Electrical Stimulation of the Neuromuscular system

Outline

• Introduction
• Neuro-muscular junction, myelin sheet
• Examples of neuromuscular prostheses
  – Upper extremity
  – Lower extremity
  – Bladder stimulation
• Derivatives (\(\nabla\)) and cross, dot products.
• Mathematical formulation of the effect of current stimulation from electrode immersed in conductive media.
The neuromuscular junction

- [http://www.youtube.com/watch?v=ZscXOvDgCmQ](http://www.youtube.com/watch?v=ZscXOvDgCmQ) (1min)
- [http://www.youtube.com/watch?v=YnVY4Waimwg](http://www.youtube.com/watch?v=YnVY4Waimwg) (3min, McGrawHill book)

Neurons, revisited
Membrane potential: how does it come about?

- Charge in each compartment is balanced
  - Outside the cell, sum of anions = sum of cations
    - $[\text{Na}^+] + 2[\text{Ca}^{++}] + [\text{K}^+] = [\text{Cl}^-]$
  - Inside the cell, sum of anions = sum of cations
    - $[\text{Na}^+] + 2[\text{Ca}^{++}] + [\text{K}^+] = [\text{Cl}^-] + [\text{A}^-]$
  - $\text{A}^-$ are other anions, which are mostly proteins
  - Anions are impermeant to the membrane

\[ \Delta \text{ membrane potential} = \Delta \text{ V}_{\text{membrane}} \text{ } \frac{1}{R_{\text{membrane}}} \Delta \text{ [K]} \]
Identifying parts of a stained neuron:

How does a spike happen?
http://www.tvdsb.on.ca/westmin/science/sbioac/homeo/action.htm
Ion channel states

Closed Channel - No Current Flows

Open Channel - Current Flows

Closed (and inactivated) Channel - No Current Flows

Inactivated Channel - No Current Flows

Activation

Deactivation

Removal of Inactivation

= Activation Gate

= Inactivation Gate

Ion channels, Agonists, antagonists.
Neurons, Myelin sheath, Synapses
Passive and active responses, Ion channel states

Saltatory conduction
Myotactic reflex

1. Hammer tap stretches tendon, which, in turn, stretches sensory receptors in leg extensor muscle

2. (A) Sensory neuron synapses with and excites motor neuron in the spinal cord
   (B) Sensory neuron also excites spinal interneuron
   (C) Interneuron synapses inhibits motor neuron to flexor muscles

3. (A) Motor neuron conducts action potential to synapses on extensor muscle fibers, causing contraction
   (B) Flexor muscle relaxes because the activity of its motor neuron has been inhibited

4. Leg extends

Intracellular responses during the myotactic reflex

1. Microdialysis to measure intracellular potential

2. (A) Sensory neuron
   (B) Motor neuron (extensor)
   (C) Interneuron
   (D) Motor neuron (flexor)

3. (A) Action potential
   (B) Motor neuron (extensor)
   (C) Interneuron
   (D) Motor neuron (flexor)

4. Time (ms)
Reflex as result of sensory neuron stimulation

A sensory neuron transforms a physical stimulus into an electrical signal. The duration of the input signal determines the number of action potentials. Thus, the greater the stimulus, the greater the number of action potentials produced.

Figure 2-10 A sensory neuron transforms a physical stimulus into an electrical signal of varying amplitude. The duration of the input signal determines the number of action potentials. Thus, the greater the stimulus, the greater the number of action potentials produced.

Figure 2-11 The sequence of signals that produces a reflex action.
References – previous 18 slides.

Action potential animation:
http://www.tvdsb.on.ca/westmin/science/sbioac/homeo/action.htm

Books available online:

Neuroscience book where I took most figures from:

Vertebrate motoneuron

**FIGURE 2.4**
The components of a vertebrate motor neuron
The cell body of a motor neuron is located in the spinal cord. The various parts are not drawn to scale; in particular, a real axon is much longer in proportion to the size of the soma.
Myelin

- Tight wrapping of cell membrane around axon
- Cytoplasm of glial cell is gradually squeezed out as cell wraps around
- Result is concentric layers of closely apposed membrane
- Acts as electrical insulator
- Huge increase in speed of action potential transmission

Myelinated axons, nodes of Ranvier

Axon (transversal section)

Myelin sheath (transversal section)
Unmyelinated axons


Myelin is produced by glia
- Oligodendrocytes in CNS
- Schwann cells in PNS

vv.carleton.ca/~neil/neural/neuron-a.html
Nodes of Ranvier

Unmyelinated axon

Myelinated axon

Saltatory conduction (Ranvier nodes), and second derivative of the extracellular potential.

Electrode-tissue interface

• Constant current x constant voltage stimulation

• Tissue damage:
  – Passive: presence of foreign object (mechanical)
  – Active: passage of current (electrochemical)

Damage to biological tissue

• Passive: vascular or neural
  – How to overcome this?
    • Change electrode size, tip geometry, substrate, anchoring

• Active:
  – primary (reaction products from electrochemistry);
  – secondary (physiological changes associated with neural excitation).
Effect of waveform

- Strength-duration curve (obtained empirically):
  - PW = pulsewidth
  - $I_{th}$ = threshold current
  - $I_{rh}$ = rheobase current, minimum current amplitude if $PW \rightarrow \infty$
  - $T_{ch}$ = chronaxie time $PW$ to excite neuron with $2I_{rh}$
  - $I_{th} = I_{rh} + (I_{th} T_{ch} / PW)$

Anodic vs cathodic stimulation
**Neuromuscular junctions**

*TUTORIAL:*
As it approaches the surface of a target muscle fiber, a **motor neuron axon** sheds its myelin sheath and splits into a small cluster of fine **terminal branches**.

Each terminal branch sits in a shallow groove in the muscle fiber membrane (sarcolemma) called a **motor end plate** (side plate). Please note that many authorities prefer, instead, to use the term motor end plate to refer to the entire neuromuscular junction.

The tips of the terminal branches, which often expand into **synaptic knobs** (= synaptic bulbs or terminal buttons), contain many mitochondria and **secretory vesicles** filled with acetylcholine (ACh). A non-myelinating **Schwann cell** (idioglia) covers the terminal branches and motor end plates.

A small space known as the **synaptic cleft** exists between the synaptic knob and motor end plate. Acetylcholine molecules, after being released from the synaptic knob, diffuse across this space and bind with receptors on the motor end plate.

Many junction folds occur along the motor end plate. The added surface area provided by these folds increases the amount of membrane available for acetylcholine receptors.

[Link to animation](http://www.getbodysmart.com/ap/muscletissue/nervesupply/junction/animation.html)

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**Neuromuscular prostheses**

Nervous system injury = impairment of motor functions.

Motor functions: body functions; limb movement.

**Objectives of neuroprostheses**: restore lost function, increase independence of disabled individuals; reduce economic impact of disability.

Current neuroprostheses use FES (functional electrical stimulation) to activate motoneurons.

**Motoneurons**: neurons that innervate muscles. Muscles are the actuators (for the desired function).

Current target patients: stroke (750,000/year incidence); SCI (10,000/year incidence, higher prevalence).
Recruitment properties

Magnitude of muscular contraction depends on: (1) electrode type; (2) stimulation waveform shape, time, amplitude; (3) location of electrode relative to motoneuron.

**Force modulation** can be achieved by: (1) rate modulation (2) recruitment

(1) **rate modulation**: there’s summation of muscular contraction if high enough frequency is used, but the muscle is more prone to fatigue. Higher frequency leads to higher (faster) fatigue.

(2) **recruitment**: number of motoneurons stimulated: more neurons means more muscles.

Muscular recruitment through electrical stimulation

A: where the electrode is located. If the stimulus intensity is low, this is the only activated area.
B: (white area) if slightly higher current, only muscle 1 would contract.
C: possibly higher force exerted by both muscles now.
D: everybody is stimulated (both muscles, through activation of both motoneuron.)
Recruitment properties

Nonlinearities should be dealt with in the implant: how to measure and deal with fatigue.

There are high gain regions, and plateau regions (why?).

Spillover should also be avoided (they contribute to the nonlinearities)
Muscle stimulation?

• With rare exceptions, neuroprostheses activate paralyzed **neurons** at different levels of the nervous system:
  – Spinal cord
  – Spinal roots
  – Peripheral nerves
  – Intramuscular nerve branches

Electrode types

• Surface:
  – Skin has high resistance, and high current needs to be passed before muscle is activated. (Large area is stimulated, unpleasant side effects).

• Implantable:
  – Epimysial (next slide)
  – Intramuscular
The Tissue Response to Epimysial Electrodes for Diaphragm Pacing in Dogs
Brian D. Schmidt, Michael W. Keith, Kevin L. Kilgore, Julie H. Grill, Kathy S. Wuolle, Geoffrey B. Thrope, Peter Gorman

Fig. 1. (a) Electrode Type 1. This electrode is characterized by a stimulating surface placed within a well to reduce high-current densities at the edge of the stimulating surface. A Dacron mesh was molded into the tabs on the sides of the stimulating disk for reinforcement during staple attachment to the muscle. Sixteen Type 1 electrodes were implanted in four dogs. (b) Electrode Type 2. This electrode type has a hemispherical stimulating surface for uniform current density. The tabs are Dacron-free to reduce electrode stiffness. Eighteen Type 2 electrodes were implanted in a total of five dogs. The absence of Dacron reinforcement resulted in staple tearing of the tabs and displacement of the electrodes from the muscle surface in ten samples. (c) Electrode Type 3. This electrode type has a hemispherical stimulating surface for uniform current density. An exposed Dacron mesh was tacke to the electrode on the surface that opposes the muscle. The Dacron was incorporated into the design to reinforce the tabs and to promote tissue ingrowth and mechanical anchoring of the electrode. Ten Type 3 electrodes were implanted in four dogs.

A MULTICENTER STUDY OF AN IMPLANTED NEUROPROSTHESIS FOR RESTORING HAND GRASP IN TETRAPLEGIA
P. Hunter Peckham, PhD†‡, Michael W. Keith, MD†‡, Kevin L. Kilgore, PhD†‡, Julie H. Grill, MS§, Kathy S. Wuolle, OTR/L, CHT§, Geoffrey B. Thrope§, Peter Gorman, MDxx¶

http://www.ifess.org/cdrom_target/ifess01/oral1/peckhamPH.htm
Epimysial versus intramuscular electrodes

- Epimysial and intramuscular are invasive.
- **Epimysial** touches the epimysia (outer sheath of the muscle), near the entry point of the nerve, and is subcutaneously secured.
- **Intramuscular**: inserted through a needle, the needle is retracted, the barbed tips of the “wire” secure it in the muscle.
Upper extremity applications

- Restoring hand grasp and release
- Handmaster (Ness, Israel)
- Bionic Glove (Prochazka)
- Freehand system (NeuroControl)
The NESS H200 is a non-invasive, portable device for combating and treating the consequences of brain damage.

This personal system is the outcome of many years of development. It is an incorporation and integration of the most effective state of the art upper limb rehabilitation technologies in a single system. It brings the fruits of the latest clinical laboratory research and expertise into the homes of patients for independent use.
Urinary Bladder: location and activation

Fig 1. The Bionic Glove. (A) Self-adhesive electrodes are placed over motor points of the muscles to be stimulated. (B) The glove is donned and tightened onto the electrodes, making electrical contact with them (Fig 2). (C) Voluntary tension of the wrist to a preset trigger angle initiates stimulation of the muscles that open the hand. (D) Extending the wrist to another trigger angle directs stimulation to the muscles that produce grasp.

http://www.polystim.polymtl.ca/anglais/urinaire/intrurin.html
**Urinary Bladder: histology**

**Tutorial Name:** Neoplasia  
**Concept Name:** In situ carcinoma  
**Slide Name:** Bladder Transitional Epithelium

**Image Description:** Transitional epithelium is found only in the conducting passages of the urinary system. Note the columnar surface cells with their large nuclei and prominent nucleoli. These are typical of transitional epithelium.

<table>
<thead>
<tr>
<th>Structures</th>
<th>Structure Descriptions</th>
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<tr>
<td>lamina propria</td>
<td>In the bladder, this is the rather dense connective tissue layer beneath the epithelium.</td>
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<tr>
<td>transitional epithelium</td>
<td>When the bladder is not distended (as in this slide), the line of swollen cells at the surface is particularly evident.</td>
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**Image Description:** Transient epithelium is found only in the conducting passages of the urinary system. Note the columnar surface cells with their large nuclei and prominent nucleoli. These are typical of transitional epithelium.

**Slide 17 Bladder Wall**  
The bladder has transitional epithelium and a thick lamina propria to allow for expansion. You will be thankful for this on those long days in lab. Bar = 250 Microns

http://www.kumc.edu/instruction/medicine/anatomy/histoweb/urinary/renal17.htm
Urinary Bladder: how does it really look?

http://www.deltagen.com/target/histologyatlas/atlas_files/genitourinary/urinary_bladder_4x.jpg

Urinary Bladder Implant. How would you do it?

http://library.thinkquest.org/15401/images/organs urinarybladder.jpg

Implantable bladder stimulator

X-rays show the sphincter contracted before stimulation (a) and loosen during stimulation (b). Also, the graph above shows that the stimulation efficiency is enhanced by more than 50% with selective stimulation, leading to an average residual volume of 9%. These results are taken from studies on 8 different subjects.

http://www.polystim.polymtl.ca/anglais/urinaire/implant.html
Medtronic’s InterStim™ Bladder Stimulator

It measures 2.4 inches (6cm) by 2.2 (5.5cm) by 0.4 inches (1cm), with a weight of 1.5 ounces (42 grams)

Spinal Reflex – what is it?

http://137.222.110.150/calnet/LMN/LMN.htm
Homework 7

1. Find, in the literature (IEEE, for example) a paper presenting a graph or numbers of FES results, with stimulus intensity versus force (by the muscle). Copy the figure or make one (out of the numbers) and explain (one paragraph is enough) what the implant is for, and what the regions you see are (plateau, high gain, linear, etc).

2. Write me an email with the time and day you can come present your project. It should be a 20min deal. I would like to see all of you on Monday, but if you can’t make it, my available days and times are:
   - Monday, Nov 6th, either between 9am and 3pm, or from 5:15 to 7pm.
   - Tuesday Nov 7th, afternoon (12pm to 3:30pm)
   - Wednesday Nov 8th, from 8am to 4pm.

   You should bring a small presentation on your project. Maximum of 10 slides. Be ready to answer questions. This will be the second phase of your project, and you will be graded for it (not as a homework).
Electrical Stimulation of the Neuromuscular system: mathematical derivations and simulations

The “del” operator (nabla, or $\nabla$)

$$\nabla = i \frac{\partial}{\partial x} + j \frac{\partial}{\partial y} + k \frac{\partial}{\partial z}$$

Gradient of $p$ (where $p$ is a scalar field): a vector field!

If we simply multiply a scalar field such as $p(x,y,z)$ by the del operator, the result is a vector field, and the components of the vector at each point are just the partial derivatives of the scalar field at that point, i.e.,

$$\nabla p = i \frac{\partial p}{\partial x} + j \frac{\partial p}{\partial y} + k \frac{\partial p}{\partial z}$$
Now we want to multiply a vector field $\mathbf{v}$ by the gradient.

Dot product between vectors $\mathbf{a}(x,y,z)$ and $\mathbf{b}(x,y,z)$:

Cross product between same vectors:

1) Dot product between gradient and $\mathbf{v}(x,y,z)$:
   Defined as the DIVERGENCE of $\mathbf{v}$ (it's a scalar!)

\[
\nabla \cdot \mathbf{v} = \frac{\partial v_x}{\partial x} + \frac{\partial v_y}{\partial y} + \frac{\partial v_z}{\partial z}
\]

2) Cross product between gradient and $\mathbf{v}(x,y,z)$:
   Defined as the CURL of $\mathbf{v}$ (it's a vector!)

\[
\nabla \times \mathbf{v} = \left( \frac{\partial v_z}{\partial y} - \frac{\partial v_y}{\partial z} \right) \mathbf{i} + \left( \frac{\partial v_x}{\partial z} - \frac{\partial v_z}{\partial x} \right) \mathbf{j} + \left( \frac{\partial v_y}{\partial x} - \frac{\partial v_x}{\partial y} \right) \mathbf{k}
\]
Laplacian operator ($\nabla^2$): divergence of the gradient. Scalar field!

\[ \nabla \cdot \nabla = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \]

**Introduction**

- Restoring function is not immediate in paralysis. Ex. FreeHand (by NeuroControl™)

- FES (functional electrical stimulation): stimulate the neuromuscular junction, neuron is stimulated first (less charge needed)

- Phrenic nerve stimulation: restore respiration (ventilation)
Quasi-static formulation of Maxwell's equations

Equivalence between dielectric and conductive media:
It helps to look in static fields (due to point charges) and relate to fields due to current sources and sinks.

\[ J = J_\Omega + J_s = \sigma E + J_s \]  \hspace{1cm} (5.5)

Using Eq. (5.1)

\[ \nabla \cdot J = \nabla \cdot (\sigma E) + \nabla \cdot J_s = 0 \]  \hspace{1cm} (5.6)

Assuming a homogeneous volume conductor, \( \nabla \cdot (\sigma E) = \sigma (\nabla \cdot E) \); therefore

\[ \nabla \cdot E = -\nabla \cdot J_s \sigma \]  \hspace{1cm} (5.7)

Because \( E = -\nabla V \)

\[ \nabla^2 V = \nabla \cdot J_s \sigma = -I_s / \sigma \]  \hspace{1cm} (5.8)

where \( I_s \) is a volume current in A/m\(^3\) and \( \nabla^2 \) is the Laplacian operator. The volume current \( I_s \) can be calculated from the knowledge of the distribution of sources in the volume conductor. This equation is the equivalent of the Poisson equation derived for dielectrics:

\[ \nabla^2 V = -\rho / \varepsilon \]  \hspace{1cm} (5.9)

derived for dielectric media. Using the following equivalence,

\[ \rho \leftrightarrow I_s \]
\[ \varepsilon \leftrightarrow \sigma \]

the solution of the Poisson equation for dielectric problems can be applied to the calculation of the current and voltage distribution in volume conductors.
Now let’s derive the voltage at a point along the axon of a neuron being stimulated by an electrode with a monopolar current source.

(See notes)
The Matlab code should be either VERY simple, or understandable (if you have never programmed in Matlab in your life).

\begin{verbatim}
i=1e-3; % current. Assume I=1mA

sigma=linspace(.12, 1, 4); % conductivity range

r=linspace(.001, .05, 100); % axon distance range (in meters)

for k=1:4;
    for j=1:100;
        v(k,j)=i/(4*pi*sigma(k)*r(j));
    end;
end;

plot(r*100,v*1000);
grid
xlabel('r[cm]');
ylabel('V[mV]');
title('Plot of Monopole Potential V=I/4*pi*sigma*r for Typical Brain Conductances');
\end{verbatim}
Voltage along the axon due to a bipolar source. Current through one electrode has the same amplitude (but opposite sign) as current through the other electrode.
Now plot both sides of an axon – orthodromic and antidromic – for the bipolar stimulation.
Analysis of Models for Extracellular Fiber Stimulation

FRANK RATTAY

\[ f = \frac{3V_r}{4\pi} - \frac{\rho A_d}{4\pi} (x^2 + z^2)^{-3} (2x^2 - z^2). \]

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Fig. 2. Stimulation with a monopolar electrode. (a) Change of the extracellular potential along the fiber caused by anodal stimulation. Activating function for anodic (b) and cathodic (c) stimulation. (d) Shows the position of the electrode to get the upper traces. The border between depolarizing and hyperpolarizing regions is given by an angle of 70.5° and this angle does not depend on fiber parameters or the conductance of the extracellular medium [1]. Removing a negative electrode from the axon means to obtain a broader stimulating part; in the case of a myelinated axon more nodes are stimulated.
\[ f = \frac{\partial^2 V}{\partial x^2} = \frac{\rho_e l}{\pi} \left( x^2 + z^2 \right)^{-\frac{3}{2}} \left( 2x^2 - z^2 \right). \]

Iel = 1 mA, rhoe = 1 kOhm.m, z = 10 mm
COMPARING STIMULATION FOR DEPOLARIZATION OR HYPERPOLARIZATION

V (mV)

x along axon (cm)

cathode
anode