

# Molecular Synergy in the Nano-networks

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## ABSTRACT

The heterogeneity of technology in the products or object fabrication system, where the external control system usually is based on silicon technology, the interface e.g. transducers or robots represents mixed technology, and the controlled process another, leads to the material and energy losses, and the waste production. Surprisingly high effectiveness of objects creation can be reached in homogeneous processes with internal control, namely molecular. The paper discusses the systems where the molecular programs in cooperation with intermolecular modifiers create the molecular objects which, may have a new behavioral properties. This is caused by a specific molecular synergy observed in the nanoprocesses running inside the molecular nano-networks.

**Keywords:** molecular nanotechnology, nano-networks, signal cascades, simulation, synergy

## 1 INTRODUCTION

Among a different implementations of molecular nanotechnology in the molecular products and object fabrication like a manipulation with atoms or classical chemical reactions, these kind of molecular process can be classified as a processes with external control [10, 16, 18]. These processes are characterized by heterogeneity of technologies of the whole system. The control part of the production system usually is based on silicon technology, the interface e.g. converters, transducers or robots (in mobile cases) represents mixed technology, and the process itself an another technology. This non-homogeneity leads to the material and energy losses, the low reliability, and the waste production.

Surprisingly high effectiveness of object creation can be reached in the homogeneous processes with internal control where the control programs use the same technology as the products obtained, namely molecular. In these molecular nanotechnology the set of individual processes is performed in a closed spaces surrounded by the borders (permeable for reaction substrates) of nanoprocess forming a specific nano-network (Fig. 1). The molecular programs create the molecular objects through the molecular interface which, together, have greater effect than the sum of their individual effects, this means that not only the main goal of the system is fulfilled i.e. the desired product or objects creation but also the new behavioral forms like a function modification, amplification, self-organization, self-replication [19, 28] and self-destruction (similar to apoptosis in biological systems) of the nanoprocess can be activated with a possibility of future reuse of broken elements.

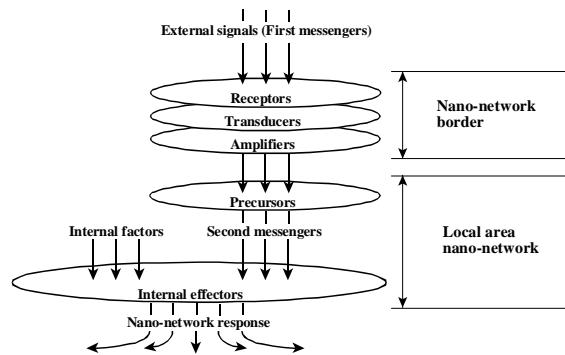


Figure 1: Signals system levels in a local nano-network

This is caused by a specific molecular synergy of nanoprocesses because of the direct contacts between the programs execution, modification elements and products in the same environment possible.

The characteristic elements of *{information processing}/{object generation}* in the selected track of nanoprocess (the pattern after the living cell) is presented in Fig. 2.

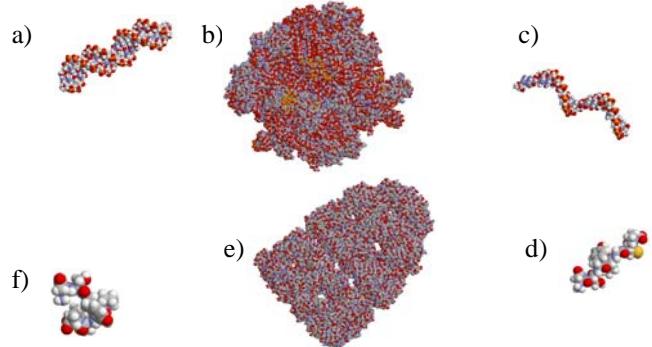


Figure 2: Elements of nanoprocess (the scales are different): a) a molecular program, b) and c) the molecular tools, d) molecular intermediate product, e) molecular modifier, f) the final molecular product.

Presented in Fig. 2 the track of modified molecule creation (Fig. 2f) consists a molecular program (a), the tools (b and c), an intermediate product (d), a modifier (e), and a final product (f). In this biological example the main elements represent the basic points of the protein translation process (the protein production track).

The molecular program determining the linear chain of e.g. seven amino acids:

asn – ser – tyr – pro – gly – cys – pro

expected in the desired polypeptide is coded in DNA double helix molecule (a). As a result of transcription, the molecule of mRNA strand (c) is created as a complementary to its DNA template getting the following form:

5' – AAUAGGUUAUCCUGGUUGUCCU – 3'

where 5' and 3' denote the ends of strand determining direction of the molecule of polypeptide elongation in the molecule of ribosome (b) [2]. The mRNA helix, which establishes the “gluey matrix” [26] in cooperation with ribosome concentrates and integrates freely moving molecules of amino acids forming the needed intermediate molecule (d). In the last stage, the molecule of chaperonin (e) in the post-translational modification process helps the intermediate polypeptide molecule to get the properly folded shape forming the desired conformation of product. This “gluey matrix” approach, in parallel with self-replication and self-organization are basis for the systems of informatics of the direct materials nano-fabrication [27].

In this simplified view of protein creation at least in two points the synergy of acting jointly molecules is evident, firstly, when the program (a) is translated into cooperating tools (b and c), and secondly, when the intermediate shape of molecule (d) is converted into the desired final conformation (f). This is possible when we state the existence of molecular information networks including signal transduction cascades, metabolic pathways, and a regulation of particular part of molecular program execution (gene expression) [1, 3, 4, 6, 7, 17, 25]. Biochemical style of a signal dependencies in particular cascades [4] is presented in Fig. 3.

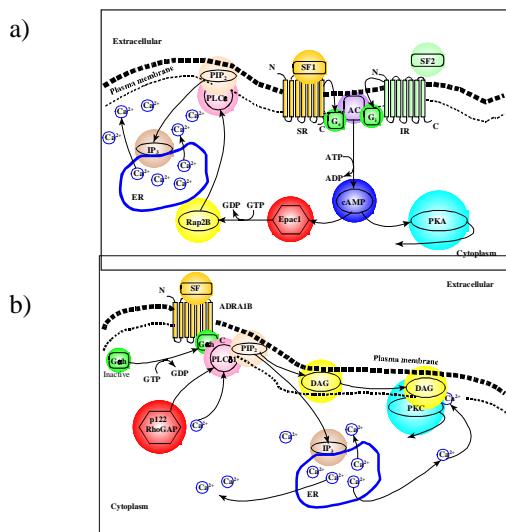


Figure 3: Exemplary signal cascade pathways: a) adenylate cyclase signal cascade pathways ( $\text{Ca}^{2+}$ , kinase A), b) phosphoinositide signal cascade pathways ( $\text{Ca}^{2+}$ , kinase C).

## 2 MOLECULAR RECURSION INSIDE THE NANOPROCESSES

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 the wide area nano-networks. 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 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 nanoprocess.

One of the most promising and exciting property of nanoprocesses (different from heterogeneity of the classic production system based on computer control) is possibility to modify the control molecular program from the body of the function created and performed on the basis of this exactly control program basing on homogeneity of nanoprocesses. This is in general recursion performed in hardware, the process leading to the models of processing in the informatics systems which can be different from classically understood, leading to the material and objects production directly from stored data.

## 3 MODIFICATIONS OF CONFORMATION IN NANO-NETWORKS

An example of synergy in the intermolecular interactions are the processes of modifications in the translation process of polypeptides. The final properties of formed polypeptide depend on molecule conformation. However, in many cases this desired conformation can not be reached before the proper modifications of the nascent polypeptide take place. These modifications are performed directly by the other molecule or indirectly through the environment parameters changes caused by influence of signal cascades in the nanoprocess. The direct interaction as early as in nascent phase of polypeptide creation is interaction between ribosome and nascent polypeptide chain when the initial part of chain is fixed in ribosome. Similar situation takes place when we observe the chaperone or chaperonine-mediated partially or improperly folded polypeptide chain [15, 23, 29]. These interactions do not change the configuration of chain, only change the conformation. The other group of direct interactions changes chemical structure of the chain through the covalence modifications, disrupting non covalent bonds (e.g. hydrogen bonds) or cleavage of polypeptide chain. The activities of many polypeptides (or proteins) are indirectly modulated by the environment pH changes through protonation of histidine side chains [15, 31].

The polypeptide forms a chain of the molecules of residues connected together through peptide bonds constituting a rotational bonds determined by the set of torsion angles [14]  $\phi$  (rotation around the nitrogen- $\alpha$ -carbon bond), and  $\psi$  (rotation around the  $\alpha$ -carbon-carbon bond in the chain of the polypeptide). The force powered the conformation changes, is a tendency of the chain of polypeptide to get minimal conformational energy [9, 31]. Basing on simulation we'll illustrate selected modifications of the polypeptide chain conformations caused by intermolecular interactions.

## 4 NUMERICAL EXAMPLES

In the numerical examples we apply the new, non-gradient, two-phase sequential algorithm for simulation of the conformation changes in case of nascent polypeptide folding, the cleavage of formed polypeptide chain, a protonation of histidine side chain [30] and a switching effects of phosphorylation process. The basic assumption for the construction of simulation algorithm is an observation, that the new amino acid appearing from the ribosome rotates the existing chain of amino acids in a such manner, that the torsion angles on the new peptide bond, accordingly with minimization of potential energy of the structure *{new amino acid}/{existing amino acid chain}* are determined, and next, the conformation of the whole structure is somewhat modified to minimize the potential energy of *{new existing amino acid chain}*. In the Initialization and First Phase of simulation the search for energy decreasing is performed in the discretized, allowed ranges of torsion angles for glycine, proline and all 18 remaining amino acids specifically, predicted as modified Ramachandran plots[22] based on X-ray crystallography [11]. In the Second Phase of simulation during the chain “shaking” process, only the generated torsion angles which remain in the allowed ranges are used. The energy computations apply the AMBER (*Assisted Model Building with Energy Refinement*) force field and the Tinker subroutines [21].

### 4.1 Nascent Folding

An illustration of nascent polypeptide folding when leaves the ribosome molecule are the intermediate and final results in simulation of elongation process and conformational changes of the small protein containing thirty eight amino acids:

asn – ser – tyr – pro – gly – cys – pro – ser – ser – tyr – asp – gly – tyr – cys – leu – asn – gly – gly – val – cys – met – his – ile – glu – ser – leu – asp – ser – tyr – thr – cys – asn – cys – val – ile – gly – tyr – ser.

The initialization phase of simulation based on the minimization of conformational energy, gives the dipeptide *asn-ser* with four torsion angles. After processing [30] the conformation of dipeptide and the set of torsion angles is the initial condition for the next steps of elongation. When the third amino acid appears i.e. tyrosine, in the first phase of simulation for the elongated tripeptide the minimization of tyrosine torsion angles takes place with remaining angles unchanged. Continuing this process, the eight amino acids chain obtains the conformation after the first and second phase of simulation presented in Fig. 4. Finally, the whole 38 amino acids chain adopts the conformation after first and second phase of simulation presented in Fig. 5.

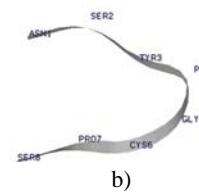
### 4.2 Cleavage of Chain

The cleavage mechanism performed by other molecule is an irreversible process of cutting of the long peptide sequences into sub-chains with the basically different properties than the sub-chains inside the origin. The reason is the switching of its conformations to the new shapes.

The interesting observation can be do refer to the conformations of the same polypeptide sub-chain during the elongation phase and post-translational modifications namely cleavage of the main chain.

asn	-61.000	-74.000
ser	-146.000	108.000
tyr	-163.000	127.000
pro	-47.000	114.000
gly	132.000	-153.000
cys	-116.000	92.000
pro	-86.000	171.000
ser	-122.000	135.000

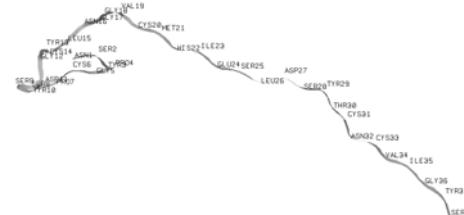
a)



b)

Figure 4: Final conformation of eight amino acids nascent protein after the second phase of simulation: a) torsion angles, b) backbone of molecule (spacefill visual representation [24]).

In Fig. 6 the conformation of the initial eight amino acids cleaved from the whole chain has been presented. Comparing this conformation with the conformations of the same sub-chain of polypeptide in elongation phase (Fig. 4b) we see the difference in the spatial nanostructures’ shapes. It suggests that the folding process of polypeptide depends on the sequence of external intermolecular events preceding the final conformation (no global minimization).



energetic optimal and the torsion angles are (symbol PB denotes the peptide bond):

$$(-63.0^\circ, 154.0^\circ)_{\text{his}} \rightarrow \text{PB} \rightarrow (-115.0^\circ, 112.0^\circ)_{\text{cys}},$$

and

$$(-61.0^\circ, 143.0^\circ)_{\text{his}} \rightarrow \text{PB} \rightarrow (-145.0^\circ, 145.0^\circ)_{\text{cys}}.$$

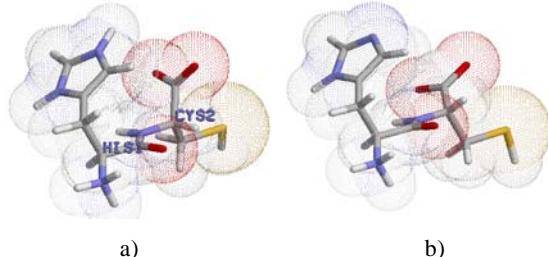


Figure 7: Protonation – change of the charge of histidine side chain: a) pH 5.8, b) pH 7.8.

#### 4.4 Reversible Covalent Modification

The functional properties of many proteins are switched by the most common process of reversible covalent modification i.e. phosphorylation performed by the covalent attachment of phosphoryl groups to the specific amino acids (e.g. threonine, serine) residues in the phosphorylated protein. The activation (the specific conformation forcing of the phosphorylated protein) is catalyzed by the protein kinases (on) and on the other hand, the protein phosphatases remove the effects of kinases (off) by the catalyzing the hydrolysis process of phosphoryl groups attached to the chain of amino acids.

As an example of phosphorylation process forcing the conformation switching [5], in Fig. 8 the results of conformation changes in the middle part of the selected protein (in this case the human CDK2 kinase, ID: 1B38 protein in the DataBase – (PDB, 2006)) before (Fig. 8a) and after phosphorylation (Fig. 8b) are presented. In this case, the threonine residue is a central point of phosphorylation (Fig. 8 presents the extraction of the middle seven amino acids from the whole chain in the ATP complex) leading to the CDK2 protein change of activity.

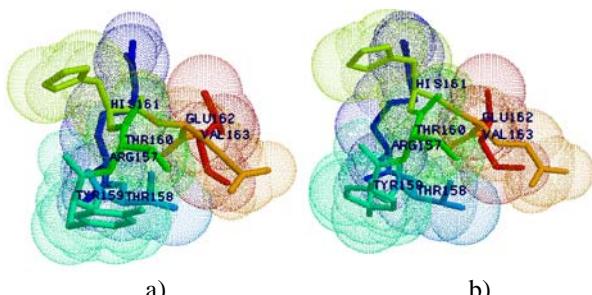


Figure 8: Phosphorylation: a) sticks representation with the van der Waal's dot surfaces of the conformation in a middle part (residues 157-163) of the non-phosphorylated CDK2 (the threonine 160 in the center of view), b) the same view of CDK2 in a middle part of the amino acids chain (residues 157-163) presenting the results of phosphorylation of threonine 160 on the conformation switching of the whole CDK2 structure.

## 5 CONCLUSIONS

Basing on a few selected numerical examples of intermolecular interactions (for biomolecules): ribosome/nascent polypeptide, cutting the polypeptide, protonation caused by environment pH, and phosphorylation, the paper presents characteristic feature of synergy in the molecular processes observed in the signal cascades of the nano-networks.

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