РОЗДІЛ II
Біофізика та біохімія

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Cell Biology From a Self-organization Theory Perspective

Self-organization is a universal functioning property of cellular systems. Still, due to nonlinear nature of biological entities, revealing the primary mechanisms of the process is an intricate task. Here we discuss recent progress in this respect focusing on examples from cytoskeleton, cardiomyocytes and neurons.

Key words: nonlinear system, cell, self-organization, order parameter.

Introduction. It is widely understood to date, that dynamic self-organization dominates functioning of cellular systems. A number of properties, comprising (i) continuous matter and energy exchange of cellular system with environment, (ii) pronounced nonlinearities facilitated by strong *feedback* interactions between system's elements, (iii) time hierarchy for system's variables that suggests existence of the *order parameters*, and (iv) dissipation that accompanies the system's functioning, were evidenced by experimental studies and also by very successful modeling and support the application of the dynamic self-organization concepts in formulation of Prigogine [1] in cell biology research [2–4]. It is important that nonlinear connectivity and variability within a cellular system may be a requisite for health. Breakdown of these normal nonlinear rhythms may produce «pathological rhythms», which may underlie disease states. Improved identification and recognition of such rhythms may help in diagnosing illness at an earlier stage.

The number of research papers on self-organization effects in cell biology has mounted exponentially during the last decades. This review summarizes some of the most interesting, recently reported phenomena related to cytoskeleton, cardiac myocytes, and neurons. **The study aims** to pinpoint feedback mechanisms, order parameters, and *control parameters* needed to completely define the self-organized behavior of a particular system.

Materials and Methods. In preparation for this paper, a review of the scientific literature was performed primarily by searching the PubMed database for the time period 1966 through 2017. Keywords used in the search included «complex», «nonlinear dynamics», «systems», «self-organization», «feedback», «control parameter», and «order parameter».

Results and Discussion. *Cytoskeleton*. One of the central questions in modern cell biology is how large macroscopic cellular structures are formed and maintained. It is unknown what determines the various shapes and sizes of cellular organelles, why specific structures form in particular places, and how cellular architecture is affected by function and vice versa. Recent discovery demonstrated how the size of the cells could be controlled: motor proteins walk along the microtubules, reaching the end, at which point they collectively depolymerize longer microtubules faster than shorter ones, providing feedback necessary to control the length [5].

The cytoskeleton, an organized network of filamentous proteins, is an essential component of all eukaryotic cells. It plays a major role in morphogenesis, transport, motility, and cell division. An important cytoskeletal structure in various cell types is the cortical rings formed by bundles of filaments that wrap around the cell. Such rings form within the cell cortex, a thin layer of filament network located close to the cell membrane. As a result of continuous consumption of fuel (ATP) and related active processes, dynamic patterns of filament orientation and density emerge via instabilities, leading to the formation of stationary and oscillating rings via self-organization and coherency phenomena [3]. Recent experimental and theoretical

studies of spatiotemporal dynamics of actomyosin networks exemplified nonlinear dynamical properties of cytoskeleton [6], suggesting the global alignment of filament movement as the order parameter and using actin concentrations and myosin surface densities as control parameters.

The periodic changes in the cell's shape caused by interactions within a complex network of feedbacks between the components of the cell were known for over 25 years [7]. Cells' contractility relies on a contractile complex of actin and myosin (actomyosin), in which myosin molecular motors convert chemical energy from ATP hydrolysis into forces on actin filaments. Most recent works demonstrated that periodic deformation of the shell shape could not be explained within the linear models of interaction between the components of the cell, but could be readily attributed to effects of nonlinear couplings between various dynamic modes of actomyosin networks, responsible for the cell motility. The motions of cells and organelles are highly coordinated via mechanical signaling, driven by motor proteins moving along cytoskeletal filaments. Moreover, actomyosin can self-organize and respond to mechanical stimuli through multiple types of biomechanical feedback [8].

The cells' contractility was suggested to occur above a threshold concentration of myosin motors and at a critical distance between the bundles of motors and within a window of cross-link concentration. The suggested mechanism of contraction was based on myosin filaments pulling neighboring bundles together into a cooperative, aggregated structure. The microscopic dynamic models of experimentally observed pulsatile behavior incorporated essential aspects of actomyosin self-organization: the asymmetric load response of individual filaments, the correlated motor-driven events of motor-induced filament sliding, and the complex competition of crosslinking molecules and motor filaments in the network [9].

The models developed thus far suggested various possibilities to define the order parameters that drive the system's dynamics – the number of motor proteins per cluster within a filament, free energy change for the constituents, polarization of polar filaments, and geometrical variables (e.g. a cortical layer thickness). These studies considered using the ATP, calcium, and myosin concentrations, connectivity and coupling in the network of filaments and motor proteins, as well as the asymmetry of a filament load response as control parameters that influence cytoskeleton nonlinear dynamics. A coupling between the activity of the cortical layer and calcium channels in the outer membrane, which are gated by the local stretching of the cortical layer, was also suggested as the control parameter. An increase of the extracellular calcium density inhances the actomyosin contractility in the cortical layer, providing the necessary feedback and facilitating sustained shape oscillations of the shell, see e.g. [10].

Cardiac Myocytes. Cardiac myocytes' behavior is commonly considered in terms of dynamic self-organization formalism, see e.g. [11]. Spatiotemporal calcium dynamics within the cell has been demonstrated to occur as calcium sparks, short lived calcium waves, full calcium waves, and spiral waves initiated by groups of calcium channels – calcium release units (CRUs) [11, 12]. At the whole-cell level, these sub-cellular calcium dynamics give rise to the whole-cell calcium transients (and following beats) as a response to action potential, with the transient strongly dependent on the form of the sub-cellular calcium waves [11].

Recent studies facilitated deeper insights into the mechanisms of calcium beat alternants in myocytes, demonstrating how disordered behaviors dominated by stochastic processes at the subcellular level become organized into beats alternating patterns at the whole cell level [13]. Calcium release by an individual CRU was suggested to maintain the coherent pattern of release producing macroscopic alternations of calcium release, stable against stochastic de-phasing. The coherence within individual CRU and between CRU's was found to be facilitated by local coupling through calcium diffusion or globally by interactions through the membrane voltage. This result demonstrated that the emergence of calcium alternants at the whole cell level is a strongly cooperative phenomenon mediated by the diffusive coupling of a large number of CRUs. The transition from the «no alternants» to «sustained alternants» regime represents an onset of a new ordered pattern in calcium release by the whole cell through bifurcations, a fundamental topic of dynamic self-organization in open systems far from thermodynamic equilibrium.

Theoretical descriptions of self-organized behaviors on the sub-cellular level suggested the transmembrane potential and intracellular calcium concentration as order parameters in nonlinear dynamical models. On the cellular and tissue levels, the calcium alternants amplitude and number of synchronized sparks in a single beat were used as the order parameters with a variety of control parameters – the coupling efficiency between voltage and calcium concentration, coupling between neighboring CRUs, CRU recovering rate, cell-to-cell conduction, and others.

The pathological voltage oscillations, called early after-depolarizations, have been widely observed under disease conditions in cardiac cells. Recent studies proved their bifurcation origin using Lyapunov exponents analysis and other approaches [14]. During period pacing, chaos always occurs at the transition to early after-depolarizations as the stimulation frequency decreases, providing a distinct explanation for the irregular voltage oscillations observed in experiments.

Numerous works on spiral waves propagation in cardiac tissues discussed experimental observations using the concepts of nonlinear dynamics. These features of cardiac myocytes were suggested to affect functioning of a higher-level organization system – tissues and organs [15]. The cardiac myocytes as the components of an organ alter the behavior of the heart and the heart in turn alters the behavior of the components, yet both components and the heart are integrated in a higher multi-cellular structure, the organism. Apparently, such multi-level organization with feedback supports usage of dynamic self-organization ideas to describe the system function. However, it also calls for additional experimental and theoretical studies within the systems biology paradigm, also emphasizing the importance of relating specific order parameters to biophysical properties of calcium channels currents and pumps.

Neurons and Neural Networks. Early applications of nonlinear dynamics paradigm in neuroscience targeted mainly higher organization level entities – neural networks, tissues, and the whole brain, emphasizing the feedbacks between different complexity layers [16]. Accumulation of experimental data and further theoretical developments facilitated deeper understanding of self-organization properties of neurons, synapses, and neural networks, which we analyze briefly below.

Multiple experimental and theoretical works proved nonlinear dynamic behavior of single neurons (e.g. [17] for review). In response to external stimuli, neurons generate electrical spikes and chemical signals, switching between different functional modes (attractors), showing bistability, multistability, oscillations, and chaotic behavior. Such switching between attractors is a typical dynamic self-organization process for a system far from thermodynamic equilibrium. Various mathematical models were applied to describe such emergent properties, allowing additional prediction of important functional details in neurons.

As an example, the models derived from Hodgkin-Huxsley approach [18] demonstrated the onset of mutistability, oscillations, bursting, and deterministic chaos using the gating variables describing the mean fraction of open gates of the sodium and potassium channels as the order parameters [19]. The models used ion concentrations, transient input stimuli, coupling strength of the dendrite internal feedback connection, and the feedback time delay as control parameters that switch the neuron between attractors. Using Lyapunov exponents analysis of the chaotic neuron model, the internal state of the neuron – the generalized structural variable – was suggested as the order parameter to model the onset of deterministic chaos, using the strength of the refractoriness and external stimuli as control parameters.

Complex functional properties have been proven for the components of a neuron, calling for application of nonlinear dynamics models on the lower organization level entities, see works on dynamics of dendritic spines [20], dendritic branch-specific plasticity [21], and vesicle transport dynamics [22].

Synapses are the macromolecular structures responsible for transmitting electrical or chemical signals between neurons. The first description by Hebb proposed a basic mechanism for synaptic plasticity, suggesting the imperative role of repeated interactions between neurons to accumulate and increase synaptic efficacy [23]. Such accumulation occurs through a versatile network of feedbacks acting on largely different time scales within a synapse, thereby suggesting the slaving principle and providing prerequisites for dynamic self-organization.

Synapses reveal complex dynamics that depend on the frequency and timing of presynaptic spike firing, dendtritic spine dynamics, intracellular signaling, and other factors (e.g. [24, 25]). Most recent biologically relevant models of synaptic plasticity emphasize their nonlinear dynamical behavior. One of the nonlinear models introduced the mechanism that adjusts the synaptic coupling to the neural activity through spike timing-dependent plasticity, allowing the synaptic strength to be either facilitated or depressed depending on the order of the spikes of pre- and post-synaptic neurons [26].

Synaptic strength was shown to depend on a crosstalk coming from neighboring synapses. The crosstalk may be due to various factors, e.g. dendritic diffusion of calcium or other intracellular diffusion processes, creating bifurcations in developmental synaptic plasticity and tending to destroy it. The related nonlinear dynamic models revealed switching to emergent functioning modes – oscillations or other attractors [27]. Some studies showed, however, that the crosstalk might facilitate synaptic strength leading to self-organization of the synaptic connectivity. At an optimal crosstalk level, the amount of synaptic coupling

gets maximal in a resonance-like manner preserving the existing level of collective dynamics in the brain by neutralizing the impact of random perturbations [28]. The corresponding nonlinear dynamic models used synaptic strength and synchronization parameter that characterized the phase difference of firing neurons as the order parameters, with the magnitude of a random synaptic input (crosstalk) as one of the control parameters.

Multiple studies indicated that a cooperative amplification of the synaptic efficiency by dentritic spines promotes nonlinear dendritic processing and associated forms of plasticity and storage, thus fundamentally enhancing the computational capabilities of neurons [29]. The sign of synaptic plasticity was shown to be regulated by the action potential feedback to the synapse, thereby providing a mechanism for associative learning through a nonlinear dynamic mechanism [30].

Neural networks are multifunctional – they transduce sensory information, recover hidden signals, and generate new information. Researchers unanimously agree that neural networks function as self-organized systems far from the thermodynamic equilibrium. Below we will analyze only a few representative examples to demonstrate important features of biologically relevant nonlinear dynamic models.

Self-organization in neural networks relies on feedback processes that optimize biologic functions by correlating firing of groups of neurons to strengthen or modify synaptic connections between them, while the strengthened connections will in turn amplify the correlated firing of the neurons. Multiple experimental and theoretical studies explored nonlinear dynamic behaviors in groups and networks of neurons, confirming typical self-organized properties of their functioning like cell self-assembly, formation of standing patterns and other spatial structures, population bursts, consolidation of the synaptic changes, deterministic chaos, oscillating and propagating waves in synaptically-coupled networks, etc., as well as analyzing conditions of switching between different regimes of functioning (see e.g. [31] and references therein).

Successful models for excitatory and inhibitory neural networks were developed showing multi-stability onset with oscillations, spiral waves, and chaos. These models used the portion of cells receiving at least threshold excitation and average activity level of neuronal population as the order parameters [32]. The control parameters included the external stimulus intensity, proportion of firing inhibitory cell, synaptic firing rate, and number of synaptic connections.

Most of the models based on the chaotic neural networks used Lyapunov exponents and metric entropy analysis to explore the onset and properties of deterministic chaos and other dynamic regimes in neural networks, see for example [33].

The «self-organizing recurrent network» introduced recently combines several distinct forms of (nonlinear) synaptic plasticity to explore spatio-temporal patterns that mimic the properties of the biological systems [34]. It was shown that all of the analyzed plasticity mechanisms were essential for the onset of emergent properties through self-organization. The model produced bursts, oscillations, steady-state operation dependently on connections and switching of synaptic activities. The fraction of active excitatory neurons was chosen as the order parameter, with the synaptic strength and extent of connections between cells as the control parameters.

Other Examples at Cell and Tissue Levels. Multiple studies confirmed that the dynamic properties of cellular structures are consistent with a role for self-organization in their formation, maintenance, and function; therefore, self-organization is considered to be a general principle in tissue organization and function [4].

Meiotic nuclear oscillations crucial for proper chromosome pairing and recombination in yeast cells [35] as well as cellular biochemical processes responsible for e.g. self-regulating gene networks and phosphorylation-dephosphorylation signaling [36] were also widely discussed within the concept of dynamic self-organization in far from thermodynamic equilibrium systems with feedback.

Conclusions and Further Perspectives. Considerable progress in experimental and theoretical studies achieved during the last decades provides an additional motivation for development of realistic self-organization models in cell biology. Future work will focus on the improved definition of order parameters through multiple local interactions in cellular structures. The impact of widely different time scales of system dynamics on order parameters will receive special attention. Another topic of interest will be coordinated study of physiologically relevant models, which may favor a deeper understanding of the state and development of diseases and thereby provide powerful tools for healthcare research and medicine

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Гуща Тетяна, Гуща Олександр. Клітинна біологія з погляду теорії самоорганізації. Самоорганізацію визнано універсальною властивістю, яка притаманна відкритим системам, зокрема біологічним об'єктам і живим організмам. Потік енергії або речовини, що протікає через систему, унаслідок кооперативної взаємодії її складників, спричинює перехід системи до нового впорядкованого стану. Система функціонує в стані, далекому від термодинамічної рівноваги, а переходи між станами описуються за допомогою нелінійних моделей. Аналіз такої поведінки дає підставу зібрати корисну інформацію про емерджентні властивості певної системи, що, як правило, неможливо зробити іншими засобами. У цьому огляді зібрано деякі найбільш цікаві з недавно опублікованих явищ, пов'язаних із динамічною самоорганізацією в клітинній біології. Основну увагу приділено процесам, які відбуваються в цитоскелеті, кардіоміоцитах та нейронах. Проаналізовано механізми зворотного зв'язку, контролюючі параметри й параметри порядку, необхідні для повної характеристики самоорганізованої поведінки кожної системи.

Ключові слова: нелінійна система, клітина, самоорганізація, параметр порядку.

Гуща Татьяна, Гуща Александр. Клеточная биология с точки зрения теории самоорганизации. Самоорганизация признана универсальным свойством, присущим открытым системам, в частности биологическим объектам и живым организмам. Поток энергии или вещества, протекающий через систему, вследствие кооперативного взаимодействия ее составляющих, приводит к переходу системы в новое упорядоченное состояние. Система функционирует в состоянии, далеком от термодинамического равновесия, а переходы между состояниями описываются с помощью нелинейных моделей. Анализ такого поведения позволяет собрать полезную информацию об эмерджентных свойствах определенной системы, чего, как правило, невозможно достигнуть другими способами. В этом обзоре собраны некоторые наиболее интересные из недавно опубликованных явлений, связанных с динамической самоорганизацией в клеточной биологии. Особое внимание уделяется процессам, протекающим в цитоскелете, кардиомиоцитах и нейронах. Проанализированы механизмы обратной связи, контролирующие параметры и параметры порядка, необходимые для полной характеристики самоорганизованного поведения каждой из систем.

Ключевые слова: нелинейная система, клетка, самоорганизация, параметр порядка.

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Вищі карбонові кислоти олії насіння чорниці звичайної (*Vaccinium myrtillus* L.)

Із насіння чорниці звичайної (V*accinium myrtillus* L.) методом вичерпної екстракції *н*-гексаном отримано олію світло-жовтого кольору з показником заломлення 1,4742. Вихід станвить 18 %.