Problem Set 3.2

Neuromuscular Transmission, Muscle Force, and Energetics

1. At rest in muscle cells, the E_m is not constant but shows seemingly random fluctuations that appear to be in units of about 0.5 mV. These are called **miniature end-plate potentials** and are due to the fusion of a single vesicle containing acetylcholine with the presynaptic nerve terminal membrane.
   A. If the muscle cell is 50 μm in diameter and 10 cm long, and its specific capacitance is $1\ \mu F\ cm^{-2}$, how much charge must flow for this 0.5 mV change due to a single vesicle fusion event?
   B. If $E_{Na} = +66$ mV and $E_m = -85$ mV, and the MEPP rises in 0.5 ms, what is the average conductance increase in the membrane due to the single fusion event? Assume the current is all carried by Na^+.
   C. How many channels do you think open during the MEPP? Use 40 pS for the unitary conductance of the acetylcholine receptor.
2. Synapse A on a motoneuron results in a EPSP with a peak depolarization of 2 mV. Synapse B also results in an EPSP with a peak depolarization of 2 mV. Synapse C results in an IPSP peak of hyperpolarization of 2.5 mV. The resting potential of the nerve is −70 mV.
   A. Simultaneous firing of A and B results in what peak potential? What is this phenomenon called? Do you think it is enough to reach threshold?
   B. Simultaneous firing of A and C results in what peak potential? What is this phenomenon called? Do you think it is enough to reach threshold?
   C. Simultaneous firing of A, B, and C results in what peak potential?
3. The membrane potential of a cell is −70 mV. E_{Na} is +65 mV, $E_K = -95$ mV, $E_{Cl} = -75$ mV.
   A. If a Na channel was to open, in which direction would Na^+ go? Is this a negative or positive current?
   B. If a K channel was to open, in which direction would K^+ go? Is this a negative or positive current?
   C. If a Cl channel was to open, in which direction would Cl^- go? Is this a negative or positive current?
4. Neuron A makes a synapse on a dendrite on a motor neuron and neurotransmission at this synapse produces a 5 mV depolarization immediately adjacent to the synapse.
   A. Why is the EPSP less when measured further away?
   B. Would you expect the EPSP to be larger in the soma or further away from the synapse up the dendrite? Why?
   C. Repetitive firing of the neuron should result in a larger depolarization. What is this phenomenon called?
5. Consider the sarcomere shown in Figures 3.5.3 and 3.5.4. Assume that the myofibril is about 1 μm thick.
   A. What is the approximate maximum distance between the nearest RyR on the SR and the TnC on the thin filament?
   B. Assume the diffusion coefficient of Ca^{2+} in the cytosol is about $0.4 \times 10^{-5}\ cm^2\ s^{-1}$. What is the time of diffusion from the nearest RyR to the furthest TnC?
6. Assume that the sarcomere length is 2.8 μm.
   A. How much overlap is there between the thick and thin filaments?
   B. What fraction of the force generators on the thick filament do not overlap with the thin filament?
7. A.V. Hill derived an empirical equation to describe the force–velocity relationship. He wrote

$$(T + \alpha)(v + \beta) = (T_0 + \alpha)\beta$$

   where T is the tension, or force, v is the velocity, and T_0 is the force at which $v = 0$, the isometric tension.
   A. Derive an expression for the maximum velocity (recall that maximum velocity occurs when $T = 0$) in terms of T_0, α, and β.
   B. Hill's equation can be written in a normalized form, where $v' = v/v_{max}$ and $T' = T/T_0$. Show that this normalization results in

$$v' = (1 - T')/(1 + T'/k) \quad \text{where } k = \alpha/T_0 = \beta/v_{max}$$

   C. Derive an expression for power $(T \times v)$ in terms of v, T_0, α, and β.
8. Consider muscle fibers that are 8 cm long and that develop a maximum of $20\ N\ cm^{-2}$ force. Consider a muscle that has a volume of $20\ cm^3$ with the fibers aligned with the direction of the tendon ($\theta = 0$).

DOI: http://dx.doi.org/10.1016/B978-0-12-800883-6.00031-8

A. What is the maximum force developed by this muscle?
B. If partial recruitment results in activation of 10% of the muscle fibers (assuming they are all of equal size), how much force could the muscle generate?
C. If the muscle fibers contract 15% of their length in 50 ms under no load, what is the maximum muscle velocity?
D. Suppose the muscle fibers were oriented at 15° relative to the tendon axis, with the same volume of muscle. What is the maximum force delivered to the tendon? What is the maximum velocity?

9. Suppose that the amount of TnC in fast-twitch muscle fibers is about 70 μM. The density of muscle is about 1.06 g cm^{-3}.
A. From the structure of the thin and thick filaments, estimate the amount of myosin heads. Convert this to nmol per g of tissue.
B. Suppose that the muscle activation is 75 ms and that the turnover of the heads is 10 s^{-1}. About how many ATP would be hydrolyzed in a single twitch per g tissue? Use a step function for activation: it is on or off with a 75-ms duration. This is not how the muscle works, but reality is a lot more complicated to simulate. We are doing a crude estimate here.
C. Assume that the TnC binds 2 Ca^{2+}. How much ATP would be split by the SERCA pumps to return activating Ca^{2+} to the SR per g tissue? Suppose now that we consider a slow-twitch muscle fiber which has TnC1 that binds only 1 Ca^{2+} per TnC and has a turnover of 3 s^{-1} and a twitch time of 200 ms.
D. Estimate the number of ATP hydrolyzed by the cross-bridges during the twitch.
E. Estimate the ATP hydrolyzed by the SERCA pumps to return activating Ca^{2+} to the SR per g tissue.
F. Do you think there would be more or less SR necessary in slow-twitch muscle fibers?