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Mathematical issues in body water volume estimation using bio impedance analysis in e-Health

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Abstract

BioImpedance Analysis (BIA) is a safe, simple, and noninvasive technology to measure body composition. The principle is to determine the electric impedance of an electric current passing through body tissues. This technique is currently integrated into numerous connected devices, for quick and easy self-assessment of health condition. However, these measurements are indirectly related to body composition and intensively bear on strong assumptions related to mathematical models that are limited and imprecise. This situation is the source of several methodological and experimental issues. In this study, we analyze in details these issues based on a complete and recent survey of literature.

Obtained results suggest that it is clearly needed to multiply references, to define personalized models, and to adjust mathematical assumptions to improve BIA reliability and adoption in e-health or specific applications.

Keywords: BIA, bio impedance analysis, body composition, body compartments, e-health, model, prediction equations, mathematical, hydric volumes, body water.

I. INTRODUCTION

BioImpedance Analysis (BIA) is a safe, simple, noninvasive, low cost and widely applied approach in clinical applications to assess body composition and fluid distribution. Mainly, BIA measures the body tissue's opposition to the flow of a low alternate current and converts electrical data into body composition. This technique shows a strong potential for clinical applications. Indeed, due to ease of use of BIA, many researchers studied body composition disorders in various diseases such as *Toso et al.*[1] for staging lung cancer, *Zlochiver et al.* [2] for pulmonary edema monitoring, *Cumming et al.* [3] for hydration status and hyponatremia in elderly, *Chen et al.*[4] for hypertension detection in nephrology, *Chamney et al.*[5] for dry weight estimation in kidney failure, *Mereu et al.* [6] [for neural system diseases such as Alzheimer, *Moreno et al.* [7] for anorexia nervosa, *Ring et al.*[8] for muscular activity monitoring.

Furthermore, recent technological progress opened new possibilities for e-health applications such as BIA integration in smartwatches[9] and smart scales[10] for quick and health condition self-assessment. Now, body composition can be measured in multiple locations like home, training centers, drugstores... However, measurements precision may be discussed according to the context (wellness or clinical).

BIA is based on electrical resistance and reactance at different frequencies of human tissues and fluid to estimate hydric volumes such as Total Body Water (TBW). BIA is not a straightforward technology since physiological parameters are deducted indirectly from mathematical models. Furthermore, the approach suffers from a blackbox effect: many equations are parametric and empirical variables were obtained based on regression methods to correlate the raw electrical measurements to body composition vs. reference methods like Dual-Energy X-ray Absorption (DEXA) and isotopes dilution, validated in healthy subjects.

The objective of this review is to discuss the issues and limitations of the mathematical equations used for hydric volume estimation when the standard conditions are not met or when they are applied to clinical cases. We identified five major issues:

Issue 1: Rheological modeling precision. To analyze body water compartments, human body is represented as an electrical circuit made of resistors and capacitors to reflect electrical properties of tissues at different frequencies. In the literature, several rheological models were proposed [11]. Each model is based on various electrical descriptions leading to diverse results and precision.

Issue 2: Body compartments. Human body is modeled as a combination of cylinders different tissues type and fluids volumes. The complexity of the model relies on the number of compartments. 2 to 5 compartments models are commonly used, depending on the physiological parameters targeted (TBW, fat

mass (FM), fat-free mass (FFM), total body protein (TBPro), bone mineral content (BMC)). Accuracy of the results depends on the number of compartments considered.

Issue 3: Physiological approximations. Bio statistic anthropometric data [12] are used in body composition modeling, they refer to an ancient population from 1975 (Caucasian, body mass index (BMI), height, age, health status...). This is a strong bias when applying models to other populations or a recent generation.

In addition, hydric volumes estimations are based on multiple hydration status hypotheses that also influence the results.

Issue 4: Predefined constants. Bioimpedance analysis uses predefined constants to predict body composition, especially hydric volumes, such as equivalent resistivity of intra and extracellular fluids, body density, shape factor... These constants were calculated on healthy subjects and misleading when used in a population with health disorders.

Issue 5: Electrical stimulation frequency choice. The impedance measures depend on the frequency of the alternative current applied. To differentiate tissues, BIA must consider multiple frequencies. Also, there is a characteristic frequency determining if the current can cross cell membranes to measure whole body composition. That's why the results are affected by frequencies values.

II. BIA PRINCIPLE AND METHODS

A. Principle of BIA

BIA consists in injecting an imperceptible electric current of very low amplitude (μA) into the body, at various low (1 to 30 kHz) and high (≥ 50 kHz) frequencies., Conductive electrodes are placed with skin contact. As the body behaves as an electric circuit (Fig. 1), it is possible to measure of total impedance (Z), resistance (R) and reactance (X_c) according to Ohm's law.

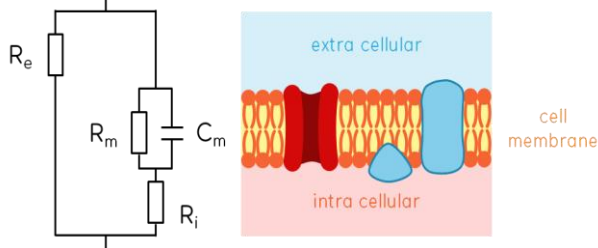


Figure 1. Frick circuit equivalent circuit of a cell membrane

B. Body Compartments

As BIA aims to analyze body composition, the most popular physiological model introduces the concept of compartments. Different tissues have specific electrical properties, in particular they will show a different resistance to current flow. Figure 2

shows the models of body composition. In the two-compartments model (2-C), the body is divided into FM and FFM. In the three-compartments model (3-C), the FFM is then divided into BMC and lean body mass (LBM). In the four-compartment model (4-C), LBM is divided into TBPro and TBW. In the five-compartments model (5-C), the TBW is divided into intracellular water (ICW) and extracellular water (ECW). Different methods and assumptions are considered for each model and will be discussed.

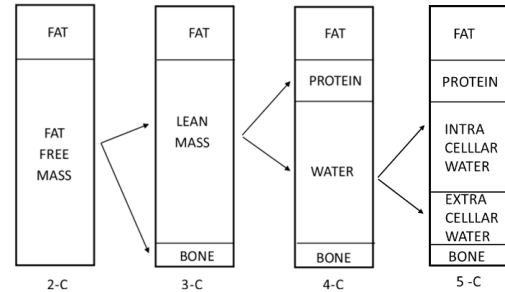


Figure 2. Modeling of body composition in two-compartments (2-C), three-compartments (3-C), four-compartments (4-C) and 5-compartments (5-C).

C. Whole Body vs. Segmental Analysis

Several technologies for applying bioelectrical impedance analysis were developed based on:

- the number of frequencies (single or multiple frequencies)
- the sections of the body crossed by the current.

BIA can be operated with different frequencies strategies: single frequency (SF-BIA), multiple frequency (MF-BIA) and a spectroscopy of frequencies (BIS).

With SF-BIA, a 50 kHz electrical current is injected through the body assuming this single frequency of 50 KHz passes across all body cells of all tissues.

Electrical properties are characteristic of each tissue that will show different responses to the flow of current at different frequency. MF-BIA requires to use at least 2 frequencies to differentiate extracellular compartment from intracellular one: at least one low (1–5 kHz) and one high (50–1000 kHz) frequencies.

A poor reproducibility was observed with frequencies below 5 kHz and above 200 kHz [13] [14]. Unlike MF-BIA, BIS uses a broad range of frequencies, typically about 50 frequencies ranging from 1 to 1000 kHz and follows the Cole's approach (R values are extrapolated at zero and infinite limit frequencies) to predict hydric volumes ECW and TBW respectively. ICW is the difference between TBW and ECW.

Two BIA approaches depend on the sections of the body considered: the whole body (WB-BIA) and the segmental BIA (S-BIA). The WB-BIA method measures total body impedance, typically between wrist and ankle: whole body is modelled as a

single cylinder. The WB-BIA method measures total body impedance, typically between wrist and ankle: whole body is modelled as a single cylinder (figure 3). S-BIA measures the impedance of individual segments modeled as independent cylinders (arms, trunk, and legs).

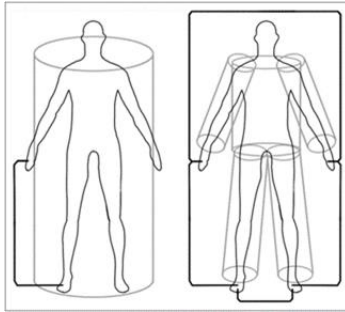


Figure 3. bioelectric impedance analysis approaches: whole-body impedance model as one cylinder vs. segmental BIA considering five separate cylinders.

D. Hydric volumes

Analysis of body composition by BIA assumes that resistance to a determined electrical current is inversely proportional to the distribution of water and electrolytes. The resistance (R) of a homogeneous conductive material (figure 4) is proportional to its length (L) and inversely proportional to its uniform cross-sectional area (A).

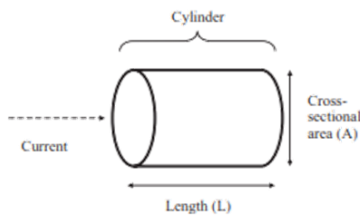


Figure 4. modelling human body by a homogeneous cylinder of length (l), cross sectional area (a) and resistivity (ρ).

For a given fluid resistivity (ρ), the resistance is:

$$R = \rho \frac{L}{A} \quad (1)$$

where R is the resistance, ρ fluid resistivity, L length of a cylinder et A is a cross sectional area.

By substituting surface area (A) with body volume (V_b) considering an even distribution of fluids, SF-BIA can estimate TBW. Impedance is inversely proportional to the TBW. The conductive path of the electric current is represented as:

$$V_b = \rho \frac{L^2}{R} \quad (2)$$

where body volume (V_b), ρ fluid resistivity, L length of a cylinder and R is the resistance.

The major attribute of BIA is the capability to approximate TBW. It is common to estimate TBW from FFM because there is a constant relationship between TBW and FFM (FFM/TBW constant ratio = 0.732) [15]. TBW can be refined to assess the

volumes and concentrations of ICW and ECW with MF-BIA.

III. LITERATURE REVIEW AND DISCUSSION

We made an exhaustive review of the literature. We discuss in the section the mathematical issues listed in the introduction to point out limitations.

Issue 1: Rheological models

Many rheological models simulating human body electrical properties were proposed to determine TBW. The 50-kHz serial model was the most common for in vivo analysis of body water volume based on the linear correlation between the resistance index (H²/R_{50s}) and TBW[16]:

$$TBW = mH^2/R_{50s} + c \quad (3)$$

Where H is the height and R_{50s} the serial resistance at 50 kHz. m and c are constants determined from linear regression of TBW vs. the ratio H²/R_{50s} in a reference population.

The 50-kHz parallel model assumes that the body behaves as resistance-capacitance circuits arranged in parallel and linearly related to ECW and ICW as shown in Eq 3 and 4.

$$ICW = k_i \cdot W \cdot (H^2/R_i) \quad (4)$$

$$ECW = k_e \cdot W \cdot (H^2/R_e) \quad (5)$$

Where K_i is the intracellular fluid coefficient, W weight, H height, R_i intracellular resistance, K_e is the extracellular fluid coefficient and R_e extracellular resistance.

To differentiate both intracellular and extracellular compartments at different frequency, a 5/500-kHz serial model assumes the signal pathway at 5 kHz is exclusively extracellular thus the resistance index is linearly related to ECW and the resistance index at 500 kHz is linearly related to TBW.

To separate the intra- and extra-cellular components of bioimpedance, the Cole-Cole theory considers the human body as a 0 to ∞-kHz parallel model, based on the β-dispersion (10 kHz to 10 MHz) of the bioimpedance cell response. The resistance and reactance measures from a range of frequencies between 5 and 500 kHz are plotted in a semicircular figure by nonlinear, least-squares analysis, allowing a depressed centroid. R₀ equals all the resistances of extracellular fluid (R_e). R_∞ sums all the intracellular resistances (R_i) and all R_e. R_e and R_i are linearly related to ECW and ICW, respectively.

When we compare the three models, the serial model uses constants derived from linear regressions and the equations perform poorly when applied to subjects where normal conditions (e.g., normohydration, homogeneous fluid distribution, normal BMI...) are not met. The Cole-Cole model doesn't consider real life cases where the resistance of

conducting body fluids will increase with the concentration of nonconducting particles in suspension, that may come from physiologic variations or disorders[17] . This explains why raw physiological data show shifted values at high frequency, why characteristic frequency may vary from one subject to another, and how hydration status influences the results. In the parallel model, the resistance representative of the extracellular water volume can be calculated with $f_{min} = 1$ kHz, the value is $R_1 = 560.97 \Omega$, which is almost the same as $R_e = 562 \Omega$ from the Cole model [18] . The resistance representative of the intracellular water volume can be calculated for $f_{max} = 1000$ kHz, the value is 314.97Ω , unlike $R_i = 352.69 \Omega$ from the Cole model [18].

According to experimental data (figure 5), body water volume prediction is improved when considering a parallel model [18]. The RC (resistive capacitive) parallel model is considered as a reduction of the Cole-Cole model, and accurate for a range of frequencies below 500 kHz. It is very interesting to see that R_1 has a similar value to R_e in the Cole model, being equivalent to the resistance for $f = 0$ Hz. This circuit can be viewed as a generalization of the Cole model. The two branch models

include only Re, Ri, Ci. As the frequency range of interest is extended to higher frequencies, a model with a greater number of branches is needed.

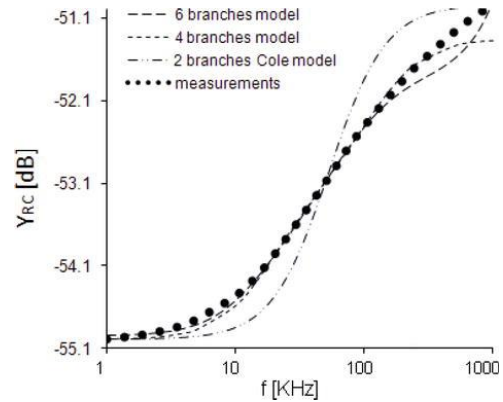


Figure 5. The measured frequency characteristic and proposed electrical models with 2, 4 and 6 branches [18]

Author	Population included	Subjects number	Reference method	BIA (MF SF)	Total body water (TBW) prediction equations
Deurenberg [19] 1995	Healthy subject	139 139	Dilution deuterium oxide $^2\text{H}_2\text{O}$	MF-BIA	$TBW = 6.69 + \frac{H^2}{Z_{100}} + 0.17065 W - 0.11 A + 2.66 \text{ sex}$ $TBW = 6.53 + \frac{H^2}{Z_{50}} + 0.17531 W - 0.11 A + 2.83 \text{ sex}$
Cornish [20] 1996	Healthy subjects	60	dilution deuterium oxide $^2\text{H}_2\text{O}$	MF-BIA	$TBW = 0.6 + 0.50 \frac{H^2}{R_0} + 0.186 W$
Heitmann [21] 1990	Healthy subjects 35-65	139	dilution deuterium oxide $^2\text{H}_2\text{O}$	SF-BIA	$TBW = -17.58 + 0.240 \frac{H^2}{R_{50}} - 0.172 W + 0.04 W \cdot \text{sex} + 0.165 H$
Kotler [22] 1996	Healthy multi ethnicity subjects	206 126	dilution deuterium oxide $^2\text{H}_2\text{O}$	SF-BIA	Men: $TBW = -3.66 + 0.58 \left(\frac{H^{1.62}}{Z_{50}^{0.7} 1.35} \right) + 0.32 W$ Women.: $TBW = -0.86 + 0.78 \left(\frac{H^{1.99}}{Z_{50}^{0.58} 18.91} \right) + 0.14 W$
Kushner and Schoeller [23] 1986	Healthy subjects 17-66	40 40	dilution deuterium oxide $^2\text{H}_2\text{O}$	SF-BIA	Men: $TBW = 8.399 + 0.396 \frac{H^2}{R_{50}} + 0.143 W$ Women: $TBW = 8.315 + 0.382 \frac{H^2}{R_{50}} + 0.105 W$ $TBW = 1.726 + 0.5561 \frac{H^2}{R_{50}} - 0.0955 W$
Sun[24] 2003	Healthy subjects 12-94	734 1095	?	Sf-BIA	Men: $TBW = 1.203 + 0.449 \frac{H^2}{R_{50}} + 0.176 W$ Women: $TBW = 3.747 + 0.450 \frac{H^2}{R_{50}} + 0.113 W$
Vache [25] 1998	Elderly subjects	58	Dilution ^{18}O	MF-BIA	$TBW = 3.026 + 0.358 \frac{H^2}{R_{50}} + 0.149 W + 2.924 \text{ sex}$ $TBW = 2.896 + 0.366 \frac{H^2}{R_{100}} + 0.137 W + 2.485 \text{ sex}$
Van Loan [26] 1992	Healthy subjects 19-65	60	dilution deuterium oxide $^2\text{H}_2\text{O}$	MF-BIA	$TBW = 14.0107 + 0.29753 \frac{H^2}{R_{224}} + 0.14739 W - 3.63734 \text{ sex} - 0.07299 A$

Visser[27] 1995	Elderly subjects 63–87	117	dilution deuterium oxide $^2\text{H}_2\text{O}$	MF-BIA	Men: $TBW = 8.3 + 0.3228 \frac{H^2}{Z_{50}} + 0.1652 W$ Women: $TBW = 11.9 + 0.2715 \frac{H^2}{Z_{50}} + 0.1087 W$
Cox-Reijnen and Soeter [28] 2000	Healthy non-obese and obese subject	90	dilution deuterium oxide $^2\text{H}_2\text{O}$	MF-BIA	$TBW = 0.08 + 0.458 \frac{H^2}{R_{tbw}} + 0.06 W$
De Lorenzo [29] 1997	Obese women	55	dilution deuterium oxide $^2\text{H}_2\text{O}$	MF-BIA	$TBW = 23.898 + 0.0154 \frac{V}{Z_1} + 0.3315 \frac{V}{Z_1 Z_{100} / Z_1 - Z_{100}}$
Hannan [30] 1994	Surgical patients	43 43 43	Dilution tritium oxide $^3\text{H}_2\text{O}$	MF-BIA	$TBW = 5.82 + 0.446 \frac{H^2}{R_{50}} + 0.129 W$ $TBW = 5.69 + 0.399 \frac{H^2}{R_{500}} + 0.114 W$ $TBW = -1.04 + 0.45 \frac{H^2}{R_{500}} + 0.46 APT + 0.0119 \frac{H^2}{X_{c50}} - 0.0106 \frac{H^2}{X_{c500}}$
Delorenzo[17] 1999	Healthy subjects	?	Dilution tritium oxide $^3\text{H}_2\text{O}$	MF-BIA	$TBW = ECW + ICW$ $ECW = k_e \times \left(\frac{H^2 W^{0.5}}{R_e} \right)^{\frac{2}{3}}$ $\left(1 + \frac{ICW}{ECW} \right)^{\frac{5}{2}} = \frac{R_e + R_i}{R_i} \left(1 + k_p \frac{ICW}{ECW} \right)$
Jaffrin[31] 2006	Healthy subjects 15-50	74	BIS spectroscopy	MF-BIA	$TBW = 0.01 \times \left(\frac{k_b \times \rho_{\infty} \times H^2 \times \left(\frac{W}{D_b} \right)^{\frac{1}{2}}}{R_{\infty}} \right)^{\frac{2}{3}}$

Table 1. Equations in literature to estimate TBW

TBK total body potassium; NaBr dilution by sodium bromide; KBr dilution by potassium bromide; $^3\text{H}_2\text{O}$ dilution by tritium; $^2\text{H}_2\text{O}$ dilution by deuterium oxide; SF-BIA single frequency bio impedance analysis; MF-BIA multiple frequency bio impedance analysis; H height; W weight; A age; sex 1 for men, 0 for women unless otherwise stated; health (healthy=1; ill=2); R_i intracellular resistance; R_e , extracellular resistance; R_{tbw} total body water resistance $R_{tbw} = (R_i R_e) / (R_i + R_e)$; K_e extracellular fluid coefficient ; K_p ratio intracellular to extracellular fluid resistivity; ρ_{∞} fluid resistivity at infinite frequency; K_b shape coefficient; D_b body density; V body volume; APT maximum thickness long full length of sternum ; R resistance; X_c reactance; Z impedance; R_0 resistance at 0 KHz; R_1 resistance at 1 KHz; Z_1 impedance at 1 KHz; Z_5 impedance at 5 KHz; R_5 resistance at 5 KHz; R_{50} resistance at 50 KHz; X_{c50} reactance at 50 KHz; Z_{50} impedance at 50 KHz; R_{100} resistance at 100 KHz; Z_{100} impedance at 100 KHz; R_{224} resistance at 224 khz; R_{500} resistance at 500 KHz; X_{c500} reactance at 500 KHz; R_{∞} resistance at infinite frequency.

Issue 2: Body Compartments

To represent human body as numerous compartments, many hypotheses were elevated. The FM of a 2-C model is assumed to have a density of 0.9007 g/cm^3 [32] and to be anhydrous, whereas the FFM is assumed to have a density of 1.1000 g/cm^3 and a water content of 73.72% [33]. The errors associated with a 2-C model doesn't lay in the technical accuracy of the measurements but in the validity of the previously outlined assumptions, which are based on the analysis of only three male cadavers (70.4 , 77.56 and 72.62%) [33] and which vary by age, gender, genetic endowment, ethnicity, training... Due to this oversimplified limitation, a 3-C model was suggested [34] and based on the measurements of both body density and TBW while a constant mineral-to-protein ratio of 0.35 is assumed. Therefore, this model controls for interindividual variation in FFM hydration. With the advent of the use of DEXA, which yields values for FM and BMC, it became easier to assess FFM components and 4-C model has therefore emerged [11]. This model is theoretically more valid than the three-compartment model because it controls for biological variability in both BMC and TBW. Furthermore, a 5-C model was proposed [35] for the advent of differentiating ECW and ICW to create a more complex model representing body composition. A comparison between these models is established to validate the accuracy of

the 3-C model over 2-C model because it controls for variability in TBW, but additional control for interindividual variability in BMC via the 4-C model achieves little extra accuracy. The complexity of the equations is then related to compartments number and the application.

Issue 3: Physiological approximations

The equations include variables such as weight, arm and thigh circumferences, gender, ethnicity, age, height, and body mass index (BMI). Tissues hydration and segments compositions vary with age, with a remarkable structural difference between genders. Then, the equations perform poorly when applied to independent or specific samples or subjects. Regrading ethnicity, there are structural differences between trunk, limbs and FFM hydration that highlight the need of use ethnicity specific equations. Body composition equations for calculation of hydric volumes require measurement of length (height) and weight. Thus, inaccurate measurement of height or weight would affect estimation of body composition. When applying the cross-validated multiple-regression equation for prediction of TBW developed by *Kushner et al.* [36], an over or underestimation of 2.5 cm in height leads to an error of 1 liter in TBW estimation. Similarly, an error of 1 kg in weight results in an error of 0.2 liters in TBW and, more significantly, an error of 0.7 kg in body fat.

TBW estimation using the impedance measurement at a fixed frequency of 50 kHz was calculated with the sex-specific regression equations of *Sun et al.* [24] in a large population, with a standard error of estimate (SEE) of 3.8 (bias 0.5) and 2.6 liters (bias 0.3) in healthy males and females, respectively. Most of BIA equations are validated on healthy subjects and performed on Caucasian adults. Equations established for adults may not be applicable to children or elderly people[37]. Studies also reported an increased bias when using BIA in adults with obesity compared to normal weight subjects[38]. In severely malnourished and anorexia nervosa patients (BMI <16 kg/m²), BIA results are affected by the variation of tissue hydration. In patients with extremes BMI (<16 or >34 kg/m²), prediction errors appear to be important[39]. Finally, BIA may not be a suitable method to assess body composition of athletes with abnormal hydration status[40], even small changes in fluid balance during endurance training may be interpreted as a change in body fat content.

Despite its ease of use and high reproducibility, BIA may result in less precise estimations in situations of altered hydration status. The hydration of body tissues may change the electrical resistance and affect results. Intense physical activity, alcohol or fluid intake before measurement, states of dehydration or water retention, use of diuretics and the menstrual cycle may also represent a limitation[41] of the use of BIA to predict hydric volumes.

Moreover, considerable changes in body weight and body composition were observed during the last decades [42]. Thus, the reference man data used for BIA validation may be outdated and not a suitable reference for nowadays populations. *Later et al.*[12] compared the *Reference Man (1975)* to show great differences in body composition, indicating the need to update reference data.

In general, the equations bias was not critically analyzed, and correction factors were not proposed. Therefore, a new validation and bias analysis would provide adjustments to close the gap between initial equation development and current implementation[43]. In other terms, it is a common knowledge that BIA equations to estimate fluids distribution or any body composition compartment are only precise, accurate and unbiased in populations with similar characteristics to the sample or ethnic group where it was generated [35].

Issue 4: Predefined constants

The hydric volumes of DeLorenzo (ECW and ICW) were predicted from the modeled extracellular resistance (R_e) and intracellular resistance (R_i) assuming the apparent resistivity (ρ) of a conductive material and the volumetric concentration (C) of nonconductive elements in the body at low and high frequencies. These equations consider K_b as a constant factor for relative proportions of the leg, arm, torso, and height; ρ_f as an invariable water resistivity and D_b as body density.... However, K_b is based on *standard anthropometric ratios* and is independent of any electrical characteristic of the body.

Van Loan et al. [26] determined the coefficient k_e from the equation of ECW of DeLorenzo by dilution measurement and R_e measured by multifrequency bioimpedance to estimate $k_e = 0.306$ for men and 0.316 for women respectively. These coefficients are only valid if applied to the same healthy population aged between 19 to 65 years. The resistivities corresponding to this k_e value are respectively 40.3 $\Omega \cdot \text{cm}$ for men and 42.3 $\Omega \cdot \text{cm}$. Considering K_p as the ratio between ρ_{icw} and ρ_{ecw} *De Lorenzo et al.* determined the values of K_p from dilution measurements and found 3.82 for men and 3.4 for women. They also determined K_e to be 0.229 in women; ρ_{ecw} to be 40.5 $\Omega \cdot \text{cm}$ and 39.0 $\Omega \cdot \text{cm}$ for men and women, respectively; the ratio between ρ_{icw} and ρ_{ecw} to be 6.76 for men and 6.79 for women. Again, these values relate to healthy patients with a balanced fluid resistivity between intracellular and extracellular medium. Any fluid disorder will shift extracellular resistivity and result in a biased estimation of ECW. Many more constants are predefined. They limit the interpretation of BIA measures to assess nonstandard or unhealthy subjects.

Issue 5: Electrical stimulation frequency choice

There is no capacitive effect at high frequency ($\geq 50\text{kHz}$), the current will pass through all conducting materials. Theoretically, this enables to measure ECW as well as ICW, based on their relative resistivities, then TBW. At 50 kHz the current is often not completely conducted by TBW, hence the use of SF-BIA is questionable [44]. Indeed, SF-BIA assumes 50 kHz current passes through all cell's membranes, then measures whole body, whereas at least two frequencies are required to differentiate intracellular and extracellular fluids. *Bedogni et al.* demonstrated the accuracy and precision of estimating TBW with MF-BIA [45]. TBW contains both ICW and ECW, a 50 kHz frequency may not account for all the ICW because it may not cross cell membranes a 100 kHz frequency[46], so higher frequencies are preferred.

For ECW assessment at low frequency, BIA assumes that cell membranes are impermeable, so ICW compartment does not interfere. The body is not a uniform cylinder as considered by WB-BIA. Conductivity is not constant to establish an empirical relation between the coefficient of impedance (Length^2 / R) and the volume of water. This approach considers the human body as a one conductive section of homogeneous properties and less complex than five cylinders representing the trunk, upper and lower members. A fundamental assumption made by all bioimpedance devices is that the human body is composed of uniform cylinders where fluid is evenly distributed, and body segmental lengths are proportional to segmental circumferences[17]. Another complication is that body segments have uneven influence on impedance measures. For example, the torso is about half the body weight but accounts for 5 to 12% of total body impedance. Changes in hydration within the torso will have less impact on impedance than analogous changes in the limbs. *Kyle et al.*[47] pointed out that total bioimpedance measurement assesses mainly the upper and

lower limb compartments and shows some limitation to predict water compartments of the trunk.

BIA measures TBW, and LBM is calculated assuming that all tissues have the same degree of hydration. Such an assumption rises another error factor, e.g., in patients with oedema. Due to the variability in the body proportions associated with sex, age, ethnicity, and from one subject to another, it is not possible to apply the same equations in all populations, especially in patients with nonstandard body structure (low or high height, deformations, amputations...).

S-BIA method may allow more accurate measurements [39]. Results obtained using WB-BIA general equations should be interpreted with caution. But regarding the low contribution of trunk impedance and the complexity of electrodes positioning with S-BIA, WB-BIA remains an interesting and reliable method.

IV. CONCLUSION AND PERSPECTIVES

BIA is simple, easy to use, and noninvasive technique integrated in portable, wearable, and connected health solutions. It is commonly used to acquire electrical data in humans and correlate them with body composition. However, after a deep literature analysis, we highlighted five methodological and experimental issues. The first one concerns the complexity (compartment number, electrical assumptions) of rheological models which is not sufficient to precisely depict the experimental reality. The compartment number used for tissue modelling is the second issue and is critical for result accuracy. The commonly used configurations are the 3-C and 5-C ones. The third issue focuses on numerous physiological assumptions used in the existing models. In fact, BIA equations are often designed from the same population standard without considering cohort characteristics (gender, ethnicity, age, healthy status). Furthermore, in the fourth issue, the models assume the use of constant values that are generic, imprecise, and estimated on limited healthy population. Finally, the last issue points out the necessity to multiply electrical stimulation at different frequency to consider different type of tissue. From this study, it becomes urgent to acquire more data, at several electrical stimulation frequency and in different contexts (healthy and pathological status, ethnics, age, comorbidities...) to enrich references and constant values. This will help to define personalized models and adjust mathematical assumptions to improve BIA reliability and adoption.

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