Update on a 12-Channel, Laboratory, Neuroprosthetic Platform for SCI: Respiration, Urinary, and Muscle Disuse Atrophy Applications

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Abbreviations
SCI-spinal cord injury
DBWS-direct bladder wall stimulation
NOAB-neurogenic overactive bladder
FES-functional electrical stimulation
DSD-detrusor-sphincter-dyssynergia

Abstract:

The NeuRx® Diaphragm Pacing System (Synapse Biomedical Inc, Oberlin, Ohio) is used by individuals with tetraplegic spinal cord injury and includes Permaloc® electrodes that are placed on the ventral side of the diaphragm to stimulate the phrenic nerve for respiration as a functional electrical stimulation (FES) intervention. A new 12-Channel, Laboratory, Neuroprosthetic Platform is being developed as a collaborative effort between Synapse Biomedical Inc and our neuroprosthetic Laboratory at Hines VA Hospital Research Service. Several types of electrodes are in development for the platform: surface electrodes, Mapping Electrodes, Modified Intramuscular Electrodes, Suture Electrodes, a Multi-Lead Cable with Connectors. Multiple FES applications are being proposed: adding extradiaphragmatic muscles to diaphragm pacing for improved respiration and cough, urinary control using direct bladder wall stimulation and neuromodulation of the pudendal nerve, and management of muscle atrophy to reduce the risk of pressure ulcers. Thus, this new platform is reviewed for FES approaches and applications, device development and current results; future work is proposed.

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Introduction:

SCI inhibits physiological activity of multiple muscle groups, the number of which depends on the extent of the spinal cord injury. Thus, the amount of disuse muscle atrophy that occurs in these patients varies from minimal to potentially complete loss of function in multiple muscle groups including somatic and visceral. As a result, SCI patients may suffer from respiratory, bladder, and somatic muscle dysfunction that renders them dependent on mechanical ventilation and urinary catheterization along with the high risk for chronic decubitus sacral and other skin ulcers [1-3]. To restore function and improve quality of life, functional electrical stimulation (FES) programs for central and peripheral nerves have been developed. Neuroprosthetic platforms are developed to deliver FES interventions [3].

The NeuRx® Diaphragm Pacing System with Permaloc® Electrodes is a neuroprosthetic platform with an FES application that is used in quadriplegic SCI patients. The electrode is an intramuscular barb type with a polypropylene anchor; the electrode evolved from the original Peterson Intramuscular Electrode used for diaphragmatic pacing in quadriplegic SCI patients at Case Western Reserve University and Cleveland Veterans Administration FES Center [4]. The NeuRx® system was commercialized by Synapse Biomedical, Inc. in Oberlin, Ohio [1,5] and uses four Permaloc® electrodes implanted in the diaphragm and a fifth electrode implanted under the skin as a return electrode for monopolar stimulation. All five electrode leads pass through the skin at separate exit sites that are situated close together, and are connected to a small, battery-powered external stimulator, the NeuRx® Diaphragm Pacing System. Successful respiratory pacing with this system has been reported in over 100 SCI patients with up to ten years of use [1,5].

Hines VA Hospital Research Service in collaboration with Synapse Biomedical Inc. is developing a general-purpose platform for FES**,** a 12-Channel, Laboratory, Neuroprosthetic Platform. Stimulation is driven by a computer-controlled device delivering biphasic pulses with adjustable current amplitude. The stimulation parameters are customized for each application [6,7]. Several new and established types of electrodes are proposed for the platform: *One*, a Mapping Electrode for identification of effective chronic implant sites; *Two*, Modified Intramuscular Electrode with adjustment to the location of

the securing barb for urinary applications; *Three*, a Suture Electrode that has a long exposed stimulating wire to stimulate more nerves and a long needle at the end of the electrode for implantation; and, *Four*, Multi-Lead Cable with Connectors for up to five separate electrode leads.

Promising results are being shown with the new platform in animal studies. Surface or implanted electrodes stimulating extradiaphragmatic muscles leads to large respiratory responses [6,8-11]. Bladder emptying with Modified Intramuscular and related electrodes has been demonstrated [7,12,14], and FES for muscle maintenance is a promising application shown by others [3,15-17]. Thus, the new laboratory neuroprosthetic platform warrants further research to provide assistive technology to those with SCI.

Development of the 12-Channel, Laboratory, Neuroprosthetic Platform

There are many facets to the new platform. The use of surface electrodes is always promising as they are noninvasive. Implanted electrodes are conducted with only a needle or laparoscope techniques [6,7]. Twelve channels of stimulation will allow for multiple FES applications. A new multi-lead cable will limit the number of cables passing through the skin [6,7].

The following list summarizes the devices under development for the 12-Channel, Laboratory, Neuroprosthetic Platform. Figures 1, 2, and 3 show the stimulator settings as well as the various proposed electrodes, cables and connectors:

1. Surface Electrodes (Not Shown): Multiple commercial surface electrodes can be used with this platform. Surface electrodes will be tested first in extradiaphragmatic respiratory and lower limb muscles before considering sites for chronic electrode implantation.

2. Mapping Electrodes (Figure 1A): These electrodes are supplied by Synapse Biomedical Inc and are implanted with a 19-gauge needle. They are proposed for mapping effective sites for implantation [6].

3. Modified Intramuscular Electrode (Figure 1B): This electrode is similar to Permaloc® electrodes. The modification is to attach the self-securing polypropylene anchor at the edge of the Teflon® insulation to expose all of the stimulating wire on the outside of the anchor [1]. This modified electrode is proposed for urinary applications.

4. Suture Electrodes (Figure 1C): This electrode has 5 to 10 cm of exposed stimulating wire surface as needed to stimulate multiple nerves and muscles and has the polypropylene anchoring barb on the end. The

electrode implantation needle, on the right in the figure, is shown attached to the end of the exposed stimulating wire, dashed line in figure, just distal to the polypropylene securing barb. The needle is cut off after implantation leaving the stimulating wire and barb for a secure implant. The length of exposed wire and length and radius of curvature of the insertion needle can be adjusted as needed for different applications including stimulation of diaphragmatic, abdominal respiratory, and upper thoracic respiratory muscles as well as the lower limb muscles.

5. Multi-lead Cables and Connectors (Figure D1 and D2): This device can be implanted or used externally and the multi-lead cable can connect the stimulator to as many as five electrode leads. Connectors are FDA approved devices (Synapse Biomedical Inc) and consist of a spring applied to pins at the ends of their electrodes and stimulator leads, are electrically isolated by placing them inside Silastic tubing and closing the ends of the tubing with ties. The multi-lead cables and connectors is expected to be used in all proposed applications.

6. Twelve-Channel Laboratory Stimulator (Figure 2 and 3): The computer-controlled 12-Channel Stimulator produces a maximal stimulating current of 100 mA for each channel [6,7]. It uses standard push-pull amplifiers to generate electrically isolated biphasic stimulating waveforms with equal positive and negative charge injections and can deliver appropriate pulse-durations appropriate for each proposed application. Stimulating parameters are selectable, and all twelve channels of stimulation are selectable for each application.

The New Neuroprosthetic Platform for Respiratory Pacing and Cough

Approximately 4% of the 12,000 new SCI patients each year are ventilator-dependent [1,5]. Diaphragmatic pacing with the current NeuRx® Diaphragm Pacing System is an alternative to mechanical ventilation, and early implantation of this system after SCI improves patient-outcomes including percent obtaining 24 hour pacing. Also, the system is now approved for respiratory pacing in amyotrophic lateral sclerosis patients [1,18]. Diaphragmatic pacing is a laparoscopic, minimally invasive two-step procedure. First, the diaphragm is mapped using a laparoscopic dissector (Maryland type, a surgical instrument similar to forceps that is electrically insulated to the tip) is placed against the abdominal side of the diaphragm. Presence of an intact phrenic nerve is confirmed by a strong downward movement of the

diaphragm during stimulation. The best implantation location is determined by the strongest diaphragm-contraction. Next, two Permaloc® Electrodes are implanted at a maximal stimulation site in each hemi-diaphragm. Implantation of multiple electrodes provides an important safety factor for life-supporting chronic diaphragmatic pacing because if one electrode should fail the second electrode and hemi-diaphragm are still intact to sustain ventilation. A useful YouTube video of detailed methods of implanting electrodes in the diaphragm of patients is available [18].

One possible limitation of placing two short 1.2 cm electrodes near each other on the diaphragm is that some branches of the phrenic nerve in the diaphragm may not be stimulated [19]. To address this issue a trans-mediastinal approach for placement of Permaloc® electrodes directly on the phrenic nerve in the chest demonstrated high tidal volumes in animal models [20]. As another alternative, implantation of the Suture Electrode (Figure 1C) is proposed on the abdominal side of the diaphragm muscle, similar to current methods, but over a distance of 5 to 7 cm parallel to the central tendon. The Suture Electrode for this application should have a short needle with a small radius of curvature so that the stimulating wire can be woven across the diaphragm muscle at approximately 5 mm intervals. The Suture Electrode will be tested for improve diaphragm recruitment and reduction of the total number of electrodes that must be implanted [1,5].

Aside from direct diaphragmatic stimulation, improved respiratory function occurs with the simultaneously recruitment of extradiaphragmatic, upper-thorax inspiratory, and abdominal expiratory muscles. For cough, abdominal muscle recruitment is an obligatory requirement to produce the high pressures and volumes required for cough. Clinical [21-28] and preclinical [8,9,29] studies stimulating accessory muscles of inspiration and abdominal muscles for cough have used either spinal epidural electrodes or, in the periphery, implanted and surface electrodes. Though large respiratory volumes have been induced, none of the methods are currently available commercially.

The new neuroprosthetic platform has been tested for extradiaphragmatic respiratory muscle-stimulation using peripheral electrodes, both surface and implanted. In moderately sized canines during hyperventilation induced respiratory apnea, abdominal muscle stimulation was

conducted with four bilateral sets of Permaloc® Electrodes implanted 4 cm dorsal to the abdominal lateral line at the eighth thoracic to the first lumbar interspace [6,10,11]. Pacing at 50 Hz with 100 mA of stimulating current per stimulating channel induced expiratory volumes of 153 ± 20 mL (n = 4). Similar volumes were induced with surface electrodes in the same locations. In larger canines larger expiratory volumes of 300 to 400 ml were induced with similar electrodes and stimulation parameters (*manuscript in preparation*); such large expiratory volumes are suitable for respiration and cough in large canines. Importantly, simultaneous channel stimulation induced nearly 100% greater expiratory responses than with staggered channel stimulation. Given that maximal expiratory responses with surface and implanted electrodes were similar, surface electrodes should be tested first. One limitation of abdominal respiratory muscle stimulation with implanted electrodes is the need for eight electrodes. The proposed Suture Electrode should help resolve this limitation with fewer electrodes needed to cross multiple intercostal spaces (Figure 1C). the electrode design for this application should include long exposed stimulating wire and a long implantation needle having a radius of curvature large enough to cover the required distances.

In the upper thorax, four bilateral sets of Permaloc® Electrodes were implanted 4 cm ventral to the axilla from the second to the fifth intercostal spaces in moderate size canines and induce large inspiratory volumes of 310 ± 41 mL (n = 4) [6] at 60 to 100 mA current. More recent experiments in larger canines produced inspiratory volumes of 250 ml to 350 ml (*manuscript in preparation*). As with abdominal respiratory muscle stimulation, a limitation was use of a large number of implanted electrodes; as already discussed, the Suture Electrodes should address this concern. Work in our laboratory is also demonstrating effective methods of upper-thoracic stimulation with surface electrode to produce adequate volumes without adverse forelimb movements. In another area, extradiaphragmatic muscle stimulation increases metabolic demand and oxygen use. Simultaneous stimulation of antagonistic respiratory muscles, such as the internal and external intercostal, not only increases metabolic activity but will actually reduce tidal volume. Thus, metabolic studies of oxygen use during extradiaphragmatic muscle pacing are needed to evaluate the metabolic demand of non-specific muscle

activation with the benefit of increased ventilation during respiratory muscle pacing [6].

The New Neuroprosthetic Platform for Inducing Effective Emptying of the Urinary Bladder and Incontinence Management

A major source of morbidity for patients with SCI includes bladder and renal pathology that is primarily associated with the use of catheters [2,30]. Thus, several different types of neuroprosthetic platforms are being developed for urinary management including devices that must control both voiding and incontinence [3,7,31-33]. A commercial device in this area is the sacral anterior root stimulator (Vocare Finetech-Brindley System) [31-35]. A recent clinical review of the sacral stimulation method concluded that most SCI individuals obtained catheter-free daily voiding without the side effect of incontinence or infection [31]; however, this method requires invasive surgery that entails two different vertebral laminectomies as well as bilateral sacral root afferent neurectomy and implantation of bilateral electrodes on sacral motor nerve roots [7]. Sacral root afferent neurectomy is also a concern because it compromises or completely eliminates bladder, bowel, and sexual reflexes. Bowel and bladder emptying are usually restored with stimulation but erectile sexual function is seldom reestablished. Thus, it is important to develop methods for inducing bladder emptying that do not require bilateral sacral root afferent neurectomy.

Studies from our laboratory demonstrated that sacral root stimulation in chronic SCI felines with intact sacral roots did not induce post-stimulation voiding [36]. In these studies, a thoracic SCI had been created four-months previously, and Interstim® electrodes (Medtronic Inc. Minneapolis, MN) were implanted in the sacral canal at the time of SCI. The sacral root stimulation produced high bladder pressures with little or no voiding. Recordings from the skeletal urethral sphincter revealed contractions both during and after stimulation that prevented voiding. We further demonstrated that this adverse high urethral resistance before and after stimulation was caused by the period of stimulation. This was determined based on results with direct bladder wall stimulation (DBWS) conducted in the same animals using wire hook electrodes implanted in the wall at the time of testing. DBWS stimulation not only induced high bladder pressures but also produced effective voiding both during and after stimulation; the adverse urethral contractions seen with

sacral root stimulation were not present with DBWS. We conclude that in this SCI animal model sacral-nerve-root stimulation leads to ineffective post-stimulation voiding and that DBWS is a more effective neuroprosthetic approach [36].

Six early clinical studies of DBWS involving a total of 30 patients, many of whom had SCI, used four implanted electrodes of various types on the bladder wall [38-42]. In several patients daily voiding was induced with stimulation, but surprisingly in a few subjects the return of micturition control occurred and this subset of patients did not need to continue DBWS. The problems encountered in some patients included electrode migration, patient discomfort, and high urethral resistance. Follow-up studies in 1976 and 1986 by Magasi, et al addressed some of these concerns [43,44]. Their implanted stimulator (PMS-3-Electrical-Vesical-Stimulator®, Physico-Medical Inc, Canada) included eight platinum-iridium disk electrodes sutured to the bladder wall. Magasi, et al enrolled 32 patients using daily catheterization; of these, 21 had peripheral neural injuries and eleven had central injuries, the majority of which were localized to the spinal cord. Stimulation frequencies used were 30 to 40 Hz and current amplitudes increased until voiding started and continued until voiding stopped. Repeated stimulations were needed in some cases but daily voiding was induced in all 32 patients over a one-to-two-year period. High urethral resistance during bladder contractions due to proximal urethral closure, presumably caused by increased sympathetic activity, was a problem in three patients; these patients were managed by proximal urethral resection that allowed effective voiding with stimulation. These favorable outcomes were attributed to implantation of more electrodes and assurance that electrodes close to the ureters and neurovascular bundle were functioning.

No further clinical DBWS studies have been conducted since those by Magasi, et al and our experience strongly suggests that further studies in animal models and patients are warranted [7,36]. The pivotal studies demonstrating advantages of DBWS compared to sacral anterior root stimulation were published in 1992 [36]. Between 1993 and 1999, our laboratory conducted animal model studies utilizing woven-eye and suture-electrodes on the bladder wall [45-47] and in 2005 reported on bladder wall stimulation using microstimulators [48]; in 2008 we tested hook electrodes in the bladder wall [12]. Animal models used in these studies included acute and chronic felines with either intact nervous systems or with upper or lower motor

neuron lesions; similar acute studies in canines were also conducted. In these animal studies, DBWS stimulation induced high bladder pressures with minimal side effects.

More recent work from this laboratory, 2012, however, was less promising [13]. Seven female swine were investigated under anesthesia with four bipolar Permaloc® Electrodes implanted as two bilateral sets of electrodes on the bladder wall. Using 40 mA of current only 10 ± 2 cm H_2O peak bladder pressure was obtained. The likely cause of this poor response was the animal model, as swine bladders showed no contractions during cystometric filling up to 500 ml. Perhaps, in swine, the anesthetic Isoflurane that we used prevented contractions. Because of our concern with anesthesia and the requirement for high cystometric volumes before bladder contractions in swine, we concluded that future studies should be conducted in feline or canine models [7]. Another limitation of this most recent study was that we used four electrodes with a short separation distance of 5 mm between bipolar sets of Permaloc type electrodes; Magasi et al, in contrast, used more electrodes with wider electrode separation in their successful clinical DBWS studies. Future DBWS animal studies should use the Modified Intramuscular Electrodes that have the entire wire-stimulating surface on the outside of the polypropylene barb (Figure 1B). This will allow for close apposition of the electrode stimulating wire to the bladder innervation and should be compared to the Magasi's disk electrode. Future DBWS studies also should include optimization of stimulation-parameters such as pulse duration, current amplitude, and stimulation frequency [45-47].

Detrusor-sphincter-dyssynergia (DSD) produces high urethral resistance during bladder contractions and is another complication for SCI patients that must be managed in a DBWS program [7]. DSD results from the loss of pontine micturition center control, due to the spinal cord injury, that normally elicits sphincter-relaxation during voiding. Two different urethral muscles can cause these unwanted urethral contractions: proximal urethral smooth muscles or distal skeletal muscle sphincter. Currently, when unwanted skeletal urethral sphincter contractions occur there are two available clinical interventions: *One*, sphincterotomy involves incisions of the skeletal urethral sphincter to reduce urethral resistance, but this method greatly increases the risk for stress-urinary incontinence, impotence, urethral stricture, and urinary tract infections [2, 49-51]; *Two*, botulinum toxin injections into the urethral skeletal sphincter

to paralyze the sphincter [2,52,53]. For the proposed DBWS programs we plan to utilize botulinum toxin-injections as the first line therapy for DSD. Repeat botulinum toxin-injections at 6 to 9 month intervals may be needed, but, if daily voiding is achieved then the inconvenience is worthwhile as it avoids catheterization. DSD caused by proximal urethral smooth muscle contractions involves sympathetic nervous activation and reflex activation of the sphincter [2]. Three interventions are currently available for management of sympathetic DSD: *One,* alpha-1 receptor blocking medication [54]; *Two*, botulinum toxin injections into the proximal urethra and bladder neck; and, *Three*, proximal urethral resection or combined bladder neck and proximal urethral resection [43,44]. In the DBWS studies by Magasi et al [43,44] only three patients had DSD complications warranting similar treatments because incision of the proximal urethra provided effective management for most. For the proposed DBWS program, treatment of sympathetic DSD should include the three interventions with alpha-blockers as the first line approach and botulinum toxin and proximal urethral resection as secondary.

The third lower urinary tract complication following SCI is neurogenic overactive bladder that causes urinary incontinence; management of NOAB involves methods for inhibition of bladder contractions [2,55,56]. An important criterion for appropriate bladder inhibition in DBWS programs is that inhibition can be stopped for induction of voiding. Neuromodulation meets these condition and several methods are currently available. Dorsal penile nerve stimulation with both surface and implanted electrodes is in clinical development [3] and sacral and pudendal nerve stimulation with small implanted electrodes (Medtronic) is commercially available. Limited success for bladder inhibition with Interstim in SCI patients has been reported following unilateral stimulation and when starting neuro-modulation late after SCI. In contrast, bilateral stimulation early after injury has demonstrated effective long-term management of NOAB and incontinence [57,58]. Finally, in three SCI patients, Interstim electrodes sutured bilaterally to the pudendal nerve demonstrated profound inhibition of bladder contractions [33]. The new neuroprosthetic platform is being developed for bilateral pudendal nerve stimulation and neuromodulation. Preliminary testing in this area with Permaloc® Electrodes were complicated by current spread and leg muscle-contractions [14]. Modified Intramuscular Electrodes (Figure 1B) are expected to perform better because stimulating

wires can be implanted closer to the pudendal nerves. Further optimization of neuromodulation should include a comparison of ON-and-OFF duty-cycles to continuous programs, stimulating currents, and stimulating frequencies [3,33].

The Neuroprosthetic Platform for Maintenance of Skeletal Muscles

Atrophy of skeletal muscles is a serious complication for SCI patient that increases the risk of pressure sores and deep vein thrombosis; [59-61]. This most commonly occurs in the buttocks, or gluteal muscles, and leg muscles. An important goal of electrical stimulation of these muscles has been maintenance of muscles or restoration of muscle function. Effects of electrical stimulation therapy on leg muscle atrophy can be measured by leg girth and ultrasound measurements of muscle volume. Successful muscle maintenance occurs when initiation of the stimulation program occurs within one year of SCI [15-17,62]. After one year of chronic muscle disuse and atrophy, actin and myosin proteins in myofibrils become disorganized and are not easily restored physiologically even with electrical stimulation [63].

Leg muscle stimulations can be either isometric or isotonic: for isometric contractions both extensors and flexors are activated simultaneously with limited limb movement. A beneficial practical feature of this approach is that no additional devices beyond the stimulator and electrodes are required. When isotonic leg movement is used, resistance devices such as weights or cycling devices are necessary. One previous study found that isometric contractions of hand and wrist muscles soon after SCI did not prevent muscle atrophy [64]; however, these investigators used low stimulating currents and infrequent stimulation-periods that may have limited efficacy. In contrast, isotonic stimulation early after SCI using leg cycle ergometry and high stimulating currents prevented development of leg muscle atrophy [15-17,65]. Another application of the same technology is intermittent electrical stimulation for pressure-ulcer prevention with 10 sec of stimulation applied every 10 min that leads to pressure redistribution and increases tissue oxygenation [3]. Clinical outcomes have been promising for decreasing the risk of pressure-ulcers; however, restoration of gluteal and leg muscle mass has, thus far, not been demonstrated [3]. Given the limitations of prior SCI stimulation studies to manage disuse-atrophy of skeletal muscles, isometric stimulation methods with more frequent stimulation periods and greater stimulation currents warrant further

investigation [64,65]. The new Neuroprosthetic Platform is promising for these applications because of the large number of available stimulation channels and high maximal stimulating currents that can be produced. This application should start with surface electrodes and can be followed by use of implantable Suture Electrodes (Figure 1C), if warranted.

Technology Transfer for the New Neuroprosthetic Platform

Important collaboration for this program includes Synapse Biomedical Inc, our Neuroprosthetics Laboratory at Hines VA Hospital and the Veterans Administration, which has funded this research. Synapse Biomedical can provide the Neuroprosthetic Platform to any group doing research in this area [6,20]. Plans for testing the platform in acute animal models are highlighted above. Additional chronic animal studies will be necessary in order to demonstrate long-term effectiveness of these devices. Clinical trials will also be needed to obtain Food and Drug Administration approval for comer-cialization. Fortunately, modifications to devices currently in clinical use should expedite progression through regulatory pathways.

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Electrodes for the Neuroprosthetic Platform

A. Mapping Electrode

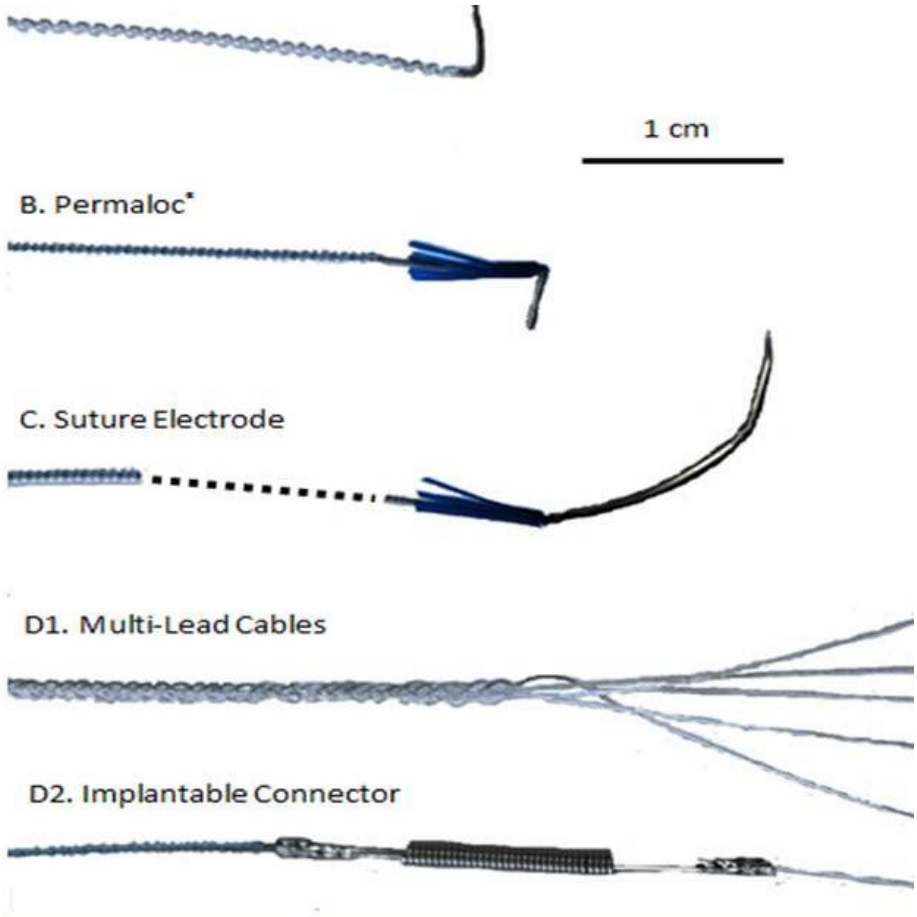

Figure 1. Electrodes current used and in development for the Neuroprosthetic Platform. **A.** Mapping Electrodes are used for locating effective implant sites and have 1 cm of deinsulated helical wire serving as the stimulating surface distal to the right angle bend. **B.** Commercial Permaloc® Electrodes are currently used in SCI patients for diaphragmatic pacing. One cm of helical stimulating wire surface is shown starting 2 mm distal to the polypropylene anchoring barb and extending for 5 mm from the barb. A modified Intramuscular Electrode (not FDA registered) is proposed for urinary applications; the anchoring barb will be moved to the insulated part of the electrode thereby exposing the entire stimulating wire. **C.** Suture Electrodes are used for chronic implantation for respiratory assistance and mitigation of muscle atrophy. The polypropylene barb is next to the implantation needle; dashed line represents variable length of deinsulated stimulating surface. **D1.** Multi-Lead Cable separating distally into five connectors for attachment to electrode leads; not shown on the left is the cable containing a wire from each distal lead, thus allowing for connection to five channels. **D2.** Spring Connector situated between cable leads and electrode; Silastic tubing that covers the spring connector and also provides electrical insulation is not shown. All devices by Synapse Biomedical Inc.

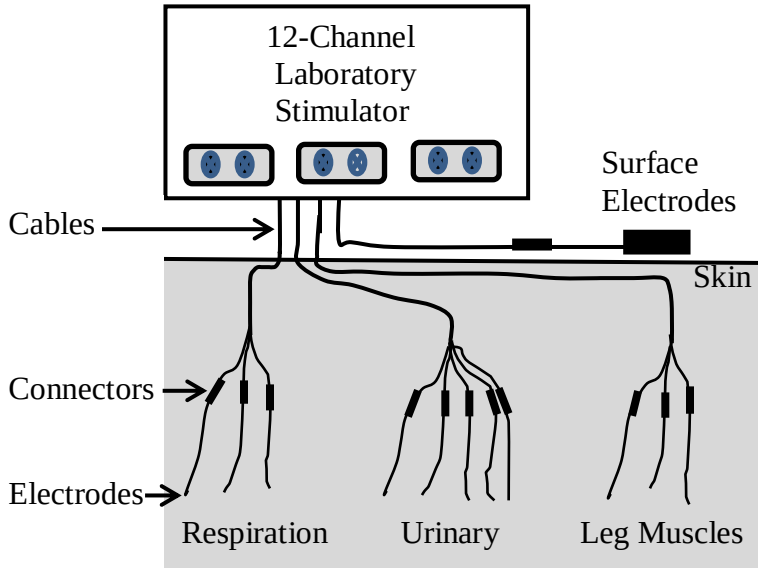

Figure 2. New Neuroprosthetic Platform with computer controlled 12-Channel Laboratory Stimulator and three Multi-Lead Cables with connectors for surface or implanted electrodes. Proposed applications for different organs as well as cable leads that pass through the skin are shown. The number of electrodes needed for each application varies and leads within one cable can be used for different applications.

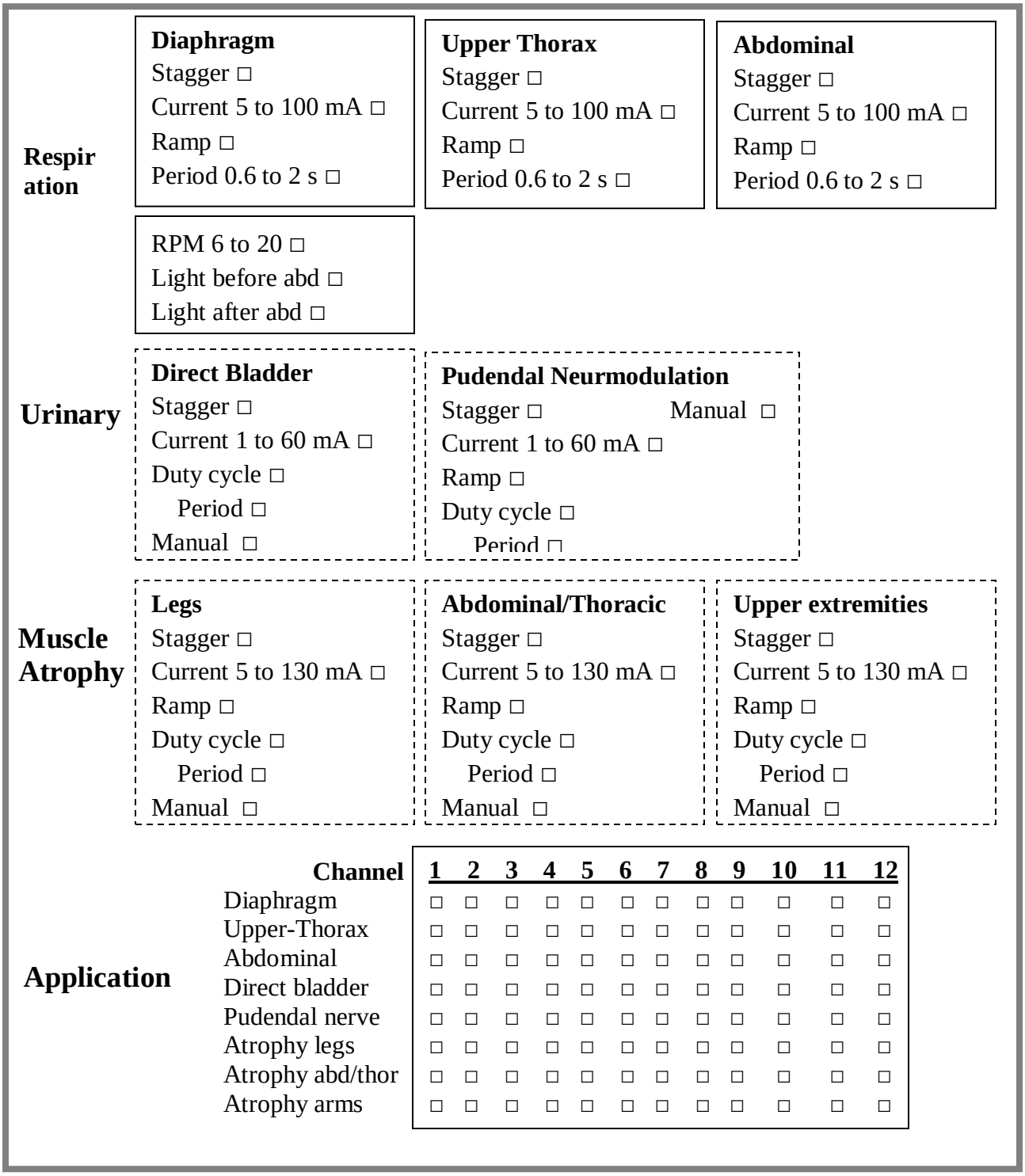

Figure 3. Computer "screen-shot" of settings for the 12-Channel Laboratory Stimulator with selection areas for the three applications. Selection boxes include yes and no answers or a selection of current or stimulation periods. In the 'Application and Channel' area, all channels are available for each application. The urinary and disuse atrophy area are shown in dashed boxes to indicate that they are in development.