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Biocomputing system of living cells

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Abstract

The aim of this paper [1] is to show that the process of gene transcription can be represented as a finite automaton illustrating the processing of input/output signals in living cells at DNA level. It is proved that the expression regulation process of λ-phage genes cI and cro represents a molecular-genetic trigger (MGT) which is a self-organizing structure with two stable states. It is shown that MGT can be described as a finite automaton fulfilling logical function $NOT\ AND$. A living cell can be represented as DNA-based molecular-genetic machine which has the following characteristics: input, output, transition states, language of computation, predetermined genetic program, memory and energy source.

We propose a formal model of biocomputing system (having depth two) that consists of three *E.coli* bacterium cell cultures. This model corresponding to an elementary logical scheme can solve a class of formula in the conjunctive normal form (like formula (1)).

Introduction

The phenomenon of self-organization in physical, chemical and biological systems is intensively investigated during the last decades. This scientific direction named also "Synergetics" studies the processes of self - organizing of time, spatial, time-spatial and functional structures in cooperative systems [1, 2].

From synergetic point of view an information system must have some special properties. In order that the system contains the information it is necessary that it should be multistationary. It might exist

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in several stationary states, some of them being stable. At least an information system should be bistable, i.e. it should have two stable states (attractors) [2].

Each cell possesses a set of possible functioning alternative regimes (stable states). A cell functions only in one of them in every moment. The switching from one stable state to another one can hold as a response to internal and external factors: UV radiation, pH, temperature, concentrations of specific molecules, etc. These stimuli can be considered as input signals.

We note that the trigger models describe adequate one of significant properties of biological system – their ability to switch from one functioning regime to another one. The self-organizing bistable genetic structures, so-called molecular-genetic triggers (MGT), are investigated in molecular biology since the well-known work of Jacob and Monod [3]. In the paper [4] it is proved that the expression regulation process of λ-phage genes cI and cro represents a molecular-genetic trigger (MGT). Mathematical models of MGT are considered in details in the papers [4]–[7]. MGT represents a genetic system possessing two stable states (attractors) which can switch from one stable state (i.e. functioning regime) to another one. These two stable states of MGT correspond to the processes of transcription of two genes: cI and cro. The purpose of this paper is to show that MGT can be represented as a deterministic finite automaton fulfilling logical function $NOTAND$.

Thus, as cells react to environmental stimuli which in our case can play a role of input signals, we can control and direct intercellular processes (the process of gene expression) on the basis of mathematical and stochastic models [4]–[7]. Real values of molecule concentrations (input/output signals), the numerical evaluations of switching time of genes from active states to inactive ones (computation time) and the role of fluctuations in destruction process of dynamic memory (trigger effect) in MGT system are obtained on the basis of mathematical and stochastic models of MGT.

We propose a formal model of biocomputing system consisting of three *E.coli* bacterium cell cultures (infected by three strains of λ-phage, respectively). It corresponds to an elementary scheme (see

Fig. 5). It is shown that this biosystem is able to solve a class of formula in the conjunctive normal form (like formula (1)). The gene regulation processes of these cells correspond to three MGT-s ($MGT1, MGT2, MGT3$, i.e. finite automata). The cellular computing is a new research direction of DNA-based molecular computing. Some works in this direction were already carried out [8, 9].

This result was presented at the DNA8 conference held on June 10-13, 2002 in Sapporo, Japan, and it was published as an abstract in the conference pre-proceedings [14]. Here we present the full version of the paper.

1 λ-phage genome switching

Regulation process of gene expression is one of the main problems in molecular biology. A molecular mechanism of λ- phage genome switching is very well investigated and is based on a lot of experimental researches [10]. Prokaryotes are relative simple cells without nucleus. In prokaryotes (for example, bacteria) genes are active while the processes of gene transcription and $mRNA$ formation are holding. In the opposite case genes are considered inactive. The genes are transcribed with formation of $mRNA$ under the action of an enzyme named RNA polymerase. A promoter is a place where the process of gene transcription starts. RNA polymerase binding with a promoter starts to move along a gene synthesizing $mRNA$ (gene transcript). As a result of $mRNA$ translation process the protein molecules are synthesized by cell.

In Fig. 1 it is represented the structure of O_R right operon which contains three operator sites O_R3, O_R2, O_R1. Two promoters P_{RM} and P_R represent the places where the transcription process of genes cI and cro (in the opposite directions) begins. When RNA polymerase binds with the promoter P_{RM} the transcription process of cI gene (on the left) starts, but when it interacts with the promoter P_R the transcription process of cro gene (on the right) starts.

cI gene encodes λ-repressor molecules, cro gene encodes Cro protein molecules. λ-repressor dimer is denoted by R^d. Activation and

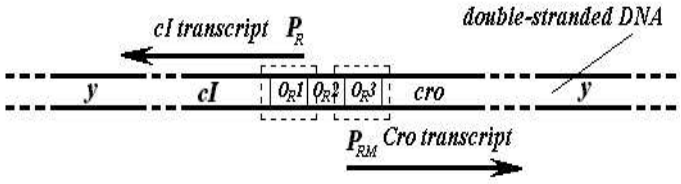

Fig. 1. The scheme of structure of O_R right operon which contains three operator sites O_R3, O_R2, O_R1. Two promoters P_{RM}, P_R start RNA polymerase in the opposite directions.

repression of genes depend on the state of O_R3, O_R2, O_R1 operator sites of O_R operon (Fig. 2). RNA polymerase binds with P_{RM} promoter only in case if dimers are interacted by O_R2 and O_R1 sites. In this case R^d dimers act on RNA polymerase as activators and the transcription process of cI gene starts (feedback). At the same time R^d dimers interacting with O_R1 block the transcription process of cro gene (cro gene is inactivated).

Because many of genes are under control of both of P_{RM} and P_R promoters we consider that y gene is one of these genes. It is located on the left and on the right sides of O_R right operon. The products of these genes (of molecular nature) are considered as output signals. Thus the output signals are produced by cells whenever cro or cI transcription process happens. Conversely, in case if both of genes are repressed the output signals are absent.

We examine 12 possible states of O_R right operon (Fig. 2). We observe some distinct situations. In O_2, O_5, O_7, O_9 states RNA polymerase binding with one of two promoters transcribes cro or cI genes (cI or cro transcript held). Thus, in these states the output signals are synthesized by cells. In O_{10}, O_{12} states both of genes are repressed and the output signals (molecules) are not produced in cellular computing system.

In Fig.2 by C is denoted a molecule of Cro protein which is encoded by cro gene; R^d denotes a molecule of λ-repressor dimer which is encoded by cI gene; P denotes a molecule of RNA polymerase which starts the process of gene activation. These molecules reversible inter-

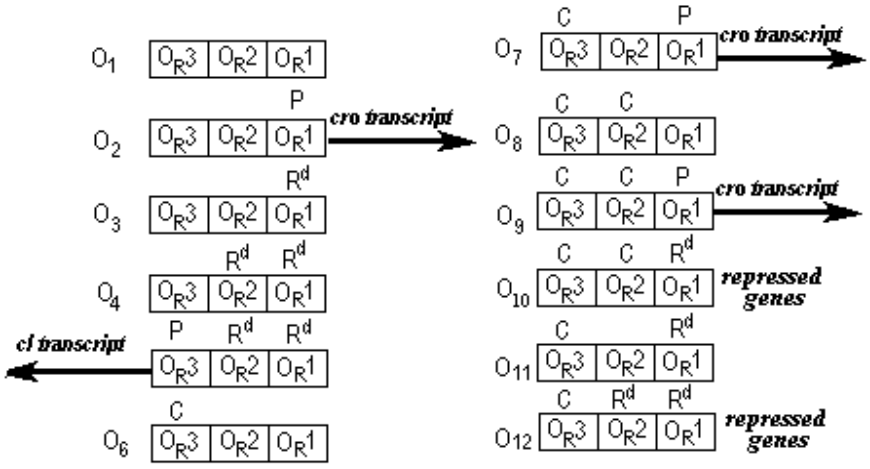

Fig. 2. Scheme of predetermined genetic regulatory system of λ-phage genome. It is represented the reversible interaction process of λ-repressor (R^d), molecule Cro (C) and RNA polymerase (P) with O_R3, O_R2, O_R1 operator sites of O_R right operon.

act with three operon sites in specific mode by predetermined genetic algorithm as it is illustrated in Fig. 2.

Let O_1 be the probability that sites O_R3, O_R2, O_R1 are free;

Let O_2 be the probability that RNA polymerase (P) interacts with O_R1 operator site and the transcription of cro gene process begins;

Let O_3 be the probability that R^d repressor dimer reversibly interacts with O_R1 operator site and repress the transcription process of cro gene;

Let O_4 be the probability that R^d dimers reversibly interact with O_R2 and O_R1 operator sites while the site O_R3 is free;

Let O_5 be the probability that RNA polymerase interacts with O_R3 operator site (cI gene is active), O_R2 and O_R1 sites are occupied by R^d repressor dimers;

Let O_6 be the probability that Cro molecule interacts with O_R3 operator site. Sites O_R2 and O_R1 are free;

Let O_7 be the probability that Cro molecule and RNA polymerase

interact with O_R3 and O_R1 operator sites, respectively. O_R2 is free;

Let O_8 be the probability that Cro molecules interact with O_R3 and O_R2 operator sites. O_R1 is free;

Let O_9 be the probability that Cro molecules interact with O_R3 and O_R2 operator sites. RNA polymerase interacts with O_R1 operator site (cro transcript);

Let O_{10} be the probability that Cro molecules interact with O_R3 and O_R2 operator sites. The molecule of λ-repressor (R^d) interacts with O_R1 operator site. In this case the genes cro and cI are repressed;

Let O_{11} be the probability that the molecule Cro interacts with the operator site O_R3. The molecule of λ-repressor (R^d) interacts with operator site O_R1;

Let O_{12} be the probability that the molecule Cro interacts with O_R3 operator site. Molecules of λ-repressor (R^d) interact with O_R2 and O_R1 operator sites. In this case cro and cI genes are repressed.

The sum of probabilities [4] is

$$O_1 + O_2 + O_3 + O_4 + O_5 + O_6 + O_7 + O_8 + O_9 + O_{10} + O_{11} + O_{12} = 1.$$

Other possible states are neglected because their probabilities are minor.

2 Living cell as a deterministic finite automaton

In this section it is described the mechanism of genetic λ-phage switching using the concept of a deterministic finite automaton [11]. A finite automaton is determined as a quintuple

$$M = (Q, \Sigma, \delta, q_1, F),$$

where $Q = \{q_1, q_2^0, q_3, q_4, q_5^0, q_6, q_7^0, q_8, q_9^0, q_{10}^0, q_{11}, q_{12}^0\}$ is the set of automaton states; $\Sigma = \{\varepsilon, r, p, c, 1, 0\}$ is the alphabet of terminals. Denote by symbol ε an empty state of automaton tape cell, by r a dimer of λ-repressor, by symbol p an enzyme molecule of RNA polymerase

and by c a molecule of protein Cro; 1 and 0 denote the values $true$ and $false$, respectively, for the output signals produced by cells as a result of the input signals processing at DNA level (see Fig. 2-4); δ is the function of transitions (Table 1); q_1 is the initial state of the finite automaton M; F is the set of final automaton states $(q_2^0, q_5^0, q_7^0, q_9^0, q_{10}^0, q_{12}^0)$;

δ	ε	r	p	c	$1(true)$	$0(false)$
state q_1	q_1	q_3	q_2^0	q_6	$\emptyset$	$\emptyset$
q_2^0	q_1	$\emptyset$	$\emptyset$	$\emptyset$	1	$\emptyset$
q_3	q_1	q_4	$\emptyset$	$\emptyset$	$\emptyset$	$\emptyset$
q_4	q_3	$\emptyset$	q_5^0	$\emptyset$	$\emptyset$	$\emptyset$
q_5^0	q_4	$\emptyset$	$\emptyset$	$\emptyset$	1	$\emptyset$
q_6	q_1	$\emptyset$	q_7^0	q_8	$\emptyset$	$\emptyset$
q_7^0	q_6	$\emptyset$	$\emptyset$	$\emptyset$	1	$\emptyset$
q_8	q_6	$\emptyset$	q_9^0	$\emptyset$	$\emptyset$	$\emptyset$
q_9^0	q_8	$\emptyset$	$\emptyset$	$\emptyset$	1	$\emptyset$
q_{10}^0	q_8	$\emptyset$	$\emptyset$	$\emptyset$	$\emptyset$	0
q_{11}	q_6	q_{12}^0	$\emptyset$	$\emptyset$	$\emptyset$	$\emptyset$
q_{12}^0	q_{11}	$\emptyset$	$\emptyset$	$\emptyset$	$\emptyset$	0

Table 1.

If $\delta(q_i, \sigma) = \emptyset$, where $\emptyset$ is empty set, for some $q_i \in Q, \sigma \in \Sigma$, then it means that the transition function is not defined.

The initial state q_1 of finite automaton corresponds to the case when all three operator sites of O_R right operon are free (contains the empty symbols) (Fig. 3); the final states q_2^0, q_7^0 and q_9^0 correspond to the states when RNA polymerase transcribes cro gene; the final state q_5^0 corresponds to the state when RNA polymerase transcribes cI gene. Thus, the final states q_2^0, q_5^0, q_7^0 and q_9^0 correspond to automaton state $1(true)$ when at least one of genes (cI or cro) is active and living cells produce the output signals of molecular nature. The final states q_{10}^0, q_{12}^0 correspond to automaton state $0(false)$ when both of genes are repressed and the output signals are not produced by cells.

The finite automaton tape consists of three cells which correspond to O_R3, O_R2, O_R1 operator sites of O_R right operon of λ-phage (Fig. 2, 3). Each cell of the automaton tape can be in one of the finite set states: ε, r, p, c. The process of reversible molecule interaction with three operator sites corresponds to a writing operation of a symbol in an automaton tape cell.

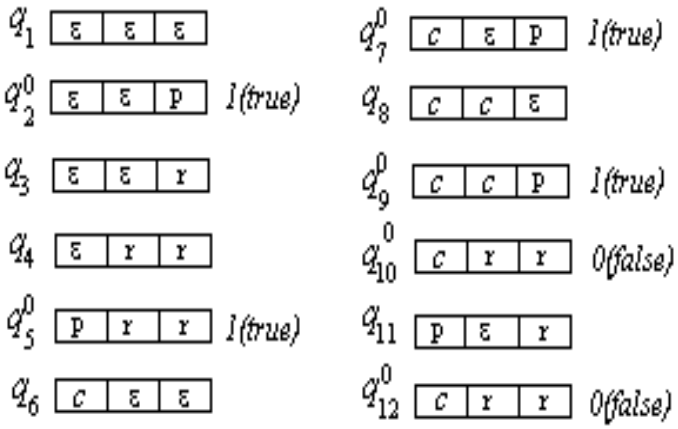

Fig.3. 12 genetic predetermined automaton states and 12 states of automaton tape cells, respectively.

Now let us examine the sequences of machine words corresponding to lysogenic and lytic paths of development of λ-phage. These are the following:

1. Lysogen way (cI gene is active and cro gene is inactive). By virtue of its structure the automaton M will consecutively pass from the initial state q_1 up to the final state q_5^0:

$$q_1\varepsilon \models q_3 r \models q_3\varepsilon r \models q_4 rr \models q_4\varepsilon rr \models q_5^0 prr.$$

2. The lytic path (cro gene is active, cI gene is inactive).

a) The first variant. The finite automaton work begins from the initial state q_1:

$$q_1 \models q_2^0 p$$

and in the converse case

$$q_2^0 p \models q_1 \varepsilon.$$

b) The second variant. Switching of cI, cro genes. The finite automaton M begins the work from the state q_5^0 (cI is active) into the state q_2^0 (cro gene is active). The automaton consecutively takes the following states:

$$q_5^0 prr \models q_4 \varepsilon rr \models q_4 rr \models q_3 \varepsilon r \models q_3 r \models q_1 \varepsilon \models q_2^0 p.$$

For convenience it is described only the process of reversible interaction of λ-repressors and RNA polymerase with three operator sites. Similarly can be written sequences of automaton words that correspond to reversible interaction process of protein Cro molecules with three operator sites (automaton tape cells).

Thus, the switching of genetic system of λ-phage is described as the finite deterministic automaton M that executes a computation by a predetermined genetic algorithm. Succession of regulatory events of each path of development of λ-phage (lysogenic state, lytic growth) represents the cascade mechanism when genes cI and cro are activated or are inactivated according to the predetermined genetic program (Fig. 4).

In Fig. 4 it is represented the diagram of the finite automaton M:

$$M = (\{q_1, q_2^0, q_3, q_4, q_5^0, q_6, q_7^0, q_8, q_9^0, q_{10}^0, q_{11}, q_{12}^0\},$$
$$\{\varepsilon, r, p, c, 1, 0\}, \delta, q_1, \{q_2^0, q_5^0, q_7^0, q_9^0, q_{10}^0, q_{12}^0\}).$$

In dependence of the molecule concentration of λ-repressor or Cro protein the certain branches of gene switching cascade mechanism are realized. The high value of molecule concentration is represented below by 1 and low value – by 0. Because MGT mathematical model of λ-phage gene switching is two-dimensional we have two input signals: x_1, x_2. The input signals corresponding to x_1, x_2 variables must regulate the transcription process of genes cI and cro and control the level of molecules concentration of λ-repressors (R^d) and Cro. Also,

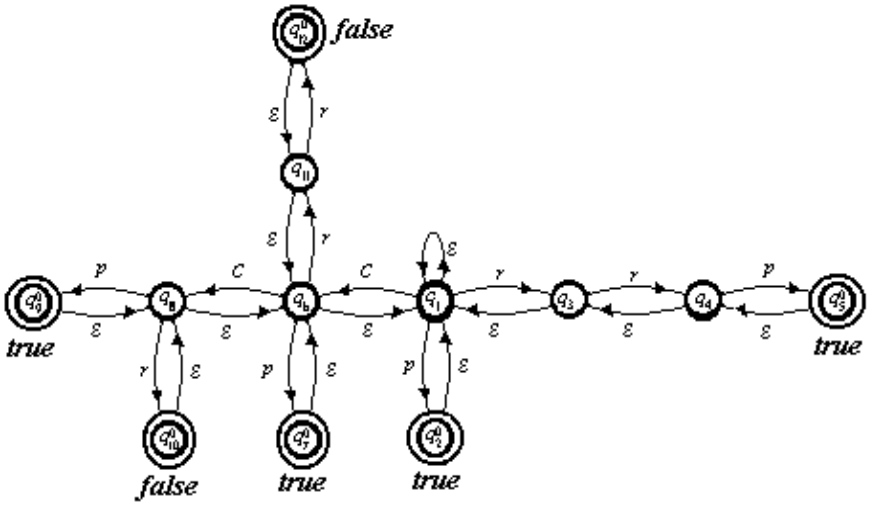

Fig. 4. The diagram of the finite automaton M. Arrows indicate reversible molecules interaction processes with three operon sites at DNA level.

they regulate the process of synthesizing by cells of the output signals (Fig. 4). For convenience, we consider that x_1 and x_2 correspond to concentration molecules of λ-repressor (r) and Cro protein (c), respectively. Boolean values *true* of the output signal will be denoted by 1, and values *false* – by 0. For instance, the state q_2^0 is realized whenever Cro protein and λ-repressor are absent, i.e. the respective molecule concentrations are low (i.e. are 0). In this case cro gene is activated and the output signal $1(true)$ of molecular nature (molecules encoding by y gene (Fig. 1)) is produced by cells. The state q_5^0 is realized, i.e. cI gene is activated, whenever the molecule concentration of λ-repressor will be high (i.e. is 1). The output signal synthesized by cell also is $1(true)$. If both of input signals are equal to 1 ($x_1 = 1, x_2 = 1$), then both of genes are repressed and the output signal is $0(false)$ (see Table 2).

INPUT		OUTPUT
x_1	x_2	y
0	0	1 $(true)$
0	1	1 $(true)$
1	0	1 $(true)$
1	1	0 $(false)$

Table 2. (LOGICAL FUNCTION $NOT\ AND$). Table of the output signals y depending on the input signals x_1 and x_2.

A language defined by automaton M (denoted by $L(M)$) [11] is a set of input chains which is recognized by automaton M. For instance, for the input chain prr there exists the unique configuration sequence of the automaton M, namely:

$$\begin{aligned}(q_5^0, prr) &\models (q_4, \varepsilon rr)\\ &\models (q_4, rr)\\ &\models (q_3, \varepsilon r)\\ &\models (q_3, r)\\ &\models (q_1, \varepsilon)\\ &\models (q_1, e)\end{aligned}$$

Thus, the chain prr belongs to language $L(M)$ ($prr \in L(M)$), where e is the empty chain. Thus, the formal language $L(M)$ consists, for example, of the following chains: $\varepsilon\varepsilon\varepsilon$, $\varepsilon\varepsilon p$, $\varepsilon\varepsilon r$, εrr, prr, $c\varepsilon\varepsilon$, $c\varepsilon p$, $cc\varepsilon$, etc. Our deterministic finite automaton can read chains as well from left to right as from right to left. For instance, if chains ccp, $c\varepsilon\varepsilon$ are recognized by M reading them from left to right, then these chains belong to $L(M)$. If the chain prr is recognized by M reading it from right to left, then it also belongs to $L(M)$.

Obviously, in this case we can say that *E.coli* bacterium cell (infected by strain of λ-phage) can be represented as a deterministic finite automaton having two inputs and one output. It fulfills logical function $NOTAND$. It is an example of DNA–based molecular-genetic machine which has the following characteristics: input, output, transition states, language of computation, predetermined genetic program, memory and energy source.

3 Self-organizing biocomputing model solving a logical problem

We propose a formal model of cellular computing system that consists of three living *E.coli* bacterium cell cultures (infected by three strains of λ-phage) which can be represented as finite automata fulfilling logical function $NOTAND$. The gene regulation processes of these three cell cultures correspond to three MGT : $MGT1, MGT2, MGT3$. They correspond to three finite deterministic automata $(A1, A2, A3)$ fulfilling logical functions $NOTAND$ (Fig. 5).

In this paper we show that the self-organizing system of finite automata can solve the concrete example of logical problem in the conjunctive normal form like this one:

$$\beta = (x_1 \vee x_2) \wedge (\neg x_1 \vee \neg x_2) \tag{1}$$

We have two variables x_1, x_2 and two clauses. It is satisfying when any of the following *truth*-assignments make formula (1) *true*:

$$(x_1 = false, x_2 = true), (\neg x_1 = true, \neg x_2 = false), \tag{2}$$

$$(x_1 = true, x_2 = false), (\neg x_1 = false, \neg x_2 = true). \tag{3}$$

We use three connectives: or, and, negation.

It is known that a living cell (bacterium) reacts to internal and external factors considered as input signals. In dependence of genetic construction of promoter regulatory sites of genes we can organize the Input of initial data for biosystem using signals of wave or molecular nature. Values 1 and 0 are continuous values of molecule concentrations or intensities. The high (1) and low (0) concentrations of specific molecules (for example, activators, repressors, hormones, toxins, etc.) can be used as signals of molecular nature and binding with promoter regulatory sites they control the transcription processes of genes. In case of light-induced gene [12] the input signals of wave nature may be utilized.

There are 2^n (n is the number of variables in (1), $n = 2$) different sets of initial values. All possible combinations of two input signals are:

00, 01, 10, 11. The input signals corresponding to x_1, x_2 variables must regulate the transcription process of genes cI and cro and control the level of molecules concentration of λ-repressors (R^d) and Cro. Also, they regulate the process of synthesizing by cells of output signals.

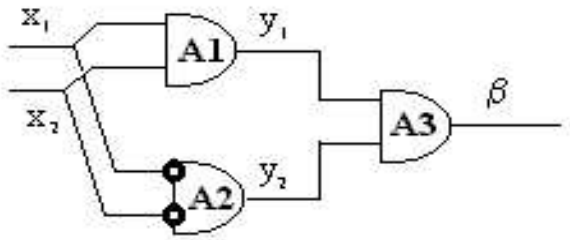

Fig. 5. The elementary scheme of two levels cellular computing system consisting of three finite automata which can solve a class of propositional formula in the conjunctive normal form (like formula 1).

The living cells that form a biosystem communicate among themselves by means of intercellular signals. Cells (emitters) secrete output signals of molecular nature. The molecules diffuse in the surrounding medium of cellular computing system and the signals are transferred from emitter cells to receptor cells. For the trigger switch the concentrations of molecules or light intensities have to be higher than a critical value [4]–[7]. We remark that the computation process based on MGT, i.e. finite automata for solving formula (1) can be associated with a binary tree structure consisting of 2 levels. The number of levels (the depth) determines the formula (1) calculation time. The first level cells receive in parallel the initial input signals and produce output signals that are input signals for the second level cells. Cells, whose gene transcription process correspond to $A1$ and $A2$ belong to the first level cells. They receive in parallel input signals x_1, x_2 and $\neg x_1, \neg x_2$, respectively. Their output signals y_1, y_2 are the input signals for cells, whose gene regulation processes correspond to $A3$ and belong to the second level cells.

If input signals are $x_1 = 1$, $x_2 = 1$ (state q^0_{10} or q^0_{12}, Fig. 3, Table 2), then output signal y_1 is weak and we can neglect with him ($y_1 = 0(false)$). In this case the process of gene transcription does not hold

because the genes (cI and cro) are repressed (are inactive). Let the input signals be $x_1 = 0$, $x_2 = 0$ (i.e. molecules of λ-repressors and protein Cro are absent), then the output signal y_1 is $1(true)$ (Table 3), i.e. the genes are active (the process of gene transcription happens). The cells, corresponding to $A1, A2, A3$, adjusted by methods of genetic engineering will receive only a concrete set of input signals (and will not react to other signals do not belonging to the given set). At the same time these cells secrete only specific output signals of molecular nature.

From genetics point of view, logical element NOT can be associated with the transcription process of a gene which is under control of some promoter with a negative type of gene regulation. In Fig. 5 logical element NOT is designed by a circle. The repressor molecules may serve as input signals for logical element NOT, and binding with the promoter they stop the gene transcription process (gene is repressed). The gene is active whenever the repressor molecules (input signals) are absent.

In Table 3 the evolution process of input/output signals at DNA level and the communication process of cellular computing system components (living cells) are represented.

	x_1	x_2	$\neg x_1$	$\neg x_2$	y_1	y_2	β
1	0	0	1	1	1	0	0
2	0	1	1	0	1	1	1
3	1	0	0	1	1	1	1
4	1	1	0	0	0	1	0

Table 3. Dependence of β output signal of the cellular computing system on the input signals x_1, x_2.

The presence of output signals β secreted by cells, whose gene transcription regulation processes correspond to $A3$ ($MGT3$), designs that the first level cells of cellular computing system receive a combination of the input signals which satisfy equation (1). Note that the computation process of cellular computing model for solving formula (1) can be

associated with a binary tree structure consisting of 2 levels. The number of levels (the depth) determines formula (1) calculation time. The mathematical and stochastic models permit us to effectuate numerical evaluation of genes switching time (computation time). We can calculate the necessary computation time (as a function of environmental stimuli), i.e. duration in which $1(true)$ output signal (molecules β) has to appear in cellular computing system. We consider that the output signals are $0(false)$ if $1(true)$ signals do not appear in the evaluated computation time. The proposed cellular computing model (having depth 2) can calculate a class of propositional formula in the conjunctive normal form (like formula (1)) with two variables (n=2) and two clauses in two parallel-consecutive steps with parallel gates fulfilling logical functions $NOT\ AND$.

Final remarks

In this paper it is assumed that MGT, i.e. the regulation process of gene transcription in living cells may be represented as a deterministic finite automaton. A living cell is an example of DNA-based molecular-genetic machine fulfilling logical function $NOT\ AND$. It is shown that the cellular computing model (having depth 2) can calculate a class of formula in the conjunctive normal form (like formula (1)) in parallel-consecutive mode (in two steps). We consider that the cellular computing system is able to solve P-complete problems in polynomial time due to high degree of computation parallelism (for instance, the well-known $n - SAT$ problem).

MGT (i.e. finite automaton) being an analogous of transistors can be of several types in dependence of genetic construction of cells. A simplest types of MGT may be represented as a deterministic finite automata with 3 automaton states having alphabets of 5 symbols. Variables $true$ and $false$ correspond to active and inactive states of gene, respectively. There are different types of MGT both with positive and negative type of gene transcription regulation process. They can fulfill logical functions OR, XOR, $NOT\ AND$, AND [4]–[7], [13]. Theoretically, it is possible to form a biosystem of living cells (fulfilling

logical functions) that correspond to any logical scheme.

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