

**FREQUENCY ENCODING OF INTRACELLULAR Ca<sup>2+</sup> SIGNALS**

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**Abstract:** In a very recent theoretical study [1], we showed that simple mitochondrial kinetics, originally proposed by Marhl *et al.* [2], could be easily used as a plug-in element in other models describing intracellular Ca<sup>2+</sup> dynamics. We analysed several previously published models and showed that mitochondria could indeed maintain the constant amplitude of intracellular Ca<sup>2+</sup> oscillations very effectively. We also pointed out the importance of amplitude regulation for the frequency encoding of intracellular Ca<sup>2+</sup> signals. This paper focuses on giving a more exhaustive demonstration of this phenomenon of frequency encoding for the model of Dupont *et al.* [3].

**Keywords:** Calcium Oscillations, Frequency Encoding, Mitochondria

Oscillatory changes in free cytosolic Ca<sup>2+</sup> concentration are known as calcium oscillations, and play an important role in cell signalling. Many cellular processes, e.g. egg fertilisation or cell secretion, are regulated by agonist evoked Ca<sup>2+</sup> oscillations. Experiments show that, in a number of different cells, depending on the agonist type and its concentration, the frequency of Ca<sup>2+</sup> oscillations changes much more significantly than their amplitude, which remains almost constant [4]. This probably allows the cell to encode information in the frequency of Ca<sup>2+</sup> oscillations. This idea was already suggested in some very early papers [4]. However, until recently, experimental evidence was lacking. Now it has been shown that altering the frequency of Ca<sup>2+</sup> oscillations indeed affects several cellular processes, such as gene expression [5] and enzymatic activities [6].

A question arises about what the mechanism is which enables frequency encoding of Ca<sup>2+</sup> signals. For a particular mathematical model [2], it has been shown that Ca<sup>2+</sup> sequestration in mitochondria could be a key part of the mechanism maintaining the constant amplitudes of cytosolic Ca<sup>2+</sup> oscillations with a broad spectrum of different oscillatory frequencies. In this model, simple plausible rate laws for Ca<sup>2+</sup> fluxes across the inner mitochondrial membrane are used. Recently, we have shown that it is possible to use the same rate laws as a plug-in element in other existing mathematical models and obtain the same effect on amplitude regulation [1]. Herewith the role of mitochondria in frequency encoding is generalised, and we could argue that the amplitude of Ca<sup>2+</sup> oscillations is regulated by the sequestration of Ca<sup>2+</sup> in mitochondria, at least for those cells in which mitochondrial Ca<sup>2+</sup> uptake follows the rapid mode

mechanism (RaM) [cf. 1]. This mechanism effectively cuts off  $\text{Ca}^{2+}$  peaks at about the threshold level of  $\text{Ca}^{2+}$  uptake.

In [1], we presented bifurcation analysis for several existing mathematical models. Here, for one of those models, probably the most intensely studied mathematical model for  $\text{Ca}^{2+}$  oscillations [3], the phenomenon of frequency encoding is more exhaustively demonstrated for the case in which mitochondria are added to the original model. In Fig. 1, oscillations of free  $\text{Ca}^{2+}$  concentration in the cytosol are shown for two different values of model parameter  $b$ , reflecting two different agonist concentrations.

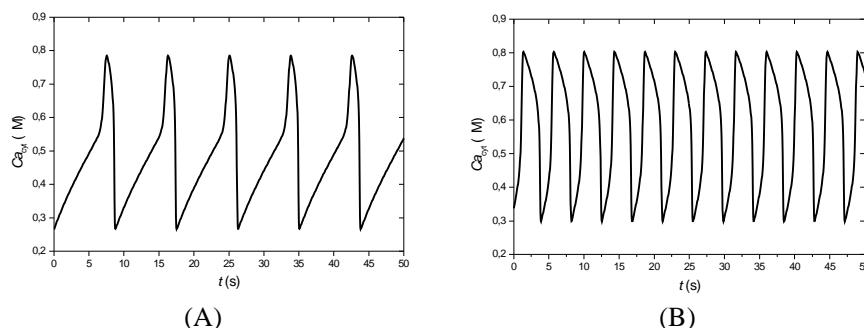


Fig. 1. Frequency encoding in the model from [3] with additional consideration of mitochondrial  $\text{Ca}^{2+}$  sequestration.  $\text{Ca}^{2+}$  oscillations are shown for two different agonist stimulations: (A)  $b=1,824$ , (B)  $b=2,45$ . For other parameter values see [3].

The results are promising and clearly suggest further experiments. The  $\text{Ca}^{2+}$  dynamics in cells which feature the RaM mechanism should be compared with those which do not. According to our calculations, the former should show a clear tendency to maintain a constant amplitude of  $\text{Ca}^{2+}$  oscillation.

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