PERSPECTIVE

Mobileular morphology digital circuits and mathematical modelling

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ABSTRACT

Application of systems biology principles using examples of neuronal dopamine signaling pathways. The model presented is based on two approaches: cell morphology electronic circuits and mathematical modeling. Transcription and phosphorylation of DARPP32 were modeled by analog circuits based on the well-known approach. Circuit applications have been shown to help receive signal vibrations similar to to those described in real biological systems. This combination, on the one hand, offers the possibility of simplifying computations, and on the other hand, the possibility of showing the dynamics of these signal paths. Considering the expected effects of changes in calcium channel function, a mathematical model of system component interactions is proposed. The average frequency of calcium current oscillations due to the presence of dopamine in the presented model is 30 Hz, which is consistent with the literature, and the frequency of such oscillations is up to tens of Hz.

INTRODUCTION

There are many approaches to accounting for cellular processes at the genetic level, extending the idea of considering a single biological sy-stem as a complex of multiple subsystems. For example, the similarities between synthetic biological circuits and electrical circuits are being actively discussed today. The operating process of electrical circuit elements simulates the natural conditioning process within a cell. Similarities have also been shown between the dynamics of biochemical reactions and the flow of electrons in a transistor. This makes it possible to expand the scope of the idea of using electronic circuits with the help of transistors. The similar electron flow of sub-threshold transistors and the similar molecular flow of chemical reactions are described by surprisingly similar log electrochemical potentials according to the Boltzmann exponential law of thermodynamics.

Therefore, cell morphology circuits help map the circuit design between the electronic and biochemical domains. Therefore, along with many similarities between different processes in cells and transistors, circuit implementations of dynamic processes of transcription and translation in living cells have been proposed. The signalling network plays a central role in the regulation of processes within a single cell and throughout the body. Dopaminergic signalling pathways were selected for the subject. Dopamine is involved in the development of certain cellular responses, such as changes in the conductance of calcium channels in neurons. It also plays an important role in ensuring cognitive activity, and lack of dopaminergic transmission is one of the causes of various cognitive disorders such as. B. Parkinson's disease. Symptoms include motor tremors, difficulty initiating behaviour, and ultimately catatonia and anhedonia.

On the other hand, when dopamine neurons are operating normally, when rewards (unexpected joy) occur, short bursts of dopamine reach the neocortex and other brain regions, and when unexpected rewards occur, activity decreases. increase. The phosphoprotein DARPP32 (dopamine and cAMP-regulated phosphoprotein, Mr 32,000 kD) plays an important biological role in dopamine-responsive neurons. A recent combination of experimental and modelling studies suggest that DARPP32 is a powerful signal integrator whose main role may be to increase the reliability of information decoding. mediated by dopamine, as well as other inputs (such as glutamate).

It is located mainly in dopaminergic endoplasmic receptacle regions and is present in virtually all medium-sized spiny neurons in the striatum. DARPP32 plays a key role in the dopaminergic signalling pathway. Regulation of the phosphorylation state of DARPP32 provides a mechanism to integrate information to dopaminoceptreceptor neurons, in several regions of the brain, via a variety of neurotransmitters, and neuromodulators, neuropeptides and steroid hormones. DARPP32 phosphorylation can be controlled by synaptic dopamine release, and the phosphoprotein is involved in the regulation and management of dopamine-induced transsynaptic effects, achieved through binding of receptors D1 with the activation of adenylyl cyclase, which induces the synthesis of cAMP. cAMP in turn activates protein kinase A through the release of catalytic subunits when cAMP levels are increased in response to dopamine signalling. The catalytic activity of adenylyl cyclase, and thus the efficiency of PKA phosphorylation, is regulated by various molecules, including G protein, that can stimulate and inhibit the activity of PKA.

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Under normal conditions, the activity of DARPP32 is dependent on the phosphorylation status at several regulatory sites, including Thr34, Thr75 and in addition Ser97, and Ser130. The phosphorylation pattern itself depends on the dynamic balance between phosphatase and protein kinase activation.

Phosphorylation at Thr34 by PKA converts DARPP32 to a protein phosphatase 1 (PP1) inhibitor, and phosphorylation at Thr75 by kinase 5 converts DARPP32 to a PKA inhibitor. It turns out that the mechanism of influence of CDK5 on the dopamine signalling pathway in neurons is closely related to the activity of coronin 1 protein, which interacts with and binds to G protein, thereby directly affecting the cAMP synthesis via adenylyl cyclase. Activation by dopamine of the D1 receptor and, therefore, of this signalling pathway increases the level of PDARPP32Thr34, which is an inhibitor of PP1, and stimulates the PKA-sensitive regulatory subunit, protein phosphatase 2A, in turn, dephosphorylate residues Thr75.Degradation of the Thr75 residue directly leads to the inhibition of PKA. Thus, in the dopaminergic signalling pathway, One of the effects of dopamine exposure and thus activation of the D1 receptor signalling pathway is an alteration in the properties of ion channels, for example, their electrical conductivity.As with existing models of DARPP32 activity, the approach is essentially the same, all chemical reactions described as protein-protein interactions or as enzymatic reactions are written as Michaelis-Menten.

CONCLUSION

Taken together, these results demonstrate the ability to relatively accurately simulate the activity of biological objects such as signalling pathways using an analogue circuit approach through cell morphological transistor-based circuit equivalents increase. With this tool, scientists can not only model some biochemical reactions but also consider more realistic simulations that include biological molecular noise, so the robust response of complex reaction networks to input signals. Can be analyzed. Based on good correlation with known experimental data, the model presented on paper based on a combination of analogue electronic circuits of cell morphology and mathematical approaches is good with data previously published in the literature. We can conclude that the correlation can give satisfactory results.