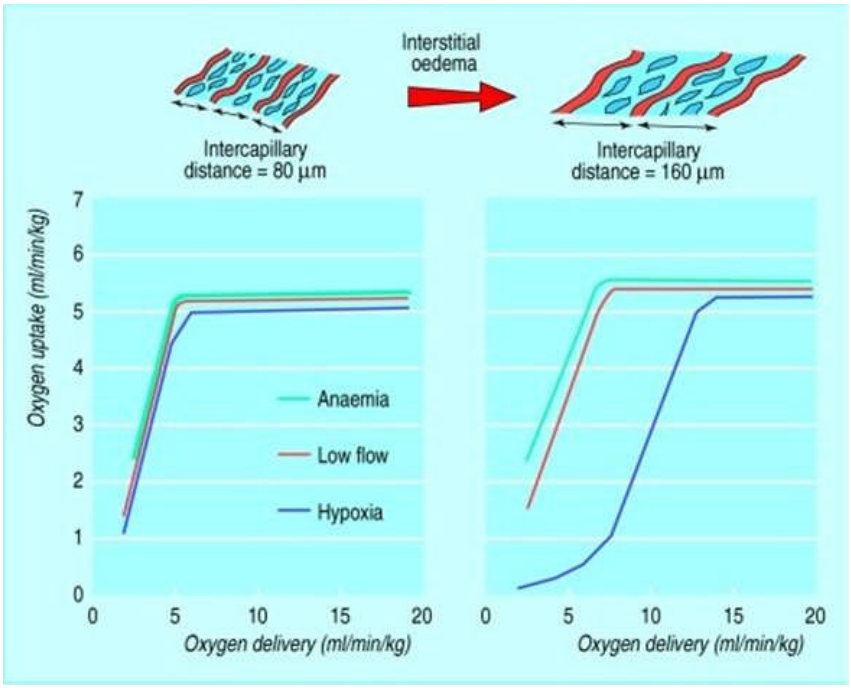


Fig.4 Oxygen delivery and interstitial volume

Effect of intercapillary distance on relation between oxygen delivery and consumption when delivery is reduced by hypoxia (a fall in Pa_{O_2}), reduced flow (stagnant), and anaemia (fall in haemoglobin concentration)
BMJ. 1998 November 14; 317(7169): 1370–1373.

Cells activity and ionic equilibrium

The EIS system can calculate the interstitial fluid volume and according to the interstitial fluid knowledge , the sodium pool.

When the sodium concentration decreases in the interstitial fluid, the sodium moves inside the cell and affects the tissue(s) as follows:
1. Cellular volume increases
2. Mitochondrial activity decreases and ATP production decreases
3. Oxygen consumption decreases
4. Intracellular exit of K+ and H+ ions to the interstitial fluid causing an interstitial acidosis and an intracellular alkalosis. Note that the interstitial and intracellular acid base balance are according to cells activity due to the absence of haemoglobin and proteins (buffers)
5. An interstitial Chlorine retention and a corresponding retention of intracellular bicarbonate
6. CO2 increases interstitially resulting in an increase in the elimination of CO2 via blood circulation by the lungs
7. Interstitial fluid volume decreases, the oncotic pressure is more high that the hydrostatic pressure
8. Blood microcirculation: vasodilatation and blood viscosity decreases

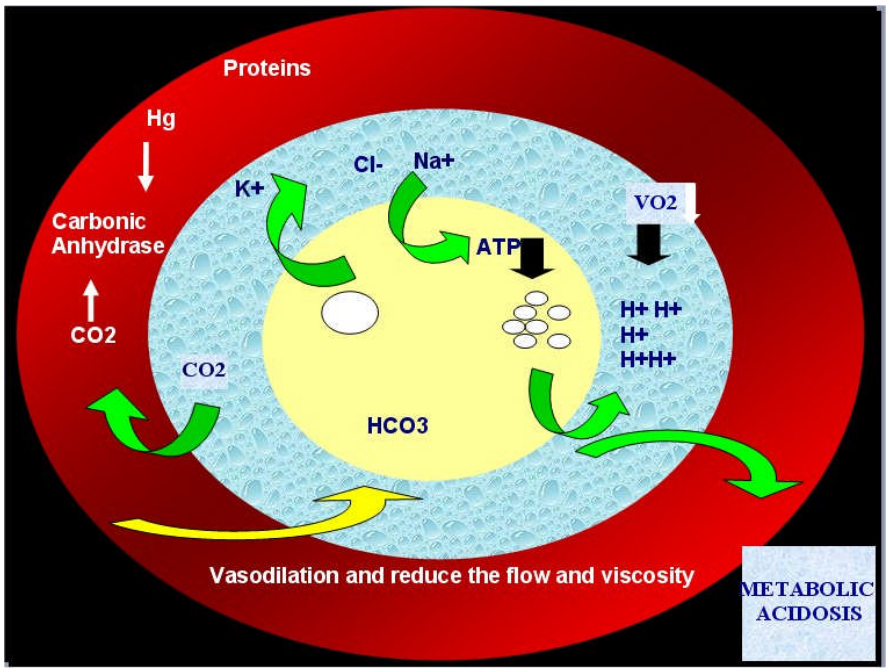


Fig 5. Results in electrolytic balance of Na+ cell income

When the sodium concentration increases in the interstitial fluid, the sodium moves outside of the cell and affects the tissue(s) as follows:
1. Cellular volume decreases
2. Mitochondria activity increase and ATP production increases
3. Oxygen consumption increases
4. Interstitial K+ and H+ ions move into the cell causing an interstitial alkalosis and an intracellular acidosis
5. Interstitial Chlorine moves to intracellular space, and a corresponding intracellular decrease of bicarbonate
6. Interstitial CO2 decreases and a corresponding decrease in the elimination of CO2 via blood circulation by the lungs
7. Interstitial fluid volume increases, the hydrostatic pressure is more high that the oncotic pressure
8. Blood microcirculation, vasoconstriction and blood viscosity increases

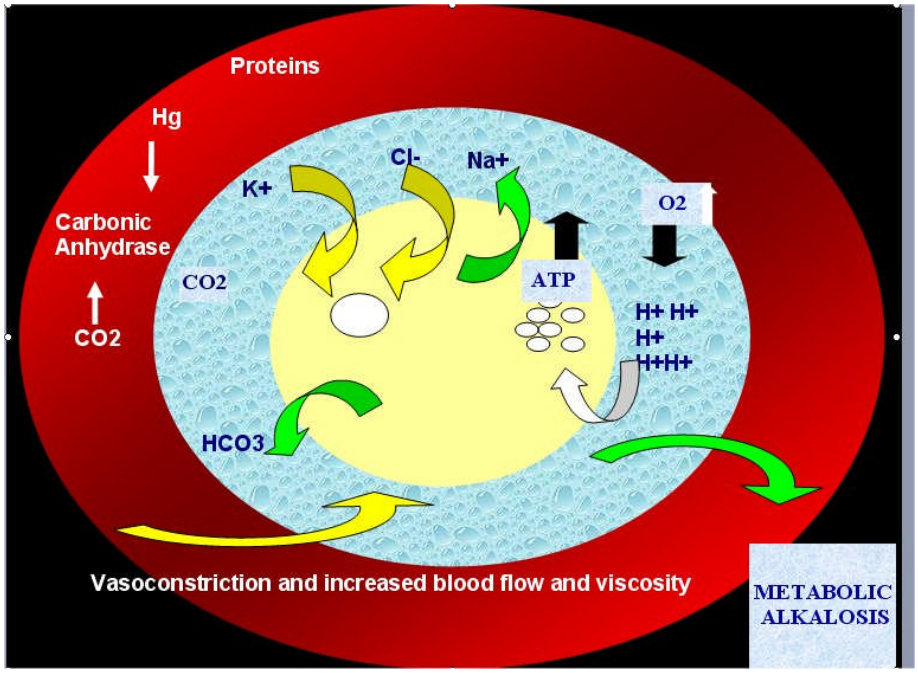


Fig 6. Results in electrolytic balance of Na+ cell outcome

Since D.C. electric current only passes through the interstitial fluid, it has been proposed that an abnormality in the chemical composition of the interstitial fluid and physiological tissue parameters could be detected with an adequately sensitive D.C. BIM device

Correspondence of the interstitial and blood biochemical values: Table 1
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
Table 1.

biochemical constants	**Venous blood**	**Arterial blood**	**Capillar blood**	**Interstitial fluid**	**Intracellular**
Na+ mEq/l	130	137	135	130	10
K+ mEq/l	4	4	4	3.17	140
Ca ++ mEq/l	2.5	2.2	2.3	1.55	0.0001
Mg mEq/l	0.64	0.62	0.60	0.50	58
Cl- mEq/l	104	101	103	106	4
HCO^3 mEq/l	22	24	23	24	10
P mEq/l	2.5	2.3	2	0.70	75
SO 4 mEq/l	0.8	0.6	0.5	0	2
Glucose mg / dl	1	1	1.01	0.90	0 à 20
Cholesterol mg/dl	0.65	0.630	0.676	0.188	0.2
Po^2 mmHg	80	90	89	87.2	20
Pco^2 mmHg	46	40	42	46	50
Ph	7.35	7.4	7.35	7.33	7.0
Proteins gm/dl	72	74	73.7	20.6	68

2. Modeling

Foreword on modeling: (30)

The E.I.S device allows a modeling of the human body.

What is a modeling?

The modelization 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 centered on the computer.

Human body, Electric activity and modeling
The human body has measurable electric activity using cutaneous electrodes utilizing the principle of bio electric impedance. The direct problem is simulating the generated electric potential starting from a power source. . (30) (31) (32)
The modeling will be the results of mathematical algorithms named direct and inverse problems
(64)

Mathematical formula for direct methods: Maxwell's equations
As with all the problems of electromagnetism, Maxwell's equations are the starting point.

$$\epsilon_0 \approx 8.85\,10^{-12} Fm^{-}$$

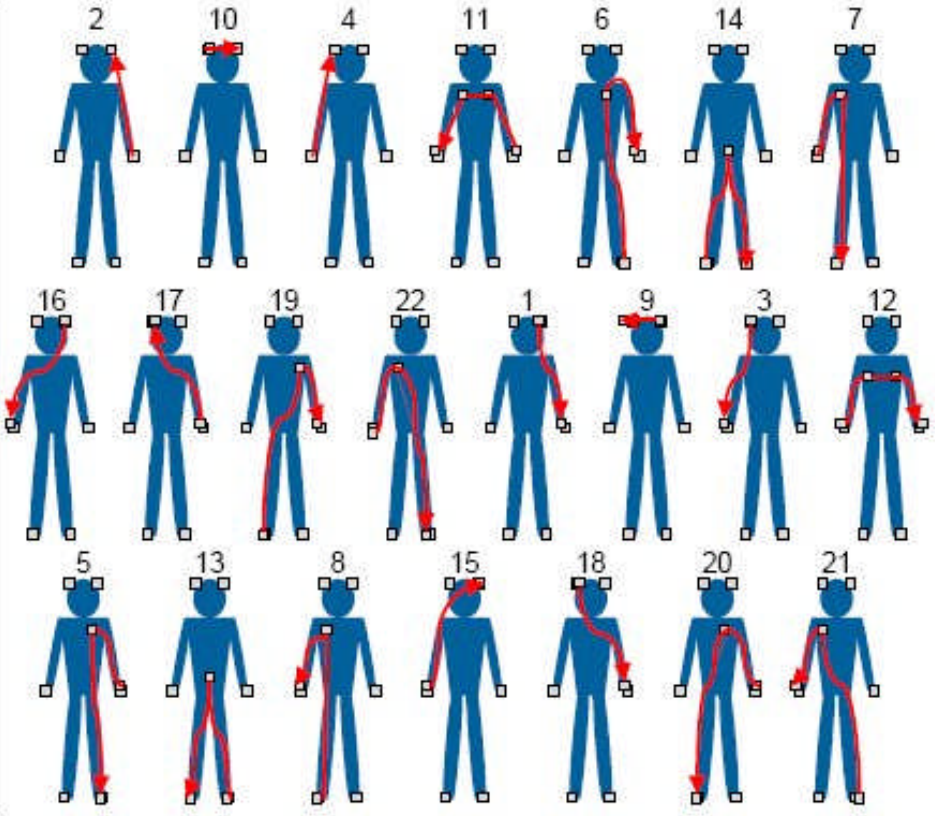
$$\nabla \cdot \mathbf{E} = \frac{\rho}{\epsilon_0}$$

E and ρ represent the electric field respectively

Direct problem in EIS system

Table 2. The 22 volumes and sequence of recording

	Anode		Cathode
2.	L hand	→	L forehead
10.	R forehead	→	L forehead
4.	R hand	→	R forehead
11.	L hand	→	R hand
6.	L foot	→	L hand
14.	R foot	→	L foot
7.	R hand	→	R foot
16.	L forehead	→	R hand
17.	L hand	→	R forehead
19.	R foot	→	L hand
22.	R hand	→	L foot
1.	L forehead	→	L hand
9.	L forehead	→	R forehead
3.	R forehead	→	R hand
12.	R hand	→	L hand
5.	L hand	→	L foot
13.	L foot	→	R foot
8.	R foot	→	R hand
15.	R hand	→	L forehead
18.	R forehead	→	L hand
20.	L hand	→	R foot
21.	L foot	→	R hand



Direct evaluation: Venn diagrams

A first localization of organs by direct problems came out through application of the mathematical calculation of Venn diagrams. However, this area of localization of different organs is not precise enough since several organs may be included in the same area.

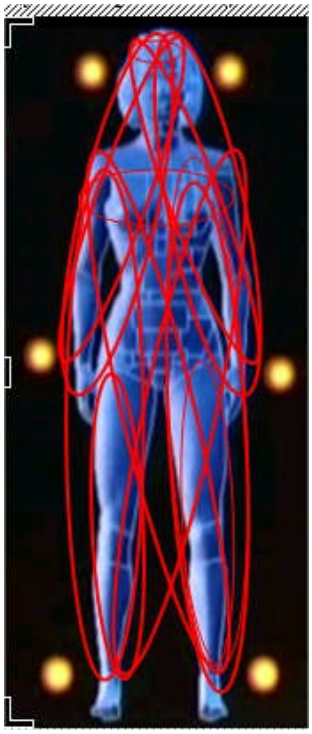


Fig.7. Venn diagrams in EIS modeling

The precision of localizing different organs requires the application of inverse problems

Methods for the inverses problem:

The mathematical algorithms of the "inverse problems" based upon the following principle: *"Each phenomenon is governed by equations with parameters like the initial conditions or various coefficients; when some of these parameters are unknown, we are within the framework of the inverse problems and to find them using experimental measurements amounts to solving the problem."*

Inverse problem in EIS system
With the aid of the ESG graph (see below) as a reference and criterion of judgment, in order to establish algorithms of inverse problems of localization, different clinical trials were undertaken. (See clinical tests)

3. The chronoamperometry: The Cottrell's equation (2) (27)

The chronoamperometry and the Cottrell equation is used in laboratory tests devices for the measurement of weak concentration of biochemical values. This technique was also used for the measurement of the serotonin (49) (50).

In chronoamperometry, the working electrode potential is suddenly stepped from an initial potential to a final potential, and the step usually crosses the formal potential of the analyte. The solution is not stirred. The initial potential is chosen so that no current flows (i.e., the electrode is held at a potential that neither oxidizes nor reduces the predominant form of the analyte). Then, the potential is stepped to a potential that either oxidizes or reduces the analyte, and a current begins to flow at the electrode. This current is quite large at first, but it rapidly decays as the analyte near the electrode is consumed, and a transient signal is observed.

If the point in time when the potential is stepped is taken as time zero, then the Cottrell equation describes the how the current, I, decays as a function of time, t:

Cottrell equation and mathematical transformation for the calculation of the concentration in EIS system

$$I = nFA\, c_o \sqrt{\frac{D}{\pi t}}$$

The Cottrell equation

$$c_o = \frac{i}{nFA\sqrt{\frac{D}{\pi t}}}$$

F = Faraday constant (96500 C/mole)
A= Electrode area (en cm2)
Co = Ionic concentration (mol/ cm3)
n =number of electrons per molecule
D= Diffusion coefficient (cm2/ s)
t= Measurement time in seconds

Although the current decay may appear to be exponential (in the case of adsorbed redox species), it actually decays as the reciprocal of the square root of time. This dependence on the square root of time reflects the fact that physical diffusion is responsible for transport of the analyte to the electrode surface.

4. Clinical investigations:

The clinical studies from 2002 to date (July 2007) of The EIS System have validated the following:

Pre-study Gustave Roussy Institute GRI 2002:

This study was conducted to validate the following:

- Monitor the acid base balance
- Monitor tissue oxygen
- Monitor the effects chemotherapy

Clinical investigation Botkin Hospital 2003

This study was conducted to validate the following:

- The inverse problem for the modeling of the human body using The EIS System.
- As a marker for unipolar depression with reference to an estimation of interstitial fluid of the cerebral serotonin level
- As a marker for hypothyroid

The screening and follow up of:

- Hypertension
- Arrhythmia
- Type I Diabetes
- Hepatitis, viral ABC
- Heart attack
- Circulatory problems

For the monitoring of the following pathologies:

- Spasmodic colitis
- Gastritis
- Duodenal ulcer
- Angina
- Type II Diabetes
- Pancreatitis
- Hepatitis, alimentary
- Chronic bronchitis and asthma:
- COPD
- Cancer

Investigation Marfino 2004

This study was conducted to validate the following:

- The values of the interstitial ionogramme
- The statistical estimation of the blood biochemical constants (Atherogenic Index, Glucose, Urea, Creatinine, Triglycerides) for the subjects not on current medication.
- To validate the estimation of the fat mass.

Pre- study St Louis Hospital 2005

This study was conducted to validate the following:

- The measurement of stress and catecholamine

Clinical investigation Botkin hospital 2006

This study was conducted to validate the following:

- The screening of 4 pathologies:
  - Hypothyroid
  - Hyper pressure
  - Atherosclerosis
  - Unipolar depression
- For monitoring the follow up of 4 pathologies
  - Hypothyroid
  - Hyper pressure
  - Atherosclerosis
  - Unipolar depression
- The production of thyroid (this was achieved by comparing the value of thyroid modelling using The EIS System with TSH laboratory test)

ADHD children 2007 Dr.Caudal Frederique

This study was conducted to validate the following:

- The EIS could be used as a marker for the determination of ADHD in children
- The EIS System could provide an estimation of the measurement of dopamine

Protocols and clinical investigation in progress
IRB FDA approval: Harvard Medical School
McLean Hospital: New possibility of diagnostic of unipolar and bipolar depression

5. Statistical Analysis:

The Statistical databases are from the clinical tests but also from Hospitals, clinics and private offices worldwide.

The data will be analyzed using the statistical methods (section, above). Statistics will be computed with STATISTICA™ software (version 7.0). The impedance and clinical data will be transferred from their respective Microsoft Excel databases into the STATISTICA program database. The first step will be to run the STATISTICA version of the Shapiro-Wilk W test to examine whether the impedance data has a normal (Gaussian) distribution. Skewed (non-Gaussian) data will be analyzed with nonparametric methods and data with a normal (Gaussian) will be analyzed with parametric methods (see Table2, below).

Table 3: Choice of Statistical Tests

Objective	Type of Data		
	Normal (Gaussian) distribution	Non-Gaussian distribution	Categorical (binomial)
Compare 2 unpaired groups	Unpaired *t* test	Mean Plot: Whisker: Mean	Fisher's Exact test (chi-square test for large sample sizes)
Compare 2 paired groups	Paired *t* test	Wilcoxon test	McNemar's test
Compare ≥ 3 unmatched groups	One-way ANOVA	Box & whisker plot by group	Chi-square test
Compare ≥ 3 matched groups	Repeated-measures ANOVA	Friedman test	Cochrane Q test
Quantify association between 2 variables	Pearson correlation	Categorized histograms by group	Contingency coefficients

Definition of Biofeedback device

Biofeedback is a form of alternative medicine that involves measuring a subject's bodily processes such as blood pressure, heart rate, skin temperature, galvanic skin response (sweating), and muscle tension and conveying such information to him or her in real-time in order to raise his or her awareness and conscious control of the related physiological activities.

Neurofeedback has become a popular treatment for ADHD; electromyogram (muscle tension) biofeedback has been widely studied and accepted as a treatment for incontinence disorders, and small home biofeedback machines are becoming available for a variety of uses. Its role in controlling hypertension is becoming recognized.

Biofeedback Devices examples

- Electromyogram (EMG)
- Peripheral skin temperature
- Galvanic skin response training
- Electroencephalography (EEG)
- Heart rate variability (HRV)

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