Electrical stimulation of nerves usually activates all the axons within the influence of the electrical field. To achieve functional goals, it is necessary to be able to stimulate select subpopulations of axons directed towards specific targets. The nervous system evolved mechanisms to signal specific locations with specific neurotransmitters. The individual axons distribute these signals spatially to achieve desired function. Electrical intervention to establish the same capacity needs to be able to provide signals in a similar pattern. This requires the ability to selectively activate sets of axons within a peripheral nerve.

Advantages may be taken of gross anatomical paths, fascicle distribution within nerves, differences in axon diameters or utilize reflex pathways. The applied electrical field can be varied temporally to manipulate the non-linear properties of the axonic ion-channels to generate required firing patterns.

The creation of technology to selectively activate specific populations of neurons and electronically reposition “virtual excitation sites” will bring neural prostheses that have tunable electrodes. Very often the site of injection of applied current, the electrode contact, of an implanted electrode is not at the best location to electrically activate a desired population of neurons. With a tunable electrode, we would be able to create a “virtual electrode site” at a desired position without physically moving the electrode.

There are at least four phenomena that we can draw upon to create these electronically steerable electrodes:

1) The electrically induced potential is inversely related to the separation between the site of current injection and the point of interest,
2) Current injected from separate contacts generate electrical potentials that are linearly additive,
3) Voltage-gated sodium ion channels are not uniformly distributed over the surface of the neuron; and
4) Voltage-gated sodium ion channels exhibit an inactivatable state.

The fact that the potential falls off inversely with distance means that the effects of an applied current are more pronounced on neurons that are closer to the contact site than those that are further way from the current injection site; usually this is taken to mean that neurons closer to the electrode require lower currents to activate, but as we will discover there is more to this statement. The fact that voltage-gated sodium ion channels are concentrated in specific regions of a neuron, the axon hillock and the nodes of Ranvier, means that potential
changes only in those regions can effect propagated action potentials. The fact that voltage-gated sodium ion channels can be put into an inactivatable state open opportunities to alter the excitability of neurons close to the contact. Using these phenomena we will show how the normal recruitment order, large diameter to small diameter axons, can be reversed, currents from several electrodes can be used to “field steer” an excitation site, and the inactivation property can enable us to effect excitation of neurons further from a current injection site without exciting neurons closer to the electrode.

The reader is encouraged to think of other phenomena that might be useful in creating steerable “virtual electrode sites”.

Selective Activation of Peripheral Nerves

Electrodes applied to most peripheral nerves can electrically access a large number of axons within the nerve. In many cases, advantage may be taken of the fascicular arrangement of the axons within the nerve trunk. By placing multiple electrode contacts around or within the nerve, the field of influence of the applied electrical stimulus can be directed to selectively activate subsets of axons within the nerve. In the figure, a radial arrangement of four electrical contacts is shown arrayed around a nerve trunk with four fascicles. By orchestrating the electrical field spatially and temporally from specific contacts, different subpopulations of the axons may be selectively activated.

Numerical Analysis of Electric Field Generated by a Nerve Cuff Electrode.

A 3-D finite element model of an unifascicular nerve was developed to study the potential distribution from a nerve cuff electrode [1]. A schematic model nerve is shown in the figure. The z-axis runs in the direction of the axons in the nerve trunk. The 3-D domain representing the nerve, surrounding tissue and the electrode were assumed purely resistive. The nerve model consisted of 28 layers with 256 volume elements along the axis of the nerve. A finer mesh was used in the region inside and close to the electrode.

The x-y and the x-z planes were considered to be two planes of symmetry. Therefore, only one-fourth of the problem was modeled using 7769 nodes and 1680 volume elements. The electrical potential distribution was obtained by solving the Laplace Equation within a 3-D domain. The solution was obtained by minimizing a functional given by

$$F(\Phi) = \int_D \left[ \sigma_x (\partial \Phi / \partial x)^2 + \sigma_y (\partial \Phi / \partial y)^2 + \sigma_z (\partial \Phi / \partial z)^2 \right] dx dy dz$$
Geometry of the Nerve

The geometry of the represented nerve is shown in the figure. It was modeled as a three-mm. diameter, unifascicular anisotropic structure with $\sigma_{\text{longitudinal}} = 1.0 \text{ S/m}$ and $\sigma_{\text{transverse}} = 0.1 \text{ S/m}$, surrounded by a 30 $\mu$m perineurium with $\sigma = 0.00063 \text{ S/m}$.

Two layers of encapsulation tissue, a 150 $\mu$m loose layer with $\sigma = 1.0 \text{ S/m}$ and a 50 $\mu$m tight layer with $\sigma = 0.0659 \text{ S/m}$ (so that the effective $\sigma = 0.22/m$) and a 50 $\mu$m layer of 0.9% saline ($\sigma = 2.0 \text{ S/m}$) were considered between the nerve and the electrode.

Electrode Contacts

The electrode contacts were 30 $\mu$m thick with $\sigma = 10^4 \text{ S/m}$ and with a surface area of 1.57 sq. mm. They were embedded on the inner surface of a 1 mm thick insulated nerve cuff ($\sigma = 10^{-6} \text{ S/m}$). The surrounding body fluid was represented by a 20 mm layer of saline.

Electrode Configurations

The four electrode configurations modeled are shown in the figure. The monopolar configuration considered a single cathodic contact in the x-y plane of symmetry at the center of the nerve cuff. The monopolar with steering configuration added an anodic contact placed radially 180 degrees opposite to the cathodic contact.

The tripolar configuration considered a single cathodic contact flanked by two anodes. The tripolar with steering configuration added an anodic contact placed radially 180 degrees opposite to the cathodic contact of the tripole.

Nerve Activation Model

A cable model of myelinated axons by McNeal [2] was used for analysis of the electric field from the electrode. An equivalent driving function, as defined by Warmen et al. [3] was used to predict axon excitation. The solution to the cable equation gave the transmembrane potential $V_m$ induced at a node of Ranvier.

Using parameters of the cable based on properties of mammalian myelinated axons [4], threshold current for a 100$\mu$sec pulse from a point source was determined. The equivalent driving force $DF(i)$ was calculated for 10 micron and 20 micron diameter axons at nodes of Ranvier in the X-Y plane. $DF(i)$ being independent of fiber diameter and distance from electrode. An axon was considered to be activated when $DF(i)$ was equal to or greater than threshold.
Solution to the cable equation gives the transmembrane potential $V_m$ induced in an axon at the node of Ranvier $i$.

$$
V_m(i,t) = R_{in} G_a [V_e(i-1,t) - 2V_e(i-1,t) + V_e(i,t)] 
+ \sum_{j \neq i} R_{in} G_a \Psi_j(i,t) [V_e(j-1,t) - 2V_e(j-1,t) + V_e(j,t)]
$$

where $V_e$ is the extracellular potential, $R_{in}$ is the input resistance at node $i$, $G_a$ is the axoplasmic resistance, $\Psi_j(i,t)$ is the induced transmembrane potential at node of Ranvier $i$, per unit of source current at node of ranvier $j$.

**Activation Contour Plots**

A reference point ‘A’ was located midway between the center of the nerve and the center of the cathode (1.25 mm radially from the center). The driving function at point A due to a stimulus of −1 V at the cathode was calculated. The threshold current density was determined to be 4.88 mA/sq. cm. $V_{thr}(A/10\mu m)$ was defined to be the threshold voltage stimulus required to activate a 10 µm axon at point A and was calculated by scaling −1 Volt, with the ratio of 4.88 mA/sq.cm. to the driving function DF(i). If the value of the driving function for a 10 µm diameter axon at location ‘A’ was half of threshold with a stimulus of $V$ volts, then a stimulus of 2$V$ volts would be needed to activate the axon.

The threshold stimulus was found to be lowest at nodes of Ranvier in the X-Y plane passing through the center of the cathode. Finite element solutions were found for stimulus of −1 V at the cathode. In the figure, equivalent driving function DF(i) contours for threshold current density of 4.88 mA/sq. cm (J) and for 2.44 mA/sq. cm (2J) are shown for 10 µm and 20 µm axons. All the axons of a particular diameter are activated in the region between the Jth contour line and the nerve surface towards the electrode. A voltage of twice threshold is required to activate fibers in the region between contour lines 2Jth and the surface of the nerve towards the electrode.


Effect of Tissue Conductivity

In an isotropic, homogenous, unifascicular nerve, with conductivity equal to saline, (left of figure), $V_{thr} (A/10\mu m)$ (the threshold voltage stimulus required to activate a 10 µm axon at point A) was determined to be −0.1043 Volts. The Jth and 2Jth contours for 10 Mm axons are shown. All 20 µm axons were activated at 2J, twice the $V_{thr} (A/10\mu m)$.

The activation contours in an anisotropic nerve, with longitudinal conductivity of 1.0 S/m and transverse conductivity of 0.1 S/m, is shown in the center of the figure. The $V_{thr} (A/10\mu m)$ increased to −0.1651.

With a perineurium of conductivity 0.00063 S/m, the $V_{thr} (A/10\mu m)$ increased to −0.5161 Volts, the activation contours are shown in right side of figure. All 20 µm axons were activated with 2J (twice threshold for 10 µm axons).

Effect of Electrode Configuration

The tripolar electrode configuration had two anodes located 3 mm from the central cathode. In the figure, the activation contours for monopolar and tripolar configurations are shown. A higher $V_{thr} (A/10\mu m)$ was required for the tripolar electrode. In the monopolar, all 20 µm axons were activated, whereas with the tripolar the Jth and 2Jth contours for the 20 µm axons can be seen.

Steering:

A positive 0.557 Volts was applied to the steering Anode across from the central Cathode. This was the subthreshold amplitude for 20 µm axons at location A. With the monopolar electrode, a significant change can be seen with addition of a steering voltage (Top right of figure).

The effect of steering with the tripolar configuration can be seen in the bottom right of the figure. The contours were similar to the Monopolar with steering, but the 2Jth area for the 20µm axons were further reduced.
Effect of Encapsulation and Cuff Fit

With chronic electrode implants, the interface tissue between the contact and the nerve changes due to development of encapsulation tissues. With a proper cuff-fit and growth of encapsulation tissues, model shows a change in the activation contours (center of figure) from acute implants (without encapsulation, left of figure) and from a loose cuff-fit (right of figure).

Effect of Contact Spacing

The effect of distance between the contacts of the tripolar configuration, 3mm (left) and 6 mm (right) are shown in the figure. The threshold was lowered with increase in contact spacing. There was a shift in the activation contour of the 20 µm axons for both the Jth and 2Jth values. The results appear to show that smaller inter-contact distances are more efficient in localizing the applied currents.

Conclusions

Anisotropy, perineurium and connective tissue were barriers to the current flow between the electrode and the nerve fiber. Perineurium and connective tissue decrease the selectivity of excitation of specific regions of the nerve. Anodic current from an electrode across from the cathode improved the selective excitation of specific regions for both monopolar and tripolar electrode configurations. Tripolar electrodes provided greater selectivity than monopolar electrodes. Smaller spacing between the anodes and the cathode in a tripolar configuration was more efficient in confining the current to regions closer to the electrode. Snugly fitting cuff reduced the scattering effect of the saline layer present between the implanted cuff and the nerve.

Selective Stimulation of Nerve Fascicles

When multicontact cuff electrodes are placed around a peripheral nerve, the contacts may not be aligned with target fascicles. With multiple available contacts, virtual excitation sites can be created by superimposing the electric fields generated by simultaneous application of currents to two or more contacts in the electrode assembly, “field steering”.

Field steering has been explored as a technique
for creating virtual excitation sites that are different from the physical location of an actual stimulating contact [1]. These were carried out with self-sizing spiral cuff electrodes, containing four radial contacts, implanted on feline sciatic nerve. The feline sciatic nerve is ~3mm in diameter and contains four major motor fascicles. In about two-thirds of the tests one of the four contacts was positioned to excite selectively and controllably one of the four motor fascicles in the sciatic nerve. In those cases where a single contact could not activate a target fascicle, field steering was shown to be an effective means of creating a virtual excitation site confined to a target fascicle.

Monopolar and tripolar-cuff electrode configurations and schematics of the resulting current flow are shown in the figure. With the tripolar configuration (above), the current flows between the center contact (cathode) and the two outer contacts (anodes). With the monopolar configuration (below), the current flows between the central contact (cathode) and the remote contact (distant anode), creating a virtual anode at each end of the cuff.


**Monopolar and Tripolar Electrodes**

Both Monopolar and Tripolar configurations can be used to create virtual excitation sites or tunable electrodes. The experiments described here were intended to bring out any differences in the recruitment characteristics between the two electrode configurations. The coordinates of the plot, in the Figure, are ankle torques in two dimensions, Planter Flexion/Dorsi-Flexion and Medial/Lateral Rotation. Data shown are for evoked ankle torque resulting from stimulation applied to various contacts within a self-sizing spiral cuff electrode. Also shown in this figure are torque measurements recorded when stimuli were applied to each of the four isolated motor nerves, labeled T, CP, MG and LG (shown by grey lines). The drawing, shown in the lower right hand portion of the figure, provides an approximation for the nerve anatomy relative to the position of the four electrode contacts labeled O°, 90°, 180° and 270°. Single dots represent data collected at different stimulus levels. In this experiment, the Medial Gastrocnemius (MG), the Lateral Gastrocnemius (LG) and the Tibialis (T) branches were selectively activated over their full range by contacts 90°, 180° and 0° respectively. Stimuli applied to the 270° contact appeared to activate both the tibial and common peroneal fascicles.

**Similarity of Activation**

Quantitative comparisons of the torque trajectories recorded for the monopolar and tripolar configurations have been made using a method developed by Tyler and Durand [1] to compare two torque curves in space. The similarity of two recruitment curve was defined as the percent of one curve that was not statistically different from a second curve at a 98% level of confidence. The 98% confidence level for the data may be found using the Student's
t distribution and the standard deviation of points achieved by supra-maximal stimulation of the nerve. Results achieved after supra-maximal stimulation were selected since, by definition, no additional torque may be achieved and therefore any variability in the measured torque was a characteristic of the experimental system and not due to changes in the number of fibers activated. Using the 98% confidence level, each point along one curve, the test curve, was tested against each point on the other curve, the reference curve.

A summary of the similarity of values found for monopolar and tripolar configurations is shown in the figure. The similarity achieved using the same tripolar configuration at different times (above) and the similarity achieved using the same monopolar configuration at different times (second from top) were found to be 78% and 79%, respectively. The monopolar output torque compared to the tripolar output torque (middle), at a value of 76%, was not found to be significantly different than either the monopolar or tripolar repeatability at a 98% confidence level. The similarity values found for the torque outputs produced by stimulation applied to two different locations around the nerve were found to be 19% and 15%, respectively. The number of comparisons (n) was equal to the sum of every combination of two trials that satisfied the comparison of interest.


**Threshold and Torque Gain**

The threshold current, $I_{\text{thresh}}$, was defined as the current required to achieve 10% of the above defined maximum torque output. The torque gains for the monopolar and tripolar configurations were defined as the slope of the torque recruitment curve between the points that produced 10% and 90% of the maximum torque output.

The torque gains for the monopolar and tripolar configurations in the example shown in the Figure, are $-0.4$ and $-0.2$ N-cm/μA respectively.

**Summary**

Summaries for the ratio of monopolar to tripolar threshold current, maximum torque output before spillover and torque output gain, across six experiments, are shown in the Figure.

The histograms are the ratio of monopolar to tripolar threshold current, maximum torque before spillover and torque output gain. Data located on the left side (less than 1) indicate...
monopolar values that were smaller than the value measured using a tripolar configuration. Data located on the right side (greater than 1) indicate that monopolar values were larger than tripolar values. Monopolar current required to produce 10% of the maximum torque output (threshold) was found to be less than tripolar threshold at a 99% significance level. The mean of the ratio of maximum torque outputs before spillover was found to be between 0.85 and 1.2 with a ratio equal to 1.0 +/- 0.2 at a 99% significance level. The torque output gain of monopolar stimulation was found to be greater than tripolar stimulation at a 99% significance level.

The results of these tests indicate that, provided one can accommodate a higher gain and a lower threshold, a monopolar cuff electrode will perform as well as a tripolar cuff. An advantage of the monopolar configuration over the tripolar configuration is that it has fewer electrode contacts and requiring fewer separate lead wires, making them simpler to manufacture.

**Fascicular Selectivity:**

For a multicontact cuff electrode to be functional all target fascicles must be accessible. This can be achieved if there are sufficient numbers of contact to cover all possible positions of nerves inside a cuff or techniques must be developed to create steerable excitation sites. The development of techniques to steer (or move a virtual excitation sites) would make it possible to manufacture functional multicontact cuff type electrodes with fewer contacts, leads and simpler connectors. In the following section we show that “field steering” can be use to position an excitation site (a virtual excitation site) at a point in space where there is no actual contact in the cuff electrode.

**Anodic Steering:**

A comparison was made of the torque outputs produced by direct stimulation of each branch of the Sciatic nerve, labeled as Tib, MG, LG and CP, to the torque produced by stimulation of each contact in the cuff electrode, labeled 0°, 90°, 180° and 270°, in a feline. Based on the torque outputs, the Tib, MG, and LG branches of the sciatic were activated by the 0°, 90°, and 180° contacts on the sciatic nerve. No single contact activated the common peroneal by itself. The addition of anodic steering current from the 0° position to the 270° position (labeled c270°a0°) was found to produce the same torque output as was produced by stimulation of the common peroneal branch. The inset in the bottom right corner is a reconstruction of the nerve cross section and the relative locations of each contact. A schematic of the configuration used to apply current for the multiple contact stimulation is also shown.
Cathodic Steering:
In this experiment, no single contact activated the Medial Gastrocnemius (MG) by itself. The addition of cathodic steering current from the 90° position to the 180° position (labeled c90°c180°) was found to activate the MG selectively over its entire range. The inset in the top left corner is a reconstruction of the nerve cross-section and the relative locations of each contact. This schematic depicts the current configuration used to apply the steering currents.

Summary
Stimulation combinations used at the level of the sciatic nerve to achieve the same torque output as each corresponding fascicle for each experiment are shown in this table.
In each case in which the same torque output as the corresponding nerve branch was achieved, four placeholders were entered to represent how the four corresponding contacts (0°, 90°, 180° and 270°) were used.
An open circle (o) represents a contact that was not used for that particular configuration.
A minus sign (-) indicates that the corresponding contact was pulsed in the cathodic direction.
A plus sign (+) indicates that the corresponding contact was pulsed in the anodic direction.
Four filled circles (● ● ● ●) indicate that the particular torque was not achieved fully with single contact stimulation but not targeted using steering currents due to time limitations. In no case was a particular torque not achieved when multiple contact stimulation was attempted. The shaded cells are the cases in which “collision block addition” was used to verify the corresponding fascicle was fully and selectively activated.

The results of these experiments indicate that a four contact, self-sizing, cuff electrode can be used to target activation of any one of four motor fascicles, over its entire range, provided the stimulator is capable of effecting “field steering” by the application of positive or negative currents to any of the four contacts on demand and simultaneously.