AURA Devices
Bioimpedance Analysis

Introduction

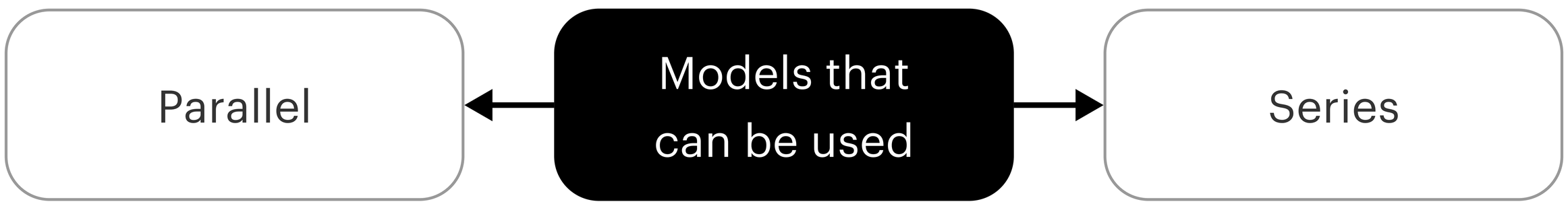
AURA Devices is developing and manufacturing wearable devices that can measure hydration levels and body composition. Bioimpedance analysis (BIA) generates data for calculating % or abs of the user's body muscle and fat tissues, and water level. AURA Devices' products gather and analyze these data to assess each user's fitness performance and health status.

In this document, we discuss our core technology — bioimpedance analysis, its concept, application and accuracy validation. This document will help you to understand the real value of bioimpedance analysis, how it has been implemented in AURA Devices' products, and provide answers to possible questions about these topics.

Basic technology

Bioimpedance analysis is a non-invasive way to get data about fat, muscle tissues, and hydration levels. It is a passive electrical property of body tissues: the ability to oppose (impede) electric current flow. Bioimpedance methods use electrodes with galvanic coupling to the tissue. Most tissues are regarded as predominantly electrolyte conductors (i.e., substances with ions as charge carriers) or dielectric (a capacitive property) in response to alternating current (AC) at different frequencies from 10kHz to 500 kHz.

To implement such a type of measurement in our device we first need to represent the human body as a correct electric scheme or BIA model.



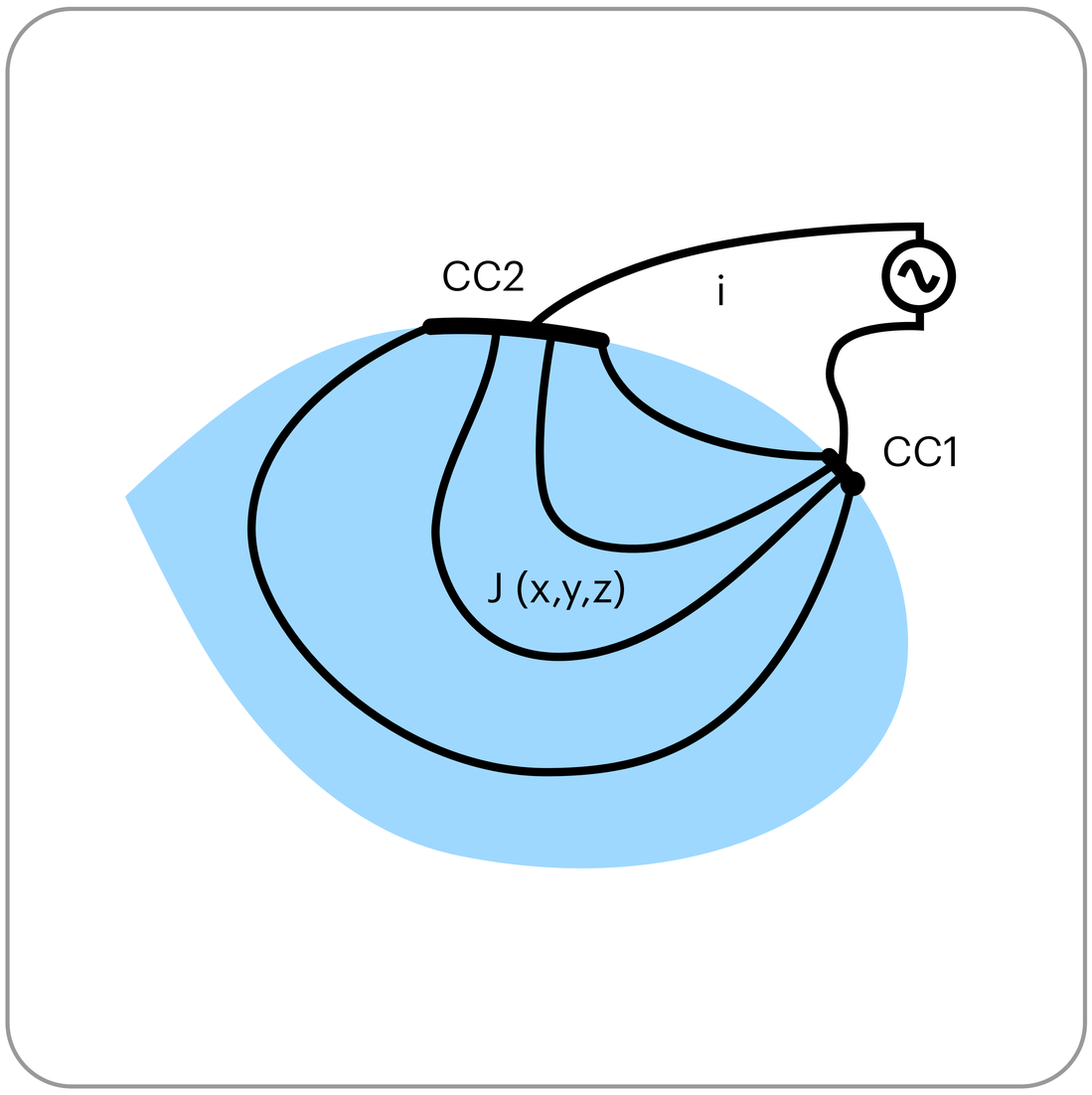
Some devices can use a series model in BIA for processes that actually occur physically in parallel, and vice versa. Another challenge is that we need to choose between a number of other models like a dispersion BIA model or a conductor volume (‘volumetric-based’) BIA model.

The dispersion BIA model in contrast to the ‘volumetric-based’ BIA model presupposes that the measured volume is independent of the frequency of the applied current. In fact, how to select or limit the measured volume is part of a general problem in bioimpedance.

Classic models for bioimpedance are models with mathematical equations, but others include statistical models, which are used to determine the correspondence between bioelectrical measurements and physiological variables (e.g., tissue characterization).

At present, we're using the 'conductor volume' or 'volumetric-based' BIA model (Fig. 1). Since the body cell membrane is a good capacitor due to its specific structure, a low-frequency current is forced to flow through only liquid located outside the body cells (extracellular water). However, a high-frequency current penetrates the cell membrane easily and flows through the whole body liquid (through extracellular water as well as intracellular water).

Figure 1.
Volumetric-based BIA model. Current i [A] in the electrode wires and current density J [A/m2] in the tissue volume are presented. The lines drawn in the tissue show current flow direction, the proximity of two lines is the current density magnitude. i [A] is easily measured and known; the J(x,y,z) field is difficult to map, often unknown, and its effect related to BIA results is adjusted to individual stature or inter-electrode distance, weight, and population-derived regression coefficients (Adapted from Grimnes and Martinsen, 2014).



It is necessary to take into account that blood vessels contain a lot of liquid which also is a good conductor (intravascular water). In this case, body impedance can be presented as a parallel electrical chain with R_{ecw} (resistance of extracellular water including intravascular and interstitial fluids) on one branch and R_{icw} (resistance of intracellular water) and C_{cell} (cell membrane capacity) on another branch with resistance (R) and reactance or capacitor (Xc) parts of bioimpedance obtained by the parallel measurement schema of alternating current transmission (Fig. 2).
This model uses BIA-derived and demographic measures such as length^2/R or stature^2/R as a predictor adjusted to populationally-derived regression coefficients and individual weights in the same equation.

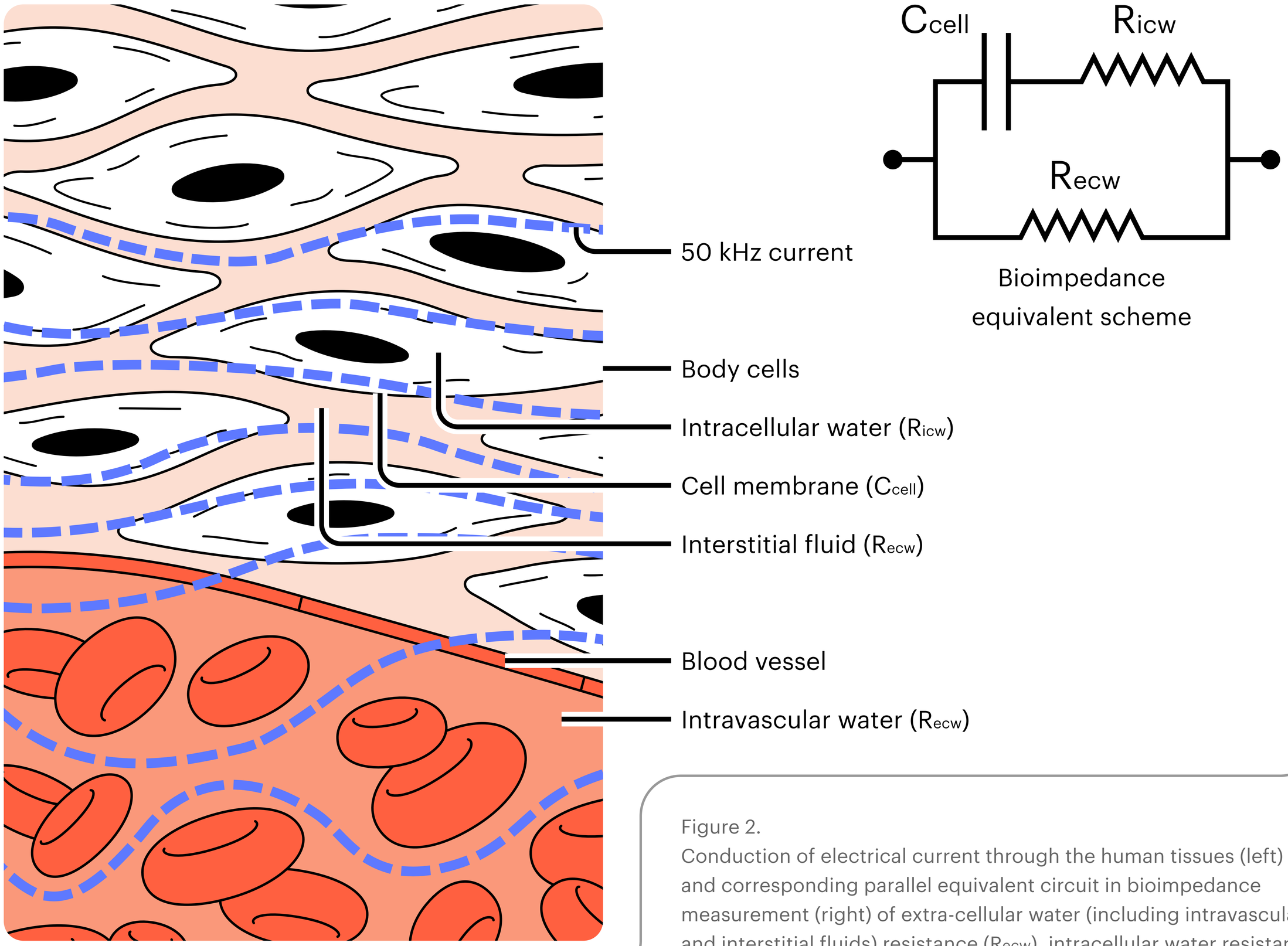
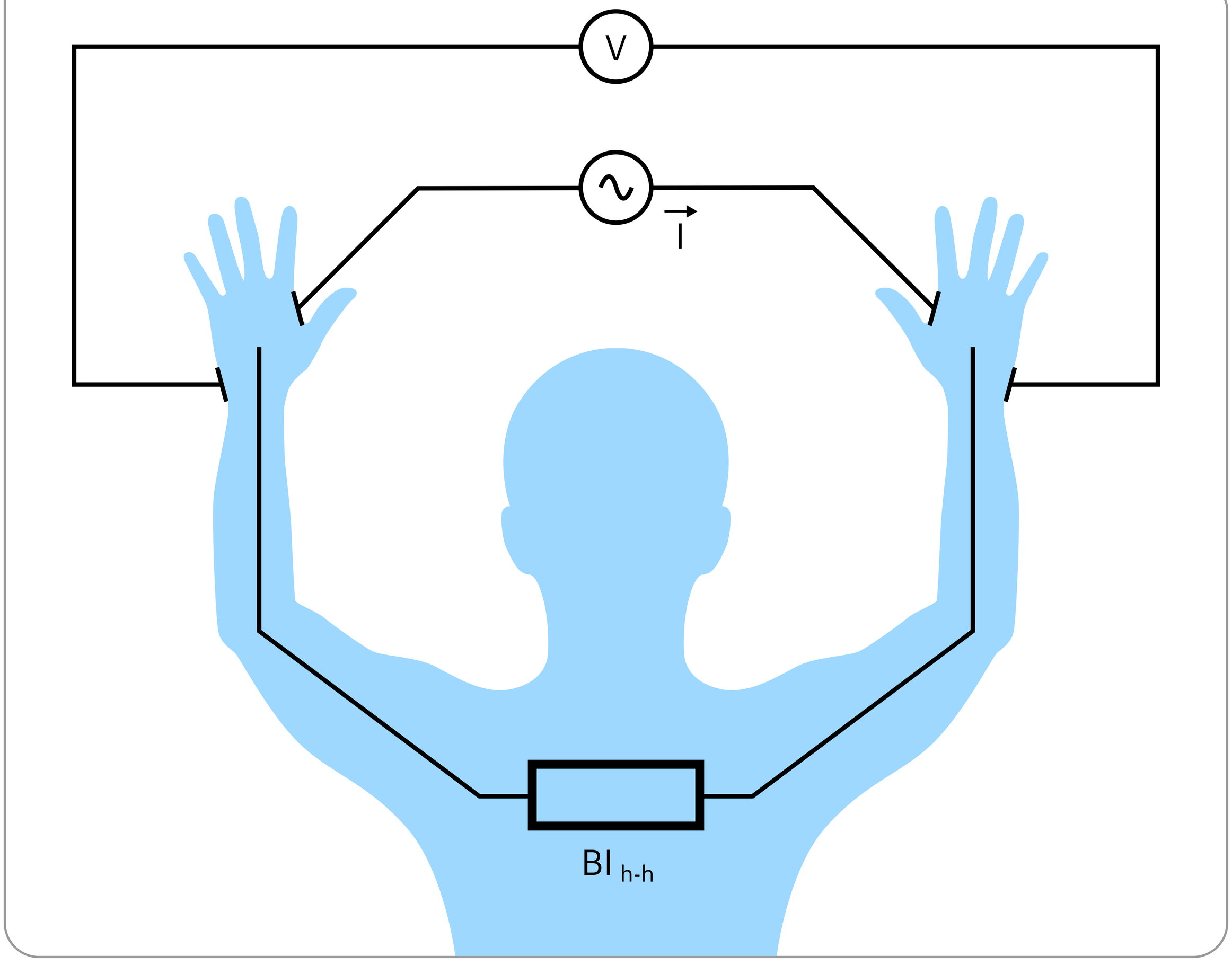


Figure 2.
Conduction of electrical current through the human tissues (left) and corresponding parallel equivalent circuit in bioimpedance measurement (right) of extra-cellular water (including intravascular and interstitial fluids) resistance (R_{ecw}), intracellular water resistance (R_{icw}) and cellular capacitance (C_{cell}).

Our goal was to build a compact device to measure body compartments and hydration status. The most convenient way that provides enough level of useability with sufficient accuracy is to make a segmental BIA of the upper body by transmitting alternating current from hand to hand through the chest (Fig. 3).

In order to achieve the maximum precision of bioimpedance determination the 4-point measurement scheme was chosen (Fig. 3).

Figure 3.
Hand-to-hand communication schema of impedance measurement (Adapted from Ratner et al., 2009).



To make the measurement the user needs first to attach the device as a watch on his/her wrist for skin-contacting two internal electrodes, then start measurement in the app, by touching the other two, external electrodes on the external side of the device by the second hand for 30 seconds. The measurement is triggered and the device starts to transmit alternating current and to measure real and imaginary components of bioimpedance. Then the device transmits the obtained data to the smartphone with AURA App for their further analysis and computation of body compartments.

Current Status

At present AURA Devices has two products (Fig. 4) in its line-up for mobile assessment of body fat, muscle and hydration status:

AURA Band
A stand-alone fitness tracker assesses BIA along with monitoring heart rate and activity

AURA Strap for Apple Watch
an extension accessory enriches the Apple device with hydration and body composition measurement features.

Figure 4.
AURA Band and AURA Strap for Apple Watch.

In general, we’re providing body composition and hydration assessment features in our products for fitness performance tracking. Users can make a measurement regularly on demand by touching the electrodes on the devices with their hands for 30 seconds. After a series of measurements day-by-day, our app builds a graph that shows how their body changes after the exercises and fitness activity. It’s useful to track hydration levels for semi-/pro-athletes before and after a game/match to understand if they perform well or not with respect to their health/performance balance.

In the next updates, we’re planning to provide a heart disease risk assessment feature that uses additional data presented in BIA for breath tracking and PPG sensor for pulse rate calculation. These two metrics allow us to predict problems with the heart at an early stage through analysis of breathing and pulse activities coherence (correspondence in fluctuations of the activities) and phase (negative, zero, or positive time shift in fluctuations of the activities) (Fig. 5). If the coherence declines and the phase changes between breathing and pulse rate from negative to positive, the risk of heart failure increases (Patent US10463260).

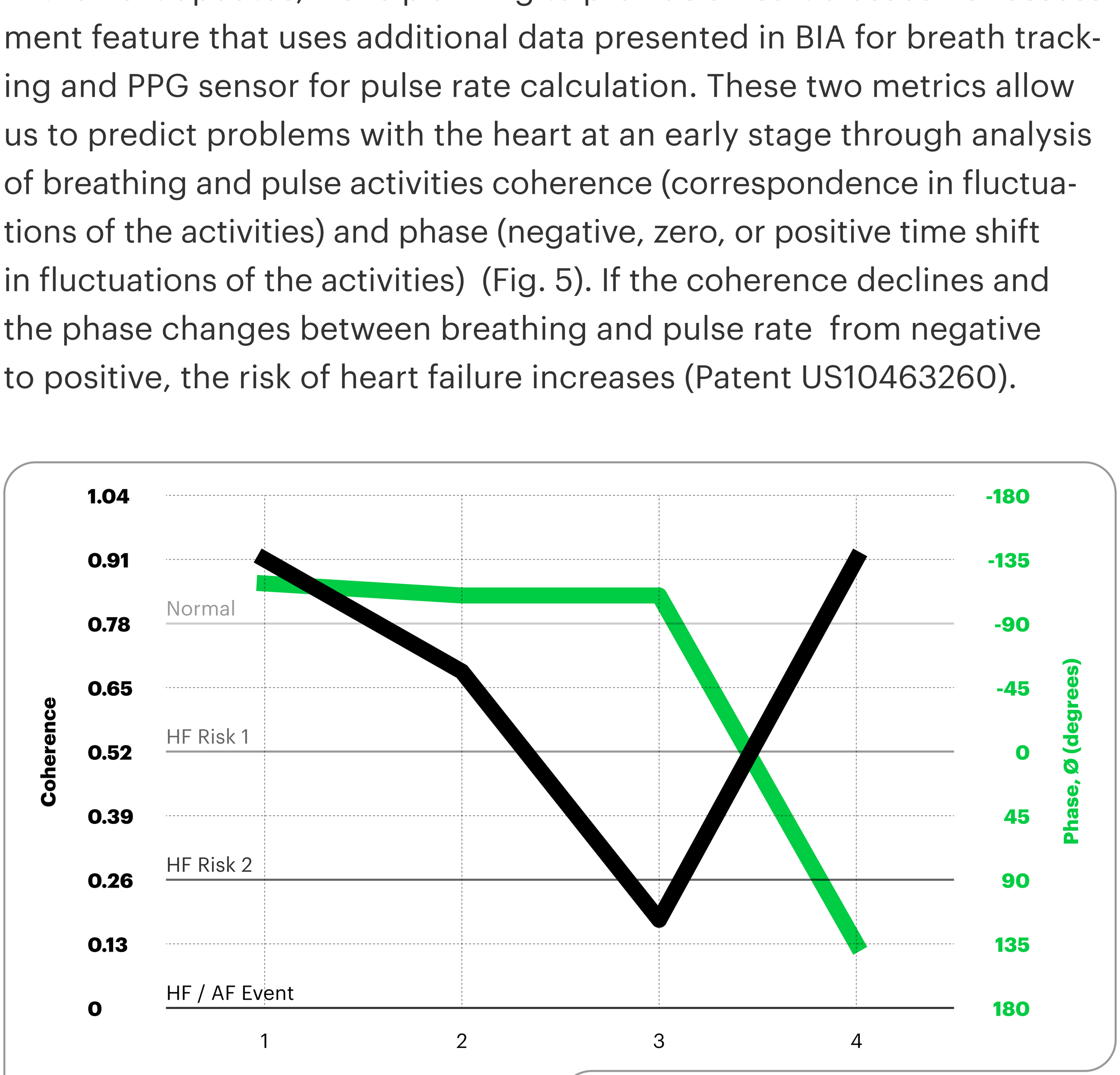


Figure 5.
A schema of heart failure risk prediction by coherence and phase between breathing and pulse rate.

Shortcomings & Solutions

The BIA technology and related devices have been developed to measure meaningful (non-random or non-occasional) within-subject changes and meaningful (non-random or non-occasional) between-subject differences in body composition including hydration status. However, the BIA has its own shortcomings that may cause low accuracy or bad user experience.

For example, it has issues related to short-term or acute physiological and metabolic processes regulating body fluids redistribution like temporal water, protein, and electrolyte transfer between extra and intracellular spaces, and arterial, venous, and lymph redistribution between body's parts affected by:

— Cardiovascular processes
— Excretion
— Thermoregulation
— Perspiration
— Respiration
— Physical movements
— Various responses to stress
— Posture changes
— Central arousal (emotional and cognitive)
— Other challenges

Another issue is related to proper contacts of the BIA electrodes with the body. A challenge with various BIA equations and models for body compartments assessment and calculation also attracts our attention. In the next few pages we're showing a part of approaches that help to resolve these challenges.

Technology validation studies

The Company has conducted studies on effects with respect to various BIA schemas and BIA models to prove the high accuracy and reliability of the BIA technology itself using a more direct and reliable assessment of body compartment compared to isotope dilution and dual-energy X-ray absorptiometry (DEXA) methods that have their own shortcoming (see further). Other studies have assessed the confounding and moderation effects of electrode models, sex, race/ethnicity, and reactivity phenotypes on the accuracy and reliability of the BIA technology.

Reliability and validity of AURA's BIA devices and incorporated BIA models and equations have been explored using different protocols in various biological, laboratory, clinical and population studies. Some studies have already been conducted, others are ongoing or in planning and pending lists.

Main and moderation analyses using Generalized Linear Mixed-Effects Models (GLMM) with the Akaike Information Criterion (AIC) for obtaining and selecting the highest significant and best model-fitting results are used in the studies.

A study of best-fitting BIA models on a biological object (fish)

The physiology of the body may be represented by the equivalent electrical circuits when Extra Cellular Water (ECW) and Intra Cellular Water (ICW) as the major electrical conductors in the body reside adjacent to each other in a parallel arrangement, with the ICW (measured as R_{icw} or X_c) being isolated from the ECW (measured as R_{ecw}) by a nonconducting membrane (C_{cell}) similar to the insulating material within a capacitor (Fig. 2) (Gudivaka, Schoeller, Kushner, & Bolt, 1999).

Other models consider that the ECW and ICW pathways are composed of a resistor and a capacitor in series, but do not run side by side, and thus the resistance (Recw) and reactance (R_{icw} or Xc) are additives (Gudivaka et al., 1999). 50 kHz bioimpedance obtained by a serial schema is proposed to primarily reflect the ECW space, which represents a constant proportion of Total Body Water (TBW) in normal conditions (Kyle et al., 2004). On the other hand, a parallel bioimpedance model appears to be sensitive to changes in ICW, but not to changes in ECW.

However, the most exploited ‘volumetric-based’ approach in obtaining BIA measures has brought contention regarding the utility of the technique in predicting body compartments. Nevertheless, most reference methods assessing body compartments in humans like isotope dilution and dual-energy X-ray absorptiometry (DEXA) methods have their own shortcomings to assert this contention (Branski et al., 2010). It was proposed that the assessment of body compartments by the most direct lethal method could resolve the challenge.

Thus, the comparison of various BIA models in the prediction of direct lethal measures of body compartments using proximate composition analysis of water, proteins, and ash as the reference or criterion points was the main objective of AURA's first study in fish as the biological model. (Davydov, Boev, & Gorbunov, 2021)

This study using this biological model and the proximate composition analysis showed that the 'volumetric-based' parallelly-obtained BIA measures like distance²/Rp could be the best approach in predicting ECW in the 'whole-body' schema (GLMM: t(p) = 2.22 (0.03); 95% CI = 0.02 to 0.44; AIC = 214) compared to 'dispersion' models (all were non-significant) and to 'volumetric-based' serially-obtained schema (GLMM: t(p) = 1.93 (0.06); 95% CI = -0.004 to 0.40; AIC = 215). However, segmental BIA like in the AURA Devices should use 'dispersion' models with serially-obtained measures for the best fitting body compartments prediction (GLMM: t(p) = -4.16 (0.001); 95% CI = -2.58 to -0.92; AIC = 845 for serial Xc) compared to 'volumetric-based' (all were non-significant) and to parallely-obtained 'dispersion' models (GLMM: t(p) = -2.11 (0.04); 95% CI = -0.52 to -0.02; AIC = 850 for parallel Xc).

Moreover, other findings of the study showed that the 50kHz single frequency of alternating current used in the devices can separately predict extra- and intra-cellular water compartments using resistance (GLMM: t(p) = 2.08 (0.04); 95% CI = 0.001 to 0.059) and reactance (GLMM: t(p) = -2.69 (0.01); 95% CI = -0.80 to -0.12) measures of total impedance obtained by the segmental BIA schema. Thus, AURA Devices will be using serially-obtained measures to increase the validity of BIA measures.

Davydov, D. M., Boev, A., & Gorbunov, S. (2021).
Making the choice between bioelectrical impedance measures for body hydration status assessment. Scientific Reports, 11, 7685.
https://doi.org/10.1038/s41598-021-87253-4

Human studies of the method reliability and the model validity

The next objective of our studies was to assess the reliability and validity of the application of the technology in our devices and alike techno-logies in similar devices compared with different references. For example, we added in the study a smart scale with the BIA of the lower part of the body. Our goal was to understand how accurate our BIA device was compared with the BIA of the smart scale in the prediction of clinical references of body hydration state and a fat compartment using, respectively, a heart rate response to orthostatic challenge and an empirical fat calculating formula from skin folds in within- and between-subject analyses.

The parallelly-obtained BIA measures currently incorporated in the AURA Devices and BIA data obtained from the smart scale showed similar validity:

— In correspondence to hydration status: rs = 0.78-0.98, where rs - correlation coefficients, (in different sexes) assessed by indirect clinical indicators of hydration: heart rate response to orthostatic challenge.

— In correspondence to fat compartment: rs = 0.79-0.93, where rs - correlation coefficients, (in different sexes) assessed by empiri-cal fat calculating formula from skin folds - the sum of the triceps, subscapular, suprailiac, and midthigh skinfold thicknesses w/out and with additional adjustment to age, height, and BMI according to Peterson et al. (Peterson, Czerwinski, & Siervogel, 2003).

It is expected that serially-obtained segmental BIA measures in future AURA Devices will increase the validity of BIA measures compared with such commercial BIA scales.

At the same time, our human studies found lower reliability of AURA's BIA measures (consistency of BIA measures of water and fat across time: rs=.80-.81, where rs - correlation coefficients) compared with the BIA measures obtained by the smart scale (consistency of BIA measures of water and fat across time: rs = 0.98-0.99). However, another study showed that this was a result of low compliance (adherence) of the user with the instruction (see Fig. 6).

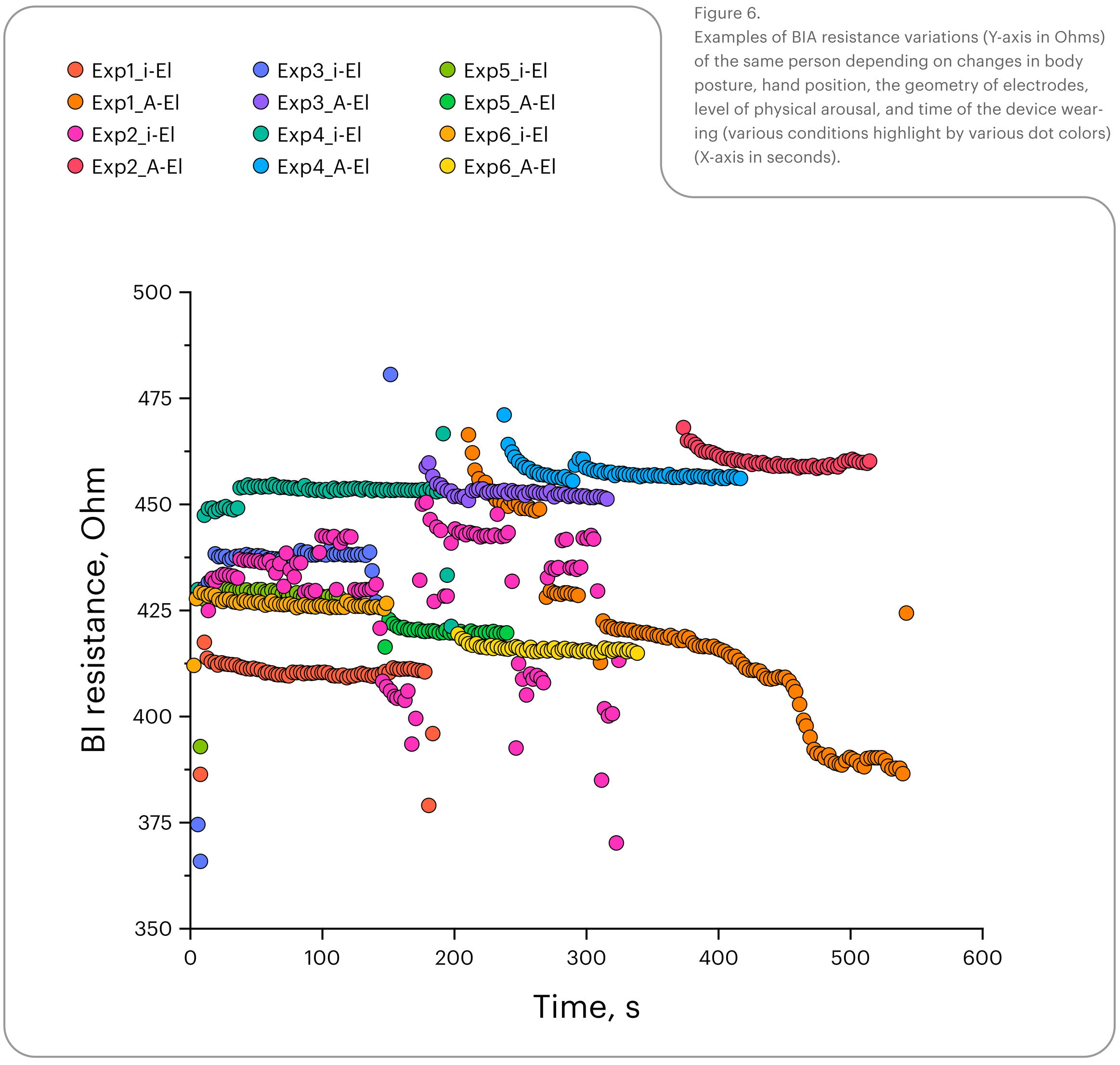


Figure 6.
Examples of BIA resistance variations (Y-axis in Ohms) of the same person depending on changes in body posture, hand position, the geometry of electrodes, level of physical arousal, and time of the device wearing (various conditions highlight by various dot colors) (X-axis in seconds).

For example, an improper hand and/or body position can affect the reliability of the BIA measurements in the current AURA Devices products that are related to hydrostatic pressure and/or blood volume variations (Tables 1 and 2).

Fixed Coefficients[1]

Model Term	Coefficient	Std. Error	t	Sig.	95% Confidence Interval	
					Lower	Upper
Intercept	-1075.784	40.6862	-26.441	.000	-1157.634	-993.934
Hand_Positions=Chest	-13.861	4.1616	-3.331	.002	-22.233	-5.488
Hand_Positions=Abdomen	0[2]	—	—	—	—	—

Probability distribution: Normal
Link function: Identity
1 — Target: BIA resistance
2 — This coefficient is set to zero because it is redundant.

Table 1.
Generalized Linear Mixed Models for hand position (chest vs. abdomen level) effect on resistance measurement.

Fixed Coefficients[1]

Model Term	Coefficient	Std. Error	t	Sig.	95% Confidence Interval	
					Lower	Upper
Intercept	1515.175	50.3992	30.063	.000	1413.785	1616.565
Hand_Positions=Chest	23.175	4.8628	4.766	.000	13.392	32.958
Hand_Positions=Abdomen	0[2]	—	—	—	—	—

Probability distribution: Normal
Link function: Identity
1 — Target: reactance
2 — This coefficient is set to zero because it is redundant.

Table 2.
Generalized Linear Mixed Models for hand position (chest vs. abdomen level) effect on reactance measurement.

Physical activity (e.g., handgrip force vs. arm relaxing) during the measurement can further decrease BIA measurement reliability (Fig. 7).

Thus, the reliability of the AURA Devices measurements can be increased by the consistency in posture, arm positions, and arousal level between measurement sessions. Moreover, reliability can further be increased by a longer (>2 min) wearing of the current AURA Devices, which decreases effects related to the electrode to skin impedance (resistance) variation (Fig. 6). In this case validity in prediction of body muscle increases from 1 min (rs = 0.756-0.757, where rs - correlation coefficients) to 5 min (rs = 0.833-0.834, where rs - correlation coefficients) compared with a reference.

Sweating is considered to be the factor improving the contact and thus the electrical conductance between the skin and the dry electrodes in time. It is also possible to decrease the time until the accurate measurement through stabilizing the signal quality by applying a short breath toward the dry electrode or the skin before the attachment of the electrodes (Grimnes & Martinsen, 2014).

Before electrodes attachment, the water content of the superficial layers of the skin is determined by the partial pressure of water vapor in the surrounding air and on the recent sweat activity. After some time passed from the attachment of the electrodes, the condition between electrodes and skin becomes more like the applied wet gel case due to non-evaporated sweat under electrodes and this improves the electrical contact and the reliability of the BIA measurement. Washing the skin with tap water before the attachment of the electrodes also lowers the impedance.

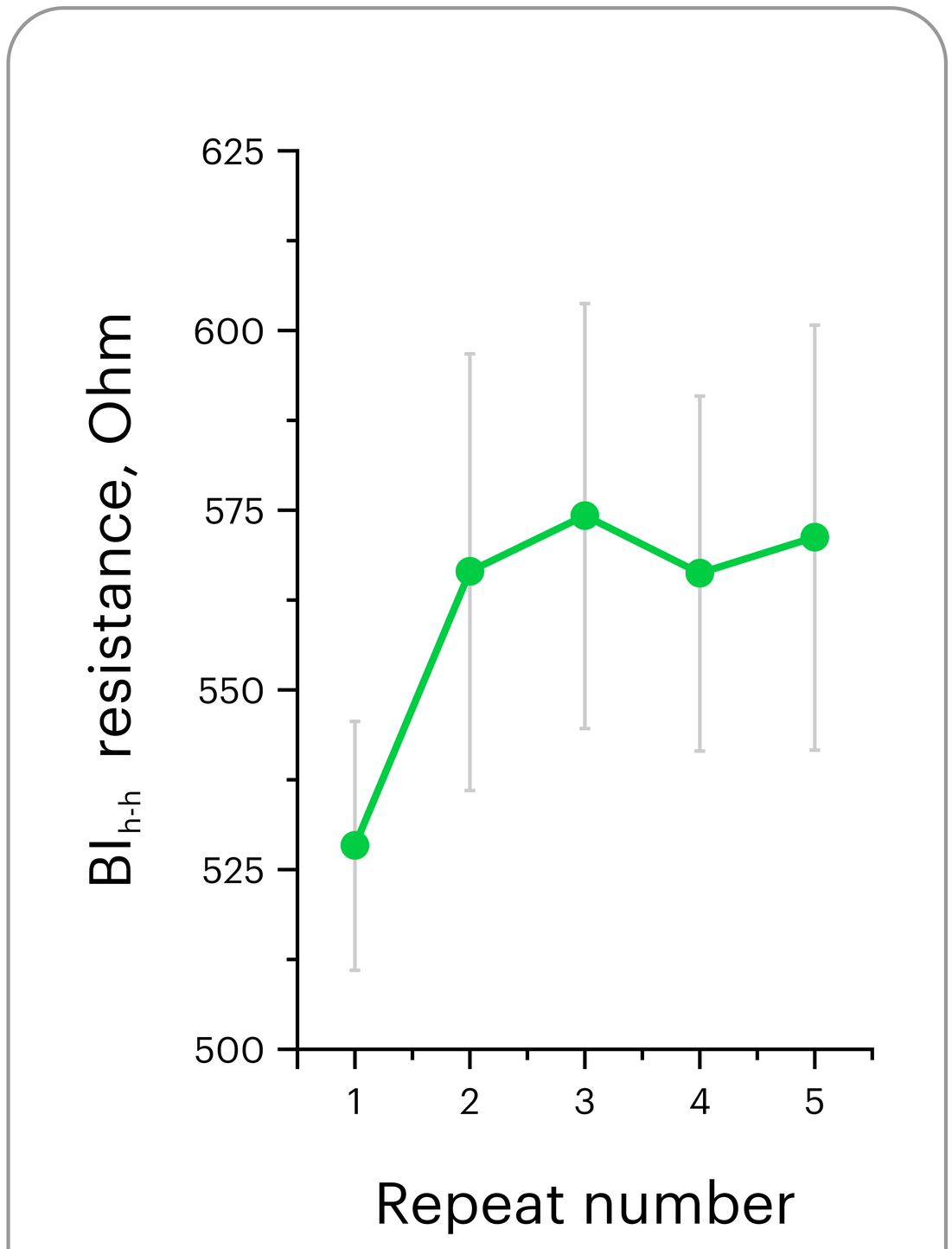


Fig. 7.
Hand-to-hand BIA resistance (BIhh in Ohm) at different times of wearing (Repeats) from 1 to 5 min.

Pilot experimental studies showed that a new geometry of electrodes covering more sweat glands and switching to a new electrical compensation schema of alternating current transmission (with skin conductance measurement) can improve the reliability.

This can adjust the final impedance measurement to within- and between-subject variations in the sweat-related conductance and decrease the time until stable BIA measurement after attaching the device to 10-15 seconds (Fig. 8).

An equation for the compensation in skin-electrode resistance fluctuation is being incorporated in the current models of the AURA Band and Strap.

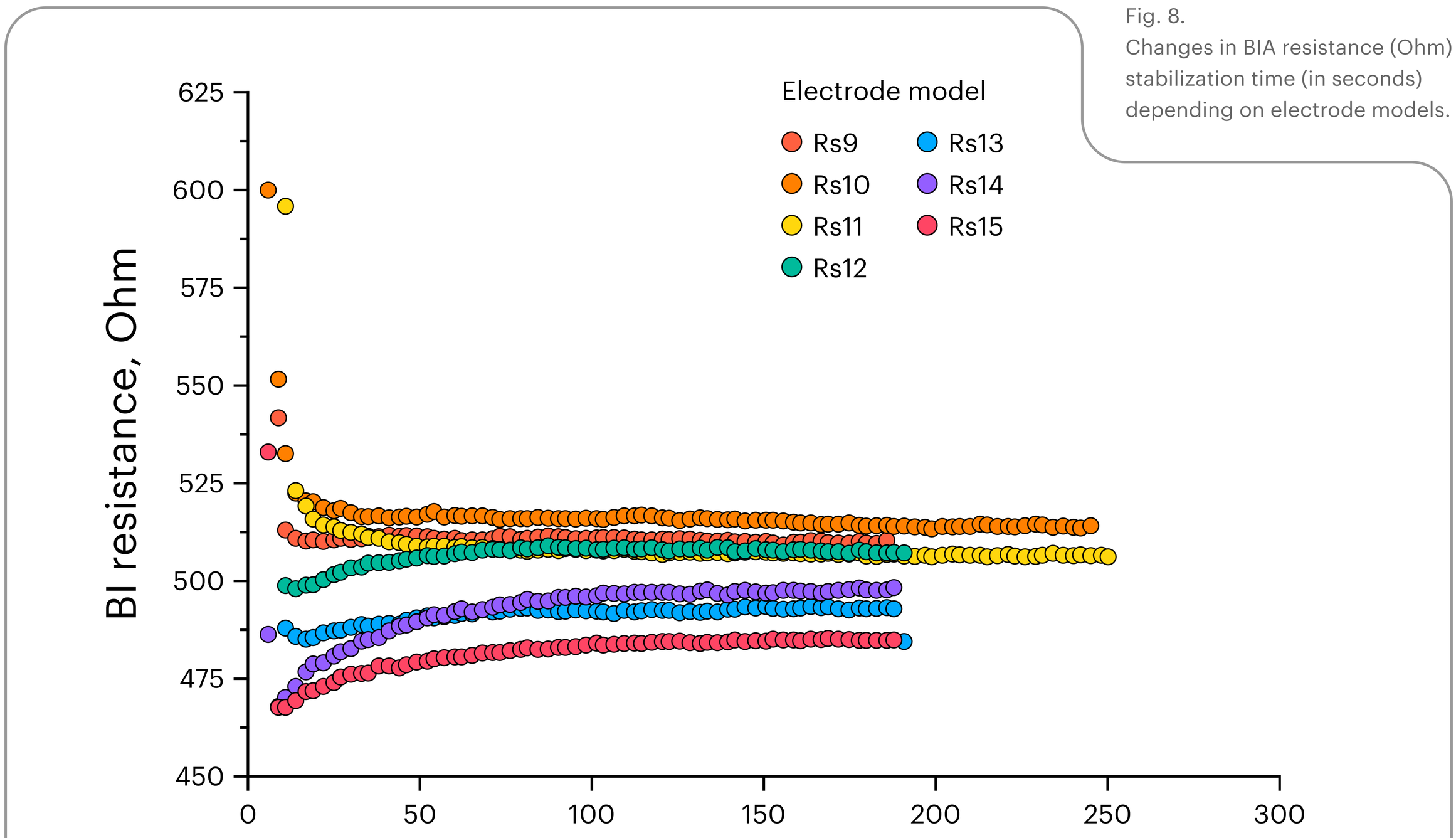


Fig. 8.
Changes in BIA resistance (Ohm) stabilization time (in seconds) depending on electrode models.

Experiments with food and fluid intake showed that the segmental schema of BIA measurement used in AURA Devices is less sensitive to their confounding effects (4-5 Ohm in resistance change) than the regular ‘whole-body’ schema of BIA.

A study of main and interaction effects of ethnicity and sex on BIA-corrected metabolic or energy activity at rest

There are some differences in metabolic and cardiovascular activity that are related to ethnic differences. E.g., some mutations in genes like one responsible for the synthesis of peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) are more distributed in some ethnic groups, but not in others (see, e.g., athletes from Jamaica). PGC-1α is a key regulator of energy metabolism (Liang and Ward, 2006).

PGC-1α stimulates mitochondrial biogenesis and promotes the remodeling of muscle tissue to a fiber-type composition that is metabolically more oxidative and less glycolytic in nature, and it participates in the regulation of both carbohydrate and lipid metabolism. It is highly likely that PGC-1α is intimately involved in disorders such as obesity, diabetes, and cardiomyopathy. However, it is more important not mutations in genes themselves, but gene activity regulated by epigenetic factors like methylation.

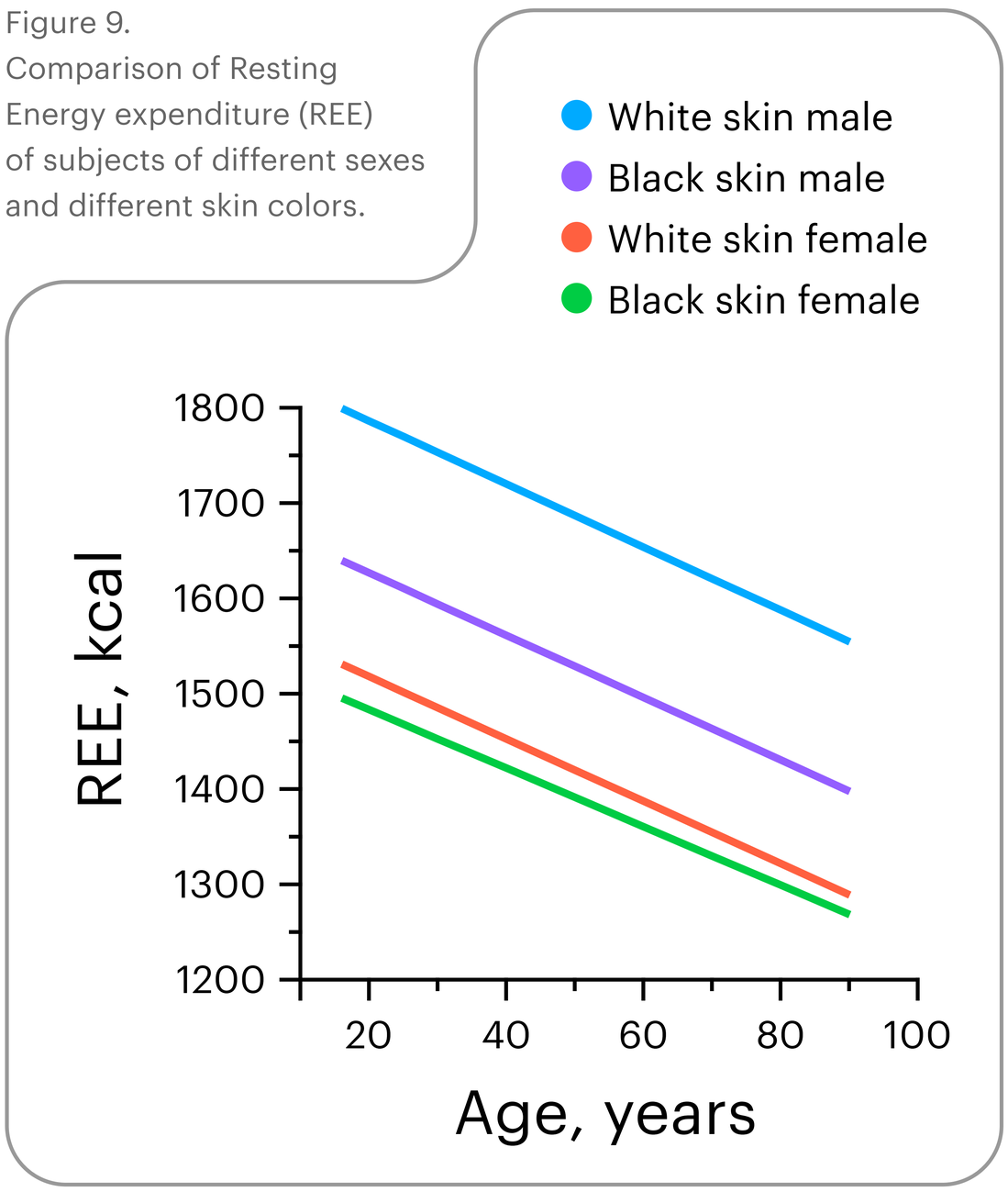
Such genes activity affects basal (resting) metabolic (energy) rate (expenditure) and metabolic efficiency in response to physical activity. This rate of expenditure has different names and respective abbreviations, but the same meaning in scientific literature and among commercial services: BMR, RMR, BEE, REE, where B - basal, R - resting, M - metabolic, E - energy, R- rate, E - expenditure.

The basal energy expenditure determines the energy necessary for the vital functioning of the body at rest and is the largest influencing factor in total energy consumption. However, at present, it is difficult to get the correct information regarding ethnicity, and genetic analysis for the genes affecting metabolic activity is still expensive. Instead, it was proposed to use skin color as a proxy of the effect. Skin color depends on the amount of melanin, and that, in turn, on the amount of melanin-concentrating hormone and sensitivity of respective receptors to it (MCH1R and MCH2R) that affect the basal metabolic rate (Diniz and Bittencourt, 2017; Hervieu, 2006;).

The expression of such factors like PGC-1α is also critical in the melanogenic system (Grabacka et al., 2017; Shoag et al., 2013). Overexpression of PGC-1α induces pigment formation and regulates human tanning or skin color. Thus, AURA takes into account the skin color of users using the Fitzpatrick human skin color scale to correct basal metabolic rate formulas for women and men (Fig. 9). Sex also showed a different effect on metabolic activity and this was considered to be related to the hormone estrogen (17b-estradiol) regulating metabolism and eating behavior (Xu and López, 2018).

Thus, the study showed that the BIA-obtained measures of individual metabolic activity should be adjusted to the skin color and sex of the individual in calculating the individual level of basally burned calories during a day and this algorithm was incorporated in the current versions of Aura devices as an option for more accurate assessment of resting or basal energy rate.

Figure 9.
Comparison of Resting Energy expenditure (REE) of subjects of different sexes and different skin colors.



A clinical prospective study

A collaborative prospective clinical study is conducted on people with metabolic and cardiovascular disorders, using Aura band devices with clinical BIA and DEXA-scan references along with biochemical clinical indicators of hydration and metabolic status and activity. Different populationally and individually derived regression coefficients are expected to obtained for these populations after the study.

An experimental, proof-of-concept ‘hydration’ study

An experimental, proof-of-concept study is ongoing to develop a device for measuring hydration status using a local one-hand BIA with referen-ces to weight change during exercises and thermal bathing along with other cardiovascular and sensorial measures as indicators of the within-subject dehydration and rehydration processes.

Hydration status evaluation differs from the body water composition analysis.

First, hydration status is evaluated according to individual, but not popu-lational health-centric targets:

— Individual level of dehydration (hypohydration)
— Individual level of normal hydration
— Individual level of amount of rehydration for recovery
— Individual level of overhydration

They are related to individual healthy (homeostatic) hydration range as the reference (i.e., an individual health tracking solution) in contrast to absolute or relative water amount as a component of body composition with normal population references (i.e., a regular fitness tracking solution).

Second, the hydration status can be assessed by specific homeostatic referent indicators. For example:

— Short-term body weight changes (hours, days)

— Haematological indices: plasma volume through concentration of haemoglobin and haematocrit

— Levels of plasma osmolality and sodium concentration

— Urinary indices: urine specific gravity, urine osmolality

— Salivary indices: saliva osmolality and volume, saliva specific gravity

— Cardiovascular indices: systolic blood pressure drop on standing; rapid pulse; postural pulse increment

— Subjective indices: e.g., postural dizziness; thirst; fatigue

Other ongoing and future studies to assess and compare effects on the reliability of different BIA measures with respect to

— Different single and multiple BIA frequencies schemas

— Different time from or between event schemas (activity, substance intake, circadian or diurnal rhythms, ultradian and infradian rhythms in normal and abnormal situations like jet lag, sleep and mood disorders, shift work conditions) with and without compensation algorithms

— Different person-location schemas (altitude, weather, climate) with and without compensation

— Different time and position compensation technologies using other sensors against events related to external and internal processes affecting BIA measurements like temperature and humidity changes, changes in hydrostatic, arterial, and venous pressures, blood, and lymph volume redistribution, central arousal effects on skin conductance, vasoconstriction, and muscle tonus, etc.

— Sensors with other physical and/or electrotechnical principles of biological signals acquiring within- (in time and place [body, hands, electrodes positions]) and between-subject designs by assessment of their relationships to references.

Conclusion

In summary, by this date, the studies of the company showed that variables obtained by the BIA technology allowed reliable prediction of direct measures of body compositions and that the accuracy of this prediction depended on correctly selected models and schemas of the BIA.

rs = 0.78-0.98 as the validity compared
with references [r_{max} = 1.0] and rs=.80-.81
as the reliability or repeatedness [r_{max} = 1.0]

Other studies showed that some specific schemas of BIA measurement require a specific voluntary-control (via compliance to instruction) or automatic machine-control (using additional sensors and algorithms) of a current user's behavior and/or state during the measurement to increase the validity and reliability of the results.

Additional findings showed that the accuracy of BIA-related measures could further be improved by adding in their processing a moderation effect related to genetic and epigenetic modifications of the basal metabolic activity assessed by individual skin color. Other ongoing and planning studies are expected to show other directions of the technology application and of further improvement of its accuracy.

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