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SIGNAL CASCADES IN NANO-NETWORKS *)

Summary. Signal transduction executed in the signal cascades is the common term used to define a divers biochemical mechanisms that regulate processes in the nano-networks. In the paper, basing on a selected biological examples, the properties of signal cascades in the nano-networks are discussed.

Keywords: nanotechnology, nano-networks, Petri nets, signal cascade, signal transduction.

KASKADY SYGNAŁOWE W NANOSIECIACH

Streszczenie. Translokacja sygnału zachodząca w kaskadach sygnałowych jest terminem określającym szereg mechanizmów biochemicznych regulujących procesy w izolowanych nanosieciach stymulowanych molekularnymi sygnałami otaczającego środowiska. W pracy, bazując na wybranych przykładach biologicznych, przedyskutowano właściwości kaskad sygnałowych w nanosieciach.

Słowa kluczowe: kaskada sygnałowa, translokacja sygnału, nanotechnologia, nanosieci, sieci Petri.

1. Introduction

Nanotechnology is in a very early stage of development. Besides few examples, development of commercial nanotechnology-based products will most likely be possible in next several years. Therefore, it should come as no surprise that the first approach to implement the nano-processes would be coping biocompatible standards in design and implementation phase of such nano-processes. Those processes can be performed in a closed area of space

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containing proper quantities of substrates and a set of molecules working in a predefined manner determined by their chemical construction, including changes of chemical activity reached usually by the conformational changes. These molecules play a role of a control system, which is stimulated by external signal molecules (and of course performing homeostatic functions) coming from outside of the closed area of space to its surface, fulfilling the function of nano-process border. The molecular control system performs its control tasks in fixed cycles of transformations called signal cascades. We shall call this kind of system performing nano-process a nano-netwoks. In determined conditions, the selected substrates (inorganic ions and most of metabolites e.g. sugars, amino acids, and nucleotides) and final products can penetrate through the border of the process. Excluding selected ions fulfilling the control functions in the signal cascades, the external stimulating signal molecules only activate the receptors placed in the border of a nano-network. The process of internal transformations and conversions of control molecules in signal cascades expressed as a control of nano-processes in a nano-network, is called a signal transduction.

The paper discusses the properties of signal cascades in the nano-networks based on selected biological examples [1, 2, 3, 4, 5].

2. Problem Formulation

Generally, we can talk about wide area and local nano-networks. In living organisms, an electro-chemical net (e.g. nervous system) and extracellular communication net (e.g. immune and hormone systems), represent nano-networks [6]. A cell represents a local area nano-network. One of the most natural (but not simple) approach to build the local nano-network performing a desired production process, which can be modified through the external control, is exploitation of a living cell. The fundamental condition, which have to be fulfilled for the cell, is an assurance of survival requirements. The control needs stimulation of inputs of the signal cascades in a cell from its environment. The signal cascades existing in the different type of cells for selected processes, can be retrieved from the biochemical research available in the databases. Finally, we can determine a sequence of stimuli signals for desired process. As an illustration, we will briefly discuss the signal cascades in the process of translation [9], which can be used for selected proteins production (Fig. 1).

The translation process takes place in a ribosome structure (complex of subunits 40S and 60S rRNA) in presence of at least one kind of tRNA and activating enzyme for each amino acid, along the mRNA chain. Protein synthesis takes place in initiation, elongation, and termination stages. The *initiation stage* results in connecting of the initiator tRNA to the start signal in mRNA. The *termination stage* takes place when a stop signal in the mRNA is read

by the protein release factor. Each nucleotide triplet, or codon, in mRNA chain encodes a specific amino acid. In the *elongation stage*, each molecule of tRNA binds only the amino acid proper to a particular codon, and tRNA recognize a codon by means of a complementary nucleotide sequence named anticodon. The movement of the ribosome to the next codon is powered by the hydrolysis of GTP. When the termination stage occurs, a completed polypeptide is released from the ribosome [5, 7].

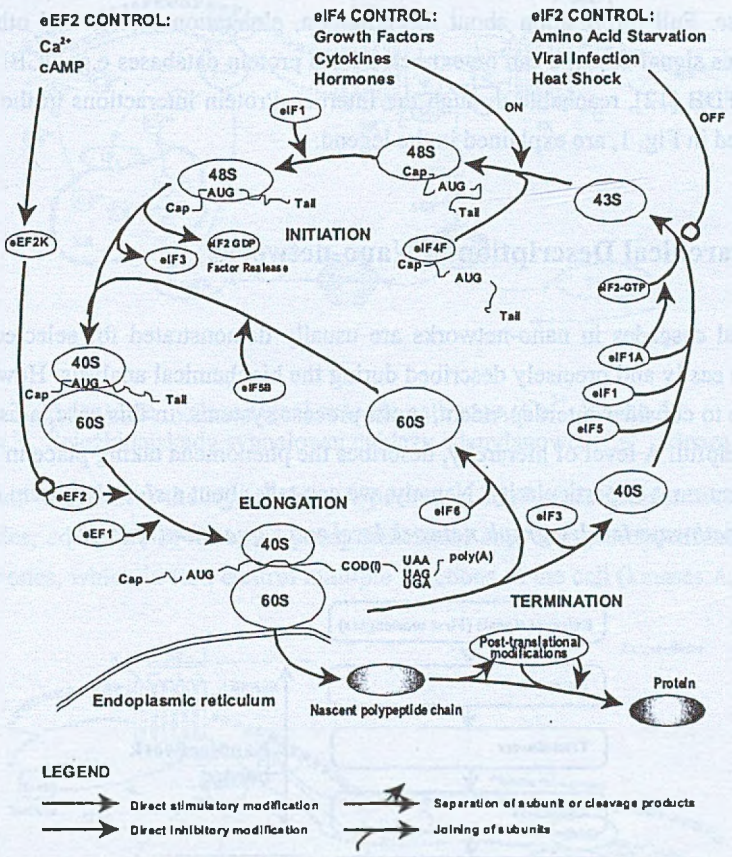

Fig. 1. The signal cascade in a nano-network (translation control)
Rys. 1. Kaskada sygnałowa w nanosieci (sterowanie translacją)

Next, the processes of modifications after translation take place [8]. Synthesis of a new protein is highly controlled process that allows rapid cellular responses to diverse stimuli [9, 10]. Initiation of protein synthesis begins after a separation of the ribosome into its 40S and 60S subunits. Different eukaryotic initiation factors (eIFs) represented by protein molecules, catalyze the assembly of a functional ribosomal complex including the 40S subunit, mRNA and tRNA. Cap-binding proteins bind the cap of mRNA (Fig. 1). They are joined by eIF4F

factor, which finds the AUG codon closest to the 5' end [5] of mRNA. Symbol Tail in Fig. 1, denotes sequence of codons COD(i) ended with the stop code (UAA, UAG, or UGA codons) with following few hundreds of A (adenosine nucleotide in mRNA) – poly(A). Finally the 60S subunit before the first peptide bond is formed. Most regulatory stimuli, such as growth factors and heat shock, control steps of the initiation process by either stimulating or inhibiting specific eIFs. Elevated levels of Ca^{2+} ions or cAMP (cyclic adenosine monophosphate) can also attenuate translation by blocking the action of elongation factor eEF2 through the eEF2K kinase. Full information about the initiation, elongation factors and other proteins existing in this signal cascade can be extracted from protein databases e.g. NCBI EntrezProtein [11] or PDB [12], reachable through the Internet. Protein interactions in the signal cascade presented in Fig. 1, are explained in the legend.

3. Hierarchical Description of Nano-networks

The signal cascades in nano-networks are usually demonstrated for selected processes which can be easily and precisely described during the biochemical analysis. However, in realty, we have to consider interdependent, multi-process systems. In this case, a use of hierarchy can be helpful. A level of hierarchy, describes the phenomena taking place in the process with a different rank of particularity. Namely, we can talk about a ***signals system level***, a ***signal cascade pathways level***, a ***graph network level*** and a ***quantitative level.***

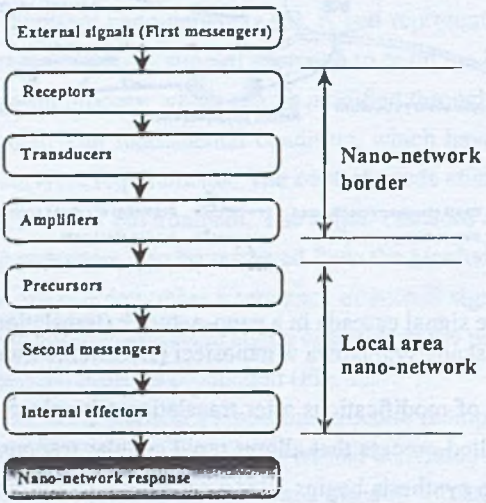

Fig. 2. Signals system level in a local nano-network
Rys. 2. Poziom sygnałów systemu w lokalnej nanosieci

In Fig. 2 the ***signals system level*** for the local nano-network is presented. First messengers are the external signal molecules arriving at receptor molecules on the border of a nano-network (plasma membrane of the cell). Second messengers are signal molecules in the interior of the local nano-network (e.g. in the cell, these are: cyclic adenosine monophosphate – cAMP, diaglycerol – DAG or inositol triphosphate – IP_3).

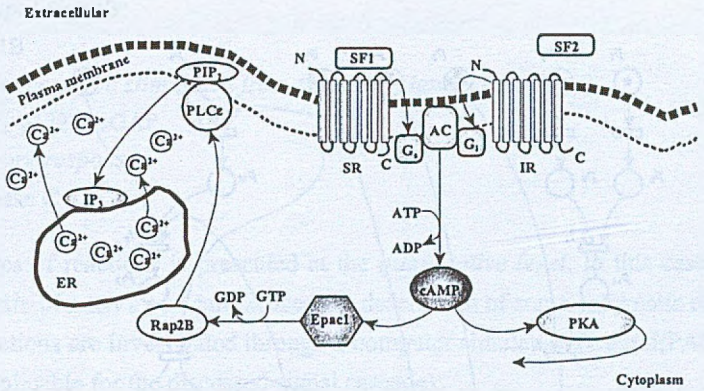

Fig. 3. Adenylate cyclase signal cascade pathways (Ca^{2+}, kinase A)
Rys. 3. Ścieżki kaskady sygnałowej cyklazy adenylanowej (Ca^{2+}, kinaza A)

Figs. 3 and 4, illustrate the ***signal cascade pathways level***, presented for two fundamental cell's cascades; adenylate cyclase and phosphoinositide converting extracellular signals into intracellular ones, which in turn control multiple functions of the cell (kinases A, C, and ions Ca^{2+}).

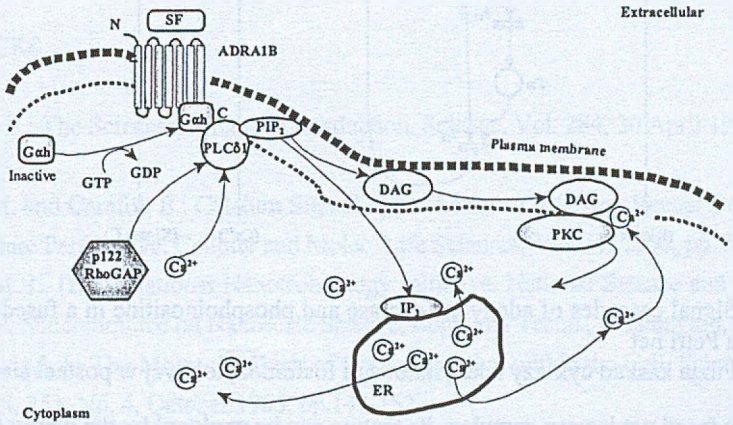

Fig. 4. Phosphoinosidite signal cascade pathways (Ca^{2+}, kinase C)
Rys. 4. Ścieżki kaskady sygnałowej fosfoinozytolu (Ca^{2+}, kinaza C)

The signal cascade pathways shown in Figs. 3 and 4 are described in [14, 15].

The signal cascades from Figs. 3 and 4 are fused in Fig 5, representing the ***graph network level***, in a form of extended Petri net [13]. Places are expressed by circles, transitions by bars, inhibitor arcs have small circles instead of arrows, the initial marking is represented by dots inside circles, and the firing rate and choice functions are given as additional descriptions of transitions resulting from Figs. 3 and 4.

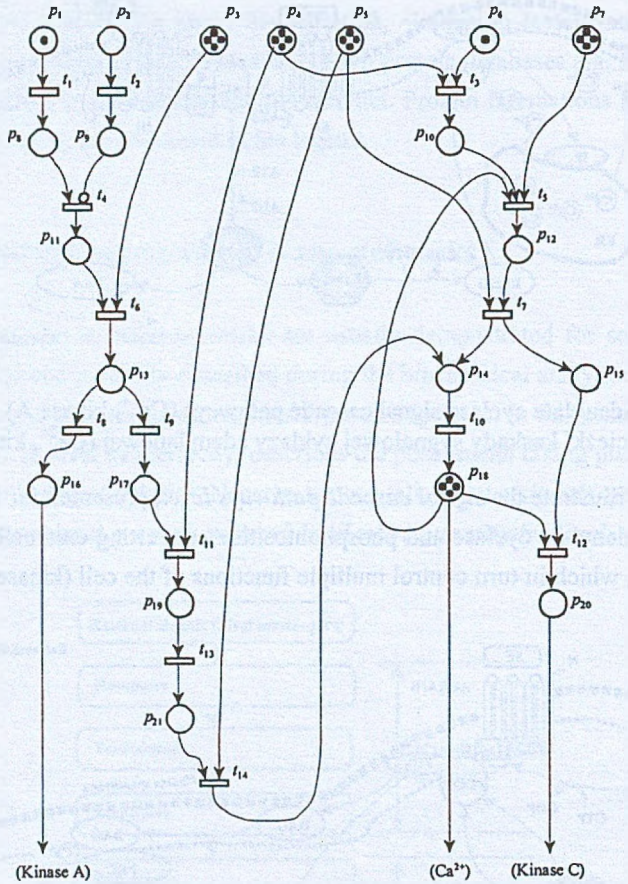

Fig. 5. Signal cascades of adenylate cyclase and phosphoinositide in a fused form of a Petri net

Rys. 5. Fuzja kaskad cyklazy adenylanowej i fosfoinozytolowej w postaci sieci Petri

When the fused net is very complex, its feature can be explored by the theory of Petri nets or analyzed by a computer program. In the signal cascades analysis, the liveness of a net is critical, because the dead branches or deadlock can degrade the functionality of the considered signal cascades [13].

Symbols in Fig. 5 correspond to the symbols from Figs. 3 and 4 in a following manner:

places:

p_1 – SR, p_2 – IR, p_3 – ATP, p_4 – GTP, p_5 – PIP_2, p_6 – ADRA1B,
p_7 – p122RhoGAP, p_8 – G_s, p_9 – G_i, p_{10} – Gαh, p_{11} – AC,
p_{12} – PLCδ1, p_{13} – cAMP, p_{14} – IP_3, p_{15} – DAG, p_{16} – PKA, p_{17} – PIP_2,
p_{18} – Ca^{2+}, p_{19} – Rap28, p_{20} – PKC, p_{21} – PLCε.

external input signals:

SR, IR, ADRA1B

signals, that could be stimulated from the other signal cascades:

ATP, GTP, PIP_2, p122RhoGAP

nano-network response:

Kinase A, Kinase C, Ca^{2+}.

The kinetics of reactions is presented at the ***quantitative level***. In this case, the models like of Michaelis-Menten's one can be used for description of some enzymatic reactions. The composite reactions are investigated through a computer simulation (e.g. GEPASI 3 program [16], if it is applicable for the discussed signal cascade).

4. Conclusions

The paper presents selected paradigms for the analysis of signal cascades in nano-networks, with emphasis on the fusion of few cascades.

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Streszczenie

W pracy przedstawiono zagadnienia translokacji sygnałów, występujące w kaskadach sygnałowych w izolowanych nanosieciach stymulowanych molekularnymi sygnałami otaczającego środowiska (rys. 2). Bazując na wybranych przykładach biologicznych (rys. 3 i 4), przedyskutowano niektóre właściwości złożonych kaskad.

Adres

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