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A Phase-Based Electrical Plethysmography Approach to Bladder Volume Measurement

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Abstract—Neuromodulation approaches to treating lower urinary tract dysfunction could be substantially improved by a sensor able to detect when the bladder is full. A number of approaches to this problem have been proposed, but none has been found entirely satisfactory. Electrical plethysmography approaches attempt to relate the electrical impedance of the bladder to its volume, but have previously focused only on the amplitudes of the measured signals. We investigated whether the phase relationships between sinusoidal currents applied through a pair of stimulating electrodes and measured through a pair of recording electrodes could provide information about bladder volume. Acute experiments in a rabbit model were used to investigate how phase-to-volume or amplitude-to-volume regression models could be used to predict bladder volumes in future recordings, with and without changes to the saline conductivity. Volume prediction errors were found to be 6.63 ± 1.12 mL using the phase information and 8.32 ± 3.88 mL using the amplitude information ($p = 0.44$ when comparing the phase and amplitude results, $n = 6$), where the volume of the filled bladder was about 25 mL. When a full/empty binary decision rule was applied based on the regression model, the difference between the actual threshold that would result from this rule and the desired threshold was found to be 4.24 ± 0.65 mL using the phase information and 106.92 ± 189.82 mL using the amplitude information ($p = 0.03$, $n = 6$). Our results suggest that phase information can form the basis for more effective and robust electrical plethysmography approaches to bladder volume measurement.

Keywords—Bladder volume, Bladder neuromodulation, Lower urinary tract dysfunction, Electrical plethysmography, Bladder impedance.

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INTRODUCTION

Lower urinary tract (LUT) dysfunction is a situation that can occur after a disruption to the neural control of the bladder, for example after spinal cord injury (SCI), multiple sclerosis (MS), stroke, diabetes and Parkinson's disease. LUT dysfunction can manifest itself as impairments of the two main functions of the bladder, namely storage of urine and micturition (voiding).[6] These impairments in turn can result in compromised renal function and repeated urinar tract infections, leading to increased morbidity and mortality. These symptoms are highly detrimental to the quality of life of the affected individuals. For example, after SCI, individuals with paraplegia have reported that recovery of bladder and bowel functions is their second highest priority, after sexual function.[2]

A number of treatment modalities exist for LUT dysfunction, most notably pharmacological intervention, surgery (denervation or augmentation procedures), behavioral therapy, and sacral neuromodulation.[23] Indications for sacral neuromodulation have included urge incontinence, urge frequency, and nonobstructive urinary retention.[6,7,20] Neuromodulation techniques use electrical stimulation to directly alter activity in the neural circuitry of the bladder, and are appealing because they can be applied *via* minimally invasive interventions and avoid the side-effects that can occur with pharmacotherapy.[30]

Neuromodulation systems designed to treat impaired voiding generally require the user to manually activate the device in order to induce voiding. Similarly, neuromodulation systems designed to treat incontinence inhibit the voiding function most of the time by stimulating the storage function of the bladder, but again require manual intervention when voiding is

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required. In individuals who have impaired bladder sensation and cannot detect when the bladder is full (e.g., after SCI), the voiding is performed at regular intervals, which has two drawbacks: (i) the user's quality of life is reduced by the need to adhere to a rigid voiding schedule that depends mainly on the fluid consumption, and (ii) if the bladder fills too much before the scheduled voiding time, the high bladder pressures may result in kidney damage. Neuromodulation systems for LUT dysfunction could therefore be improved by incorporating implanted sensors that can monitor bladder volume reliably and accurately, and allow users to activate voiding only when needed. A number of different approaches have been suggested for monitoring bladder volume, highlighting the clinical importance of this goal, but so far no method has been found to be entirely satisfactory for chronic use in humans.[21]

Intravesical pressure measurement has been suggested as a surrogate for bladder volume, and can be measured using pressure transducers attached to the bladder wall. This method is limited by the complex relationship between bladder volume and intravesical pressure, by the difficulty of achieving stable placement of the sensors over long periods of time, and by its susceptibility to movement artifacts.[5,15,29] Strain-gage plethysmography offers to measure the bladder volume by using sensors that measure deformations on the outer wall of the bladder, which occur as a result of distention or contraction. The challenge in this method is to develop sensitive and biocompatible sensors that can remain in place over long periods of time and provide accurate information despite the irregular and variable shape of the bladder.[27] Wearable ultrasound devices have also been used to measure bladder volume. Although the technique works under well-controlled conditions, it is sensitive to probe movement, posture and interfering factors such as bowel function.[16,25] An implantable miniaturized ultrasound probe was explored in an animal model in 2004,[28] but to the best of our knowledge has not been tested clinically.

Electroneurographic signals have also been proposed to monitor bladder volume. The extraction of bladder information from peripheral nerve recordings using nerve cuffs has been demonstrated in a number of animal models[9–11,18,31] as well as in humans.[17] Whereas many of these studies focused on detecting bladder contractions, bladder volume information is more tonic in nature and has proven more difficult to detect reliably. Jezernik *et al.* and Kurstjens *et al.* in separate studies obtained partial success in obtaining bladder volume information (in pig and human, respectively), but both noted that these recordings were more difficult to obtain reliably than bladder contraction signals.[11,17] Recent studies by Bruns *et al.* demonstrated that bladder afferent information could also be extracted from the dorsal root ganglia of the sacral roots using microelectrode arrays,[3] though the chronic viability in humans of these devices has not yet been established. Mendez *et al.* have demonstrated that bladder volume information can be extracted from afferent activity in the sacral roots, using recordings from dissected fine filaments, but the potential of this method to be translated clinically is currently uncertain.[22]

Electrical impedance plethysmography functions by using a pair of electrodes to inject current into the bladder, either non-invasively through the abdominal wall or using implanted electrodes placed directly on the bladder wall. This process gives information about the electrical impedance of the bladder, which is related to its volume. On the other hand, this relationship has been found by many investigators to be weak. The effectiveness of electrical impedance plethysmography has further been found to be limited by a number of confounding factors, including electrode placement, the variable conductivity of urine, and body fat.[1,8,12,14,26,32]

The previous studies that have examined the electrical impedance of the bladder using implanted electrodes have focused on the resistance component of the impedance.[8,12,26] As the bladder fills with urine and the distance between the electrodes changes, however, it is possible that capacitive effects will also play a role and lead to a change in the reactance component as well. These effects may in turn be manifested as changes in the phase relationships between an injected current sinusoid and the waveforms measured by pairs of recording electrodes on the bladder wall. The objective of this study was to determine whether such phase relationships can provide information about bladder volume, and whether this relationship is robust in the presence of confounding factors that have been shown to reduce the usefulness of resistance-based predictions, in particular variations in urine composition.

MATERIALS AND METHODS

Nine adult male New Zealand white rabbits (Charles River Laboratories, MA, USA) were used in this study, weighing approximately 3.6 kg on average. Incomplete datasets were obtained in three rabbits, and so in the following we report data from six rabbits. All procedures were approved by the University of Toronto Animal Care Committee.

Surgical Methods and Data Acquisition

The rabbits were given glycopyrrolate and acepromazine *via* subcutaneous injection, following which anesthesia was induced using isoflurane. Anesthesia was maintained continuously throughout the experiment with inhaled isoflurane (2 %). Hydration was maintained using an intravenous catheter introduced into the marginal ear vein. Blood gasses (SpO2) and heart rate were continuously monitored using a pulse oximeter. The rabbit was placed on a circulating warm water pad. A midline abdominal incision was used to gain access to the lower abdominal cavity. A urinary catheter (3.5 Fr) was inserted through the urethra and its location inside the bladder confirmed by visual inspection. The bladder was voided manually and the other end of the catheter was attached to a 30 cc syringe filled with room temperature saline (0.9 %). The bladder was then gently exposed and kept out of the abdominal cavity *via* the abdominal incision. EEG Electrodes (Chalgren Entreprises, CA, USA) loaded with electrolyte paste were attached to the bladder dome using VetBond tissue adhesive such that the adhesive formed a good seal around the circular electrode perimeter. Either three ($n = 2$) or four ($n = 4$) electrode pairs were attached to the bladder, depending on the surface area available. Stimulating electrodes were always placed closest to the bladder neck, while consecutive pairs of recording electrodes were positioned towards the apex (Fig. 1a). The electrodes were attached while the bladder was full, in order to facilitate the placement procedure. A reference needle electrode (Ambu Neuroline monopolar needle, Denmark) was placed in muscle tissue in the abdominal cavity adjacent to the bladder. The bladder was covered with a gauze pad which was wetted periodically with saline throughout the experiment to prevent the bladder from drying out.

A function generator (33220A, Agilent, CA, USA) was connected to the stimulating electrodes *via* an analog stimulus isolator (Model 2200, A-M Systems, WA, USA). The function generator was used to pass 50 mV peak-to-peak sine waves of 250, 500, 750 Hz, 1, 2, 3, 4, 5, 6 and 7 kHz across the bladder (in the first of the six rabbits, only stimuli from 1 to 7 kHz were used). Each stimulation period lasted 10 s. The order of the frequency applied was randomized in three rabbits in order to avoid confounding the stimulation frequency variable with time; in the other three rabbits the frequencies were applied in increasing order. Current flowing through the stimulating electrodes was measured by placing a 1 Ω resistor in series between the isolator and the positive stimulating electrode and recording the potential difference across the resistor. This potential was amplified 1000× using a DC-

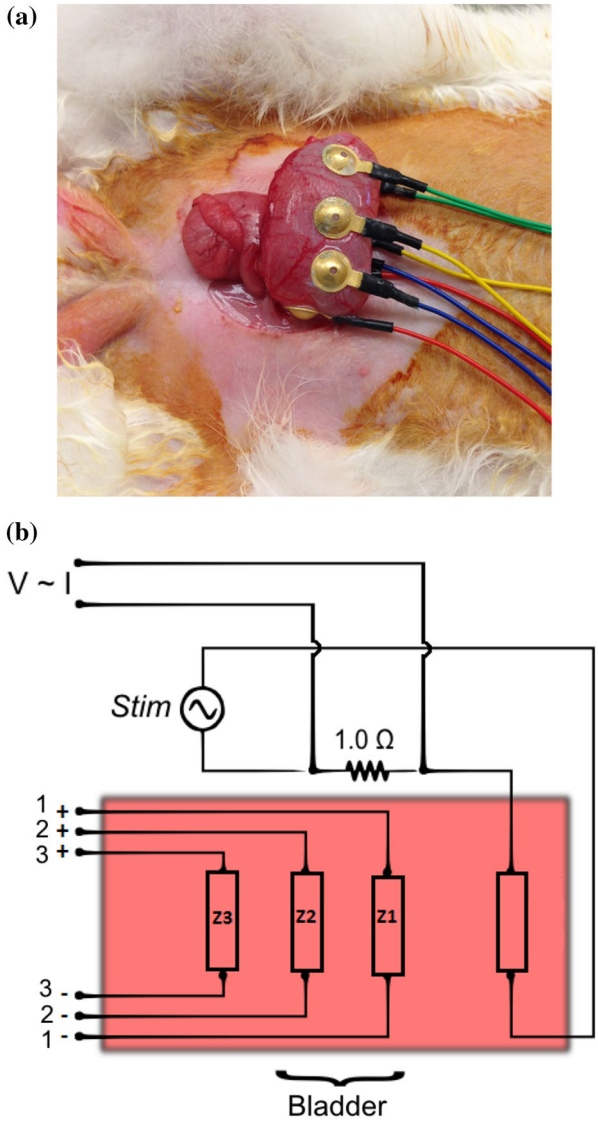

FIGURE 1. (a) Example of the electrode placement on the bladder wall. (b) Schematic representation of the stimulation and recording circuit.

amplifier (ETH-256C, iWorx Systems, Inc., NH, USA) before being recorded by the data acquisition system. Signals from individual recording electrodes were acquired vs. the remote reference, and the potential difference across each pair of recording electrodes was then computed (Fig. 1b). All signals were sampled at 30 kHz and acquired using a Cerebus Data Acquisition System (Blackrock Microsystems, Utah).

The experiment was completed in three sets. Starting with a completely empty bladder, the bladder was sequentially filled to 5, 10, 15, 20, and 25 mL, and a complete frequency sweep performed at each step (including empty). The injections were performed manually, at a rate of approximately 10–20 s per 5 mL. The bladder's distension during each step occurred

smoothly. Following the completion of the first frequency/volume set (hereafter referred to as Set 1), the syringe was removed and the bladder was allowed to drain passively. The experiment was repeated after 1 h in order to investigate the effect of potentially time-varying properties of the electrode/bladder interface (Set 2). Finally, the experiment was repeated immediately after Set 2 with a higher concentration of saline (~2 %) in order to investigate effect of changes in urine conductivity on the measurements (Set 3).

Extraction of Amplitude and Phase Information

Following acquisition, all data were imported into MATLAB for offline analysis. The acquired sinusoidal waveforms from the stimulation and recording electrodes were filtered with a 10th order Butterworth bandpass filter with corner frequencies of ±100 Hz of the stimulation frequency for each trial. A forward–backward application of the filter was used to achieve zero phase distortion. Next, the power spectra of the "input" (stimulating) electrode and "output" (recording) electrodes were computed using Welch's modified periodogram. This was done by dividing each signal into 16 non-overlapping segments, windowing with a Hanning window, and averaging the result. The amplitude of each sine wave at the stimulation frequency was recovered by integrating the power spectra at 10 indices about the center of the stimulation frequency band, multiplying by the frequency increment, and adjusting for digitization and windowing effects (Eq. (1)):

$$x_{\mathrm{a}} = \sqrt{\sum_{k=i-5}^{i+5} P_{\mathrm{xx}}[k].\mathrm{df}.\sqrt{2}.\left(\frac{4}{8/3}\right)}, \tag{1}$$

where x_{a} denotes the amplitude of the sinewave in the frequency band of interest, i is the index corresponding to the stimulation frequency in the power spectrum, P_{xx} is the power spectrum, and df is the frequency increment when 10 s of data are collected at a rate of 30 kHz. In order to recover the amplitude of the waveform, the expression on the right hand side of the equation is further scaled by $\sqrt{2}$ in order to adjust for RMS amplitude scaling, and the factor $\frac{4}{8/3}$ is used to adjust for windowing and discretization effects. Let x_{a} be the amplitude of the input sinewave (recorded across the 1 Ω resistor) and y_{a} the amplitude of the output sinewave from one of the recording electrode pairs, computed in the same way. The ratio $y_{\mathrm{a}}/x_{\mathrm{a}}$ is used in the remainder of the analysis to quantify the amplitude of the recorded sinusoids.

The phase relationship φ between the input and output sinusoids was estimated by computing the cross-power spectral density of the input and output electrode signals, and taking the mean of the phase estimates about the stimulation frequency band (Eq. (2)).

$$\widehat{\varphi} = \frac{1}{10}.\sum_{k=i-5}^{i+4} \tan^{-1}\frac{-\mathrm{Im}\left(P_{\mathrm{xy}}[k]\right)}{\mathrm{Re}\left(P_{\mathrm{xy}}[k]\right)}. \tag{2}$$

Volume Prediction

Relationships between phase and bladder volume and between amplitude and bladder volume were established based on the data in Set 1, then used to predict bladder volume in Sets 2 and 3.A linear regression was applied in each case to obtain a relationship of the form shown in Eq. (3).

$$v_{f,e} = c_{1,f,e}x_{f,e} + c_{2,f,e}, \tag{3}$$

where the subscripts f and e refer to the stimulation frequency and recording electrode pair used, respectively, $v_{f,e}$ is the volume in milliliters, $x_{f,e}$ is either the amplitude or the phase (depending on the variable being examined), and the $c_{1,f,e}$ and $c_{2,f,e}$ are the regression coefficients.

Bladder volumes in Set 2 and Set 3 were predicted using the regression obtained from Set 1 and the phase or amplitude values measured in Sets 2 and 3, respectively. The root-mean-square (RMS) value of the prediction error was computed and used to evaluate the quality of the prediction. In each rabbit, in order to select the best combination of stimulation frequency and electrode pair, the RMS values produced by the Set 1 regression in Set 1, Set 2 and Set 3 were averaged, for each frequency/electrode combination. The frequency/electrode combination producing the lowest average RMS value was selected. However, the error reported below is the average only of the RMS values in Set 2 and Set 3.

Threshold Determination

The motivation for obtaining information about the bladder volume is to create a sensor that can detect bladder fullness and inform the user that voiding is needed. Thus, in some cases, the objective is not to predict bladder volume as precisely as possible, but rather to develop a robust binary decision rule to distinguish "full" and "empty" bladder states.

We used the Set 1 regression models developed in the volume prediction step to select a phase or amplitude value corresponding to a desired volume threshold. Unless specified otherwise, the volume threshold was set to 15 mL, corresponding to approximately 60 % of the bladder capacity. The phase or amplitude value obtained was then used to predict a volume threshold using the regression models derived for Sets

2 and 3. The absolute difference between the actual threshold obtained using this phase or amplitude value and the desired threshold value (15 mL) was used as our error metric (Fig. 2). For example, if the desired threshold is 15 mL, but the selected phase (or amplitude) value is such that the "full" decision will actually be reached at 18 mL, then the threshold error is 3 mL. The mean of the error value for Set 2 and Set 3 was computed for each combination of stimulation frequency and electrode pair, and the combination yielding the lowest mean error was selected.

Statistical Analysis

In order to compare the performance of the amplitude and phase predictions, Wilcoxon signed-rank tests were applied for each error metric, with the significance level set at 0.05. Comparing regression coefficients of determination between Sets 1, 2 and 3 was accomplished using a Friedman test. *Post-hoc* comparisons were conducted using pair-wise Wilcoxon signed-rank tests with Bonferroni correction.

RESULTS

Volume Prediction

We first investigated how well the phase and amplitude measurements could be used to predict bladder volumes in the presence of changes in electrode impedance (due to time) and saline conductivity. We further examined if there was a significant difference in the performance of phase and amplitude for this task. An example of the sinusoidal waveforms obtained is provided in Fig. 3.

We first examined the quality of the linear regression models build using the phase information. The coefficients of determination (R^2) for the phase regression models across all rabbits, stimulation frequencies and electrode pairs had a mean (±standard deviation) of 0.64 ± 0.32 for Set 1, 0.58 ± 0.31 for Set 2, and 0.52 ± 0.32 for Set 3. An example of a phase-to-volume relationship is provided in Fig. 4. A Friedman test revealed a significant difference between the R^2 statistics on the three sets ($\chi^2(2) = 10.8$, $p = 0.0046$). *Post-hoc* comparisons found a significant difference only between Set 1 and Set 3 ($p = 0.0018$).

We next examined the volume prediction error based on the regression models developed above. The mean RMS value of the prediction error in Set 1, Set 2 and Set 3 was used to select a stimulation frequency and electrode pair for each rabbit. The selected combination for each rabbit is provided in Table 1. Using these combinations, the mean volume prediction error in Set 2 and Set 3 across all rabbits was 6.63 ± 1.12 mL (Fig. 5), out of a bladder capacity of approximately 25 mL.

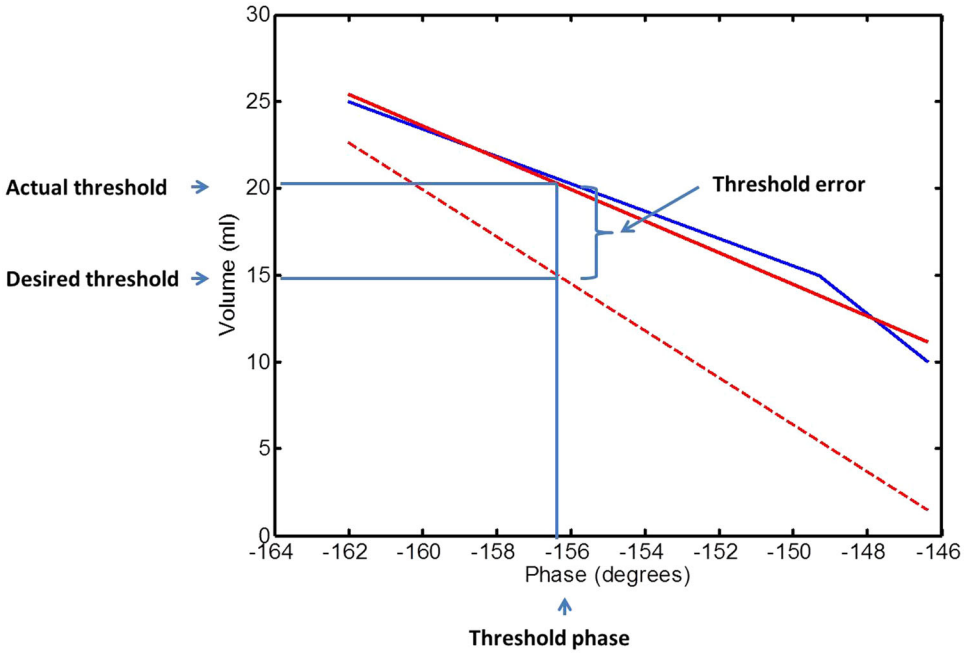

FIGURE 2. Illustration of the threshold determination process. A threshold phase is determined based on the desired threshold and the linear fit from Set 1 (dashed red line). Then, using this threshold phase, the actual threshold that would be obtained from the Set 2 (or Set 3) regression (solid red line) is computed. The threshold error is the difference between the desired and actual threshold. The experimental data is shown by the blue line.

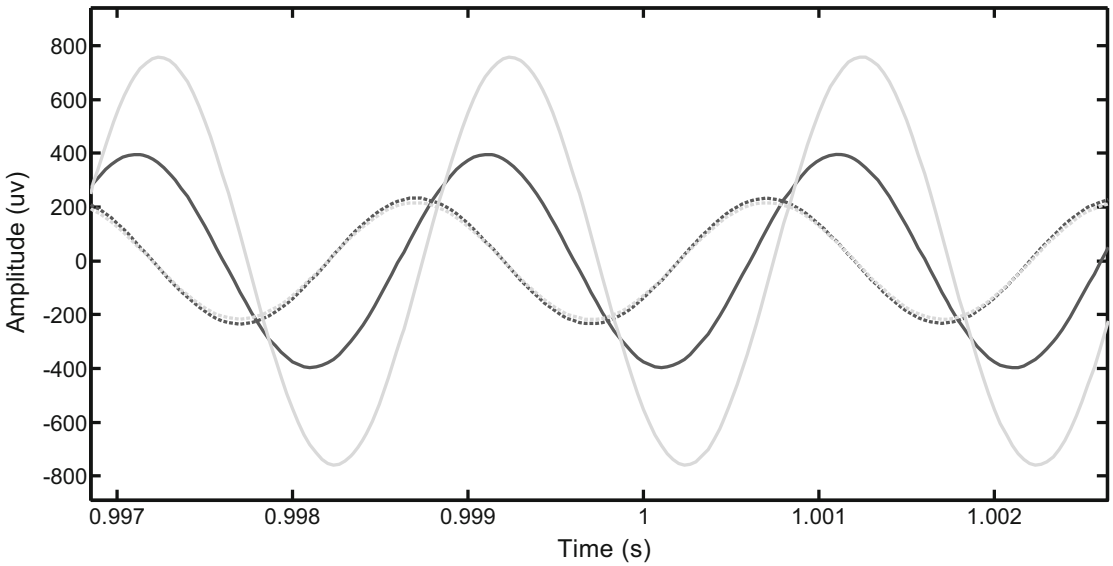

FIGURE 3. Example of the recorded waveforms, at two different bladder volumes. In this case, the stimulating frequency was 500 Hz. The dark gray lines were obtained with a bladder volume of 5 mL, and the light gray lines with a bladder volume of 25 mL. The dashed lines are the input waveforms obtained by recording the voltage across the 1 Ω resistor. The solid lines are the output waveforms obtained from a pair of recording electrodes. Both the amplitude and phase changes are visible between the two different bladder volumes.

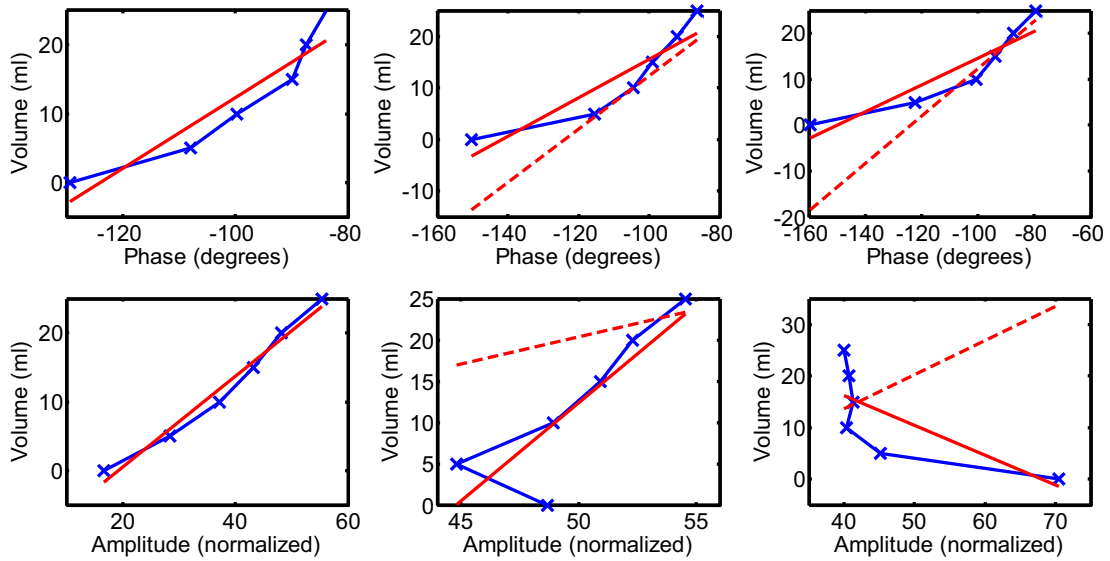

FIGURE 4. Top row: Bladder volume as a function of phase as well as linear fit of the relationship for Set 1 (left), Set 2 (middle) and Set 3 (right), in a single experiment. In each figure the blue line is the experimental data, where the abscissa shows the phase values that were measured at different volume levels, and the ordinate shows the corresponding volumes. In Sets 2 and 3, the solid red line represents the linear fit using the data from that set, whereas the dashed red line is the relationship obtained using the data from Set 1. Bottom row: Analogous results to the top row, using the amplitude instead of the phase information. The phase results are shown for the frequency-electrode pair that maximized performance for the phase-based volume prediction error, whereas the amplitude results are shown for the pair that maximized performance for the amplitude-based volume prediction error. The shapes of the responses observed varied between experiments; the data presented in this figure is from one experiment only and is intended only to illustrate our analysis.

These procedures were repeated for the amplitude regression models. The R^2 statistics across all rabbits, stimulation frequencies and electrode pairs had a mean of 0.59 ± 0.34 for Set 1, 0.60 ± 0.27 for Set 2, and 0.57 ± 0.24 for Set 3. An example amplitude-to-volume relationship is provided in Fig. 4. An Friedman test found no significant differences between the three sets ($\chi^2(2) = 0.57$, $p = 0.75$).

The selected combination of frequency and electrode pair for each rabbit using the amplitude

TABLE 1. Combination of stimulation frequency and electrode pair yielding the best performance, according to each performance measure.

Rabbit	Volume prediction error using phase	Volume prediction error using amplitude	Threshold prediction error using phase	Threshold prediction error using amplitude
1	2 kHz, Pair 1	1 kHz, Pair 2	2 kHz, Pair 1	1 kHz, Pair 1
2	7 kHz, Pair 1	4 kHz, Pair 3	4 kHz, Pair 2	250 Hz, Pair 3
3	7 kHz, Pair 1	250 Hz, Pair 2	7 kHz, Pair 1	1 kHz, Pair 3
4	7 kHz, Pair 1	6 kHz, Pair 2	1 kHz, Pair 1	1 kHz, Pair 1
5	500 Hz, Pair 1	5 Hz, Pair 2	750 Hz, Pair 1	1 kHz, Pair 1
6	500 Hz, Pair 2	250 Hz, Pair 1	500 Hz, Pair 2	250 Hz, Pair 2

The selected combination is the one with the best averaged performance across all three recording sets.

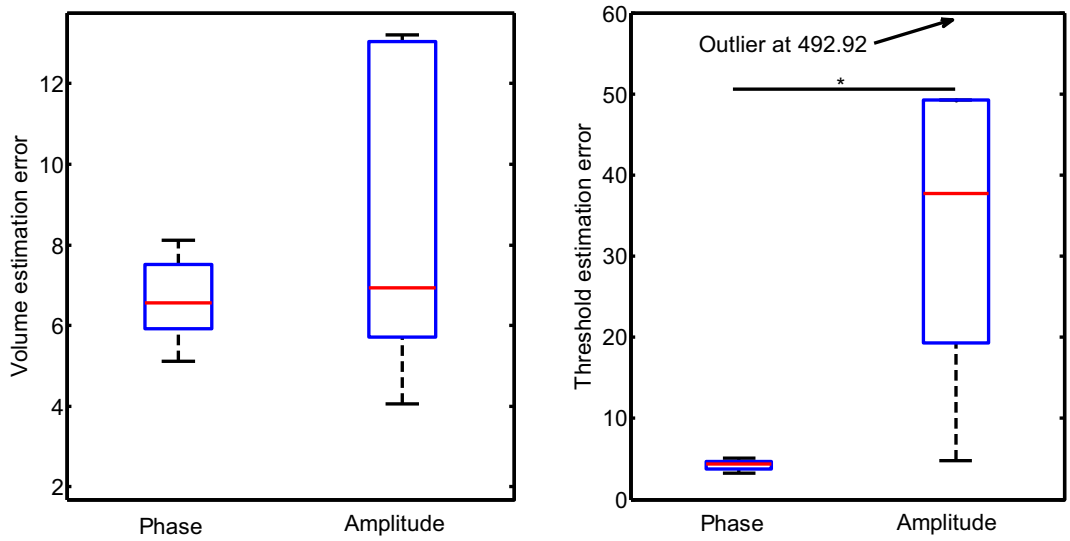

FIGURE 5. Comparison of the results obtained using the phase and amplitude information, according to the volume prediction error (left) and the threshold estimation error (right). $n = 6$ in all cases. The box plots use the median and quartiles of the data.

regression models is provided in Table 1. Using these combinations, the mean volume prediction error in Set 2 and Set 3 across all rabbits was 8.32 ± 3.88 mL (Fig. 5).

We compared the performance of the phase and amplitude approaches. When only the best-performing frequency-electrode combinations in each rabbit were considered, the volume prediction errors using the phase regressions was not significantly different from the errors using the amplitude regressions ($p = 0.44$ in a Wilcoxon signed-rank test, $n = 6$). However, when all frequency-electrode combinations were considered, the phase regressions gave significantly lower volume prediction errors than the amplitude regressions (16.88 ± 19.37 mL vs. 23.71 ± 20.91 mL, $p < 0.001$ in a Wilcoxon signed-rank test with $n = 151$).

Threshold Determination

Our second step was to investigate how well the phase and amplitude measurements could be used to obtain an empty/full binary decision rule, and to compare the performance of the two approaches for this task.

First using the phase regressions, the mean fullness threshold error in Set 2 and Set 3 (for a target threshold of 15 mL) was used to select a stimulation frequency and electrode pair for each rabbit. The selected combination for each rabbit is provided in Table 1. Using these combinations, the mean threshold error across all rabbits based on the phase regressions was 4.24 ± 0.65 mL.

Next, using the amplitude regression models, the combinations of frequency and electrode pairs selected are also provided in Table 1. Using these combinations, the mean volume threshold error across all rabbits using the amplitude regressions was 106.93 ± 189.82 mL (Fig. 5). Note that the threshold error may be larger than the actual bladder volume (25 mL) if the linear regression on the Set 2 (or Set 3) data is poor or very different than the Set 1 regression: the amplitude threshold selected from Set 1 may not be in the range

of amplitudes actually observed in Set 2 (or Set 3), leading to a predicted volume that could be outside the range 0–25 mL. Notably, as can be seen in Fig. 5, there is one large outlier in the amplitude threshold estimation results; if this value is excluded, the mean volume threshold error becomes 29.73 ± 18.57 mL.

We compared the performance of the phase and amplitude approaches. When only the best-performing frequency-electrode combinations in each rabbit were considered, the threshold errors using the phase regressions was significantly lower than the errors using the amplitude regressions ($p = 0.03$ in a Wilcoxon signed-rank test, $n = 6$; if the outlier discussed in the previous paragraph is excluded, significance is narrowly missed with $p = 0.06$, $n = 5$). Likewise, when all frequency-electrode combinations were considered, the phase regressions gave significantly lower threshold errors than the amplitude regressions (14.97 ± 16.70 mL vs. 26.37 ± 46.51, $p < 0.001$ in a Wilcoxon signed-rank test with $n = 151$).

The variations in the threshold errors as a function of the desired threshold are shown in Fig. 6 (using the best frequency-electrode combination for each rabbit). The choice of threshold was not found to qualitatively affect any of the conclusions that can be drawn from our analysis.

DISCUSSION

We evaluated the accuracy of bladder volume estimation using a phase-based electrical plethysmography approach. By injecting a sinusoidal waveform through a pair of stimulating electrodes, and measuring from pairs of recording electrodes placed on the outside of the bladder wall, we found clear relationships between the phase shift in the recorded sinusoid and the volume of saline in the bladder. The phase-based estimation was found to be more accurate than estimation based on the amplitude of the recorded sinusoids.

The most important difference was found when a binary empty/full decision rule was derived based on the regression models. With the phase information, a threshold error of 4.24 ± 0.65 mL was obtained, corresponding to approximately 15 % of the bladder volume. This error is well within the range of clinical relevance for this application, since a 15 % error would still be able to provide a user with very meaningful feedback about when they need to void their bladder. With the amplitude regression models, the threshold errors were very large and did not suggest any translational potential.

Importantly, the phase-based approached provided improved performance even in the presence of variations in the concentration of the saline. This was particularly evident when the volume threshold metric was used (4.24 ± 0.65 mL threshold error, as discussed in the previous paragraph). Variations in urine conductivity have previously been reported to have a significant impact on the performance of impedance-based volume estimation methods,[8] and are considered to be an important obstacle to the robustness of implanted bladder volume estimation devices in a chronic *in vivo* situation.[21] Previous studies examined only the relationship of the amplitude with bladder volume.[8,12,26] Our study is the first to examine whether the phase information might also be useful for predicting bladder volume. Thus, the finding that phase information can help overcome changes in urine conductivity is novel and has high clinical relevance.

Interestingly, there was found to be a significant difference in the R^2 values of the Set 1 and Set 3 phase regression models, but not for the amplitude regressions. This suggests that the saline conductivity had a stronger effect of the linearity of the relationship with the phase models. Nonetheless, as discussed above, the phase models yielded better volume predictions and considerably better threshold estimations. This finding suggests that, although the phase relationship became less linear with changes in conductivity, the approximate range of the phase values was not dramatically different between Set 1 and Set 3, such that meaningful volume predictions remained possible. With the amplitude models, on the other hand, the range of the values measured shifted in Sets 2 and 3, making volume prediction difficult. As illustrated by the example in Fig. 4, there was also more variability in the shape of the amplitude response, further complicating amplitude-based predictions.

Examining the combinations of stimulation frequency and electrode pair that yielded the best performance for each rabbit and performance metric did not reveal any obvious trends (Table 1). This suggests that selecting these parameters *a priori* will likely not be possible, and that some type of calibration process will be required for the electrode site and the stimulation parameters. The reasons for the heterogeneity of these results are not certain, but are likely related to inter-subject variations in the anatomy and electrical properties of the bladder, the exact placement of the electrodes, and the contact impedance achieved when attaching the electrodes.

We considered only univariate regression models linking the volume to the phase or amplitude from a single recording electrode pair. It is possible that multiple regression approaches combining phase and amplitude information from one or several recording pairs may improve performance. However, as the number of predictor variables increases, so does the amount of data points needed to avoid overfitting the

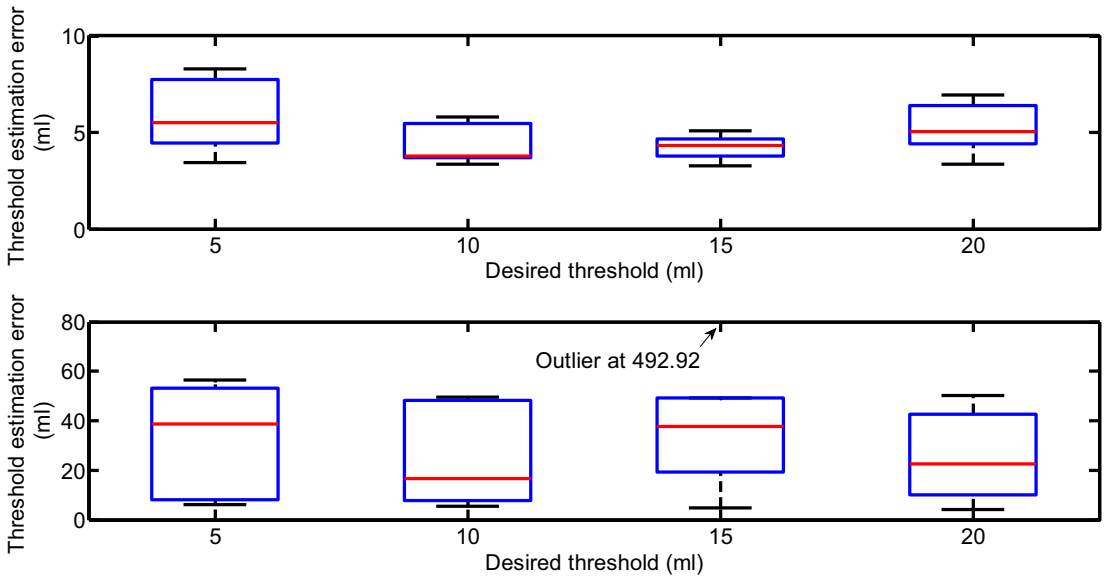

FIGURE 6. Variation in the threshold estimation error as a function of the desired threshold. Top plot: results using phase information. Bottom plot: results using amplitude information. $N = 6$ in all cases.

model. The dataset used in this study is not large enough to support an investigation into multivariate models, and the issue has therefore not been explored here. On the other hand, as mentioned above, even with a single variable model there will be a need for a calibration procedure when the method is implemented in a chronic application. In a multivariate model the amount of calibration or training data would be substantially higher. If the encouraging results presented here are found to translate well to chronic studies, it is not certain that any performance improvements that can be derived from multivariate models would be worth the added complexity of implementation. Similarly, non-linear univariate models would require a consistent response shape between experiments and sets in order to justify a particular model form. Given the variability that we observed, there was not sufficient justification for choosing a non-linear model, and we opted to for the simplicity of the linear model.

One limitation of this study is the use of a small animal model. The rabbit bladders were filled to only 25 mL. Gill *et al.* previously reported that the performance of an impedance-based bladder volume estimation method (using amplitude) decreased at higher volumes as the relationship became non-linear.[8] It will be crucial to investigate the variations of the phase information for bladder volumes up to the 400–600 mL range and characterize the phase-to-volume relationship in more detail. This will require future studies in larger models. Note that a non-linear relationship is not an obstacle to a reliable system, if that relationship can be well characterized.

Another potential limitation is that the use of sinusoidal stimulation in the kilohertz range may lead to nerve block effects[13] and alter the behavior of the physiological system. However, it is important to note that the stimulation would not need to be applied continuously. A few seconds of stimulation every few minutes would be sufficient to obtain a measurement and make a decision on whether the bladder has exceeded a fullness threshold. It is unlikely that this type of relatively infrequent stimulation would have any deleterious effects due to nerve block, but this will have to be confirmed in future studies.

It is possible that the conclusions presented here may have been affected by the fact that the bladder was outside the abdomen. With the bladder re-inserted, leakage currents through the bladder wall to surrounding tissues may exist and complicate the relationship between the applied and measured sinusoidal waveforms. Re-inserting the bladder into the abdomen was not possible with the current version of our instrumentation, but will need to be explored in future work. Additionally, because Set 1 was performed immediately after placing the electrodes, it is possible that a transient settling period of the electrode-tissue interface may have accounted for the different amplitude ranges observed between Set 1 and Set 2. Although this eventuality will have to be investigated in more detail in future work, even if such a transient effect was present, the fact would remain that the phase-based approach was more robust than the amplitude-based approach to these variations in the electrode-tissue interface.

Recent studies have demonstrated that recordings of afferent neural signals can be used to extract information about bladder volume. Recording sites have included dissected filaments in the sacral roots,[22] the sacral dorsal root ganglia,[4] the pudendal nerve,[19] and the spinal cord.[24] The use of afferent recordings is appealing because it is taking advantage of information naturally present in the physiological system, in contrast to the artificial perturbations on which electrical impedance-based measures rely. On the other hand, none of the afferent recording methods that have been proposed have a clear potential for clinical translation. The surgeries involved are generally complex, and the chronic stability of the recordings has not been demonstrated. Methods based on sensors placed on the bladder wall, such as the one proposed here, may be more easily implemented in humans. The use of artificial signals is also likely to provide more robust recordings over time than natural neural signals with low signal-to-noise ratio and high sensitivity to small electrode movements. However, future chronic studies in larger models are needed to confirm this.

Electrical plethysmography approaches to bladder volume measurement and fullness detection can be improved by the use of the phase information in sinusoidal stimulation waveforms. Accurate estimation of a fullness threshold (to within approximately 15 % of bladder capacity) was achieved even in the presence of large changes in the composition of the saline and variations over time of the electrode-tissue interface. These findings suggest that an implanted sensor based on phase-based electrical plethysmography is a promising solution to the problem of bladder fullness detection in neuromodulation systems for LUT dysfunction, with a high translational potential.

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