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Impedance Ratio Method for Urine Conductivity-Invariant Estimation of Bladder Volume.

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Abstract

Non-invasive estimation of bladder volume could help patients with impaired bladder volume sensation to determine the right moment for catheterisation. Continuous, non-invasive impedance measurement is a promising technology in this scenario, although influences of body posture and unknown urine conductivity limit wide clinical use today. We studied impedance changes related to bladder volume by simulation, in-vitro and in-vivo measurements with pigs. In this work, we present a method to reduce the influence of urine conductivity to cystovolumetry and bring bioimpedance cystovolumetry closer to a clinical application.

Keywords: Impedance tomography, cystovolumetry, volume estimation

Introduction

Unobtrusive measurement of urinary bladder volume could help to introduce better treatment of the overactive bladder syndrome (OBS). OBS is characterized by urinary urgency and increased urination frequency, often paired with urinary urgency incontinence. Roughly 12–17 % of the population are affected [1]. OBS patients often develop depressions, social isolation, show a reduced quality of life and decreased general health status. Especially in the elderly, falls while rushing to the toilet are frequent incidents [2].

A variety of common treatment options exist, including dietary modifications, pelvic floor muscle exercise, behavioural training, bladder training, drug treatment and surgery.

Dietary modifications aim on reducing the intake of bladder irritants (like caffeine or alcohol) to reduce urgency, while pelvic floor muscle exercises help to hold the urine in a 'freeze and squeeze' manner: during urgency sensation the patient stays still focusing on pelvic floor muscle contraction to avoid incontinence until the end of the urgency period instead of rushing to the bathroom.

Behavioural training and bladder training both aim at extending the time between visits to the bathroom: To improve bladder storage capacity and reduce urgency sensation, micturition is deferred until significant urine has accumulated in the bladder. Usually, the patients try to meet a specific individual micturition volume goal which can be increased from time to time during the training period. Studies have shown that behavioural training and bladder training both significantly improve OBS symptoms [1, 2, 3, 4]. Today, bladder volume is roughly estimated on time basis from historical data from the patient's micturition diary.

A wearable monitor would eliminate the need for drinking and micturition diaries and could inform the patient about the appropriate time to visit the bathroom as well as provide feedback on training progress. Although frequent ultrasound examinations to estimate bladder volume are possible, continuous and unobtrusive measurement is desirable. One promising technology towards a non-invasive, unobtrusive bladder volume monitor is continuous bioimpedance measurement. Early measurements by Denniston and Baker in 1975 [5] revealed a linear dependence of extracorporal impedance and bladder volume in dogs, which could be reproduced in humans [6].

Recently, both our group [7] and He et al. [8] presented the extension of the extracorporal bioimpedance approach to multi-electrode electrical impedance tomography measurements (EIT). It is expected that 3D multi-electrode measurements can help to reduce distorting influences and provide more accurate bladder volume estimates than a single tetrapolar measurement could do.

One issue with extracorporal bioimpedance for bladder volume estimation is the influence of urine conductivity which varies throughout the day depending on a wide variety of influences like food and drink intake or sweating.

The aim of this work is to present a method to compensate extracorporal bioimpedance measurements for the influence of varying urine conductivity by referencing three tetrapolar measurements. Our measurements were done using an EIT device, although not required by the presented method.

Materials and Methods

EIT for cystovolumetry

To the knowledge of the authors, the first application of EIT for cystovolumetry has been reported by our group in 2011 [7]. In this study, nine male paraplegic patients have been monitored by EIT during regular urodynamic examination. A total volume of 99–585 ml contrast agent (conductivity of 13.35 mS/cm) has been instilled. An elastic electrode belt of 16 conductive silicone electrodes has been attached to the lower torso of the patient and an experimental EIT System (EEK2, Dräger Medical, Lübeck, Germany) was connected for impedance measurement. The device uses adjacent injection and measurement patterns, which means

that neighbouring electrodes are used for current injection as well as voltage measurement. This pattern results in a total of 208 readings per measurement (so called frame, for further details on the EIT measurement method, the interested reader is referred to the literature [9]). For image reconstruction, a reference measurement at empty bladder has been used. By summation of the pixel values of the reconstructed impedance-change image, the global impedance is obtained which was correlated with infused bladder volume. The results show excellent linearity of global impedance with bladder volume, with Pearson's correlation coefficients of up to -0.97958.

A different EIT-based approach was presented and evaluated in an in-vitro agar phantom by He et al. [8] in 2012. They used a planar 8×8 array of metal electrodes for ventral placement with a dorsal ground electrode. Current was injected between one of the ventral array electrodes and the dorsal common ground electrode, voltage measurements are taken from the remaining 63 electrodes, therefore implying a tripolar measurement. A total of $64 \cdot 63 = 4032$ readings was recorded per measurement. Bladder volume calculation was performed in terms of boundary detection in the reconstructed images in 3 D and volume of the extracted closed surface is calculated. For evaluation, an agar phantom with a cylindrical cavity filled with sodium chloride solution has been designed. In-vitro evaluation showed excellent estimation accuracy of up to 1 ml.

Impact of urine conductivity on impedance cystovolumetry

When thinking of an impedance-based bladder volume monitor it is evident that electrical impedance is not only influenced by volume but also by urine conductivity. In the human body, the kidneys are in charge of maintaining constant blood osmolarity, mainly by regulation of its sodium concentration [10]. In consequence, urine conductivity is highly dependent on renal activity and can not be assumed constant. Early experiments identified the influence of different urine conductivities on bladder volume estimation from impedance measurements [11, 12] and suggested further research in this field.

To quantify intra- and inter-individual variability of urine conductivity, we collected 81 urine samples from nine hospitalized patients (five female, four male, age 47.5 ± 17.9 years). All patients have sensorimotor defects (paraplegia) of different severity (ASIA A to ASIA D, cervical to lumbal). Subject 2 had antidiuretic medication which affects urine concentration, all other subjects had medication without known impact on urine concentration. Urine samples were taken at three consecutive days, each day at 8:00, 12:00 and 16:00. Urine conductivity has been measured using an HI 8733 (Hanna Instruments, Woonsocket, USA) conductivity meter. Results are shown in Figure 1, grouped for each patient as a box plot. The box contains 50% of all measurements with a horizontal bar indicating the mean value. The whiskers to the top and bottom of the box represent

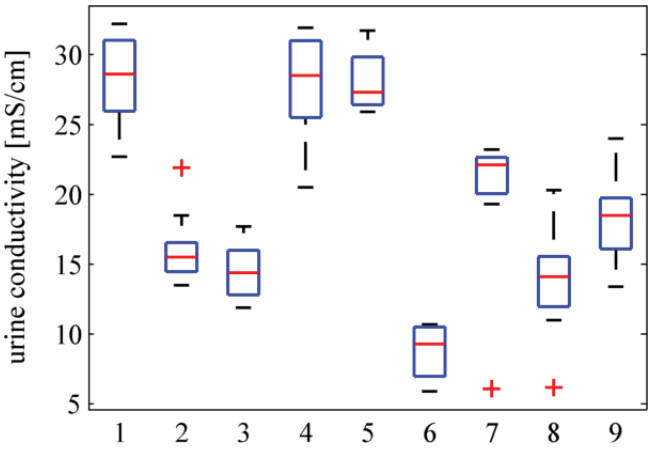


Fig. 1: Variability of urine conductivity in nine patients: Even in a hospitalized environment, high intra- and inter-individual variations are apparent.

the 1.5 interquartile range, while the plus signs indicate outliers. There was no obvious information from the time series data so that this data representation emphasizing the conductivity variation $\Delta\sigma$ has been chosen. From Figure 1, high inter-individual variation of urine conductivity in the range of 5.9…32.2 mS/cm is apparent, although intra-individual variation is lower. Intra-individual variation ranged from $\Delta\sigma = 4.8$ mS/cm (subject 6) to $\Delta\sigma = 17.1$ mS/cm (subject 7). From this results we can conclude that even for hospitalized patients with comparable daily routine and meals, urine conductivity can not be assumed constant and its influence on impedance-based volume estimation has to be taken into account.

To evaluate the influence of urine conductivity on EIT global impedance, experiments comparable to an urodynamic examination have been performed in a freshly euthanized pig (≤ 30 min). For EIT measurement, the set-up has been kept close to the human experiment performed in 2007 [7] incorporating an EEK1 (Dräger Medical, Lübeck, Germany) EIT device with adjacent injection and measurement pattern as well as an elastic belt with 16 conductive rubber electrodes. Solutions of demineralized water with sodium chloride concentrations of 0%, 0.9% and 1.8% accoding to conductivities of $\sim$0 mS/cm, $\sim$15 mS/cm and $\sim$28 mS/cm have been prepared. As shown in Figure 2, a 50 ml syringe and two three-way taps have been used to perform urodynamic examination-like filling and emptying of the bladder through an intravesical catheter. The electrode belt has been attached as caudal as possible while maintaining stable electrode contact, resulting in the electrode belt placed cranial of the iliac crest.

Before starting the experiment, the bladder was drained completely and EIT reference baseline was recorded. Then, the bladder was filled successively by 50 ml syringe fillings with 0.9% sodium chloride solution until a total volume of 200 ml was reached and successive emptying in 50 ml syringe fillings followed. The whole procedure was then repeated for 1.8% and 0% sodium chloride solutions.

The resulting global impedance from the experiment is shown in Figure 3. For each solution concentration, global

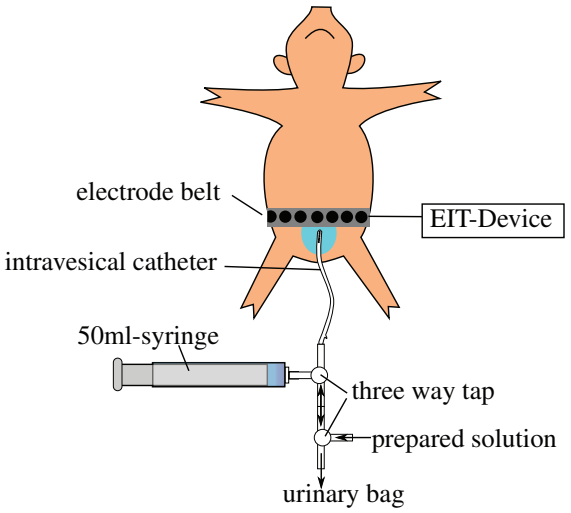


Fig. 2: Experimental set-up of in-vivo measurement for controlled volume instillation: The EIT belt is placed cranial of the iliac crest and a standard urinary balloon catheter is used for fluid instillation by a 50 ml syringe.

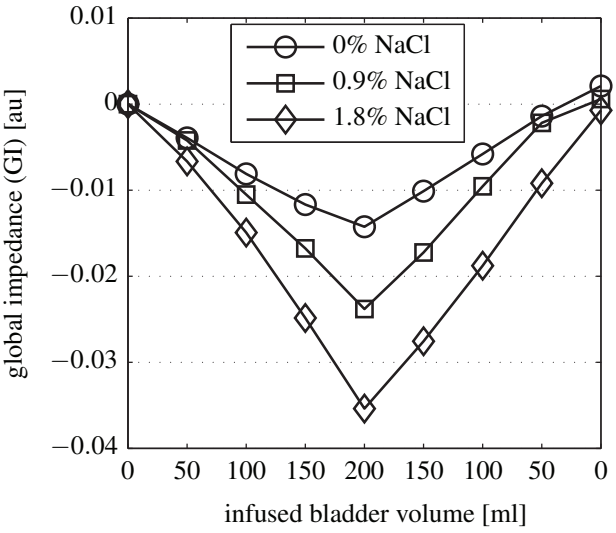


Fig. 3: Influence of urine conductivity on EIT global impedance: the slope of the impedance-volume-mapping is influenced by urine conductivity.

impedance decreases with increasing volume which confirms the negative correlation of volume and extracorporal impedance reported earlier [12, 5]. Additionally, the experiment reveals great dependence of the slope of impedance change on solution conductivity. The higher the conductivity the steeper the negative slope of global impedance with volume.

From this results we conclude that varying urine conductivity has to be taken into account for accurate, impedance-based bladder volume estimation.

Impedance Ratio Method

The general idea of the Impedance Ratio Method is to correlate volume with a ratio of three different impedances measured at bladder level around the abdomen to reduce the influence of unknown urine conductivity on the volume estimate. The sensitivity of a bioimpedance measurement system is normally highest nearby the electrodes due to

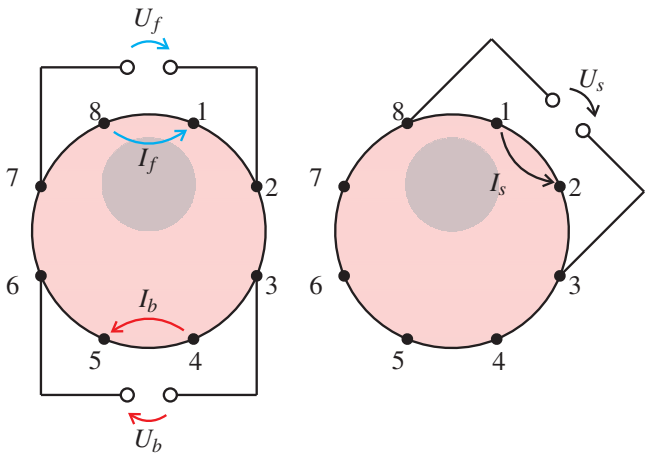
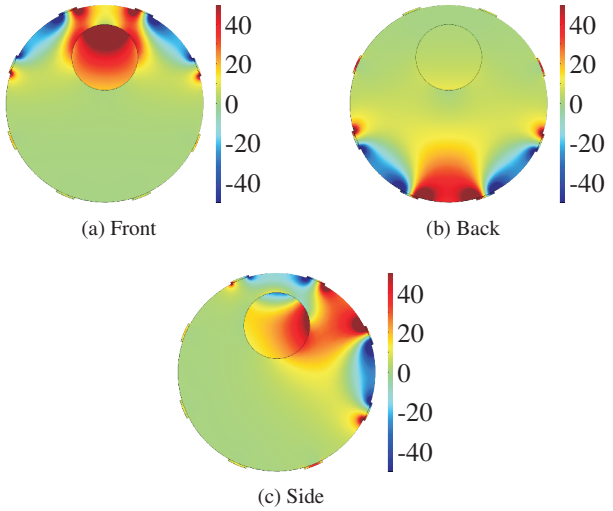


Fig. 4: The Impedance Ratio Method uses three tetrapolar measurements at front (ventral, U_f/I_f), side (U_s/I_s) and back (dorsal, U_b/I_b) positions.



(a) Front (b) Back

(c) Side

Fig. 5: Sensitivity field of the measurement positions showing the spatial difference in sensitivity regions, $[1/m^4]$.

higher current densities [13]. With increasing volume, the bladder extends and displaces surrounding tissue. To exploit the spatial change, three spatially distributed impedance measurements have been chosen, which are shown in Fig. 4. The first measurement (U_f/I_f, front) is located ventrally in front of the bladder, the second measurement (U_b/I_b, back) is located dorsally and a third measurement (U_s/I_s, side) is located at the patient's side. To justify the chosen electrode placements, sensitivity simulations inspired by the work of Kauppinen et al. [14] have been calculated. As Fig. 5 visualizes, the front measurement is very sensitive to bladder impedance changes, while the back measurement has only low sensitivity in the bladder region and is used as a baseline impedance reference. The sensitivity of the side measurement is dependent on bladder size and therefore bladder volume: the influence of the bladder to the side impedance measurement increases with increasing bladder size.

The Impedance Ratio is defined as

$$IR = \frac{Z_s - Z_f}{Z_b - Z_f} \tag{1}$$

where Z_s is the measured impedance at side position, Z_f at front position and Z_b at back position, respectively.

It can be understood as a measure to quantify the influence of the bladder on abdominal impedance inhomogeneity, which correlates with its volume.

Especially for low bladder volumes, the impedance differences are very small and the division by a small difference amplifies measurement errors. Therefore, we define a trust factor (TF) to quantify the amount of impedance difference in the pelvis:

$$TF = \frac{Z_b - Z_f}{Z_b} \tag{2}$$

Below a certain threshold of TF, IR is assumed to be susceptible to measurement errors.

Three different versions of the Impedance Ratio Method have been taken into account in this work:

- The first version is based on *absolute values* of the impedance measurements and well suited for use with a wide variety of medical devices for impedance measurement.
- The second version is based on *imaginary parts* of the measured impedances requiring a complex impedance measurement.
- The third version substitutes each Z_x in the formulas above by a *frequency differential* impedance $Z_{x,2} - Z_{x,1}$ requiring a multi-frequency measurement device.

While tissue shows a complex, frequency dependent impedance, urine can be assumed purely resistive in the bioimpedance measurement range below 1 MHz. Therefore, a decreased imaginary part or decreased frequency differential impedance indicates increased bladder volume.

During an initial calibration measurement, a mapping of IR values to bladder volume has to be found, which is used for volume calculation in all subsequent measurements.

Simulative environment

For the simulative analysis, the EIDORS toolkit for Matlab [15] has been used. A cylinder of 30 cm diameter and 3.9 cm height modelling our in-vitro tank phantom has been defined with a cylindrical cavity located eccentrically to model the bladder. The frequency dependent impedance of muscle based on the Gabriel database [16] has been assigned to the material surrounding the cavity, resulting in 3.492 mS/cm + i0.235 mS/cm at 37.5 kHz and 3.825 mS/cm + i0.695 mS/cm at 193 kHz, respectively. Conductivities of 4 mS/cm, 12 mS/cm, 20 mS/cm and 28 mS/cm have been assigned to the material inside the cylindrical cavity to represent varying urine conductivity. The measurement at 20 mS/cm has been selected for calibration of the IR to volume mapping.

To test the noise tolerance of the algorithm variants, white uncorrelated noise was added to the simulated EIT impedance measurements in the following manner:

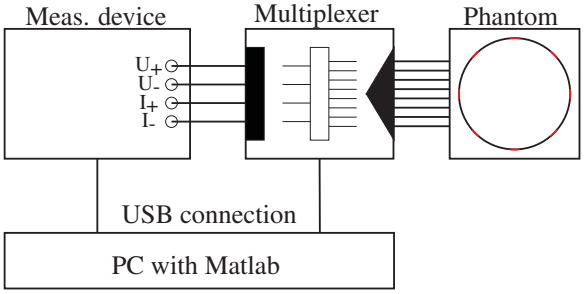


Fig. 6: Measurement system schematics with Agilent E4980 impedance measurement device, custom built multiplexer and phantom. A PC is used to control injection frequency and selection of current injection and voltage measurement electrodes.

$$\eta = \frac{\text{noise}}{|\text{noise}|} \cdot \frac{|\text{signal}|}{\text{SNR}} \tag{3}$$

$$Z_{i,noise} = Z_i + \eta \tag{4}$$

Here, *SNR* defines the desired signal-to-noise ratio, Z_i the measured impedance raw data vector and *noise* the generated noise. Noisy impedance raw data $Z_{i,noise}$ are calculated by superimposing the noise-free measurements Z_i with the scaled noise η. Considering that patient impedance recordings and dummy test measurements using a Goe MF II EIT device (Abimek, Friedland, Germany) showed noise levels between 42 dB SNR and 156 dB SNR, this paper focuses on noisy test data with levels of 40, 50, 60 and ∞ dB SNR.

In-vitro measurements

A 30 cm diameter perspex tank phantom with sixteen equally spaced stainless steel screws as electrodes (of which eight have been used in this work) has been used for in-vitro measurements. A dispersive agar-sodium-chloride filling has been used to model frequency-dependent tissue impedance. Although neither exact muscle impedance nor a Cole-like dispersion curve can be modelled using agar, the set-up provides a dispersive surrounding around the cavity representing the bladder, thus allowing to evaluate the suitability of the Impedance Ratio Method.

A commercial precision LCR meter (E4980, Agilent Technologies, Santa Clara, CA, United States) connected to a custom-built multiplexer intended for 8-electrode multifrequency electrical impedance tomography has been used for all measurements. A schematic drawing of the measurement set-up is shown in Fig. 6. Although the E4980 does not provide a tetrapolar measurement eliminating the influence of varying contact impedances, the resulting error can at least be assumed to be constant for measurements at one frequency.

To model the bladder, a cylindrical cavity has been cut into the agar filling, as shown in Fig. 7. De-mineralized water, 0.9 % and 1.8 % sodium-chloride solution have been used to represent urine of varying conductivity in the cylindrical cavity, thus resulting in a smaller fluid filled cylinder inside the agar cylinder (see upper left sketch in Fig. 7). The

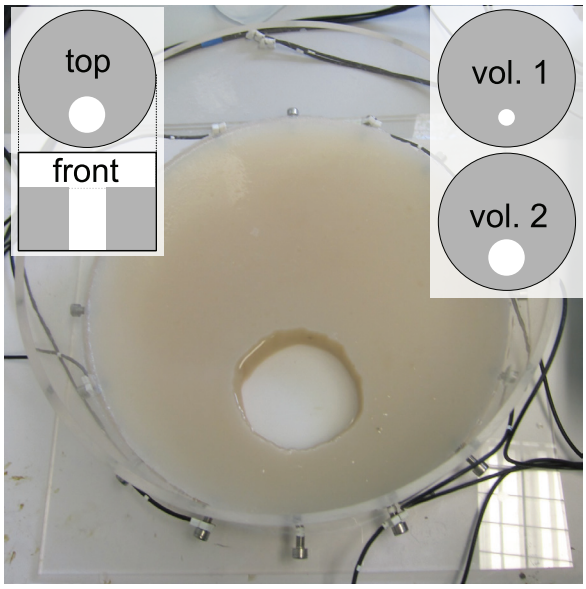


Fig. 7: In-vitro tank filled with agar as a multi-frequency EIT phantom: A cylindrical cavity is cut into the agar and filled with solutions of different conductivities to model varying urine conductivity. The sketches visualize the spatial arrangement (left) and variation in cavity size (right).

measurements were started with a small cylindrical cavity, then measurements for all three conductivities were recorded before the cavity was enlarged with greater radius as shown in the upper right sketch of Fig. 7. Then, measurements of all three conductivities started over again for the next volume. Between all measurements, the fluid has been drained completely from the cavity. For each cavity size, the volume was measured once by instilling fluid using a syringe. The measurement with 0.9 % sodium-chloride solution has been used to calibrate the IR to volume mapping.

Results

Volume accuracy

For all three algorithm variants, four plots presenting simulation results are shown in the Figures 8–10, respectively. The top plot shows the estimated to instilled volume for all four conductivities, while the lower three plots show the volume error over instilled volume, the error mean (blue line) and 1.96 standard deviation of the error (red lines).

Common to all three variants is a high volume error at very low bladder volumes. At low volumes, the measured differential voltages are very small and noise as well as numerical effects get amplified by the division, which is also represented by the trust factor value.

The single frequency variant using absolute values shows high errors for low urine conductivities in the range of surrounding tissue impedances ($\sigma = 4\,\mathrm{mS/cm}$), as shown in Fig. 8. For higher conductivities, the method works as expected: the volume estimation result is independent of the urine conductivity to a great extend.

If using a complex impedance measurement device, the error at low urine conductivities can be reduced by using the imaginary parts of the impedances, as shown in Fig. 9. This

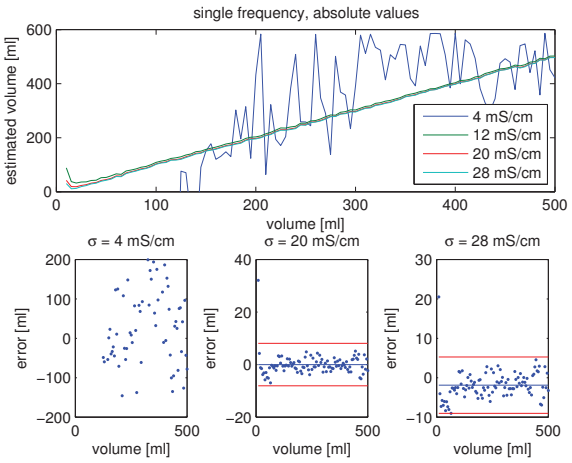


Fig. 8: In-silico results for single-frequency variant using absolute values: The method is unreliable for urine conductivities in the range of surrounding tissue impedances (4 mS/cm in this case).

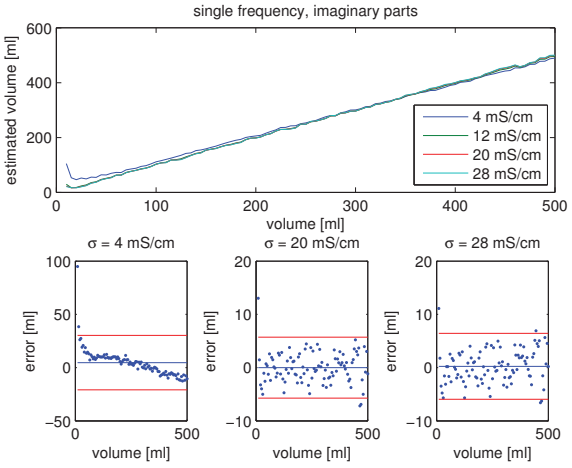


Fig. 9: In-silico results for single-frequency variant using imaginary parts: For urine volumes higher than 100 ml the method works as expected.

is because surrounding tissue shows dispersive effects while urine can be assumed purely resistive in our measurement frequency range and a displacement of dispersive tissue in favour of more purely resistive urine introduces a phase change in the measured impedance.

The frequency differential variant using absolute values in Fig. 10 shows comparable results to the single frequency variant with imaginary parts. The reason for comparable performance is the same for both methods: tissue shows a frequency-dependent impedance while the conductivity of urine can be assumed constant in our frequency range. The higher the bladder volume, the less impedance changes between both frequencies can be measured.

Noise tolerance

Fig. 11 visualizes the influence of noise on volume estimation by all three variants. Both single frequency variants show acceptable noise influence, while the frequency differential variant shows much higher noise susceptibility. This results from the drastically reduced amplitude of the impedance difference vector compared to a single frequency vector.

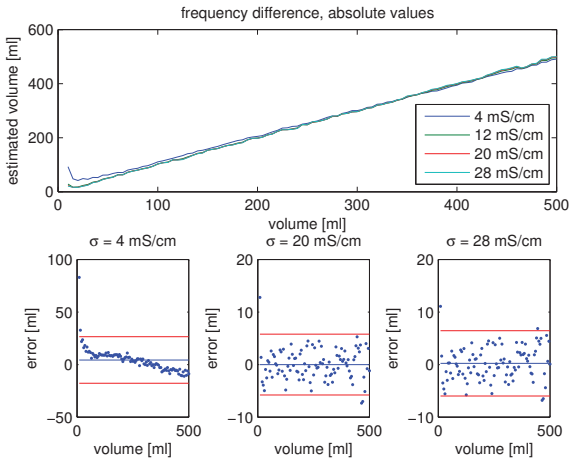


Fig. 10: In-silico results for frequency-differential variant using absolute values: Comparable result to the single-frequency variant using imaginary parts.

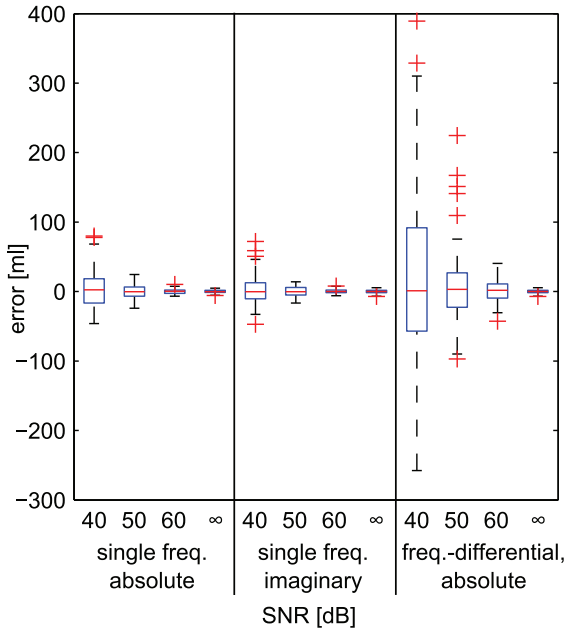


Fig. 11: Noise susceptibility of the three methods for given SNR: Due to the smaller amplitude of the impedance differences, the multi-frequency method is much more susceptible to noise than the single frequency method.

However, since diuresis is a very slow process compared to impedance measurement time, temporal filtering can be applied for further noise reduction, which has not been taken into account in this work.

In-vitro evaluation

The measurement results for our Agar tank phantom measurements are shown in figure 12 (single frequency, absolute values), figure 13 (single frequency, imaginary parts), and figure 14 (multi-frequency, absolute values). Common to all variants is a higher variation in estimated volume compared to the results from simulated measurements. The narrowest band of variation shows the single frequency variant using imaginary parts in Fig. 13, followed by the single frequency variant using absolute values. The high variation in the multi-frequency measurement may result from varying electrode

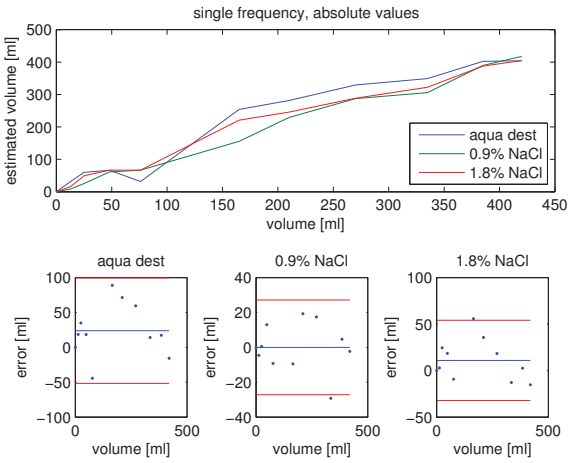


Fig. 12: In-vitro results for single-frequency variant using absolute values: the influence of urine conductivity is not suppressed completely.

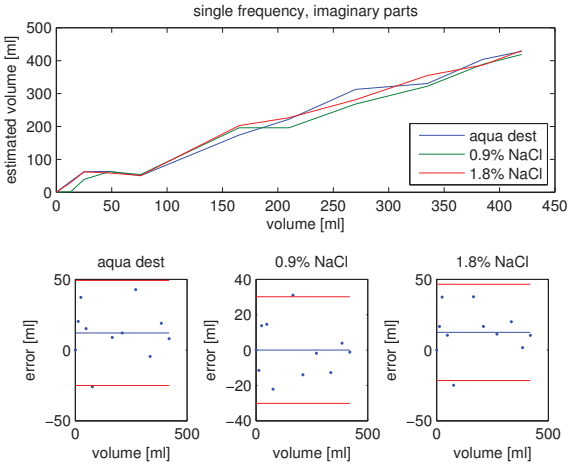


Fig. 13: In-vitro results for single-frequency variant using imaginary parts: good suppression of urine conductivity variation in the volume estimation result.

contact impedances, which are affecting the measured impedance in our set up. For greater impedance changes (0.9% and 1.8% saline solution), all methods show acceptable estimation errors below 50 ml.

Discussion

In this work, we showed high intra- and inter-individual variation in urine conductivity for nine hospitalized patients. Even when daily activities and meals are rather comparable for hospitalized patients, significant inter and intra individual urine conductivity variation can be assumed for a wide patient group.

In-vivo EIT measurements during an urodynamic-like procedure with instillation liquids of different conductivities showed significant effects of urine conductivity on global impedance, affecting the estimation accuracy of global impedance-based volume estimation methods.

One way to reduce the influence of urine conductivity on volume estimation is provided by the Impedance Ratio Method introduced in this paper. Three different versions of the method were presented and evaluated in-silico and in-

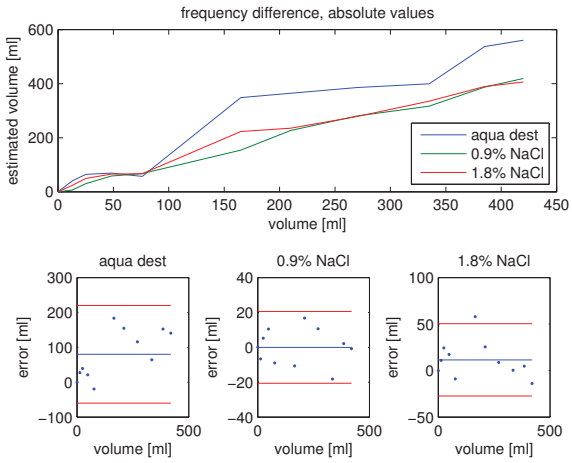


Fig. 14: In-vitro results for frequency-differential variant using absolute values: the results from simulation could not be reproduced, probably by an impact of varying electrode contact impedances on the measurement device.

vitro. All versions show promising results in conductivity variation suppression on volume estimation.

Best results in the simulative analysis as well as our in-vitro measurements showed the single frequency variant based on imaginary parts of the measured impedance. Common to all variants are high volume errors for low bladder volumes. As long as the method is used to determine the right time for micturition and not for residual urine measurements, this is not of any consequence in practical applications. Further, the TF parameter provides a trust measure for the volume estimate, so unreliable estimates at low bladder volumes can be discarded.

During a calibration measurement, the mapping of Impedance Ratio values to known bladder volumes has to be determined for each individual at least once. Continuous, simultaneous impedance and uroflow measurements provide enough data tuples to find a mapping.

Still in question is if and to which extend this mapping is influenced by changes in body posture, body movement or intestine content. Unfortunately, our measurement device is not yet certified for human use, so we have to leave this question open for future research.

Nevertheless, to the best knowledge of the authors, the presented Impedance Ratio Method is the first approach to conductivity-independent bladder volume estimation by non-invasive electrical impedance measurement and therefore a significant step towards a practical application.

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