Active Implantable Device for Erectile Dysfunction

Garrett Corcoran and Ryan Peck
University of California, Berkeley
Electrical Engineering

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Abstract

Erectile dysfunction affects a large portion of the population but is not a life threatening condition. For this reason, publicly available research papers on treatment methods are lacking, even though the technology is available in private industry. In this paper, we will discuss an active implantable medical device to treat erectile dysfunction. We will start with a discussion of the types of erectile dysfunction we aim to treat and current methods of treating erectile dysfunction. Then, we will use patents on similar devices and research papers on stimulation techniques to create a feasible device design. We will show that such a device is possible to create with existing technologies and implantation procedures. It is our hope that collecting this information outside of industry will be helpful to future researchers and the further improvement of erectile dysfunction treatment.

1 Introduction

1.1 Erectile Dysfunction

Erectile dysfunction (ED), the inability to maintain an erection sufficient for sexual intercourse, affects about 50% of men in some capacity by the time they are 60 years old [1]. This condition, while not by any means fatal, has the potential to greatly decrease the quality of life for men who suffer from it, as they lose an important way to connect with their spouse or partner as well as a source of confidence. The following lists classifications of ED [2].

1. Organic
    - 1.1. Vasculogenic
        - 1.1.1. Arteriogenic
        - 1.1.2. Cavernosal
        - 1.1.3. Mixed
    - 1.2. Neurogenic
    - 1.3. Anatomic
    - 1.4. Endocrinologic
2. Psychogenic
    - 2.1. Generalized
    - 2.2. Situational

Vasculogenic ED is caused by insufficient blood flow into the penis (arteriogenic), a failure to keep blood in an erect penis (cavernosal), or both. Anatomic ED is caused by structural damage to the penis. These types of ED would not be able to be treated by our proposed device, since that device would rely on the body's natural blood flow and penile structure in order to function. Psychogenic ED, which most men with ED at least partially suffer from, provides a very promising use case since the anatomy in many of these cases is entirely intact and the afflicted population is so large [3]. However, neurogenic ED is the type of ED studied in most of the prior work we review [4, 5].

It is estimated that 10 to 19% of ED is of neurogenic origin, with the large range being attributed to the difficulty doctors encounter in confirming that a patient's ED does not stem from another cause as well as neurogenic [3]. Neurological diseases such as Parkinson's can cause ED in a patient, as can spinal cord injuries. Prostatectomy procedures frequently result in damage to the pelvic plexus, which in turn causes impotence in the patient. The incidence of impotence from various pelvic procedures has dropped from 100% to 30-50% as a result of improved surgical procedures, but this can also be helped by implanting a device which could counteract that nerve damage by providing stimulation to those potentially damaged nerve sites [6] Neurogenic ED presents another viable opportunity for an active implantable device, as it can be solved by well-placed stimulation.

1.2 Current Treatments

Many implantable devices exist on the market today to treat ED, the most established being implantable inflatable pumps and semi-rigid rods that go inside the penis to assist in erectile function [7, 8]. It should be noted, however, that these devices merely assist the penis in holding its erect shape but do not increase sexual pleasure on their own. The pump implant involves a very invasive procedure, replacing existing tissue, and the semi-rigid rod implant results in a penis that is always somewhat erect. While these devices have been very successful in the marketplace, the experience is not completely natural. With an active implantable device, a stimulation procedure can start the natural chain of events that leads to an erection, resulting in a natural erection with all of the associated sensation.

Other treatments for ED include oral medications such as Sildenafil, Tadalafil, Vardenafil, and Avanafil [9]. These medications work by increasing the response of vascular muscles in the penis to nitric oxide released by the penile nerves upon stimulation. These drugs could potentially increase the effectivity of an active implantable device since that device would be stimulating the release of nitric oxide. Other alternatives for various forms of ED include injectable drugs, testosterone supplements, penile pumps, and counseling. All of these suffer from drawbacks including requiring significant time to take effect and additional stimulation for full functionality.

1.3 Proposed Treatment

Here we propose a device that stimulates the cavernous nerves of the penis to produce an erection. It has been proven that non-invasive, external magnetic stimulation of the cavernous nerves is effective in producing both an increase in intracorporeal pressure and a full penile erection in both healthy patients and those suffering from neurogenic ED [5]. Invasive, internal stimulation has also been proven effective in both humans and rats [4, 10]. In fact, US patents exist for a device very similar to the one we propose [11, 12, 13, 14, 15, 16, 17, 18]. We intend to design an externally controlled implantable device which stimulates the cavernous nerves using electrodes. Figure 1 illustrates the anatomy of the nervous system surrounding the penis including the cavernous nerves. The location of the cavernous nerves is at a shallow depth beneath the skin, so the implantation of a device there will be a relatively uncomplicated surgery. The figure also shows that the cavernous nerves are downstream from the pelvic plexus. Damage to the pelvic plexus due to a prostatectomy, as mentioned in the prior section, would interfere with the body's ability to send a signal to the cavernous nerves but would not affect the ability of the cavernous nerves to function if they are stimulated by an implantable device.

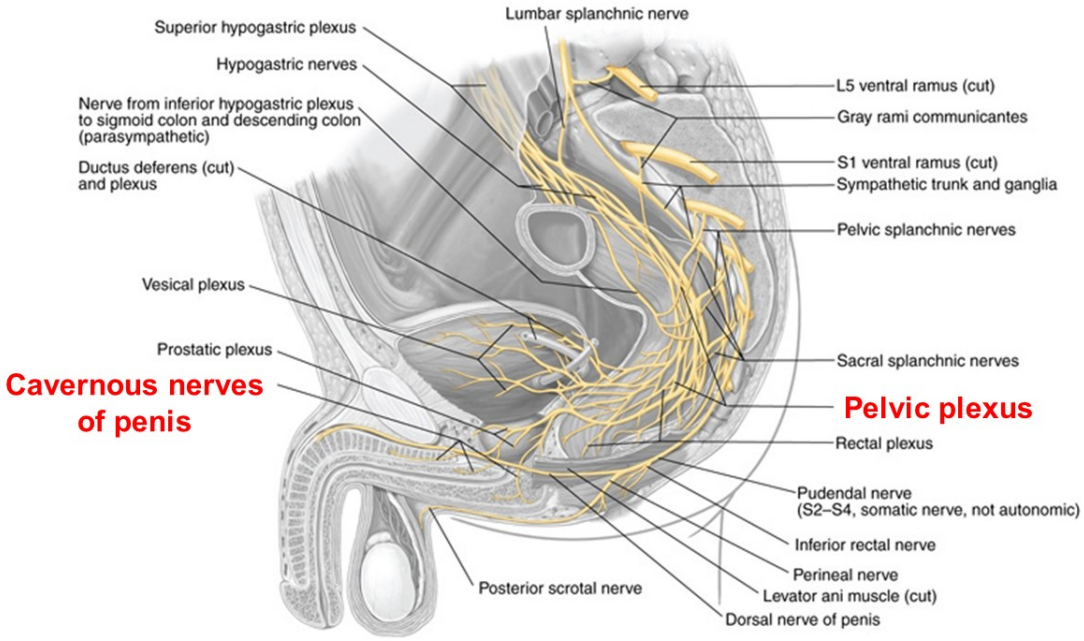

Figure 1: Anatomy of the nervous system surrounding the penis including the pelvic plexus and cavernous nerves [19]

2 Results

The following table shows a summary of the parameters of our device. Our methods for arriving at these parameters will be presented in the following sections.

Parameter	Value
Electrode Material	Platinum
Electrode Type	Cuff
Cuff Inner Diameter	2 mm
Number of Contacts	2
Electrode Configuration	Bipolar
Contact Dimensions	100 μm $\times$ 3 mm
Stimulation Current	1.5 mA
Stimulation Frequency	60 Hz
Stimulation Pulse Width	160 μs
Stimulation Configuration	Balanced Biphasic
Biphasic Delay	50 μs
Power Consumption	144 μW
Battery Type	Lithium-Ion
Battery Size	31.42 mm^3
Recharging Method	Inductive Coupling
Recharging Time	$\approx$ 7.5 min
Communication	Backscatter

Table 1: Device parameters

3 Methods

The efficacy of using a bipolar platinum cuff electrode to stimulate the cavernous nerve and induce erection has been shown in humans [4]. This study, however, failed to mention several important factors such as surgical procedure, stimulation parameters, power requirements, and justification for electrode design. A recently published guide on the stimulation of the cavernous nerve in rats will help provide some of this information. Another paper provides stimulation parameters and discusses the surgical procedure in rats [10]. Patent literature discusses device and electrode sizing, but frequently does not mention communication. By combining these sources and industry standards for safe stimulation, we hope to outline a modern device for human use in greater detail than previously done.

3.1 Electrode Sizing and Materials

Several constraints need to be considered in choosing the proper electrodes to be used in this application. The cavernous nerves are relatively small compared the nerve sites targeted in most peripheral nerve stimulation applications, so we will need to choose a small electrode. In a study on the selectivity of three different types of stimulating electrodes - transverse intrafascicular multichannel electrodes (TIME), longitudinal intrafasicular multichannel electrodes (LIFE), and cuff electrodes - it was was shown that cuff electrodes require higher current (800 μA for cuff vs. 300 μA for TIME and LIFE) to stimulate particular fascicles within a rat sciatic nerve due to the greater distance separating the electrode poles and the fascicle [20]. However, the cavernous nerves of a human are much smaller in diameter than the rat sciatic nerve, so the nerve tissue thickness that the stimulation needs to overcome will not be as great of a consideration for this application. The main concern with stimulating through tissue is the skeletal muscle between the nerve and the inner diameter of the cuff, since the cuff will not wrap flush around the nerve. Additionally, cuff electrodes reside on the periphery of the nerve rather than being implanted straight through it, so the cuff electrode is a less invasive option which reduces the risk of nerve damage. Due to the small diameter of the human cavernous nerves, we will utilize a small cuff electrode, 2 mm in diameter and with two 100-μm x 3 mm leads (one stimulating and one reference) in a bipolar configuration which will provide adequate charge for stimulation, as will be explained in the Power Requirements section.

Aside from the spatial and mechanical design of the electrode, proper materials must also be considered. In choosing proper implanted electrode materials, tissue response, allergic response, electrode-tissue impedance, and radiographic visibility are the four most important criteria to consider [21]. It is easy to eliminate materials such as silver, copper, and nickel based on the tissue and allergenic responses, since the former two are known to be highly toxic and the latter is known to be highly allergenic [22]. The electrode-tissue impedance is the criteria we are most interested in designing for in this investigation. It is dependent on the temperature and tissue type in the surrounding environment, the selected material, and the surface area of the electrode. We can control the latter two of those four constraints, while we know the surrounding tissue is going to be held at a relatively constant 37° C, and the resistance of the surrounding skeletal muscle is known. Of the materials presented in table 1 in Geddes's 2003 study [21], platinum-black and its alloys have the highest capacitance by more than one order of magnitude. Capacitance values for platinum-black range from 4,950-149,700 μF/cm^2 depending on its density and what materials it is alloyed with. However, platinum-black is also expensive and more of an experimental material, so it would not be a good choice for a commercial product such as the one we are attempting to propose here. Stainless steel and platinum have the highest capacitance of the remaining materials discussed in Geddes which aren't toxic, with capacitance of 161 μF/cm^2 and 21.6 μF/cm^2, respectively. Platinum is ranked higher on the list of favorable immune responses given in Geddes than stainless steel, making it the best material for stimulation despite its lower capacitance value. We can afford to have slightly lower material capacitance because the impedance can still be modulated by the surface area of the electrode, which is a design parameter we can control.

3.2 Power Requirements

From Hox et. al [10], stimulation parameters of 1.5 mA, 16 Hz, 3 V, and 5 ms pulse width in a bipolar electrode configuration successfully stimulated the cavernous nerves of a rat and are within the safety limits. It is not possible to control for both voltage and current, so we will select current control as our parameter of choice due to its superior ability to mitigate electrode impedance changes over time [23]. From A. Shafik, 60 Hz was the minimum frequency required to induce a full erection with a pulse width of 200 μs [4]. This study, however, did not mention current, voltage, or phase configuration parameters. From these baselines and the discussion in the previous section, we will establish the following parameters:

To calculate the safe stimulation parameters, we can use the equation $Q_{safe} \leq \sqrt{A \times 10^k}$, where Q_{safe} is the maximum safe charge limit, and A is the area of the lead in cm^2, k is the safety parameter (we choose a conservative value of 1.5), and t is the pulse width. Using 100 μm x 3 mm leads diameter leads and a 2 mm diameter cuff (from product catalog [24]), we know the surface area of the electrode is $3 \times 10^{-3} cm^2$. Using 1.5 mA stimulation (from [10]) and the equation $I = \frac{Q}{t}$, we can solve for the maximum safe pulse width, which is calculated to be 2.053×10^{-4} s, about 200 μs. Using the electrode we have chosen, the 5 ms pulsewidth recommended by Hox [10] is well outside of the safe range. If we wished to safely use those stimulation parameters, we would need to choose a different electrode, but we can also simply lower our pulse width to 160 μs, close to the recommendation by A. Shafik. Changes in electrode surface area will result in changes in maximum pulsewidth proportional to the square root of the change in surface area. The minimum required charge to stimulate peripheral nerves is 30 μC/cm^2 when using macroelectrodes [25]. Therefore, the threshold (minimum) charge for stimulation is 0.09000 μC, or 90 nC. Using 1.5 mA current and a 160 μs pulsewidth, 0.24 μC of charge is injected into the tissue in each pulse, which exceeds the threshold charge. Therefore, it has been determined that our stimulation parameters are both safe and efficacious. For now, we suggest using a frequency of 60 Hz, a pulsewidth of 160 μs, and a current of 1.5 mA. Our pulse width is about 80% of the safety limit, so there should not be danger of tissue damage. The device will use charge balanced biphasic stimulation with a delay of 50 μs in order to help the neurons regain their original polarity before the next phase of stimulation. Neither of the previous studies nor the patent literature mention monophasic or biphasic stimulation, but biphasic appears to be safe and industry standard. This would mean each phase is 370 μs with one 160 μs stimulation pulse, a 50 μs delay, and a 160 μs reversal pulse. At a frequency of 60 Hz, there will be 16.3 ms between phases.

Calculating the power consumed by the device will require stimulation pulse width, frequency, current, electrode impedance, and tissue impedance. We have now obtained all but the impedance values. To calculate the resistance of tissue stimulated by our device, we can model the tissue between the cuff electrode poles as muscle, since that is the predominant tissue type in the pelvic floor. Skeletal muscle can be modeled as having a resistivity of 171 Ω-cm [26]. The spread resistance for an electrode in tissue (which we approximate as having infinite volume) is given by Equation 1, where ρ is the resistivity of the tissue in Ω-cm and a is the characteristic length of the electrode, in this case 3 mm, or the longer of the two sides.

$$R_s = \frac{\rho}{a} \tag{1}$$

For our selected electrode area, the spread resistance of the tissue is 570 Ω. The capacitance of platinum is 21.6 $\mu F/cm^2$, and the surface area of the electrode we intend to use is 3×10^{-3} cm^2, so the effective capacitance is 6.480×10^{-8} F, or 64.8 nF. We can determine the compliance voltage, or the maximum voltage that can be produced with our chosen current of 1.5 mA, for our application as a function of pulsewidth using Equation 2, where $I_{compliance}$ is the threshold current in A, C is the electrode capacitance in F, V is the voltage in V, R_s is the spread resistance of the tissue in Ω, and t is the pulsewidth in s. For a pulsewidth of 160 μs and current of 1.5 mA, the compliance voltage is 4.217 V. The possible stimulation parameters are summarized by Figure 2. Note that the device parameters must fall above the threshold line to be effective, below the safety curve to be safe, and below the compliance voltage curve if a battery of that voltage is to be used effectively.

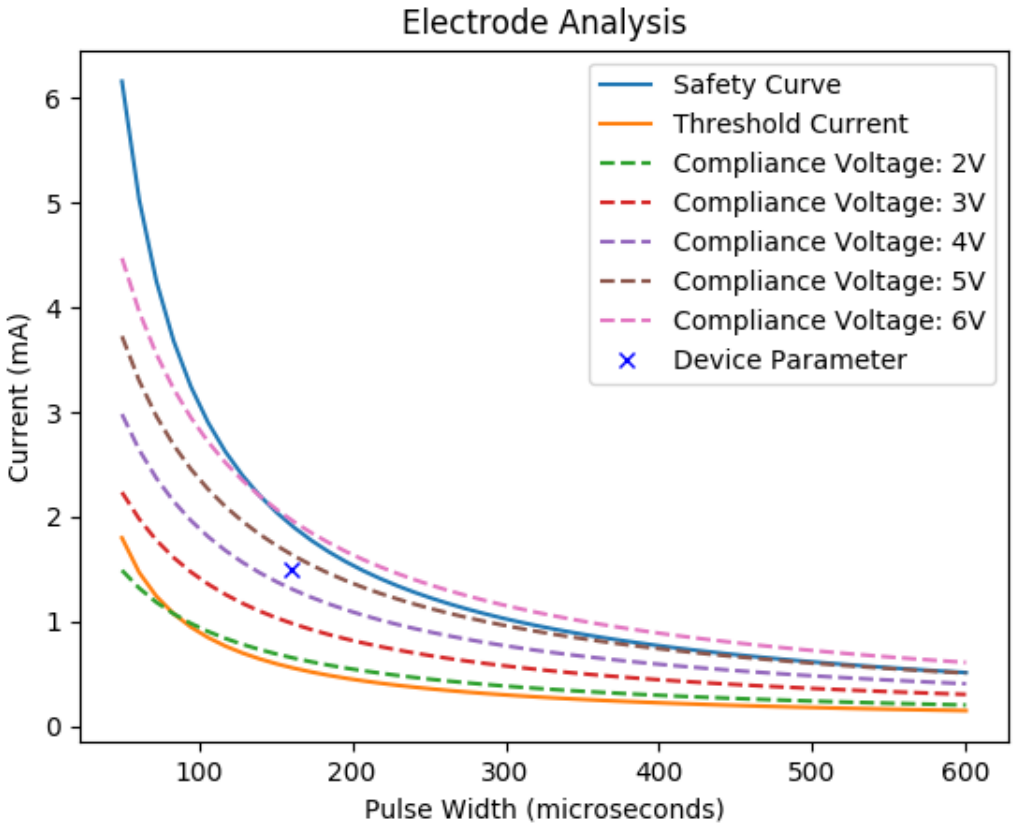

Figure 2: Probe design parameters

$$I_{compliance} = \frac{CV}{R_s C + t}$$
$$V_{compliance} = \frac{I \times (R_s C + t)}{C} \tag{2}$$

The power consumed during stimulation can be calculated using Equation 3, where I_{stim} is our stimulation current (1.5 mA), t_{pulse} is our chosen pulsewidth (200 μs), f_{stim} is the stimulation frequency (60 Hz), and V_{DDH} is the supply voltage. The term $I_{stim} t_{pulse} f_{stim}$ is the average current, and multiplying by the supply voltage gives the average power consumption during stimulation. The whole equation is multiplied by 2 because the stimulation is biphasic, as described earlier, which results in twice the power consumption.

$$P_{stim} = 2 I_{stim} t_{pulse} f_{stim} V_{DDH} \tag{3}$$

Using this equation, the power consumption of the device by stimulation is 144 μW. If we use a rechargeable Li/I_2 battery with an energy density of 240 mW-Hr/cm^3 [27, 28], a radius of 1 mm, and a length of 10 mm, then the available energy in the fully-charged battery is 7.540 mW-Hr, and it would be able to support stimulation for 52.34 hours if no power was used on communication. To ensure that the battery is not discharged more than halfway, we will suggest that the patient recharge the device after 20 hours of operation.

When approximating sizing and power constraints, we must consider thermal safety along with efficacy. Figure 3 shows the received power as a function of the size of the receive antenna [29]. This size is the measure of one side of a single square loop. We can see here that with a 100 mm^2 receiving antenna we can achieve roughly 0.03 W of safe energy transfer. To recharge the battery from halfway, the user would need to charge for roughly $\frac{3.77\times10^{-3}}{.03} = 7.5$ minutes. This number is a very rough estimate, but shows that the user would not be terribly inconvenienced by recharging.

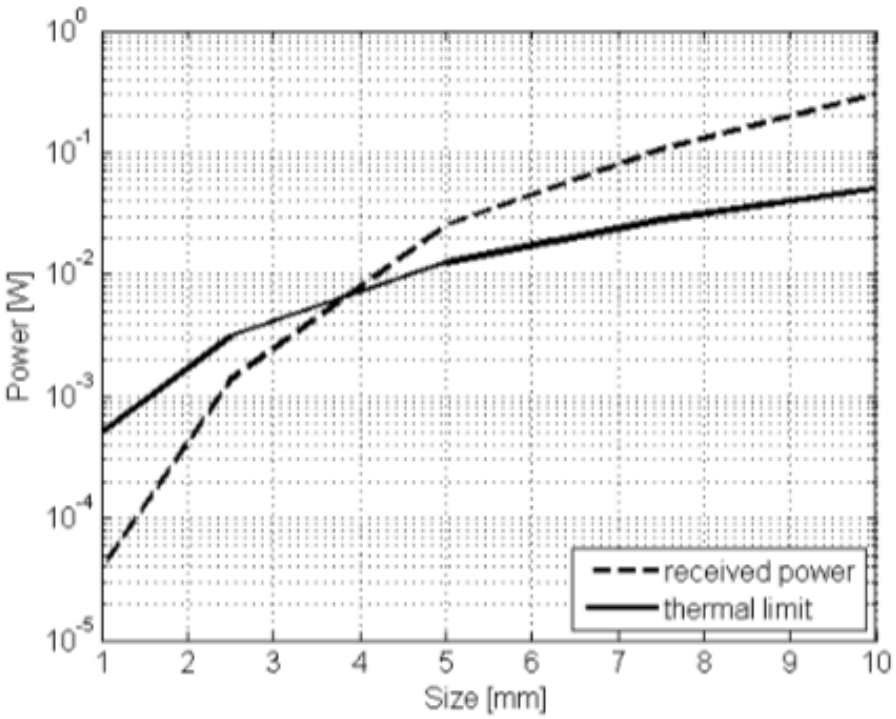

Figure 3: Received power considering thermal safety [29]

3.3 Communication

This device will primarily be focused on stimulation. Communication will be in the form of small and infrequent bidirectional packets. For example, an external transmitter could send a "stimulate" command and a "stop stimulating" command. The internal device could be expected to respond with a status code indicating whether it had started stimulating or had stopped stimulating successfully, and optionally a power level indicator. Due to this very simple communication scheme, we recommend relying on backscatter as our communication method. Backscattering will make our communication power consumption negligible [30]. An overview of the communication and charging scheme can be seen in Figure 4.

The external device will have three modes:

1. Stimulate: Whenever he wishes to induce an erection, the user switches the external device to "stimulate" mode and holds it against his skin where the internal device is implanted. The external device sends a command to stimulate, and the internal device begins the stimulation procedure to induce an erection.

2. Stop Stimulation: When the user wishes to stop his erection, he switches the external device to "stop stimulation" mode and holds it against his skin where the internal device is implanted. The external device sends a command to stop stimulating, and the internal device ceases stimulation, leading to a loss of erection. As

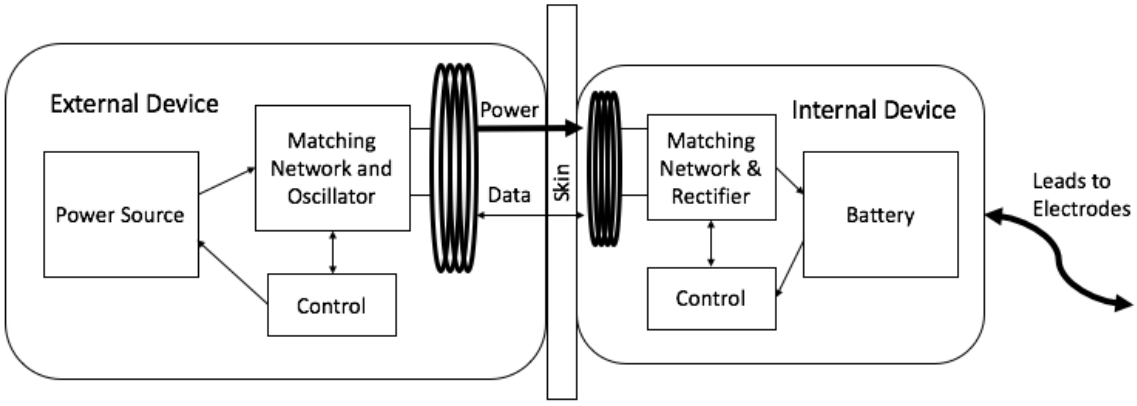

Figure 4: An overview of the external and internal power and communication design

a safety procedure, an internal clock could stop the stimulation at some predetermined length of time, about 2 hours.

3. Recharge: When the user wishes to only recharge the internal device, he switches the external device to "recharge" mode and holds or fastens it to his skin where the internal device is implanted. As calculated above, recharging the device would take up to about 7.5 minutes if we do not allow it to be more than halfway discharged.

This method of activation allows the device to operate at exceptionally low power while providing limited obstruction to the user and increased security over other communication methods. The user only needs to use the external device to start and stop his erection since the battery can provide power after the device receives a stimulation command.

3.4 Implantation Procedure

A Shafik and Marten Hox et al. both explain surgical procedures in their respective studies [4, 10]. Building off of their work, we would plan to insert the device through an incision as illustrated in Figure 5.

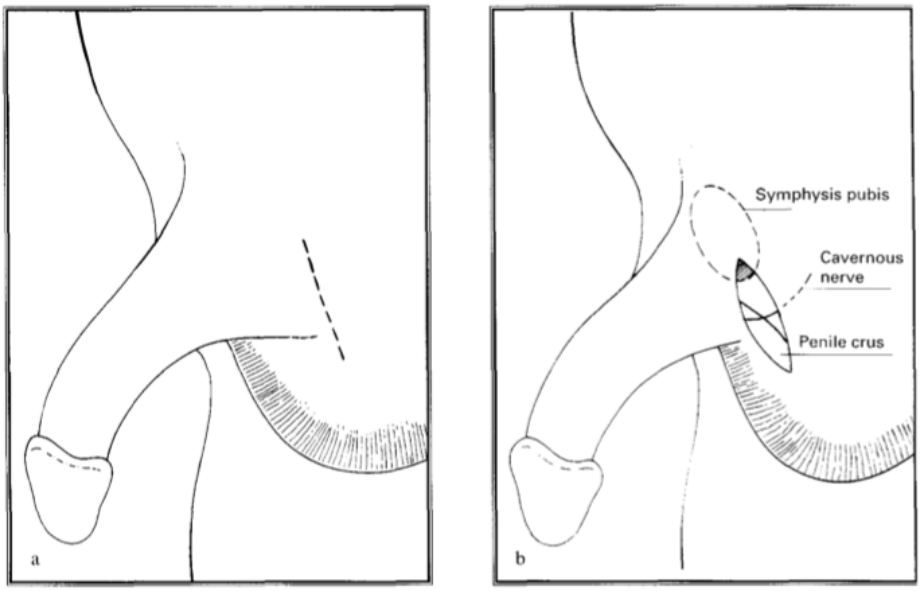

Figure 5: a) The incision to be made. b) where the cavernous nerve lies relative to the incision [4]

After making the incision on the left side of the penis, some fascia tissue may need to be removed before placing a ligature under the nerve [10]. Additionally, the suspensory ligament may need to be divided [4]. By pulling on the resulting suture, the cavernous nerve can be exposed, allowing for implantation of the cuff electrode. Now, the internal device shown on the right side of Figure 4 can be implanted just underneath the skin on the left side of the penis. The device is exceptionally small, so it should not require the rearranging of any nearby tissue. Finally, the wound can be sutured, and the device will be ready to operate.

4 Existing Patents and Intellectual Property

Numerous patents have cited A. Shafik's 1996 paper on extrapelvic stimulation of the cavernous nerves in humans. Of particular interest is a series of patents submitted by Todd Whitehurst while he worked with Boston Scientific Neuromodulation approved between 2003 and 2011 on a fully implantable device which stimulates the cavernous nerves to treat erectile dysfunction as well as other sexual dysfunction [11]. This patent broadly covers sizing and spacing of electrodes, materials, power, frequency, external communication, and open- and closed-loop control for a device of this nature in 24 claims. The power, frequency, stimulation, and electrode type specified in the patent all match the specifications laid out in this proposal. The one area where we initially thought our device may be able to circumvent the patent language is in our method of external communication. However, claim 20 broadly covers stimulation parameters determined by at least one external device, which encompasses our communication method. This patent is set to expire in December 2021, so if we wait 2.5 years until then we will not be infringing on it.

Another patent authored by Whitehurst which is particularly relevant to this work is on stimulation of the cavernous nerves via unidirectional propagation of action potentials (UPAPs), which details an electrode configuration and stimulation timing which prevents the action potential from traveling in the afferent direction (towards the central nervous system) and instead directs it only in the efferent direction (towards the penis) [13]. This is done by using one electrode as an anode block in the afferent direction and through virtual cathode elimination at one of the other electrode sites. The patent discusses the use of cuff electrodes that range from 3 mm to 26 mm in diameter to achieve UPAPs in the cavernous nerves, so our 2 mm electrode is smaller, which seems appropriate given the small size of the cavernous nerves. Also included in this group's work are patents for control units for timed drug delivery and/or electrical stimulation to treat erectile dysfunction in the pelvic plexus as well as in the spinal cord [12, 14, 15]. Despite all the research that went into these patents, we could not find any FDA-approved devices by Boston Scientific Neuromodulation which used the technology described, nor could we find any devices that were otherwise commercially available. The only devices that Boston Scientific has available to treat erectile dystfunction are inflatable penile prostheses such as the AMS Spectra [31]. The project was probably discontinued by the company because they would need to charge more for the devices than their target audience would be willing to pay to make up the research and development expenditures, and insurance companies would not cover the devices since they do not treat a life-threatening condition. On top of that, feasibility studies would be more difficult to conduct because the device would likely need to be filed as Class III due to the nature of the treatment via electrical stimulation within the body.

Medtronic also owns a series of approved patents on treating disorders of the pelvic floor, including incontinence and erectile dysfunction, by stimulating the pudendal and/or sacral nerves and by delivering drugs which cite Boston Scientific Neuromolduation's first patent on a device to stimulate the cavernous nerves [16, 17, 18]. This research was geared more towards bladder control to treat incontinence than treating erectile dysfunction, however, and this shows in their line of available products, including the Interstim II and the Nuro which are both marketed as bladder control devices [32].

5 Contributions

While several studies have shown that stimulation of the cavernous nerves results in an erection, and several patents have claimed ownership of devices designed to take advantage of this phenomenon, there is a remarkable lack of publicly available information on devices that can stimulate cavernous nerves on a safe and regular basis. There is even a lack of thorough clinical studies despite some early recorded success. No single source that we could find shows stimulation, power, implantation, and communication details like the ones in this paper. It is our hope that this paper assists future researchers by collecting this knowledge and making it publicly available.

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Code Used for Probe Design Curves

```
import matplotlib.pyplot as plt
import numpy as np

# area is in cm^2
A = (100*10**-4)*.3

# interested in pulse-widths from 50-600 microseconds
t = np.linspace(50*10**-6, 600*10**-6)

# the following equations are from class slides
Q_thresh = (30*10**-6)*A
I_thresh = Q_thresh/t

# conservative
k = 1.5
Q_safe = np.sqrt(A*10**k)
I_safe = Q_safe/t

fig, ax = plt.subplots()
ax.plot(t*10**6, I_safe*10**-3, label="Safety Curve")
ax.plot(t*10**6, I_thresh*10**3, label="Threshold Current")

cap = (21.6*10**-6)*A
R_s = 171/.3
for v in [2, 3, 4, 5, 6]:
        I_compliance = v*cap/(R_s*cap + t)
        ax.plot(t*10**6, I_compliance*10**3, linestyle="dashed", label="Compliance Voltage:

ax.plot(160, 1.5,'bx', label='Device Parameter')
ax.legend()
plt.title('Electrode Analysis')
plt.ylabel('Current (mA)')
plt.xlabel('Pulse Width (microseconds)')
plt.show()
```