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DYNAMICAL ANALYSIS OF CALCIUM MODEL OF MUSCLE AT REST

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Abstract. The present paper is concerned with a calcium model of muscle at rest and a dynamical analysis of it. We show that the model is well-posed; that is, the solution representing the state of the model inside a special pyramid never leaves it as time evolves. Moreover, an analysis of its steady states is given.

Keywords: Calcium model of muscle at rest; steady state; exponential stability; Routh-Hurwitz Theorem.

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1 Introduction

In this paper we analyze the dynamics of a physiological model (see the diagrams (A) and (B) below) near equilibrium, see [9]. The full model accounts for a complete set of chemical states associated with calcium regulation of vertebrate striated muscle, but the analysis here is confined to the subset

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of states directly related to calcium binding. These are states that are physically confined to the thin filament of muscle. Specifically, we focus on two reversible reactions, namely, an interaction between the protein complexes, troponin (T) and actin, and the interaction between T and calcium. An interaction with actin is required for tropomyosin in the ground state (C) to transition to an excited state (B). To simplify the analysis here, we do not consider a competing reaction responsible for the transition of C to another excited state (M). The competing reaction is prevented in a muscle stretched beyond the overlap between thin and thick filaments. Given the overstretched condition, we examine how the states of the thin filament in our model evolve in time following a perturbation by calcium.

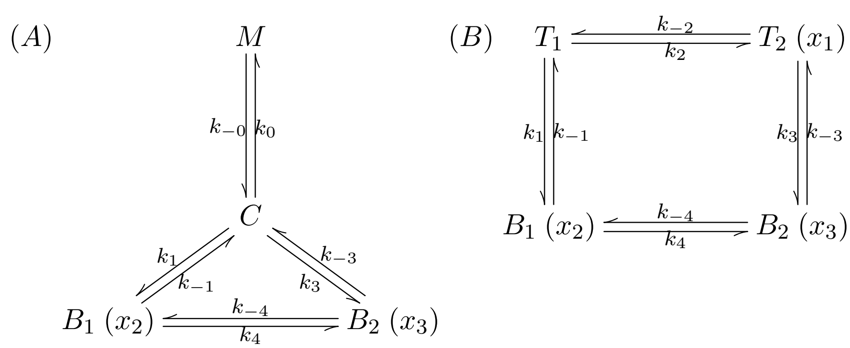
Mathematically, the dynamics of the model (A) & (B) can be described by the system of ordinary differential equations (3.1) or (3.2). Biologically, for our study to make sense, a special pyramid in the 3-dimensional Euclidean space $\mathbb{R}^3$, namely, $\{(x_1, x_2, x_3) \in \mathbb{R}^3 : x_1 \geq 0, x_2 \geq 0, x_3 \geq 0, x_1 + x_2 + x_3 = 1\}$, is of our interest. We will show that the system of equations (3.2) generates a dynamical system that leaves the pyramid invariant as time evolves forward (Theorems 3.1). This yields a sequence of mathematical conclusions on the general behavior of the system. For example, we will show that the system should have at least one steady state inside the pyramid (Corollary (3.2)). And, this leads to an investigation of the behavior of the system around all possible steady states (Corollary 3.4). In addition to the proofs of Theorem 3.1, Corollary 3.2, which are given in a traditional, way we propose a proof of Corollary 3.4 with assistance of a software to verify the conditions of Routh-Hurwitz Theorem for the exponential stability of linear systems of differential equations.

For related works on calcium dynamics in muscle we refer the reader to [7, 5] and especially to [6] and the references therein, as well as [4]. A thorough understanding of the qualitative properties of the dynamical systems modeling the calcium dynamics would lead to predictions as discussed in [7].

2 Preliminaries

2.1 Diagram Model and System of ODE

In [9] we have proposed a model of muscle regulation with the following diagram model that depicts the essential chemical states of the model.



The equilibrium relationships among the complete set of states are as expressed as follows:

$$M = \frac{k_0}{k_{-0}} C\,U^n\,, \quad B_1 = \frac{k_1}{k_{-1}} C\,T_1\,, \quad B_2 = \frac{k_3}{k_{-3}} C\,T_2\,, \quad T_2 = \frac{k_2}{k_{-2}}\,, \quad B_2 = \frac{k_4}{k_{-4}}\,, \tag{2.1}$$

where, as in [9], $U = 1 + (\alpha - 1)M$, k_i's are rate constants. Only the latter four equations above operate under the conditions of the present analysis, i.e. reactions of the thin filament absent thick filament overlap. We introduce the calcium concentration $[Ca^{2+}]$ as a variable that enters in the variables k_2 and k_4.

3 Dynamical Analysis of the Model

3.1 The ODE Model of Overstretched Muscle Near Equilibrium

From the above diagram the following system of equations describes the dynamics of the chemical states

$$\begin{cases} \frac{\mathrm{d}M}{\mathrm{d}t} = k_0\,C\,(1 + (\alpha - 1)M)^n - k_{-0}\,M. \\ \frac{\mathrm{d}B_1}{\mathrm{d}t} = k_1\,C\,T_1 + k_{-4}\,B_2 - (k_{-1} + k_4)\,B_1 \\ \frac{\mathrm{d}B_2}{\mathrm{d}t} = k_3\,C\,T_2 + k_4\,B_1 - (k_{-4} + k_{-3})\,B_2 \\ \frac{\mathrm{d}T_2}{\mathrm{d}t} = k_2\,T_1 + k_{-3}\,B_2 - (k_3\,C + k_{-2})\,T_2\,, \end{cases} \tag{3.1}$$

where $C = 1 - B_1 - B_2$ and $T_1 = 1 - B_1 - B_2 - T_2$.

For our convenience we will re-write (3.1) in the following form:

$$\begin{cases} \frac{\mathrm{d}M}{\mathrm{d}t} = k_0\,C\,(1 + (\alpha - 1)\,M)^n - k_{-0}\,M \\ \frac{\mathrm{d}x_1}{\mathrm{d}t} = k_2\,(1 - \sum_{i=1}^3 x_i) + k_{-3}\,x_3 - (k_{-2} + k_3(1 - x_2 - x_3))\,x_1 \\ \frac{\mathrm{d}x_2}{\mathrm{d}t} = k_1\,(1 - x_2 - x_3)(1 - \sum_{i=1}^3 x_i) + k_{-4}\,x_3 - (k_{-1} + k_4)\,x_2 \\ \frac{\mathrm{d}x_3}{\mathrm{d}t} = k_4\,x_2 + k_3\,x_1(1 - x_2 - x_3) - (k_{-4} + k_{-3})\,x_3. \end{cases} \tag{3.2}$$

that is obtained from (3.1) by replacing T_1, B_1, B_2 with x_1, x_2, x_3, and C with $(1 - x_2 - x_3)$, T_2 by $(1 - x_1 - x_2 - x_3)$, respectively.

We will study the behavior of the system when $M = 0$ (or more reasonably, $k_0 = 0$). Then, the system of equations takes the form

$$\begin{cases} \frac{\mathrm{d}x_1}{\mathrm{d}t} = k_2\,(1 - \sum_{i=1}^3 x_i) + k_{-3}\,x_3 - (k_{-2} + k_3\,(1 - x_2 - x_3))\,x_1 \\ \frac{\mathrm{d}x_2}{\mathrm{d}t} = k_1\,(1 - x_2 - x_3)\,(1 - \sum_{i=1}^3 x_i) + k_{-4}\,x_3 - (k_{-1} + k_4)\,x_2 \\ \frac{\mathrm{d}x_3}{\mathrm{d}t} = k_4\,x_2 + k_3\,x_1\,(1 - x_2 - x_3) - (k_{-4} + k_{-3})\,x_3\,. \end{cases} \tag{3.3}$$

with (x_1, x_2, x_3) in the pyramid $\{(x_1, x_2, x_3) \in \mathbb{R}^3 : x_1 \geq 0,\ x_2 \geq 0,\ x_3 \geq 0,\ x_1 + x_2 + x_3 = 1\}$.

For simplicity we will use the vector form of the system of equations (3.3) in which $X := (x_1, x_2, x_3)^T$ and $F(X) = (F_1(X), F_2(X), F_3(X))^T$ denotes the vector field, that is, the right hand side of the equation. Therefore, the equation is of the form

$$\frac{\mathrm{d}X}{\mathrm{d}t} = F(X).$$

Below we will denote by $\langle a, b\rangle$ the inner product of two given vectors a, b in the space $\mathbb{R}^3$, that is, if $a = (a_1, a_2, a_3)^T$ and $b = (b_1, b_2, b_3)^T$, then

$$\langle a, b\rangle := \sum_{j=1}^{3} a_j\, b_j.$$

3.2 Analysis of the model

Biologically, the following theorem on the invariance of the pyramid $P := \{(x_1, x_2, x_3) \in \mathbb{R}^3 \mid 0 \le x_1; 0 \le x_2;\ 0 \le x_3;\ x_1 + x_2 + x_3 \le 1\}$ means that if the muscle is started at a state it must evolve, but does not disappear as time evolves. Therefore, this question is of our primary concern.

Theorem 3.1 *Let all parameters k_i, $i = 1, 2, 3, 4$, k_{-i}, $i = 1, 2, 3, 4$ in the model (3.3) be positive. Then the system generates a dynamical system that leaves the pyramid P invariant as time evolves. This means every solution starting from a point within the pyramid remains in the pyramid for all later time.*

Proof. The main idea of the proof is to show that every solution starting from a point of the pyramid cannot escape from the pyramid. We refer the reader to [1], [2] for a more detailed explanation of the idea.

Step 1: *We show that except for the four vertices each solution cannot cross the four planes*. In fact, for the plane $1 - x_1 - x_2 - x_3 = 0$: At each point on the plane the normal vector is $\vec{n} = (1, 1, 1)$, so we have

$$\begin{aligned}
\langle F, \vec{n}\rangle &= k_2(1 - \sum_{i=1}^{3} x_i) + k_{-3}x_3 - (k_{-2} + k_3(1 - x_2 - x_3))x_1 \\
&\quad + k_1(1 - x_2 - x_3)(1 - \sum_{i=1}^{3} x_i) + k_{-4}x_3 - (k_{-1} + k_4)x_2 \\
&\quad + k_4x_2 + k_3x_1(1 - x_2 - x_3) - (k_{-4} + k_{-3})x_3 \\
&= k_{-4}x_3 - (k_{-1} + k_4)x_2 + k_4x_2 + k_3x_1(1 - x_2 - x_3) \\
&\quad - (k_{-4} + k_{-3})x_3 + k_{-3}x_3 - (k_{-2} + k_3(1 - x_2 - x_3))x_1 \\
&= -k_{-2}x_1 - k_{-1}x_2 \\
&< 0
\end{aligned}$$

whenever $x_1^2 + x_2^2 \neq 0$. Therefore, the solutions starting from the inside the pyramid cannot cross this plane except for the vertex $(0, 0, 1)$.

Similarly, we show that each solution starting out from inside the pyramid cannot cross the plane $x_2 = 0$. At each point on this plane the outward normal vector is of the form $\vec{m}(0, -1, 0)$. Therefore,

$$\begin{aligned} \langle F, \vec{m} \rangle &= -k_1 (1 - x_3)(1 - x_1 - x_3) - k_{-4}\, x_3 \\ &< 0, \end{aligned}$$

unless $x_3 = 0$ and $x_1 = 1$. The only possibility for all solutions starting out from the inside of the pyramid to cross the plane $x_2 = 0$ is via the vertex $(1, 0, 0)$.

Similarly, we show that each solution starting out from the inside of the pyramid cannot cross the plane $x_3 = 0$. In fact, the inner product of the vector filed at each point on the plane and the outward normal vector $\vec{p} = (0, 0, -1)$ of the plane is

$$\begin{aligned} \langle F, \vec{p} \rangle &= -k_4 x_2 - k_3 x_1 (1 - x_2) \\ &< 0, \end{aligned}$$

unless the point is $(0, 0, 1)$.

Next, we show that each solution starting out from inside the pyramid cannot cross the plane $x_1 = 0$. In fact, the inner product of the vector filed at each point on the plane and the outward normal vector $\vec{q} = (-1, 0, 0)$ of the plane is

$$\begin{aligned} \langle F, \vec{q} \rangle &= -k_2 (1 - \sum_{i=1}^{3} x_i) - k_{-3} x_3 \\ &< 0, \end{aligned}$$

if the point is not the vertex $(1, 0, 0)$.

Step 2:: *Vector field at the four vertices:*
(i) At the origin $X_0 := (0, 0, 0)$. The vector field at this point is

$$\overrightarrow{F}(0, 0, 0) = (k_2, k_1, 0).$$

Let $Y(t) = (x_1(t), x_2(t), x_3(t))$ be the solution starting from $X_0 = (0, 0, 0)$. Since the vector field is analytic for sufficiently small $t > 0$ the components $x_1(t), x_2(t)$ may be approximated by $k_1 t, k_2 t$, respectively. Therefore, $x_1(t), x_2(t)$ will be positive for sufficiently small $t > 0$. To show that $Y(t)$ is directed inward the pyramid it suffices to prove that $x_3(t)$ is positive for sufficiently small $t > 0$.

Referring to the vector field, we have that $x_1(t) = k_2\, t + o(t)$, $x_2(t) = k_1\, t + o(t)$, so

$$\begin{aligned} \dot{x}_3 &\simeq k_4 k_1 t + k_3 k_2 t (1 - k_1 t - x_3) - (k_{-4} + k_{-3}) x_3 \\ &= k_4 k_1 t + k_3 k_2 t - k_3 k_2 k_1 t^2 - k_3 k_2 t x_3 - (k_{-4} + k_{-3}) x_3 \\ &= -(k_{-4} + k_{-3} - k_3 k_2 t) x_3 + (k_4 k_1 + k_3 k_2) t - k_3 k_2 k_1 t^2 \\ &= a(t) x_3 + b(t), \end{aligned}$$

where

$$\begin{aligned} a(t) &= -(k_{-4} + k_{-3} - k_3 k_2 t) \\ b(t) &= (k_4 k_1 + k_3 k_2) t - k_3 k_2 k_1 t^2. \end{aligned}$$

Therefore, for $x_3(0) = 0$, if we set

$$U(t,\xi) := e^{\int_\xi^t a(\eta)\,\mathrm{d}\eta},$$

then, by the Variation-of-Constants Formula,

$$\begin{aligned} x_3(t) &\simeq U(t,0)x_3(0) + \int_0^t U(t,\xi)b(\xi)\,\mathrm{d}\xi = \int_0^t U(t,\xi)b(\xi)\,\mathrm{d}\xi \\ &= \int_0^t e^{\int_\xi^t a(\eta)\,\mathrm{d}\eta} \left((k_4k_1 + k_3k_2)\xi - k_3k_2k_1\xi^2\right)\,\mathrm{d}\xi. \end{aligned}$$

For sufficiently small $t > 0$, since all parameters $k_i > 0$, for $0 \le \xi \le t$ we have $(k_4k_1 + k_3k_2)\xi - k_3k_2k_1\xi^2 > 0$. Therefore, from this formula $x_3(t)$ should be positive for sufficiently small $t > 0$.

(ii) At the vertex $X_2 = (0,1,0)$ the vector field at this point is

$$\overrightarrow{F}(0,1,0) = (0, -(k_{-1} + k_4), k_4).$$

To show that the solution starting out from this vertex is attracted inward the pyramid it suffices to prove that $x_1(t)$ is positive for sufficiently small $t > 0$. We will use the idea as above. At this vertex for small $t > 0$ we have

$$\begin{aligned} x_2(t) &= 1 - (k_{-1} + k_4)t + o(t) \\ x_3(t) &= k_4t + o(t). \end{aligned}$$

Therefore, referring to the vector field we arrive at

$$\begin{aligned} \dot{x}_1 &\simeq k_2[1 - (1 - (k_{-1} + k_4)t) - k_4t] + k_{-3}k_4t \\ &\qquad -[k_{-2} + k_3(1 - (1 - (k_{-1} + k_4)t) - k_4t)]x_1 \\ &= -[k_{-2} + k_3(k_{-1} + 2k_4)t]x_1 + [k_2(k_{-1} + 2k_4) + k_{-3}k_4]t \\ &= c(t)x_1 + d(t), \end{aligned}$$

where

$$\begin{aligned} c(t) &= -[k_{-2} + k_3(k_{-1} + 2k_4)t] \\ d(t) &= [k_2(k_{-1} + 2k_4) + k_{-3}k_4]t. \end{aligned}$$

Using exactly an estimate similar to the above we can show that both $x_1(t)$ and its derivative $\dot{x}_1(t)$ should be positive for small $t > 0$. And hence, the solution starting out from this vertex should be attracted inward the pyramid.

(iii) At the vertex $X_3 := (0,0,1)$: the field vector at this point is of the form

$$\overrightarrow{F}(0,0,1) = (k_{-3}, k_{-4}, -(k_{-4} + k_{-3})).$$

This vector is directed inward the triangle with vertices being $X_1 := (1,0,0), X_2 := (0,1,0), X_3 := (0,0,1)$. We are going to show that the solution starting out from the vertex X_3 will be attracted inward the pyramid. Let $X(t) = (x_1(t), x_2(t), x_3(t))$ be that solution. We will show that for sufficiently small ϵ, and $0 < t < \epsilon$, if $\phi(t) := \langle X(t), \overrightarrow{n} \rangle$, then $\phi(t) < 0$. For sufficiently small $\epsilon > 0$ and $0 \le t < \epsilon$ we have

$$\begin{aligned}
\frac{\mathrm{d}\phi(t)}{\mathrm{d}t} &= \frac{\mathrm{d}}{\mathrm{d}t}\left(x_1(t) + x_2(t) + x_3(t)\right) \\
&= \frac{\mathrm{d}}{\mathrm{d}t}\left(-k_{-1}\, x_2(t) - k_{-2}\, x_1(t)\right) \\
&= -k_{-1}\frac{\mathrm{d}x_2(t)}{\mathrm{d}t} - k_{-2}\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} \\
&\simeq -k_{-1}\, k_{-4} - k_{-2}\, k_{-3} \\
&< 0.
\end{aligned}$$

This shows that $\phi(t)$ is decreasing, so $\phi(t) < \phi(0) = 0$. Therefore, $X(t)$ cannot enter the region $x_1 + x_2 + x_3 > 1$ for $t > 0$.

Similarly we can show that $X(t)$ cannot enter the regions $x_2 < 0$ and $x_1 < 0$. This yields that each solution starting out from inside the pyramid cannot cross the plane $1 - x_1 - x_2 - x_3 = 0$.

(iv) At the vertex $X_1 = (1, 0, 0)$ the vector field at this point is

$$\overrightarrow{F}(1, 0, 0) = (-(k_{-2} + k_3), 0, k_3).$$

Therefore, we have

$$\begin{aligned}
x_1(t) &= 1 - (k_{-2} + k_3)\, t + o(t) \\
x_3(t) &= k_3\, t + o(t).
\end{aligned}$$

Referring to the vector field at this vertex we arrive at

$$\begin{aligned}
\dot{x}_2 &\simeq k_1(1 - x_2 - k_3 t)(1 - x_2 - k_3 t - (1 - (k_{-2} + k_3)t)) + k_{-4}k_3 t \\
&\qquad -(k_{-1} + k_4)x_2 \\
&= k_1 x_2^2 - (k_1 + k_{-1} + k_4 + k_1 k_{-2} t - k_1 k_3 t)x_2 \\
&\qquad k_1 k_2 t + k_3 k_{-4} t - k_1 k_3 k_{-2} t^2 \\
&= k_1 x_2^2 + \alpha(t)x_2 + \beta(t),
\end{aligned}$$

where

$$\begin{aligned}
\alpha(t) &= -(k_1 + k_{-1} + k_4 + k_1 k_{-2} t - k_1 k_3 t) \\
\beta(t) &= k_1 k_2 t + k_3 k_{-4} t - k_1 k_3 k_{-2} t^2.
\end{aligned}$$

If we take sufficiently small ϵ, then $\alpha(t) > 0, \beta(t) \ge 0$ for $t \in [0, \epsilon]$. If we set $\gamma(t) = k_1 x_2^2(t) + \beta(t)$ for $t \in [0, \epsilon]$, then, $\gamma(t) > 0$ for $t \in (0, \epsilon]$, and

$$\dot{x}_2 = \alpha(t)x_2 + \gamma(t), \quad t \in [0, \epsilon]. \tag{3.4}$$

Next, we use the same idea as above to show that $x_2(t)$ and its derivative must be positive for small $t > 0$. Therefore, the solution starting out from this vertex is directed inward the pyramid. This completes the proof of the theorem. □

Corollary 3.2 *There exists at least a steady state inside the pyramid.*

Proof. This theorem is deduced from a general result from Topology (see e.g. [1]). In fact, we can show that since every solution starting from any point of the pyramid cannot escape from the pyramid the system generates a forward dynamical system in the pyramid P mentioned above, that is, a mapping $F : \mathbb{R}^+ \times P \to P$ that is continuous such that $F(t,x)$ is the solution starting from $x \in P$. By the properties of the autonomous equations, $F(t+s,x) = F(t,F(s,x))$ for any $t, s \geq 0,\ x \in P$. As P is convex and compact subset of $\mathbb{R}^3$, for each fixed $T \in \mathbb{R}^+$, by the Brouwer Theorem on the fixed points there is a fixed point for $F(T,\cdot)$ that corresponds to a T-periodic solution of the equation. We may choose a sequence of numbers $\{T_n\}_{n=1}^{\infty}$ such that $T_n = 1/2^n$. Then, there exists a sequence $X_n(\cdot)$ of T_n-periodic solutions contained inside the pyramid. Since the pyramid is compact, there should be a limit point P of the sequence of their trajectories. By the Ascoli Theorem and the Existence and Continuous Dependence Theorem we can show that there exists a subsequence of solutions mentioned above that is convergent to the solution $X_0(\cdot)$ starting out from the limit point P uniformly on the interval $[0,1]$. As all these solutions $X_n(\cdot)$ are 1-periodic the subsequence must be convergent uniformly on the whole real line. This show that the solution $X_0(\cdot)$ is T_n-periodic for any n. That is, for each positive integer n and each real t,

$$X_0(t) = X_0\left(t + \frac{1}{2^n}\right).$$

Using the uniform continuity of this function on the compact interval $[0,1]$ we end up with X_0 being a constant function, that is, it is a steady state of the dynamical system. □

3.3 Behavior around the steady states

We are now investigating the behavior of the system around the steady states by using the local theory of dynamical systems. Set $X := (x_1, x_2, x_3)^T$,

$$\begin{cases} F_1(X) = k_2(1 - \sum_{i=1}^{3} x_i) + k_{-3}x_3 - (k_{-2} + k_3(1 - x_2 - x_3))\, x_1 \\ F_2(X) = k_1(1 - x_2 - x_3)(1 - \sum_{i=1}^{3} x_i) + k_{-4}\, x_3 - (k_{-1} + k_4)\, x_2 \\ F_3(X) = k_4\, x_2 + k_3\, x_1(1 - x_2 - x_3) - (k_{-4} + k_{-3})\, x_3. \end{cases} \tag{3.5}$$

The vector field at each point X can be re-written with $F_1,\ F_2,\ F_3$ of the form

$$\begin{aligned} F_1(X) &= k_2 - (k_2 + k_{-2} + k_3)x_1 - k_2x_2 + (k_{-3} - k_2)x_3 \\ &\qquad + k_3x_1x_2 + k_3x_1x_3 \\ F_2(X) &= k_1 - k_1x_1 - (2k_1 + k_{-1} + k_4)x_2 - (2k_1 - k_{-4})x_3 \\ &\qquad + (x_2 + x_3)(x_1 + x_2 + x_3) \\ F_3(X) &= k_3x_1 + k_4x_2 - (k_{-4} + k_{-3})x_3 - k_3x_1(x_2 + x_3). \end{aligned}$$

Next, we consider an equilibrium of the system in the pyramid, say $(c_1, c_2, c_3)^T$. It is easy to see that the Jacobian of the vector field at this point is of the form

$$J = \begin{pmatrix} -(k_2+k_{-2}+k_3)+k_3(c_2+c_3) & -k_2+k_3c_1 & k_{-3}-k_2+k_3c_1 \\ -k_1+(2c_1+2c_2+c_3) & -(2k_1+k_{-1}+k_4)+2c_1+2c_2+c_3 & -(2k_1-k_{-4})+c_2+c_3 \\ k_3-k_3(c_2+c_3) & k_4-k_3c_1 & -(k_{-4}+k_{-3})-k_3c_1 \end{pmatrix} \tag{3.6}$$

Below we set

$$\begin{aligned} K_1 &:= k_1-(2\,c_1+2\,c_2+c_3) \\ K_{-1} &:= k_{-1}-(2\,c_1+2\,c_2+c_3) \\ K_2 &:= k_2-k_3\,c_1 \\ K_3 &:= k_3-k_3\,(c_2+c_3) \\ K_{-3} &:= k_{-3}+k_3\,c_1 \\ K_4 &:= k_4-k_3\,c_1 \\ K_{-4} &:= k_{-4}+c_2+c_3. \end{aligned}$$

Below we will assume that all these parameters k_i are positive for all $i = 1,2,3,4$ or $i = -1,-2,-3,-4$. In addition, we need the following conditions on $k_i,\ k_{-i}$ for $K_i,\ K_{-i}$ to be positive as well:

$$k_1 \geq 2\,,\ k_{-1} \geq 2\,,\ k_2 \geq k_3\,,\ k_4 \geq k_3\,. \tag{3.7}$$

With the above notation, the matrix J is now looks like

$$\begin{pmatrix} -(k_2+k_{-2}+K_3) & -K_2 & k_{-3}-K_2 \\ -K_1 & -(K_1+k_1+k_{-1}+k_4) & -(2\,k_1-K_{-4}) \\ K_3 & K_4 & -(K_{-4}+k_{-3}) \end{pmatrix}. \tag{3.8}$$

Suppose that the characteristic polynomial of this matrix is of the form

$$P(\lambda) = p_0\,\lambda^3+p_1\,\lambda^2+p_2\,\lambda+p_3\,. \tag{3.9}$$

In order to study the stability of the dynamical system we associate with the characteristic polynomial $P(\lambda)$ the following determinants whose positivity needs to be verified

$$\Delta_1 := p_1\,, \tag{3.10}$$

$$\Delta_2 := \det\begin{pmatrix} p_1 & p_3 \\ p_0 & p_2 \end{pmatrix}, \tag{3.11}$$

$$\Delta_3 := p_3\Delta_2\,. \tag{3.12}$$

Next we are going to find the polynomial $P(\lambda)$. We have

$$\begin{aligned} P(\lambda) \;:=\; & \lambda^3 + (K_{-4} + k_{-3} + K_1 + k_1 + k_{-1} + k_4 + k_2 + k_{-2} + K_3)\,\lambda^2 \\ & -(K_1K_2 - 2k_1k_2 - 2k_1k_{-2} - 2k_1K_3 - k_4k_2 - k_4k_{-2} - k_4K_3 - K_3K_2 - 2K_4k_1 \\ & +K_4K_{-4} - k_2k_{-3} - k_{-2}k_{-3} - 2k_1K_{-4} - k_4K_{-4} - K_{-4}k_2 - K_{-4}k_{-2} - K_{-4}K_3 \\ & -2k_{-3}k_1 - k_{-3}k_4 - K_{-1}k_2 - K_{-1}k_{-2} - K_{-1}K_3 - K_{-1}K_{-4} - k_{-3}K_{-1})\lambda \\ & +K_3K_2K_{-1} + K_{-4}K_{-1}k_2 + K_{-4}K_{-1}k_{-2} + K_{-4}K_{-1}K_3 + k_{-3}K_{-1}k_2 + k_{-3}K_{-1}k_{-2} \\ & +K_3K_2K_{-4} + K_4K_1k_{-3} - K_4K_1K_2 + K_3K_2k_4 + 2K_4k_1k_2 + 2K_4k_1k_{-2} \\ & +2K_4k_1K_3 - K_4K_{-4}k_2 - K_4K_{-4}k_{-2} - K_4K_{-4}K_3 - K_{-4}K_1K_2 + 2K_{-4}k_1k_2 \\ & +2K_{-4}k_1k_{-2} + 2K_{-4}k_1K_3 + K_{-4}k_4k_2 + K_{-4}k_4k_{-2} + K_{-4}k_4K_3 \\ & -k_{-3}K_1K_2 + 2k_{-3}k_1k_2 + 2k_{-3}k_1k_{-2} + k_{-3}k_4k_2 + k_{-3}k_4k_{-2}. \end{aligned}$$

Therefore,

$$\begin{aligned} p_1 :=\, & K_4 + k_{-3} + K_1 + k_1 + k_{-1} + k_4 + k_2 + k_{-2} + K_3, \\ p_2 :=\, & -K_1K_2 + K_1k_2 + K_1k_{-2} + K_1K_3 + k_1k_2 \\ & + k_1k_{-2} + k_1K_3 + k_{-1}k_2 + k_{-1}k_{-2} \\ & + k_{-1}K_3 + k_4k_2 + k_4k_{-2} + k_4K_3 + K_3K_2 \\ & + 2\,K_4k_1 - K_4K_{-4} + k_2k_{-3} + k_{-2}k_{-3} \\ & + K_1k_{-3} + K_1K_{-4} + k_1K_{-4} + k_{-1}K_{-4} \\ & + k_4K_{-4} + K_{-4}k_2 + K_{-4}k_{-2} + K_{-4}K_3 \\ & + k_{-3}k_1 + k_{-3}k_{-1} + k_{-3}k_4\,. \end{aligned}$$

Notice that $p_1 > 0$. As for p_2, since

$$-K_1\,K_2 + K_1\,k_2 = K_1\,(k_2 - K_2) = K_1\,k_3\,c_1 > 0$$

and

$$k_4\,K_{-4} - K_4\,K_{-4} = k_3\,c_1\,K_{-4} > 0\,,$$

we have

$$p_2 > 0. \tag{3.13}$$

As for p_3 since

$$\begin{aligned} 2\,K_4\,k_1\,k_2 - K_4\,K_1\,K_2 &\geq 0 \\ K_{-4}\,k_4\,k_2 - K_4\,K_{-4}\,k_2 &\geq 0 \\ K_{-4}\,k_4\,k_{-2} - K_4\,K_{-4}\,k_{-2} &\geq 0 \\ K_{-4}\,k_4\,K_3 - K_4\,K_{-4}\,K_3 &\geq 0 \\ 2K_{-4}\,k_1\,k_2 - K_{-4}\,K_1K_2 &\geq 0 \\ 2k_{-3}\,k_1\,k_2 - k_{-3}\,K_1K_2 &\geq 0 \end{aligned}$$

we have

$$p_3 > 0\,. \tag{3.14}$$

Next, we have

$$
\begin{aligned}
\Delta_2 \;:=\;& p_1 \cdot p_2 - p_3 \\
=\;& 2\,K_{-4}K_{-1}k_{-2} + 2\,K_{-4}K_{-1}K_3 + 2\,k_{-3}K_{-1}k_2 + 2\,K_{-4}K_{-1}k_2 \\
&+2\,K_3K_2k_1 - K_4K_1k_{-3} + 2\,k_{-3}K_{-1}k_{-2} \\
&+2\,k_{-3}k_4k_2 + K_4K_1K_2 + K_4K_{-4}k_2 + K_4K_{-4}K_3 + K_{-4}K_1K_2 + K_4K_{-4}k_{-2} \\
&+3\,K_{-4}k_1k_2 + 4\,K_{-4}k_1k_{-2} + K_{-4}k_4K_3 + 4\,K_{-4}k_1K_3 + K_{-4}k_4k_2 + K_{-4}k_4k_{-2} \\
&+k_{-3}K_1K_2 + 3\,k_{-3}k_1k_2 + 4\,k_{-3}k_1k_{-2} + 2\,k_{-3}k_4k_{-2} + 2\,K_{-4}k_{-2}k_{-3} \\
&+3\,k_1k_4k_2 + k_3c_1K_{-4} + K_{-1}k_3c_1 + 2\,K_{-1}k_4k_{-2} + 2\,K_{-1}K_4k_1 + 4\,k_1k_4K_3 \\
&+4\,k_{-3}k_1K_3 + 2\,k_1k_3c_1 + K_{-4}k_{-3}k_4 + 2\,k_{-3}K_{-1}K_3 + 2\,K_{-4}k_{-3}K_{-1} \\
&+4\,k_1K_{-1}k_{-2} + k_{-3}K_3K_2 + 2\,K_{-1}k_4K_3 + 4\,k_1k_{-3}K_{-1} + 2\,K_{-1}k_4k_2 + 4\,k_1K_{-1}K_3 \\
&+3\,k_1K_{-1}k_2 + 2\,K_{-4}k_2k_{-3} + 2\,k_{-3}k_4K_3 + k_3c_1{K_{-4}}^2 + 4\,k_1K_{-1}K_{-4} + 2\,K_{-4}K_4k_1 \\
&+2\,k_{-3}K_4k_1 + k_{-3}k_3c_1 + k_{-3}K_{-4}K_3 + 4\,k_1k_{-3}k_4 + 4\,K_{-4}k_{-3}k_1 + 2\,K_{-1}k_{-3}k_4 \\
&+4\,k_1k_4k_{-2} + k_4K_{-1}K_{-4} + 2\,k_4k_1K_{-4} + k_4k_3c_1 + 3\,k_2k_1k_{-2} + 2\,k_2k_4k_{-2} \\
&+3\,k_2k_1K_3 + k_2K_3K_2 + 2\,k_2k_4K_3 + 2\,k_4K_4k_1 + 2\,k_2K_{-4}k_{-2} + 2\,k_2k_{-2}k_{-3} \\
&+2\,k_2K_{-4}K_3 + k_2k_3c_1 + 2\,k_2K_{-1}k_{-2} + 2\,k_2K_{-1}K_3 + 2\,k_1{K_{-4}}^2 + 4\,k_{-2}k_1K_3 \\
&+2\,k_{-2}k_4K_3 + k_{-2}K_3K_2 + 2\,k_{-2}K_{-4}K_3 + k_{-2}k_3c_1 + 2\,k_{-2}K_{-1}K_3 + K_3k_{-2}k_{-3} \\
&+K_3k_2k_{-3} + K_3k_3c_1 + 2\,k_{-3}c_2 + {K_{-4}}^2k_2 + {K_{-4}}^2k_{-2} + {K_{-4}}^2K_3 + 2\,K_{-4}c_1 \\
&+2\,K_{-4}c_2 + K_{-4}c_3 + K_{-1}{K_{-4}}^2 + k_2{k_{-3}}^2 + k_{-2}{k_{-3}}^2 + 2\,{k_{-3}}^2k_1 + {k_{-3}}^2k_4 \\
&+2\,k_{-3}c_1 + 4\,k_1c_2 + k_{-3}c_3 + {k_{-3}}^2K_{-1} + 2\,{k_1}^2k_2 + 4\,{k_1}^2k_{-2} + 4\,{k_1}^2K_3 + 4\,K_4{k_1}^2 \\
&+4\,{k_1}^2K_{-4} + 4\,k_{-3}{k_1}^2 + 4\,k_1c_1 + 2\,k_1c_3 + 2\,K_{-1}c_1 + 2\,K_{-1}c_2 + K_{-1}c_3 + {K_{-1}}^2k_2 \\
&+{K_{-1}}^2k_{-2} + {K_{-1}}^2K_3 + {K_{-1}}^2K_{-4} + k_{-3}{K_{-1}}^2 + k_4{k_2}^2 + {k_4}^2k_2 + {k_4}^2k_{-2} \\
&+{k_4}^2K_3 + k_{-3}{k_4}^2 + 2\,k_4c_1 + 2\,k_4c_2 + k_4c_3 + k_1{k_2}^2 + k_4{k_{-2}}^2 + {k_2}^2k_{-3} + K_{-4}{k_2}^2 \\
&+2\,k_2c_1 + 2\,k_2c_2 + k_2c_3 + K_{-1}{k_2}^2 + 2\,k_1{k_{-2}}^2 + 2\,k_1{K_3}^2 + {k_{-2}}^2k_{-3} + K_{-4}{k_{-2}}^2 \\
&+2\,k_{-2}c_1 + 2\,k_{-2}c_2 + k_{-2}c_3 + K_{-1}{k_{-2}}^2 + K_{-4}{K_3}^2 + 2\,K_3c_1 + 2\,K_3c_2 + K_3c_3 \\
&+k_4{K_3}^2 + {K_3}^2K_2 + k_{-3}k_3c_1K_{-4} + 2\,k_1k_3c_1K_{-4} + K_{-1}k_3c_1K_{-4} + k_4k_3c_1K_{-4} \\
&+k_2k_3c_1K_{-4} + K_{-1}{K_3}^2 + k_{-2}k_3c_1K_{-4} + K_3k_3c_1K_{-4}\,.
\end{aligned}
$$

Proposition 3.3 *Let all parameters $k_i,\ K_i,\ i = 1,2,3,4$ and $k_{-i},\ K_{-i},\ i = 1,2,3,4$ be positive. Then, all eigenvalues of the matrix J have negative real parts.*

Proof. First we notice that no equilibrium lies on the boundary of the pyramid, so we may assume $c_1 > 0,\ c_2 > 0,\ c_3 > 0$, where $(c_1, c_2, c_3)^T$ is assumed to be an equilibrium of the dynamical system in the pyramid. To show this proposition we will apply the Routh-Hurwitz Theorem (see [3]). We can easily check (by hand and by any math software as above) that

$$p_0 \;=\; 1$$

and p_1, p_2, p_3 are determined by the above formulas. Since all parameters in the matrix J are positive we have

$$\Delta_1 \;=\; p_1 > 0\,.$$

$$\Delta_2 \quad = \quad p_1 \cdot p_2 - p_3 > 0$$

because $k_1\, k_{-3}\, k_4 - K_1\, K_4\, k_{-3} > 0$. Therefore,

$$\Delta_3 \quad = \quad p_3\, \Delta_2 > 0\,.$$

Finally, if all parameters in the equations are positive, then $\Delta_1, \Delta_2, \Delta_3$ are all positive, so by the Routh-Hurwitz Theorem (see [3], and [8]) all real parts of the eigenvalues of the matrix J are positive. □

Corollary 3.4 *Let all parameters $k_i,\ i = 1, 2, 3, 4$ and $k_{-i},\ i = 1, 2, 3, 4$ be positive. Then, all steady states of the systems inside the pyramid are exponentially stable.*

Proof. By the general theory of stability of dynamical systems at steady states this corollary follows from the fact that all real parts of the linearized part are positive. □

References

[1] V. I. Arnold, *Geometrical methods in the theory of ordinary differential equations*. Second edition. Grundlehren der Mathematischen Wissenschaften **250**. Springer-Verlag, New York, 1988.

[2] S. N. Chow, J. K. Hale, *Methods of Bifurcation Theory*. Grundlehren der Mathematischen Wissenschaften **251**. Springer-Verlag, New York–Berlin, 1982.

[3] F. R. Gantmacher, *Matrix Theory*, Vol. II. Chelsea Publishing Company, New York, 1959.

[4] J. D. Murray, *Mathematical Biology*. Springer-Verlag, Berlin–Heidelberg–New York, 1993.

[5] J. J. Rice, F. Wang, D. Bers, P. P. de Tombe, *Approximate model of cooperative activation and crossbridge cycling in cardiac muscle using ordinary differential equations*. IBM Report RC24343 (W0709-017), September 6, 2007.

[6] J. Sneyd (Ed.), *Tutorials in Mathematical Biosciences II. Mathematical Modeling of Calcium Dynamics and Signal Transduction*. Lecture Notes in Mathematics **1867**. Springer-Verlag, Berlin–Heidelberg, 2005.

[7] Y. Tang, H. Othmer, *A model of calcium dynamics in cardiac myocytes based on the kinetics of Ryanodine-sensitive calcium channels,* Biophysical Journal **67** (1994), 2223–2235.

[8] B. Zhang, *Formulas of Liapunov functions for systems of linear ordinary and delay differential equations*. Funkcialaj Ekvacioj **44** (2001), 253–278.

[9] H. G. Zot, J. E. Hasbun, N. Van Minh, *Striated muscle regulation of isometric tension by multiple equilibria*. PLoS One **4** (2009), e8052.