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A new reduced mathematical model to simulate the action potential in end plate of skeletal muscle fibers

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Abstract Usually mathematicians use Hodgkin-Huxley model or FitzHugh-Nagumo model to simulate action potentials of skeletal muscle fibers. These models are electrically excitable, but skeletal muscle fibers are stimulated chemically. To investigate skeletal muscle fibers we use a model with six ordinary differential equations. This dynamical system is sensitive to initial value of some variables so it is more realistic. Studying qualitative behavior and propagation of action potential through a cell with this model is time consuming .In this paper we try to use properties of variables of this model to reduced dimension of this dynamical model. We study qualitative behavior of obtained model and illustrate that this new model treats like the original model.

Keywords. Dynamical systems, Skeletal muscle, Qualitative behavior, Action potential.
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1. Introduction

Mathematical models have been used to study different properties of biological events like infectious disease, membrane action potential, population growth and so on.

In this paper we focus on studying membrane action potential. The majority of researches in this field are about action potential in neurons [1, 7, 10]. Forasmuch as skeletal muscle cells are the body's engine analysis of their features is important; So we focus on these kind of cells. The Huxley model and the Hill model are two famous model describing contraction features in muscle fibers. Despite lots of other mathematical models have been proposed based of these two models for simulating contraction of skeletal muscle fibers [6, 8, 14], few studies have been done on features of their membrane action potential.

Since an action potential is the beginning of the process of muscle contraction we think that studying this aspect of muscle is as important as muscle contraction. In

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this paper, we investigate a mathematical model which describes an action potential changes in a skeletal muscle fibers. We try to reduce the number of equations when preserving dynamical behavior of the system. In this way we first explain what happens during an action potential after that we introduce the model.

Each cell has a membrane that like a boundary separates the internal of the cell from its external environment. More importantly, it is selectively permeable. That means it allows passage of specific ions. Both the intracellular and extracellular environments consist of, Among many other things, Na^+, K^+ and Cl^- ions. Different ionic concentration between inside and outside of a cell membrane leading to the potential difference across the membrane. This potential difference is called membrane potential, and will change during an action potential. All cells are divided into two categories: excitable, and non-excitable. If a chemical or electrical or mechanical stimulus leads to sudden changes in membrane potential, that cell is called an excitable, otherwise it is non excitable. Neurons, skeletal muscles, and cardiac cells are examples of excitable cells.

A skeletal muscle is made up of individual muscle fibers. Muscle fibers are arranged in parallel between the tendon ends. Each muscle fiber is a single, long, and cylindrical cell, which is surrounded by a cell membrane. This membrane is called sarcolemma [5]. Skeletal muscle fibers are stimulated by nerve fibers. There is neuromuscular junction at the end of each nerve fiber which connects it to the midpoint of the muscle fiber.

When an impulse reaches the neuromuscular junction acetylcholine releases from the terminal into the synaptic space. There are very small acetylcholine receptors on the gated ion channels in a muscle fiber membrane which acetylcholine attaches them and opens ion channels. Mostly sodium ions can pass through these channels. Chloride, and potassium ions cannot pass because of potential, and concentration gradient. From these opened channels large number of sodium ions go into the fiber. This cause a local positive charge inside the muscle fiber membrane, called the end plate potential. The end plate potential initiates an action potential that spreads along the muscle membrane and causes muscle contraction [4].

It is common to use Hodgkin and Huxley model (HHM) for simulating action potential in a muscle fiber. Hodgkin and Huxley were the first scientists who provided a model for action potential changes in a giant neuron based on the flow of sodium and potassium ions [1, 7, 8]. They added a leak current instead of the $Na - K$ pump, chloride, and inward rectifier potassium currents. The HHM is stimulated by electrical current, but as we mentioned before in skeletal muscle fibers acetylcholine, which is a chemical stimulator, leads to open sodium channels, so the original HHM model is not a realistic model for muscle fibers because it is not sensitive to the initial values of variables. We should use a model that is sensitive to the initial value of sodium gates.

In paper [13], Wallinga et al. studied action potential of mammalian skeletal muscle fibers using following system:

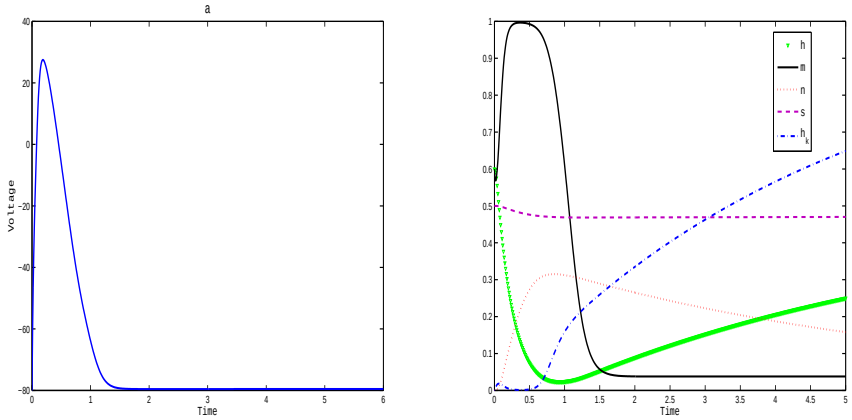
$$\begin{cases} \frac{dV}{dt} = -\hat{g}_{Na} m^3 h S(V - E_{Na}) - \hat{g}_K n^4 h_K (V - E_K) - I, \\ \frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m, \\ \frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n, \\ \frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h, \\ \frac{dS}{dt} = \frac{S_\infty - S}{\tau_S}, \\ \frac{dh_K}{dt} = \frac{h_{K_\infty} - h_K}{\tau_{h_K}}, \end{cases} \tag{1.1}$$

where

$$\begin{cases} I = g_{IR}(V - E_{IR}) + g_{Cl}(V - E_{Cl}) + I_{NaK}, \\ g_{Cl} = \hat{g}_{Cl} a^4, \\ g_{IR} = \hat{g}_{IR} y, \\ y = 1 - [1 + \frac{1}{[S]_i^2 e^{2(1-\delta)VF/RT}}(1 + \frac{[K]_R^2}{K_K})]^{-1}, \\ [K]_R = [K]_o e^{-\delta E_K F/RT}, \\ I_{NaK} = \hat{I}_{NaK} f(V), \\ \hat{I}_{NaK} = \frac{F \hat{J}_{NaK}}{(1 + K_{mK}/[K]+o)^2 (1 + K_{mNa}/[Na]_i)^3}, \\ f(V) = (1 + 0.12 e^{-0.1VF/RT} + 0.04\sigma e^{-VF/RT})^{-1}, \\ \sigma = \frac{1}{7}(e^{[Na]_o/67.3}), \\ a = \frac{1}{1 + e^{\frac{V - V_a}{A_a}}}, \\ \alpha_n(V) = \frac{\hat{\alpha}(V - V_n)}{1 - exp\frac{-(V - V_n)}{K_{\alpha_n}}}, \\ \beta_n(V) = \hat{\beta}_n \exp(\frac{-(V - V_n)}{K_{\beta_n}}), \\ \alpha_m(V) = \frac{\hat{\alpha}_m(V - V_m)}{1 - exp\frac{-(V - V_m)}{K_{\alpha_m}}}, \\ \beta_m(V) = \hat{\beta}_m \exp(\frac{-(V - V_m)}{K_{\beta_m}}), \\ \alpha_h(V) = \hat{\alpha}_h \exp(\frac{-(V - V_h)}{K_{\alpha_h}}), \\ \beta_h(V) = \frac{\hat{\beta}_h}{1 + exp\frac{-(V - V_h)}{K_{\beta_h}}}, \\ \tau_s = \frac{60}{0.2 + 5.65(\frac{V+90}{100})^2}, \\ \tau_{h_K} = exp\frac{-(V+40)}{25.75}, \\ h_{K_\infty} = \frac{1}{1 + e^{\frac{V - V_{h_K}}{A_{h_K}}}}, \\ S_\infty = \frac{1}{1 + e^{\frac{V - V_S}{A_S}}}. \end{cases} \tag{1.2}$$

This system is sensitive to the initial value of some variables [12]. Just like the HHM m, h, and n are sodium activation and inactivation gates and potassium gate respectively, and V describes potential differences. Since skeletal muscle fibers are slower than neurons, then two slow variables S (for sodium channel), and h_K (for potassium channel) are added to the HHM; Moreover, inward rectifier potassium current and sodium-potassium pump current are added. This model is in accordance with experimental data. For more details about this model and parameters, you can

FIGURE 1. Rigth–hand side: An action potential for end plate in a muscle fiber, Left– hand side diagram shows how gate variables change as time goes on.

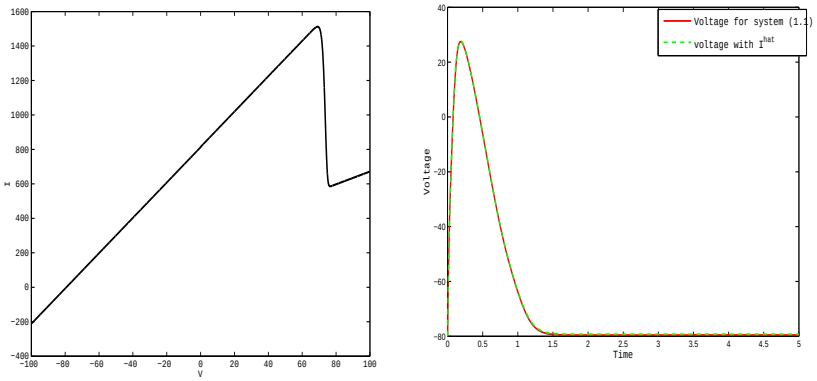


see [13, 2, 3].
Given that this system contains lots of parameters and complicated mathematical relationships, studying its mathematical feature will be difficult. In this paper, we try to study the dynamical behavior of variables and use their properties to introduce a reduced dynamical model. We study the qualitative behavior of obtained model, and illustrate that our model treats like the original model (1.1). Since our proposed model has fewer differential equations respect to the original model, studying its quality behavior will be much easier than the original one.

2. Describing the reduced model

One single end plate action potential for system (1.1) is as shown in Figure 1. When acetylcholine opens enough channels, sodium ions go into the cell, and potential goes up therefor there will be a spike. In other words, if m_0 and h_0, which are initial values for activation and inactivation sodium gates are more than a threshold we can see a spike. From now on we just tell *potential* instead of end plat action potential. In this section, we want to find a reduced system that acts just like the system (2.3). Let's start with current I. Definition of this current contains lots of parameters and complex mathematical relationships. In this part, we try to replace a new easier current with the same behavior instead of I. To study the behavior of current I, we plot Na-K pump current pulse chloride, and inward rectifier potassium currents in terms of V in Figure 2. As you can see in this figure, the current is almost linear about V, with a positive slope until $V = 69.1$. At this point, it goes down very fast until $V = 76.5$, after that it again increases. We approximate these three almost

FIGURE 2. Right–hand side:Current I as a function of potential, Left side: Action potential for system (1.1) before and after replacing $\hat{I}$ instead of I.



linear relationships with $\hat{I}$ which is defined as follows:

$$I \simeq \hat{I} = \begin{cases} 10.25V + 812.57, & V < 69.1, \\ -261V + 20235, & 69.1 \leq V < 76.5, \\ 3.65V + 306.25, & V \geq 76.5. \end{cases} \tag{2.1}$$

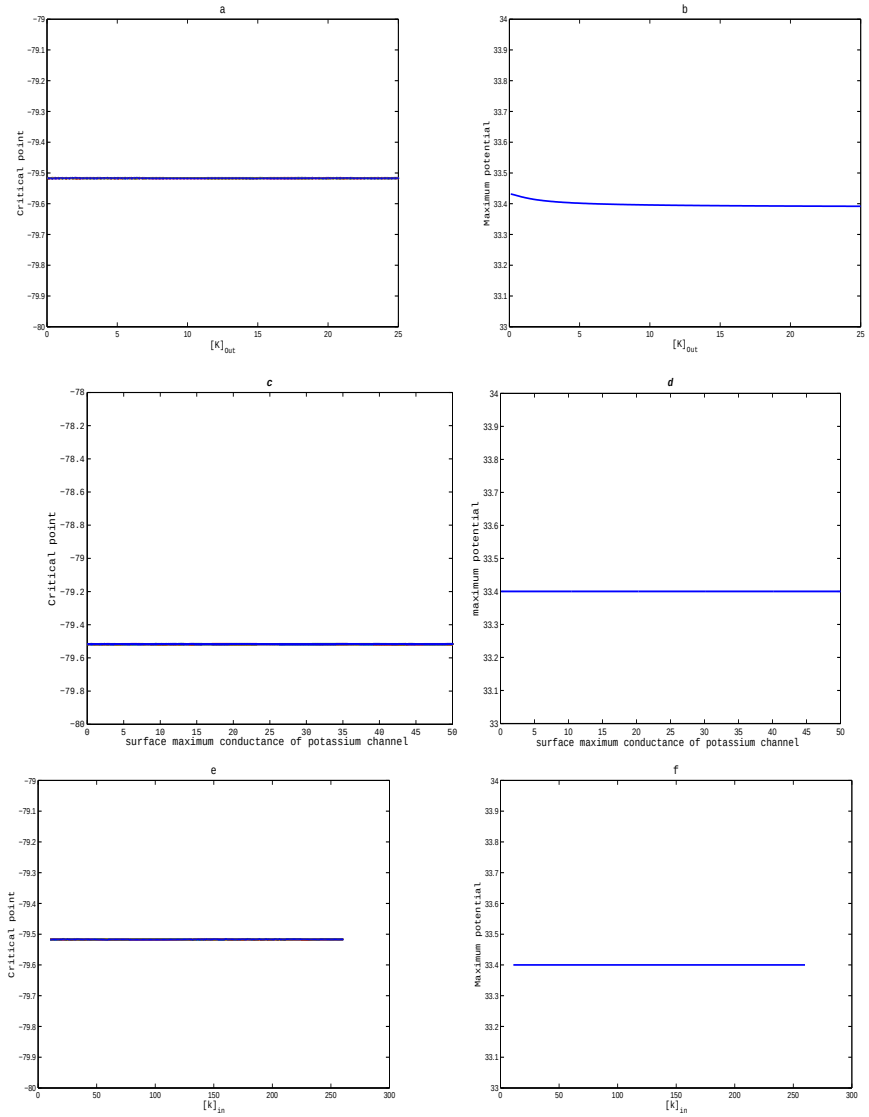
The efficiency of this approximation is shown in Figure 2. In this figure, you can see clearly that the replacement of the (2.1) preserves dynamical behavior of the original model (1.1). Potential is almost equal in both cases and their mean difference is less than 0.28. Therefor with this replacement we have a system with fewer parameters respect to the original model, but with the same qualitative behavior. Our next goal is reducing the number of equations. For this purpose, we peruse dynamical behavior of variables. In Figure 1-b you can see how variables change as time goes on. During the time that n increases h_k is almost zero. When h_k starts to increase n decreases, so the product of these two variables is always low. Due to the fact that the flow of potassium is product of fourth power of n and first power of h_k maybe we can omit the potassium current from system (1.1).

To verify effects of potassium current on action potential we alter different parameters related to potassium current and show how maximum amount of potential and critical point change and draw results in Figure 3. As it is obvious in this figure different amount of $[k]_{in}, [k]_{out}$, and $\hat{g}_k$ do not change the maximum amount of potential and rest potential(critical point).

Moreover, if we define ratio of length of each current interval to each other as follows

$$r_{I_i,I_j} = |\frac{MaxI_i - MinI_i}{MaxI_j - MinI_j}| \quad i,j = Na, K, cl, ... \tag{2.2}$$

FIGURE 3. Altering potassium current parameters, first row: $[K]_{Out}$, second row: $\hat{g}_h$, and third row:$[K]_{in}$. right side: effects on the critical point, left side: effects on maximum end plate potential.

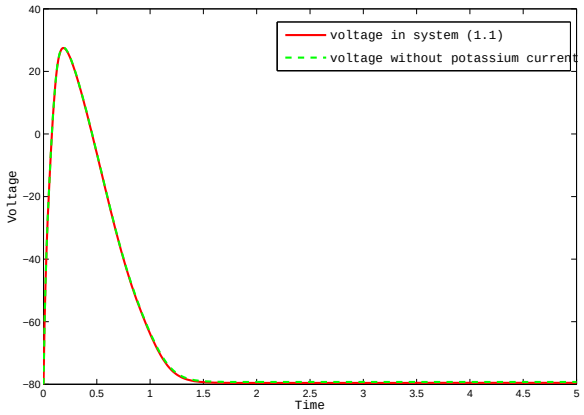


then

$$|r_{I_k,\hat{I}}| < \frac{0.25}{1600} < 1.6 \times 10^{-4}.$$

Since this ratio is very low and because of discussions conducted in the last two paragraphs, we can eliminate potassium current. Figure 4 shows the action potential for system (1.1) before and after this elimination. These two diagrams almost coincide and their mean differences are less than 0.07; So the action potential is almost the same for original and reduced models.

FIGURE 4. Action potential for system (1.1) with and without potassium current.



Now if you look carefully to the Figure 5. you can see that variable S is almost unchanged after $t = 1$. Since the variable S is really slow we can replace it with a fixed value. This value is only dependent on initial value of S. Let $S = 0.95S_0$, where S_0 is the initial value of $S(t)$. Replaceing it in the original system instead of $S(t)$ will simplify the original system and reduces its dimension.

FIGURE 5. S(t) is ploted for three different initial values.

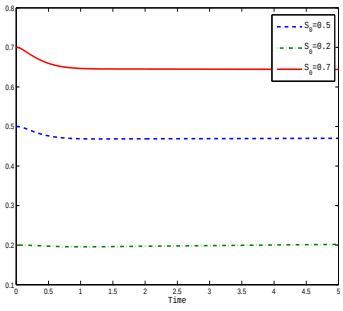
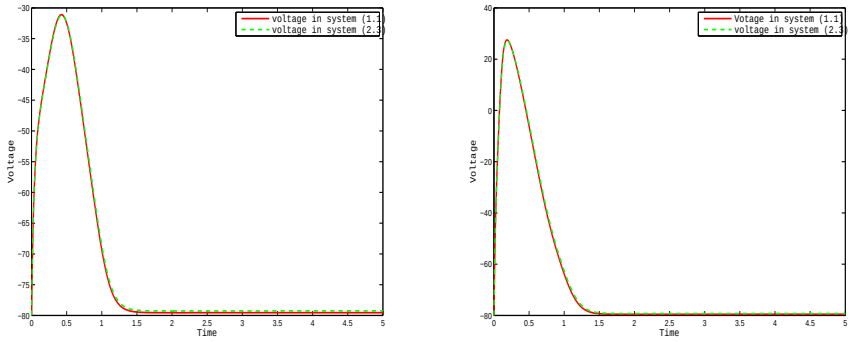


FIGURE 6. Action potential for system (1.1) and (2.3): Left hand side diagram for $S_0 = 0.2$, right hand side diagram for $S_0 = 0.5$.



Now we apply all of these simplifications to the system (1.1) to have a new reduced system as follows:

$$\begin{cases} \frac{dV}{dt} = -0.95 S_0 g_{Na} m^3 h (V - E_{NA}) - \hat{I}, \\ \frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V) m, \\ \frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V) h. \end{cases} \tag{2.3}$$

This new system has three equations, and the number of its parameters is less than (1.1). In Figure 6. we compare action potential changes in the system (1.1) with (2.3). This figure is plotted for different initial values of S. In this figure, red diagrams are corresponding to voltage changes for the system (1.1) and green ones show changes in voltage for the reduced system (2.3). The mean difference of potential between these two systems is less than 0.34. Since the behavior of the action potential of both systems is similar, and dimension of the system (2.3) is less than system (1.1), the former system (2.3) is a perfect choice for studying the qualitative behavior of skeletal muscle cells. It is easier to study critical points, bifurcation and propagation action potential and other dynamical behavior of the reduced dynamical system; Besides discussing all of the different properties in the reduced system needs less time and memory space for processing.

3. Qualitative behavior of the reduced system

In this section, we will find critical points of the system(2.3). In this way, we let $S_0 = 0.2, m_0 = 0.7$ and $h_0 = 0.7$ and discuss the critical point in this particular case then we analyze the system in general.

One way to find critical points of the system (2.3) is putting second and third equations in the system (2.3) equal to zero to find a relationship between m, and V and between h and V as follows:

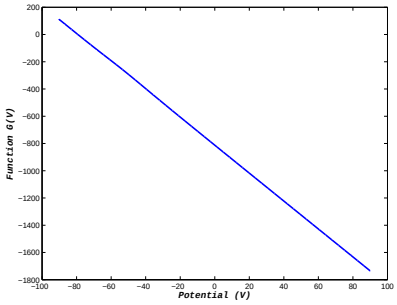
$$X_\infty(V) = \frac{\alpha_x(V)}{\alpha_X(V) + \beta_X(V)}, \quad \text{where } X = m, h. \tag{3.1}$$

By replacing (3.1) in the first equation of (2.3) we have

$$\frac{dV}{dt} = G(V) = -0.95 S_0 g_{Na} m_\infty^3 h_\infty (V - E_{NA}) - \hat{I}. \tag{3.2}$$

If we can find V^* such that $G(V^*) = 0$ then the point $(V^*, m_\infty(V^*), h_\infty(V^*))$ will be a critical point for system (2.3). We plot diagram of $G(V)$ in Figure 7. As you can see this function has only one root in an interval that is physiologically justified; As a result system (2.3) has only one explainable critical point when $h_0 = 0.7, m_0 = 0.7$ and $S_0 = 0.2$. To analyze the stability of this point we use Routh-Hurwitz criterion.

FIGURE 7. Diagram of $G(V)$.



The Routh-Hurwitz Criterion. Consider the polynomial

$$P(\lambda) = \lambda^n + a_{n-1}\lambda^{n-1} + ... + a_1\lambda + a_0. \tag{3.3}$$

Roots of $P(\lambda)$ have negative real parts if and only if

$$det(H_j) > 0 \quad \text{for} \quad \text{j=1...n},$$

where,

$$H_1 = a_{n-1},\ H_2 = \begin{pmatrix} a_{n-1} & 1 \\ a_{n-3} & a_{n-2} \end{pmatrix}, H_3 = \begin{pmatrix} a_{n-1} & 1 & 0 \\ a_{n-3} & a_{n-2} & a_{n-1} \\ a_{n-5} & a_{n-4} & a_{n-3} \end{pmatrix}. \tag{3.4}$$

For more details see [1].
To apply this criterion to the system (2.3) we should linearize system about its critical point and then evaluate characteristic polynomial for it. Let $S_0 = 0.2$ and $h_0 = 0.7$, so we have

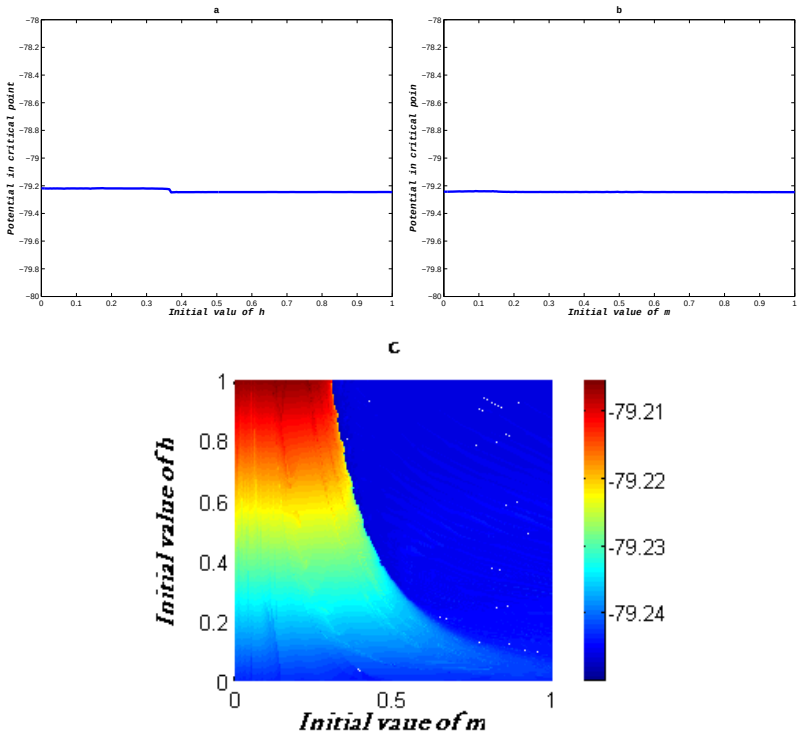
$$A = \begin{pmatrix} -10.2509 & 9.86 & 0.433 \\ 0.080 & -25.74 & 0 \\ -0.004 & 0 & -0.1050 \end{pmatrix} \tag{3.5}$$

$$p_A(\lambda) = -\lambda^3 - 36.1\lambda^2 - 266.85\lambda - 2316. \tag{3.6}$$

By applying Routh-Hurwitz Criterion, we have

$$H_1 = 36.1,\ det(H_2) = 9656.445.$$

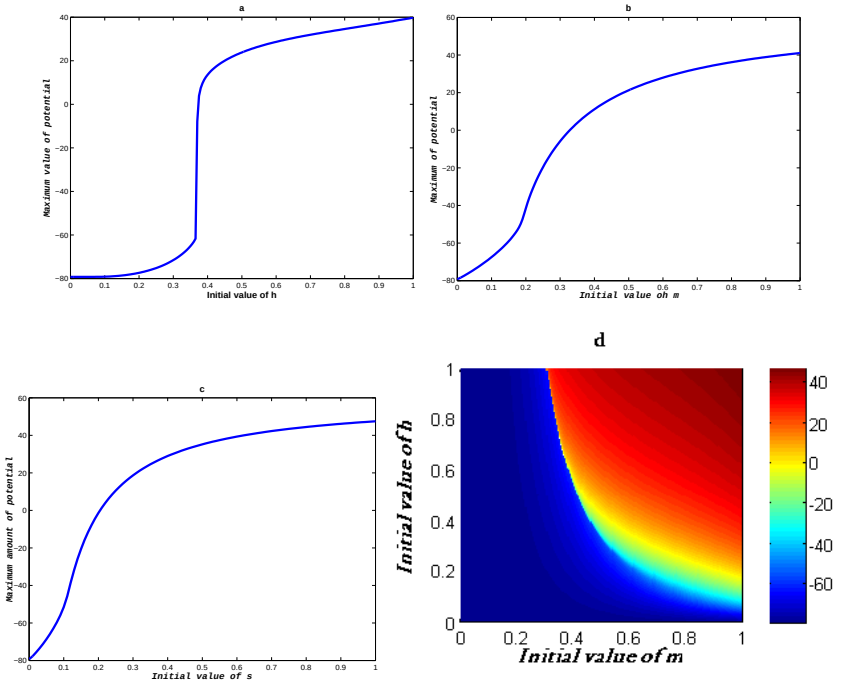
FIGURE 8. Position of critical point: a) let $S_0 = 0.5$ and $m_0 = 0.7$ and altering h_0, b) let $s_0 = 0.5$ and $h_0 = 0.7$ then altering m_0, c) let $s_0 = 0.5$ and altering m_0 and h_0.



Since H_1 and $det(H_2)$ are positive then real parts of eigenvalues are negative, thus critical point is stable when $S_0 = 0.2, m_0 = 0.7$ and $h_0 = 0.7$. To evaluate the effect of S_0, m_0 and h_0 on qualitative behavior of critical point we can plot diagram of critical point as a function of initial values. Figure 8. shows the sensitivity of critical point to initial values of h, and m. Clearly, in both cases the critical point remains stable; Moreover, its position changed a little and remains in the interval $[-79.26., -79.20]$. The same story happens for the initial value of S.

At this point, we show that unlike the critical point, maximum amount of potential is sensitive to initial values. As it is obvious in Figure 9. maximum amount of this potential alters in a range between -80 and 50. When it is around -80 it means that there is no spike in those initial values. It means that if acetylcholine opens activation and inactivation sodium gated channels less than a certain value potential will stay near critical or rest point.

FIGURE 9. Maximum amount of potential in three different cases: a) fixed $s_0 = 0.5$ and $m_0 = 0.7$ and altering h_0, b) fixed $s_0 = 0.5$ and $h_0 = 0.7$ and altering m_0, c)fixed $m_0 = 0.7$ and $h_0 = 0.7$ and altering s_0. d) fixed $s_0 = 0.5$ and ltering h_0 and m_0.



4. CONCLUSION

In this paper, we studied a mathematical model for skeletal muscle fibers which was used by Wallinga, et al. We found that some of the variables in the model are omissible. According to this, we introduced a new reduced model with three variables and fewer parameters respect to the original model.We studied some properties of the new system. With some computational methods, we determine that critical point of the system is stable. Despite the simplicity of the presented model, we illustrated that it is as efficient as the original model in studying the qualitative behavior of the action potential.

REFERENCES

[1] B. Ermentrout, *Mathematical foundation on neuroscience*, The MIT Press Cambridge, Massachusetts London, England, 2007, 1–27

[2] M. Fortune and M. M. Lowery, *Effect of extra cellular potassium accumulation on muscle fiber conduction velocity: A simulation study*, Annals of Biomedical Engineering, *37* (2009), 2105-2117.

[3] E. Fortune and M. M. Lowery, *Effect of membrane properties on skeletal muscle fiber excitability: a sensitive analysis*, Med. Bio. Eng. Comput., *50* (2012), 617–629.

[4] A. C. Guyton and J. E. Hall, *Text book of medical physiology*, Elsevier Inc. , Philadelphia, Pennsylvania, 2006, 57–78.
[5] W. F. Ganong, *Review of medical physiology*, McGraw-Hill Companies, Inc, United State, 2005, 51–70.
[6] B. Hernandez-Gascon, J. Grasa, B. Calve, and J. F. Rodriquez, *A 3D electro–mechanical continuum model for simulating skeletal muscle contraction*, Journal of theoretical biology, *335* (2013), 108–118.
[7] E. M. Izhikevich, *Dynamical systems in neuroscience*, The MIT Press Cambridge, Massachusetts London, England, 2007, 215–223.
[8] J. Keener and J. Sneyd, *Mathematical Physiology*, Springer, new york, 1998, 542–577.
[9] V. I. Krinski and I. u. M. Kokoz, *Analysis of the equations of excitable membranes. I. Reduction of the Hodgking-Huxley equations to a 2d order system*, Biozika, *18* (1973), 506–511.
[10] T. A. M. Langlands, B. I. Henry, and S. L. Wearne, *Fractional cable equation models for anomalous electrodiffusion in nerve cells: finite domain solutions*, SIAM J., *71* (2011), 1168–1203.
[11] S. Lynch, *Dynamical systems with applications using Maple*, Springer, Birkhauser Boston, 2010, 43–140.
[12] S. Shahi and H. Kheiri, *Dynamical behavior of a skeletal muscle fiber model*, Global conference on applied physics and mathematics, Italy-Rome, 2016.
[13] W. Wallinga, S.L. Meijer et. al, Modelling action potentials and membrane currents of mammalian skeletal muscle fibers in coherence with potassium concentration changes in the T-tubular system, *Eur Simulation*, 8 (2007) 317-329.
[14] M. Xi, G. Yun, and B. Narsu, *A mathematical model on stressstrain of the epimysium of skeletal muscles*, Journal of theoretical biology, *365* (2015), 175–180.