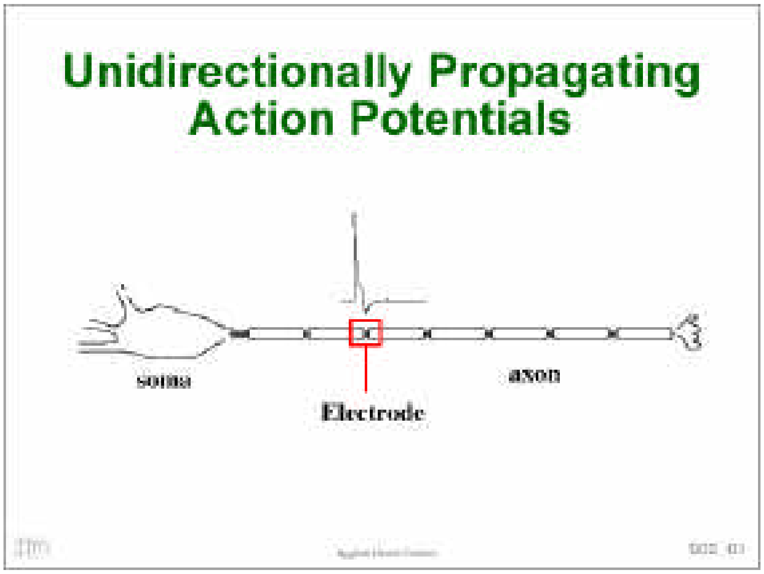
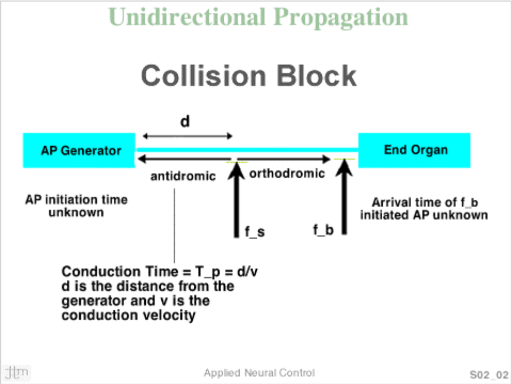


Unidirectionally Propagating Action Potentials

jtm S02_01

Under physiological conditions, a nerve **action potential** (AP) is generated at one end of an axon and proceeds towards its other end. Electrical nerve stimulation of an axon normally produces two propagating APs, one in the orthodromic direction (towards the terminal end where the neurotransmitter is released) and one propagating in the antidromic direction (towards the soma). Techniques have been developed to prevent the AP from propagating in one of these directions, while allowing it to travel in the other. Such **unidirectionally** propagating APs can be used for **collision block** of naturally incoming nerve signals to a target. This may be of clinical utility in conditions of spasticity of skeletal muscles or in preventing undesirable sensory inputs. They can be directed towards the target (orthodromic) without activating the soma and resulting central reflexes.

Collision Block of Action Potentials.



Unidirectional Propagation

Collision Block

d
AP Generator
End Organ
antidromic
orthodromic
AP initiation time unknown
Arrival time of f_b initiated AP unknown
f_s
f_b
Conduction Time = T_p = d/v
d is the distance from the generator and v is the conduction velocity

jtm Applied Neural Control S02_02

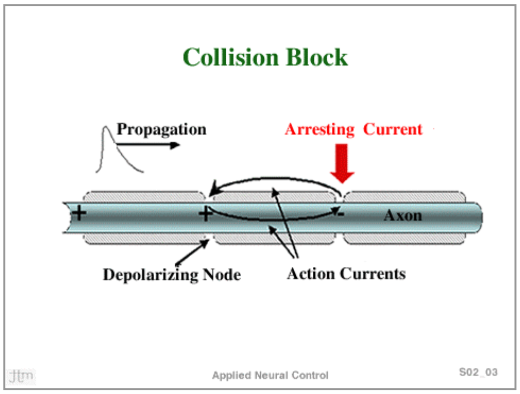
An electrically initiated action potential (AP) can be sent towards an oncoming naturally generated AP to neutralize it and stop propagation, **collision block**. To effect 100% collision block of Action Potentials (AP) from a source, the stimulation frequency will depend on

1. the distance of the stimulation site from the action potential generator (APG),
2. the conduction velocity of the axons,
3. and the refractory period.

In the left side of the figure is shown an APG, such as the soma of a motor neuron. On the right is the target that receives the signals.
The arrow at $\mathbf{f}_s$ is the input from stimulation at frequency of $\mathbf{f}_s$ Hz.
The conduction time (**Tp**) of an AP from the generator to the stimulation point is **d/v** where **d** is the distance between the generator and the stimulation point and **v** is the conduction velocity.
Let $\mathbf{f}_s = 0$ for $t < 0$

Any AP initiated by the generator between zero and $\mathbf{Tp}$ will be annihilated by the stimulator initiated AP occurring at t=0.
Any AP initiated by the generator between t = $\mathbf{Tp}$ and 2$\mathbf{Tp}$ will be annihilated by the stimulation initiated AP occurring at t=2$\mathbf{Tp}$
Therefore the collision window is $\mathbf{Tc} = 2\mathbf{Tp}$
If we include the refractory period, $\mathbf{Tc} = 2\mathbf{Tp} + \mathbf{r}$
Then the escape window is $\mathbf{Te = Ts - Tc}$
For 100% block of the incoming APs, $\mathbf{Te} = 0$, so $\mathbf{Ts = Tc}$,
or $\mathbf{Ts} = 2\mathbf{Tp} + \mathbf{r} = \mathbf{2d/v + r}$
Which means that the frequency $\mathbf{f_s}$ needs to be $(2d/v + r)^{-1}$
For example, if v=100 m/s, d = 10 cm and r = 2 ms then $\mathbf{f_s} = 250$ Hz. If the stimulator frequency were less than 250 Hz, there is a possibility that a naturally occurring AP would not be annihilated by a stimulator produced AP.

Arresting the Action Potential

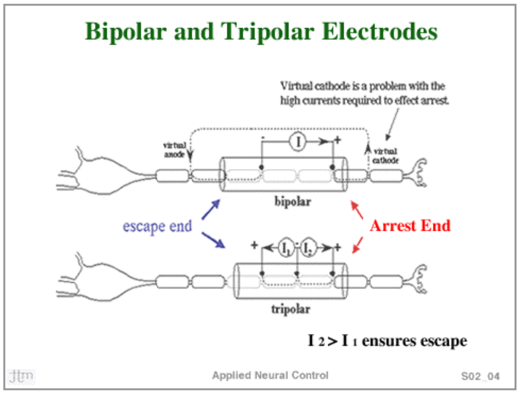

Collision Block

Action Potentials (AP) propagation initiated by electrical stimulation with a nerve electrode can be stopped by applying an arresting current.

- To arrest the incoming AP, the current has to be applied at the time the propagating AP arrives at the arrest site.
- The arresting current has to persist for the time that excitation currents from the preceding node are flowing in to depolarize the adjacent node.
- When the distance between the location providing the arrest current and the location initiating the AP initiation is small, the temporal dispersion of arriving APs on axons of different diameters will be small. This suggests that the distance between the initiation site and the arrest site should be small.

A nerve **electrode** with multiple contact surfaces for injecting currents can be placed around a nerve trunk to initiate APs and arrest propagation in one direction.

Bipolar and Tripolar cuff electrodes.


Bipolar and Tripolar Electrodes

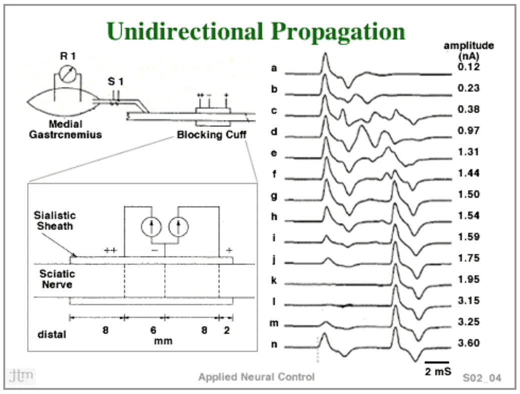
Virtual cathode is a problem with the high currents required to effect arrest.

A **bipolar nerve cuff electrode** has two contacts for current flow. One contact, the **'cathode'**, depolarizes the membrane (towards more positive potentials), where the Action Potential(AP) is generated. The other, an **'anode'** injects current and hyperpolarizes the axon membrane potential (towards more negative potentials) and can arrest AP propagation.

Because current flows in all directions, pathways at the open end of the nerve cuff form 'virtual' contacts that act on the axons. A **'virtual cathode'** outside the 'anodic' end of the electrode, and a **'virtual anode'** outside the 'cathodic' end. APs may be generated at this 'virtual cathode' when the current flow at this location causes threshold depolarization.

In a **tripolar cuff electrode**, a central 'cathode' is flanked by a pair of 'anodes'. The total current to the 'cathode' is divided between these two 'anodic' contacts. Since there is current flowing to both anodes, the potential at each end is similar and there is a reduced tendency for current to flow outside the cuff. This ensures that most of the current is contained within the insulating walls of the electrode, limiting the formation of 'virtual' cathodes outside the two 'anodic' ends of the cuff. By distributing the currents unequally to the two anodes, one of them can arrest the 'cathode' initiated APs coming to it and the other can suppress the tendency for a virtual cathode to develop outside the arresting end yet allow the evoled AP to 'escape' and propagate at the other end, called the escape end.

Generation of Unidirectionally Propagated Action Potentials -1



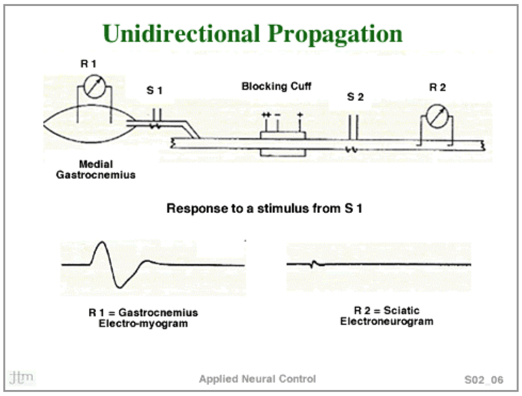
A **tripolar nerve cuff** applied around a nerve trunk can be used to initiate action potentials (AP) under a central 'cathodic' contact, while arresting AP propagation by a flanking 'anode'. By making one anode carry more current than the other or spacing the escape anode further from the centrally placed cathode, the AP can be arrested at the end carrying the greater current while the other allows the AP to escape. A shorter anode to cathode distance on the left (towards the medial Gastrocnemius muscle) lowers the electrical resistance and allows more current to flow through that anode. This acts as the arresting end of the electrode. The other end of the electrode allows the propagating APs to continue travel. This can ensure **arrest** of the bidirectionally propagating AP at one end, allowing **'escape'** at the other.

Experimental preparation is shown on top left of Figure. R1 is the electromyogram recording site and S1 hook electrode for stimulation. In the bottom, left part of the figure is a detail of an insulated tripolar electrode, shown above as the 'Blocking Cuff'. The dashed lines on the Sciatic nerve represent ring contacts around the nerve inside the insulating silicone rubber sheath. The applied current is unequally divided to the two flanking contacts by using separate stimulators.

In the right side of figure is shown the Medial Gastrocnemius EMG responses to 8 mS square pulses applied through the cuff electrode, with the central contact as the Cathode. There are two distinct responses, a short latency response, which is presumed to have been initiated at the cathode, and the long latency compound AP, which is presumed to have been initiated by an “anodic break” response arising from the left most anode (designated ++) because it is highly correlated with the lagging edge of the 8 ms current pulse. In (a) maximum EMG response at 0.12 mA. In (b to f) growth and then decline of asynchronous activity. (f and g) appearance of post stimulus anodic break response. (h to l) decline and disappearance of direct response (initial deflections) at 1.95 to 3.15 mA. In (k) and (l) a unidirectionally propagating AP, initiated at the cathode, is presumed to have occurred. In(m and n) reappearance of the direct response at higher current amplitudes, but at a slightly shorter latency, presumably arising from a virtual cathode located to the left of the electrode. The “anodic break” response can be eliminated by making the tailing edge of the stimulus pulse decay exponentially.

> van den Honert, C. and J. T. Mortimer (1981). “A technique for collision block of peripheral nerve: single stimulus analysis.” IEEE Trans Biomed Engg. 28(5): 373-8.

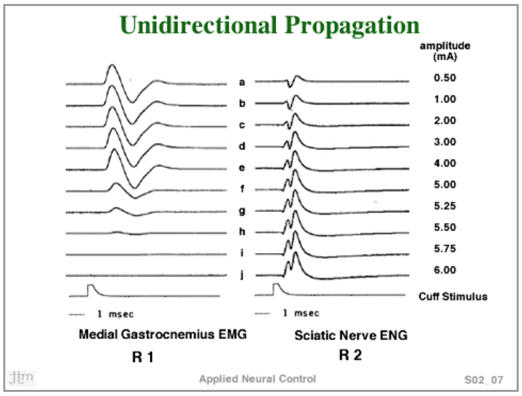
Generation of Unidirectionally Propagated Action Potentials -2



The experimental preparation is shown in the top of the Figure was designed to test the hypothesis that unidirectionally propagating action potentials were actually generated. R1 and R2 are electro-myogram and electro- neurogram recording sites respectively. S1 and S2 are hook electrodes used to apply currents to the nerve trunk for test stimuli. The **tripolar nerve cuff** is in the center, around the nerve trunk. Action Potentials (APs) generated under the central contact ('cathode') are arrested at the contact on the left, which carries more current than the one on the right and allowed to propagate to the right, because the contact on the right carries less current than the one on the left but just enough current to suppress the development of a virtual cathode on the left side.

Response to a test stimulus at S1 is shown on the bottom of figure. A maximum Gastrocnemius EMG response is recorded at R1 and a Compound Action Potential from the Sciatic nerve at R2.

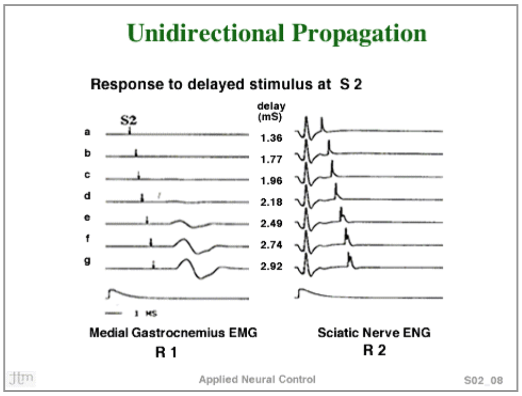
Responses to 'block' stimulus.



Above a certain current amplitude, the cuff electrode causes **arrest** of APs towards the muscle (left) while allowing them to **escape** to the right.

Stimuli applied to tripolar nerve cuff: 350 µsec plateau phase, 350 µsec falling phase time constant, of increasing amplitude from 0.50 to 6.00 mA. Gastrocnemius EMG recorded at R1 and Sciatic ENG recorded at R2. As the current amplitude is increased, the maximum EMG response (a-e) diminishes (f, g) and then disappears (i,j). The sciatic ENG shows compound action potentials at all amplitudes.

Responses to delayed stimuli at S2 during 'block' stimulus.


Unidirectional Propagation

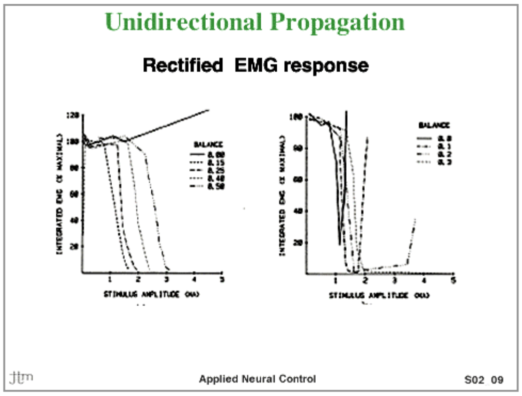
Response to delayed stimulus at S 2

Applied Neural Control S02_08

If unidirectionally propagating (moving to the right) were actually generated at the cuff electrode, the nerve fibers carrying these APs would be refractory for a period of time after the APs had passed the region of the S2 electrode. The experimental data shown in the figure support the hypothesis. Stimuli from the tripolar electrode **'arrests'** APs propagating towards the Gastrocnemius, while allowing them to **escape** antidromically. Only when the S2 stimuli were applied at delays greater than 2.4 msec was the S2 stimulus capable of exciting the nerve to cause muscle contraction. This implies that a unidirctionally propagating pulse was generated and the refractory period was greater than 2.18 msec.

van den Honert, C. and J. T. Mortimer (1979). “Generation of unidirectionally propagated action potentials in a peripheral nerve by brief stimuli.” **Science** 206(4424): 1311-2.

EMG Response


Unidirectional Propagation

Rectified EMG response

Applied Neural Control S02 09

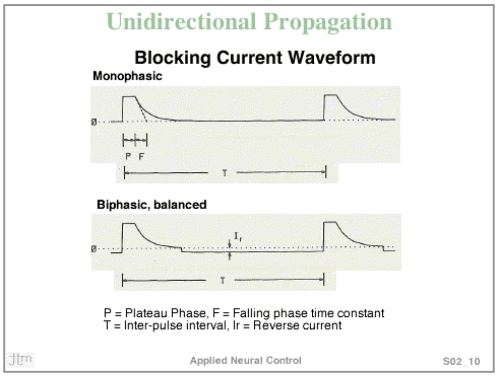
Asymmetric current injection, with more current flowing in the distal 'blocking anode' could arrest APs at lower amplitudes, resulting in decrease in the rectified, integrated EMG response.

The rectified, **integrated EMG** responses (excluding any anodic break response) are shown in the figure as a function of the stimulus amplitude, from two different experiments, on the left and right.

The proximal 'anode' was 8 mm from the 'cathode', and the distal 'anode' was 6 mm away. Rectangular pulses of 8 mS duration were applied. The maximum response was determined with 100µsec square pulses. The **balance** refers to the fraction of the total applied current that is flowing through the proximal 'anode'. The EMG was recorded from the medial Gastrocnemius with bipolar intramuscular electrodes, digitized and processed.

On the left, at zero balance(solid line, no current through the distal, 'blocking anode') APs were not arrested. With increasing current in the distal ‘anode’, EMG diminished and then disappeared. On the right, the direct response returns at higher amplitudes from the 'virtual cathode' initiated APs. The experimental results, shown in the figure, indicate that the current required to arrest APs increases as a larger percent of the current is diverted to the escape anode. These results also show that window between when arrest occurs and the virtual cathode become sufficient to cause excitation increases as a greater proportion of the anodic current is delivered to the escape anode.

Current Pulse Waveform


Unidirectional Propagation

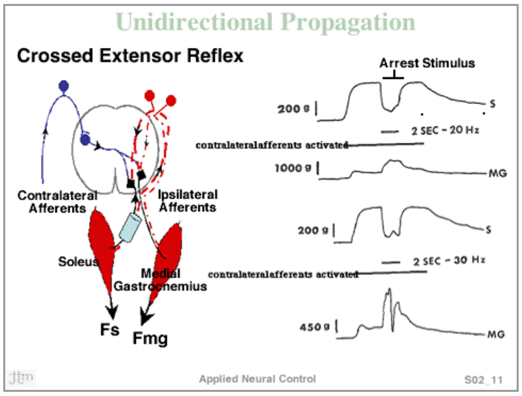
Blocking Current Waveform

P = Plateau Phase, F = Falling phase time constant
T = Inter-pulse interval, Ir = Reverse current

Applied Neural Control S02_10

Monophasic (above) and balanced biphasic (bottom) blocking current waveforms applied to tripolar nerve cuff electrode. Total current divided unequally between proximal and distal contacts ('anodes'). The central contact (the 'cathode') receives the opposite current phase, negative stimulus pulse followed by positive reversal current (if any). In the bottom figure, the reversal current I_r shown exaggerated for clarity.

Suppression of Crossed Extensor Reflex .


Unidirectional Propagation

Crossed Extensor Reflex

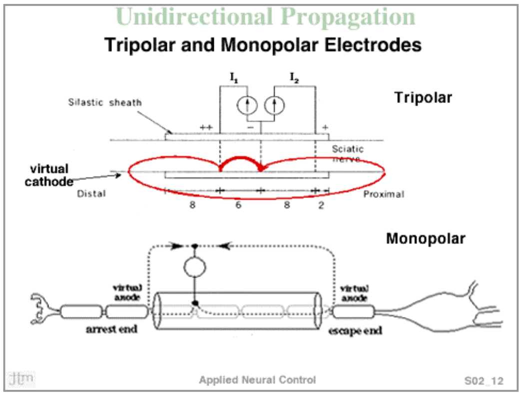
Applied Neural Control S02_11

Force developed in the Soleus muscle (Fs) by spinal reflex from skin afferents on the other hind limb could be blocked by pulse trains on the Soleus motor nerve(left side of figure). In a decerebrate preparation, cutaneous stimulation of the contra-lateral hind limb developed a background force in the Soleus (S) and Medial Gastrocnemius (MG) muscles. Application of a 2 second train of blocking pulses (3.0 mA, 0.5 mS plateau phase, 0.7 mS decay time constant) to the nerve to the Soleus, during this procedure, resulted in a 80% force reduction at 20 Hz. (right top) and a 90% reduction at 30 Hz. (right bottom)

Decerebration was done at the level of the superior colliculi. All nerve branches of the Sciatic beyond the poplitial fossa, other than branches to the Soleus and Medial gastrocnemius were severed. A blocking electrode was placed on the Soleus nerve branch. Isometric forces were recorded from the two muscles.

van den Honert, C. and J. T. Mortimer (1981). “A technique for collision block of peripheral nerve: frequency dependence.” **IEEE Trans Biomed Eng**. 28(5): 379-82.

Monopolar Nerve Cuff


Unidirectional Propagation

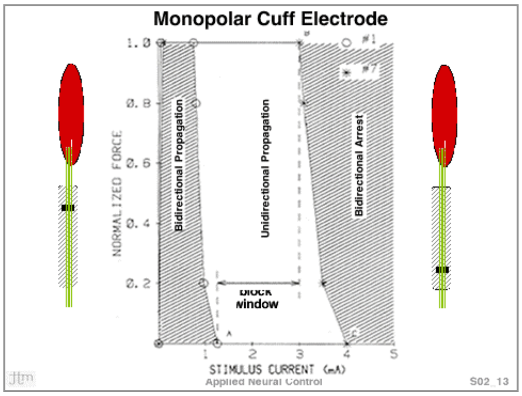
Tripolar and Monopolar Electrodes

Applied Neural Control S02_12

A monopolar nerve electrode requires less hardware than a tripolar electrode and is simpler to implement. Tripolar cuff electrode (above in Figure) uses the two flanking contacts as 'anodes' and, can create 'virtual cathodes' that may initiate action potentials (AP)

The **monopolar** electrode configuration simplifies design by having a single contact that acts as the **'cathode'** and creates **'virtual anodes'**. Relative current flow at the two ends of the electrode can be determined by the position of the contact within the insulating electrode sheath. The relative amplitudes of the stimulus pulse at the 'virtual anodes' allow **arrest** or **escape** of the propagating AP.

Propagation and arrest with Monopolar Electrodes.



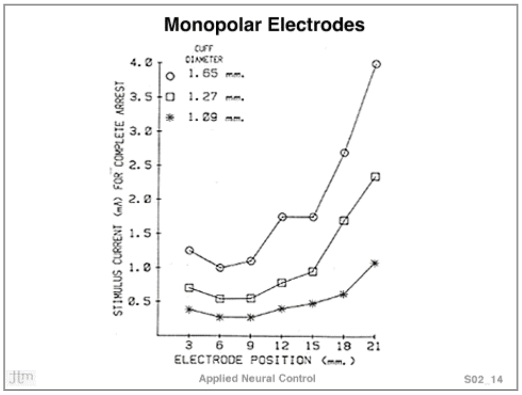
With monopolar cathode near the **distal** end of the electrode (open circles), maximum muscle force was generated below 1 mA current amplitude and AP propagation was arrested distally at higher amplitudes. With monopolar cathode near the **proximal** end of the electrode (asterisks), maximum muscle force was generated until 3 mA current amplitude.

Muscle force (normalized to the maximum force) in the cat Gastrocnemius during stimulation of the Sciatic nerve with a monopolar nerve cuff is shown in the figure. A 24 mm long cylindrical electrode was placed on the Sciatic nerve and isometric Gastrocnemius forces were recorded.

Open circles - monopolar contact was 3 mm from distal end of electrode and 21 mm from proximal end (schematic on left). Asterisks - monopolar contact was 21 mm from distal end of electrode and 3 mm from proximal end (schematic on right). Red ovals represent the distal Gastrocnemius muscle. Stimulus pulse were of 320 µsec plateau phase and falling phase time constant of 600 µsec.

The 'block window' is defined as the range of current amplitudes between complete arrest of propagation by a 'distal cathode' (point A on graph) to the onset of arrest by a 'proximal cathode' (point B on graph). Beyond point C on the graph, the 'virtual anodes arrested the APs at both ends of the electrode.

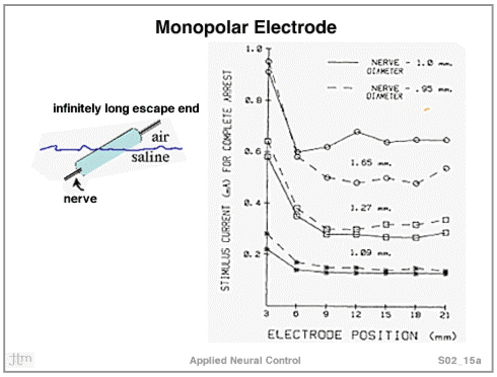
Effect of Position of the Contacts.



Minimum current to produce arrest in cuffs of 17 - 24 mm overall length occurred when the contact was 5 - 9 mm from the distal end of the cuff.

Current amplitudes for complete orthodromic arrest of propagation (at the distal end of the cuff) in relation to the contact position is shown in the figure. The position (mm) is the distance of the monopolar contact from the end of the cuff. Nerve cuffs of three different internal diameters (1.09, 1.27 and 1.65 mm) were applied on a nerve of ~ 1 mm diameter. Stimulus pulse widths were between 300 to 400 µsec. Absolute current values and slope increased with larger cuff diameters.

Electrical Isolation of Proximal End

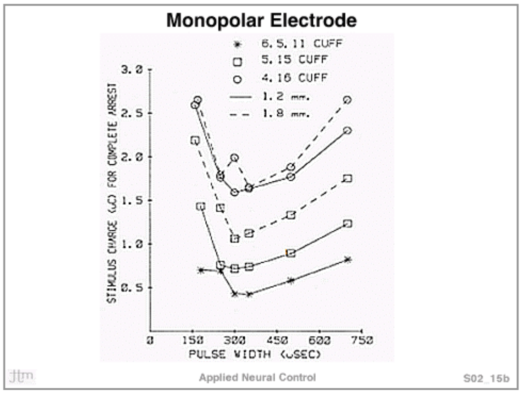


The proximal end of the electrode was electrically isolated by raising it from the saline pool around the nerve. This allowed all the applied current to flow at the distal 'virtual anode'.

As all the current flows distally, they reach a plateau for varying contact distances. Current amplitudes show increase with increasing cuff diameter. These results suggest that the electrode contact for the monopolar cuff should be positioned about 6mm from the end of the cuff. The larger the asymmetry between the arrest end and the escape end the larger the “block window”. An asymmetry of 3 yields a marginally useful window where an asymmetry of 7 is more desirable. With an asymmetry of 7 and electrode would be of the order of 5 cm in length, which may be too long for some applications.

Stimulus current amplitude for **complete arrest** of evoked APs are shown in the Figure. Results are for two different preparations, with cuff electrodes of three different diameters (1.09, 1.27 and 1.65 mm). Pulse widths were 350µsec with a minimum exponential decay phase.

Pulse Width and Charge Injection.

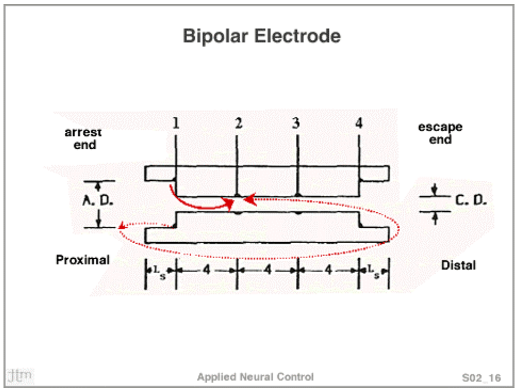


Minimum charge injection was with pulse widths between 300 to 400 µsec with falling phase time constant held at a minimum. Electrodes with monopolar contacts closer to the distal (**'arrest'**) end of the cuff required more charge injection for complete arrest.

Charge injected at distal end of cuff for electrodes with varying contact position and diameters shown in figure. The 6.5,11 (asterisk) is with the monopolar contact 6.5 mm from the distal cuff end and 11 mm from the proximal end. The 5,15 (open square) is with the monopolar contact 5 mm from the distal cuff end and 15 mm from the proximal end and 4, 16 (open circle) 4 mm from distal and 16 mm from proximal. Two cuff diameters of 1.2 and 1.8 mm were applied around a nerve of ~ 0.9 mm diameter.

Ungar, I. J., J. T. Mortimer, et al. (1986). “Generation of unidirectionally propagating action potentials using a monopolar electrode cuff.” **Ann Biomed Eng** 14(5): 437-50.

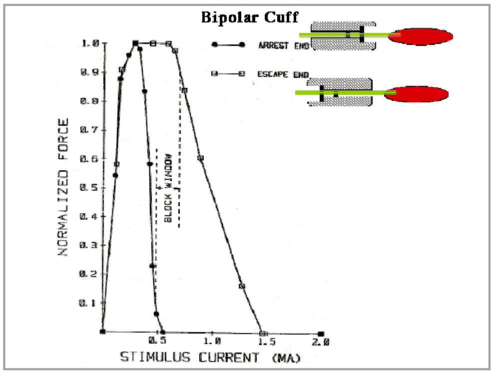
Bipolar Electrodes



A bipolar electrode configuration is less complicated to implement than a tripolar electrode. It may be better suited for clinical use than the monopolar configurations because it can be useful at shorter electrode lengths.

An experimental asymmetric electrode with two pairs of contacts is shown in the figure. A.D. is the internal cuff diameter of the primary Anodes (1 and 4) and C.D. is the internal cuff diameter of the primary Cathodes (2 and 3). L-s is the length of insulation housing the Anodes. Red arrows show the current paths from anode to cathode, internal and external to the insulating cuff.

Electrode was placed around nerve to the Medial Gastrocnemius. EMG and muscle force were recorded during electrical stimulation. Orthodromic conduction block was tested with contact 3 as cathode and 4 as the anode ('Arrest End'). Antidromic escape was tested with contacts 1 and 2 ('escape end').

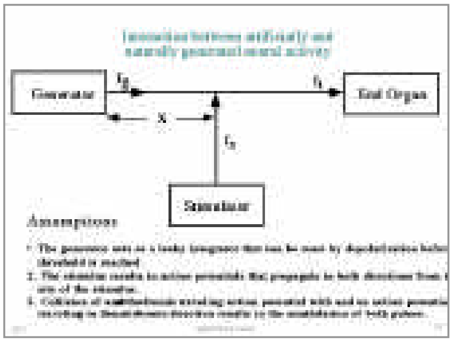


Example of twitch force, (normalized to maximum elicited by supramaximal rectangular pulse) recorded from Medial Gastrocnemius is shown in the figure, plotted against the stimulus current amplitude. The pulse width of the plateau phase was 300 µsec. In addition, the exponential decay phase was 500 µsec. Filled circles are the results for the 'arrest end', with contacts 3 and 4. Open circles are the results for the 'escape end', with contacts 1 and 2.

For the 'arrest end', force started to decline at 0.28 mA, and was down to 10% at 0.48 mA. Conduction arrest at the 'escape end' resulted in a fall of 90% of maximum force at 0.69 mA. The 'block window' is defined by the 90% maximal current at the 'escape end' minus the 10% maximal current at the 'arrest end'.

Sweeney, J. D. and J. T. Mortimer (1986). "An asymmetric two electrode cuff for generation of unidirectionally propagated action potentials." **IEEE Trans Biomed Eng.** 33(6): 541-9.

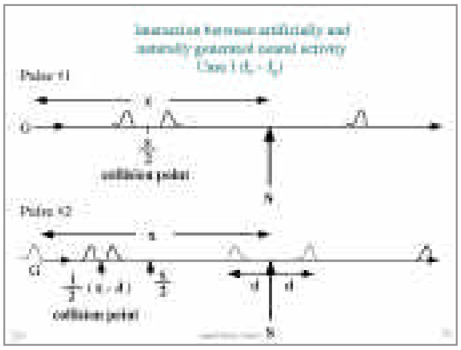
Interaction between Artificial and Naturally Generated Neural Activity



The question we want to answer here is ‘What is the effective rate action potentials are received when an electrical stimulus is applied to a nerve carrying naturally generated action potentials?’ To answer this question several assumptions will be made:

1. The generator acts as a leaky integrator that can be reset by depolarization before threshold is reached.
2. The stimulus results in action potentials that propagate in both directions from the site of the stimulus.
3. Collision of and orthodromic traveling action potential with and an action potential traveling in the antidromic direction results in the annihilation of both pulses.

Case I ($f_s > f_g$)



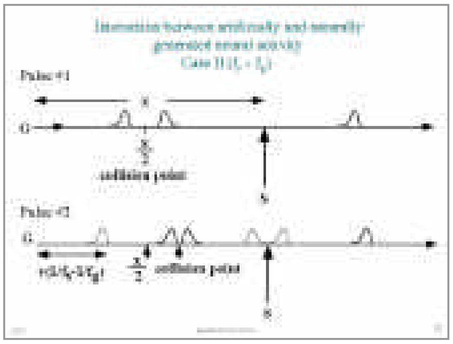
<u>PULSE # 1</u> At t =(x/2)/v the action potential initiated at the generator and the one initiated at the stimulator collide at x/2.

<u>PULSE # 2</u> At t = $1/f_s$ a stimulator action potential is initiated and at Δt later an action potential is initiated at the generator, where Δt = $1/f_g - 1/f_s$. At the time Δt the stimulator initiated action potential has moved away from the stimulation site a distance d= v Δt, where v is the conduction velocity of the action potential. The collision point for the second two action potentials is closer to the generator site than was the site for the first two action potentials.

<u>PULSE # 3</u> At 2Δt the action potentials have traveled a distance d’ away from the stimulus site before the third action potential has been initiated at the generator site, where d’=2v Δt or 2d. The collision site for the third pair of action potentials is 1/2(x-2d).

<u>PULSE #n</u> The collision point for the n^{th} pair of action potentials is 1/2[x-(n-1)d] = $1/2[x-(n-1)v(1/f_g-1/f_s)]$. When $(n-1)v(1/f_g-1/f_s)\geq x$ the stimulator initiated action potential invades the generator and all succeeding stimulator generated pulses reset the generator before the generator pulses are initiated. Note that at the nerve terminal the end organ receives an action potential for each stimulator initiated pulse and a frequency that is equal to f_s.

Case II ($f_s < f_g$)



PULSE # 2

At a time $v(1f_s-1/f_g)$ after the second action potential has been initiated at the generator and action potential will be initiated at the stimulator site

The collision site will be closer to the stimulation site than x/2. The new collision site will be

$v(1/f_s-1/f_g) + 1/2[x-v(1/f_s-1/f_g)] = 1/2[x+v(1/f_s-1/f_g)]$.

PULSE #n

The collision site for the n^{th} pair of action potentials will be $1/2[x+(n-1)v(1/f_s-1/f_g)]$. However, when $(n-1)v(1/f_s-1/f_g)>x$ a generator initiated action potential will be beyond the stimulation site and thus escape annihilation by collision. Up until this each generator initiated action potential was annihilated by a stimulator initiated action potential and for every annihilated generator initiated action potential a stimulator initiated action potential was sent to the end organ at a frequency f_s. However, when a generator initiated action potential escapes annihilation and is transmitted to the end organ the instantaneous frequency will no longer be f_s but would required to be greater than f_s. Since an action potential is received for every generator initiated action potential the average frequency for the end organ received action potentials must be f_g, with the lowest observe frequency being f_s.