I have attached a report about epidural stimulation which is useful both for our discussion on pain next week and as an example of a product analysis document similar to the report assignments. While somewhat out of date, it would still be appreciated if people would use this only for their own info and not circulate it. Please post the doc with this message on our class webpage.

Thanks,
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Strategic Opportunities in Epidural Stimulation

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Background

Electrical stimulation of the spinal cord is used to treat chronic pain and, less commonly, motor disorders such as spasticity. One or more arrays of electrode contacts are inserted into the epidural space between the inner wall of the spinal canal and the dural sac that contains the spinal cord bathed in cerebrospinal fluid (CSF). Electrical stimulation pulses applied among various combinations of these contacts excite transversely and/or longitudinally oriented nerve bundles that run along the surface of the spinal cord in the white matter. This results in sensory or motor effects that are referred to the body part that is supplied by the activated neurons.

Pain

When treating pain, epidural stimulation is targeted primarily at the dorsal roots and columns, producing bodily sensations of tingling and vibration called paresthesias. When the apparent location of the paresthesias overlaps the apparent location of the pain, the sensation of pain is reduced. Several mechanisms are probably involved, including short-term “masking” in which the presence of one sensation distracts from another, mid-term release of the neuromodulator endorphin (a naturally occurring form of morphine produced by certain nerve cells in the spinal cord), and long-term reorganization of connections among neurons as a result of the stimulated activity.

Spasticity

When treating spasticity, the target of the stimulation may include sensory columns responsible for proprioception (sense of posture and muscle effort) and the lateral and ventral columns, which convey motor commands from the brain to the spinal cord. Relief may be immediate or develop slowly and may outlast the stimulation itself. The mechanisms are unclear but probably include effects related to masking, neuromodulation and synaptic reorganization.

State of the Art

Most of the epidural device development work to date has concentrated on variations in the design and placement of epidural electrode arrays. This is because clinical outcome appears to depend somewhat capriciously on the exact placement of the contacts with respect to the target nerve tracts. It is difficult to control the course of an array in the epidural space as it is pushed through a needle wedged between the vertebrae, particularly if there is scarring from previous trauma or surgical interventions, as is often the case. Some physicians implant the associated electronics at the same time that the stimulation electrodes are inserted while others insert only the electrode and use a trial period of percutaneous stimulation to determine efficacy of the electrode placement before implanting the electronics package.

The commercially available implantable stimulators have been relatively primitive, permitting limited combinations of electrode contacts into a few different multipolar sources.
of simple biphasic pulses. Stimulation systems can be divided into externally powered, RF-coupled systems that send stimulation pulses by inductive coupling to electronically simple implants and battery-powered implants that can be programmed like pacemakers to produce preset sequences of stimulation pulses autonomously. The lack of electronic sophistication stems partly from limited technological competition in this field and partly from the fact that neurosurgeons are more comfortable with mechanical rather than electrophysiological specifications. This is changing, however, as indicated by the attached patent by Holsheimer and Struijk (1996; assigned to Medtronic) and references cited therein (checked items on request for ABC files).

Enabling Science

It is instructive to contrast the principles and goals of epidural stimulation with those of cochlear stimulation, the only other commercially important neural prosthetic implant. In the cochlea, the multiple parallel channels of high-data rate communication are achieved by complex patterns of electrical stimulation. The appropriate distribution of these patterns among multiple electrode contacts is easily determined by the law of tonotopic representation of acoustic pitch along the cochlea. Technological competition has been based on the parameters and programming of electrical output patterns. Little effort has been spent on cochlear electrode design because improvements are difficult to demonstrate clinically and carry high regulatory risks. Nevertheless, electrode design is critical to achieving the channel selectivity required for further improvements. As the improvements obtainable with electronic circuitry alone are tending to plateau, the competition is turning toward electrode design.

In spinal cord stimulation, the goal is not multiple independent channels of stimulation but rather the creation of one homogeneous distribution of neural activation whose anatomical extent exactly matches the extent of the patient’s pathology. The reason for having multiple independent contacts in the electrode arrays is to provide as many different fall-back options as possible to deal with uncertainty about the ideal neural targets and the vagaries of electrode placement and effect. These options are explored mostly by trial and error, limiting the amount of stimulus waveform and channel complexity that the clinician can usefully exploit.

In fact, there is a substantial body of biophysical knowledge that could be used to design complex, multipolar stimulation patterns in order to tailor their effects to a particular patient (see citations in patent by Holsheimer and Struijk, 1996, attached). The volume-conductive properties of the spinal cord, CSF and surrounding spinal canal walls are well-known. The effects of various temporospatial distributions of voltage gradients on the recruitment of different types of nerve fibers are also well-understood. Given a sufficient number of electrode contacts with a sufficient spatial distribution around the spinal cord, it is possible to compute the optimal temporospatial pattern of current sources and sinks required to target a particular fiber tract in the spinal cord. The computations are complex and not intuitively obvious to the clinician, but they can be hidden in an expert layer of software so that the clinician can go directly from an anatomical specification of the target to a complex set of suggested stimulus parameters.
Proposed System Components

Electrode Array

The main requirement is to distribute contacts over the extent of the target region. Ideally, the whole spinal cord would be surrounded in three dimensions (rostro-caudal, medial-lateral, antero-ventral). In practice, at least a few contacts arranged more or less longitudinally in two or more laterally separated lines would be very powerful. The simplest way to achieve this would be to insert separately two parallel, narrow strips with about 8 contacts each, aimed in different lateral directions. More complex electrode arrays (e.g. lateral fins or bifurcating tines) are possible, but they are probably unnecessary and tend to play into our competitors’ strengths in terms of both patent protection and market reputation. Our advantage comes from shifting the clinician’s focus away from the electrode array and onto our strengths in stimulus waveform control, rechargeable batteries, RF-communications and clinical fitting software.

Multichannel Stimulator

Parallel Source-Sink Drivers

The key requirement is that each electrode contact be connected to a separate current-regulated driver whose polarity and timing are independently controlled. All of the output drivers must be capable of being turned on in any sequential, overlapping or simultaneous pattern to produce a given multipolar, multiphasic output waveform. This is essentially the CLARION-2 output system, with scaled-up maximal current output.

Stored Programs

A stimulation program would consist of one to a few such multipolar-multiphasic output waveforms delivered with variable amplitude and/or frequency in one to a few repetitive patterns.

Wearable Controller

Patients will require varying degrees of on-line control of their implants, ranging from simple on-off a few times a day to frequent selections of different programs and/or adjustments of stimulus intensity.

Rechargeable Battery

Implants in different patients can be expected to vary enormously in the power consumed by electrical stimulation, depending on the extent and complexity of the source-sink patterns, the pulse train frequency, and the daily duty cycle. The implant should be capable of producing continuous stimulation for at least a few days with little or no input from the wearable controller. There needs to be a warning system when recharge is required. Recharge should take less than an hour. The batteries should withstand sufficient recharge cycles to last 10 years. The electrode connection system should permit replacement of the implanted electronics package with its internal rechargeable batteries if necessary, without dislodging the epidural electrode array(s).
Surgical Disconnect

All epidural stimulator types employ multicontact surgical disconnects, mostly of a coaxial cylindrical form that slips into screw terminals through a silicone boot. These have been the source of considerable clinical problems, mostly related to electrical leakage. There is an opportunity to use our pressure disconnect technology to advantage here.

**Clinician’s Programming Software**

Fitting Procedure

1. Identify goals of treatment to expert-software
2. Obtain suggested electrode placement from expert-software
3. Implant electrodes
4. Input electrode locations from x-ray to expert-software
5. Select initial anatomical target graphically
6. Apply stimulation according to parameters computed by targeting algorithm
7. Obtain feedback from patient on effects of stimulation
8. Adjust anatomical target and stimulation parameters iteratively on basis of patient feedback.

Anatomical Targeting Algorithm

This is the main competitive advantage of the proposed product, with a user-friendly interface for the clinician backed up by a sophisticated but hidden model of stimulation biophysics:

- a 3D graphical interactive display of the spinal cord with the approximate location of the patient’s electrodes (from x-ray) and a click-and-drag icon representing the target;
- the biophysical algorithm for setting stimulation parameters according to the target location and extent selected by the physician;
- an optional waveform design and control panel that lets the physician fine-tune the stimulation waveform computed by the algorithm (ideally such alterations would propagate backwards to alter the target icon; in practice, this may be difficult).

The use of on-line expert-software that uses biophysical models to compute stimulation parameters for a given patient is probably novel and patentable intellectual property. Given the flurry of activity in this area in the past 4 years, however, there may already be interfering patent applications pending.
Patient Feedback

A graphical representation of the patient’s body that permits the patient and/or the physician to indicate and track the location and extent of the sensations produced by different stimulation waveforms. This makes it possible for the physician to shift the target icon in a direction that seems promising empirically even when the anatomical basis becomes obscure. Dr. Richard North, Johns Hopkins University, has reported on a system called Pain Doc that includes a touch-sensitive screen operated by the patient (this may have been developed with Neuromed - a search is underway).

Product Development Cycle

A key feature of this approach is that it permits both the clinicians and the fitting software to get smarter with experience. If the targeting algorithm is at least reasonably orderly in its behavior, the clinicians will learn to associate certain anatomical target displays with the desired physiological effects, even if the anatomical location of the actual neural target is not correctly represented. Conversely, clinical data about the location of the paresthesias and other physiological effects can be used to improve the targeting algorithm, which requires only a software release. Such information could be gathered simply by uploading fitting records from the field.

New biophysical research into the location and responsiveness of target neurons and the design of even more complex temporospatial fields can be used to take advantage of the electronic sophistication of the implant without the clinician having to deal with ever-increasing numbers of stimulus parameters. For example, the orientation and duration of potential gradients required to stimulate spinal roots and grey matter are distinctly different from those required for longitudinally oriented white-matter tracts. If the clinician positions the target icon to include such structures, the program could automatically introduce a mix of stimulus waveforms that would be tailored separately for each, providing the clinician with a simple intensity control for each waveform.