BIOMATH
https://biomath.math.bas.bg/biomath/index.php/biomath
Biomath Forum
ORIGINAL ARTICLE

A Simple Integrated Mathematical Model of Neuromuscular Activation

Zdravka D. Ivanova, Tihomir B. Ivanov

Faculty of Mathematics and Informatics,
Sofia University "St. Kliment Ohridski", Bulgaria
zivanova@fmi.uni-sofia.bg
tbivanov@fmi.uni-sofia.bg

Received: May 13, 2022, Accepted: October 11, 2022, Published: November 14, 2022

Abstract: **In the present work, we propose a new integrated mathematical model of neuromuscular activation. It combines the Izhikevich model of neural activity with the Williams model of calcium activity inside the muscle cell and a Hill-type model for the resultant muscle force. The coupling is done using a heuristic approach. The aim is to construct a simple model, which has biophysically meaningful parameters and is applicable to the study of neuromuscular diseases. Then, we study numerically the properties of the model solutions with respect to the main parameters. To that end, we study the effect of various firing patterns of the motoneuron, variations in the properties of the end-plate as well as the rates, corresponding to the calcium dynamics inside the muscle cell.**

Keywords: **Neuromuscular Activation, Neuromuscular Diseases, Mathematical Modelling, Parametric Analysis, ODE Systems, Multiphysics Simulations, Computational Experiments**

I. Introduction

The neuromuscular system combines the nervous system and muscles to work together and permit movement. Neuromuscular diseases are diseases that affect the normal functioning of the muscles and/or their control from the nervous system. Such diseases are caused by autoimmune or genetic disorders as well as contact with environmental chemical substances or other influences [1]. Therefore, to model such a disease one should apply a detailed integrated approach—modelling of the nervous system, the resulting muscle activity and the connection between them. The process of muscle contraction can be modelled as the result of four consecutive processes—propagation of nerve impulses, neurotransmitter release and transport in the neuromuscular junction, the resulting biochemical reactions in the muscle, and the generated contraction. The mechanisms behind neuromuscular activation are discussed in more detail in a previous work of the authors [2], so we refer to that article for more information. We shall, nevertheless, state the main steps of the activation process:

1) An impulse travels through the axon of the motor neuron to its terminal;
2) At the axon terminal there are voltage-gated calcium channels, which open due to the action potential and calcium ions diffuse into the terminal;
3) The calcium presence in the axon terminal opens the so-called synaptic vesicles to release a neurotransmitter, called acetylcholine (ACh);
4) The released ACh diffuses, crosses the synaptic cleft between the motoneuron and muscle cell and binds to ACh receptors on the motor end-plate of the muscle fiber, which contains cation channels. The cation channels open and sodium ions enter the muscle fiber, causing potassium ions to exit the muscle fiber;

Citation: Zdravka D. Ivanova, Tihomir B. Ivanov, A Simple Integrated Mathematical Model of Neuromuscular Activation, Biomath 11 (2022), 2210119, https://doi.org/10.55630/j.biomath.2022.10.119

5) The input flux of the sodium ions changes the membrane potential, causing depolarization or the so-called end-plate potential (EPP). Once the membrane potential reaches a threshold value, an action potential propagates along the sarcolemma;
6) Inside the muscle cell, the sarcoplasmic reticulum (SR), which is a network of tubules that regulates calcium concentration, then releases calcium so that it can bind to contractile filaments (actin and myosin filaments) in the muscle fiber. The binding of calcium to the contractile filaments (CFs) allows them to bind to each other and further leads to muscle cell contraction.

We are interested here in constructing a mathematical model, which meets the following goals:

- Relative simplicity, which allows for a mathematical and/or computational analysis,
- Sufficient flexibility, which allows for simulating various realistic scenarios of neuromuscular activity,
- Ability to study the effect of various malfunctions of the neuromuscular system. To that end, one must have model parameters that have biophysical meaning and, furthermore, be directly connected to the effect of some known problems of the neuromuscular system.

To the best of our knowledge, such models in the scientific literature (if any) are very few. The work of Meredith [3] is a step in the direction we aim, but it covers only "half" of the complete process. It lacks the ability of modelling realistic nerve impulses as well as having a realistic description of the ACh transport in the neuromuscular junction. It focuses on what happens after the electrical and chemical signals have reached the end-plate of the muscle cell. Thus, our aim is to step on some ideas, proposed in [3], and extend them in such a way that a more complete (though sufficiently simplified) model of the process is obtained as a step towards a successful mathematical modelling of various neuromuscular diseases and accomplishing the goals, formulated above. To that end, basically, we shall consider an implementation of the following more general scheme, see Figure 1.

This general scheme allows for many possible choices for the modelling of each individual stage as well as the coupling between the consecutive stages. Therefore, we believe that a hierarchy of mathematical models needs to be constructed by choosing appropriate models for each stage and coupling them in a suitable way. Thus, one would indeed obtain a hierarchy of

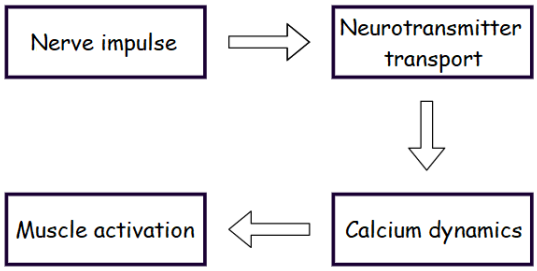


Fig. 1: General scheme of the process of neuromuscular activation.

mathematical models with various levels of detailedness, which would hopefully shed light on various aspects of this very complex, yet, highly important process and become useful for the study of various neuromuscular diseases.

Of course, when one undertakes such a goal, one must start simple. This is the reason for the requirements that we posed above for the model we aim to construct in this article. It should serve as a foundation for this hierarchy of mathematical models. Various parts of it should be later gradually improved, complicated, made more detailed. But, now, we would like to establish the general setting and a general approach for obtaining some useful results.

We shall combine the following models:

- Izhikevich model for the action potential [4,5],
- A model, proposed by Williams [6], of the calcium dynamics inside the muscle cell,
- Hill-type model for the muscle contraction [7,8].

The coupling between the nerve impulse and the resulting calcium activity is made using a heuristic approach, following [3].

The model, which we consider, expands the results in [3], due to the simulation of realistic nerve impulses and, furthermore, shows a general approach, which can be extended for taking into account more aspects of the process.

The present work is structured as follows. In Section II, the mathematical model is formulated. Then, its solutions for various combinations of the model parameters are studied numerically in Section III. In particular, in Section III-A different firing patterns are simulated with the Izhikevich model and their effect on the model solutions is studied. In Section III-B, the properties of the end-plate are varied, and in Section III-C, the effect of the reaction rates of calcium binding and unbinding in the muscle cell are studied. Section IV summarizes the main findings of the article.

II. Mathematical model

Let us formulate here the Izhikevich model of neural impulse [4, 5]:

$$\begin{aligned} \frac{dv}{dt} &= 0.04v^2 + 5v + 140 - u + I, \\ \frac{du}{dt} &= a(bv - u), \end{aligned} \tag{1}$$

with the auxiliary rule that if $v = 30$mV holds, then, $v \leftarrow v_{reset}, u \leftarrow u + u_{reset}$, i.e. the variables v and u are reset after each spike (or, equivalently, when v gets to 30mV) to values v_{reset} and $u + u_{reset}$, correspondingly. Here, v means the transmembrane voltage and u is a recovery variable. The parameters $a, b, u_{reset}, v_{reset}$ are positive constants and I is the input current. The result of the latter model is coupled with the following model of calcium dynamics inside the muscle cell and a Hill-type model for the muscle activity. The model was proposed by Williams [6] and used in a similar context to ours in [3]. It can be reduced to the following system of 3 ODEs after proper rescaling of the participating quantities (see [6], [3]).

$$\begin{aligned} \frac{dc}{dt} &= (k_4 f_b - k_3 c)(1 - f_b) + k_1(C - c - f_b) \\ &\quad + k_2 c(C - S - c - f_b), \\ \frac{df_b}{dt} &= -(k_4 f_b - k_3 c)(1 - f_b), \\ \frac{dP_s}{dt} &= k_5 \mu_s \frac{P_0 \lambda(P_s) f_b - P_s}{\mu_s + k_5 P_0 \lambda(P_s) \alpha f_b}, \\ \alpha &= \begin{cases} \alpha_p, & v_c \geq 0, \\ \alpha_m, & v_c < 0. \end{cases} \end{aligned} \tag{2}$$

In the latter model, c is the nondimensionalised concentration of free calcium ions inside the muscle cell, f_b is the nondimensionalised concentration of bound CF sites. The concentrations are scaled with the total amount of CF sites per unit volume. P_s is the resultant muscle force, k_1, k_2, k_3, k_4 are the rates of release of calcium ions from the SR, binding of calcium ions to the SR, binding of calcium ions to the CFs, and release of calcium ions from the CFs, correspondingly; C and S are the total nondimensionalised amounts of calcium and SR sites per unit volume. Further, if l_{s0}, l_{c0} are the resting lengths of the spring and contractive elements (in the sense of a Hill model [8]), correspondingly, L is the muscle length, μ_s is the stiffness coefficient, and $v_c = dP_s/dt$ is the velocity of the contractile element in Hill's model, then

$$\lambda(P_s) = 1 + A\left(L - l_{s0} - \frac{P_s}{\mu_s} - l_{c0}\right)^2.$$

Models (1) and (2) are coupled via the coefficient k_1. Following [3], the latter is chosen to be

$$k_1 = \sum_{i=1}^{M} k_{10} \exp\left(-\frac{|t - t_i|}{\tau_q(i)}\right),$$

where t_i are the times of the peaks of the neural stimuli, i.e. the peaks in the solution of (1), M is their number, $\tau_q(i)$ is the decay time parameter for the i-th impulse (we shall further assume that $\tau_q(i) \equiv \tau_q = const$), and k_{10} is the maximum resultant end-plate potential. In other words, we stimulate the muscle cell with exponential stimuli at a rate, consistent with the simulated neural activity. The parameter k_2 is taken to be

$$k_2 = \begin{cases} k_{20}, & \text{if } \left|\frac{dk_1}{dt}\right| < tol, \\ 0, & \text{otherwise,} \end{cases}$$

where k_{20} is a positive parameter. In this way, we manage to couple the activity of the muscle cell with a realistic description of a neural impulse, which is the main improvement on the model in [3].

III. Parametric analysis

We are interested in studying how varying the different parameters affects the model solutions. It is important to understand those mechanisms in order to associate such simulations with various malfunctions of the neuromuscular system. In particular, we study consecutively the effects of:

- applying various neural stimuli,
- varying the properties of the end-plate of the muscle cell,
- varying the properties of the calcium dynamics inside the muscle cell.

Those are the main factors, which can be accounted for by the presented mathematical model.

Let us note that the asymptotic behaviour of the model solutions of (2) in two important limiting cases was studied in a previous work of the authors [2]. For convenience of the reader, we state one of the main propositions in [2] here.

Proposition. *Consider the case $k_1 = const > 0$, $k_2 = 0$ in (2). The conditions for the existence and stability of the equilibrium points, corresponding to the first two equations,*

$$E_1 = (C - 1, 1) \text{ and } E_2 = \left(\frac{Ck_4}{k_3 + k_4}, \frac{Ck_3}{k_3 + k_4}\right)$$

in terms of C are given in the table below:

C	$0 < C < 1$	$1 < C < \frac{k_3 + k_4}{k_3}$	$C > \frac{k_3 + k_4}{k_3}$
E_1	$\nexists$	saddle	stable
E_2	stable	stable	$\nexists$

A. Result of various neural stimuli

We conduct numerical experiments with various values of the model parameters in (1), corresponding to different firing patterns of the nerve cell and we simulate the corresponding generated muscle forces, according to the formulated model.

For the next experiments, we shall fix the following parameter values, following [3] and [4]:

$$A = -2.23,\ b = 0.2,\ C = 2,\ I = 10,\ k_3 = 65,$$
$$k_4 = 45,\ k_5 = 100,\ k_{10} = 9.6/M,\ k_{20} = 5.9,$$
$$L = 2.7,\ l_{c0} = 2.6,\ l_{s0} = 0.234,\ M = 20,$$
$$\mu_s = 600,\ P_0 = 60.86,\ S = 6,\ tol = 5,\ \tau_q = 0.01.$$

The ODE systems are solved using the classical fourth order Runge–Kutta method [9].

First, we study the effect of changing the firing pattern of the motoneuron. We consider the following possibilities:

- Regular spiking (RS)—we choose the parameter values in (1) to be $a = 0.02$, $u_{reset} = 8$, $v_{reset} = -65$;
- Intrinsically bursting (IB)—we choose parameter values $a = 0.02$, $u_{reset} = 4$, $v_{reset} = -55$;
- Chattering (CH)—we choose parameter values $a = 0.02$, $u_{reset} = 2$, $v_{reset} = -50$;
- Fast spiking (FS)—we choose parameter values $a = 0.1$, $u_{reset} = 2$, $v_{reset} = -65$.

Solving equations (1) and (2) numerically, we obtain the results in Figures 2–3. Changing the firing pattern has several well-noticeable effects on the calcium dynamics inside the muscle cell. First, the higher frequency leads to a quicker increase and higher values of the calcium levels inside the muscle cell and, correspondingly, in the bound calcium sites in the CFs and the resultant muscle force.

Furthermore, if one has local bursting activity (as in the CH pattern or the beginning of the IB pattern), this leads to a quick local increase in the calcium levels (the higher the frequency, the steeper the increase) and corresponding quicker increase in f_b and P_s.

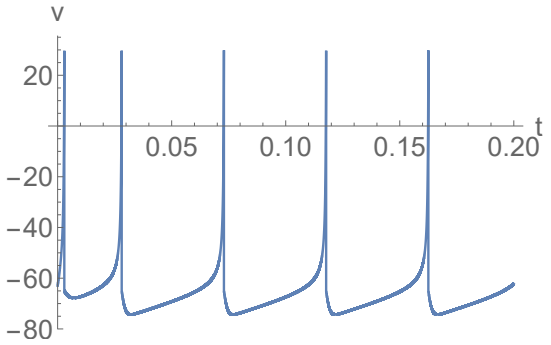
Lower frequency or long time intervals without stimulus also lead to higher fluctuations in the calcium levels. One thing that is interesting to note is that the amplitudes of the fluctuations in c are greater than those of f_b, and the fluctuations in P_s have the least amplitudes. In some sense, those fluctuations get less noticeable in each consecutive process. Furthermore, if the frequency is high enough (like in the case of fast spiking pattern) the increase in f_b and P_s is (almost) monotonic, even though some oscillations can be observed in c.

In order to better understand those results, let us also consider what happens with the coefficients k_1 and k_2 as functions of time for the various neural stimuli (see the results, depicted in Figure 4). That is, we study the rates of binding and unbinding of calcium to the SR. As one can see from the first graph, the different firing patterns lead to substantial differences in the rates of calcium release from the SR. (Locally) higher rates of neural spiking lead to higher rates of calcium release, k_1, e.g. CH and FS patterns as well as the beginning of the IB pattern. The amplitude is highest for the CH pattern, because it has the highest (locally) bursting activity. It is also important to note that higher amplitudes, e.g., in the CH pattern lead to higher fluctuation in the values of k_1 (which, as we have seen, lead further to higher fluctuation in c and f_b). On the other hand, the FS activity leads to relatively low fluctuations in k_1 and, thus, in calcium levels inside the muscle cell. Furthermore, the rate of binding of calcium to the SR is positive only for very short moments of time for the FS pattern (see Figure 4b). The time intervals of binding are much larger, when one considers the other firing patterns.

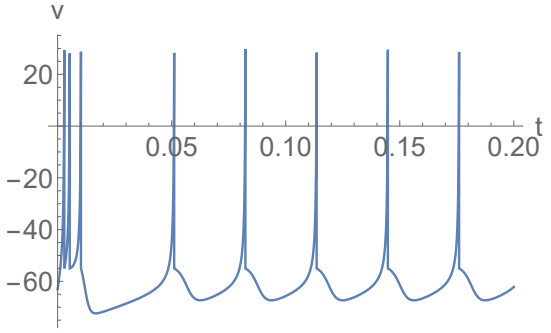
B. Changes in the end-plate potential

Let us now study numerically the effect of varying some of the parameters in the model, which could possibly be associated with a neuromuscular disease, affecting the end-plate of the muscle cell. In particular, we are interested in the effect of decreasing the maximum EPP (associated with such illnesses as Myasthenia Gravis) as well as variations in τ_q, associated with various states of the acetylcholine receptors inside the neuromuscular junction.

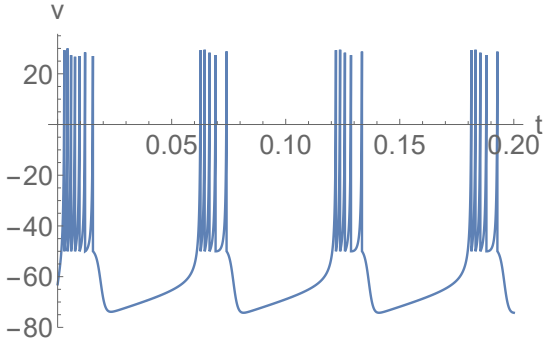
The maximum EPP can be reduced due to various diseases of the neuromuscular junction. We shall thus study here the effect of decreasing the parameter k_{10}. We depict the results from the numerical experiments for regular spiking in Figure 5a. We compute the values of c and f_b, corresponding to $k_{10} = 1, 5, 10, 20, 40, 80, 100$. The last values seem to be unrealistically large, but we nevertheless choose them for illustrative purposes, so that we can also show the asymptotic behaviour of the model solutions. As one can see, the decrease in k_{10} leads to a decrease in the free calcium levels and corresponding values of



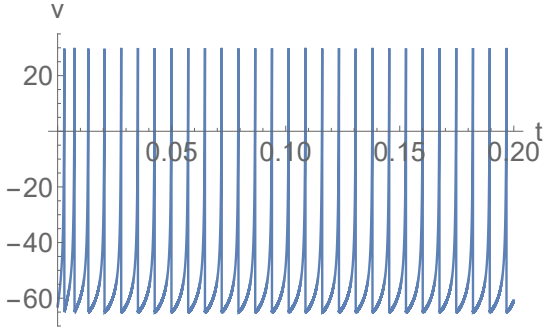
(a) Regular spiking (RS)



(b) Intrinsically bursting (IB)



(c) Chattering (CH)



(d) Fast spiking (FS)

Fig. 2: Spiking patterns.

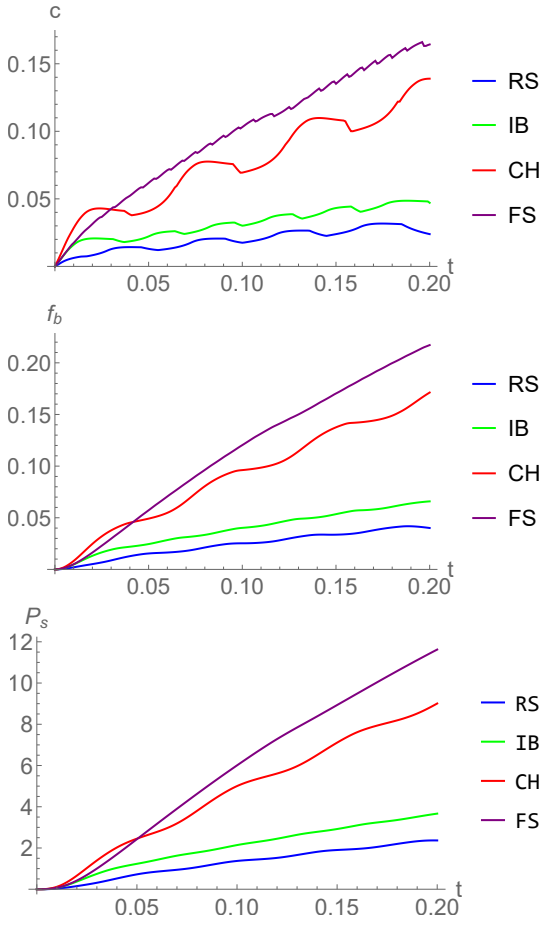
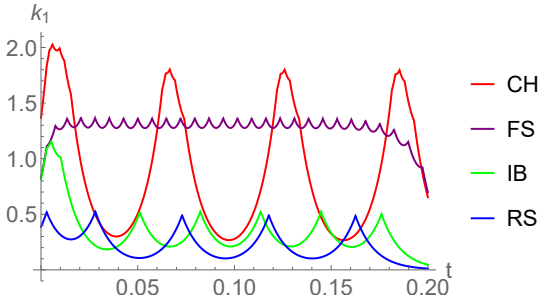
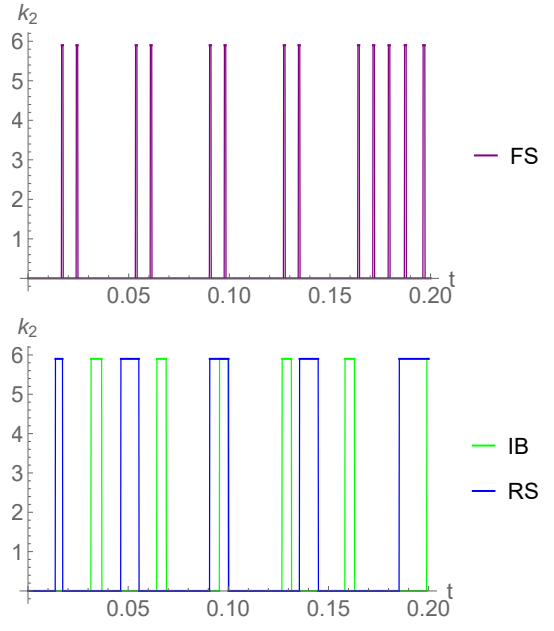


Fig. 3: Concentration of free Ca, bound Ca, and generated muscle force.

f_b. It takes significantly longer to reach the maximum levels of calcium concentration inside the muscle cell. The effect is much more noticeable for lower values of k_{10}, than for higher values. The results for the other firing patterns are qualitatively similar in the following sense—the decrease in k_{10} leads to a decrease in the free calcium levels and corresponding values of f_b in an analogous manner to what we saw for regular spiking, see Figure 5b, i.e. the difference between the curves, corresponding to different values of k_{10} follows the same trend as for regular spiking. For this reason, we shall not include results for all firing patterns, when discussing the change in c and f_b in our further experiments. Naturally, what we said about the effect of varying the firing pattern itself on c and f_b (see III.A) holds here as well—the higher frequency of the CH pattern means quicker increase in c and f_b, i.e. the



(a) Calcium release from the SR



(b) Binding of calcium to the SR

Fig. 4: Coefficients, corresponding to binding and unbinding of calcium to the SR.

effect of the various firing patterns for a fixed value of k_{10} is as described in III.A. Thus, in the following experiments we shall only give the results for regular spiking and state that the rest are qualitatively similar.

Let us further discuss the implications of the different values of k_{10} to the resultant muscle force. We compare the times for reaching the maximal force at each value of k_{10} as well as the forces reached for a fixed time of 0.2 s, see Figure 5c. One can see that the increase of k_{10} leads to an increase in the force, which can be obtained for a fixed time and a corresponding decrease in the time, needed for reaching maximal force. What is important to note is that this effect is most noticeable for small values of k_{10} (where the curves $P_s(k_{10})$ are steepest). Furthermore, firing patterns with higher frequencies (fast spiking and chattering from our examples) mean weaker effect of the variation in k_{10} (unless k_{10} is extremely small, e.g., $t_{maxforce}$ is almost constant). More precisely, the effect would be noticed on a much shorter time scale.

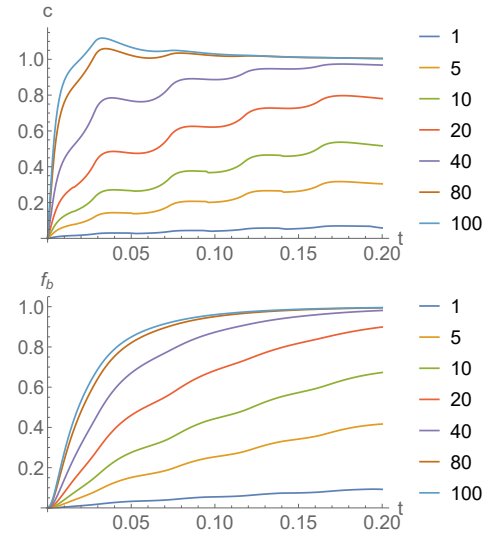
Let us consider next the variation in τ_q. We present in Figure 6a, again, simulations for regular spiking and the rest are qualitatively similar. We choose the following values of τ_q—0.005, 0.01, 0.02, 0.03, 0.04, 0.05. In some sense, the effect of lower maximal EPP can be compensated by higher values of τ_q and vice-versa. Furthermore, the increase in τ_q reduces the fluctuations in the calcium levels. The intervals of decrease become shorter and have much lesser amplitude with respect to the intervals of increase. Again, we also consider the effect of varying τ_q on the generated muscle force and present the results in Figure 6b.

C. Calcium binding properties inside the muscle cell

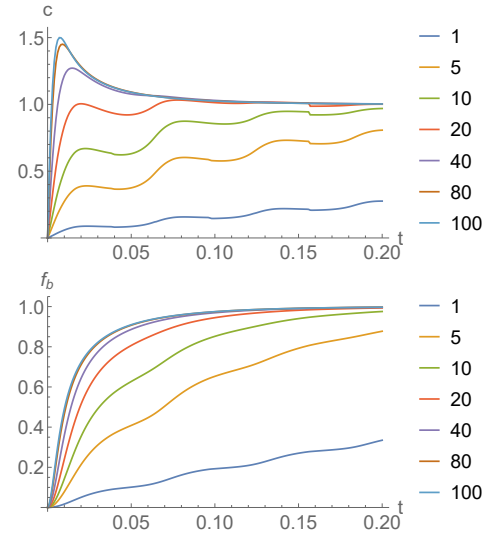
Let us now discuss the effect of varying the parameters k_3 and k_4 on the complete process. As can be naturally supposed, those parameters have opposite effects. This can be easily seen from Figure 7a and Figure 8a—when k_3 is increased, the concentration of free calcium decreases and the bound calcium increases (because of the higher binding rate), while the effect of increasing k_4 is exactly opposite.

However, it is interesting to pay special attention to the following. Our numerical experiments so far have shown that if one varies the properties of the end-plate or the firing pattern, this could have a serious effect on the generated muscle force for a fixed period of time (in our simulations, 0.2) as well as the time, needed for reaching the maximal force, which can be exerted by the motor unit. Nevertheless, at least in theory, this maximal force could be reached if there is a sufficiently long neural stimulus (for any of the patterns we study and within the scope of the numerical experiments we have carried out).

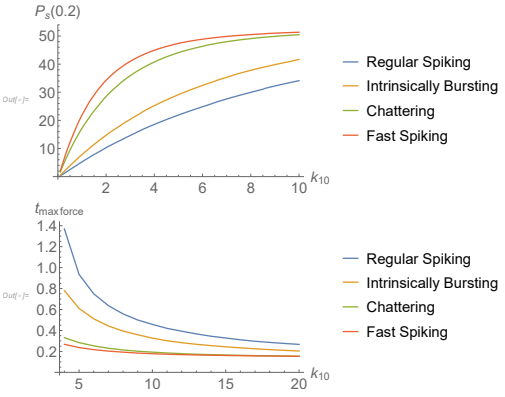
On the other hand as stated in the Proposition from the Section III, k_3 and k_4 are the parameters which control (for C being fixed) the asymptotic behaviour of the calcium dynamics in the muscle cell when there is a constant neural stimulus. It was proven that if $C > 1 + k_4/k_3$, then, the point $(c, f_b) = (C - 1, 1)$ is stable, if $1 < C < 1 + k_4/k_3$, then the point $(Ck_4/(k_3 + k_4), Ck_3/(k_3 + k_4))$ is stable. The latter means that if k_4 is large or, equivalently, if k_3 is small (in the case of our experiment, where $C = 2$, this would mean $k_4 > k_3$), then, f_b cannot reach its



(a) Effect on calcium dynamics for regular spiking

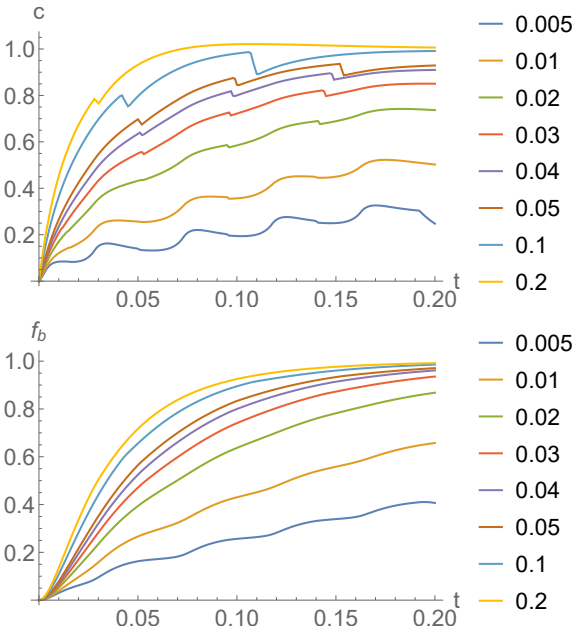


(b) Effect on calcium dynamics for chattering

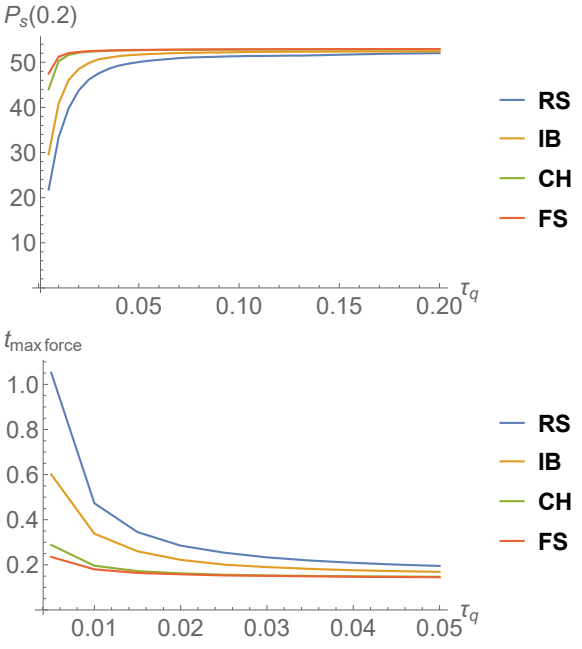


(c) Effect on muscle force

Fig. 5: Effect of varying the parameter k_{10}.

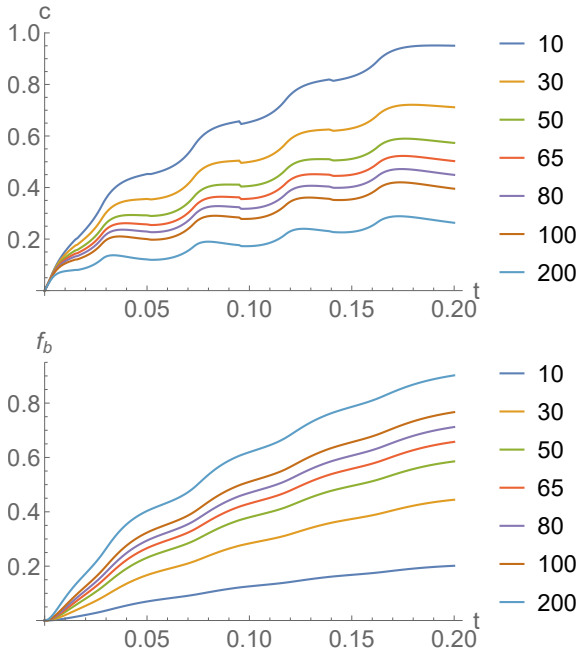


(a) Effect on calcium dynamics

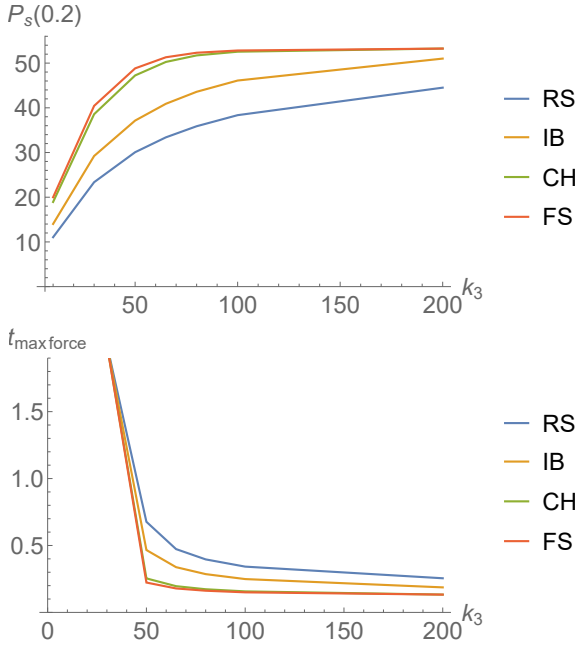


(b) Effect on muscle force

Fig. 6: Effect of varying the parameter τ_q.

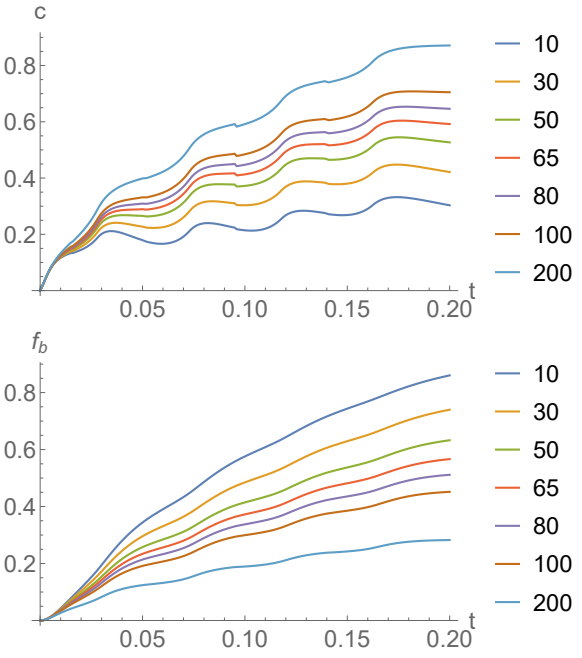


(a) Effect on calcium dynamics

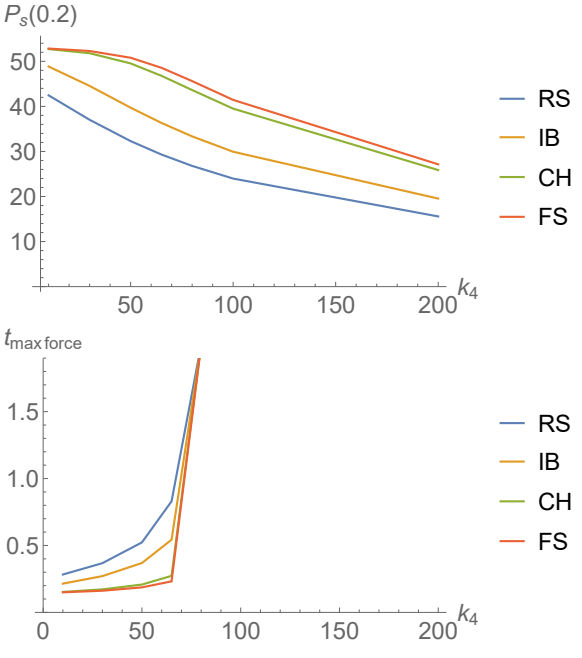


(b) Effect on muscle force

Fig. 7: Effect of varying the parameter k_3.



(a) Effect on calcium dynamics



(b) Effect on muscle force

Fig. 8: Effect of varying the parameter k_4.

maximal value of 1, which leads to the results, depicted in Figure 7b—for $k_3 < k_4 = 45$ and in Figure 8b—for $k_4 > k_3 = 65$, the maximal force cannot be reached, no matter what the firing pattern of the neuron is. This is further illustrated by the fact that the muscle force, obtained for fixed time of 0.2, decreases greatly, when k_4 is increased or k_3 is decreased for all firing patterns, unlike the experiments we have provided from varying the remaining parameters. In the previous experiments, the curves were smooth, while here we observe a discontinuity in the derivative in the first graphs in Figure 7b and Figure 8b.

IV. Conclusion and discussion

In the present work, we have proposed a mathematical model of neuromuscular activity, which takes into account some of the most important biochemical and biophysical mechanisms, known to be associated with the process. We have shown how some of the parameters in the model affect the solutions. Those parameters could be related to various malfunctions of the neuromuscular system. In particular, we have shown what the effects of various spiking patterns as well as variations in the properties of the end-plate and rates of calcium binding to the CFs are. Our main focus here was on presenting (some of) the descriptive capabilities of the model. It is a step further in modelling the process with respect to [3], thanks to the coupling with a nerve impulse model, which allows for the study of realistic stimuli in the motor unit and the dependence on their properties, which highly enriches its descriptive abilities in terms of different spiking patterns, possible effects of demyelination diseases, etc. Furthermore, we have carried out numerical experiments, which study in much more detail the dependencies of the model solutions on the most important parameters in the model.

We hope that the approach, we propose here, can, thus, be used to study the effect of underlying mechanisms in different diseases. To that end, as a future work, we aim to classify known neuromuscular diseases in terms of what they affect and, correspondingly, which parameters in the model they are related to. Then, numerical experiments will be carried out, in order to study some of the mechanisms of those diseases. The results should be compared to what is known (at present, mainly qualitative comparison can be done).

Another aspect that should be mentioned is the need of using some more detailed models in those stages of the process, which are identified to be crucial from the corresponding experiments. In particular, a more detailed model of the neuromuscular junction, simulating the acetylcholine transport should be used to connect the neural activity to the calcium dynamics inside the muscle cell (see, e.g. [10]).

In terms of the generated muscle forces, some detailed phenomenological models can also be used. One can consider, e.g., the model in [11]. Furthermore, a validation in terms of experimental data of generated force must be done.

Acknowledgments

The work of the first author was partially funded under contract КП-06-М47/6 with Bulgarian National Science Fund. The work of the second author was funded under contract 22-813/26.03.2021 with Sofia University.

References

[1] Neuromuscular disease, *Wikipedia*, Retrieved on [18/10/2022], https://en.wikipedia.org/wiki/Neuromuscular_disease.

[2] Z.D. Nedyalkova, T.B. Ivanov, "Qualitative analysis of a mathematical model of calcium dynamics inside the muscle cell", *Annual of Sofia University "St. Kliment Ohridski", Faculty of Mathematics and Informatics*, 106:127-151, 2019.

[3] T. Meredith, "A Mathematical Model of the Neuromuscular Junction and Muscle Force Generation in the Pathological Condition Myasthenia Gravis", *Semantic Scholar*, Art. 52036412, 2018.

[4] E.M. Izhikevich, "Simple model of spiking neurons", *IEEE Transactions on Neural Networks*, 14(6):1569-1572, 2003.

[5] E.M. Izhikevich, *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting*, MIT Press, 2007.

[6] T. Williams, G. Bowtell, N.A. Curtin, "Predicting force generation by lamprey muscle during applied sinusoidal movement using a simple dynamic model", *Journal of Experimental Biology*, 201(6):869-875, 1998.

[7] A.V. Hill, "The heat of shortening and the dynamic constants of muscle", *Proceedings of the Royal Society of London. Series B – Biological Sciences*, 126(843):136-195, 1938.

[8] J. Keener, J. Sneyd, *Mathematical Physiology II: Systems Physiology*, Second Edition, Springer-Verlag, New York, 2009.

[9] J.C. Butcher, *Numerical Methods for Ordinary Differential Equations*, Third Edition, John Wiley & Sons, 2016.

[10] T. Naka, K. Shiba, N. Sakamoto, "A two-dimensional compartment model for the reaction-diffusion system of acetylcholine in the synaptic cleft at the neuromuscular junction", *Biosystems*, 41(1):17-27, 1997.

[11] R. Raikova, H. Aladjov, "The Influence of the Way the Muscle Force is Modeled on the Predicted Results Obtained by Solving Indeterminate Problems for a Fast Elbow Flexion", *Computer Methods in Biomechanics and Biomedical Engineering*, 6(3):181-196, 2003.