Feasibility of Real-Time Conditional Sacral Neuromodulation Using Wireless Bladder Pressure Sensor

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***Abstract*— Continuous sacral neuromodulation (SNM) is used to treat overactive bladder, reducing urine leakage and increasing capacity. Conditional SNM applies stimulation in response to changing bladder conditions, and is an opportunity to study neuromodulation effects in various disease states. A key advantage of this approach is saving power consumed by stimulation pulses. This study demonstrated feasibility of automatically applying neuromodulation using a wireless bladder pressure sensor, a real-time control algorithm, and the Medtronic Summit™ RC+S neurostimulation research system. This study tested feasibility of four conditional SNM paradigms over five days in 4 female sheep. Primary outcomes assessed proof of concept of closed-loop system function. While the bladder pressure sensor correlated only weakly to simultaneous catheter-based pressure measurement (correlation 0.26-0.89, median r = 0.52), the sensor and algorithm were accurate enough to automatically trigger SNM appropriately. The neurostimulator executed 98.5% of transmitted stimulation commands with a median latency of 72 ms (n = 1,206), suggesting that rapid decision-making and control is feasible with this platform. On average, bladder capacity increased for continuous SNM and algorithm-controlled paradigms. Some animals responded more strongly to conditional SNM, suggesting that treatment could be individualized. Future research in conditional SNM may elucidate the physiologic underpinnings of differential response and enable clinical translation.**

***Index Terms*— Implants, biomedical transducers, biomedical signal processing, pressure sensors, classification algorithms, neural engineering.**

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I. Introduction

SACRAL neuromodulation (SNM) is clinically approved for the treatment of refractory fecal incontinence, non-obstructive urinary retention, and urinary incontinence [1]–[3]. Patients who show a >50% improvement in symptoms during a trialing period may receive an implantable neurostimulator (INS) for long-term treatment (e.g. Medtronic InterStim®). The lead contacts are placed in close proximity to a sacral nerve and the treatment paradigm is continuous, open loop neuromodulation. Because SNM is used over periods of years, tissue matrix remodeling in pelvic organs or other physiologic changes can change the underlying physiology and symptoms of incontinence [4]. As a result, optimum SNM parameters may change over time, so SNM devices allow limited parameter changes by the patient. More significant waveform changes must be performed during a clinic visit. However, as next-generation neurostimulators are incorporating wirelessly rechargeable batteries, real-time adjustment of stimulation parameters based on changing physiologic conditions—closed-loop or conditional SNM—could be considered in the development of future treatments. For example, stimulation levels could be auto-adjusted to track physiological changes that occur during aging or as a manifestation of improved continence during SNM treatment.

To date, research has focused on conditional stimulation, where SNM is applied during only part of the bladder filling cycle, or only during periods of active detrusor contraction [5]. A key advantage of this approach is saving power to reduce INS size and improve battery life since most INS power is consumed by stimulation pulses. In addition, stimulation is feasible and effective on nerves other than the sacral [6]–[9]. Different nerves may inhibit the bladder differently than SNM [10], but are not widely targeted clinically due to surgical difficulty and risk.

Recent studies have indicated that continuous SNM delivery may not be necessary to elicit equivalent functional outcomes [11]. Studies in anesthetized rats [6] and cats [12] showed that conditional SNM can outperform continuous SNM in increasing bladder capacity. Experiments in an anesthetized rat model demonstrated a possible physiological mechanism. SNM delivered during the latter half, but not the first half, of the bladder filling cycle significantly increased

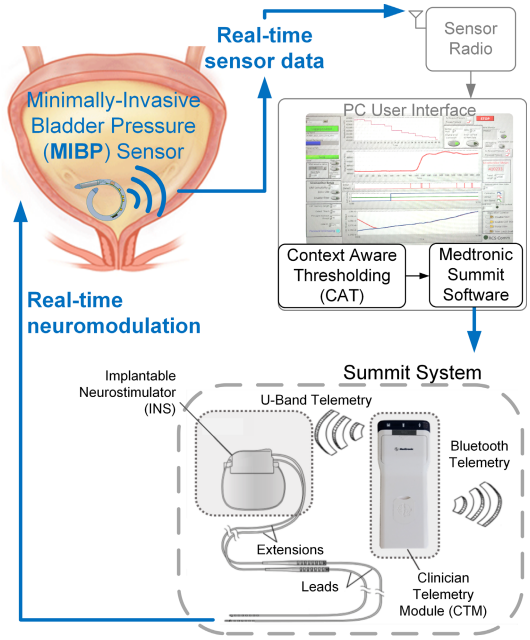

Fig. 1. Closed-loop bladder stimulation used a wireless minimally invasive bladder pressure (MIBP) sensor which transmitted pressure data to a data acquisition program on a computer. A bladder contraction detection algorithm communicated in real time to the Medtronic Summit control software. This enabled communication via a clinician telemetry module (CTM) to control an implanted neurostimulator (INS) configured for sacral neuromodulation.

bladder capacity similar to SNM applied for the entire fill cycle [13]. Clinically, a recent prospective randomized study demonstrated that cycling SNM (e.g. 10 mins on followed by 10 mins off) provided similar reduction in urinary incontinence episodes compared to continuous SNM [14] which suggests that closed-loop or conditional SNM could be used to more efficiently deliver therapy based on physiological signals in a patient specific way.

A critical element for conditional SNM is a signal to determine when to optimally apply stimulation. Researchers have used signals from catheter-based bladder pressure measurement, sensory nerves, bladder strain, and rectal activity among other measures [5]–[9], [12], [15]. These methods are either surgically invasive or require catheter placement. In this study, we investigated physiologically-triggered SNM using a minimally invasive wireless catheter-free bladder pressure monitor to provide feedback in real time. An algorithm was used to alter SNM programming on an INS based on four conditional SNM paradigms. Feasibility was demonstrated in an established, fully conscious sheep model [16] over 5 days, using clinically standard electrodes in use today. To our knowledge this study represents the first demonstration of the feasibility of a telemetry-based catheter-free bladder pressure monitor to automatically communicate with an INS in response to changing bladder pressure in real time.

II. Hardware and Software for Conditional Bladder Neuromodulation

A. Closed-Loop Bladder Neuromodulation Approach

The conditional SNM system consisted of three essential components: a minimally invasive bladder pressure sensor (MIBP), a contraction detection algorithm running in real-time on a PC, and the Medtronic Summit™ RC+S neurostimulation system consisting of an INS and control software (Fig. 1). Briefly, the MIBP transmitted bladder pressure data to an external radio connected to a PC. The PC ran the contraction detection software as well as software to communicate to the Summit system. The algorithm analyzed temporal patterns in bladder pressures, with the assumption that an active detrusor contraction produces a characteristic rise in vesical pressure over a specific time course [17]. With this assumption, voiding and non-voiding contractions are detected from pressure data alone, and abdominal pressure artifacts can be algorithmically ruled out. When a contraction was detected, the algorithm transmitted an event to the Summit software, which commanded the INS to turn on stimulation. After the bladder contraction ended, or during voiding, the software communicated to the Summit system to turn off stimulation.

B. Summit INS & System

The Summit system is an investigational research system that includes an INS with both stimulation and sensing capabilities [18]. The Summit system has been previously described [19]. We therefore detail only relevant features here. The Summit system is a rechargeable, 16-channel constant current stimulation system with bidirectional wireless communication. This study used the bidirectional communication to implement distributed closed-loop sacral neuromodulation using a minimally invasive bladder pressure (MIBP) sensor device.

The INS is one part of the Investigational Summit System, which also includes a clinician telemetry module (CTM) and research lab programmer (RLP). The CTM enables wireless, bi-directional communication between the INS and the RLP. The RLP can then be used to remotely select electrode configurations and set stimulation parameters including pulse width, frequency, amplitude, and ramp time within predefined safety limits. Finally, the Summit System also provides an application programming interface (API) that allows for distributed control of Summit RC+S sensing and stimulation as well as device data logging from a host computer. In this study, stimulation parameters were established at the beginning of each experimental session for each animal. A custom API was used to toggle stimulation based on the control policy determined from the MIBP and stimulation algorithm. The MIBP algorithm issued commands to the Summit API using user datagram protocol (UDP) packets to turn stimulation on and off in real time (Fig. 1). While UDP would allow networked communication, both the MIBP software and the Summit API ran on the same host computer in order to facilitate timestamping of events.

C. Minimally Invasive Bladder Pressure Sensing

Pressure-sensing catheters are not suitable for long-term use or in free-moving humans or animals. To improve future animal research studies, and to support translation to clinical testing in humans, a MIBP sensor was developed (Fig. 2). It consisted of a thin-walled, highly flexible and curled silicone

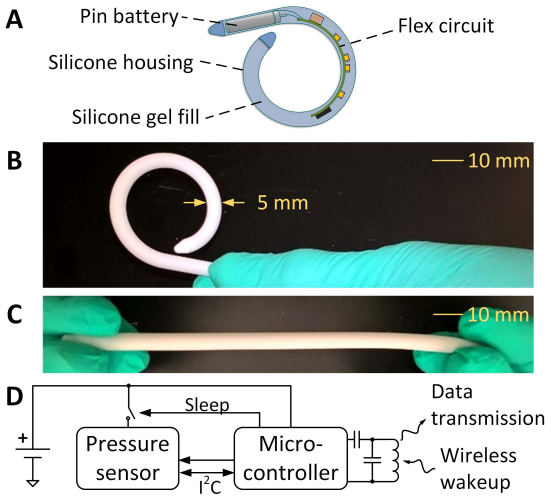

Fig. 2. The minimally invasive bladder pressure sensor (MIBP) (A) uses a flexible circuit board within a flexible 5-mm diameter housing. The MIBP curled into shape (B) within the bladder, but was flexible to pass through the urethra (C). The MIBP electronics (D) relies on ultra-low-power components to transmit pressure data in real time while consuming only 86 μA from a primary cell battery.

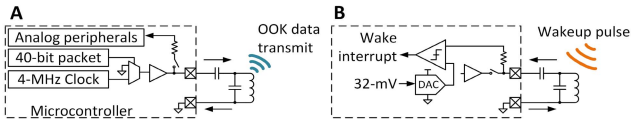

Fig. 3. The minimally invasive bladder pressure sensor (MIBP) transmitted OOK wireless radio signals using an inductive antenna with matching circuit (A). The MIBP was woken from sleep mode by inductively coupling energy into the transmit antenna (B).

TABLE I
MINIMALLY INVASIVE BLADDER PRESSURE SENSOR (MIBP) SPECIFICATIONS

Symbol	Measured/nominal value
MIBP dimensions	5 mm diameter, 13.5 cm straightened length
Pressure sampling rate	75 Hz
Pressure transmission rate	10 Hz
Pressure sensor bandwidth	0.5 Hz
Pressure range[a]	0 – 250 cm H_2O
Pressure resolution	24 bit
Pressure error[a] (0-250 cmH_2O)	7.8 cm H_2O RMS
(0-100 cmH_2O)	0.9 cm H_2O RMS
Transmission distance	30 cm, using 8-cm loop antenna
Wireless wakeup distance	20 cm, using 10-W transmission pulse
Current draw, average in measure mode	86 µA
Peak current draw in radio transmission	2.2 mA
Current draw, average in sleep mode	2.3 µA
Battery lifespan in measure mode	290 hours
Battery lifespan in sleep mode, estimated	452 days

[a] Represents deviation from straight-line fit over limited range of testing for packaged pressure sensor.

tube measuring 5 mm in diameter with internal electronics on a polyimide flex circuit. The MIBP is intended to be inserted through the urethra similarly to a catheter, and to curl into shape when in the bladder. This curled shape prevents the MIBP from obstructing or entering the urethra during voiding, so the MIBP remains in the bladder until manually removed. The MIBP housing was fabricated via silicone injection molding in a pre-curled shape to ensure that it curls up after entering the bladder.

The sensor circuitry consisted of a low-power microcontroller (PIC12, Microchip Technology, Chandler, AZ) and solid-state pressure transducer (LPS22HB, ST Microelectronic, Geneva, Switzerland), a 25 mAh pin battery (BR425, Panasonic, Osaka, Japan), and components enabling wireless data transmission and wireless wakeup. All components were soldered to a 110-μm flexible polyimide printed circuit board with 10-μm polyimide coverlay on both sides. Flexible epoxy (M-121HP, Henkel Loctite, Düsseldorf, Germany) was applied around all components and solder joints for stress relief. Circuits were then placed inside the silicone housing of the MIBP and the housing was filled with silicone gel (Sylgard 527, Dow Corning, Midland, MI) to protect the electronics and transmit pressure equally throughout the tube. Finally, endcaps were glued on with silicone adhesive (Silbione 4300, Elkem, Oslo Norway), providing a biocompatible silicone packaging for the electronics.

The MIBP was controlled by embedded firmware, with two major modes: measure and sleep. In measure mode, 24-bit pressure data were over-sampled at 75 Hz to increase accuracy and to reduce aliasing of high-frequency abdominal pressures [17], then filtered to a 0.5-Hz bandwidth using an exponential moving average filter. Samples were then transmitted at 10 Hz using On-Off-Keyed (OOK) digital transmission at 4 MHz. OOK pulse width was 10 μs; total time to transmit each 40-bit packet was 400 μs. Intermittent OOK further reduced power consumption such that the average transmitter active time was only 0.3% for typical pressure data [20]. Each transmission packet used an 8-bit synchronization pulse (0xFF) followed by an 8-bit header containing ancillary data, and a 24-bit pressure sample. The MIBP used an inductive antenna and a matching circuit for passive voltage gain and bipolar antenna current (Fig. 3a). During transmission the microcontroller directly drove the antenna circuit with a 4-MHz carrier from an output pin. With this simple method, data transmission range up to 30 cm was measured in the lab setting, using an external 8-cm loop antenna and a low-noise radio receiver. The radio receiver used a 4-MHz bandpass filter, 31-dB gain low-noise amplifier, a 95-dB logarithmic amplifier, and a baseband comparator to recover binary OOK transmission packets. An Arduino Due processed transmitted data into USB serial format for communication to a PC. Data were decimated to a rate of 1 Hz after exponential moving average as part of the contraction detection algorithm [17].

Measured current draw for the MIBP in measure mode was 86 μA average with peak current of 2.2 mA occurring during radio transmission which met the minimum specifications for the MIBP devices to be used in the experiment (Table I). Bench-testing of 16 devices in a water-filled pressure chamber demonstrated pressure sensing RMS error of 7.8 cmH_2O over the range of 0–250 cmH_2O and 0.9 cmH_2O on the range of 0–100 cmH_2O (Fig. 4). Before packaging, pressure error on

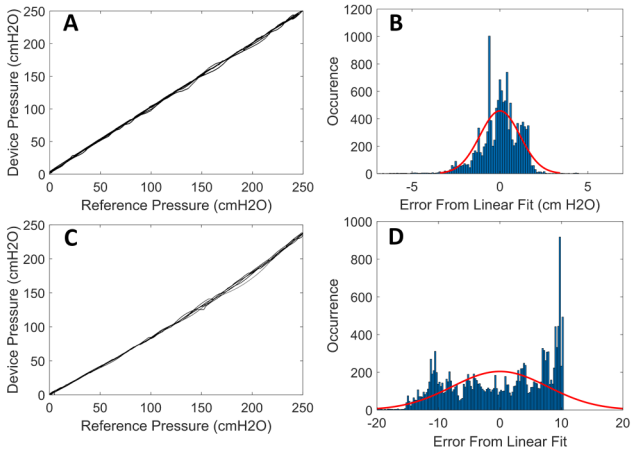

Fig. 4. Example outcomes of bench testing the minimally invasive bladder pressure sensor (MIBP) in a pressure chamber. Before packaging, MIBPs showed high linearity (0.65% error, n = 13,026 points) (A) with random errors due to thermal noise (B). After packaging, sensor deviation from linear fit increased (3.40%, n = 17,103 points) (C). Residual analysis showed a response dominated by fitting errors indicating slight nonlinear response at high pressure values (D).

the same range was 1.5 cmH_2O, indicating that the package introduced slight nonlinearity in the pressure sensing response.

After running for 4 hours, MIBPs automatically entered sleep mode. A watchdog timer woke the system every 500 ms to check for a wakeup signal. Wakeup used the same antenna as data transmission, but the microcontroller pin was configured as an input. An external Class-E power amplifier was used to transmit magnetic bursts at 4 MHz, which were received by the MIBP antenna through inductive coupling (Fig. 3b). An internal comparator and digital-to-analog (DAC) peripheral were used to detect if the energy received by the antenna exceeded 32 mV in any wake period. Current draw in sleep mode was dominated by the pressure sensor standby current. With an average measured sleep mode current of 2.3 μA, MIBPs discharged 0.2% of the battery voltage per day in sleep mode.

Wireless activation of the MIBP used a 15-cm diameter, 6-turn coil antenna placed near the skin surface. The coil was driven by a 4 MHz, 10-Watt power amplifier to provide 20 ms energy bursts every 250 ms. The MIBP was wirelessly activated at up to 20 cm implant depth (Table I).

D. Context-Aware Thresholding (CAT) Algorithm

This study implemented closed-loop SNM using the context aware thresholding (CAT) algorithm to detect the onset of contractions in real time (less than 100 ms). The CAT algorithm was developed to differentiate real bladder contractions from pressure artifacts and was validated on human cystometric data with a detection accuracy of 97% [17]. In this study, we programmed a real-time version of the algorithm in Labview (National Instruments, Austin, TX) software (Fig. 5a). While CAT previously was demonstrated on pre-recorded data, the real-time implementation of CAT performed the same signal processing using a sample buffer.

The CAT implementation had three parameters, described here briefly. First, pressure data were filtered by an exponential moving average with parameter α defining the cutoff

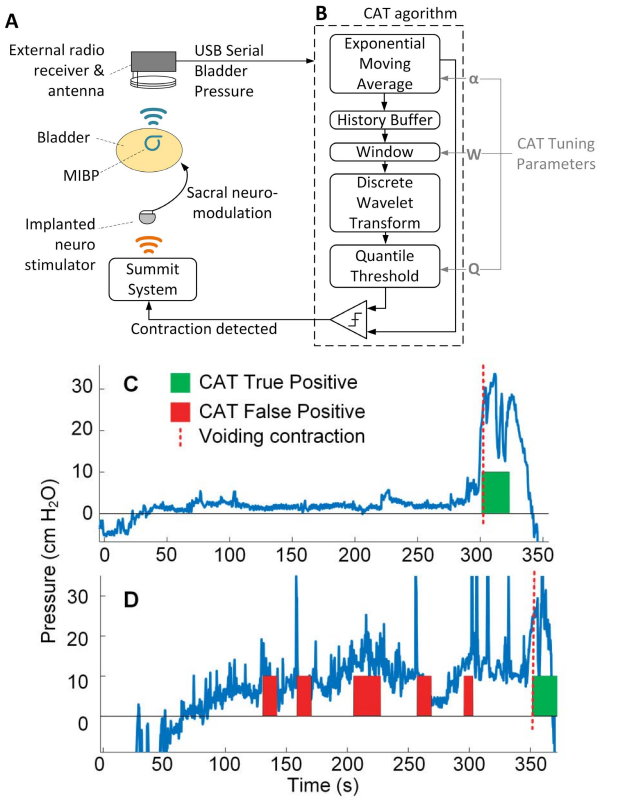

Fig. 5. Conditional sacral neuromodulation (SNM) trials (A) used the context aware thresholding (CAT) algorithm (B) to detect contractions in real time and control SNM. CAT detected 97% of voiding contractions in cystometry data from sheep (C) with a false positive rate of 1.87 detections per fill. False positives were possibly non-voiding contractions of the bladder or artifacts (D).

frequency. Next, a 3rd-order discrete wavelet transform (DWT) was performed using the db2 wavelet. Only approximation coefficients were selected; detail coefficients correspond to higher frequency abdominal pressure changes and were not used. The DWT approximation coefficients were then thresholded using a context-aware threshold. Positive threshold crossings were counted as contraction onset. The threshold sensitivity was determined by two other parameters: window length (W) and quantile (Q). The percentile value correlating to parameter Q from the values in the range of data in window W was selected as the detection threshold. For each new pressure sample, a new DWT waveform of length W was calculated, and quantile Q was determined. Finally, bladder contraction was detected simply by comparing the newest pressure value to percentile Q. Pressures exceeding Q indicate an ongoing contraction.

The performance of the real-time CAT implementation was validated on pre-recorded data from the same sheep used for neuromodulation studies. In these studies, the bladder was filled with saline while pressure was recorded. Volume was linearly infused until the bladder reflexively emptied via voiding contraction. Therefore, in each cystometric cycle one voiding contraction was observed, which simplified validation. Data were processed through the CAT algorithm while varying parameters α, W, and Q. A figure of merit established in prior work [17] was used to select an optimized parameter

set from a dataset of 140 catheter-based cystometric fills from 4 conscious sheep. The best-performing parameters were calculated as: $\alpha = 0.095$, W = 165, Q = 0.95. These parameters produced a mean true positive detection rate of 97% and a false positive rate of 187%. The high false positive rate in this case was an artifact of the validation method, which assumed only a single bladder contraction per cystometric trial, the voiding contraction (Fig. 5c). While voiding contractions were simple to identify visually, non-voiding contractions are more subtle and were therefore not analyzed in manual annotation and counted as false positives in this analysis (Fig. 5d). Nonetheless, non-voiding contractions are a normal and well-documented phenomenon in bladder physiology [5], [21], [22]. Combining terms, an average of 2.84 (range: 1-6) contractions were detected by CAT per bladder filling cycle.

III. Experimental Methods for Conditional Neuromodulation

A. Implantation of Pulse Generator

This study was performed on four female polypay sheep (age: 15.9 ± 1.1 months; weight: 57.3 ± 2.4 kg) with each sheep acting as its own control in compliance with a protocol approved by the Medtronic Physiological Research Laboratories Institutional Animal Care and Use Committee. Basic surgical and urological monitoring methods and implantation procedures used in these experiments were described previously [16]. Briefly, animals were anesthetized with an intramuscular injection of morphine (0.5 mg/kg) followed by intravenous propofol and maintained with isoflurane. Two Model 3889 InterStim® (Medtronic, Minneapolis, MN) quadripolar leads were inserted through the sacral foramen on the left and right side using a percutaneous technique implanted under fluoroscopic guidance with the sheep in sternal recumbency. S3 was initially targeted and stimulation was used to verify appropriate motor response described as perianal tail or bellows contractions with minimal leg contraction. In the absence of an appropriate motor response at levels less than 4 V, the lead was moved to S4 and motor response was reevaluated. In two sheep, leads were implanted in right and left S3 and in the other two sheep, leads were implanted in right and left S4. Leads were then connected to extensions (Model 37083, Medtronic, Minneapolis, MN) and tunneled to a subdermal pocked on the left flank and connected to an INS (Summit RC+S, B35300R, Medtronic, Minneapolis, MN). All incisions were closed, and animals were recovered prior to cystometry.

B. Catheter Cystometry in Conscious Animal Model

Repeat, single fill cytometry protocols were used through this study [16]. Bladder pressures were recorded through a pressure sensor line (Mikro-Cath™, Millar, Houston, TX) fed through a 12 Fr urinary catheter (Lubri-Sil®, Bard Medical, Covington, GA). In one animal, an 8 Fr catheter was used due to sensitivity exhibited with use of a 12 Fr catheter. A Foley balloon was filled with saline to maintain catheter placement and warmed saline was infused at 30 ml per minute (Flo-Gard R pump, Baxter, Deerfield, IL). Saline infusion was promptly terminated when bladder pressure sharply increased past 30 mm Hg and the sheep assumed the voiding posture or after bladder pressure was 30 mm Hg for more than five seconds with no postural response. Capacity was defined as the amount of saline infused prior to voiding as described. The catheter was then pushed forward to allow voiding and the bladder was manually emptied before starting the subsequent trial.

Prior to system implant, this cystometry protocol was used to screen sheep for ability to accept bladder catheterization and for consistency in capacity over ten fills. Following system implant, this protocol was used to determine effects of continuous stimulation. Previous work has demonstrated significant increases in bladder capacity when stimulating at maximum tolerable amplitude (MTA; [16]). In that study, five of the six sheep had significant increases in capacity with an average increase across all sheep of 60% in response to continuous SNM. MTAs were determined for each electrode configuration on each lead. MTA was defined as the highest current comfortably tolerated by the sheep such that the animal was still weight bearing. The same stimulation waveform was used (10 Hz, 0.21 ms pulse width) but MTA varied from 0.4 – 8.5 mA across all animals.

C. MIBP Insertion in Conscious Animal Model

Prior to insertion, gas-sterilized MIBPs were wirelessly activated and functionally-tested while in the sterilization bag. MIBPs were then inserted in the bladders of conscious animals just after baseline conscious cystometry and after removing cystometric catheters. Animals did not receive any antibiotics or analgesics to minimize immediate impact to bladder capacity. MIBPs were lubricated with Surgi-lube and inserted through the urethra similarly to catheterization. Patency of each MIBP was verified by palpating the urethra from within the vagina to ensure that the MIBP was fully in the bladder lumen. After insertion, the wireless receiving antenna was placed near the animal's hip to validate reception of MIBP pressure data.

D. Sacral Neuromodulation Paradigms Tested

Five stimulation paradigms were tested in this proof-of-concept study for use of a wireless catheter-free pressure sensor to trigger stimulation. Continuous stimulation was tested as a control. In addition, two physiologically-timed paradigms and two pressure-triggered stimulation paradigms were investigated (Fig. 6). For all stimulation paradigms, SNM was manually disabled at the onset of visible voiding. These stimulation modes were chosen as potential use cases for wireless, catheter-free bladder pressure for neuromodulation feedback.

For the physiologically-timed paradigms, stimulation was either delivered during the first half of the fill cycle or the second half of the fill cycle. Fill cycle duration and half capacity was determined for each sheep, on each day by averaging the two, no-stimulation fills that were completed at the beginning of each test session. The two pressure-triggered stimulation paradigms were oscillating and latched-stimulation. In the

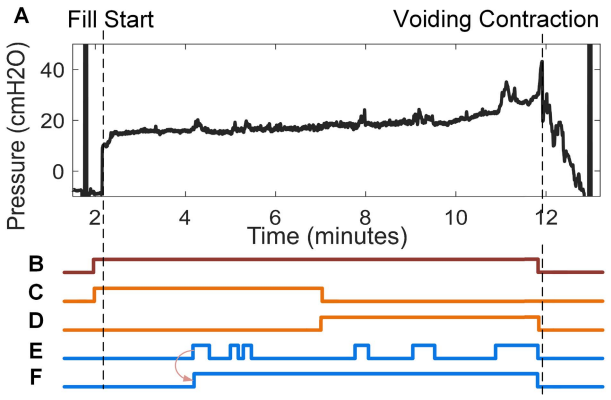

Fig. 6. Bladder filling cystometry measured pressure while filling the bladder with saline at a constant rate (A). Illustrative stimulation paradigms (high value indicates stimulation applied) included continuous stimulation (B), or conditional methods such as first half (C), second half (D), oscillating (E), or latched (F). Latched stimulation is initially triggered as in oscillating (orange arrow), but thereafter remains continuous.

TABLE II
BLADDER CAPACITIES BEFORE AND AFTER MIBP INSERTION, VALUES ARE MEAN [RANGE] (n = 3 FOR ANIMALS 1-2)

Animal	Baseline	After Insertion	Retained Capacity
1	86.7 mL [80 - 93]	56.7 mL [48 - 64]	65%
2	82.7 mL [61 - 109]	65.7 mL [27 - 91]	80%
3	-	167.4 mL [146 - 171]	-
4	-	83.0 mL [76 - 89]	-

oscillating paradigm, the pressure signal was used to trigger stimulation on and off based on the CAT algorithm. Since a conditional neuromodulation system should stimulate with nonvoiding contractions, the oscillating stimulation paradigm was set to stimulate with all contractions identified by the CAT algorithm. The latched paradigm used CAT to detect the start of bladder contractions after an initial lockout period, then started and maintained stimulation until the void. The lockout period was based on the typical void measure of each animal such that it was half the average time fill time.

IV. EXPERIMENTAL OUTCOMES

A. Impact of MIBP on Bladder Capacity

Bladder capacity was measured before and after MIBP insertion using filling cystometry (n = 3 per animal). Insertion and resumption of cystometric testing took less than 30 minutes. After the MIBP was inserted, cystometric catheters were re-inserted to measure capacity. Mean bladder capacity decreased (Table II) after MIBP insertion, however, this effect was not statistically verifiable due to the low number of observations. Because of day-to-day variation, bladder capacity after insertion is only reported for cystometric trials on the same day as MIBP insertion.

Additionally, animals were monitored for signs of weight loss, increased voiding frequency, or behavioral changes indicating discomfort caused by the MIBP device. No animals showed any indications of discomfort with the MIBP device.

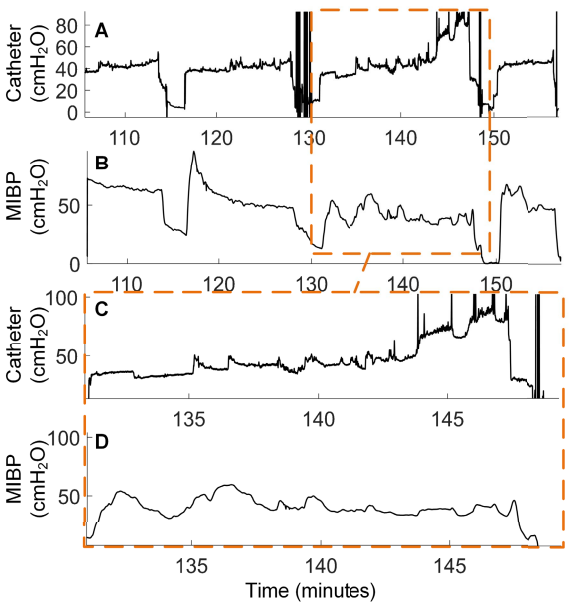

Fig. 7. During cystometry, catheter (A) and MIBP pressures (B) showed pressure increases at the start and end of filling cycles. Catheter (C) and MIBP data (D) correlated during contractions but showed large differences in static values. These data suggest local forces from the detrusor muscle pressing on the MIBP influenced pressure accuracy. Orange dashed lines in (A) and (B) delineate data magnified in panels (C) and (D).

B. MIBP Bladder Pressure Accuracy

MIBP pressures showed a pressurization/depressurization artifact occurring at the beginning and end of each fill cycle (Fig. 7a,b) giving them greater error than that measured with benchtop testing in a pressure chamber, as in Fig. 4. This was likely due to the local forces of the detrusor muscle pressing on the MIBP when the bladder was empty and during voiding. During the filling cycle, MIBP pressures correlated with bladder contractions most strongly after the bladder was partially filled (Fig. 7c,d). Including all valid cystometric trials (n = 114), median MIBP and catheter data correlation coefficient was $r = 0.52$ (range: 0.26-0.89). 21 trials were excluded from analysis due to poor recording quality caused by wireless radio artifacts.

C. Stimulation Paradigms Tested

In this study we tested five SNM stimulation paradigms (Fig. 8). In all cases stimulation was manually disabled during voiding. In physiologic paradigms SNM was triggered manually when the prescribed bladder capacity was reached during volumetric infusion. Closed-loop SNM paradigms used real-time pressure data from the MIBP device and the CAT algorithm to activate SNM (Fig. 9). In latched SNM, due to CAT false positives occurring during the initial pressurization phase of filling cystometry, a 30-s timeout was used which prevented early latched stimulation.

D. Stimulation Timing Latency

The MIBP algorithm changed stimulation with a latency of 72.4 ± 21.2 ms (n = 1,224 commands) (Fig. 10). This latency encompassed the time delay from MIBP algorithm

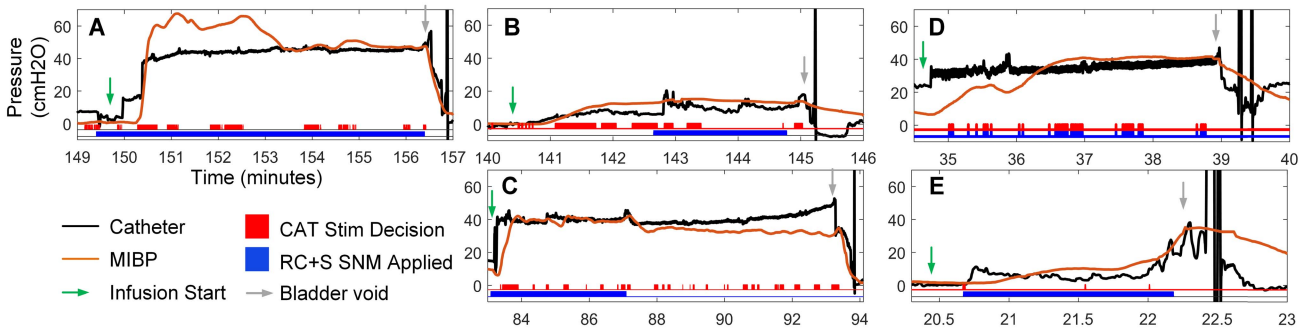

Fig. 8. Stimulation paradigms included (A) continuous SNM through the entire filling cycle, (B) second-half stimulation, and (C) first-half stimulation. Real-time data from the MIBP was processed by the CAT algorithm to enable (D) rapid oscillating stimulation and (E) conditional latched stimulation.

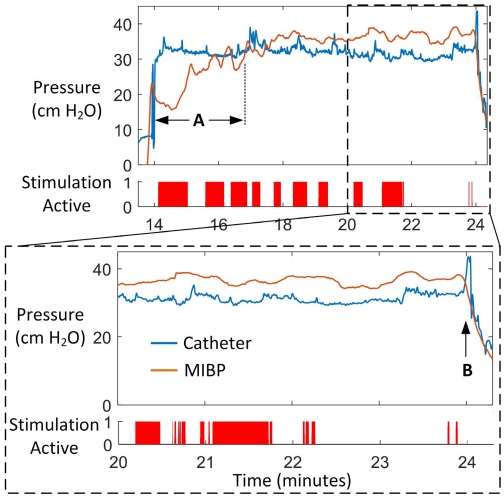

Fig. 9. Example of oscillating stimulation controlled by CAT algorithm. After the pressurization artifact (A), CAT turned SNM on/off automatically. Generally, CAT activated SNM within one second of contraction onset. SNM was disabled manually during voiding (B). Black dashed lines in the top panel delineate data magnified in the bottom panel.

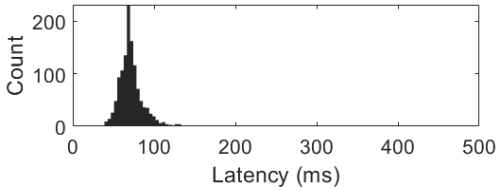

Fig. 10. Stimulation change latency. The latency is the time delay from MIBP algorithm output to change in therapy on the device (median: 70 ms, mean ± std: 72.4 ± 21.2 ms, range: 39–432 ms) (n = 1,224 commands).

issued UDP command to Summit RC+S change in stimulation. Only 18 out of 1,224 stim commands were issued and not executed possibly due to host computer CPU load (1.5%).

E. Impact of Stimulation on Bladder Capacity

Different stimulation paradigms were tested in each animal based on overall response to SNM and on cystometry and catheterization tolerability. Some animals showed reduced bladder capacity due to catheterization as well as increased sensitivity. Due to this sensitivity and time constraints, not all parameters could be meaningfully tested on each animal.

TABLE III
CONDITIONAL SNM BLADDER CAPACITY CHANGES FROM BASELINE, VALUES ARE MEAN [RANGE]

Animal	Continuous	Oscillating	Latched	First Half	Second Half
1	185% [96-367]	167% [75-332]	-	-	318% [307-327]
2	140%*	-	94% [56-146]	-	-
3	135% [78-171]	97% [75-113]	166% [145-208]	89% [53-129]	-
4	136% [89-200]	106% [96-114]	108% [72-154]	63%*	120%*
Pooled Mean	157% (n=32)	147% (n=21)	112% (n=29)	84% (n=5)	268% (n=4)

*only tested in one cystometric trial in this study.

All experiments started with several filling trials without stimulation to determine the baseline bladder capacity. Baseline capacity was calculated as the average of all no-stimulation trials per animal, per day (n = 3-6 per day).

Across four animals all paradigms were tested during cystometry: baseline filling (no stimulation) (n = 54), continuous SNM (n = 32), physiologic first-half SNM (n = 5), physiologic second-half SNM (n = 4), CAT oscillating SNM (n = 21), and CAT latched SNM (n = 29).

Capacity change during stimulation was then calculated for each stimulation trial and represented as a percentage to normalize comparisons between animals. In most cases, each stimulation paradigm was tested 3-10 times per animal. Some paradigms were only tested once in some animals due to experimental time constraints. Cystometry trials with capacity below 50% of the daily baseline were dropped from analysis. As a result, 13 trials were omitted from analysis (2-5 outliers per animal). Average capacity change relative to the mean capacity of the two initial baseline, no-stimulation fills done in each animal to start each test period, was calculated for each stimulation paradigm for each animal. Capacity change was also pooled across animals for each stimulation paradigm and calculated (Table III). One-way ANOVA was used to detect differences in stimulation effects but was inconclusive due to wide intra-animal variance. Therefore, data in Table III are presented without further statistical analysis.

V. Discussion

The primary aim of this work was to demonstrate the feasibility of automatic, real-time activation of sacral neuromodulation based on wireless sensor feedback. Similar paradigms on different pelvic nerves have been previously demonstrated in anesthetized animals [11], [12], [23], [9] and with patients themselves closing the loop [24], but in most cases used either catheter-based pressure data or self-observed sensations to trigger stimulation. To our knowledge, this study is the first to demonstrate a fully wireless catheter-free system using real-time bladder pressure data to automatically trigger SNM from an implanted stimulator. While our approach was limited to conscious animals and required short-range communication to wearable radios and PC software, an integrated system could be developed in future work. Implementation with a wearable external radio—or even with intra-body communication between sensor and stimulator—could improve closed-loop stimulation for bladder control; perhaps similar to the neural reflex pathways which normally provide continence.

Our findings demonstrate technology platform feasibility for real-time, automatic, closed-loop sacral neuromodulation research. The MIBP sensor was sufficiently accurate for this proof-of-concept study. Most critically, the MIBP was easy to insert and extract without anesthesia or analgesia and did not cause any noticeable animal discomfort or urinary tract infections. After the MIBP was extracted, all animals in this study survived without urinary tract complications. In addition, the CAT algorithm was sufficiently accurate to detect voiding contractions in this animal model. CAT performed well in a real-time implementation, partly because the algorithm was designed to be implemented on-chip or in low-power mobile hardware [25].

The Summit RC+S platform demonstrated robust, low-latency performance, generally responding to new stimulation commands faster than 100 ms. Electrode stability was assessed by impedance testing each day and no out of range values were detected. Additionally, motor threshold testing showed minimal change, consistent with the animal model [16].

Throughout filling cystometry, MIBP pressure data varied greatly compared to catheter pressures. MIBP data was only moderately correlated to catheter-measured pressure (median $r = 0.52$). Pressures correlated more strongly on shorter time scales, while occasionally differing greatly in static bladder pressure accuracy (e.g. Fig. 7c,d demonstrated this effect). Interestingly, in some cases MIBP pressure varied widely enough to trigger SNM, while catheter pressures remained relatively smooth. Pressures varied most widely immediately after the initial bladder pressurization, suggesting a physiological basis to MIBP pressure artifact. Because this effect was not seen in bench testing, this could be caused by detrusor contact force on the MIBP. Ultimately this effect limited the pressure accuracy of the device. However, since the CAT algorithm used a self-adjusting threshold, this did not seem to limit system performance after the initial pressurization period.

This study had several limitations which prevent conclusions on the efficacy or mechanisms of different conditional SNM paradigms. First, it was limited to 5 days of observation. Second, conditional SNM was tested on only four animals, and each stimulation paradigm was tested a variable number of times (1-6) per animal. Furthermore, animals in this study showed a wide variation in bladder capacity day-to-day, which might have been caused by repeated catheterizations leading to variability between trials; variability is common for the ovine animal model [16]. Because this was a non-statistically powered, proof of concept study, we cannot statistically distinguish the effects of each stimulation paradigm.

This study used a urologically normal animal model which has been shown to demonstrate increased bladder capacity during continuous SNM [16]. Intermittent, physiologically-timed SNM has also been demonstrated to affect bladder capacity in this continent model [13]. However, conditional neuromodulation could perform differently in the case of an incontinent individual, particularly if incontinence is due to an underlying neurogenic condition, spinal cord injury, or neurodegenerative disorder [9], [15], [26], [27]. Conditional SNM might also be an alternative approach to improve incontinence treatment for these populations, or to reinforce recovery of reflex pathways. The current study provides the proof-of-concept data to justify future research investigating different conditional SNM paradigms in human subjects using the Summit system or similar technology, possibly with individualized tuning of the CAT algorithm to enable personalized therapy.

This feasibility study hinted at a few trends for conditional stimulation. We observed that continuous SNM improved bladder capacity as described previously [16]. This confirmatory finding suggested that programmed settings and sacral lead implant locations were effective. We did not extensively test physiologic paradigms other than to demonstrate they were feasible with this hardware system, but our limited results are consistent with previously published results showing SNM delivered in the first half of the fill cycle is not as effective as SNM delivered during the second-half [13]. Physiologic stimulation based on bladder volume can possibly be implemented through real-time estimates of bladder volume from neural decoding [5], but in this study we timed it based on cystometric fill volume. Finally, this study showed that both algorithm-controlled paradigms were feasible. Outcomes from oscillating and latched paradigms suggested that some animals responded more strongly than others. This could have been due to confounding variables, but might also represent a neurological underpinning, especially as the effectiveness of SNM in general varies between individuals [28], [29]. Future research with greater statistical power could quantify the efficacy of conditional SNM for improving bladder capacity.

VI. Conclusion

This study demonstrated the feasibility of automatic, conditional sacral neuromodulation of the bladder using a research platform. This feasibility study demonstrated several neuromodulation paradigms which were enabled using continuous, catheter-free measurements of bladder pressure from an implanted sensor. A real-time algorithm allowed sub-second, automated decision making for when to start and stop neurostimulation based on detected bladder contractions. Future research could focus on quantifying the efficacy of different stimulation paradigms on specific urologic conditions. Chronic

demonstration of closed-loop stimulation is also an important next step in the validation of this approach.

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