QUALITATIVE ANALYSIS OF A MODEL FOR SYNAPTIC SLOW WAVES*

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Abstract

A four-dimensional mass action kinetic model of the synaptic slow waves has previously been investigated by numerical methods. Here, a slightly simplified version of the model is shown to produce Andronov–Hopf bifurcation at certain values of the reaction rate constants. It turns out that the model leads to a unique stable limit cycle within each simplex corresponding to a fixed value of total mass.

1. Introduction

Neurochemical and neurophysiological oscillatory phenomena appear at three different hierarchical levels of synaptic transmission. The rapid oscillation and the slow wave of free cytoplasmic acetylcholine (ACh) were reported by Dunant et al. [3]. The third oscillatory phenomenon is the series of miniature end-plate potentials (Fatt and Katz [9]).

These three oscillatory phenomena have been summarized in the "Three Coupled Oscillators" model by Érdi and Tóth [7] and put into a broader framework by Érdi [4]. Érdi and Tóth [7] have also provided alternative models for these oscillatory phenoma.

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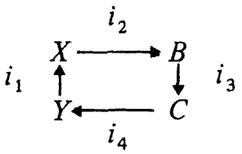
In the present paper, our interest is focused on the slow wave. This type of oscillation is the result of integrated activity of the synaptic metabolic subprocesses. Our model, based upon the transmitter recycling hypothesis and constructed upon the principles proposed by Császár et al. [2], is a mass action type kinetic model with the elementary reactions as follows:



$$2X + Y \xrightarrow{i_5} 3X . \tag{1}$$

In this model, the chemical components or species are:

X: cytoplasmic ACh,
Y: choline,
B: ACh at the postsynaptic membrane surface,
C: choline.

The elementary reactions are:

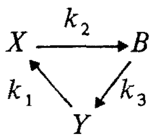
1: re-uptake of choline,
2: diffusion of ACh, cleft processes,
3: hydrolysis of ACh,
4: diffusion of choline,
5: autocatalytic synthesis of ACh.

The system of differential equations describing the change of the concentrations x, y, b, c of the components in time is:

$$\left.\begin{aligned}\dot{x} &= -i_2 x + i_1 y + i_5 x^2 y \\ \dot{y} &= -i_1 y + i_4 c - i_5 x^2 y \\ \dot{b} &= i_2 x - i_3 b \\ \dot{c} &= i_3 b - i_4 c\end{aligned}\right\} \tag{2}$$

according to the usual mass action type deterministic model of reaction kinetics. Partially published numerical results (see, for example, [8,6,12]) show that at certain values of the parameters called reaction rate constants, the system represented by the set of equations (2) has periodic solutions. The form and location of the periodic solution also depends on $M := x + y + b + c$, a linear first integral (meaning the sum of the concentrations) of the system.

In the present paper, a slight simplification of the model will be made in order to make it more amenable for qualitative investigations. This simplification means that the components Y and C will be united and the fourth elementary reaction will be disregarded. Thus, the object of our theoretical investigations will be the reaction



$$2X + Y \xrightarrow{k_4} 3X \tag{3}$$

with the kinetic differential equation

$$\begin{aligned} \frac{dx}{d\tau} &= -k_2 x + k_1 y + k_4 x^2 y \\ \frac{dy}{d\tau} &= -k_1 y + k_3 b - k_4 x^2 y \\ \frac{db}{d\tau} &= k_2 x - k_3 b\,. \end{aligned} \tag{4}$$

(This system has also been investigated numerically and analogous results to those mentioned above were obtained.)

The system represented by (4) can obviously be reduced to a two-dimensional one. Furthermore, it is more convenient to have a simpler, dimensionless form. In order to achieve this, let us introduce the following transformation:

$$t := k_2 \tau \qquad x_1 := \sqrt{k_4/k_1}\,x \qquad x_2 := \sqrt{k_1 k_4/k_2}\,y\,, \tag{5}$$

and let us denote the constant $x + y + b$ by M. We thus obtain

$$\begin{aligned} \frac{dx_1}{dt} &= -x_1 + x_2 + x_1^2 x_2 \\ \frac{dx_2}{dt} &= -\frac{k_1 k_3}{k_2^2} x_1 - \left(\frac{k_1}{k_2} + \frac{k_3}{k_2}\right) x_2 - \frac{k_1}{k_2} x_1^2 x_2 + \frac{k_3}{k_2^2} \sqrt{k_1 k_4}\, M. \end{aligned} \tag{6}$$

It is this system of differential equations that we now treat by the methods of the qualitative theory of differential equations in order to establish the biologically interesting features that have been suggested by numerical calculations. A specific feature of our investigations is that not only the occurrence of bifurcation and stability of the emerging limit cycle will be stated, but also the bifuraction direction.

2. Qualitative analysis

As a result of preliminary considerations, we consider the differential system obtained from (6) by introducing the notation $K_i := k_i/k_2$, $i = 1, 3, 4$, for the "relative rate constants":

$$\frac{dx_1}{dt} = -x_1 + x_2 + x_1^2 x_2 =: f_1(x_1, x_2)$$

$$\frac{dx_2}{dt} = K_3 \sqrt{K_1 K_4}\, M - K_1 K_3 x_1 - (K_1 + K_3) x_2 - K_1 x_1^2 x_2 =: f_2(x_1, x_2), \tag{7}$$

where K_1, K_3, K_4, M are positive constants. We shall seek conditions guaranteeing the existence of a periodic solution in the positive quadrant. To this end, we apply a theorem on the bifurcation of a periodic solution from an equilibrium point (Andronov–Hopf bifurcation, see theorem A_1 in the appendix).

Let us introduce the parameters

$$m := \sqrt{K_4}\, M, \qquad k := \frac{K_3}{K_1(1 + K_3)}, \tag{8}$$

where m will be considered as the bifurcation parameter. An equilibrium point $\tilde{x} := (\tilde{x}_1, \tilde{x}_2)$ of (7) is a solution of the system

$$-\tilde{x}_1 + \tilde{x}_2 + \tilde{x}_1^2 \tilde{x}_2 = 0$$

$$K_3 \sqrt{K_1}\, m - K_1 K_3 \tilde{x}_1 - (K_1 + K_3)\tilde{x}_2 - K_1 \tilde{x}_1^2 \tilde{x}_2 = 0 . \tag{9}$$

From the first equation, we find that

$$\tilde{x}_2 = \frac{\tilde{x}_1}{1 + \tilde{x}_1^2}, \tag{10}$$

such that (9) is equivalent to

$$p(\tilde{x}_1, K_1, K_3, m) := \tilde{x}_1^3 - k\sqrt{K_1}\, m\, \tilde{x}_1^2 + (k+1)\tilde{x}_1 - k\sqrt{K_1}\, m = 0. \tag{11}$$

From (10) and (11), we immediately obtain:

LEMMA 1

For any positive constants K_1, K_3, m, the system (7) has at least one equilibrium point in the positive quadrant.

Let $(\tilde{x}_1, \tilde{x}_2)$ be an equilibrium point of (7). Using the transformation $x_i = \tilde{x}_i + y_i$, $i = 1, 2$, we find from (7) that:

$$\frac{dy_1}{dt} = (2\tilde{x}_1\tilde{x}_2 - 1)y_1 + (1 + \tilde{x}_1^2)y_2 + \tilde{x}_2 y_1^2 + 2\tilde{x}_1 y_1 y_2 + y_1^2 y_2$$

$$\frac{dy_2}{dt} = -K_1(K_3 + 2\tilde{x}_1\tilde{x}_2)y_1 - (K_1 + K_3 + K_1\tilde{x}_1^2)y_2 - K_1\tilde{x}_2 y_1^2 - 2K_1\tilde{x}_1 y_1 y_2 - K_1 y_1^2 y_2. \tag{12}$$

By definition, the characteristic roots of the equilibrium point $\tilde{x} := (\tilde{x}_1, \tilde{x}_2)$ of the system (7) are the eigenvalues $\kappa_{1,2}$ of the matrix $f_x(\tilde{x})$

$$f_x(\tilde{x}) = \begin{pmatrix} 2\tilde{x}_1\tilde{x}_2 - 1 & 1 + \tilde{x}_1^2 \\ -K_1(K_3 + 2\tilde{x}_1\tilde{x}_2) & -(K_3 + K_1(1 + \tilde{x}_1^2)) \end{pmatrix}. \tag{13}$$

According to theorem A_1, the occurrence of Andronov–Hopf bifurcation in the system (7) requires the existence of an equilibrium point whose characteristic roots have vanishing real parts. From (10) and (13), this condition reads:

$$\operatorname{trace} f_x(\tilde{x}) = \frac{\tilde{x}_1^2 - 1}{\tilde{x}_1^2 + 1} - K_1(\tilde{x}_1^2 + 1) - K_3 = 0. \tag{14}$$

LEMMA 2

Let $K_1 > 0$, $K_3 > 0$ be given. Suppose the system (7) has an equilibrium point $\tilde{x}$ in the positive quadrant such that trace $f_x(\tilde{x}) = 0$. Then the constants K_1, K_3 satisfy

$$0 < K_1 \leqslant \frac{(1 - K_3)^2}{8}, \qquad 0 < K_3 < 1. \tag{15}$$

Proof

From (14) we obtain the equation:

$$(\tilde{x}_1^2)^2 + \frac{2K_1 + K_3 - 1}{K_1}\tilde{x}_1^2 + \frac{K_1 + K_3 + 1}{K_1} = 0. \tag{16}$$

This equation has the solutions

$$\begin{aligned}\tilde{x}_{1,\pm}^2 &= \frac{1}{2K_1}[1 - 2K_1 - K_3 \pm ((1 - 2K_1 - K_3)^2 - 4K_1(K_1 + K_3 + 1))^{1/2}]\\ &= \frac{1}{2K_1}[1 - 2K_1 - K_3 \pm ((1 - K_3)^2 - 8K_1)^{1/2}]\,. \end{aligned}\tag{17}$$

For $\tilde{x}_{1,\pm}^2$ to be positive, we apply the conditions:

$$1 - 2K_1 - K_3 > 0 \tag{18}$$

$$(1 - K_3)^2 - 8K_1 \geqslant 0. \tag{19}$$

Under the assumptions that $K_1 > 0$, $K_3 > 0$, we obtain from (18) and (19) the conditions:

$$0 < K_3 < 1, \quad 0 < K_1 < (1 - K_3)/2, \quad 0 < K_1 \leqslant (1 - K_3)^2/8. \tag{20}$$

It is easy to see that in the interval $0 < K_3 < 1$, the last condition implies the previous one. □

COROLLARY 2.1

Under the assumptions of lemma 2 we have $0 < K_1 < 1/8$.

Remark 2.2

If $\tilde{x}_1^2$ satisfies (16), we then have $\tilde{x}_1^2 > 1$.

LEMMA 3

For given K_1, K_3 values satisfying (15), there exist two not necessarily distinct parameter values m_+ and m_- such that the system (7) for $m = m_+$ and $m = m_-$, respectively, has an equilibrium point $\tilde{x}_+$ and $\tilde{x}_-$ whose corresponding Jacobian has a vanishing trace.

Proof

For given K_1, K_3 values satisfying (15), there are two positive numbers $\tilde{x}_{1,+}$ and $\tilde{x}_{1,-}$ satisfying (14). In order that $\tilde{x}_{1,+}$ and $\tilde{x}_{1,-}$ also be solutions of (11), we obtain for the corresponding parameter values m_+ and m_-

$$m_+ := \frac{\tilde{x}_{1,+}(1 + k + \tilde{x}_{1,+}^2)}{k\sqrt{K_1}(1 + \tilde{x}_{1,+}^2)}, \qquad m_- := \frac{\tilde{x}_{1,-}(1 + k + \tilde{x}_{1,-}^2)}{k\sqrt{K_1}(1 + \tilde{x}_{1,-}^2)}. \tag{21}$$

It is clear that the points $\tilde{x}_+$ and $\tilde{x}_-$ defined by

$$\tilde{x}_\pm := (\tilde{x}_{1,\pm}, \quad \tilde{x}_{1,\pm}/(1 + \tilde{x}_{1,\pm}^2)) \tag{22}$$

are equilibrium points of (7) to K_1, K_3, $m_\pm$.

LEMMA 4

Let $K_1 > 0, K_3 > 0$ and $\tilde{x}_\pm$ as in lemma 3. We then have

$$\begin{aligned}
\det f_x(\tilde{x}_+) > 0 \quad \text{iff} \quad & K_3 \in (0, \tfrac{1}{2}), K_1 \in (0, \tfrac{1}{8}(1 - K_3)^2) \qquad \text{or} \\
& K_3 = \tfrac{1}{2}, \ K_1 \in (0, \tfrac{1}{32}) \qquad \text{or} \\
& K_3 \in (\tfrac{1}{2}, \tfrac{1}{2}(\sqrt{5} - 1)), \ K_1 \in (0, \tfrac{1}{2} K_3^2(1 - K_3 - K_3^2))
\end{aligned} \tag{23}$$

$$\det f_x(\tilde{x}_-) > 0 \quad \text{iff} \quad K_3 \in (0, \tfrac{1}{2}), \ K_1 \in \tfrac{1}{2} K_3(1 - K_3 - K_3^2), \tfrac{1}{8}(1 - K_3)^2).$$

Proof

It is easy to verify that an equilibrium point $\tilde{x}$ of (7) with trace $f_x(\tilde{x}) = 0$ satisfies

$$\det f_x(\tilde{x}) = K_1(1 + \tilde{x}_1^2) - K_3^2 . \tag{24}$$

Hence, we have from (17):

$$\det f_x(\tilde{x}_+) > 0 \Leftrightarrow 1 - K_3 - 2K_3^2 + \sqrt{(1 - K_3)^2 - 8K_1} > 0 \tag{25}$$

$$\det f_x(\tilde{x}_-) > 0 \Leftrightarrow 1 - K_3 - 2K_3^2 - \sqrt{(1 - K_3)^2 - 8K_1} > 0 . \tag{26}$$

For $1 - K_3 - 2K_3^2 > 0$, the inequality (25) is valid for all K_1 satisfying (15). For

$K_3 > 0$, the relation $1 - K_3 - 2K_3^2 > 0$ is equivalent to $0 < K_3 < \frac{1}{2}$. In the case $K_3 = \frac{1}{2}$, the inequality (25) is equivalent to $0 < K_1 < \frac{1}{32}$. For $K_3 > \frac{1}{2}$, a simple calculation shows that the relation (25) is equivalent to $K_1 < \frac{1}{2} K_3^2(1 - K_3 - K_3^2)$. Here, the upper bound is positive only for $K_3 < \frac{1}{2}(\sqrt{5} - 1)$. The inequality (26) can be fulfilled only for $0 < K_3 < \frac{1}{2}$. It is easy to show that in this case (26) is equivalent to $\frac{1}{2} K_3^2(1 - K_3 - K_3^2) < K_1 < \frac{1}{8}(1 - K_3)^2$. □

We now introduce the regions

$$\mathcal{H}_+ := \{(K_3, K_1) : K_1 \in (0, \tfrac{1}{8}(1 - K_3)^2) \quad \text{for } K_3 \in (0, \tfrac{1}{2}],$$

$$K_1 \in (0, \tfrac{1}{2} K_3^2(1 - K_3 - K_3^2)) \quad \text{for } K_3 \in (\tfrac{1}{2}, \tfrac{1}{2}(\sqrt{5} - 1))\}, \tag{27}$$

$$\mathcal{H}_- := \{(K_3, K_1) : K_1 \in (\tfrac{1}{2} K_3^2(1 - K_3 - K_3^2), \tfrac{1}{8}(1 - K_3)^2) \quad \text{for } K_3 \in (0, \tfrac{1}{2})\}$$

which are represented in fig. 1. It is obvious that $\mathcal{H}_- \subset \mathcal{H}_+$.

According to lemma 4, $(K_3, K_1) \in \mathcal{H}_+$ implies $\det f_x(\tilde{x}_+) > 0$ and $(K_3, K_1) \in \mathcal{H}_-$ implies $\det f_x(\tilde{x}_-) > 0$. By lemmas 3 and 4, we find for each $(K_3, K_1) \in \mathcal{H}_+$ from (21) a unique parameter value m_+ such that the system (7) has an equilibrium point $\tilde{x}_+$ in the positive quadrant with trace $f_x(\tilde{x}_+) = 0$ and $\det f_x(\tilde{x}_+) > 0$. Moreover, for each $(K_3, K_1) \in \mathcal{H}_-$, we find a unique parameter value m_- such that (7) has an equilibrium point $\tilde{x}_-$ with the same properties as $\tilde{x}_+$.

As remarked above, for given $(K_3, K_1) \in \mathcal{H}_+$ we consider m as the bifurcation parameter. By theorem A_1, m_+ and m_- are possible bifurcation values for Andonov–Hopf bifurcation.

Under our conditions, there are intervals $\mathcal{J}_\pm := \{m \in \mathbb{R} : |m - m_\pm| < \delta\}$ and functions $x_\pm : \mathcal{J}_\pm \to \mathbb{R}^2$ such that $x_\pm(m)$ are simple equilibrium points of (7) for $m \in \mathcal{J}_\pm$ satisfying $x_\pm(m_\pm) = \tilde{x}_\pm$. Setting $a_\pm(m) := \frac{1}{2}$ trace $f_x(x_\pm(m))$, $b_\pm^2(m) := \det f_x(x_\pm(m)) - (\frac{1}{2}$ trace $f_x(x_\pm(m)))^2$, the characteristic roots of $x_\pm(m)$ can be written in the form

$$\kappa_{1,\pm} = a_\pm(m) + \mathrm{i}\, b_\pm(m), \quad \kappa_{2,\pm} = \bar{\kappa}_{1,\pm} \,. \tag{28}$$

To be able to apply theorem A_2, we look for a condition guaranteeing

$$\frac{\mathrm{d}}{\mathrm{d}m} a_\pm(m_\pm) \neq 0 .$$

From (14) we have

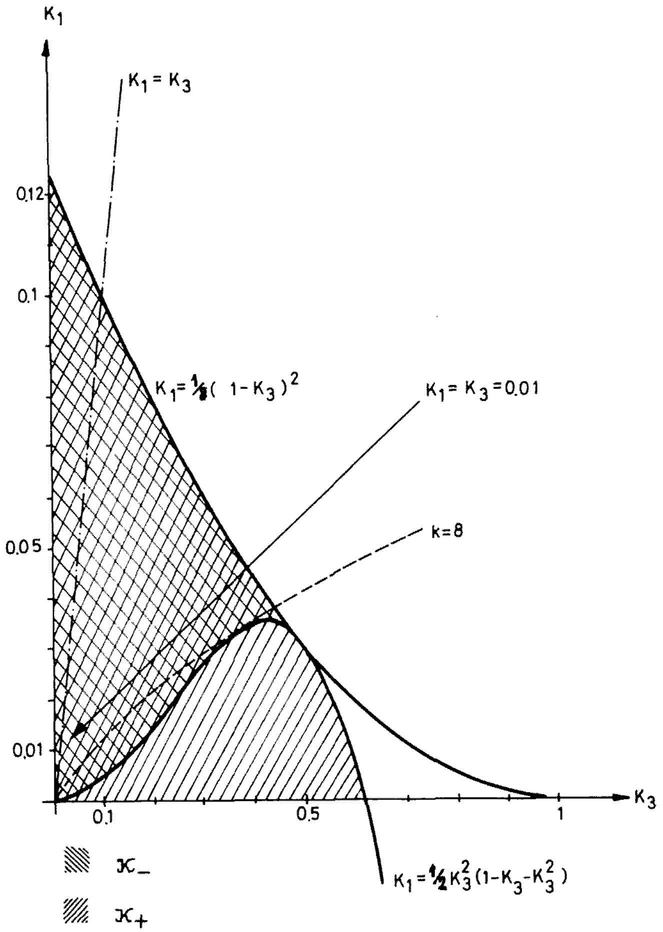


Fig. 1. Qualitatively different regions of the parameter space.

$$\frac{\mathrm{d}}{\mathrm{d}m} a_{\pm}(m)|_{m = m_{\pm}} = \frac{1}{2} \frac{\mathrm{d}}{\mathrm{d}m} \operatorname{trace} f_x(x_{\pm}(m))|_{m = m_{\pm}}$$

$$= \tilde{x}_{1,\pm} \left(\frac{2}{(\tilde{x}_{1,\pm}^2 + 1)^2} - K_1 \right) \frac{\mathrm{d}x_{1,\pm}(m)}{\mathrm{d}m} \Bigg|_{m = m_{\pm}} . \tag{29}$$

LEMMA 5

Let $\tilde{x}_{1,\pm}$ be as above; then we have

$$K_1 > \frac{2}{(\tilde{x}_{1,+}^2 + 1)^2} \quad \text{for} \quad (K_3, K_1) \in \mathcal{K}_+ \quad \text{and}$$
$$K_1 < \frac{2}{(\tilde{x}_{1,-}^2 + 1)^2} \quad \text{for} \quad (K_3, K_1) \in \mathcal{K}_- . \tag{30}$$

Proof

From (17) we find

$$\frac{2}{(\tilde{x}_{1,\pm}^2 + 1)^2} = \frac{8K_1^2}{(1 - K_3 \pm \sqrt{(1-K_3)^2 - 8K_1})^2} .$$

Hence, the relation

$$K_1 > \frac{2}{(\tilde{x}_{1,+}^2 + 1)^2}$$

is equivalent to

$$8K_1 < (1-K_3)^2 + (1-K_3)\sqrt{(1-K_3)^2 - 8K_1} . \tag{31}$$

The validity of this inequality follows immediately from $(K_3, K_1) \in \mathcal{K}_+$. The relation

$$\frac{2}{(\tilde{x}_{1,-}^2 + 1)^2} > K_1$$

is equivalent to

$$(1-K_3)\sqrt{(1-K_3)^2 - 8K_1} > (1-K_3)^2 - 8K_1 . \tag{32}$$

For $(K_3, K_1) \in \mathcal{K}_-$, both sides of (32) are positive. Therfore, (32) is equivalent to $0 > -8K_1$, which is always fulfilled. □

Accordingly, the sign of

$$\left.\frac{\mathrm{d}a_\pm}{\mathrm{d}m}\right|_{m = m_\pm}$$

is uniquely determined by the sign of

$$\left.\frac{\mathrm{d}x_{1,\pm}}{\mathrm{d}m}\right|_{m = m_\pm}$$

LEMMA 6

Assume K_1, K_3 to be positive and $x_\pm(m)$ as above. We then have

$$\operatorname{sign} \left.\frac{\mathrm{d}x_{1,\pm}}{\mathrm{d}m}\right|_{m = m_\pm} = \operatorname{sign}\left\{\tilde{x}^4_{1,\pm} + (2-k)\tilde{x}^2_{1,\pm} + k + 1\right\} . \tag{33}$$

Proof

$\tilde{x}_{1,\pm} = x_{1,\pm}(m_\pm)$ is a simple root of eq. (11) for $m = m_\pm$. Thus, we obtain from (11)

$$\left.\frac{\mathrm{d}x_{1,\pm}}{\mathrm{d}m}\right|_{m = m_\pm} = \frac{k\sqrt{K_1}(1 + \tilde{x}^2_{1,\pm})}{3\tilde{x}^2_{1,\pm} - 2k\sqrt{K_1}\, m_\pm \tilde{x}_{1,\pm} + k + 1} . \tag{34}$$

Hence,

$$\operatorname{sign} \left.\frac{\mathrm{d}x_{1,\pm}}{\mathrm{d}m}\right|_{m = m_\pm} = \operatorname{sign}\left\{3\tilde{x}^2_{1,\pm} - 2k\sqrt{K_1}\, m_\pm \tilde{x}_{1,\pm} + k + 1\right\} . \tag{35}$$

Substituting (21) into (35), we obtain (33). If we now set $q(z) := z^2 + (2-k)z + k + 1$, we can easily verify that $q(z)$ has no real zero for $k < 8$. Thus, we get from lemma 6:

COROLLARY 6.1

Assume K_1, K_3 to be positive and $k < 8$. Then

$$\left.\frac{\mathrm{d}x_1}{\mathrm{d}m}\right|_{m = m_\pm}$$

has a positive sign.

To determine the direction of the bifuraction, we need the sign of the $\tilde{\alpha}_3$ number defined in (A.6). To this end, we transform the system (12) for $m = m_\pm$ into the normalized form (A.4) at $\lambda = \lambda_0$ using

$$y_1 = (1 + \tilde{x}_{1,\pm}^2)v/\tilde{b}_\pm, \quad y_2 = u - (\tilde{x}_{1,\pm}^2 - 1)v/(\tilde{b}_\pm(\tilde{x}_{1,\pm}^2 + 1)), \tag{36}$$

where $\tilde{b}_\pm = b_\pm(m_\pm) > 0$. In this way, we obtain the system

$$\begin{aligned}\frac{\mathrm{d}u}{\mathrm{d}t} &= -\tilde{b}_\pm v + \frac{2\tilde{x}_{1,\pm}}{\tilde{b}_\pm} K_3 uv + \frac{\tilde{x}_{1,\pm}(3 - \tilde{x}_{1,\pm}^2)K_3}{\tilde{b}_\pm^2(\tilde{x}_{1,\pm}^2 + 1)} v^2 \\ &\quad + \frac{1 + \tilde{x}_{1,\pm}^2}{\tilde{b}_\pm^2} K_3 uv^2 - \frac{(\tilde{x}_{1,\pm}^2 - 1)}{\tilde{b}_\pm^3} K_3 v^3 \\ \frac{\mathrm{d}v}{\mathrm{d}t} &= \tilde{b}_\pm u + 2\tilde{x}_{1,\pm} uv + \frac{\tilde{x}_{1,\pm}(3 - \tilde{x}_{1,\pm}^2)}{\tilde{b}_\pm(\tilde{x}_{1,\pm}^2 + 1)} v^2 \\ &\quad + \frac{1 + \tilde{x}_{1,\pm}^2}{\tilde{b}_\pm} uv^2 - \frac{(\tilde{x}_{1,\pm}^2 - 1)}{\tilde{b}_\pm^2} v^3 .\end{aligned} \tag{37}$$

According to (A.6), we also obtain

$$\begin{aligned}\tilde{\alpha}_{3,\pm} &= \frac{2\tilde{x}_{1,\pm}^2(3 - \tilde{x}_{1,\pm}^2)}{\tilde{b}_\pm^2(1 + \tilde{x}_{1,\pm}^2)} \left(\frac{K_3^2}{\tilde{b}_\pm^2} + \frac{K_3(3 - \tilde{x}_{1,\pm}^2)}{\tilde{b}_\pm^2(1 + \tilde{x}_{1,\pm}^2)} - 1 \right) \\ &\quad - \frac{3(\tilde{x}_{1,\pm}^2 - 1)}{\tilde{b}_\pm^2} + \frac{K_3}{\tilde{b}_\pm^2} (\tilde{x}_{1,\pm}^2 + 1).\end{aligned} \tag{38}$$

It is easy to determine the sign of $\tilde{\alpha}_{3,\pm}$ numerically. To be able to determine this sign analytically, we restrict ourselves to the case $K_1 = K_3 =: K \ll 1$. We remark that the straight line $K_1 = K_3$ is located in the region $0 < k < 8$ (cf. fig. 1).

From (17), (21) and (24) we find the relations

$$\tilde{x}_{1,+}^2 = \frac{1}{K} - 4 + \mathrm{O}(K), \quad \tilde{b}_+^2 = \det f_x(\tilde{x}_+) = 1 - 3K + \mathrm{O}(K^2),$$

$$m_+ = \frac{1}{K} + \mathrm{O}(K)$$

$$\tilde{x}^2_{1,-} = 1 + 6K + O(K^2),\ \tilde{b}^2_- = 2K + 5K^2 + O(K^3),$$

$$m_- = \frac{1.5}{\sqrt{K}} + 4\sqrt{K} + O(K^{3/2}). \tag{39}$$

Using the relations (39), we obtain from (38):

$$\begin{aligned} \tilde{\alpha}_{3,+} &= -\frac{1}{K} - 1 + O(K) \\ \tilde{\alpha}_{3,-} &= -\frac{1}{2K} - 10.5 + O(K), \end{aligned} \tag{40}$$

which implies that both $\tilde{\alpha}_{3,+}$ and $\tilde{\alpha}_{3,-}$ have negative signs for $K_1 = K_3 = K$, with K sufficiently small.

Applying lemmas 3 and 4, corollary 6.1 and theorem A_2, we obtain the following result:

THEOREM 7

Let $K_1 = K_3 = K$, with K sufficiently small. Then there exist exactly two values m_+ and m_-, defined by (21) such that for $m > m_-$, $m - m_-$ sufficiently small, the system (7) has a unique stable limit cycle in a small neighbourhood of the equilibrium point $\tilde{x}_-$ defined by (22) and this contracts to $\tilde{x}_-$ as m tends to m_-. Moreover, for $m < m_+$, $m_+ - m$ sufficiently small, the system (7) has a unique stable limit cycle in a small neighbourhood of the equilibrium point $\tilde{x}_+$ defined by (22) and this contracts to $\tilde{x}_+$ as m tends to m_+.

3. Discussion and perspectives

The model presented and investigated in the present paper has two important characteristics:

(i) it adheres to experimental facts from neurobiology as strictly as possible;
(ii) it is straightforward in that it contains nothing more than a single brusselator-type nonlinearity plus a simple irreversible triangle reaction.

Although the model is closed with respect to mass, it is still able to produce oscillations. This is not in contradiction with the propositions of thermodynamics because neither our model nor its elaboration with reverse reactions is balanced at the detailed level.

One area of further research could involve the qualitative investigation of the four-dimensional model and the investigation of the dependence of behaviour on more than two parameters.

Numerical investigations suggest that additional elementary reactions may not disturb the presence of oscillatory solutions. This question has not been investigated by theoretical means so far. A similar question is: What kinds of nonlinearities (in regard to non-mass-action kinetics) are enough to ensure the existence of periodic solutions?

Appendix

Consider the qualitative behaviour of the trajectories of the differential system

$$\begin{aligned} \frac{dy_1}{dt} &= \sum_{1 \leqslant i+j \leqslant 3} b_{ij}^{(1)}(\lambda)\, y_1^i y_2^j + r_1(y_1, y_2, \lambda) \\ \frac{dy_2}{dt} &= \sum_{1 \leqslant i+j \leqslant 3} b_{ij}^{(2)}(\lambda)\, y_1^i y_2^j + r_2(y_1, y_2, \lambda) \end{aligned} \tag{A.1}$$

in the neighbourhood G of the origin $y = 0$ for

$$\lambda \in \Lambda_0 := \{\lambda \in \mathbb{R} : |\lambda - \lambda_0| < \delta_0, \delta_0 > 0\}$$

under the following regularity assumptions.

(H_1) For $k = 1, 2$; $1 \leqslant i + j \leqslant 3$, the coefficients $b_{ij}^{(k)} : \Lambda_0 \to \mathbb{R}$ are continuous.

(H_2) For $k = 1, 2$, the functions $r_k : G \times \Lambda_0 \to \mathbb{R}$ are differentiable with respect to y up to order 3 where all derivatives continuously depend on (y, λ) and satisfy $|r_k(y, \lambda)| = O(|y|^3)$ as $|y| \to 0$ uniformly in $\lambda \in \Lambda_0$.

We are interested in the bifurcation of a periodic solution of (A.1) from the equilibrium point $y = 0$ as λ crosses the critical value $\lambda = \lambda_0$ (Andronov–Hopf bifurcation). Let us denote by $\kappa_1(\lambda)$, $\kappa_2(\lambda)$ the characteristic roots of $y = 0$ of the system (A.1). The following theorem can be easily demonstrated:

THEOREM A_I

Assume (H_1), (H_2) to be valid. The conditions

$$\operatorname{Re} \kappa_1(\lambda_0) = \operatorname{Re} \kappa_2(\lambda_0) = 0 \tag{A.2}$$

are necessary for the bifurcation of a family of periodic solution of (A.1) from the equilibrium point $y = 0$ as λ crosses λ_0.

In the sequel, we suppose that the equilibrium point $y = 0$ of (A.1) has the characteristic roots $\kappa_{1,2} = a(\lambda) \pm \mathrm{i}\, b(\lambda)$ for $\lambda \in \Lambda_0$ satisfying (A.2) and

$$b(\lambda_0) > 0. \tag{A.3}$$

Using the transformation

$$x_2 = b(\lambda)[b_{01}^{(1)}(\lambda)]^{-1} y_1 \; x_1 = y_2 - [b_{01}^{(2)} - a(\lambda)]\, [b_{01}^{(1)}(\lambda)]^{-1} y_1 \,,$$

the system (A.1) is equivalent to the system

$$\begin{aligned}\frac{\mathrm{d}x_1}{\mathrm{d}t} &= a(\lambda)x_1 - b(\lambda)x_2 + \sum_{2 \leqslant i+j \leqslant 3} a_{ij}^{(1)}(\lambda)x_1^i x_2^j + \bar{r}_1(x_1, x_2, \lambda)\\ \frac{\mathrm{d}x_2}{\mathrm{d}t} &= b(\lambda)x_1 + a(\lambda)x_2 + \sum_{2 \leqslant i+j \leqslant 3} a_{ij}^{(2)}(\lambda)x_1^i x_2^j + \bar{r}_2(x_1, x_2, \lambda),\end{aligned} \tag{A.4}$$

where the coefficients a, b, $a_{ij}^{(k)}$ and the functions $\bar{r}_k$ have the same regularity properties as the corresponding one in (A.1).

From [1,10,11], we obtain the following result:

THEOREM A_2

The hypotheses

(H_3) $a_{ij}^{(k)}$ and r_k have the same regularity properties as the coefficients and functions in (H_1), (H_2);

(H_4) $a, b : \Lambda_0 \to \mathbb{R}$ are continuous, a is continuously differentiable satisfying (A.2), (A.3) and

$$a'(\lambda_0) \neq 0. \tag{A.5}$$

(H_5)

$$\begin{aligned}\tilde{\alpha}_3 := \Big\{ \frac{1}{b} \, [a_{11}^{(1)} (a_{20}^{(1)} + a_{02}^{(1)}) + 2(a_{02}^{(1)} a_{02}^{(2)} \\ - a_{20}^{(1)} a_{20}^{(2)}) - a_{11}^{(2)} (a_{20}^{(2)} + a_{02}^{(2)})] \\ + 3(a_{30}^{(1)} + a_{03}^{(2)}) + a_{12}^{(1)} + a_{21}^{(2)} \Big\} \Big|_{\lambda = \lambda_0} \neq 0\end{aligned} \tag{A.6}$$

are sufficient for the bifurcation of exactly one family of periodic solutions of the system (A.4) from the origin with the representation $x = p(t, \lambda)$ satisfying

$$p(t + T(\lambda), \lambda) = p(t, \lambda), \ T(\lambda) = \frac{2\pi}{b(\lambda_0)} + O(|\lambda - \lambda_0|^2)$$

$$\max_{t \in [0, T(\lambda)]} |p(t, \lambda)| = \left\{8 \left|\frac{a'(0)}{\tilde{\alpha}_3}\right| \left|\lambda - \lambda_0\right|\right\}^{1/2} + O(|\lambda - \lambda_0|).$$

The direction of bifurcation is determined by sign $[-a'(\lambda_0)\tilde{\alpha}_3]$, which implies there is a sufficiently small neighbourhood G_1 of $x = 0$ such that, if $-a'(\lambda_0)\tilde{\alpha}_3$ has positive (negative) sign, then the system (A.4) has a unique limit cycle $p(t, \lambda)$ in G_1 for $\lambda > \lambda_0$ ($\lambda < \lambda_0$) and $|\lambda - \lambda_0|$ sufficiently small, whereas (A.4) has no limit cycle in G_1 for $\lambda < \lambda_0$ ($\lambda > \lambda_0$) and $|\lambda - \lambda_0|$ sufficiently small. The stability of $p(t, \lambda)$ is opposite to that of the origin.

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