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HODGKIN-HUXLEY MODEL FOR GENERATION OF ACTION POTENTIAL

Aim

To simulate the smooth muscle cell action potential generation using Hodgkin-Huxley model

Objectives

To model the smooth muscle cell electrical activity based on physiological parameters from its genesis at the cellular level, to its propagation to the tissue level.

Apparatus required

1. Matlab

Theory

The cellular space is largely filled with body fluid with different concentrations of ions such as potassium, sodium, and chloride in the intracellular and extracellular regions due to the selective permeability of the cell membrane. The difference between the ion concentrations on either side of the cell membrane leads to a potential difference between the interior and exterior of the cell, which is also termed the membrane potential of the cell. Due to the active maintenance of homeostasis, a stable membrane potential is achieved for the resting state of the cell. This resting membrane potential is approximately – 80 mV across the cells, but it varies between cell types. For skeletal muscle, the resting membrane potential is – 50 to – 60 mV, while for skeletal muscle the range is – 70 to – 90 mV.

Cells like muscles and neurons are called excitable cells as they can undergo a reversal of resting potential under stimulation. For stimulus below the threshold level, the ion pump generally neutralizes it. The voltage-gated channels get activated for a stimulus beyond the threshold level, which in turn allows the transmission of the ions and can lead to a sequence of voltage changes across the membrane called action potential. A representative diagram of an ideal action potential is given in Figure 1.

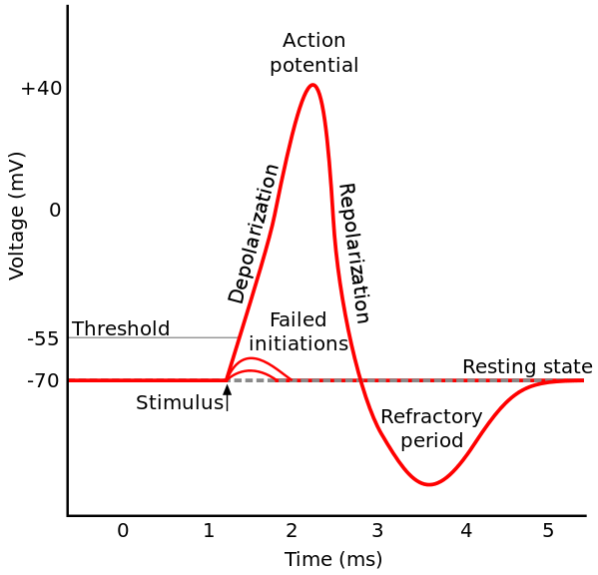


Figure 1. Representative diagram of different phases of action potential

The four main stages of action potentials are:

1. **Resting state:** The voltage-gated channels are closed and leakage is balanced.
2. **Depolarization:** Stimulus exceeding threshold would trigger open the voltage gates, resulting in huge influx of sodium ions and sharp increase in membrane potential.
3. **Repolarization:** The sodium channels close while the potassium channels are opened to allow efflux of potassium ions, resulting in decrease in the membrane potential back to resting membrane potential
4. **Hyperpolarization:** The potassium channels are slow to close, leading to a lower membrane potential, and the sodium-potassium pump functions to bring membrane potential back to the resting value.

The refractory period is the time after an action potential is generated, during which the excitable cell cannot produce another action potential. This is due to the hyperpolarization process being continued and not allowing depolarization for this period. Thus, the refractory period limits the number of action potentials that a given muscle cell can produce per unit time.

Methodology/Experimental Protocol

At the cell level, the smooth muscle electrical activity like all excitable cells, results from current flowing through ionic channels and transporters embedded in the cellular membrane. The resting membrane potential for it oscillates between -60 to -45 mV. When resting potential reaches a certain threshold, it triggers a burst of action potentials. The depolarization of the smooth muscle cell is mostly due to the influx of calcium ions to the intracellular space.

Consequently, the intracellular calcium concentration, [Ca2+]i rises, reaching a given threshold, and then triggers the muscle cell contraction. An outward current, mostly due to the outflow of potassium ions, allows the cell repolarization. Therefore, the modeling overview of a single muscle cell can be expressed by the following:

$$\frac{dV_m}{dt} = \frac{I_{stim} - I_{ion}}{C_m} = \frac{I_{stim} - I_{ca} - I_K - I_{KCa} - I_L}{C_m}$$

Where V_m is the transmembrane potential (Initial condition is -50 mV), C_m is the capacitance of cell membrane, I_{stim} is the stimulation current, $I_{ion} = \sum_i I_i$is the sum of the total ionic currents through the membrane.

$$\frac{dn_K}{dt} = \frac{h_{K_\infty} - n_K}{\tau_{n_K}}$$

$$\frac{d[Ca^{2+}]}{dt} = f_c(-\alpha I_{Ca} - k_{Ca}[Ca^{2+}])$$

Where, nk is the potassium activation variable, Kca is the calcium extraction factor, $Ca^{2+}$is the intracellular calcium concentration, The ionic currents are I_{Ca} for the voltage dependent calcium channel current, I_K for the voltage dependent potassium channel current, I_{KCa} for the calcium dependent potassium channel current and I_{leak} for the leakage current. Equations for each current are then:

$$I_{Ca} = J_{back} + G_{Ca}(V_m - E_{Ca})\frac{1}{1 + e^{\left(\frac{V_{Ca} - V_m}{R_{Ca}}\right)}}$$

$$I_K = G_k n_K (V_m - E_K)$$

$$I_{KCa} = G_{kCa}\frac{[Ca^{2+}]^2}{[Ca^{2+}]^2 + k^2}(V_m - E_K)$$

$$I_L = G_L(V_m - E_L)$$

$$E_{Ca} = \frac{RT}{2F} ln\left(\frac{[Ca^{2+}]_e}{[Ca^{2+}]_i}\right)$$

$$h_{K\infty} = \frac{1}{1 + e^{\left(\frac{4.2 - V_m}{21.1}\right)}}$$

$$\tau_{nK} = 23.75e^{\left(-\frac{V_m}{72.15}\right)}$$

Table 1. Parameters of the electrical model

Variable	Value	Description	Unit
G_k	0.064	Potassium channels conductance	mS/cm^2
G_{kCa}	0.08	Potassium/Calcium channels conductance	mS/cm^2
G_L	0.0055	Leak channels conductance	mS/cm^2
κ	0.01	Half-point potassium concentration	μmol
f_c	0.4	calcium influx probability	
α	$4e-5$	current conservation factor	$mol\ cm^2/\mu C$
k_{Ca}	0.1	Ca extraction factor	ms^{-1})
E_L	-20	Leak nerst potential	mV
E_K	-83	Potassium nerst potential	mV
R	8.314	gas constant	$JK^{-1}mol^{-1}$
T	295	Temperature	K
F	96.487	Faraday constant	kC mol
$\left[Ca^{2+}\right]_e$	3	Extracellular calcium concentration	μmol
J_{back}	0.023	Background calcium current	$\mu A/cm^2$
G_{Ca}	0.022	VOCC conductance	mS/cm^2
V_{Ca}	-20.07	Half-point of the VOCC activation sigmoid	mV
R_{Ca}	5.97	Maximum slope of the VOCC activation	mV

Sample Code

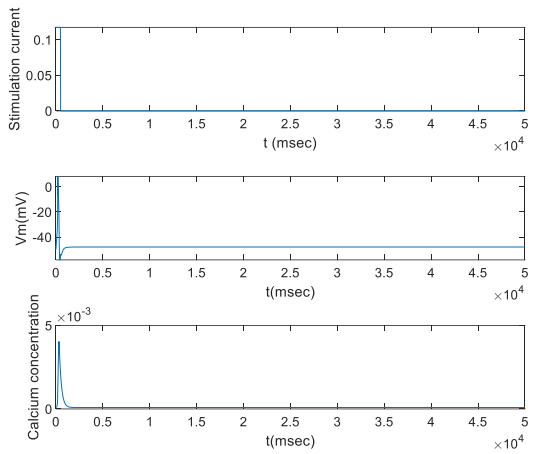
```
clc; clear all;
t0=0;h=0.5;N=100000;

Vm0=-50;nk0=0.079257;Ca0=1e-4;
t(1)=t0;Vm(1)=Vm0;nk(1)=nk0;Ca(1)=Ca0;
%parameters
Istim=zeros(N,1);
for i=1:1000
   Istim(i)=0.1175;
end

Gk=0.064; Gkca=0.08; Gl=0.0055; k=0.01;
fc=0.4; alpha=4e-5; Kca=0.01; El=-20;
Ek=-83; Gca=0.02694061; Vca=-20.07451779; Rca=5.97139101;
Jback=0.02397327; T=295; Cae=3; Cm=1;
F=96.487; R=8.314;

for n=1:1:N
   Eca=((R*T)/(2*F))*log(Cae/Ca(n));
   hk=1/(1+exp((4.2-Vm(n))/21.1));
   tnk=23.75*exp(-Vm(n)/72.15);
   Ica=Jback+Gca*(Vm(n)-Eca)/(1+exp(-(Vm(n)-Vca)/Rca));
   Ik=Gk*nk(n)*(Vm(n)-Ek);
```

```
    Ikca=Gkca*(Vm(n)-Ek)*(Ca(n).^2/(Ca(n).^2+k.^2));
    Il = Gl*(Vm(n) -El);

    t(n+1)=t(n)+h;
    Vm(n+1)=Vm(n)+(h*((Istim(n)-Ica-Ik-Ikca-Il)/Cm));
    nk(n+1)=nk(n)+(h*((hk-nk(n))/tnk));
    Ca(n+1)=Ca(n)+(h*(fc*(-alpha*Ica-Kca*Ca(n))));
end

%plot
title('Memebrane Potential at Cell level');
subplot(3,1,1);
plot(t(1:100000),Istim');
ylabel('Stimulation current')
xlabel('t (msec)')
subplot(3,1,2)
plot(t,Vm);
ylabel('Vm(mV)');
xlabel('t(msec)');

subplot(3,1,3);
plot(t,Ca);
ylabel('Calcium concentration');
xlabel('t(msec)');
```

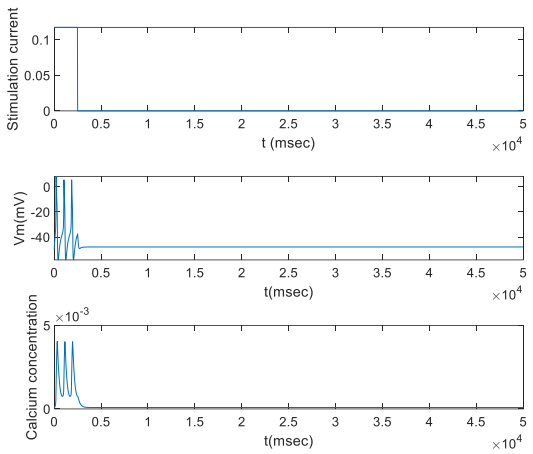
Results

Figure 2 shows the train of action potentials for different duration of simulation current simulated by experimental data found in the literature. It also represents the continuous increase in intracellular calcium concentration during the sustained action potentials.

Refraction period can be observed as the cell cannot respond to additional simulation immediately after one depolarization event.



(a) Stimulation time = 500 ms



(b) Simulation time = 2500 ms

Fig. 2 Train of action potentials and corresponding changes in the calcium concentrations

Outcomes

For the given stimulation current, membrane voltage exhibits a sudden increase with a periodic refraction. In addition, calcium concentration is also observed to vary. From that, action potential, hyperpolarization potential, duration of the phases and refractory period of muscle cells is found for given membrane characteristic.

Conclusion

This experiment presents the modeling of the action potential of the smooth muscle based on physiological data from its genesis at the cellular level, to its propagation to the tissue level. It will be used to simulate different physiological situations, like the effect of calcium blockers and gap junction distribution, on the action potential characteristics.