Learning objectives

- Explain the sliding filament mechanism of muscle fiber contraction.
- Define a motor unit, and explain its properties.
- Describe how muscles act at the joints to produce movement.
- Understand neural control principles associated with muscle physiology & mechanics.
- Read Kandel chapter 34, understand all figures.

From spinal cord to skeletal muscle:

- Parts
  - Alpha-motor neurons
  - Muscle
    - ~40% body mass
  - Fascicle = bundle
  - Fibers = cells
    - ~5 cm X 0.1 mm
  - Myofibrils

Source throughout: Kandel et al. 2000 (unless otherwise noted)
Motor unit
- ~100/muscle, 100-1000 or more fibers per mn
  - innervation ratio
- Interface: Motor end plate at the neuromuscular junction
  - ACh, action potential depolarizes all fibers to threshold simultaneously

Neuromuscular Junction

ACh

More parts:
- Myofibril
  - Striations
- Sarcomere
  - Portion of myofibril
  - 1.5-3.5 μm length
  - composed of...
- Myofilaments
  - Thick=myosin, stem and globular heads
  - Thin=actin, helical protein
  - troponin attached to tropomyosin

Contractile Mechanism: Sliding Filament Theory
- Sarcomeres squish together
- cyclical interaction between actin and myosin
- Sequence: 5 events
  - Rest: Myosin stretched outward, ADP bound, actin binding sites blocked
  - Ca+ release, Tr/TrM reveal binding site,
    Myosin head rotates, filaments pulled together (~.06 μm), fiber shortens
  - After power stroke, ATP binds to myosin, myosin detaches from actin
  - Energy from ATP → ADP+P (Mg needed) allows myosin head to reach forward to next actin binding site
Non-contractile elements
- Parallel: Connectins
  - From myosin to Z disks
  - Keep filaments aligned
- Parallel: Endomysial connective tissue
  - Collagen matrix surrounding muscle fiber
- In-series
  - Tendons, aponeuroses
    - Can stretch and store mechanical energy
    - Concentric vs eccentric stretch properties

Motor unit properties
- Length-tension curve (aka force-length rel.)
  - Degree of overlap & non-contractile element properties determine force output
  - Control issue

Motor unit properties
- Force velocity relationship
  - Faster the shortening rate, lower the force
    - Fewer active cross bridges relative to isometric condition
These two properties together affect neural control

- Nervous system must account for MU properties when making brain-output to force-output calculations during motor learning & performance.

Twitch profile of a MU

- Mechanical contraction of a muscle unit in response to an action potential is called a twitch.
- You can artificially stimulate the nerve and see exciting things:
  - At certain rates (before previous decay has ended), twitches summate.
  - Really high rates, no individual force modulations. Tetanus. Don’t ever see this in the healthy state.

- Next lecture: more interesting pathological twitching, I promise!

Peripheral Fatigue

- Less force and rate of force rise reduced after repeated activation:
  - Rise & relaxation times prolonged, frequency spectrum of muscle reduced (more power in lower frequencies).
  - Fatigue can occur anywhere along response chain.

Three motor unit sub-types
- Characteristics determined by metabolism, support (blood supply, enzymes, myoglobin)
  - Type I: Anaerobic metabolism, Large glycogen stores
  - Type IIa: Aerobic metabolism
  - Type IIb: Anaerobic metabolism, Large glycogen stores

Motor unit subtypes
- A given motor unit has only one subtype of fibers
  - Fast twitch units usually have a large # of large fibers, motor neurons have large cell bodies, large diameter axons
  - Slow twitch units, not so much

Cat gastrocnemius
- 50% of muscle, 20% of power (postural, slow movement)

Motor unit recruitment
- Size principle, helps with stability and smooth force development
Muscle action at joints

- Multiple degrees of freedom at skeletal and muscular level
  - Provides stability and adaptability

  ![Moment arm](image)

  Moment arm also affects required muscle activation for a given torque

- Muscle acts as a low pass filter for neural signals
  - Need to control the timing of muscles about a joint for different movements

  ![Signal diagrams](image)
Muscle pattern for basic movement

- Triphasic burst pattern
  - produces triphasic torque pattern

Brown & Cooke (1990b)

Sergio & Ostry (1995) EBR 105

• Multiarticular muscles
  - brain must account for actions at other joints for single-joint movements

Sergio & Ostry (1995) EBR 105

All degrees of freedom must be accounted for when programming muscle activity

• Example 1: Bicep activity for 2 df movements
• Example 2: compensation, 1df


Summary
• Motor neurons carry neural commands to skeletal muscles
• Muscles exert force to produce torque at joints via contractile mechanism
• Numerous factors affect activation:force relationship
• Different types of motor units and their behaviour allow for a rich repertoire of motor behaviour
• Physiological and mechanical properties of the muscular system have consequences for the neural control of movement

Objectives, Diseases of the Motor Unit & Spinal Reflexes
• Explain the differences and criteria for distinguishing myopathic versus neurogenic disease
• Describe different case studies for each type of disease
• Understand the neural mechanisms underlying basic reflexes and their modulation
• Read Kandel chapter 35 & 36, understand all figures.
Motor unit and Myopathic disease

- Myopathic: problems with the muscle
- Neurogenic: problems with the motor neuron and ‘pre’ motor neuron

- 3 examples of motor dysfunction
  - Muscular dystrophy(ies)
  - Amyotrophic Lateral Sclerosis (ALS)
  - Multiple Sclerosis

Characteristic of the disease depends on which component of motor unit affected

- Nerve cell body: motor unit disease
- Motor neuron axon/neuromuscular junction: peripheral neuropathy
- Muscle degeneration: myopathy

- Different clinical implications for different sources of disease

Criteria for distinguishing neurogenic versus myopathic diseases

- Myopathic
  - main symptom = muscular weakness/wasting (atrophy)
    - leads to difficulty walking, lifting, etc.
    - also myotonia, myalgia, cramps
- Neurogenic diseases have these characteristics also, though
  - tendon reflexes lost
  - gradual weakening
  - fasciculations (visible twitches)
‘Upper’ and ‘Lower’ motor neurons

- Used clinically (historically)
  - lower motor neurons directly innervate muscle
  - ‘upper’ motor neurons originate in higher brain regions and synapse with ‘lower’ motor neurons in spinal cord
    • technically ‘premotor’ neurons (but don’t confuse with premotor cortex neurons!)
- Each produces distinctive symptoms
  - upper: spasticity, overactive tendon reflex (msr), Babinski sign
  - lower: atrophy, fasciculations, loss of tendon reflex, hypotonia

Clinical and lab tests often needed to distinguish the two

EMG

- BIOPSY
  - See histochemistry differences
  - Type I and II fibres usually equal and distributed randomly
  - neuropathy: can see clustering, size changes
  - myopathy: can see damage
Neuropathies: symptom mechanisms

- Motor neuron disease: affects motor neurons leaving sensory neurons intact
  - selective lesioning of corticospinal tracts
  - fasciculation caused by something beyond spinal cord (axon? terminals? NM junction?)
- Peripheral neuropathies affect sensory and motor functions
  - often have paresthesias (numbness, tingling, etc)
- May be categorized as ‘demyelinating’ or ‘axonal’
  - demyelinating more common

Demyelination: causes ‘negative’ symptoms

- can’t conduct nerve impulse as well
  - lower conduction velocity, conduction block, impaired high impulse frequencies

  Record action potentials to determine conduction velocity

- leads to slowing of conduction velocity
  - no node (of what?) jumping, smaller diameter
  - attenuates action potential
- lose synchrony of conduction if at different velocities
  - can lead to reflex problems, odd sensations

  insulation lost

  ion channel differences
Causes

- viral: certain viruses can affect motor nerves selectively (eg, poliomyelitus)
  - virus may induce autoimmune disorder (eg, guillain-barré syndrome…and counting…)
- neonatal hypoxia (eg, cerebral palsy)
- unknown (eg, multiple sclerosis)
- genetic (eg, muscular dystrophies)

Case 1: Duchenne Muscular Dystrophy

- Description
  - Muscular dystrophies are genetic disorders characterized by progressive muscle wasting and weakness that begin with microscopic changes in the muscle.
  - As muscles degenerate over time, the person's muscle strength declines.
  - Patients begin to show signs of muscle weakness as early as age 3. The disease gradually weakens the skeletal or voluntary muscles, those in the arms, legs and trunk. By the early teens or even earlier, the heart and respiratory muscles may also be affected.

- Symptoms (boys only)
  - Children with the disorder are often late in learning to walk
    - clumsy, unsteady gait, difficulty raising arms, walk on toes
  - lose the ability to walk sometime between ages 7 and 12
  - in teen years, activities involving the arms, legs or trunk require assistance or mechanical support
  - often develop fixations of the joints, known as contractures

Gowers manoeuvre: distinct way of getting up with weak legs.
• Causes
  – In 1986, researchers identified the gene that, when flawed (mutation) causes DMD. In 1987, the protein associated with this gene was identified and named dystrophin
    - lack of dystrophin affects cytoskeleton

• Treatment
  – Physical therapy for contractures (knees, hips, feet, elbows, wrists, fingers) & spinal curvatures
    • Range-of-motion and back straightening exercises
    • Braces on the hands and lower legs
    • Tendon release surgery, spine-straightening surgery
  – Medications to slow muscle degeneration
    • Catabolic steroids (prednisone)
      – Has side effects: weight gain, bone loss, psychological distress
  – Braces, wheelchair (eventually)
  – Future: stem cell therapy

Case 2: Amyotrophic Lateral Sclerosis
• Amyotrophic: neurogenic muscle atrophy, Lateral sclerosis: hardening of lateral CS tracts
• Description
  – Upper and lower motor neuron disease
  – Motor neurons undergo shrinkage, caused by altered cytoskeleton
    • They enervate less and less musculature, and those muscles atrophy
  – Mean onset age: 56-63

Source next 4: http://www.neuro.wustl.edu/neuromuscular/spinal/als.htm
• Symptoms
  – initially, muscle weakness and stiffness
  • Usually the first muscles affected are those in the hands, arms and legs. (lateral CS tracts)
  • Speech problems, such as slurring, hoarseness, or decreased volume may also occur (dysarthria)
  – Motor neuron signs (normal sensation): atrophy, hyperactive msr, hyper/hypotonia, Babinski’s sign, spasticity, fasciculations

• Causes
  – exact causes of the neural degeneration is unknown
  – 5 to 10 % can be attributed to heredity
  • There are multiple genes in which, if mutated, may cause ALS
  – suspects: viruses, neurotoxins, heavy metals, DNA defects (especially in familial ALS), immune system abnormalities, and enzyme abnormalities

• Treatment
  – Motor deficits only. Sensory and cognitive function intact
  – Treatment focuses on relieving symptoms and maintaining an optimal quality of life
  – Medications for spasticity, discomfort, pain
  – Physical therapy for cramping, contractures

• Prognosis
  – Fifty percent of patients die within 3 years of diagnosis,
  20% live 5 years, and
  10% live 10 years, 20% longer
Case 3: Multiple sclerosis

• Description
  – In MS, myelin is lost in multiple areas, leaving scar tissue called sclerosis.
  • Damaged areas are also known as plaques or lesions.
  • Sometimes the nerve fiber itself is damaged or broken.
  – Most people with MS are diagnosed between the ages of 20 and 50.
  • Two to three times as many women as men have MS.
  – MS is a chronic, unpredictable neurological disease.
  – The majority of people with MS do not become severely disabled.

• Symptoms
  – Wide range of unpredictable symptoms, vary from person to person, time to time.
  • Can affect vision, speech, balance, bladder function, coordination, dizziness, pain, tremors can be problems.
  – Different types
    1) Relapsing-Remitting: flareups then remission (most common - 85%)
    2) Primary-progressive: slow continuous worsening (10%)
    3) Secondary-progressive: 1) followed by 2)
    4) Progressive relapsing: continuous with flareups (rare).

• Causes
  – It is believed that MS is an autoimmune disease.
  • In the case of MS, myelin is attacked.
  – Unknown what triggers the improper autoimmune reaction.
  – Several factors are involved
    • Genetics
    • Gender
    • Environmental Triggers
      – Possibilities include viruses, trauma, and heavy metals.
• Treatment
  – Medications can treat relapsing forms of MS:
    1) Synthetic interferons (Avonex, Betaseron)
       • Host cells infected with a virus produce interferons.
       Induces neighbouring cells to synthesize a protein that inhibits intracellular viral replication. First line of defense against viral infection
    2) Glatiramer Acetate (Copaxone)
       • A synthetic protein that simulates myelin basic protein
       • This drug seems to block myelin-damaging T-cells by acting as a myelin decoy
    3) Mitoxantrone (Novantrone)
       • Suppressing the activity of T cells, B cells, and macrophages that are thought to lead the attack on the myelin sheath.

...and on to: Spinal reflexes!
• Most elementary form of motor coordination (linking the contraction of independent muscles)
• Automated but adaptable response to a sensory stimulus
  – Responsible neural circuitry entirely contained within the spinal cord
• Two important features
  – Locus
  – Strength

Stretch reflex (tendon tap)
• Monosynaptic stretch reflex
  – Ia afferent synapses directly onto α motor neuron of same muscle
  – Branches of Ia afferent excite motor neurons to synergist muscles
  – Regulates muscle tone
Most spinal reflexes are polysynaptic

- Allows the reflex to be modified
- Muscle action around a joint is coordinated by inhibitory interneurons
  - Muscle group around a joint linked by a reflex pathway called a myotatic unit

Recurrent inhibition

- **Renshaw cell** (RC) receives signal from motor neuron and in turn inhibits that same neuron, and others nearby
  - can be modulated by supraspinal commands
  - affects gain of motor neuron

Reciprocal Inhibition

- **Ia afferent synapses onto Ia interneuron** (Ia IN), which inhibits motor neuron to opposing muscle
  - prevents opposing muscles from counteracting each other during application of external loads
  - the gain of this reflex can be modulated by brain
Group Ib inhibitory interneurons inhibit the homonymous $\alpha$ motor neuron

- “Tendon organ reflex”
- Regulates muscle tension
- Modulated by multiple inputs
- Depends on behavioural state of the animal
- With stretch reflex, stabilizes posture

Key concept: ‘descending’ motor signals and multisensory inputs can change the balance of inputs to interneurons

- Can alter transmission in reflex pathways
  - may lead to ‘reflex reversal’
  - (compare ‘flexor withdrawal’ to ‘extensor thrust’ reflexes discussed in reading)
- Regulates strength of spinal reflex
- Combine to regulate movements

Sites of reflex regulation
1. alpha motoneuron
2. interneuron
3. afferent axon
Sensory feedback important for tuning movements and reflexes

- Can see reflex reversal depending on the phase of the step cycle that an obstacle is encountered
  - What's the functional relevance of this?


Summary

- Diseases affecting the peripheral nervous system result in a constellation of symptoms, "lower motor neuron" signs
  - To be compared to "upper motor neuron" signs seen in stroke (FUN II)
  - Note different effects of myopathy vs. neuropathy
- Spinal reflexes are coordinated involuntary motor responses, but they can to some extent be modulated
  - Groups of interneurons receiving higher level and peripheral input are responsible for this modulation