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Effects of ionic parameters on behavior of a skeletal muscle fiber model

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Abstract. All living cells have a membrane which separates inside the cell from it's outside. There is a potential difference between inside and outside of the cell. This potential difference will change during an action potential. It is quite common to peruse action potentials of skeletal muscle fibers with the Hodgkin-Huxley model. Since Hodgkin and Huxley summarized some controlling currents like inward rectifier current or chloride current as a leak current when we try to study the sensitivity of model to some parameters we lose some details. In this paper we use a model which contains sodium, potassium, chloride, Na-K pump, and inward rectifier currents. Firstly, we find critical point of the system, and discuss on how action potential changes for different initial values of variables. Then we study sensitivity of the critical point and maximum of potential to different parameters.

Keywords: action potential, sensitive analysis, skeletal muscle.
AMS Subject Classification: 92C30, 37N25, 49Q12, 92C37.

1 Introduction

Mathematical models and dynamical systems are widely used to study biological phenomena. Some of these phenomena are population of a special species or studying behavior of special cell in the body or effects of a particular disease on the body. Some recent studies in these areas are appeared in [1,11,12,14]. In comparison with experiments, using mathematical models to analyze these issues requires less time and money. One of these wide

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rang of biological problems is studying action potential of cells. Among the many works that have been done in this field, we can remark [4, 5, 13, 15].

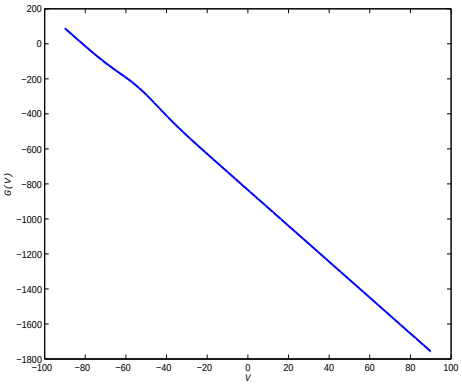

Figure 1: Diagram of $G(V)$.

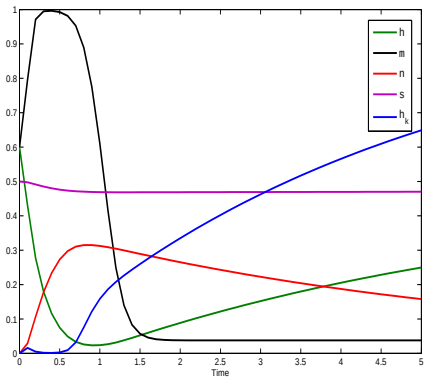

Figure 2: Red diagram is variable n, green one is related to h, blue one is for h_k, black one representees m, and purple one for s.

In this paper we try to peruse a mathematical model for skeletal muscle cells. Skeletal muscle is the most common of the three types of muscles in the body. Skeletal muscles are long cylindrical cells attached to bones by tendons. They produce all the movements of body. Since there are approximately 640 skeletal muscles within the typical human body, studying their behavior is really important. Before analyzing mathematical model of the action potential in muscle fibers, we briefly review the physiological properties of cells; Then we introduce the model and in the next section we study it's dynamical characteristics.

Every living cell is surrounded by a lipid bilayer which is called membrane. This membrane is like a boundary separates the internal of the cell from its external environment. The membrane contains channel proteins that allow for the ions to move through it. These channels are selectively permeable. That means it allows passage of specific ions [6, 7]. There are different ions within and outside of each living cell. The principle ions found on either side of the cell membrane are sodium, potassium and chloride. The potential difference arises from different ion concentrations inside and outside of the cell. Membrane potential is defined as $V_M = V_{in} - V_{out}$, where V_{in} is potential on the inside of the cell and V_{out} is outside potential.

The membrane contains channels that allow ions move between inside

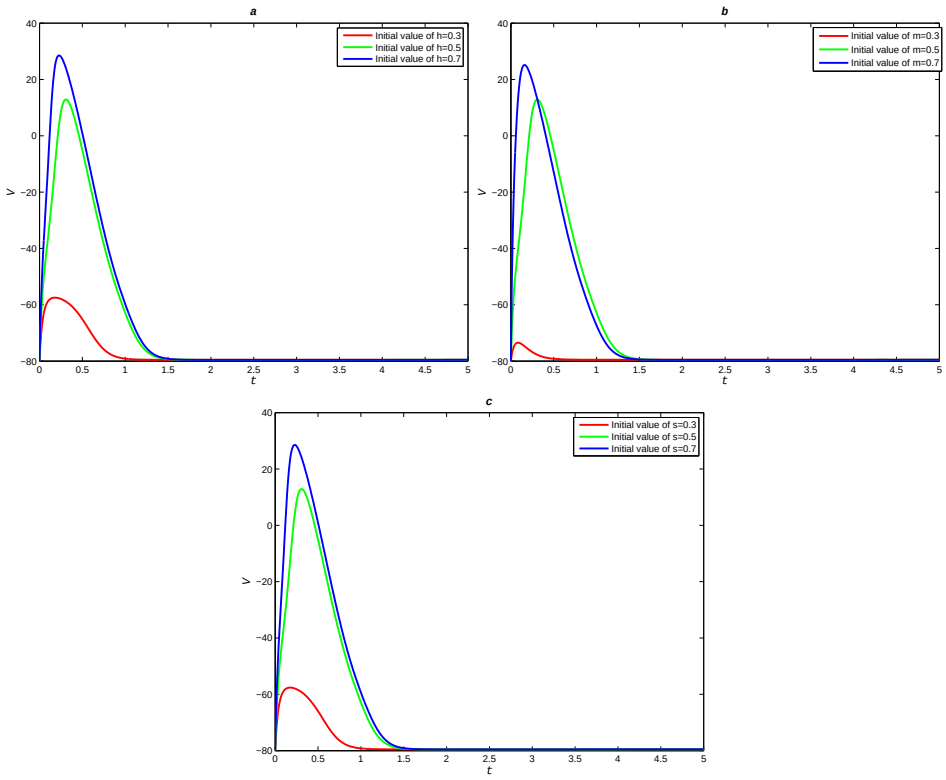

Figure 3: Action potential for different initial values: (a) $m_0, s_0 = 0.5$; (b) $h_0, s_0 = 0.5$; (c) $m_0, h_0 = 0.5$.

and outside of the cell. These channels are gated or non-gated. Gated channels are selective for a single ion [3]. When appropriate channels are open, Na^+ and Cl^- ions tend to diffuse into the cell, whereas K^+ ions tend to diffuse outward. This happens because of concentration differences for each ion between inside and outside of the cell. The resting potential of the cell is the potential at which there is a balance between these diffusions.

It is common to use Hodgkin and Huxley model (HHM) for simulating action potential in a muscle fiber [3, 8]. Since Hodgkin and huxley added a leak current instead of Na-K pump, chloride, and inward rectifier potassium currents some details are missed. To obtain more accurate information we use the following system:

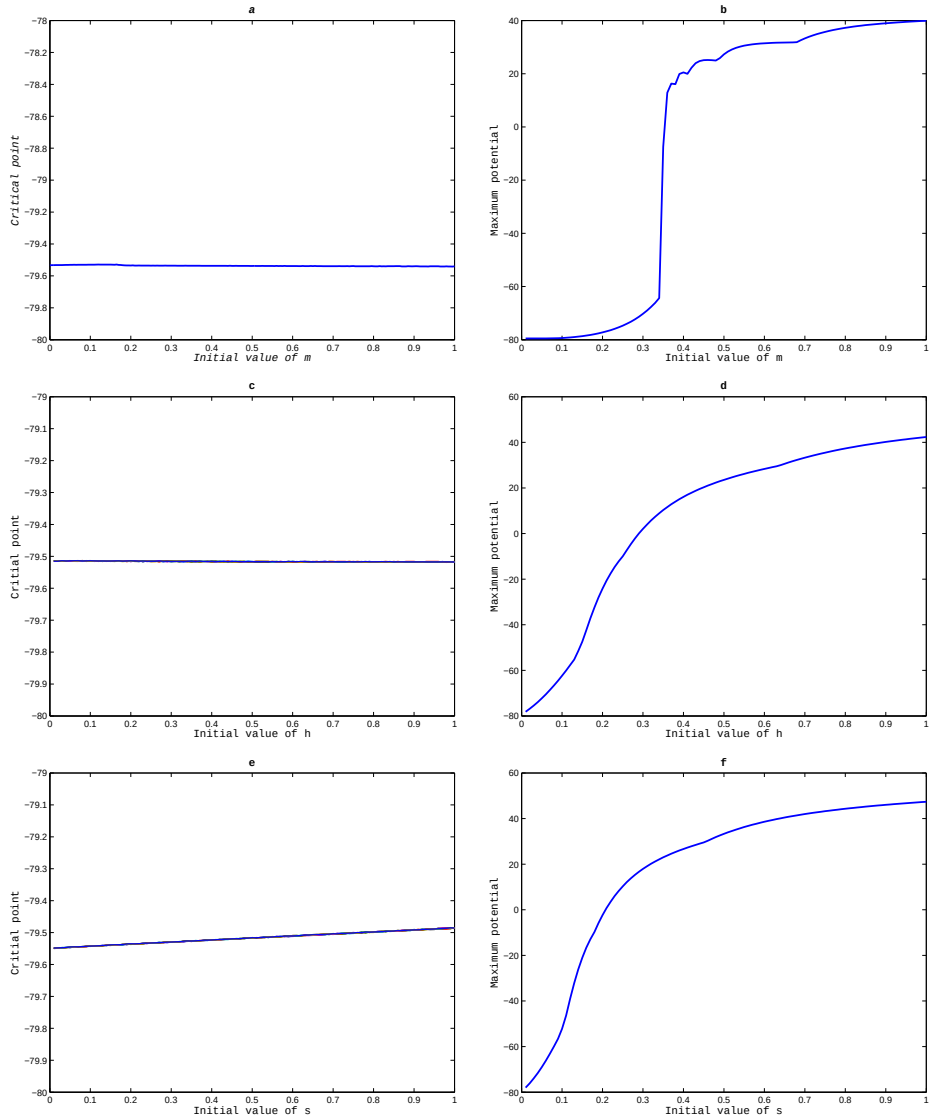

Figure 4: Altering initial value of variables in the interval $[0, 1]$: first row: changing m_0, second row: changing h_0 and third row: changing s_0. Right side: effects on critical point, Left side: effects on maximum end plate potential.

$$\begin{cases} \frac{dV}{dt} = -\hat{g}_{Na} m^3 hs(V - E_{NA}) - \hat{g}_K n^4 h_K (V - E_K) - I, \\ \frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m, \\ \frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n, \\ \frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h, \\ \frac{ds}{dt} = \frac{s_\infty - s}{\tau_s} \\ \frac{dh_K}{dt} = \frac{h_{K_\infty} - h_K}{\tau_{h_K}}, \end{cases} \tag{1}$$

where

$$\begin{cases} I = g_{IR}(V - E_{IR}) + g_{Cl}(V - E_{Cl}) + I_{NaK}, \\ g_{Cl} = \hat{g_{Cl}} a^4, \\ g_{IR} = \hat{g_{IR}} y, \\ y = 1 - [1 + \frac{1}{[S]_i^2 e^{2(1-\delta)VF/RT}}(1 + \frac{[K]_R^2}{K_K})]^{-1} \\ [K]_R = [K]_o e^{-\delta E_K F/RT}, \\ I_{NaK} = \hat{I_{NaK}} f(V), \\ \hat{I}_{NaK} = \frac{F\hat{J_{NaK}}}{(1+K_{mK}/[K]+o)^2(1+K_{mNa}/[Na]_i)^3}, \\ f(V) = (1 + 0.12e^{-0.1VF/RT} + 0.04\sigma e^{-VF/RT})^{-1} \sigma = \frac{1}{7}(e^{[Na]_o/67.3}), \\ a = \frac{1}{1+e^{\frac{V-V_a}{A_a}}}, \\ \alpha_n(V) = \frac{\hat{\alpha}(V-V_n)}{1-\exp\frac{-(V-V_n)}{K_{\alpha_n}}}, \\ \beta_n(V) = \hat{\beta_n} \exp(\frac{-(V-V_n)}{K_{\beta_n}}), \\ \alpha_m(V) = \frac{\hat{\alpha_m}(V-V_m)}{1-\exp\frac{-(V-V_m)}{K_{\alpha_m}}}, \\ \beta_m(V) = \hat{\beta_m} \exp(\frac{-(V-V_m)}{K_{\beta_m}}), \\ \alpha_h(V) = \hat{\alpha_h} \exp(\frac{-(V-V_h)}{K_{\alpha_h}}, \\ \beta_h(V) = \frac{\hat{\beta_h}}{1+\exp\frac{-(V-V_h)}{K_{\beta_h}}}, \\ \tau_s = \frac{60}{0.2+5.65\times(\frac{V+90}{100})^2}, \\ \tau_{h_K} = \exp\frac{-(V+40)}{25.75}, \\ h_{K_\infty} = \frac{1}{1+e^{\frac{V-V_{h_K}}{A_{h_K}}}}, \\ s_\infty = \frac{1}{1+e^{\frac{V-V_s}{A_s}}}. \end{cases}$$

In [15], wallinga et. al studied some properties of action potential of mammalian skeletal muscle fibers using system (1). This system contains six differential equations. Variable V represents the membrane potential. Variable m, and variable h represent activation and inactivation sodium gated channels respectively. Variable n is related to potassium gated channels. Due to this fact that gated channels of skeletal muscle fibers are slower than channels of nerve cells, two slow variables h_k, and S have been added to this model to slow down sodium and potassium currents.

In the next section we use system (1) to find resting potential of skeletal muscle fibers(critical point of the system), and analyze sensitivity of the system to some parameters.

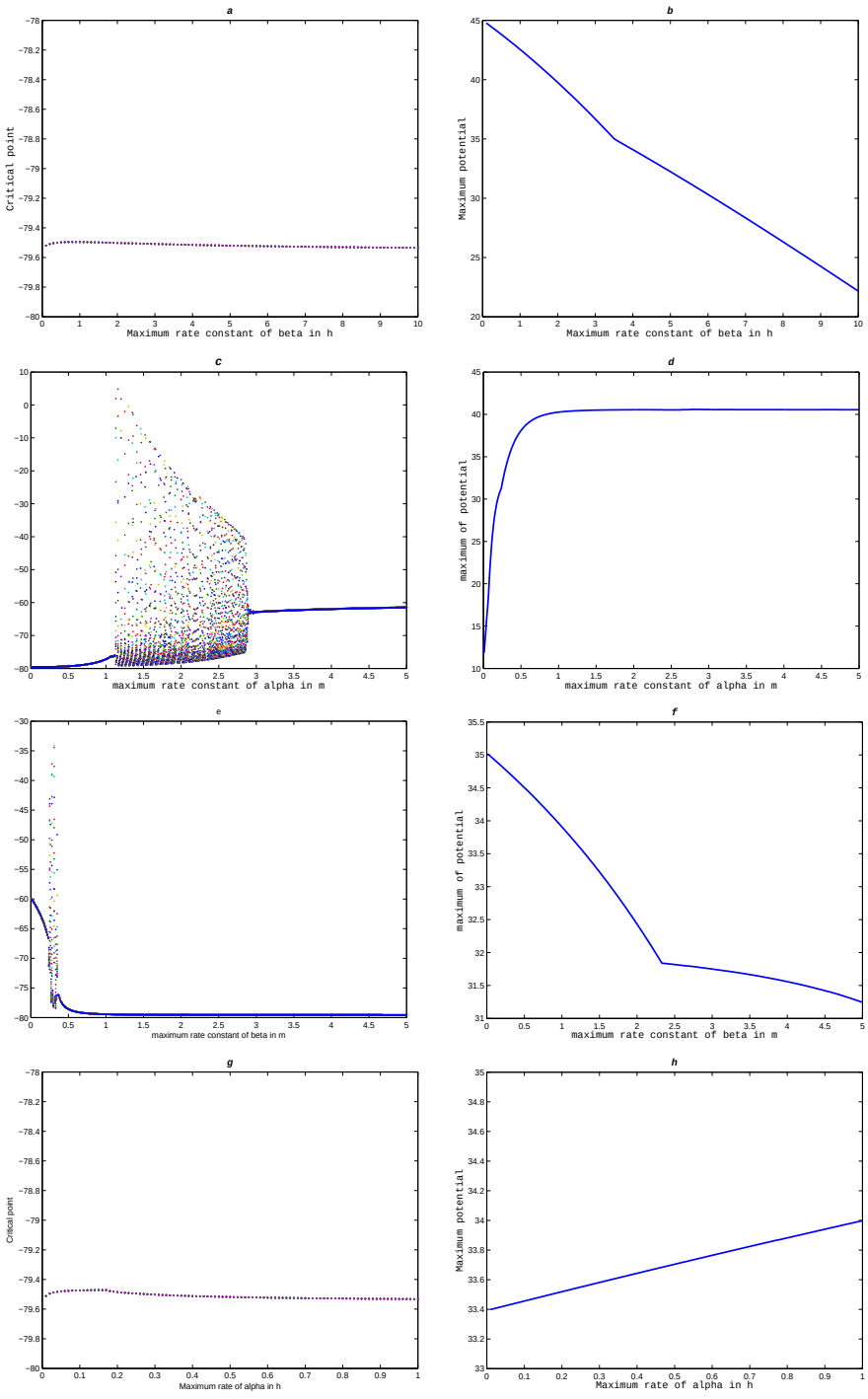

Figure 5: Altering maximum rate constant: first row: $\hat{\beta}_h$, second row: $\hat{\alpha}_m$, third row: $\hat{\beta}_m$, fourth row: $\hat{\alpha}_h$, right side: effects on critical point, left side: effects on maximum end-plate potential.

2 Analyzing the model

Each fiber is usually innervated by only one nerve ending, located near the middle of the fiber. Each nerve ending makes a junction called neurone muscular junction. The action potential initiated in the muscle fiber by the nerve signal [6]. The nerve fiber forms a complex of branching nerve terminals that invaginate into the surface of the muscle fiber but lie outside the muscle fiber membrane.

When a nerve impulse reaches the neuromuscular junction, about 125 vesicles of acetylcholine are released into the synaptic space. There are many very small acetylcholine receptors in the muscle fiber membrane. These are acetylcholine-gated channels. The opened acetylcholine channels are large enough to allow the important positive ions go into the cell; So large number of sodium ions pour to the inside of the fiber. This creates a local positive charge inside the muscle fiber membrane, called endplate potential [6, 7]. In this section we want to study properties of this end plat potential using system (1). From now on we will tell potential instead of end-plate potential.

2.1 Critical point of the system

First we aim to find the critical point of the system (1). To detect the critical point we let the right hand side of all equation in the system (1) equal to zero, except the first one to find a relation between each variable and potential at the critical point as follows

$$X_\infty(V) = \frac{\alpha_x(V)}{\alpha_X(V) + \beta_X(V)}, \quad \text{where } X = m, h, n, \tag{2}$$

and

$$h_{K_\infty}(V) = \frac{1}{1 + e^{\frac{V - V_{h_K}}{A_{h_K}}}}, \tag{3}$$

$$s_\infty(V) = \frac{1}{1 + e^{\frac{V - V_s}{A_s}}}. \tag{4}$$

After replacing (2),(3), and (4) in the first equation of system (1) we find a function of V. We call it $G(V)$ and it is defined as follows

$$G(V) = -\hat{g}_{Na} m_\infty^3 h_\infty s_\infty (V - E_{NA}) - \hat{g}_K n_\infty^4 h_{K_\infty} (V - E_K) - I. \tag{5}$$

Zeros of equation (5) are critical points of the system. We plot diagram of $G(V)$ in the Figure 1. This function is decreasing and has only one

zero before -100mv; so system (1) has one critical point. We can find this potential by numerical methods. Potential at critical point is around -79.5 mv; so critical point of this system is $(-79.5,\ m_\infty\ (-79.5)\ ,n_\infty\ (-79.5),\ h_\infty\ (-79.5),\ s_\infty\ (-79.5),\ h_{k_\infty}\ (-79.5)) = (-79.5,\ 0.038,\ 0.005,\ 0.8\ ,0.56\ ,1)$. We linearize system (1) around it's critical point and apply Hartman's theorem to show that this critical point is stable [10]. Matrix A is Jacobian matrix of the system (1) which is calculated at critical point

$$A = \begin{bmatrix} -5.58 & 72.2 & 0 & 1.14 & 1.63 & 0 \\ 0.04 & -9.22 & & & & \\ 0.002 & & -.34 & & & \\ -0.003 & & & -0.1 & & \\ -0.0002 & & & & -0.0004 & \\ -0.002 & & & & & -0.21 \end{bmatrix}.$$

Since all eigenvalue of matrix A are negative($\lambda_1 = -0.0043, \lambda_2 = -0.1, \lambda_3 = -4.86, \lambda_4 = -9.95, \lambda_5 = -0.34, \lambda_6 = -0.21$) this critical point is locally stable.

2.2 Effects of some parameters on the model

As we mentioned before released acetylcholine opens some gated channels, so initial value of m and h must be more than zero to initiate endplate potential. In Figure 2 one can see how variables change over the time. The activation sodium-gate decreases before 2ms, after that it almost remains constant and tends to the fixed point. Inactivation sodium gate decreases too, but after a short time it increases to reach a constant value. On the other hand h_k is almost zero as long as n is ascending. About the same time that n begins to decline, h_k start to increase. It is obvious that s is the slowest variable. It does not change much from the beginning time .

Since released acetylcholine influences initial value of m, and h we want to know whether these changes have effects on action potential or not; so we plot diagram of endplate potential for different initial value of m and h in Figure 3. On the other hand initial value of S changes because of some physiological characteristics; so we also check effects of changing the initial value of s in Figure 3. In this figure one can see reactions of potential to different initial values. It is clear that summit of the endplate potential varies for various initial values, but it seems that position of the critical point does not change. To clarify this conjecture, we plot Figure 4 in which we display sensitivity of critical point to different initial values of s, m, and h. These diagrams show that position of the critical point or resting potential is invariant for different initial values of m, h, and s.

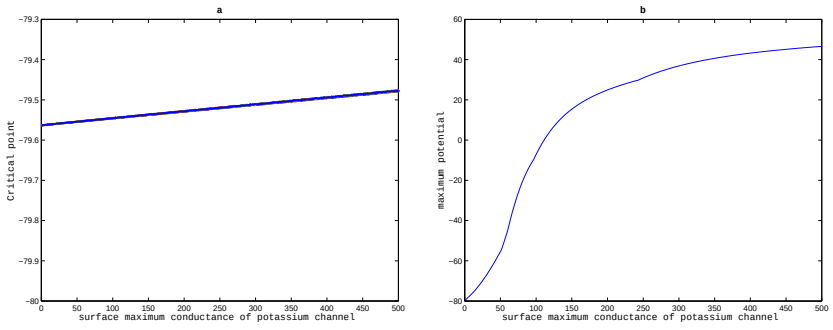

Figure 6: Right side: effects of altering surface maximum conductance $\hat{g}_{Na}$ on critical point; left side: effects on maximum end-plate potential.

As you can see in system (1), this system contains different parameters. In this part we compare sensitivity of this system to these parameters. We strat with $\hat{\alpha}_x$, and $\hat{\beta}_x$, where $x = h, m$. These are maximum rate constant in sodium gates and their values stated in [2]. We change each of these parameters in an interval based of their natural values, then plot bifurcation diagrams to show their impact on critical point (CP) and diagrams of maximum value of potential (MP) as a function of parameters. One can see the results in Figure 5. By looking carefully to all of diagrams one can see that by changing $\hat{\alpha}_h$, and $\hat{\beta}_h$ position of the critical point does not change much and it stays stable. But critical point becomes unstable for $1.1 < \hat{\alpha}_m < 2.9$, and $0.2 < \hat{\beta}_m < 0.35$. For other values of $\hat{\alpha}_m$, and $\hat{\beta}_m$ it is stable and potential at critical point changes in a range between $-80mv$ and $-60mv$. On the other hand looking carfully to diagrams in right hand side you can see that MP changes significantly just when we alter $\hat{\alpha}_m$, and $\hat{\beta}_h$. MP is almost independent of $\hat{\alpha}_h$, and $\hat{\alpha}_h$. At the next step we will check the effects of surface maximum conductance of Sodium ($\hat{g}_{Na}$). Clearly, You can see in Figure 6 that CP is almost invariable when we alter $\hat{g}_{Na}$, but MP varies in a wide range.

Since $E_{ion} = \frac{RT}{F} \ln \frac{[ion]_o}{[ion]_{in}}$, where $[ion]_o$, and $[ion]_{in}$ are concentration of each ion outside and inside the cell respectively, and T is temperature parameter (R and F are gas and Faraday's constants) we can examine their effects on CP and MP too. In Figure 7 you can see effects of concentration of sodium ion on CP and MP. Diagrams in this figure show that position of CP does not change much for different sodium concentrations. On the other hand MP varies for different concentration of this ion.

We studied effects of all parameters related to potassium gated channels;

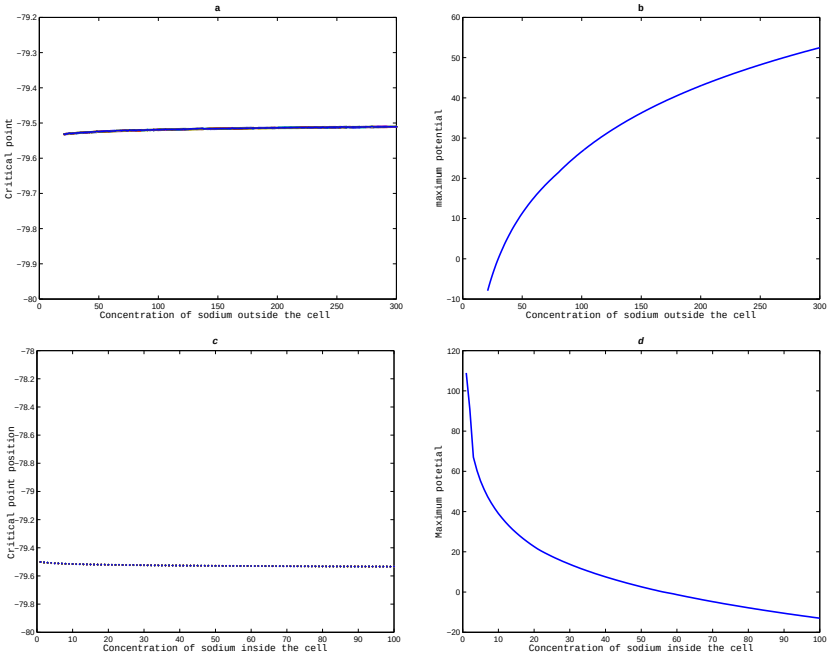

Figure 7: Altering concentration of ions: first row: $[Na]_{out}$; second row: Na_{in}; right side: effects on critical point; left side: effects on maximum end-plate potential.

Since these parameters do not change CP and MP of end-plate potential, we do not represent results.

Sensitivity of CP and MP to temperature is illustrated in Figure 8. Unlike CP, CM increases with increasing temperature.

3 Conclusion

In this paper we studied behavior of skeletal muscle fibers using a system of six ordinary differential equations. We examined sensitivity of end-plate action potential to some parameters of this system. We found that this system is more sensitive to parameters related to sodium ions than other ions.We showed that another parameter that alter position of critical point and maximum of end-plate action potential is temperature. As a result if we want to change manner of action potential for some reasons, the parameters in ion channels and temperature are the best controlling factors.

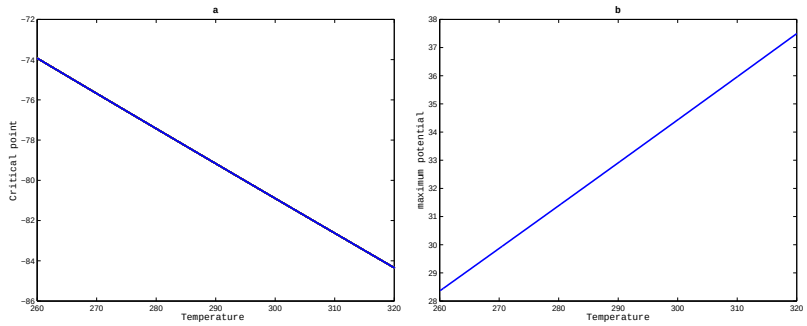

Figure 8: Altering temperature, right side effects on critical point; left side: effects on maximum end-plate potential.

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