

Monitoring of Hypohydration Caused by Physical Exercise Using a System-on-Chip-Based Bioimpedance Meter

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Abstract: This paper describes accurate monitoring of hydration using impedance variation in a human being, which accompanies extracellular fluid loss or gain. A prototype of a precision multifrequency bioimpedance meter built around advanced biomedical SoC (System on Chip) MUSEIC v.2 was used in this study. Calibration of the bioimpedance board was conducted on an RC-model of the volunteer selected for the experiments. The model was built using the averaged results of multiple impedance measurements on the subject within the 1 Hz – 100 kHz, which were repeated on different days on near-euhydrated volunteer. The sources of observed variability in bioimpedance have been studied. Several factors were spotted that affect hydration assessment but were not reported in the literature before. The specific protocols for reaching fluid shift were developed in this study. They enabled minimization of errors in altered hydration state. The bioimpedance method is shown in this research to correctly reflect hydration variation in a single person, so that there is no need for averaging over large population to observe the trend. For demonstration of sensitivity of the developed device to fluid shift, it was tested on the volunteer undergoing repeated mild dehydration and rehydration using light-effort exercise (outdoor cycling). The bioimpedance results were compared with the reference hydration. The latter was obtained using the subject weight measurement and precise counting of caloric intake, the weight of food, and also with the aid of established weight baseline prior to any planned experiment. Special attention has been paid to sodium balance, and several diets have been developed for its regulation. The predictable body fluid loss and gain was supported by measured sweating rate, and also by dehydration and rehydration diets designed for precise control of ion and water intake. The accuracy of fluid shift measurement down to a standard deviation of 200 ml is demonstrated, which essentially exceeds capabilities of known methods and devices, including ‘gold standards’ like isotope dilution for hydration assessment. Such accuracy satisfies requirements of healthcare and sport. The device has not yet been validated on population.

Keywords: Hydration, Hypohydration, Dehydration, Rehydration, Bioimpedance, System on chip, Human being.

1. Introduction to Hydration

Maintaining proper hydration is important for all living things. Almost two thirds of the weight of the

authors of this article is water. But if just a few percent of the body’s water were lost due to dehydration or insufficient water intake, it would already be difficult for them to concentrate and write a good article. An

assessment of total body water (TBW) in an individual is not precise because of the wide variety in body build and composition [1 – 4]. Thus, the percentage of hypohydration and hyperhydration is estimated in respect to body weight. A dehydration by 3 to 6 % already create problems and the number of symptoms increases starting with thirst. Such dehydration corresponds to about 5 to 10 % loss of TBW, which must be compensated by fluid intake. However, drinking itself could also become dangerous for a dehydrated person. If large volumes of pure water are consumed in a short time, dilution of body fluids can lead to death, and such cases have been reported. Therefore, both proper hydration and optimum ion intake are vital for health and optimal physical and mental performance.

The TBW can be divided in two volumes: intracellular water (ICW) and extracellular water (ECW). The most accurate classical methods for fluid assessment are based on isotope dilution for TBW, total-body potassium (TBK) using γ -ray emission for ICW, and NaBr dilution for ECW. These methods are direct and called “gold standards”, although there are always some assumptions made, i.e., they all have intrinsic errors [2, 5 – 8]. Their accuracy was not measured directly as far as there was no better reference method, except TBW on small animals compared with their desiccation, where standard deviation (SD) of 3 % was observed while some researches showed larger discrepancies in TBW assessment [7, 8]. Although administration of radioactive tracers enables TBW evaluation, it does not allow repetitive assessments of TBW often required in the clinical settings. Comparison of a sum of ICW and ECW in humans (obtained by TBK and bromide dilution methods) with TBW obtained by D₂O dilution showed that TBW, and thus hydration could be estimated with SD of about 4 l [5]. This actually means that a 99.73 % confidence interval (CI) defined as $\pm 3SD$ extends up to about ± 12 liters while TBW in a typical 70 kg man is of the order of 42 l [9]. Ref. [9] mentions accuracy for TBW of up to 5 % that corresponds to 99.73 % CI of about ± 6 liters, i.e. two-fold better than measured in [5]. People working in hot environment, workers having heavy physical load and sportsmen can rapidly lose several liters of water if they do not drink on time. For the other healthy people, daily variation of weight within the 1.5 kg and of hydration within one liter is usual in a moderate climate (as observed in this research) while a two-liter dehydration (about 3 %) has already profound effect on physical and mental performance of a person. In this study, a typical nocturnal dehydration of 0.63 l was observed in a 72 kg man, which increased to 0.8 l at high nocturnal ambient temperatures, which is normal. Because of such natural diurnal variability, a precision of ± 1 liter for hydration is widely assumed to be the ultimate goal for developers of new methods and devices for hydration assessment [10].

2. Modern Methods for Hydration Assessment

Hydration assessment is usually being conducted using a set of hydration indices (such as weight variation, urine osmolarity, its color and volume, skin elasticity) and symptoms (such as edema, mouth dryness, confusion, dizziness, tachycardia, thirst, fainting when standing up, headache, tiredness), blood test (plasma osmolarity and sodium), or, sometimes, using isotope dilution, etc. Among the methods, there are direct ones (blood tests, direct ECW sample and body weight change), those called gold standards that use some calculations (isotope and bromide dilution, TBK), and indirect methods (all others). The methods themselves and their combinations still lack precision [5, 9, 11 – 13].

Bioimpedance methods have been widely studied in application to estimation of body composition [4, 14]. The methods are based on total body water (TBW) calculation. The latter, in turn, is obtained using one of known regression equations, measured impedance of human body, and biometric data of the subject. Several regression equations were obtained for a normally hydrated general population and also for population-specific cases, see, e.g., [4]. The bioimpedance analysis (BIA) is indirect method for TBW assessment, it is quick and much easier than the classic methods used in medicine. The accuracy of bioimpedance methods compared to the “gold standards” is not better than the latter [15, 16]. However, they drastically simplify the hydration assessment and therefore are widely used, e.g., by dietologists, although the validity of conclusions based solely on the BIA is uncertain. This statement is supported by the CI reported in previous section for gold standards. It is also supported by the fact that bioimpedance methods are rarely used in clinics and never in critical situations. As reported, the CI is too large for clinical purposes [17], and that the TBW, ICW and ECW are consistent on population, but not at the individual level [18].

The rate of publications on bioimpedance methods approaches 1 paper per day [19] including this article. So far, none of researches has shown accuracy sufficient for using it in clinical practice [15 – 20]. Despite insufficient accuracy, bioimpedance methods were studied in application to hemodialysis [10, 18], where an accuracy of 1 liter would also be desirable [10]. When bioimpedance methods are used for measuring dynamic shifts in hydration, one could expect better accuracy of such relative bioimpedance variation. However, the diagnostic accuracy does not allow such relative measurements to be trusted either 5, 18, 20, 21]. For example, [22] concludes that the bioimpedance method does not provide a valid estimate of the change in TBW due to isotonic fluid loss, [23] reports that it was not valid under conditions of altered hydration, while [24] underlines that it is not

currently able to identify type and magnitude of fluid loss.

The bioimpedance regression equations obtained on the euhydrated population are not suited for the case of altered hydration. Therefore, it is not surprising that a lack of proof can be found in the literature that bioimpedance methods can assess hydration change with no need for averaging over the population. In addition to demonstrated nice statistical studies, there is a strong demand for any measurement device and method to assess TBW shift in a single healthy person, or in ambulatory application with an accuracy of about ± 1 liter. The situation in hydration assessment methods is summarized, e.g., in [25]: “As of now, there are no reliable tools to determine hydration status.” This work is devoted to demonstration of accurate TBW shift measurement with accuracy better than the one of “gold standards” to such a shift. The presented method is relative, it shows variation of hydration relative to the baseline.

3. The Bioimpedance Sensor, its Calibration and the Measurement Setup

The early hydration monitoring studies at Imec [26] were conducted using commercial bioimpedance analyzers, lock-in amplifiers and earlier versions of wearable bioimpedance sensors [27, 28]. They have indicated the need for a more accurate device, adjustment of the measurement protocol and deeper understanding of the bioimpedance variability for better assessment of hydration status. In this work, the evaluation test board, Fig. 1, was built using one of the most advanced multiparameter signal acquisition System-on-Chip (SoC) MUSEIC v.2 for personal health applications [29, 30]. The chip with a size of $8\text{ mm} \times 7\text{ mm}$ contains ten readout channels with the state-of-the-art accuracy, Fig. 2.

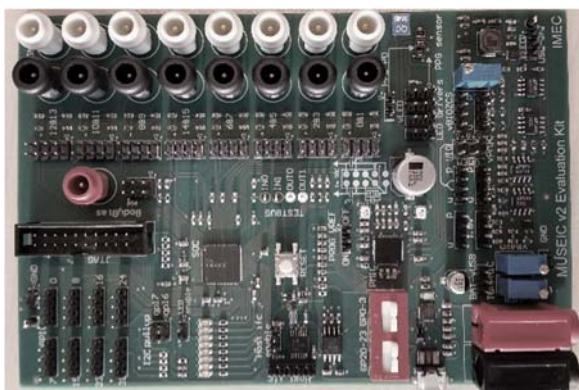


Fig. 1. Multiparameter signal acquisition test board built around SoC MUSEIC v.2.

In this work, only the multifrequency bioimpedance channel and the current generator were used. The bioimpedance sensor was used at selected

frequencies of 8, 16, 32, 64, 128, and 256 kHz at a current of $10\ \mu\text{A}$. A low-pass digital finite element response (FIR) filter selectable from 10 Hz to 150 Hz was used at 10 Hz. Variable current and gain enable selection of the most advantageous combination of sensitivity and dynamic range, depending on electrode locations on the human body. The 5-electrode configuration consists of two current electrodes, two potential electrodes, and a body bias electrode (to increase system stability and to reduce motion artifacts).

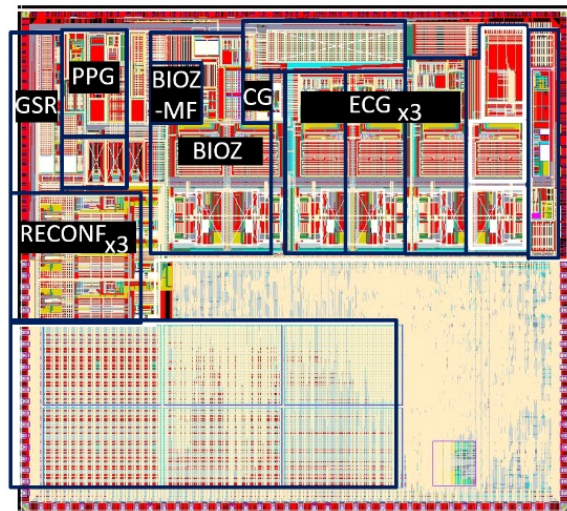


Fig. 2. MUSEIC v.2 SoC containing sensor readouts, filters, controller, and data analysis modules. Abbreviations denote current generator (CG), and readout channels for: galvanic skin response (GSR), photoplethysmography (PPG), a fixed-frequency (20 or 40 kHz) bioimpedance (BIOZ), a multifrequency bioimpedance (BIOZ-MF) within the 1 kHz to 1 MHz range. There are also three electrocardiography (ECG) and three reconfigurable (RECONF) channels that can be configured to any of readout channels mentioned above.

In this study, two basic electrode configurations were used. The first one is a classical one, with tab electrodes between the wrist and ankle, for measuring in a supine position of the subject. However, given that the device should be wearable (after miniaturization), the forearm-to-forearm configuration was mainly used in this study. The Meditrace 200 wet-gel *i*- and *v*-electrodes on the forearm were separated by at least 9 cm, otherwise the required accuracy could not be achieved.

For characterization of the bioimpedance sensor, the selected volunteer's electrical properties between the forearms and the properties of the electrode-skin pair have been repeatedly measured using EG&G 5210 lock-in amplifier within the 1 Hz – 100 kHz range for several days, averaged, and the electrical RC-model shown in Fig. 3 was obtained. It was used for calibration of the device and measurement of the system accuracy.

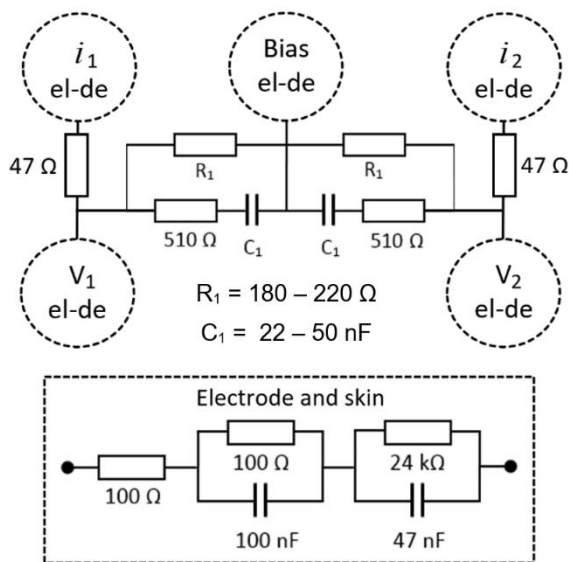


Fig. 3. Empiric RC-model of the male subject selected for the study in this work (top) and of electrode-skin pair (bottom) both suitable for 1 Hz – 128 kHz range. Typical R_1 in euhydrated state was 200Ω , and C_1 was 22 nF . The range for RC-values was used for the device calibration.

The impedance of electrode-skin pair is highly variable depending on sweating rate and skin blood flow. On average, at indoor temperatures and typical sedentary activity in the office, i.e., with no sweating, the impedance of Meditrace 200 wet-gel electrode and skin of the subject was modeled using the circuit shown in Fig. 3, top. For calibration of the bioimpedance sensor and system characterization, all five electrodes shown in Fig. 3, top, were replaced with the electrode-skin circuit shown in Fig. 3, bottom. At integration time of 16 s, a SD of resistance measured on the RC-model at 64 kHz was $45 \text{ m}\Omega$. Therefore, in absence of human-related variability, the board is sensitive enough to detect body fluid change of about 50 ml with almost 100 % probability, because resistance variation in man exceeds 6SD at such fluid shift.

4. Euhydration Baseline, the Reference Method for Hydration Estimation, and the Rate of Fluid Loss in Exercise

The impedance of a healthy and normally hydrated person fluctuates throughout the day near its stable average [26]. The human body loses water and ions through insensible perspiration, sweating, urine and feces. However, they are renewed on a regular basis through food and water intake. But before the ions from food reach the cardiovascular system, the body must secrete about one to two liters of digestion fluids. Despite the presence of many other factors affecting the results, a variation of bioimpedance associated with food intake was detected by averaging multiple measurements before and after food intake for several days using commercially available Maltron BioScan

920 bioimpedance analyzer (on earlier stages of this work, when the test board was not yet ready). The impedance was measured at 5, 50 and 100 kHz in two setups, in supine position with tab electrodes on left wrist and ankle, and between forearms while standing. The trendline for left ankle-wrist plot correlated well with the trendline for wrist-to-wrist results [31]. The peak of impedance corresponded to about 30 – 60 min after meals. This is the time when digestion fluid is secreted, thereby increasing body impedance, but electrolyte from food is not yet fully absorbed.

Apart of food intake there are other factors that lead to a change in impedance in a healthy person. The measurements show that if a person takes a supine position, the impedance drift is observed for 20 min and more after that moment [26]. Therefore, in this study, the bioimpedance measurements on a standing, or sitting subject were preferable. Although these positions do not improve repeatability of the measurements, they are more appropriate for wearable applications. Conductivity of electrolytes, including body fluids, increases with temperature [32]. Therefore, care has been taken to keep extremities warm, although skin temperature was not constant. Soft human tissue is a soft material by definition. It is therefore impossible to ideally reproduce the body shape. Even in supine position, the impedance meter was sensitive to tiny repositioning of limbs.

Replacement of electrodes also affects the impedance because of positioning accuracy. For accurate electrode positioning, marking of electrode location with a marker was not good enough. The tiny body landmarks were used instead to have positioning accuracy within 1 mm. Depending on particular electrode location, a 2 mm-shift of two v -electrodes may cause impedance variation equivalent up to 0.5 l of body fluid change. Insensible bending of limbs also affects impedance. It can be controlled in a better way in a sitting or standing subject, e.g., using a forearm support and fixed places for feet.

Cables connecting body with the device also introduce errors. The cable-to-body and cable-to-cable crosstalk is observed while using ECG leads. Such cables are however soft and work well if care is taken about separation of them from the body. However, when standard coaxial cables were used, it was found that they are too rigid and heavy for soft human tissue. They pull skin and relocate the electrode-skin couple in respect to underlying tissue thereby producing an error, and sometimes a large error.

The bioimpedance analyzers are sensitive, to certain extent, to the electrode-skin pair impedance. The difference in electrode-skin impedances between electrodes (both v - and i -electrodes) also affects the results. Therefore, the results obtained using commercial bioimpedance analyzers are influenced by the electrode-skin impedance variation. Although variations are small, they have profound influence on measurement accuracy. The high input impedance of the developed board makes it immune to this effect.

Among other factors to be accounted for, sodium intake, sweating rate and increased blood flow in

exercising muscles are the most important factors. Therefore, while using cycling in this work for dehydration, the forearm-to-forearm electrode configuration was typically used to avoid drop of impedance in legs. Finally, lactate increase, despite relatively low input in ECW conductivity, also causes decrease of the impedance during and after exercise. In this work therefore high-effort exercise was prohibited, at least for the last 1 – 2 hours of cycling.

Because of natural daily impedance variability, establishing its baseline is important for detection of small changes related to hydration. Fig. 4 illustrates typical joint effect of the aforementioned factors in a normally hydrated person. Important that uncorrelated impedance between different parts of the body, Fig. 5, observed in everyday life clearly indicates errors in impedance measurements. Indeed, hydration affects the whole body, so that the results must be correlated.

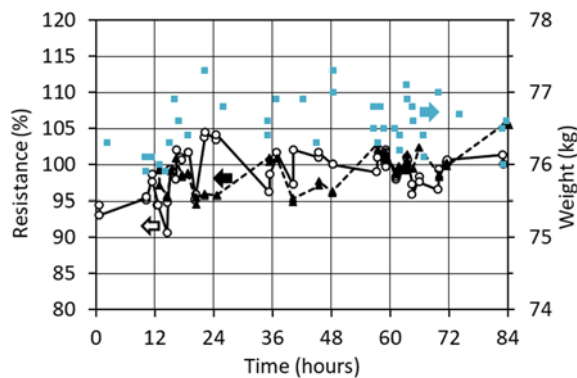


Fig. 4. Weight (squares) and impedance in a healthy person monitored in a course of three days. Shown points is impedance averaged over 5, 50, 100 and 200 kHz between forearms (circles, solid line) and between the wrist and ankle (triangles, dotted line). Measured using commercially available bioimpedance analyzer.

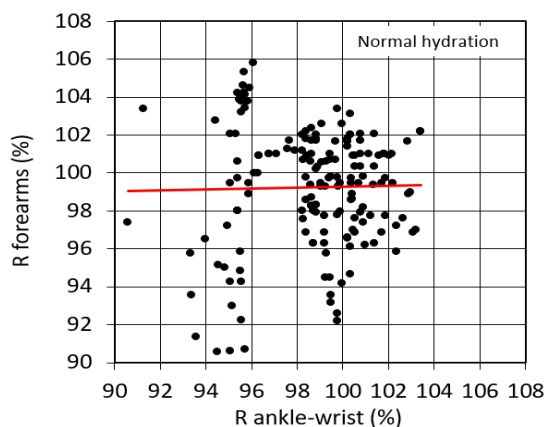


Fig. 5. Independence of resistance between forearms on resistance between wrist and ankle. Shown experimental points is impedance averaged over 5, 50, 100 and 200 kHz. Measured using commercially available bioimpedance analyzer. A part of data points is taken from Fig. 4.

Fig. 4 also illustrates daily weight variation. Using weight as a reference for fluid shift monitoring was

adopted in this work. Impedance changes were compared with this direct method for hydration assessment. It is based on weight monitoring and calculation of fluid and food intake, balanced with energy expenditure. This made it possible to obtain a reference estimate of hydration with an accuracy of about 200 ml, which is better than could be obtained using other methods. The reference method however works only in a course of several days.

To monitor hydration, a man weighing 72 kg was selected. According to several regression equations for TBW, both anthropometric and bioimpedance, the studied man had 41.0 l of TBW in euhydrated state (averaged over ten equations). Maintaining proper hydration is known to be important in heat stress for both health and safety. Therefore, simulating the workload by cycling was performed this study at moderate to high ambient temperatures. The study followed the guidelines of the protocol Stress in the Work Environment approved by the Medical Ethical Committee of KUL Hospital. Cycling for several hours at the same effort provided near-constant physical load with measured average sweating rates based on weight loss. Fig. 6 shows experimental results on fluid loss, which enabled planning of the exercise duration depending on weather conditions and the target hypohydration level. Using these results, the sweat loss was predicted for every exercise, which allowed preparation of specific diets with required deficit or excess of sodium ions in respect to optimum intake. The scattering of points observed in Fig. 6 can be explained by difference in solar radiation, clouds and humidity, and slightly different cyclist performance depending on weather.

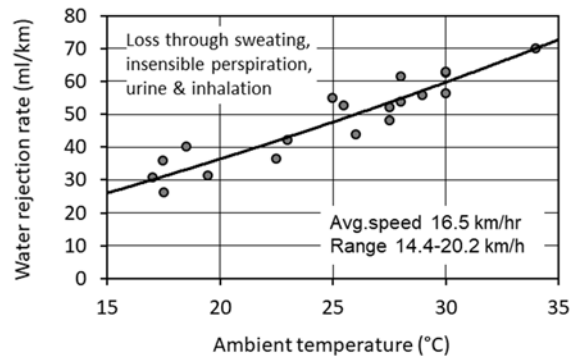


Fig. 6. Experimental rate of fluid loss depending on ambient temperature in the cyclist at a metabolic rate of 5 ± 1 MET in his several usual tracks of 40 to 60 km long. The points mark average fluid loss in 18 exercises.

5. Diets with Known Ion Content for Predictable Fluid Shift

The study preceding this project [26] has shown that uncontrolled consumption of sodium (too much table salt in food consumed in chaotic manner) resulted in dramatic daily variation of ions and water

retention in the body. Accounting for unbalanced (*ad libitum*) food intake in respect to energy expenditure, these factors typically create large variations in both subject weight and his/her impedance. Therefore, the protocol included matched diets with precise quantity of potassium and sodium per day. Furthermore, while the subject was undergoing dehydration, the sodium intake was minimized, but it was doubled during rehydration. The latter provided faster rehydration compared to using balanced sodium intake.

As an example of developed diets, the menu for exercise day included rice, potato and pasta, chocolate bars, butter, all with no added salt, apple and grape juices, tomatoes, sugar, coffee, sunflower seeds, an apple and water (50 mg sodium and 3.6 – 6.0 g potassium intake per day, per 3700 kcal). Depending on duration of exercise, the menu was corrected to match energy expenditure. Fully balanced diets have sometimes been used to stabilize impedance before exercise and after rehydration. For example, one of such diets contained bread (salted and unsalted), potatoes, cheese (Gouda), eggs, tomatoes, beef, jam, garlic (one clove), soup (curry), milk, red wine, coffee, water (3.0 g sodium and 4.64 g potassium intake per day, per 2550 kcal).

For rehydration, it is necessary to drink 50 % more water than was lost. Rehydration diet contained between 150 to 220 % of recommended sodium intake per day thereby enabling better water retention and rapid rehydration. This enabled complete fluid recovery in just one day. As an example, the rehydration diet included bread (salted), potatoes, cheese (Gouda), eggs, ham, tomatoes, sausage (turkey), sugar, table salt, jam, garlic (one clove), soup (chicken), red wine, milk, coffee, water (6.7 g sodium and 4.3 g potassium intake per day, per 2550 kcal).

6. Dehydration and Rehydration Study, the Protocols and Results

Hypohydration was provided by the combined effect of limited water intake during 2 – 3 days and 1 – 2 days of cycling in warm/hot weather for 40 – 50 km distance at about 5 ± 1 MET light effort. Low-sodium diet helped to decrease thirst and promoted water rejection. The impedance measurements were conducted on a sitting or standing subject between forearms to avoid measurements on exercising muscles (legs) of cyclist. Fig. 7 shows variation of both resistance at 64 kHz and the reference hydration of the subject during the week-long dehydration and rehydration experiment. The following protocol was used in this experiment. On first two days, a baseline of impedance was monitored together with the subject weight. Having euhydration baseline established using the average weight, it becomes possible to calculate hydration status using the subject's weight and accounting for food and water intake. Regulation of hydration began on the third day, when a balanced diet accompanied by reduced water intake enabled initial slight hypohydration. On days

4 and 5, the no- Na^+ diet was applied with reduced water intake, and cycling was used for faster dehydration. The rehydration started on fifth day, after exercise and a few measurements in hypohydrated state. The rich- Na^+ diet was used and continued on the sixth day. As mentioned in previous section, about 150 % of water was consumed on the evening of the fifth day, and on the sixth day compared with the loss of water. On the seventh day, a balanced Na^+ diet was used for fluid balance stabilization and equalization. Water intake on the seventh day was *ad libitum*. This or similar protocol was used in several experiments.

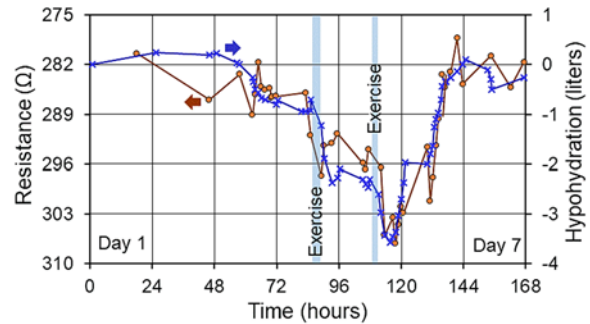


Fig. 7. Resistance between forearms at 64 kHz (circles) and the reference hydration based on weight and food intake (crosses) of a subject undergoing dehydration on days 3 to 5, cycling exercises on days 4 and 5, and rehydration on day 5 (after the 2nd exercise) and on day 6.

The results shown in Fig. 7 are still noisy, i.e., there are some impedance variations apart of those caused by fluid shift. Accounting for imperfect calculation of hydration from weight and intake, a digital low-pass FIR filter was applied to both sets of data, resistance and hydration. A simple FIR filter or just a 3-point moving average offered about the same improvement. The result of such noise reduction is shown in Fig. 8. The result of a similar processing of reactance data is shown in Fig. 9 for the same experiment.

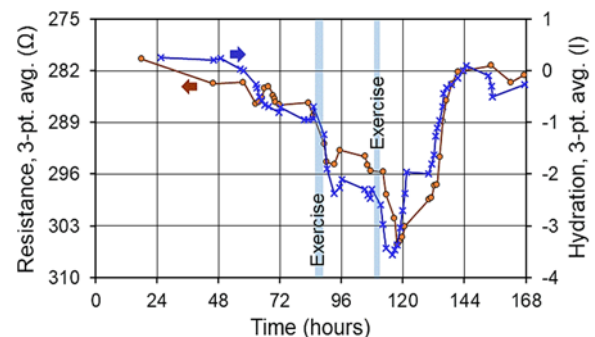


Fig. 8. Resistance between forearms at 64 kHz (circles) and the reference hydration (crosses). A low-pass filter (3-point moving average) is applied to both resistance and the reference hydration.

The remaining difference between hydration and electrical parameters shown in Figs. 7 and 8 can be explained by joint effect of different factors such as electrode placement accuracy, tiny variation of subject's posture, inaccuracy of the reference hydration calculation, limb temperature variation and delay of hydration measured electrically in respect to the weight-and-intake reference during rehydration.

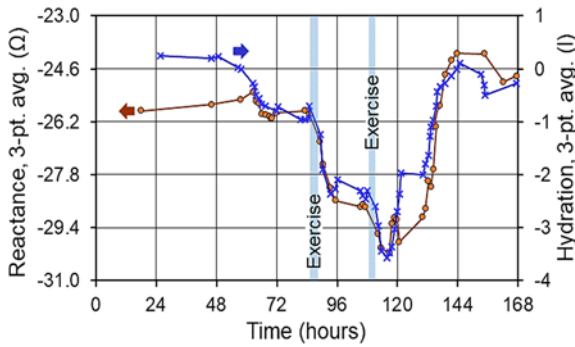


Fig. 9. Reactance between forearms at 64 kHz (circles) corresponding to the results shown in Fig. 8, and the reference hydration (crosses). A low-pass filter (3-point moving average) is applied to both reactance and hydration.

The results presented in Figs. 8, 9 can be re-plotted to obtain dependence of hydration on resistance or reactance. The example is shown in Fig. 10, where regression equation is obtained for calculation of hydration based on resistance, although reactance provides the same or similar accuracy [31].

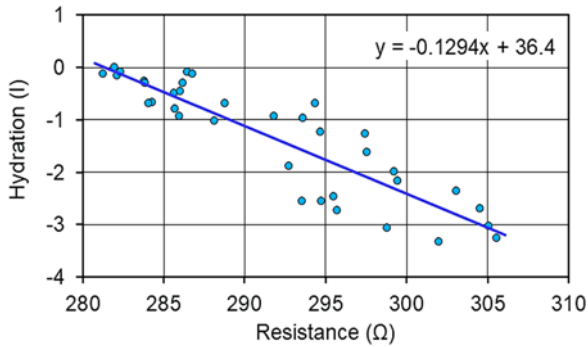


Fig. 10. Dependence of hydration on resistance between forearms at 64 kHz. A low-pass filter (3-point moving average) is applied for both resistance and hydration.

Further improvement of the method is obtained by averaging of measured impedance over several frequencies. Fig. 11 illustrates resistance averaged over several frequencies in another dehydration experiment.

Using regression equations like the one shown in Fig. 10, the results of hydration measurement with the sensor can be plotted versus the reference hydration, Fig. 12. Another way of representation of the

hydration measurements is to obtain hydration from resistance, and also from reactance, and then average over two sets of data. The example of such data processing is presented in Fig. 13.

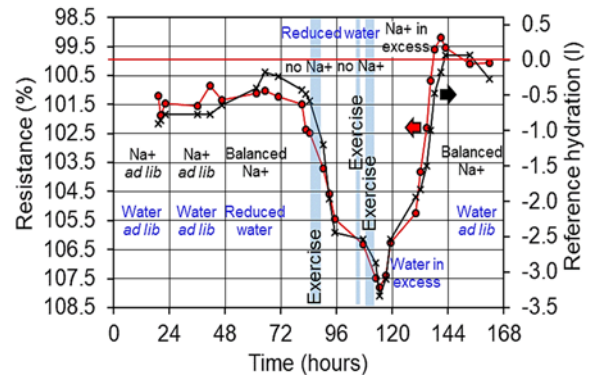


Fig. 11. Resistance between forearms averaged over 16, 64, 128 and 256 kHz (circles) and the reference hydration (crosses). A low-pass filter (3-point moving average) is applied for both resistance and the reference hydration.

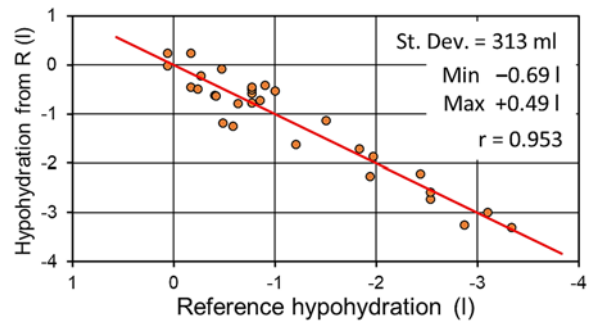


Fig. 12. Hydration measured using resistance at 128 kHz in one of the experiments and plotted versus the reference hydration based on subject weight and intake with applied digital filter (3-point moving average) for both.

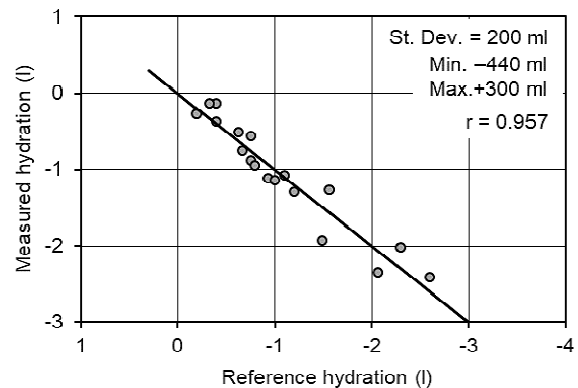


Fig. 13. Hydration obtained using resistance and reactance at 8 kHz in one of the experiments and plotted versus the reference hydration based on subject weight and intake with applied digital filter (3-point moving average) for both measured and reference hydration.

7. Discussion

Hydration in this study was successfully monitored at all studied frequencies, from 8 to 256 kHz, although the regression equations for dehydration, as clear from the RC-model, depend on frequency. For example, the slope of resistance change was 2.9 %/l at 16 kHz, and 2.3 %/l at 128 kHz. The best results were obtained so far using resistance at frequencies below 256 kHz and using reactance at low frequencies of 8 to 16 kHz, and also using averaging over hydration obtained separately using resistance and reactance. Application of data filtering, e.g., using a FIR filter, enabled further improvement of signal-to-noise ratio, where signal is hydration and noise is device-, electrode- and posture-related errors in the impedance of the subject.

Several factors were observed that usually cause instability of impedance. Among them, it is necessary to stress on variability of sodium intake, which is related to heavily salted food products available in grocery stores. Some of our initial experiments failed because volunteers consumed uncontrolled amount of cheese and ham between the measurements thereby creating chaotic electrolyte volume variation. As a result, water retention was affected, and the impedance fluctuated making hydration baseline noisy. The posture of the subject is not exactly reproduced from one measurement to another, and this is one of important factors introducing errors. Commercial impedance meters are frequently sensitive a little to electrode and skin impedances. In this relation, the body bias electrode, high CMRR (>100 dB) and high input impedance (2 G Ω) implemented in the developed device helped to eliminate some of errors observed in bioimpedance meters on the market.

The minimum SD of 200 ml for hydration variation observed in this work is seemingly largely affected by imperfect reference calculation of hydration based on food intake and weight of the subject. Indeed, the accuracy of the reference hydration was almost the same, with SD of about 100 – 150 ml on estimate, and the balance had a resolution of 100 g.

8. Conclusion

It is shown that the bioimpedance board with MUSEIC v.2 SoC enables accurate hydration monitoring in a healthy subject under condition of following a diet-based protocol. The achieved accuracy exceeds accuracy of the methods usually used for hydration shift assessment by at least a factor of ten. The method still needs both deeper studying and further validation on population. Of course, the measurement protocol and diets, which were necessary in this study for calibration of the device, could be simplified in the future for approval in hospitals and sport. Recently, a miniaturized wearable version of the device used in this work was presented [33], although it has not yet been tested as a wearable hydration monitor.

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References

- [1]. P. E. Watson, I. D. Watson, and R. D. Batt, Total body water volumes for adult males and females estimated from simple anthropometric measurements, *The American Journal of Clinical Nutrition*, Vol. 33, 1980, pp. 27-39.
- [2]. D. A. Schoeller, E. van Santen, D. W. Peterson, W. Dietz, J. Jaspán, and P. D. Klein, Total body water measurement in humans with ¹⁸O and ²H labeled water, *The American Journal of Clinical Nutrition*, Vol. 33, 1980, pp. 2686-2693.
- [3]. E. C. Hoffer, C. K. Meador, and D. C. Simpson, Correlation of whole-body impedance with total body water volume, *Journal of Applied Physiology*, Vol. 27, Issue 4, 1969, pp. 531-534.
- [4]. U. G. Kyle, I. Bosaeus, A. D. De Lorenzo, P. Deurenberg, et al., Bioelectrical impedance analysis — part I: review of principles and methods, *Clinical Nutrition*, Vol. 23, 2004, pp. 1226-1243.
- [5]. J. G. Raimann, F. Zhu, J. Wang, S. Thijssen, M. K. Kuhlmann, P. Kotanko, N. W. Levin, G. A. Kaysen, Comparison of fluid volume estimates in chronic hemodialysis patients by bioimpedance, direct isotopic, and dilution methods, *Kidney International*, Vol. 85, 2014, pp. 898-908.
- [6]. J. R. Speakman, Doubly labelled water: Theory and practice, *Chapman & Hall*, 1997.
- [7]. J. M. Culebras and F. D. Moore, Total body water and the exchangeable hydrogen. I. Theoretical calculation of nonaqueous exchangeable hydrogen in man, *American Journal of Physiology*, Vol. 232, 1977, pp. R54-R59.
- [8]. J. M. Culebras, G. F. Fitzpatrick, M. F. Brennan, C. M. Boyden, and F. D. Moore, Total body water and the exchangeable hydrogen. II. A review of comparative data from animals based on isotope dilution and desiccation, with a report of new data from the rat, *American Journal of Physiology*, Vol. 232, 1977, pp. R60-R65.
- [9]. L. E. Armstrong. Assessing hydration status: The elusive gold standards, *Journal of the American College of Nutrition*, Vol. 26, Issue 5, 2007, pp. 575S-584S.
- [10]. F. Seoane, S. Abtahi, F. Abtahi, L. Ellegård, G. Johannsson, I. Bosaeus, and L. C. Ward, Mean expected error in prediction of total body water: A true accuracy comparison between bioimpedance spectroscopy and single-frequency regression equations, *BioMed Research International*, Vol. 2015, Article ID: 656323.
- [11]. L. Hooper, A. Abdelhamid, N. J. Attreed, W. W. Campbell, et al., Clinical symptoms, signs and tests for identification of impending and current water-loss dehydration in older people, *Cochrane Database of Systematic Reviews*, April 30, 2015.
- [12]. M. N. Sawka, L. M. Burke, E. R. Eichner, R. J. Maughan, S. J. Montain, and N. S. Stachenfeld. Exercise and fluid replacement, *Medicine & Science in Sports & Exercise*, Vol. 39, Issue 2, 2007, pp. 377-390.

- [13]. L. A. Popowski, R. A. Oppliger, G. P. Lambert, R. F. Johnson, A. K. Johnson, and C. V. Gisolfi, Blood and urinary measures of hydration status during progressive acute dehydration, *Medicine & Science in Sports & Exercise*, Vol. 33, Issue 5, 2001, pp. 747-753.
- [14]. U. G. Kyle, I. Bosaeus, A. D. De Lorenzo, P. Deurenberg, et al., Bioelectrical impedance analysis — part II: utilization in clinical practice, *Clinical Nutrition*, Vol. 23, 2004, pp. 1430-1453.
- [15]. J. R. Moon, S. E. Tobkin, M. D. Roberts, V. J. Dalbo, C. M. Kerksick, M. G. Bemben, J. T. Kramer, and J. R. Stout, Total body water estimations in healthy men and women using bioimpedance spectroscopy: a deuterium oxide comparison, *Nutrition & Metabolism*, Vol. 5, 2008, Article 7.
- [16]. P. L. Cox-Reijven and P. B. Soeters, Validation of bioimpedance spectroscopy: Effects of degree of obesity and ways of calculating volumes from measured resistance values, *International Journal of Obesity*, Vol. 24, 2000, pp. 271-280.
- [17]. A. Piccoli, G. Pastori, M. Guizzo, M. Rebeschini, A. Naso, and C. Cascone, Equivalence of information from single versus multiple frequency bioimpedance vector analysis in hemodialysis, *Kidney International*, Vol. 67, 2005, pp. 301-313.
- [18]. A. Piccoli, Estimation of fluid volumes in hemodialysis patients: comparing bioimpedance with isotopic and dilution methods, *Kidney International*, Vol. 85, 2014, pp. 738-741.
- [19]. L. C. Ward, Bioelectrical impedance analysis for body composition assessment: reflections on accuracy, clinical utility, and standardisation, *European Journal of Clinical Nutrition*, Vol. 73, 2019, pp. 194-199.
- [20]. M. W. Kafri, P. K. Myint, D. Doherty, A. H. Wilson, J. F. Potter, and L. Hooper, The diagnostic accuracy of multi-frequency bioelectrical impedance analysis in diagnosing dehydration after stroke, *Medical Science Monitor*, Vol. 19, 2013, pp. 548-570.
- [21]. L. Röthlingshöfer, M. Ulbrich, S. Hahne, and S. Leonhardt, Monitoring change of body fluid during physical exercise using bioimpedance spectroscopy and finite element simulations, *Journal of Electrical Bioimpedance*, Vol. 2, 2011, pp. 79-85.
- [22]. C. O'Brien, C. J. Baker-Fulco, A. J. Young, and M. N. Sawka, Bioimpedance assessment of hypohydration, *Medicine & Science in Sports & Exercise*, Vol. 31, Issue 10, 1999, pp. 1466-1471.
- [23]. R. Gudivaka, D. A. Schoeller, R. F. Kushner, and M. J. G. Bolt, Single and multifrequency models for bioelectrical impedance analysis of body water compartments, *Journal of Applied Physiology*, Vol. 87, Issue 3, 1999, pp. 1087-1096.
- [24]. J. Castizo-Olier, M. Carrasco-Marginet, A. Roy, D. Chaverry, X. Iglesias, C. Pérez-Chirinos, F. Rodriguez and A. Irurtia, Bioelectrical impedance vector analysis (BIVA) and body mass changes in an ultra-endurance triathlon event, *Journal of Sports Science and Medicine*, Vol. 17, 2018, pp. 571-579.
- [25]. A. Bak, A. Tsiami, C. Greene, Methods of assessment of hydration status and their usefulness in detecting dehydration in the elderly, *Current Research in Nutrition and Food Science*, Vol. 5, 2017, pp. 43-54.
- [26]. V. Leonov, S. Lee, A. Londergan, R. A. Martin, W. De Raedt, and C. Van Hoof, Bioimpedance method for human body hydration assessment, in *Proceedings of the 41st Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Berlin, Germany, 23-27 July 2019, pp. 6036-6039.
- [27]. G. Squillace, S. Lee, V. van Acht, M. Vandecasteele, Bio impedance system for wearable vital sign monitoring, in *Proceedings of the 16th Conference on Electrical Bio-Impedance*, Stockholm, Sweden, 19-23 June 2016, p. 60.
- [28]. S. Lee, G. Squillace, C. Smeets, et al., Congestive heart failure patient monitoring using wearable bioimpedance sensor technology, in *Proceedings of the 37th Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Milan, Italy, 25-29 August 2015, pp. 438-441.
- [29]. Flyer on Imec's MUSEIC v2 SoC. (<http://www.imec-int.com/drupal/sites/default/files/2016-12/Imec%20Museic%20V2.pdf>)
- [30]. H. Ha, M. Konijnenburg, B. Lukita, R. van Wegberg, J. Xu, R. van den Hoven, M. Lemmens, R. Thoelen, C. Van Hoof, and N. Van Helleputte, A bio-impedance readout IC with frequency sweeping from 1k-to-1MHz for electrical impedance tomography, in *Digest of Technical Papers of the IEEE 2017 Symposium on Very-Large-Scale Integration (VLSI) Circuits*, Kyoto, Japan, 5-8 August 2017, pp. C174-C175.
- [31]. V. Leonov, M. Konijnenburg, H. Ha, B. Grundlehner, and N. Van Helleputte, Portable bioimpedance device and monitoring of hydration in a healthy person before and after exercise, in *Proceedings of the 5th International Conference on Sensors Engineering and Electronics Instrumentation Advances (SEIA' 2019)*, Tenerife (Canary Islands), Spain, 25-27 September 2019, pp. 47-50.
- [32]. R. Gudivaka, D. Schoeller, and R. F. Kushner, Effect of skin temperature on multifrequency bioelectrical impedance analysis, *Journal of Applied Physiology*, Vol. 81, Issue 2, 1996, pp. 838-845.
- [33]. S. Lee, B. Grundlehner, R. G. van der Westen, S. Polito, and C. Van Hoof, Nightingale V2: low-power compact-sized multi-sensor platform for wearable health monitoring, in *Proceedings of the 41st Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Berlin, Germany, 23-27 July 2019, pp. 1290-1293.

