ГОДИШНИК НА СОФИЙСКИЯ УНИВЕРСИТЕТ „СВ. КЛИМЕНТ ОХРИДСКИ“
ФАКУЛТЕТ ПО МАТЕМАТИКА И ИНФОРМАТИКА
Том 106

ANNUAL OF SOFIA UNIVERSITY „ST. KLIMENT OHRIDSKI“
FACULTY OF MATHEMATICS AND INFORMATICS
Volume 106

QUALITATIVE ANALYSIS OF A MATHEMATICAL MODEL OF CALCIUM DYNAMICS INSIDE THE MUSCLE CELL

ZDRAVKA D. NEDYALKOVA, TIHOMIR B. IVANOV

In this paper, we consider a mathematical model of calcium dynamics inside the muscle cell, proposed by Williams. We make a qualitative study of the model solutions. In particular, we study the existence and stability of equilibrium points of the model with respect to the model parameters in two limiting cases—when a constant stimulus is present and when there is no stimulus that triggers muscle activity. Numerical examples are given for each case, in order to illustrate the analytic results.

Keywords: Calcium dynamics, muscle cell, stability analysis, equilibrium points, dynamical system.

2010 Math. Subject Classification: 37N25.

1. INTRODUCTION

A general cross-section of a skeletal muscle can be seen in Figure 1.

The hierarchical structure in the skeletal muscle is described as follows [3]:

- A skeletal muscle is surrounded by fibrous tissue, called *epimysium.* It serves as a protection shield and protects the muscle from friction against other muscles and bones;
- Within the muscle, there is another connective tissue, the *perimysium*, which connects muscle fibers into bundles, called fascicles. A large muscle contains more fibers in each bundle, while a small one contains less;

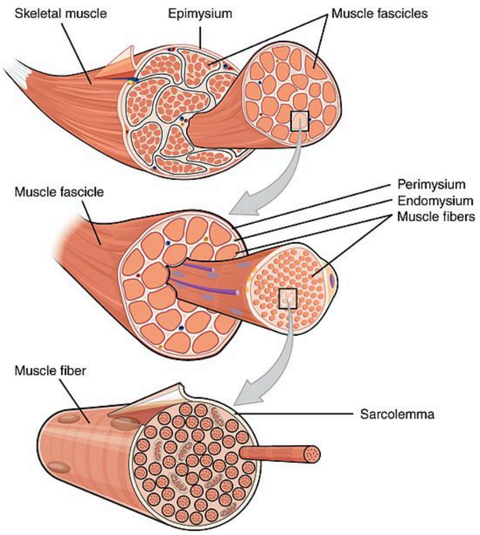

Figure 1: Skeletal muscle morphology [1].

- Inside the fascicles there is another connective tissue, which isolates each fiber, called *endomysium*;
- The endomysium contains the muscle cells/fibers or *myofibers*, formed in the process of myogenesis. Every myofiber can have a different length up to several centimeters, which is the reason that the muscle cells have multiple nuclei.

In Figure 2, the structure of a muscle fiber is shown. The membrane of the muscle cell, called sarcolemma, contains a bunch of tubes called myofibrils—the contractile units of the cell. Each muscle fiber contains hundreds or thousands of myofibrils, which are divided into segments called sarcomeres. The sarcomeres are the basis for muscle contraction theory, known as the sliding filament theory.

Each sarcomere is separated by a border, called a *Z-line* or a *Z-disc*. As in Figure 2, the sarcomere is composed of long fibrous proteins. It contains two main types of long protein chains, called **filaments**[1]—thin, made of actin protein strands, and thick—composed of myosin protein strands. Muscle contraction happens, because of thin and thick filaments sliding past each other through complex biochemical processes, triggered by calcium dynamics inside the muscle cell.

Each muscle cell has the so-called **sarcoplasmic reticulum** (SR), which is a membrane-bound network of tubules that wraps the myofibrils. **The main func-**

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[1] We have marked in bold the crucial terms related to the muscle structure that will be used throughout the paper.

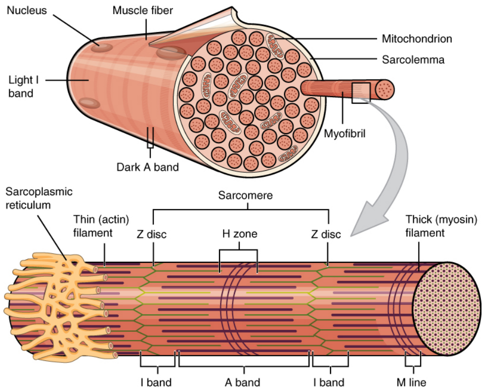


Figure 2: A muscle fiber structure [1].

tion of the SR is to store calcium ions.

It has been shown that calcium plays a central role in the process of activation of a muscle cell. In general, the process that leads to a contraction of a muscle fiber can be described in the following steps [9]:

1. An impulse travels through the axon of the motor neuron to the axon 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 and binds to ACh receptors on the motor end plate of the muscle, which contains cation channels. The cation channels open and sodium ions enter the muscle fiber, causing potassium ions to exit the muscle fiber;
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 axon 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) causes a shift in the filaments and allows them to bind to each other and contract. The latter is the so-called contractile filament theory, developed independently by two research teams in the 20th century [8].

Various authors have worked on the mathematical description of calcium dynamics inside the muscle cell, see e.g. [5, 6, 7] and the references therein. In the present work, we consider a mathematical model proposed by Williams in [7]. Here, we study the local asymptotic behaviour of the model solutions, depending on the parameter values in the two limiting cases—when a constant stimulus is present and when there is no stimulus to trigger muscle activity.

The paper is structured as follows. In Section 2, we derive the mathematical model. The general properties like existence and uniqueness, positivity, and boundedness of the solutions are shown in Section 3. An analytic study of model's dynamics is carried out in Section 4. In particular, existence and local stability study of the equilibria is derived. Numerical experiments are given in Section 5 to illustrate the analytic results and to further discuss their biological meaning in Section 6.

2. MATHEMATICAL MODEL

As discussed earlier, when a nerve impulse comes to the muscle, the action potential results in the release of Ca^{2+} ions from the SR. Ca^{2+} ions then flow into the sarcomere where the CFs are situated. Then, Ca^{2+} ions start binding to the receptors in the CFs and as a result, the filaments start sliding, causing the sarcomere to shorten. When the stimulus is turned off, the Ca^{2+} ions are transported back into the SR and the sarcomere relaxes. Having in mind the aforementioned, one needs to model the dynamics of calcium ions, SR, and CFs, in order to understand the process of muscle contraction.

For this purpose, we consider a mass action kinetics model, proposed by Williams [7], further considered by McMillen [6] and used by Meredith in [5]. The model is based on the principle of mass action kinetics, which assumes that the rate of a chemical reaction is proportional to the concentration of the reactants. Let us denote the following:

- c—concentration of free calcium ions;
- r_u—concentration of unbound sarcoplasmic reticulum sites;
- r_b—concentration of bound sarcoplasmic reticulum sites;
- f_u—concentration of unbound CF sites;
- f_b—concentration of bound CF sites;
- k_1—rate of release of calcium ions from the SR;
- k_2—rate of binding of calcium ions to the SR;
- k_3—rate of binding of calcium ions to the CFs;

- k_4—rate of release of calcium ions from the CFs.

The flow of calcium is illustrated in Figure 3:

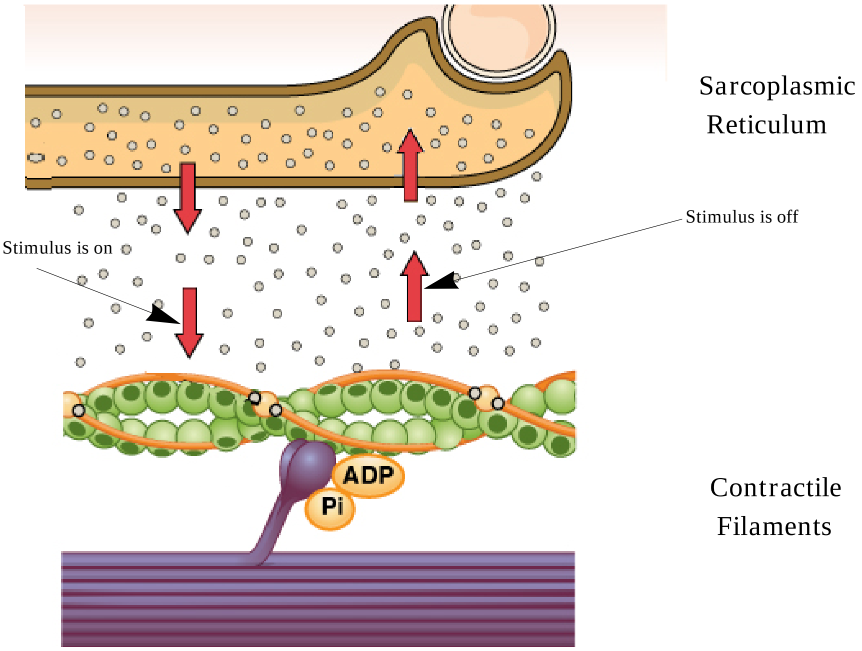


Figure 3: Flow of calcium in the muscle cell.

Based on the principle of mass action, the following statements are valid:

1. When the stimulus is on, i.e., when there is an action potential in the muscle cell, the rate of unbinding of calcium ions from the SR is proportional to the concentration of calcium-bound SR sites with a rate constant k_1;
2. When the stimulus is off, the rate of binding of calcium ions to the SR is proportional to the product of the concentrations of free calcium ions and unbound SR calcium-binding sites with a rate constant k_2;
3. The rate of binding of calcium ions to the CF sites is proportional to the product of the concentrations of free calcium ions and unbound filament sites with a rate constant k_3.

Further, because of empirical evidence, the rate of release of calcium ions from the CFs is chosen to be proportional to the product of concentration of bound and unbound filament sites with a rate constant k_4. This is meant to account for some cooperativity between the bound and unbound CF sites in the process of calcium release.

In mathematical terms, the above assumptions result in the following system of five ODEs:

$$\begin{aligned}
\frac{dc}{dt} &= k_1 r_b - k_2 r_u c - k_3 f_u c + k_4 f_b f_u, \\
\frac{dr_b}{dt} &= -k_1 r_b + k_2 r_u c, \\
\frac{dr_u}{dt} &= k_1 r_b - k_2 r_u c, \\
\frac{df_b}{dt} &= k_3 c f_u - k_4 f_b f_u, \\
\frac{df_u}{dt} &= -k_3 c f_u + k_4 f_b f_u,
\end{aligned} \tag{2.1}$$

where k_1 and k_2 are non-negative coefficients and k_3, k_4 are positive constants. Further, the following assumptions are made by Williams [7]:

1. when the stimulus is on, $k_1 > 0,\ k_2 = 0$;
2. when the stimulus is off, $k_1 = 0, k_2 > 0$.

Adding together the first, second, and fourth equations, it follows that the total amount of calcium is constant:

$$c + f_b + r_b = C. \tag{2.2}$$

Analogously, one can show that the total numbers of bound and unbound SR and CF sites are also constant, i.e,

$$\begin{aligned}
r_u + r_b &= S, \\
f_b + f_u &= F,
\end{aligned} \tag{2.3}$$

where S and F are the total numbers of SR and CF sites.

By using (2.2)–(2.3), one reduces the ODE system (2.1) to the following two-dimensional model for the concentrations of free calcium ions and calcium-bound sites:

$$\begin{aligned}
\frac{dc}{dt} &= (k_4 f_b - k_3 c)(F - f_b) + k_1 (C - c - f_b) + k_2 c (C - S - c - f_b), \\
\frac{df_b}{dt} &= -(k_4 f_b - k_3 c)(F - f_b).
\end{aligned} \tag{2.4}$$

Further, we scale the model by the total amount of the CF sites F:

$$\begin{aligned}
&\hat{f}_b = f_b/F, \quad \hat{c} = c/F, \quad \hat{C} = C/F, \quad \hat{S} = S/F, \\
&\hat{k}_2 = F k_2, \quad \hat{k}_3 = F k_3, \quad \hat{k}_4 = F k_4.
\end{aligned} \tag{2.5}$$

Substituting (2.5) in (2.4) and skipping the hats for notational simplicity, one obtains

$$\begin{aligned}\frac{dc}{dt} &= (k_4 f_b - k_3 c)(1-f_b) + k_1 (C - c - f_b) + k_2 c (C - S - c - f_b)\,,\\ \frac{df_b}{dt} &= -(k_4 f_b - k_3 c)(1-f_b)\,.\end{aligned} \tag{2.6}$$

Remark 1. The above scaling leads to certain restrictions for f_b and c, which we shall use later in the qualitative analysis of the system (2.6). Dividing both sides of (2.2) and (2.3) by F, it follows that:

$$\begin{aligned}\hat{c} + \hat{f}_b + \hat{r}_b &= \hat{C},\\ \hat{f}_b + \hat{f}_u &= 1.\end{aligned}$$

From the latter equations and the restrictions $\hat{c} \geq 0,\ \hat{f}_b \geq 0,\ \hat{r}_b \geq 0,\ \hat{f}_u \geq 0$, we obtain

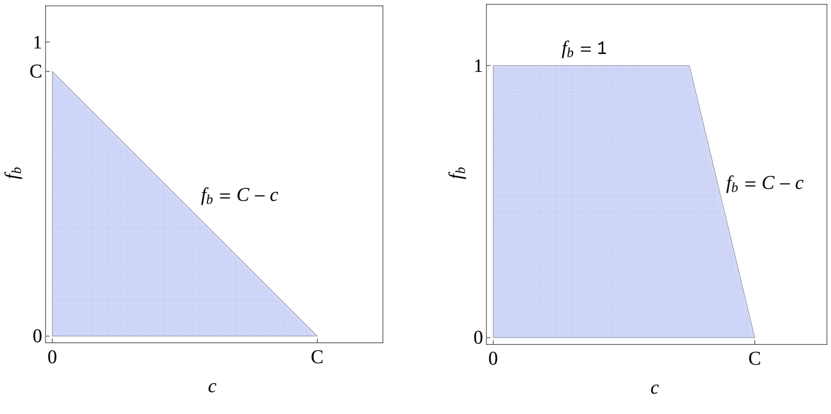
$$\begin{aligned}0 \leq \hat{c} + \hat{f}_b &\leq \hat{C},\\ 0 \leq \hat{f}_b &\leq 1.\end{aligned}$$

Therefore, system (2.6) is considered in the phase space

$$\{(c, f_b) \in \mathbb{R}^2 :\ 0 \leq c + f_b \leq C,\ 0 \leq f_b \leq 1,\ c \geq 0\}. \tag{2.7}$$

3. GENERAL PROPERTIES OF MODEL'S SOLUTIONS

Proposition 1. *The solutions of the model* (2.6) *are bounded for each choice of the model parameters.*



(a) Case $C \leq 1$.

(b) Case $C > 1$.

Figure 4: Geometry of the phase space

Proof. For the proof, we shall consider the following two cases, which determine different geometry of the phase space: $C \le 1$ and $C > 1$, see Figure 4a and Figure 4b.

Case $\boldsymbol{C \le 1}$. We shall prove that the vector field at the boundary points to the inside of the phase space. At $f_b = C - c$, it holds that

$$\frac{df_b}{dc} = -\frac{(k_4 f_b - k_3 c)(1 - f_b)}{(k_4 f_b - k_3 c)(1 - f_b) - k_2 c S} \le -1.$$

The latter means that at this part of the boundary the slope of the vectors in the vector field is less than the slope of the line $f_b = C - c$, thus, the vector field points to the inside of the phase space.

If $c = 0$, then

$$\frac{dc}{dt} = k_4 f_b (1 - f_b) + k_1 (C - f_b) > 0$$

is valid.

Finally, when $f_b = 0$,

$$\frac{df_b}{dt} = k_3 c > 0$$

holds true.

Case $\boldsymbol{C > 1}$. Let us again consider the boundary of the phase space. If $f_b = 1$, it follows that

$$\frac{df_b}{dt} = 0.$$

Thus, the solution stays on the boundary.

The results for the behaviour of the vector field on the rest boundary of the considered phase space coincide with the results in the case $C \le 1$.

Since the vector field points to the inside of the phase space at all of its boundary, it follows that the solutions of the model (2.6) are bounded for every choice of the model parameters. ☐

Now, following a standard result (see, e.g., [4, pp, 17–18]), the following proposition holds true.

Proposition 2. *For the model* (2.6)*, there exists a unique trajectory through every point* $(x_0, y_0) \in \mathbb{R}^2_+$ *and it is defined for every* $t \in [0, +\infty)$.

4. LOCAL QUALITATIVE ANALYSIS OF MODEL'S DYNAMICS IN THE LIMITING CASES $k_1 = 0$, or $k_2 = 0$

In this section, we shall study qualitatively the system of differential equations (2.6). We shall consider the two limiting cases—when the stimulus is on, i.e., when $k_2 = 0$, $k_1 = const > 0$, and when the stimulus is off, i.e., $k_1 = 0$, $k_2 = const > 0$.

4.1. CASE $k_1 = const > 0,\ k_2 = 0.$

Let us first consider the case when the rate constant for binding of calcium to the SR, k_2, is equal to zero. Thus, the system we consider is:

$$\begin{aligned} \frac{dc}{dt} &= (k_4 f_b - k_3 c)(1 - f_b) + k_1 (C - c - f_b), \\ \frac{df_b}{dt} &= -(k_4 f_b - k_3 c)(1 - f_b). \end{aligned} \tag{4.1}$$

Existence of equilibrium points

The equilibria of the system (4.1) are the solutions of the system of algebraic equations

$$\begin{aligned} (k_4 f_b - k_3 c)(1 - f_b) + k_1 (C - c - f_b) = 0, \\ -(k_4 f_b - k_3 c)(1 - f_b) = 0. \end{aligned}$$

Solving the latter system, we find two possible equilibrium points:

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

First, let us consider the conditions for the existence of the equilibrium points.

Proposition 3. *The equilibrium point E_1 exists iff $C \geq 1$. The equilibrium point E_2 exists exactly when $0 \leq C \leq \dfrac{k_3 + k_4}{k_3}$.*

Proof. In order for the equilibrium points to exist (i.e., to be in the phase space), they must satisfy the restrictions (2.7).

- Equilibrium $E_1 = (C-1, 1)$.
  We substitute $c = C - 1$ and $f_b = 1$ in (2.7) and derive the existence condition $C \geq 1$.
- Equilibrium $E_2 = \left(\dfrac{Ck_4}{k_3 + k_4}, \dfrac{Ck_3}{k_3 + k_4} \right)$.
  We substitute the latter in (2.7) and derive:

  $$0 \leq \frac{Ck_4}{k_3 + k_4} + \frac{Ck_3}{k_3 + k_4} \leq C, \qquad 0 \leq \frac{Ck_3}{k_3 + k_4} \leq 1.$$

  The first condition is trivially fulfilled, while the latter one is satisfied for $0 \leq C \leq \dfrac{k_3 + k_4}{k_3}$. □

Local stability of equilibrium points

To analyze the local stability of the equilibrium points we use the Hartman–Grobman theorem [4]. The Jacobi matrix of (4.1) as a function of the phase variables c and f_b is:

$$J(c, f_b) = \begin{pmatrix} -k_3(1-f_b)-k_1 & k_4(1-f_b)-k_4 f_b+k_3 c-k_1 \\ k_3(1-f_b) & -k_4(1-f_b)+k_4 f_b-k_3 c \end{pmatrix}.$$

Proposition 4. *The conditions for the stability of the equilibrium points* E_1 *and* E_2 *in terms of* C *are given in Table 1.*

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

Table 1: Classification of equilibria for the case $k_2 = 0$ in terms of C.

Proof. We shall analyze the stability of the equilibrium points separately.

1. Local stability of $E_1 = (C-1, 1)$.
   As derived in Proposition 3, the condition for the existence of the equilibirum point is $C \geq 1$. Substituting E_1 in the Jacobi matrix, we derive:

   $$J(E_1) = \begin{pmatrix} -k_1 & -k_4+k_3(C-1)-k_1 \\ 0 & k_4-k_3\,(C-1) \end{pmatrix}.$$

   For the eigenvalues $\lambda_1,\ \lambda_2$ of $J(E_1)$, we have

   $$\lambda_1 = -k_1 < 0,\ \lambda_2 = k_4 - k_3(C-1).$$

   Using the latter, we consider two cases for determining the stability of E_1:

   - $k_4 - k_3\,(C-1) > 0 \iff C < \dfrac{k_3+k_4}{k_3}$.
     In this case, the eigenvalues are with opposite signs. That is, the equilibrium is a saddle point.
   - $k_4 - k_3\,(C-1) < 0 \iff C > \dfrac{k_3+k_4}{k_3}$
     In this case, both eigenvalues are negative and E_1 is asymptotically stable.

2. Local stability of $E_2 = \left(\dfrac{Ck_4}{k_3+k_4}, \dfrac{Ck_3}{k_3+k_4}\right)$.
   We compute the Jacobi matrix at E_2:

$$J(E_2) = \begin{pmatrix} -k_3\left(1-\dfrac{Ck_3}{k_3+k_4}\right)-k_1 & k_4\left(1-\dfrac{Ck_3}{k_3+k_4}\right)-k_1 \\ k_3\left(1-\dfrac{Ck_3}{k_3+k_4}\right) & -k_4\left(1-\dfrac{Ck_3}{k_3+k_4}\right) \end{pmatrix}$$

and obtain

$$\begin{aligned} \lambda_1\lambda_2 &= det\ J(E_2) = k_1\left(k_4 - k_3(C-1)\right), \\ \lambda_1+\lambda_2 &= trace\ J(E_2) = -k_1 - k_4 + k_3\left(C-1\right). \end{aligned}$$

By the existence condition for E_2, derived in Proposition 3, we conclude that the determinant is always positive, with $\lambda_1 + \lambda_2 < 0$ and, therefore, the equilibrium is asymptotically stable, whenever it exists. □

4.2. CASE $k_1 = 0,\ k_2 = const > 0$.

Let us now consider the case, when the rate constant for release of calcium from the SR, k_1, is equal to zero. Thus, we consider the following system:

$$\begin{aligned} \frac{dc}{dt} &= \left(k_4 f_b - k_3 c\right)\left(1-f_b\right) + k_2 c\left(C - S - c - f_b\right), \\ \frac{df_b}{dt} &= -\left(k_4 f_b - k_3 c\right)\left(1-f_b\right). \end{aligned} \tag{4.2}$$

Existence of equilibrium points

To find the equilibrium points of the latter system of ODEs, we solve the system of algebraic equations

$$\left(k_4 f_b - k_3 c\right)\left(1-f_b\right) + k_2 c\left(C - S - c - f_b\right) = 0, \tag{4.3}$$

$$-\left(k_4 f_b - k_3 c\right)\left(1-f_b\right) = 0. \tag{4.4}$$

The solutions of (4.4) are $f_b = 1$ and $f_b = \dfrac{k_3}{k_4}\,c$. Therefore, the four possible equilibrium points to the system (4.2) are:

$$E_1 = (0,1),\ E_2 = (C-S-1,1),\ E_3 = (0,0),\ \text{and } E_4 = \left(\frac{k_4(C-S)}{k_3+k_4}, \frac{k_3(C-S)}{k_3+k_4}\right).$$

We shall derive conditions for the existence of each of the equilibrium points E_1–E_4 in terms of the total amount of calcium C.

Proposition 5. *The following statements are valid:*

- *Equilibrium point E_1 exists exactly when $C \geq 1$;*
- *Equilibrium points E_2 exists if and only if $C \geq S+1$;*
- *Equilibrium point E_3 exists for every choice of the parameters in the model* (4.2)*;*
- *Equilibrium point E_4 exists iff $S \leq C \leq S + \dfrac{k_3+k_4}{k_3}$.*

Proof. We shall derive the conditions for the existence of the equilibrium points separately.

1. Existence of $E_1 = (0,1)$.
   Taking into consideration the inequalities in (2.7) and substituting $c = 0$ and $f_b = 1$, we obtain the condition $C \geq 1$.
2. Existence of $E_2 = (C-S-1, 1)$.
   We substitute the values for c and f_b in (2.7) and derive $C \geq S+1$.
3. Existence of $E_3 = (0,0)$.
   The existence of this equilibrium is trivial since the point (0,0) satisfies the conditions in (2.7) and, therefore, exists for every choice of the parameters in the model (4.2).
4. Existence of $E_4 = \left(\dfrac{k_4(C-S)}{k_3+k_4}, \dfrac{k_3(C-S)}{k_3+k_4}\right)$.
   Substituting the latter in the inequalities in (2.7), we derive

$$0 \leq \frac{k_4(C-S)}{k_3+k_4} + \frac{k_3(C-S)}{k_3+k_4} \leq C,$$
$$0 \leq \frac{k_3(C-S)}{k_3+k_4} \leq 1.$$

Taking into consideration the positivity of the constants k_3, k_4, we derive the condition $S \leq C \leq S + \dfrac{k_3+k_4}{k_3}$. □

Local stability of equilibrium points

Proposition 6. *The conditions for the stability of the equilibrium points $E_1 = (0,1)$, $E_2 = (C-S-1,1)$, $E_3 = (0,0)$, and $E_4 = \left(\dfrac{k_4(C-S)}{k_3+k_4}, \dfrac{k_3(C-S)}{k_3+k_4}\right)$ of the system* (4.2) *in terms of C, given in Table 2 for the case $S < 1$ and in Table 3 for the case $S > 1$, are valid.*

C	$0 < C < S$	$S < C < 1$	$1 < C < S+1$	$S+1 < C < S + \frac{k_3+k_4}{k_3}$	$C > S + \frac{k_3+k_4}{k_3}$
E_1	$\nexists$	$\nexists$	saddle	unstable	unstable
E_2	$\nexists$	$\nexists$	$\nexists$	saddle	stable
E_3	stable	saddle	saddle	saddle	saddle
E_4	$\nexists$	stable	stable	stable	$\nexists$

Table 2: Classification of equilibria for the case $k_1 = 0$ in terms of the total amount of calcium ions C, when $S < 1$.

C	$0 < C < 1$	$1 < C < S$	$S < C < S+1$	$S+1 < C < S + \frac{k_3+k_4}{k_3}$	$C > S + \frac{k_3+k_4}{k_3}$
E_1	$\nexists$	saddle	saddle	unstable	unstable
E_2	$\nexists$	$\nexists$	$\nexists$	saddle	stable
E_3	stable	stable	saddle	saddle	saddle
E_4	$\nexists$	$\nexists$	stable	stable	$\nexists$

Table 3: Classification of equilibria for the case $k_1 = 0$ in terms of the total amount of calcium ions C, when $S > 1$ is valid.

Proof. Let us consider the four possible equilibrium points:

$$E_1 = (0,1),\ E_2 = (C-S-1,1),\ E_3 = (0,0),\ \text{and } E_4 = \left(\frac{k_4\,(C-S)}{k_3+k_4}, \frac{k_3\,(C-S)}{k_3+k_4}\right).$$

We linearize the system of equations (4.2) to analyze the stability of the equilibria, by using the Hartman–Grobman theorem. The Jacobi matrix of the system is

$$J(c,f_b) = \begin{pmatrix} -k_3\,(1-f_b) + k_2\,(C-S-2c-f_b) & k_4 + k_3 c - 2k_4 f_b - k_2 c \\ k_3\,(1-f_b) & -k_4 + 2k_4 f_b - k_3 c \end{pmatrix}. \tag{4.5}$$

We shall evaluate the Jacobi matrix at the four equilibrium points and determine the type of the equilibria by the signs of the eigenvalues of the matrix.

1. Equilibrium point $E_1 = (0,1)$.
   Let us first note that the point E_1 exists only for $C \geq 1$, see Proposition 5. Substituting the latter equilibrium point in (4.5), we derive:

   $$J(E_1) = \begin{pmatrix} k_2\,(C-S-1) & -k_4 \\ 0 & k_4 \end{pmatrix}.$$

   The eigenvalues of $J(E_1)$ are $\lambda_1 = k_2(C-S-1)$ and $\lambda_2 = k_4$. Then, obviously, E_1 is a saddle point if $C < S+1$ holds and an unstable node if $C > S+1$ is valid.

2. Equilibrium point $E_2 = (C - S - 1, 1)$.
   We substitute E_2 in (4.5) and obtain

$$J(E_2) = \begin{pmatrix} -k_2\,(C-S-1) & (C-S-1)\,(k_3-k_2)-k_4 \\ 0 & k_4 - k_3\,(C-S-1) \end{pmatrix}.$$

   The eigenvalues of the triangular matrix are $\lambda_1 = -k_2(C-S-1) < 0$ (from the existence condition) and $\lambda_2 = k_4 - k_3(C-S-1)$. Thus, the equilibrium point is a stable node when $k_4 < k_3(C-S-1) \iff C > \dfrac{k_4}{k_3} + S + 1$ and is a saddle point when $S + 1 < C < \dfrac{k_4}{k_3} + S + 1$.

3. Equilibrium point $E_3 = (0, 0)$. We compute the determinant and trace of the Jacobi matrix:

$$J(E_3) = \begin{pmatrix} -k_3 + k_2\,(C-S) & k_4 \\ k_3 & -k_4 \end{pmatrix}$$

   and obtain

$$det\ J(E_3) = -k_2k_4\,(C-S)\,, \quad trace\ J(E_3) = -k_3 - k_4 + k_2(C-S).$$

   The sign of the determinant in this case depends on the factor $C-S$, therefore, we shall consider the following two cases:

   - $C - S > 0$.
     In this case, the determinant is negative and, therefore, E_3 is a saddle point.
   - $C - S < 0$.
     In this case, the determinant is positive and the trace is negative. The equilibrium is, thus, asymptotically stable.

4. Equilibrium point $E_4 = \left(\dfrac{k_4(C-S)}{k_3+k_4}, \dfrac{k_3(C-S)}{k_3+k_4}\right)$.

$$J(E_4) = \begin{pmatrix} -k_3\left(1 - \dfrac{k_3(C-S)}{k_3+k_4}\right) - \dfrac{k_2k_4(C-S)}{k_3+k_4} & k_4\left(1 - \dfrac{k_3(C-S)}{k_3+k_4}\right) - \dfrac{k_2k_4(C-S)}{k_3+k_4} \\ k_3\left(1 - \dfrac{k_3(C-S)}{k_3+k_4}\right) & -k_4\left(1 - \dfrac{k_3(C-S)}{k_3+k_4}\right) \end{pmatrix}.$$

For the eigenvalues, after some computations, we obtain

$$\begin{aligned}
\lambda_1\lambda_2 &= det\ J(E_4)\\
&= \frac{k_2k_4\,(C-S)\,(k_4-k_3(C-S-1))}{k_3+k_4},\\
\lambda_1+\lambda_2 &= trace\ J(E_4)\\
&= \frac{-\,k_3(k_3+k_4-k_3(C-S))-k_2k_4(C-S)-k_4(k_3+k_4-k_3(C-S))}{k_3+k_4}\\
&= \frac{k_3k_4(-1-1+C-S)+k_3^2(-1+C-S)-k_4(k_2(C-S)+k_4)}{k_3+k_4}\\
&= \frac{k_3k_4\,(C-S-2)+k_3^2(C-S-1)-k_4\,(k_2(C-S)+k_4)}{k_3+k_4}.
\end{aligned}$$

In order for the equilibrium point to exist, using Proposition 5, we consider the case when $S < C < S + \dfrac{k_3+k_4}{k_3}$. In this case, the determinant is always positive, therefore, we have to determine the sign of the trace. Further, we shall give an upper bound for the expression of the trace:

$$\begin{aligned}
trace\ J(E_4) &= \frac{k_3k_4\,(C-S-2)+k_3^2(C-S-1)-k_4\,(k_2(C-S)+k_4)}{k_3+k_4}\\
&= \frac{k_3k_4(C-S-1)}{k_3+k_4}-\frac{k_3k_4}{k_3+k_4}+\frac{k_3^2(C-S-1)}{k_3+k_4}-\frac{k_2k_4(C-S)}{k_3+k_4}-\frac{k_4^2}{k_3+k_4}\\
&< \frac{k_3k_4^2}{k_3(k_3+k_4)}-\frac{k_3k_4}{k_3+k_4}+\frac{k_3^2k_4}{k_3(k_3+k_4)}-\frac{k_2k_4(C-S)}{k_3+k_4}-\frac{k_4^2}{k_3+k_4}\\
&= -\frac{k_2k_4(C-S)}{k_3+k_4}.
\end{aligned}$$

The latter expression is always negative for $C > S$—the case, which we are interested in. Therefore, the equilibrium is asymptotically stable. ☐

5. NUMERICAL EXAMPLES

5.1. LIMITING CASE $k_1 = const > 0, k_2 = 0$

In this section, we give example phase portraits for the three different cases, considered in the classification of the equilibria in Proposition 4. For the numerical experiments, we consider the model parameters, taken from Table 4:

$$k_1 = 9.6,\ \ k_3 = 65,\ \ k_4 = 45,$$

and $S = 2$. Let us note that the initial conditions for the system (4.1) must satisfy conditions (2.7).

Experiment 1. We consider the following parameter value: $C = 0.8$, which corresponds to the case $0 < C < 1$. Thus, as concluded in Proposition 4, in this case the point $E_1 = (C - 1, 1)$ does not exist, while $E_2 = \left(\frac{Ck_4}{k_3 + k_4}, \frac{Ck_3}{k_3 + k_4}\right)$ is asymptotically stable. The numerical results are shown in Figure 5 and are in agreement with the analytical conclusions.

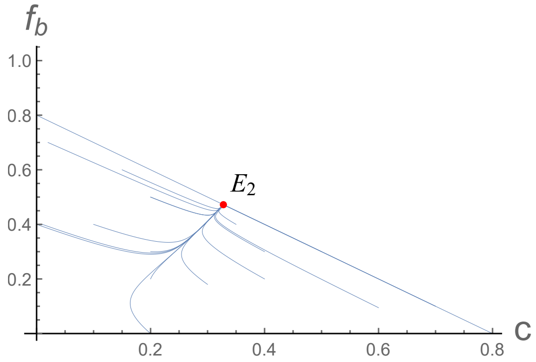


Figure 5: Phase portrait for the case $k_2 = 0$ with parameter value $C = 0.8$. E_1 does not exist, while E_2 is a stable equilibrium.

Experiment 2. We consider the parameter $C = 1.6$, which corresponds to the case $1 < C < \frac{k_3 + k_4}{k_3}$. By Proposition 4, in this case the equilibrium point $E_1 = (C - 1, 1)$ is a saddle point, while $E_2 = \left(\frac{Ck_4}{k_3 + k_4}, \frac{Ck_3}{k_3 + k_4}\right)$ is again asymptotically stable. The numerical results are in agreement with the conclusions in Proposition 4 and are depicted in Figure 6.

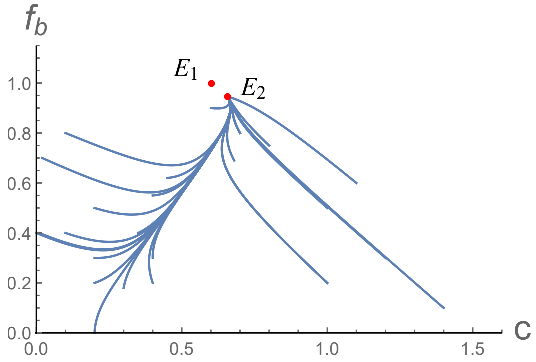


Figure 6: Phase portrait for the case $k_2 = 0$ with parameter value $C = 1.6$. E_1 is a saddle point, E_2 is a stable equilibrium.

Experiment 3. In this experiment, we consider the parameter $C = 2$, which corresponds to the case $C > \dfrac{k_3 + k_4}{k_3}$. Following Proposition 4, $E_1 = (C - 1, 1)$ is to be asymptotically stable, while $E_2 = \left(\dfrac{Ck_4}{k_3 + k_4}, \dfrac{Ck_3}{k_3 + k_4}\right)$ does not exist. The numerical results are shown in Figure 7. Again, the numerical experiments are in agreement with the analytic results.

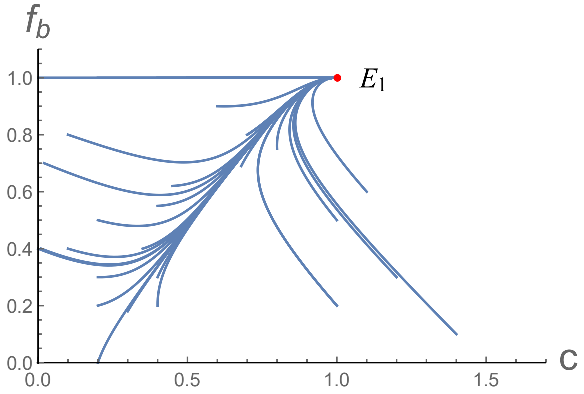


Figure 7: Phase portrait for the case $k_2 = 0$ with parameter value $C = 2$. E_1 is a stable equilibrium, E_2 does not exist.

Remark 2. By the correspoding results in Fig 5, 6, and 7, we can further suppose that the locally stable equilibrium points in each of the considered experiments are also globally asymptotically stable.

5.2. LIMITING CASE $k_1 = 0, k_2 = const > 0$

Here, we shall present several phase portraits, illustrating Proposition 6. For the numerical experiments, we consider the following values for the parameters, taken from Table 4:

$$k_2 = 5.9, \; k_3 = 65, \; k_4 = 45.$$

Let us note that the initial conditions for the system (4.2) must satisfy conditions (2.7).

Experiment 1. In this experiment, we consider the model parameters $C = 0.8$ and $S = 0.5$. Thus, we consider the case $0 < S < C < 1$. By Proposition 6, in this case $E_1 = (0, 1)$ and $E_2 = (C - S - 1, 1)$ do not exist, $E_3 = (0, 0)$ is a saddle point, and $E_4 = \left(\dfrac{k_4\,(C - S)}{k_3 + k_4}, \dfrac{k_3\,(C - S)}{k_3 + k_4}\right)$ is a stable equilibrium. The following is illustrated by the numerical results, depicted in Fig 8.

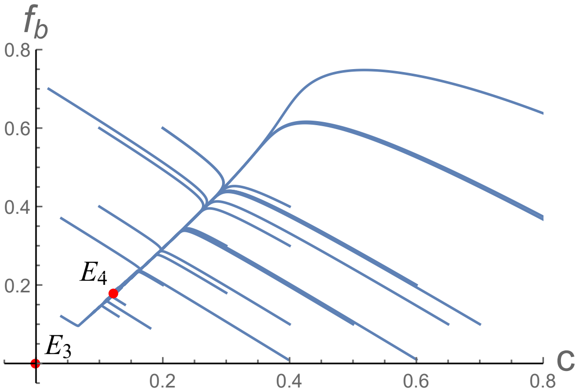


Figure 8: Phase portrait for the case $k_1 = 0$ with parameters $C = 0.8,\ S = 0.5$. E_1 and E_2 do not exist, while E_3 is a saddle and E_4 is a stable equilibrium.

Experiment 2. We consider the case $0 < C < 1 < S$, thus, we choose the model parameters $C = 0.8$ and $S = 4$. By Proposition 6, $E_1 = (0, 1)$, $E_2 = (C - S - 1, 1)$, $E_4 = \left(\dfrac{k_4\,(C-S)}{k_3 + k_4}, \dfrac{k_3\,(C-S)}{k_3 + k_4}\right)$ do not exist, while $E_3 = (0, 0)$ is a stable equilibrium. The obtained results, shown in Figure 9, illustrate the latter.

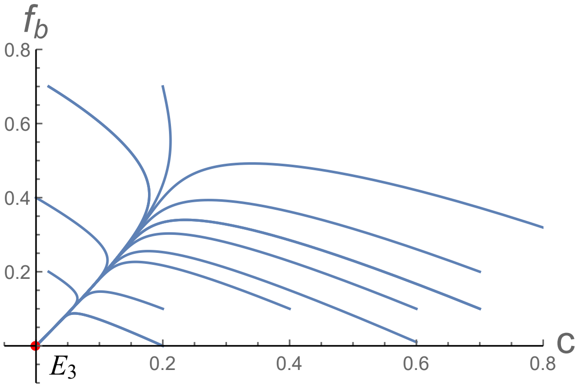


Figure 9: Phase portrait for the case $k_1 = 0$ with parameters $C = 0.8,\ S = 4$. In this case, E_1, E_2, and E_4 do not exist, while E_3 is a stable equilibrium.

Experiment 3. We shall consider model parameters $C = 4$, $S = 6$, thus, the case $1 < C < S$ holds. Following the statement of Proposition 6, equilibrium points $E_2 = (C - S - 1, 1)$ and $E_4 = \left(\dfrac{k_4\,(C-S)}{k_3 + k_4}, \dfrac{k_3\,(C-S)}{k_3 + k_4}\right)$ do not exist, while $E_1 = (0, 1)$ is a saddle point, and $E_3 = (0, 0)$ is an asymptotically stable equilibrium point. The numerical results, which illustrate the statement of Proposition 6, are shown in Figure 10.

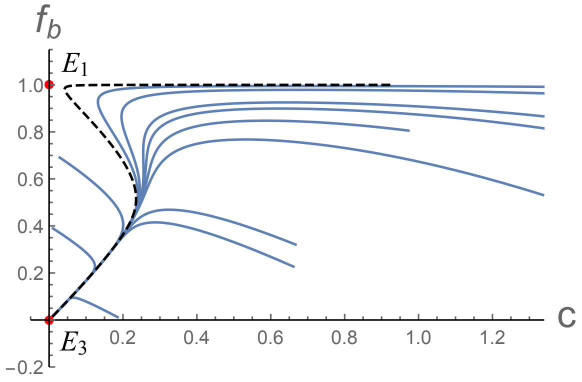


Figure 10: Phase portrait for the case $k_1 = 0$ with parameters $C = 4,\ S = 6$. In this case, E_2 and E_4 do not exist, while E_1 is a saddle and E_3 is an asymptotically stable equilibrium. Note: The dashed trajectory will be discussed further in the next section.

Experiment 4. In the following experiment, we consider the conditions $S < C < S + 1$ and choose the model parameters $C = 5.2$ and $S = 5$. Taking into account Proposition 6, in this case, E_1 and E_3 are saddle points, E_2 does not exist and E_4 is a stable equilibrium. The numerical results, illustrate the statement of the latter proposition, see Figure 11.

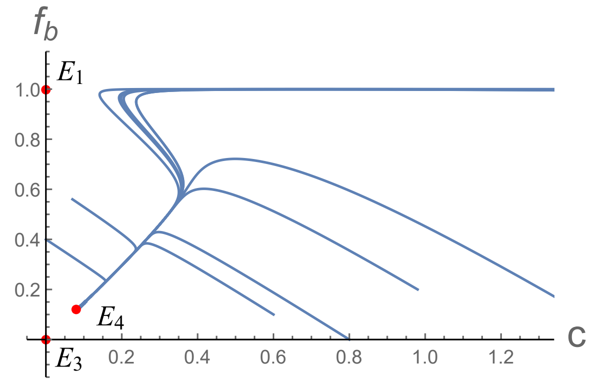


Figure 11: Phase portrait for the case $k_1 = 0$ with parameters $C = 5.2,\ S = 5$. In this case E_1 and E_3 are saddle points, E_2 does not exist, and E_4 is a stable equilibrium.

Experiment 5. For Experiment 5, we consider the case $S+1 < C < S + \dfrac{k_3 + k_4}{k_3}$

and choose model parameters $C = 5.2$ and $S = 4$. Using Proposition 6, $E_1 = (0, 1)$ is an unstable equilibrium, $E_2 = (C - S - 1, 1)$ and $E_3 = (0, 0)$ are saddle points, while $E_4 = \left(\dfrac{k_4 (C - S)}{k_3 + k_4}, \dfrac{k_3 (C - S)}{k_3 + k_4}\right)$ is asymptotically stable. The numerical results in Figure 12 are in agreement with the analytic results.

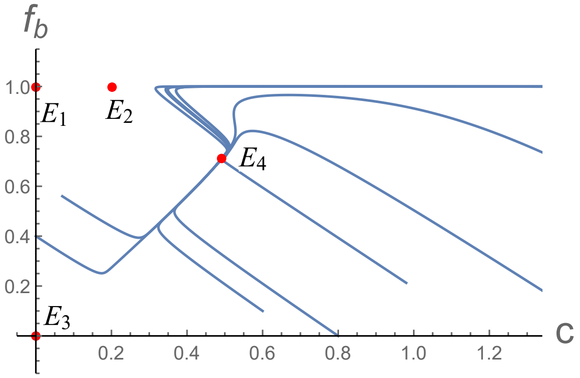


Figure 12: Phase portrait for the case $k_1 = 0$ with parameters $C = 5.2$, $S = 4$. In this case, E_1 is an unstable equilibrium, E_2 and E_3 are saddle points, and E_4 is an asymptotically stable equilibrium.

Experiment 6. Here, we shall consider the case $C > S + \dfrac{k_3 + k_4}{k_3}$ and choose model parameters $C = 7$, $S = 4$. By Proposition 6, E_1 is an unstable equilibrium, E_2 is asymptotically stable, E_3 is a saddle point, and E_4 does not exist. The numerical results in Figure 13 are in agreement with the analytic results.

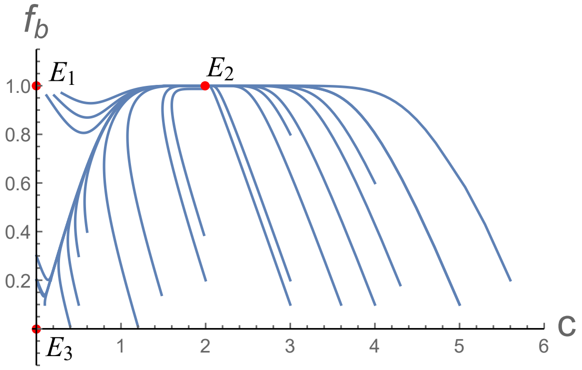


Figure 13: Phase portrait for the case $k_1 = 0$ with parameters $C = 7$, $S = 4$. In this case, E_1 is an unstable equilibrium, E_2 is a stable equilibrium, E_3 is a saddle point, and E_4 does not exist.

6. BIOLOGICAL IMPLICATIONS OF THE QUALITATIVE ANALYSIS

Based on the qualitative analysis of the model for the calcium dynamics in a muscle cell, we make the following observations:

- Case $k_1 = const > 0,\ k_2 = 0$.

  Let us first discuss the case when there is a stimulus, i.e., when $k_2 = 0$. For each choice of the parameters, depending on the ratio C between the total concentrations of calcium ions and CF sites, the biological system tends to a certain equilibrium.

  - Following Proposition 4, when $C < 1$ holds, i.e., when the total concentration of CF sites is more than the total concentration of calcium (or, stated otherwise, there is not enough calcium to fill the CF sites), the system always reaches the equilibrium point $E_2 = \left(\dfrac{Ck_4}{k_3 + k_4}, \dfrac{Ck_3}{k_3 + k_4}\right)$.
  - However, even in the case when there are sufficient calcium ions, depending on the ratio $\dfrac{k_4}{k_3}$ between the rates of binding and release from the CF sites, the system might also stabilize at this point. This is the case, when $C < 1 + \dfrac{k_4}{k_3}$, or equivalently $\dfrac{k_4}{k_3} > C - 1$, thus, the rate of binding of calcium ions to the CF is relatively small, compared to the rate of release;
  - Vice versa, if $\dfrac{k_4}{k_3} < C - 1$, then calcium ions eventually bind to all CF sites, which corresponds to the stable equilibrium $E_1 = (C-1, 1)$, where $f_b = 1$.

  Let us further note that the equilibrium state of the system does not depend on the rate of release from the SR sites k_1. Therefore, the asymptotic behaviour of the system does not depend on the strength of the incoming signal. However, it determines the rate at which the biological system tends to the equilibrium point. For the sake of example, numerical results for the concentration of free calcium ions, obtained for two different values of k_1, are shown in Figure 14.

- Case $k_1 = 0,\ k_2 = const > 0$.

  Here, we shall discuss from a biological point of view the qualitative results for the case, when there is no stimulus present in the muscle cell, i.e., when $k_1 = 0$.

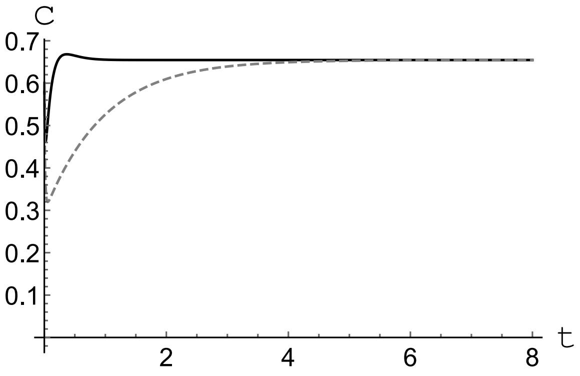


Figure 14: Concentration of free calcium ions c in time. Results for $k_1 = 1$ are depicted with dashed line, for $k_1 = 9.6$—with solid line.

- ○ Following Proposition 6, if $0 < C < S$ holds true, which biologically means that the total concentration of calcium ions is less than the total concentration of SR sites, then the system reaches the equilibrium state $c = 0$, $f_b = 0$. The latter means that all calcium ions get bound to the SR, thus, the muscle cell is relaxed. Let us emphasize that the case $0 < C < S$ is the natural one for the process, since the free calcium ions were originally released from the SR.
- ○ If, however, the total concentration C is higher than S, then different equilibrium points are reached.

We have discussed in this section the two limiting cases when k_1 and k_2 are held constant, one of them 0. Of course, in reality the process is characterized with consecutive changes in their values. Therefore, the results, presented here, will give us information for the two separate parts of the process—when the stimulus is on and off.

Let us further consider one numerical result to illustrate the process of calcium dynamics, described by model equations (2.6). Here, for model parameters we shall use values from [6], systematized in Table 4.

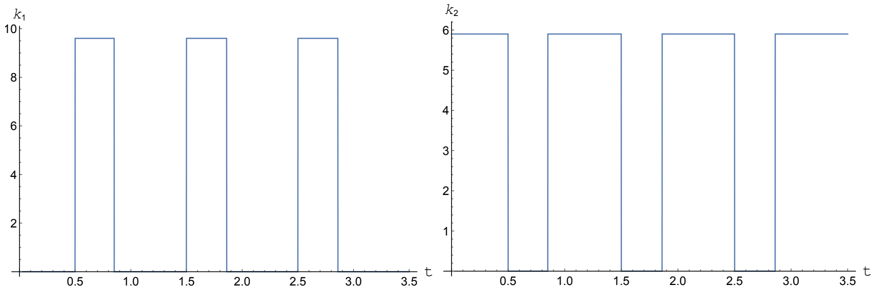
Further, we define a square wave stimulus by introducing the piecewise constant functions k_1 and k_2 in the following way:

$$k_1 = \begin{cases} k_{10}, & \text{stimulus is on,} \\ 0, & \text{stimulus is off,} \end{cases} \qquad k_2 = \begin{cases} 0, & \text{stimulus is on,} \\ k_{20}, & \text{stimulus is off.} \end{cases}$$

For our numerical experiment, we consider the particular choice of k_1 and k_2, depicted in Figure 15.

Parameter	Value	Parameter	Value
C	2	μ_s	600 mN/mm
S	6	l_{s0}	0.234 mm
k_{10}	9.6 s^{-1}	l_{c0}	2.6 mm
k_{20}	5.9 s^{-1}	a	-2.23 mm^{-2}
k_3	65 s^{-1}	α_{max}	1.8
k_4	45 s^{-1}	α_m	0.4 s/mm
L	2.7 mm	α_p	1.33 s/mm
P_0	60.86 $\mathrm{mN/mm}^2$		

Table 4: Model parameters for (2.6), taken from [6].



(a) $k_1(t)$ (b) $k_2(t)$

Figure 15: Graphs of coefficients k_1 and k_2.

The numerical solutions for the concentrations c and f_b, using fourth-order Runge–Kutta method [2] with time discretization step 10^{-3} are shown in Figure 16.

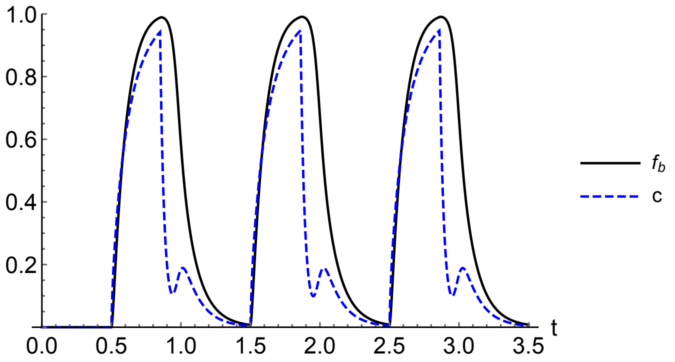


Figure 16: Modelling of calcium dynamics—concentration of free calcium ions (dashed line), concentration of filament-bound calcium sites (solid line).

To explain the numerical results, let us consider the two distinct situations in the process—when the stimulus is on and off.

- Presence of stimulus

  Let us first note that in the case, when $k_2 = 0$, this choice of parameters corresponds to the case of an asymptotically stable point $E_1 = (C-1, 1)$ in Proposition 4. Thus, for $C = 2$ and $S = 6$, the solution would "try to reach" the corresponding equilibrium point $E_1 = (1, 1)$. The latter is clearly seen from the numerical experiments in Figure 16.

- Absence of stimulus

  In the case, when the stimulus is off, or equivalently, when $k_1 = 0$, by the qualitative analysis, summarized in Proposition 6, there exist the saddle equilibrium point $E_1 = (0, 1)$ and the asymptotically stable $E_3 = (0, 0)$. The latter explains the peculiar behaviour of the solution for c, that is observed, e.g., around $t = 1$. In particular, let us consider the dashed trajectory in Figure 10, which is obtained for an initial condition corresponding to the peak of the graphs in Figure 6. When close to the saddle point, the trajectory is repelled with a change in the sign of the derivative for the concentration c, which results in a rise of the solution for c, followed by a decrease to the equilibrium $c = 0$.

7. CONCLUSION

In this paper, we have considered a mathematical model, described in terms of ordinary differential equations, for the process of calcium dynamics inside the muscle cell. We have obtained results for the qualitative behaviour of the model solutions in the two limiting cases $k_1 = 0$ and $k_2 = 0$ that to the best of our knowledge are not known in the scientific literature. On one hand, such kind of qualitative information is useful in the mathematical modelling of biological processes and it helps to better understand the dynamical properties of the mathematical model. On the other hand, it gives valuable information about the influence of the different model parameters. The latter is particularly interesting, when considering the process in different conditions, e.g., when there are certain deceases present, which affect the normal calcium activity inside the muscle cell.

ACKNOWLEDGEMENTS. The work of the authors was partially funded under contract 80-10-17/09.04.2019 with Science Fund, Sofia University.

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Received on February 6, 2020
Received in a revised form on March 23, 2020

Zdravka Nedyalkova, Tihomir Ivanov
Faculty of Mathematics and Informatics
"St. Kliment Ohridski" University of Sofia
5 James Bourchier Blvd.
BG-1164 Sofia
BULGARIA
E-mails: znedyalkova@fmi.uni-sofia.bg
tbivanov@fmi.uni-sofia.bg