BIOE 599 – Physiology for Engineers
Homework Set 3

Due: 3/16/18 at 11:59 pm to Mike Pavol

Answer the following problems.

Problems 1 and 2 will involve the use of HHSIM to run simulations for Hodgkin-Huxley (HH) non-propagating action potentials. See: http://www.cs.cmu.edu/~dst/HHsim/. It is recommended that you download the Matlab code and run that directly, rather than running HHSIM as a Windows, Mac, or Unix executable file.

A tip: Be sure to use the "Recall" feature in HHSIM to reset parameters to rest state

1. **The strength-duration exercise already mentioned in class.**

   Create a "strength-duration" curve for excitation of action potentials using HHSIM. Strength-duration curves determine the threshold current for a range of pulse widths of stimuli. In general, briefer stimulation pulses will require more current to excite the membrane. Longer duration pulses will require less current (down to a minimum for very long pulses, which is called the "rheobase" current). You will need to identify an appropriate working ranges of pulse durations, and for each duration, identify a good estimate of the threshold current. Plot the strength-duration curve and identify the value of the rheobase current.

2. **Refractory periods.**

   Use HHSIM again to explore the absolute and relative refractory periods for HH membranes. You will want to use the STIM1 settings in HHSIM to create a first stimulus to launch an action potential, and then use STIM2 to create a second stimulus in the wake of the first action potential (i.e. after a time delay relative to the first stimulus pulse). Identify over a range of delays how the threshold current needed by STIM2 is increased relative to the threshold for stimulation needed by the first pulse. Plot the current needed by STIM2, normalized to the current needed for STIM1, as a function of the time delay.

3. **Cross-bridge-based Modeling of Muscle.**

   A MATLAB program "DM_Muscle" has been written to simulate the distribution-moment model of muscle reported by Zahalak and Ma (1990). This model of muscle is based on cross-bridge kinetics, using the approach described on the slide "Cross-bridge-based Models of Muscle" in the Muscle Physiology (part 1) lecture notes. It makes the simplifying assumption that n, the number of attached cross bridges, is a Gaussian function of the normalized bond length x/h. In this model:

   - f1 = cross-bridge bonding rate function
   - g1 = cross-bridge unbonding rate function for $0 < x/h < 1$
   - g2 = cross-bridge unbonding rate function for $x/h < 0$
   - g3 = increase in cross-bridge unbonding rate function for $x/h > x_0$

   The rate at which new cross-bridges form is also a function of the number of available bonding sites, which is a function of both the sarcomere length and the sarcoplasmic free calcium concentration. Calcium dynamics are modeled as described on the slide "Active State Dynamics" in the Muscle Physiology (part 1) lecture notes. The model also includes a series elastic element, modeled as a spring of constant compliance.

DM_Muscle may be used to model isometric or isokinetic (constant velocity) muscle actions. Parameters that may be specified include:

- SimulationTime = Duration (s) of the simulation
- N_OnTime = Time (s) at which neural excitation of the muscle will begin
- N_OffTime = Time (s) at which neural excitation of the muscle will cease
- N_ExciteLevel = Level of neural excitation, as a proportion (0 – 1) of maximum
- M_StartLength = Initial length (m) of the muscle
- M_StartTime = Time (s) at which the change in muscle length will begin
- M_Velocity = Velocity (m/s) at which the muscle will lengthen
- M_Distance = Distance (m) that the muscle will lengthen

where positive values of M_Velocity and M_Distance correspond to muscle lengthening, negative values to shortening. These are applied to the length of the muscle itself, not the overall musculotendon length. There are also 14 parameters that describe the behavior of the muscle and tendon. These are as specified in the program comments, and additional explanation will be provided on request.

The output of the program includes a set of plots and a comma-delimited text file "DM_Muscle.csv" with the following variables as a function of time (s):

- Musculotendon length (m)
- Sarcoplasmic free calcium concentration (proportion of maximum)
- Musculotendon force (N)

Use this program to address the following:

a. Perform a set of isometric (constant muscle length) simulations with the following:
   - Simulation duration = 1 s
   - Neural excitation on time = 0.1 s
   - Neural excitation off time = 0.5 s
   - Neural excitation level = 1

   for 3 muscle lengths:

   1) Muscle length of 0.15 m (this is the default simulation of the program)
   2) Muscle length of 0.11 m
   3) Muscle length of 0.19 m

   Submit a graph of musculotendon force vs. time for each simulation. It is suggested that you put all 3 sets of results on the same graph.

   Briefly explain, in terms of the underlying physiology:

   i. The reasons for the observed pattern of variation in force over time;
   ii. The reason for the difference in peak force between the 3 simulations;
   iii. The reason the overall musculotendon length changed as it did during the isometric muscle actions.

b. Perform a set of isokinetic simulations with the following:
   - Simulation duration = 2 s
   - Neural excitation on time = 0.05 s
   - Neural excitation off time = 2 s
   - Neural excitation level = 1
   - Movement start time = 0.4 s

   for 3 conditions:
   1) Shorten a distance of 0.04 m at 0.03 m/s from a muscle length of 0.17 m
   2) Shorten a distance of 0.04 m at 0.06 m/s from a muscle length of 0.17 m
   3) Lengthen a distance of 0.04 m at 0.03 m/s from a muscle length of 0.13 m

   Submit a graph of musculotendon force vs. time for each simulation. It is suggested that you put all 3 sets of results on the same graph.

   Briefly explain, in terms of the underlying physiology:
   i. The reasons for the observed pattern of variation in force over time after the onset of shortening or lengthening;
   ii. The reason for the differences in force between the 3 simulations.

c. Perform a set of isometric simulations for the following:
   - Simulation duration = 1 s
   - Neural excitation on time = 0.1 s
   - Neural excitation off time = 0.5 s
   - Neural excitation level = 1
   - Muscle length = 0.15 m

   with the following changes to the muscle parameters in each of 3 simulations:
   1) f1 = 60 /s, with g1, g2, and g3 at their default values
   2) g1 = 16 /s, g2 = 340 /s, and g3 = 60 /s, with f1 at its default value
   3) The combined changes to f1, g1, g2, and g3 from (1) and (2)

   Submit a graph in which musculotendon force is plotted vs. time for all 3 simulations, together with simulation (1) from part (a).

   Briefly explain, in terms of the underlying physiology, reasons for any differences in the magnitude and rate of change of force between these simulations in part (c) and simulation (1) from part (a).

4. The Hill-type Muscle Model.

A MATLAB program "Hill_Muscle" has been written to simulate a Hill-type musculotendon unit. The dynamics of neural excitation and muscle activation are each modeled as described on the slide "Active State Dynamics" in the Muscle Physiology (part 1) lecture notes (Winters & Stark, 1985). The length-tension and force-velocity behaviors of the contractile element are derived from Kaufman et al. (1989) and Winters and Stark (1985), respectively. The parallel elastic element is modeled as a nonlinear spring: $F_{PE} = k_{1PE}e^{k_{2PE}\varepsilon_M}$. Pennation of the contractile and parallel elastic elements is modeled as in Zajac et al. (1986).

Finally, the series elastic element is modeled using Model 1 from the slide "Models of Tendon and Ligament" in the Tendon and Ligament lecture notes (Winters & Stark, 1985).

Hill_Muscle may be used to model isometric or isokinetic actions of a musculotendon unit. Parameters that may be specified include:

- SimulationTime = Duration (s) of the simulation
- N_OnTime = Time (s) at which neural excitation of the muscle will begin
- N_OffTime = Time (s) at which neural excitation of the muscle will cease
- N_ExciteLevel = Level of neural excitation, as a proportion (.01 – 1) of maximum
- MT_StartStrain = Initial strain of the muscle (relative to the muscle fiber optimal length)
- MT_StartTime = Time (s) at which the change in musculotendon length will begin
- MT_Velocity = Velocity (m/s) at which the musculotendon unit will lengthen
- MT_Distance = Distance (m) that the musculotendon unit will lengthen

where positive values of MT_Velocity and MT_Distance correspond to musculotendon lengthening, negative values to shortening. These are applied to the overall musculotendon length. There are also 13 parameters that describe the behavior of the muscle and tendon. These are as specified in the program comments, and additional explanation will be provided on request.

The output of the program includes a set of plots and a comma-delimited text file "Hill_Muscle.csv" with the following variables as a function of time (s):

- Musculotendon length (m)
- Muscle activation level (proportion of maximum)
- Musculotendon force (N)

Use this program to address the following:

a. Perform an isometric (constant musculotendon length) simulation with the following:

   - Simulation duration = 1 s
   - Neural excitation on time = 0.1 s
   - Neural excitation off time = 0.5 s
   - Neural excitation level = 1
   - Muscle strain of 0.25

   Submit a graph of musculotendon force vs. time for the simulation.

   Briefly explain, in terms of the underlying physiology, why the initial musculotendon force differs from simulation (3), conducted at a similar muscle length of 0.19 m, in part (a) of question 3.

b. Perform a pair of isokinetic simulations with the following:

   - Simulation duration = 2 s
   - Neural excitation on time = 0.05 s
   - Neural excitation off time = 2 s
   - Neural excitation level = 1
   - Movement start time = 0.4 s

   for 2 conditions:

1) Shorten a distance of 0.04 m at 0.06 m/s from a muscle strain of 0.13
2) Lengthen a distance of 0.04 m at 0.03 m/s from a muscle strain of -0.13

Submit a graph of musculotendon force vs. time for each simulation. It is suggested that you put both sets of results on the same graph.

Compare and contrast the results of these 2 simulations to the corresponding simulations [(2) and (3)] conducted in part (b) of problem 3.

c. Perform a set of isokinetic simulations with the following:
   - Simulation duration = 1.4 s
   - Neural excitation on time = 0.05 s
   - Neural excitation off time = 1.4 s
   - Neural excitation level = 1
   - Movement start time = 0.4 s
   - Shorten a distance of 0.04 m at 0.06 m/s from a muscle strain of 0.13

   for 4 conditions:
   1) Set the muscle fiber optimal length (lm0) to 0.08 m
   2) Set the maximum shortening velocity (vmax) to 2 fiber lengths/s
   3) Set the series elastic element slack length (lse0) to 0.17 m
   4) Set lm0 to 0.08 m, the pennation angle to 9°, lse0 to 0.17 m, and the maximum isometric force (Fmax) to 187 N. This muscle has the same volume and musculotendon length as that in part (b).

   Note: After each simulation, change the parameter back to the original value.

   Submit a graph of musculotendon force vs. time for each simulation. It is suggested that you include the corresponding results from simulation (1) of part (b) on the graphs where appropriate to facilitate comparisons (If you do so, be aware that the timescales differ between the .csv files).

   Based on the results, address the following:
   i. Briefly describe the influence of the fiber maximum shortening velocity on the force-generating characteristics of the musculotendon actuator;
   ii. For a given volume of muscle with a given musculotendon length, what are the benefits and drawbacks of having shorter, pennated fibers together with a longer tendon?

d. Based on the simulations you conducted, what aspects of the physiological behavior of muscle and tendon does the Hill-type model reproduce well, and what aspects does it not? Explain your answer.

e. Assume the muscle being modeled has a constant moment arm of 0.025 m about the joint it crosses. Compute the following:
   i. The change in joint angle that corresponds to a 0.04 m decrease in musculotendon length;

ii. The joint angular velocity that corresponds to a musculotendon shortening velocity of 0.06 m/s.

5. Neural Control of Muscle Force.

A MATLAB program "Force_Control" has been written to simulate the control of muscle force by the central nervous system (CNS). The program simulates the excitation-to-force behavior of a population of motor units. Parameters that may be specified include:

- SimulationTime = Duration (s) of the simulation
- Nunits = Number of motor units to simulate
- MUOnTime = Times (s) at which each motor unit's neuron will begin to fire. If the onset time is less than 0, the motor neuron will remain inactive throughout
- MUFiringRateOn = Initial rate (Hz) at which each motor unit's neuron will begin to fire
- MUdFiringRatedt = Rate (Hz/s) at which the firing rate of each motor unit's neuron will change over time. Values may be positive, negative, or zero
- MUFiringRateMax = Maximum rate (Hz) at which each motor unit's neuron will fire
- MUForce = Force (N) created by each motor unit when maximally active
- MUType = Type of muscle fiber in each motor unit. Values must be either 1 (Type I fibers) or 2 (Type II fibers)
- MUAsynchrony = Amount of random delay possible in each motor unit's onset time, as a proportion (0 – 1) of the neuron's maximum firing rate

The output of the program includes a plot of muscle force versus time, and a comma-delimited text file "Force_Control.csv" with muscle force (N) as a function of time (s).

The default configuration is a population of 10 motor neurons. The program is initially configured to run a 2 s simulation in which the motor neuron of a single type I motor unit, that with the smallest force output, fires at a constant rate of 5 Hz, starting at 0.1 s.

Run the program in its initial configuration to observe the baseline characteristics of the muscle force created by a single motor unit firing at a low frequency.

a. Perform the following simulations over a period of 2 s each. You may not modify the MUForce or MUType parameters.

   1) Simulate a single Type I motor unit whose motor neuron begins firing at 10 Hz at 0.1 s and increases in firing rate by 70 Hz/s to a maximum of 80 Hz
   2) Repeat (1) with a single Type II motor unit instead
   3) Repeat (1) with the addition of a second Type I motor unit whose motor neuron begins firing at 15 Hz at 0.6 s and increases in firing rate by 72 Hz/s to a maximum of 84 Hz
   4) Simulate the normal pattern whereby the CNS would control the firing of the 10 motor neurons to slowly ramp the muscle force output to maximum at 2 s
   5) Simulate a ballistic muscle activation by causing all 10 motor neurons to begin firing at 100 Hz at 0.1 s. From that instant, decrease the firing rates by 150 Hz/s for Type I motor units and by 400 Hz/s for Type II motor units

6) Simulate a contraction in which all 10 motor neurons begin firing at 15 Hz at 0.1 s and then increase their firing rate by 70 Hz/s to a maximum of 100 Hz, with asynchrony set to 0

Submit the following:

- A single force vs. time graph in which the results of simulations (1) and (2) are plotted, after normalizing the force to the motor unit's force when maximally active
- A set of force vs. time graphs for simulations (3), (4), (5), and (6)
- The values you used for MUOnTime, MUFiringRateOn, MUdFiringRatedt, and MUFiringRateMax in simulation (4).

b. Based on the results of part (a), briefly address each of the following:

i. In terms of the underlying physiology, why is the force increasing as the motor neuron firing rate increases in simulations (1) and (2)?

ii. What differences do you see between the results of simulations (1) and (2), and why are these differences present?

iii. In what way do changes in muscle force as a result of motor unit recruitment differ from changes as a result of altering motor neuron firing rates?

iv. In simulation (5), all of the motor neurons began firing simultaneously at their maximum rate, but the force does not peak until 50-100 ms later, when the motor neuron at firing at below this rate. What is the reason for this?

v. Simulation (6) approximates the effect of stimulating a nerve via an external electrical stimulation device. Why does the resulting muscle force output more closely approximate that in simulations (1) and (2) than that in (4)?

vi. The muscle models from Problems 3 and 4 used simplified models of neural activation of muscle. Do those simplified models seem appropriate? Why or why not?

References:

Kaufman, K.R., An, K.-N., & Chao, E.Y.S. (1989). Incorporation of muscle architecture in to the muscle length-tension relationship. *Journal of Biomechanics*, 22, 943-948.

Winters, J.M, & Stark, L. (1985). Analysis of fundamental human movement patterns through the use of in-depth antagonistic muscle models. *IEEE Transactions on Biomedical Engineering*, *32*, 826-839.

Zahalak, G.I., & Ma, S.-P. (1990). Muscle activation and contraction: Constitutive relations based directly on cross-bridge kinetics. *Journal of Biomechanical Engineering*, *112*, 52-62.

Zajac, F.E., Topp, E.L., & Stevenson, P.J. (1986). A dimensionless musculotendon model. *Proceedings of the IEEE Eighth Annual Conference of the Engineering in Medicine and Biology Society*, 601-604.