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### Calcium concentration in astrocytes: Emergence of complicated spontaneous oscillations and their cessation

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**Abstract.** The purpose of this work is to show the mechanisms of transitions between different dynamic modes of spontaneous astrocytic calcium activity. With this aim, dynamics of recently introduced Lavrentovich–Hemkin mathematical model was examined by both analytical and numerical techniques. *Methods.* In order to obtain the conditions for the oscillations cessation, the linear stability analysis for the equilibrium point was carried out. Complicated dynamics was studied numerically by calculations of time traces and bifurcation diagrams. *Results.* The mechanisms of oscillatory mode development with the increase of the maximal calcium flux out of the SERCA pump in the presence of low and high level of extracellular calcium concentration were demonstrated. It was shown that emergence of oscillations occurs via supercritical Andronov–Hopf bifurcation, and the properties of the oscillatory mode with further increase of the maximal calcium flux out of the SERCA pump are highly dependent on the value of extracellular calcium concentration. Notably, emergence of chaotic spontaneous calcium oscillations for specific level of calcium ions outside the cell was revealed. *Conclusion.* Based on the analysis of various dynamical modes of spontaneous astrocytic chemical activity, the peculiarities in astrocyte–neuron interaction in complex multicellular systems can be further investigated.

**Keywords:** mathematical modeling, calcium concentration in astrocytes, oscillatory mode, stationary mode.

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## Концентрация кальция в астроцитах: возникновение сложных спонтанных колебаний и их затухание

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**Аннотация.** Цель данной работы – показать механизмы переходов между различными динамическими режимами спонтанной кальциевой активности астроцитов. С этой целью динамика недавно представленной математической модели Лаврентовича–Хемкина была исследована как аналитическими, так и численными методами. **Методы.** Для получения условий прекращения колебаний был проведен линейный анализ устойчивости точки равновесия. Сложная динамика изучалась численно в рамках построения реализаций и бифуркационных диаграмм. **Результаты.** Продемонстрированы механизмы развития колебательных режимов с увеличением максимального потока кальция через SERCA-насос при низком и высоком уровне концентрации внеклеточного кальция. Было показано, что возникновение колебаний происходит в результате суперкритической бифуркации Андронова–Хопфа, а свойства колебательного режима при дальнейшем увеличении максимального потока кальция через SERCA-насос сильно зависят от величины концентрации внеклеточного кальция. В частности, показано, что при определенном уровне концентрации ионов кальция снаружи клетки наблюдается возникновение хаотических спонтанных кальциевых колебаний. **Заключение.** На основе анализа различных динамических режимов спонтанной химической активности астроцитов возможно дальнейшее изучение особенностей взаимодействия астроцитов и нейронов в сложных многоклеточных системах.

**Ключевые слова:** математическое моделирование, концентрация кальция в астроцитах, колебательный режим, стационарный режим.

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## Introduction

Neural networks are highly complicated collection of various interconnected structural units. Few decades ago, it was believed that only neurons define the information processing in the brain. Such representation of real neural networks allowed to obtain a lot of interesting and important results concerning the coherence and synchronization of neural elements [1–8]. At the same time, recent studies shown that a lot of factors can significantly modify the neuronal response [9–14]. Particularly, various mathematical models for neuron-astrocyte interaction were introduced and examined [15–19].

Astrocytes are glial cells of the central nervous system that are capable to generate impulses of chemical activity. This kind of chemical activity was experimentally detected by various methods

of fluorescence and confocal laser microscopy, that allowed revealing the changes in concentration of free cytosolic calcium in course of time. Extensive experimental study shown that astrocytes are characterized by both spontaneous changes in calcium concentration [10, 20, 21], and calcium signals caused by neuronal activity [22–24]. These astrocytic calcium concentration changes can be localized in synapses or spread along the astrocytic network. Peculiarity of such chemical signal is in the presence of oscillations with different amplitude in calcium concentration: the so-called *blips* and *puffs* [25]. Blips are short and weak peaks that correspond to the opening of one IP<sub>3</sub>R channel (or one tetramer of an IP<sub>3</sub>R channel), while the puffs are longer and higher peaks resulting from the coordinated opening of a group of neighboring IP<sub>3</sub>R channels (or their tetramers) through the calcium-induced calcium release principle (CICR). Recently introduced Lavrentovich–Hemkin mathematical model [26] gives clear description for these peculiarities of astrocytic response. This model allows taking into account various physiological parameters: the flow of calcium from the extracellular space into the astrocyte’s cytosol, IP<sub>3</sub>R-mediated flow of calcium from the endoplasmic reticulum (ER) to the cytosol and so on. Since the appearance of various spatiotemporal changes in calcium concentration is associated with various network functions, the analysis of the dynamic modes observed with the change of parameters in corresponding mathematical model is of particular significance.

In this work, the role of the maximal calcium flux out of the SERCA pump\* in changes of spontaneous chemical activity in astrocytes is examined.

### 1. Description of the mathematical model

In accordance with Lavrentovich–Hemkin model [26], calcium concentration changes in the cytosol of astrocytes and in its endoplasmic reticulum, and Ca<sup>2+</sup>-dependent dynamics of inositol-1,4,5-triphosphate (IP<sub>3</sub>) concentration are governed by the following equations:

$$\begin{aligned} \frac{d[\text{Ca}^{2+}]_{\text{cyt}}}{dt} &= J_{\text{in}} - k_{\text{out}}[\text{Ca}^{2+}]_{\text{cyt}} + J_{\text{CICR}} - J_{\text{serca}} + k_f([\text{Ca}^{2+}]_{\text{ER}} - [\text{Ca}^{2+}]_{\text{cyt}}), \\ \frac{d[\text{Ca}^{2+}]_{\text{ER}}}{dt} &= J_{\text{serca}} - J_{\text{CICR}} + k_f([\text{Ca}^{2+}]_{\text{cyt}} - [\text{Ca}^{2+}]_{\text{ER}}), \\ \frac{d[\text{IP}_3]_{\text{cyt}}}{dt} &= J_{\text{PLC}} - k_{\text{deg}}([\text{IP}_3]_{\text{cyt}}), \end{aligned} \quad (1)$$

where the expressions for  $J_{\text{serca}}$ ,  $J_{\text{CICR}}$  and  $J_{\text{PLC}}$  are:

$$\begin{aligned} J_{\text{serca}} &= v_{M2} \left( \frac{[\text{Ca}^{2+}]_{\text{cyt}}^2}{[\text{Ca}^{2+}]_{\text{cyt}}^2 + k_2^2} \right), \\ J_{\text{CICR}} &= 4v_{M3} \left( \frac{k_{\text{CaA}}^2 [\text{Ca}^{2+}]_{\text{cyt}}^n}{([\text{Ca}^{2+}]_{\text{cyt}}^n + k_{\text{CaA}}^n) ([\text{Ca}^{2+}]_{\text{cyt}}^n + k_{\text{CaI}}^n)} \right) \left( \frac{[\text{IP}_3]_{\text{cyt}}^m}{[\text{IP}_3]_{\text{cyt}}^m + k_{\text{ip3}}^m} \right) ([\text{Ca}^{2+}]_{\text{ER}} - [\text{Ca}^{2+}]_{\text{cyt}}), \\ J_{\text{PLC}} &= v_p \left( \frac{[\text{Ca}^{2+}]_{\text{cyt}}^2}{([\text{Ca}^{2+}]_{\text{cyt}}^2 + k_p^2)} \right). \end{aligned} \quad (2)$$

Here, we consider the following set of parameters:  $v_{M3} = 40 \text{ s}^{-1}$ ,  $v_p = 0.05 \text{ }\mu\text{M/s}$ ,  $k_2 = 0.1 \text{ }\mu\text{M}$ ,  $k_{\text{CaA}} = 0.15 \text{ }\mu\text{M}$ ,  $k_{\text{CaI}} = 0.15 \text{ }\mu\text{M}$ ,  $k_{\text{IP}_3} = 0.1 \text{ }\mu\text{M}$ ,  $k_p = 0.3 \text{ }\mu\text{M}$ ,  $k_{\text{deg}} = 0.08 \text{ s}^{-1}$ ,  $k_{\text{out}} = 0.5 \text{ s}^{-1}$ ,

\*The sarco(endo)plasmic reticulum calcium transport ATPase (SERCA) is a pump that transports calcium ions from the cytoplasm into the ER [27, 28].

$k_f = 0.5 \text{ s}^{-1}$ ,  $n = 2.02$ ,  $m = 2.2$ . In [26,29], for these parameters and  $v_{M2} = 15 \text{ }\mu\text{M/s}$ , the existence of chaotic attractor was shown. Here, we focus on role of the parameter  $v_{M2}$  in both emergence of irregular calcium activity and cessation of spontaneous calcium oscillations in the presence of various level of extracellular calcium  $J_{in}$ .

## 2. Results

### 2.1. Emergence of periodic oscillations of calcium concentration.

In order to obtain the threshold for the oscillations birth, we calculate the difference between the maximal and minimal values of  $[\text{Ca}^{2+}]_{\text{cyt}}$  with the change of parameter  $v_{M2}$ . Fig. 1 shows the curves obtained for three levels of extracellular calcium. For  $J_{in} = 0.03 \text{ }\mu\text{M/s}$ , slowly growing dependence for the amplitude of oscillations is observed. The increase of  $J_{in}$  leads to the shift of the “quiescent–oscillatory” threshold: for larger values of  $J_{in}$ , transition to oscillatory mode for larger values of  $v_{M2}$  occurs. Moreover, for  $J_{in} = 0.04 \text{ }\mu\text{M/s}$ , the growth of the amplitude is much faster then in the previous case. With further increase of  $J_{in}$ , sudden jump in amplitude is observed. It should be noted that, for all considered cases, transition to oscillatory mode occurs through the Andronov–Hopf bifurcation. To show this, the linear stability analysis for the equilibrium point was carried out. Namely, the roots of the characteristic equation were calculated. The results obtained for  $J_{in} = 0.03 \text{ }\mu\text{M/s}$  and  $J_{in} = 0.05 \text{ }\mu\text{M/s}$  are presented in Fig. 2, a and Fig. 2, b, respectively. As seen from these figures, for  $J_{in} = 0.03 \text{ }\mu\text{M/s}$ , the real part of the complex root (red curve in the figure) becomes equal to zero for  $v_{M2} \approx 2.5 \text{ }\mu\text{M/s}$  while for  $J_{in} = 0.05 \text{ }\mu\text{M/s}$  the Andronov–Hopf bifurcation is observed for  $v_{M2} \approx 11 \text{ }\mu\text{M/s}$ .

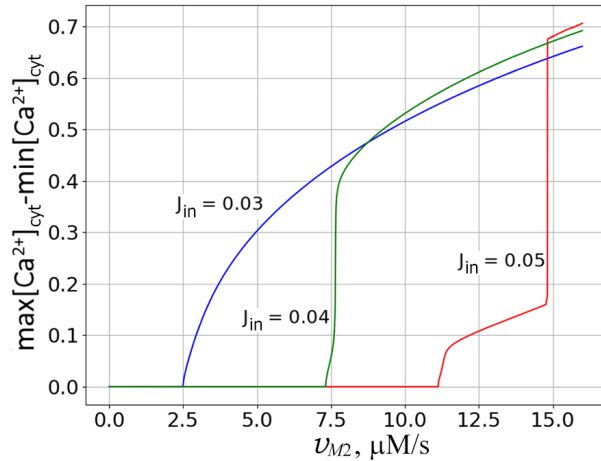


Fig. 1. Difference between the maximal and minimal values of  $[\text{Ca}^{2+}]_{\text{cyt}}$  oscillations with the change of parameter  $v_{M2}$  for three values of  $J_{in}$ :  $J_{in} = 0.05 \text{ }\mu\text{M/s}$  – red,  $J_{in} = 0.04 \text{ }\mu\text{M/s}$  – green and  $J_{in} = 0.03 \text{ }\mu\text{M/s}$  – blue curves. Zero value of the difference corresponds to the case of stable equilibrium state

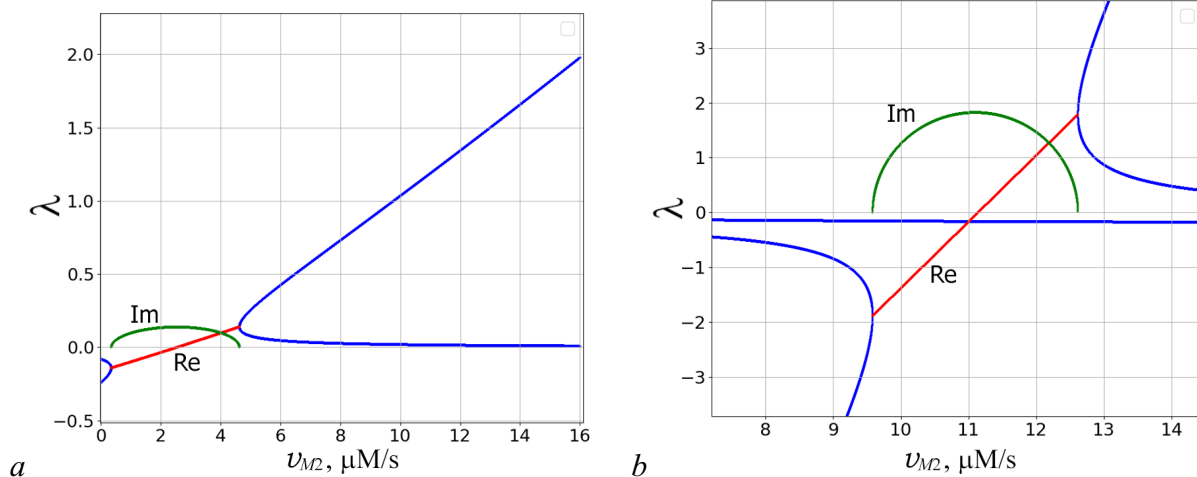


Fig. 2. Roots of the characteristic equation for two values of  $J_{in}$ :  $J_{in} = 0.03 \text{ }\mu\text{M/s}$  (a) and  $J_{in} = 0.05 \text{ }\mu\text{M/s}$  (b). Maximal values of the real roots are shown by blue color, red and green curves correspond to change of real and imaginary parts of complex roots, respectively

**2.2. Emergence of irregular oscillations of calcium concentration.** To examine the changes in oscillatory dynamics of the calcium concentration in the cytosol, we depict the values of its local maxima on diagram with the change of  $v_{M2}$  for two values of  $J_{in}$ . In Fig. 3, *a*, the diagram obtained for  $J_{in} = 0.03 \mu\text{M/s}$  is shown. These data demonstrate the appearance of additional branch for  $v_{M2} > 11.7 \mu\text{M/s}$ . This branch is due to the one-blip (weak peak after the high main peak) emergence in calcium concentration output. To show this, in Fig. 3, *b* and Fig. 3, *c*, the time traces for  $[\text{Ca}^{2+}]_{\text{cyt}}$  when  $v_{M2} = 10 \mu\text{M/s}$  and  $v_{M2} = 20 \mu\text{M/s}$  are presented. As seen from these traces, the increase of  $v_{M2}$  leads to both the increase of puff's amplitude and the increase of the interpuffs intervals, i.e. the time between subsequent high peaks of calcium concentration.

Similar calculation of  $[\text{Ca}^{2+}]_{\text{cyt}}$  local maxima for  $J_{in} = 0.04 \mu\text{M/s}$  (not shown) demonstrates the successive transition from one-blip oscillations to two-, three-, two-, and again one-blip oscillatory mode with the increase of  $v_{M2}$ . As for  $J_{in} = 0.03 \mu\text{M/s}$ , the amplitude of puffs smoothly increases with the increase of the maximal flux of the calcium ions from the cytosol to ER of the cell.

The bifurcation diagram obtained for higher level of extracellular calcium,  $J_{in} = 0.05 \mu\text{M/s}$ , looks differently. Fig. 4, *a* shows that oscillatory mode with high peak of calcium concentration (puff) appears suddenly for  $v_{M2} \approx 14.82 \mu\text{M/s}$ . To show this, in Fig. 4, *b* and Fig. 4, *c*, the time traces for  $[\text{Ca}^{2+}]_{\text{cyt}}$  when  $v_{M2} = 14.8177 \mu\text{M/s}$  and  $v_{M2} = 14.8179 \mu\text{M/s}$  are presented. It is seen that both these oscillatory modes are chaotic. It can be shown that emergence of small-amplitude chaos occurs via a period doubling cascade with the increase of  $v_{M2}$ . For  $v_{M2} > 15 \mu\text{M/s}$ , successive transition from the regime with large number of blips (six-blips to five-blips etc.) to one-blip oscillatory mode can be observed.

Finally note that, for higher levels of extracellular calcium, the chaotic dynamics of cytosolic calcium concentration is not observed.

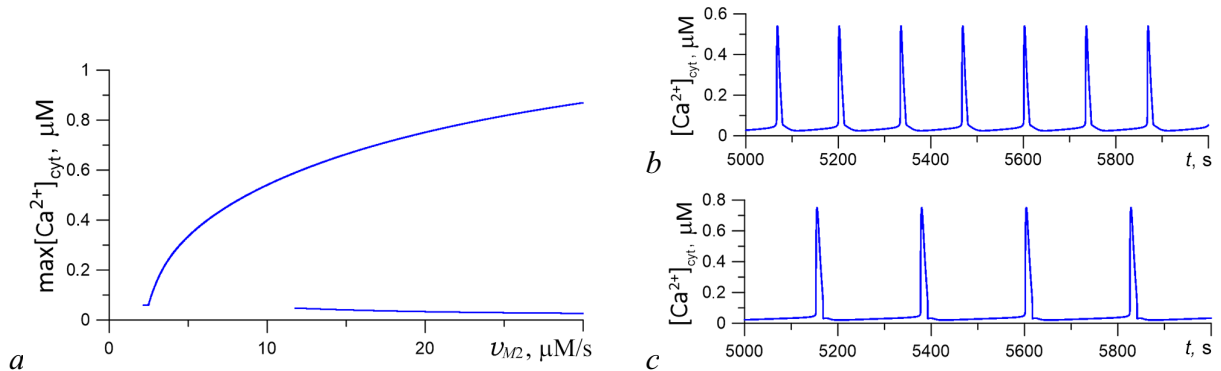


Fig. 3. *a* – Bifurcation diagram obtained for maximal values of  $[\text{Ca}^{2+}]_{\text{cyt}}$  with the change of  $v_{M2}$  for  $J_{in} = 0.03 \mu\text{M/s}$ . Time traces for  $[\text{Ca}^{2+}]_{\text{cyt}}(t)$  when  $v_{M2} = 10 \mu\text{M/s}$  and  $v_{M2} = 20 \mu\text{M/s}$  are shown in (b) and (c), respectively

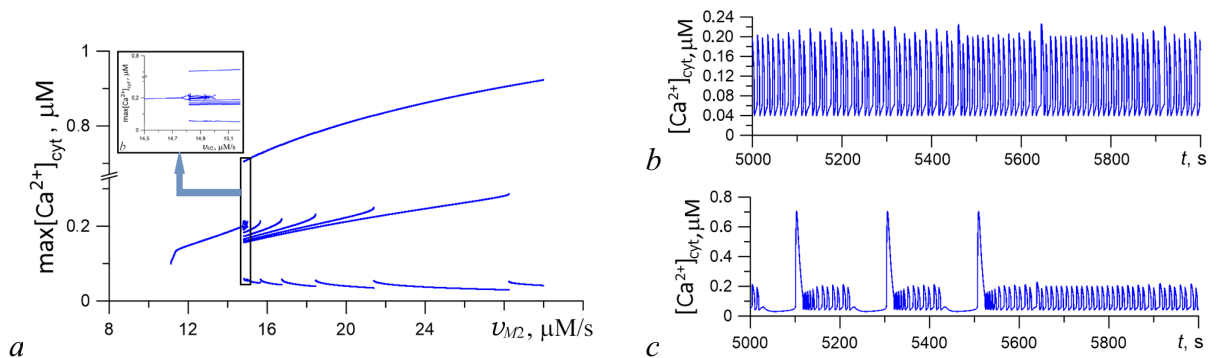


Fig. 4. *a* – Bifurcation diagrams obtained for maximal values of  $[\text{Ca}^{2+}]_{\text{cyt}}$  with the change of  $v_{M2}$ . In the inset, the enlarged part of the diagram is shown. Time traces for  $[\text{Ca}^{2+}]_{\text{cyt}}(t)$  when  $v_{M2} = 14.8177 \mu\text{M/s}$  and  $v_{M2} = 14.8179 \mu\text{M/s}$  are shown in (b) and (c), respectively.  $J_{in} = 0.05 \mu\text{M/s}$

## Conclusion

In this work, the dynamics of the astrocytic calcium concentration have been studied within the framework of the Lavrentovich–Hemkin model. The impact of the maximal flux of the calcium ions from the cytosol to endoplasmic reticulum of the cell has been analysed. The peculiarities of transition to the quiescent mode have been studied. Emergence of chaotic spontaneous calcium oscillations for specific level of calcium ions outside the cell has been revealed.

In [26], it was shown that chaos is possible in dynamics of spontaneous calcium activity. In this study, we have demonstrated that even small variation in the maximal calcium flux out of the SERCA can lead to stabilization of the spontaneous calcium dynamics: either small-amplitude periodic oscillations (for less values of  $v_{M2}$ ) or periodic oscillations with puffs (for larger values of  $v_{M2}$ ) are observed.

Since the changes in calcium concentration are able to modify the neuronal response, the conditions for emergence of spontaneous calcium oscillations, that can be chaotic, particularly, is of significance. Based on the analysis of various dynamical modes of spontaneous astrocytic chemical activity, the peculiarities in astrocyte-neuron interaction in complex multicellular systems can be further investigated. Nowadays biophysical investigations of the subcellular mechanisms of calcium signals emergence in astrocytes is required due to recently identified roles of astrocytic signalling in synaptic, neural network, and memory functions [30, 31]. Understanding the complex dynamic mechanisms of intracellular  $\text{Ca}^{2+}$  activity has remained a major challenge and will open a new therapeutic opportunities to fight against pathological and aging-induced impairments [32–34].

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