8th International Conference on DEVELOPMENT AND APPLICATION SYSTEMS
Suceava, Romania, May 25 – 27, 2006

P TRANSDUCER MODEL OF ALLELIC GENE NETWORK REGULATION

Aurelia PROFIR[1], Emil GUTULEAC[2], Elena BOIAN[3]
[1]*Institute of Applied Physics, Academy of Sciences, Chişinău, Moldova*
[1]*State University of Moldova, Chişinău, Moldova*
e-mail: aurelia@cc.acad.md
[2]*Technical University of Moldova, Chişinău, Moldova*
e-mail: egutuleac@mail.utm.md
[3]*Institute of Mathematics and Computer Science of Moldova, Academy of Sciences, Chişinău, Moldova*
e-mail: lena@math.md

Abstract. *A formal P transducer model of allelic gene network regulation is proposed to illustrate the dominance mechanism. Genes with their regulatory regions, responsible for observable treats, are encoded by continuous-time P systems of elementary membranes arranged into continuous chains. To get a clearer picture of the functional mechanism of allelic gene regulatory network and to monitoring small changes of gene activity profiles as response to external stimuli a predictive computational model of the P transducer has been built. The components of the P transducer model are encoded by the components of the descriptive Rewriting Timed Petri Nets. Both the dominance phenomena and the important characteristics of gene function such as differential gene expression, functional aspects of dynamic behaviour of gene expression regulation are demonstrated through simulation.*
Keywords: *P transducer, allelic gene, descriptive Rewriting Timed Petri Nets.*

Introduction

Membrane computing is an emergent branch of Natural Computing. P systems (membrane systems) are abstract parallel and distributed computing devices inspired by the structure and the functioning of the living cell [1]. A lot of P systems formalisms had been proposed: cell-like and tissue-like P systems, discrete, continuous-time and continuous P systems, etc. [1-4].
P systems models of gene expression regulation present a great interest in more efficient controlling ways of how cells self-regulate the expression of their genes *in vivo* and for adequate description of the cellular processes.
It is known that Systems biology is focused on understanding cellular networks (gene regulatory networks, protein networks, and membrane networks) to build integrated formal and computational models, with suitable notations, necessary to describe all cellular networks as an entire system.
In this article we introduce a P transducer model of allelic gene expression regulation for elucidation the *continuous* aspects of allelic gene structure-functional organization and the functioning of genetic machinery of the dominance phenomena. *DNA* (in genes) is mapped by means of systems of elementary membranes, arranged into chains, for capture in detail the gene structure and all relevant functional aspects of temporal behaviour of gene expression regulation. The P transducer model of the living cell provides system integration of all relevant interacting components at the main hierarchical levels of cell organization.
Using the concept of the P transducers [3] we introduce a new quantitative computational model of the living cell as a basis of analysis and simulation of real-world gene networks, which govern cellular functions, and the dynamic behavior of the living cell. This view in detail captures gene structure and all functional features of temporal behavior of gene expression regulation. On the one hand, this approach can easily describe the discrete aspects of gene regulation such as all the relevant molecular interactions one-by-one with the *DNA*. On the other hand, the continuous-valued internal state of each gene, dictated by the gene regulatory network of the living cell, is illustrated.
To simulate the dominance phenomena and to illustrate the important characteristics of gene function such as differential gene expression,

functional aspects of dynamic behaviour of gene expression regulation a predictive computational model of the P transducer has been built. The components of the P transducer model are encoded by the components of descriptive Rewriting Timed Petri Nets (RTN) [5]. Some rules are modeled by macronodes, which map subnets of the RTN structure [6].

Allelic gene expression regulation model

Let us analyse the genetic regulatory system of allelic genes linked as a regulatory network (with positive control of gene expression) [7].

Figure 1 depicts the elements of the regulatory system of one pair of allelic genes, denoted by g_1 and g_2 that code for the proteins G_1 and G_2, responsible for the observed inherited trait. The regulatory regions of the genes e and f comprise the binding site for the activator A_1 (BSA_1), the promoter P^2_1 and the binding site for the activator A_2 (BSA_2), the promoter P^2_2, respectively.
The regulatory genes l and m code for the activator molecules A_1 and A_2. The genes e and f are under the positive control of the activator molecules A_1 and A_2 and code the regulatory enzymes E_1 and E_2, respectively. Due to their proteolytical activity, the regulatory enzymes E_1 and E_2 destroy the activator molecules A_2 and A_1 of the opposite homologous chromosome.

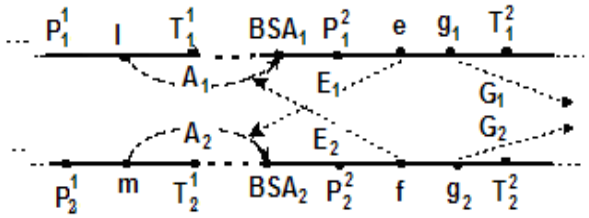

Figure 1. The scheme of the molecular regulatory mechanism of allelic gene expression with positive control.

We take into consideration that the rates of the enzymatic reaction depend on different factors (for instance, temperature, concentration of specific molecules etc.), considered as input signals. The enzymes can be either activated (E^+) or inactivated (E^-), i.e., the rates of proteolytical reaction of the enzymes E_1 and E_2 can increase or decrease as a result of action of one of the input signals. So, the activated enzymes E^+ can destroy the activator molecules A_1 or A_2 of the opposite chromosome, but the inactivated enzymes E^- – can not. Using the P transducer concept [3] we built a formal P transducer model which allows us to illustrate the direct influence of temperature on allelic gene expression.

P transducer model of dominance

Due to the fact that cells self-regulate their biochemical activities, they can adapt to different conditions, responding to stimuli. The genetic mechanism of the allelic gene switching controlled by input signals is modelled. The input signals, considered as input "marked" objects, are read from the "input tape". The proteins G_1 and G_2, designed as output "marked" objects, are sent out to the "output tape". Other factors which influence to functioning of genetic system (i.e., rates of biochemical reactions) are considered as environmental stimuli, denoted by the symbol b. The writing of ``marked`` objects on the "output tape" is associated with the cell response to the input signals.
A P transducer model of allelic gene expression regulation illustrating the molecular mechanism of allelic genes expression, controlled by regulatory enzymes, may be represented in the following way:

$$\Pi = (O_l, O_m, O_e, O_f, V, \mu_l, \mu_m, \mu_e, \mu_f, \mu_{cell}, w_{l(i)}, w_{m(i)}, w_{e(i)}, w_{f(i)}, w_1, E, R_{l(i)}, R_{m(i)}, R_{e(i)}, R_{f(i)}, R_1, R_2),$$

$i=1,2,3$,

where:

- O_l, O_m, O_e, O_f are alphabets of objects associated with systems of elementary membrane that map the genes l, m, e and f,

respectively. $O_l = \{p, p_l\}$, $O_m = \{p, p_m\}$, $O_e = \{A_1, p, p_e\}$, $O_f = \{A_2, p, p_f\}$,

where:

A_1 and A_2 represent activator molecules, encoded by the genes *l* and *m*, respectively;

p – *RNA* polymerase molecule; p_l, p_m, p_e, p_f, – *RNA* polymerase transcribing the gene *l*, *m, e* or *f* into *mRNA* copies;

- V is the alphabet of objects of the P transducer.

$$V = \{p, p_l, p_m, p_e, p_f, u_l, u_m, u_e, u_f, u, m, v, f, A_1, A_2, E_1, E_2, G_1, G_2, t, b\}, O_l, O_m, O_e, O_f \subseteq V,$$

where:

u_l, u_m, u_e, u_f represent nuclear copies of the genes *l*, *m, e* and *f*, respectively;

E_1, E_2 – regulatory enzymes, encoded by the e_1 and e_2 genes;

G_1, G_2 – output signals, encoded by the genes g_1 and g_2;

u and *m* – *mRNA* copies of the genes *l* and *m*;

v and *f* – *mRNA* copies of the genes e_1 & g_1 and e_2 & g_2, respectively;

t – temperature (input signals);

b – environmental stimuli;

- $\mu_l, \mu_m, \mu_e, \mu_f$ are elementary membranes, arranged into continuous chains that map the *l*, *m, e* and *f*.

$$\mu_l = [_{l(1)} \quad _{l(1)}|_{l(2)} \quad _{l(2)}|_{l(3)} \quad _{l(3)}]$$

is the elementary membrane structure, which represent the gene *l*. The direct communication between membranes along the chain is done in a *one-way* manner: $l(1) \rightarrow l(2) \rightarrow l(3)$. The first membrane of the chain (labelled *l(1)*) represents the *regulatory region* of this gene, it is called the *input/output* membrane. The last membrane of the chain representing the gene *transcriptional termination site* T_l^1 is named the *output* membrane. The gene-coding region is mapped by the elementary membrane labelled *l(2)*. The membrane structures μ_m, μ_e, μ_f of the genes *m, e* and *f* are similar to the membrane structure μ_l of the gene *l*;

$$\mu_{cell} = [_2 \; [_1 \quad]_1 \;]_2$$

represents the cellular membranes. Cellular membrane (the skin) is represented by membrane 2, nucleus envelope – by membrane 1;

The membrane structure of the P transducer is

$$\mu = [_2 \; [_1 \; [_{l(1)} \quad _{l(1)}|_{l(2)} \quad _{l(2)}|_{l(3)} \quad _{l(3)}] \; [_{m(1)} \quad _{m(1)}|_{m(2)} \quad _{m(2)}|_{m(3)} \quad _{m(3)}] \; [_{e(1)} \quad _{e(1)}|_{e(2)} \quad _{e(2)}|_{e(3)} \quad _{e(3)}] \; [_{f(1)} \quad _{f(1)}|_{f(2)} \quad _{f(2)}|_{f(3)} \quad _{f(3)}] \;]_1 \;]_2$$

- $w_{l(i)}$, $w_{m(i)}$, $w_{e(i)}$, $w_{f(i)}$, $(i = 1, 2, 3)$ represent the initial sets of objects over O_l, O_m, O_e, O_f, associated with each elementary membrane of the membrane structures $\mu_l, \mu_m, \mu_e, \mu_f$, respectively.
- w_1 is the initial multiset over V^* associated with the region delimited by the membrane 1 (which represents the cell nucleus).

The initial configuration of the P transducer can be represented as following:

$w_{l(2)} = \{p_l\}$; $w_{m(1)} = \{p\}$; $w_{m(3)} = \{p_m\}$; $w_{e(1)} = \{A_1, p\}$;

$w_{e(2)} = \{p_e\}$; $w_{f(2)} = \{p_f\}$;

$w_1 = \{p, p_l, p_m, p_e, u_l, u_m, u_e, u, m, v, A_1, E_1, G_1, b\}$;

- $E \in V$ is the set of objects in the environment. $E = \{t, b, G_1, G_2\}$;
- $R_{l(i)}$, $R_{m(i)}$, $R_{e(i)}$, $R_{f(i)}$, $(i = 1, 2, 3)$ are finite sets of rules associated with each elementary membrane of the membrane structures $\mu_l, \mu_m, \mu_e, \mu_f$, respectively (Table 1). All the relevant molecular interactions one–by–one with *DNA* are modelled by these rules. The rates of rule application are indicated as superscripts associated with the rules.

All rules are applied in accordance with the rates in a non-deterministic maximally parallel manner. Only one object is specified in all rules described below.

Each rule has one of the following forms:

- $(x, in)|_a^{r_m}$ (or $(x, in)|_{ab}^{r_m}$) means that from the environment the object *x* enters the input/output membrane only in the absence of

the object *a* (in the absence of the object *a* and in the presence of *b*). These conditional rules reflect the functional organization of the gene regulatory region;

- $(x, out)|^{r_m}$ means that the object *x* is sent *out* from the membrane with which the rule is associated, into the environment;
- $(x, go)|^{r_m}$ means that the object *x* leaves the membrane with which the rule is associated and passes to the next membrane of the chain.
- $(x \to (y, go))|^{r_m}$ means that the object *x* leaves the input/output membrane, it is replaced by the object *y* that passes to the next membrane of the chain.

These rules describe in detail three stages of the gene transcription process. Rules, associated with the input/output membrane, model the initiation of transcription: RNA polymerase and transcription factors (reversibly) interaction with the gene regulatory region. Rules, associated with the membranes that map the gene-coding region, model the movement of RNA polymerase along the DNA. Rules, associated with the output membrane, model the RNA polymerase leaving the end of gene;

- R_1, R_2 are finite sets of rules associated with the regions delimitated by the skin membrane of the cell-like membrane system (that map the cytoplasm) and the membrane *1* associated with the nuclear membrane (Table 1).

Biochemical reactions that evolve in the cell cytoplasm (a part of cellular protein network) are modelled by evolution rules. The evolution rules of the form $(u \to v)|^{r_m}$ mean that the objects *u* are replaced by objects *v*. The action of input signals on the living cell and the cellular response are modelled by the symport rules associated with the skin membrane of the P transducer [3, 4] (a part of cellular membrane network). All rules are applied according to their rates in a non-deterministic maximally parallel manner.

One objective of Systems biology is to create predictive quantitative models of gene regulatory networks that govern numerous cellular functions. Our aim is to model the functioning of genetic machinery to elucidate the *continuous* aspects of gene structure-functional organization.

The P transducer model of the living cell provides system integration of all interacting components at the main hierarchical levels of cell organization.

Table 1. Rules of the P transducer model of dominance.

P transducer		**P transducer**	
M	**Rules**	**M**	**Rules**
l(1)	$(p, in)\|^{r_1}$	m(1)	$(p, in)\|^{r_5}$
	$(p \to (p_l, go))\|^{r_2}$		$(p \to (p_m, go))\|^{r_6}$
l(2)	$(p_l, go)\|^{r_3}$	m(2)	$(p_m, go)\|^{r_7}$
l(3)	$(p_l, out)\|^{r_4}$	m(3)	$(p_m, out)\|^{r_8}$
e(1)	$(A_1, in)\|^{r_9}_{A_1}$	f(1)	$(A_2, in)\|^{r_{15}}_{A_2}$
	$(A_1, out)\|^{r_{10}}$		$(A_2, out)\|^{r_{16}}$
	$(p, in)\|^{r_{11}}_{pA_1}$		$(p, in)\|^{r_{17}}$
e(2)	$(p \to (p_e, go))\|^{r_{12}}$	f(2)	$(p \to (p_f, go))\|^{r_{18}}$
e(3)	$(p_e, go)\|^{r_{13}}$	f(3)	$(p_f, go)\|^{r_{19}}$
	$(p_e, out)\|^{r_{14}}$		$(p_f, out)\|^{r_{20}}$
1	$(p_l \to (pu_l))\|^{r_{21}}$	1	$(p_m \to (pu_m))\|^{r_{23}}$
	$(u_l, out)\|^{r_{22}}$		$(u_m, out)\|^{r_{24}}$
	$(p_e \to (pu_e))\|^{r_{25}}$		$(p_f \to (pu_f))\|^{r_{27}}$
	$(u_l, out)\|^{r_{26}}$		$(u_f, out)\|^{r_{28}}$
	$(A_1^5 \to A_1^4)\|^{r_{29}}$		$(A_2^5 \to A_2^4)\|^{r_{30}}$
	$(E_1^5 \to E_1^4)\|^{r_{31}}$		$(E_2^5 \to E_2^4)\|^{r_{32}}$
	$(A_2E_1 \to E_1)\|^{r_{33}}$		$(A_1E_2 \to E_2)\|^{r_{34}}$
	$((b, read), in))\|^{r_{35}}$		
2	$(u \to uA_1)\|^{r_{36}}$	2	$(m \to mA_2)\|^{r_{39}}$
	$(A_1, out_1)\|^{r_{37}}$		$(A_2, out_1)\|^{r_{40}}$
	$(u \to \lambda)\|^{d_{38}}$		$(m \to \lambda)\|^{d_{41}}$
	$(v \to vE_1G_1)\|^{r_{42}}$		$(f \to fE_2G_2)\|^{r_{45}}$
	$(E_1, out_1)\|^{r_{43}}$		$(E_2, out_1)\|^{r_{46}}$
	$(v \to \lambda)\|^{d_{44}}$		$(f \to \lambda)\|^{d_{47}}$
	$(u \to \lambda)\|^{d_{38}}$		$((G_2, write), out)\|^{r_{49}}$
	$((G_1, write), out)\|^{r_{48}}$		

Components of the descriptive RTN

Let us describe the structure of descriptive RTN:
$<P,T,Pre,Post,Test,Inh,GPri,l,\ R, G_r, \phi,\ M, \Theta>$,

where: *P, T* - finite disjoint sets of places and (immediate and timed) transitions; *Pre, Post, Test, Inh* – forward, backward, test, and inhibition functions in the multisets of *P*, which define the set of direct normal, inhibitory and test arcs; $G: T \times N_+ \rightarrow \{true, false\}$ – guard function for each transition; $Pri : T \rightarrow N_+$ – priority functions for the firing of each transition; $l: T \cup P \rightarrow L$ labelling function that assigns labels to nodes (transitions or places), *L* - set of labels; $R = \{r_1..., r_k\}$ – finite set of rewriting rules about the runtime structural modification of the net; $G_r: E \times N^{|P|} \rightarrow \{true, false\}$ – *reewriting guard function* defines the enabling of the rule $r \in R$ associated with the transition $t \in$ T, $E = T \cup P$– set of events; $\varphi \rightarrow \{T, R\}$– function defined for every transition indicating the type of event that can occur; $M : P \rightarrow N_+$ - marking functions of the places. M_o - net initial marking; Θ: $T \times N_+^{|P|} \rightarrow R_*$ – weight function mapping transitions into real numbers R_* (delay time or weight speeds).

The transition $t_j \in T$ of the event $e_j \in E$ and the rewriting rule $r_i \in R$ are enabled in current marking *M* if the enabling conditions $ec(t_j,M)$ and

$$ec(r_j,M) = ec(t_j, M) \& g_r(r_j,M)$$

are verified, respectively.

We use the concept of *DE* for analytical representation and compositional construction of RTN. A basic *DE* element (*bDE*) for a basic RTN is:

$$bDE = |_{e_j}^{a_j}\ m_i^0 p_i [W_i^+ W_i^-] |_{e_k}^{a_k}$$

where: e_j is the input event with the action a_j and e_k is the output event with the action a_k of the place p_i with initial marking $m_i^0 = M_0(p_i)$. The flow relation functions $W_i^+ = Post(e_j,p_i)$ and $W_i^- = Pre(e_k,p_i)$ return the multiplicities of the input and output arcs of p_i.

DE of RTN is either a *bDE* or a composition of *DE:*

$$DE::= bDE \mid DE*DE \mid {}^oDE,$$

where: * and ^{o} represent any binary and any unary composition operations, respectively.

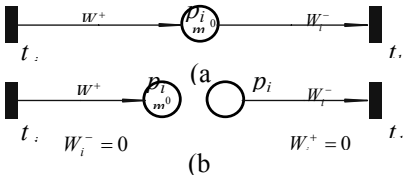

Figure 2. Translation in *bPN* (a) of *bDE* and (b) its derivatives.

Some of them are the following.

The unary inhibition " -" (p_i) or test " ~ " (p_i) operations describe the inhibitory or test arc, respectively.

The binary place-sequential operation "|" determines the logics of an interaction between two local states: precondition and post-condition, by the action (event). The specified conditions are fulfilled always.

The binary synchronization operation "•" describes the rendezvous synchronization by the event of two or more conditions, represented by places. It indicates that all preceding conditions of occurrence actions must be completed.

The binary split operation "◊" determines the causal relations between the event and its post◊-conditions: after completion of the preceding action simultaneously several other post-conditions can occur in parallel. The compositional binary competing parallelism operation "V" means that it can be applied over two RTN nets: RTN_A with $DE_A = A$, and RTN_B with $DEB_B = B$. The resulting net RTN_R with $DE_R = R$ can be represented by $DE_R = R = A \cup B$. The fused nodes, with the same names, will inherit the incidence arcs of the nodes *A* and *B*.

Introducing the macronodes we can refine RTN. This enables the refinement of a macronode a; by a subnet represented by the DE_x in the form $x \nabla DEx$. The macronodes are specified by marking-controlled *DE*s.

Simulation of the P Transducer model

The components of the P transducer model can be expressed by components of descriptive RTN using the next procedure [6]:

- to every set of objects *a (a∈V*)* associated with a region of the membrane structure of the P transducer model a place of RPN, *p = (i, a)∈ P* (Table 2) is put into correspondence. *i* is the label of region (membrane) in which the set of objects *a* is localized. The marking of the place represents the number of copies of the object *a*;

Table 2. Correspondence of the sets of objects of the P transducer model to labelled places of the descriptive RTN model.

P transducer		RTN	
Mem-brane	**Objects**	**Labelled places**	**Places**
l(1)	p	(l(1),1)	p1
l(2)	p_l	(l(2),1)	p2
l(3)	p_l	(l(3),1)	p3
e(1)	A_1	(e(1),1)	p7
	p	(e(1),1)	p8
e(2)	p_e	(e(2),1)	p9
e(3)	p_e	(e(3),1)	p10
1	p	(1,1)	p15
	p_l	(1,2)	p16
	u_l	(1,3)	p17
	p_e	(1,4)	p20
	u_e	(1,5)	p21
	A_1	(1,6)	p24
	A_2	(1,7)	p25
	E_1	(1,8)	p26
2	b	(2,1)	p29
	u	(2,2)	p30
	A_1	(2,3)	p31
	v	(2,4)	p34
	G_1	(2,5)	p35
	E_1	(2,6)	p36

- the initial state of the P transducer $w_1^0,\ldots,w_k^0$ is represented through the initial marking M_0 of descriptive RTN;
- compartimentisation of the membrane structure μ is reflected by labels of nodes (places and transitions) of descriptive RTN;
- we can remark two distinct situations connected to the mapping of rules of the P transducer into transitions of descriptive RTN models:
  - for every rule can be put into correspondence one distinct transition of the RTN, t = (j, r)∈ T, where j is the label of region with which the rule r is associated [5];
  - some rules can be modelled by two or more transitions (macronodes) (Table 3).

Table 3. Mapping of a part of rules of the P transducer model of dominance by DE.

P systems		RTN	
M	**Rules**	**T**	**DE**
e(1)	$(A_1,in)\|^{r_3}_{A_1}$	t9	$p24\|^{r_9}_{t_9}\ p7,$ $g_9=(m_7=0)$
	$(A_1,out)\|^{r_4}$	t10	$p7\|^{r_{10}}_{t_{10}}\ p24$
	$(p,in)\|^{r_{11}}_{pA_1}$	t11	$p15\|^{r_{11}}_{t11}\ p8,$ $g_{11}=(m_8=0)\&(m_7=$
	$(p\to(p_e,go))\|^{d}$	t12	$p8\|^{d_{12}}_{t_{12}}\ p9,$ $p9\triangleright\bigcup_{i=46}^{49}p_i\|^{d_i}_{t_{i+6}}\ p_{i+1}$
e(2)	$(p_e,go)\|^{d_{13}}$	t13	$p9\|^{d_{13}}_{t_{13}}\ p10,$ $d_{13}=\sum_{i=52}^{55}d_i,$ $p9\triangleright\bigcup_{i=46}^{49}p_i\|^{d_i}_{t_{i+6}}\ p_{i+1}$
e(3)	$(p_e,out)\|^{r_{14}}$	t14	$p10\|^{r_{14}}_{t_{14}}\ p20$
1	$(p_e\to(pu_e))\|^{r2}$	t25	$p20\|^{r_{25}}_{t_{25}}\ p21$
	$(u_e,out)\|^{r26}$	t26	$p21\|^{r_{26}}_{t_{26}}\ p34,$ $p34\triangleright\bigcup_{i=62}^{64}p_i\|^{d_i}_{t_{i+2}}\ p_{i+1}$
	$(A_1^5\to A_1^4)\|^{r29}$	t29	$p24[0.2m_{24}]\|^{r_{29}}_{r29}$
	$(E_1^5\to E_1^4)\|^{r31}$	t31	$p26[0.2m_{26}]\|^{r_{31}}_{t31}$
	$(A_2E_1\to E_1)\|^{r33}$	t33	$p25[m_{26}]\bullet\tilde{p}26\|^{r_{33}}_{t_{33}}$
2	$(b,read),in))\|^{r_{35}}$	t35	$p28[m_{28}]\|^{r_{35}}_{t_{35}}\ p29[m_{28}]$

	$(v \to vE_1G_1)\|^{r_{42}}$	t42	$\tilde{p}34[m_{34}]\|_{t42}^{r_{42}}$ $p36[m_{34}] \Diamond p35[m_{34}]$, $p34 \triangleright \bigcup_{i=62}^{64} p_i \|_{t_{i+2}}^{d_i} p_{i+1}$
	$(E_1, out_1)\|^{r_{43}}$	t43	$p36[m_{36}]\|_{t43}^{r_{43}} p26[m_{36}]$
	$((G_1, write), out)$	t48	$p35[m_{35}]\|_{t48}^{r_{48}} p37[m_{35}]$

The mapping of a part of rules of the P transducer model of dominance by descriptive expressions (DE) [5,6] is presented into the Table 3.

Using the P transducer concept [3] we built a computational model that allows us to illustrate the influence of temperature on allelic gene expression (Figure 3).

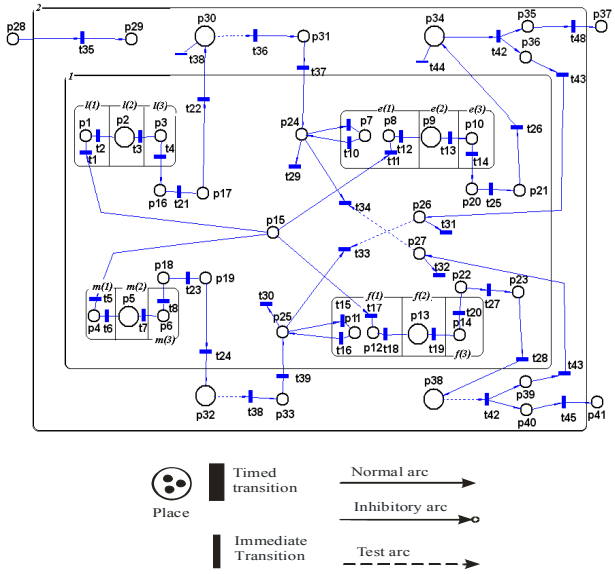

Figure 3. Screen snapshot of the descriptive *RTN* model of the P transducer model of dominance.

In Figure 3 the places *p2, p5, p9, p13, p30, p32, p34, p38* are mactonodes (macroplaces). For instance, to model the rule $(p_e, go)\|^{d_{13}}$, associated with the region delimited by the elementary membrane *e(2)*, using the DE (Table 3) we used the macroplace *p9* ($p9 \triangleright \bigcup_{i=46}^{49} p_i \|_{t_{i+6}}^{d_i} p_{i+1}$). The number of places that composes the subnet, which replaces the macroplace *p9* (Figure 4), correlates with the number of *RNA* polymerases transcribing the activated gene (Figure 3). $d_{13} = \sum_{i=52}^{55} d_i, m_9 = \sum_{i=46}^{50} m_i$.

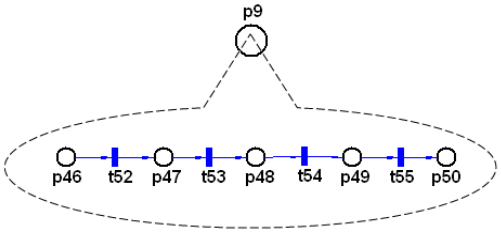

Figure 4. Subnet replacing the macronode *p9*.

Important characteristics of gene function such as differential gene expression, functional aspects of dynamic behaviour of gene expression regulation are illustrated through simulation.

Via the computational model we obtained the graphical representation of influence of temperature on allelic gene expression (Figure 5).

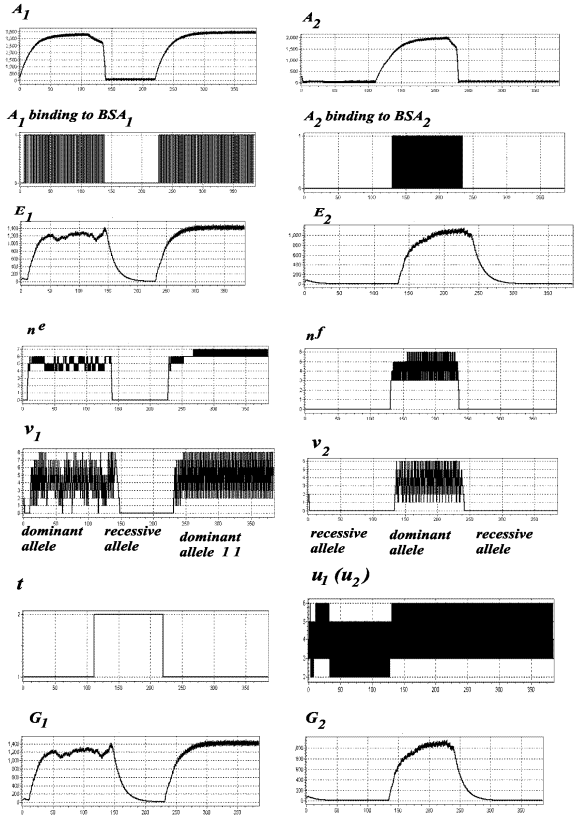

Figure 5. The simulation of the temperature dependent switching of the allelic genes.

Figure 5 illustrates that increasing the temperature from 20^0C to 35^0C the gene *f* (*e*) is transformed from a dominant (recessive) gene to a recessive (dominant) one.

Conclusions

A formal P transducer model of allelic gene network regulation is proposed to illustrate the dominance mechanism. Genes with their regulatory regions, responsible for observable treats, are encoded by continuous-time P systems of elementary membranes arranged into continuous chains. To get a clearer picture of the functional mechanism of allelic gene regulatory network and to monitoring small changes of gene activity profiles as response to external stimuli a predictive computational model of the P transducer has been built.

In the model of the P transducer of the living cell [4] the number of elementary membranes that map the gene-coding region correlates with the maximal number of RNA polymerases transcribing the activated gene.

The components of the P transducer model are encoded by the components of the descriptive Rewriting Timed Petri Nets. Both the dominance phenomena and the important characteristics of gene function such as differential gene expression, functional aspects of dynamic behaviour of gene expression regulation are demonstrated through simulation. Using of macronodes for mapping of some rules of P transducer (see Table 3) we optimized the P transducer model of the living cell, representing the gene–coding region only by one elementary membrane. On the other hand, using the macronodes we can obtain more accurate simulation results.

In this paper the allelic genes are modelled by means of the systems of elementary membranes, arranged into continuous chains, to elucidate all the relevant molecular interaction one-by-one with *DNA*, all functional aspects of real-time behaviour of allelic gene expression regulation. Our model is based on the principles of Systems biology that provides system integration of all components of hierarchical structure-functional organization of the living cell as an entire whole.

The P transducer model of the living cell permits us to develop efficient *in vivo* computational models for monitoring and prediction gene expression and protein profiles, and for determining protein interactions.

Our study is focused on elucidation of the molecular mechanisms underlying fundamental cellular processes, to decipher gene function. It is shown that the continuous-time P systems of elementary membranes, are appropriate for quantitative modelling of real gene regulatory networks.

References

[1]. Păun Gh. (2002)*Membrane Computing. An Introduction*,–Natural computing Series. ed. G. Rozenberg, Th. Back, A.E. EibenJ.N. Kok, H.P. Spaink, Leiden Center for Natural Computing, Springer – Verlag Berlin Heidelberg New York.

[2]. M.J. Perez-Jimenez, F.J. Romero (2005) "*Modelling EGFR signalling network using continuous membrane systems*`, In Proc. CMSB 2005, Edinburgh, April 3-5, , 118-129.

[3]. Ciobanu G., Păun Gh., Ştefanescu G. (2005) *P Transducers*, New Generation Computing.

[4]. Barbacari N., Profir A., Zelinschi C. (2005) *Gene regulatory network modelling by means of membrane Systems*, In Proc. WMC6 2005, Wien, Austria, July 18-21.

[5] Guţuleac E. (2004) *Descriptive Compositional Construction of GSPN Models for Performance Evaluation of Computer Systems*, In: Proceeding of 8-th International Symposium on Automatic Control and Computer Science, SACCS2004, Iaşi, România, ISBN 973-621-086-3.

[6] Profir A., Gutuleac E., Boian E., (2005) *Simulation of continuous time P systems using descriptive Timed Petri Nets,* In: Proceeding of 7-th International Symposium on Symbolic and Numeric Algorithms for Scientific Computing, SYNASC 2005, IEEE Computing Society, Timisoara, Romania, 25-29 September, 2005, pp. 458-461.

[7] Lewin B. (2004) *Genes*. Prentice Hall. Softcover.