

Modelling Molecular Genetic Triggers by Means of P Transducers* (Extended abstract)

A. PROFIR¹, E. BOIAN², N. BARBACARI³,
E. GUȚULEAC⁴, C. ZELINSCHI⁵

¹Institute of Applied Physics
Academy of Sciences of Moldova
E-mail: aurelia@cc.acad.md

²Institute of Mathematics and Computer Science
Academy of Sciences of Moldova
E-mail: lena@math.md

³Institute of Genetics
Academy of Sciences of Moldova
E-mail: nbarbacar@hotmail.com

⁴Department of Computer Science
Informatics and Microelectronics of Technical University of Moldova
E-mail: egutuleac@mail.utm.md

⁵Department of Mathematics and Computer Science
State University of Moldova
E-mail: cleozeli@usm.mail.md

Abstract

In this paper we use the concept of P transducers to model the gene expression regulatory mechanism on the basis of molecular genetic triggers in prokaryote and eukaryote cells.

A cell is a complex system where the processes of energy conversion are highly specialized. Living cells take energy from the environment (in the form of irradiation or chemical energy) and use it for the cell work, transforming it from one form into another. Due to the fact that they self-regulate its biochemical activities, cells are adapted to different conditions, responding to stimuli. Moreover, biochemical reactions evolve efficiently due to the fact that they are spatially localized and compartmentalized. Generally, living cells (prokaryote, eukaryote, neurons) which produce specific signals as a response to action of external factors might be defined as P transducers [1].

*This work is supported by IST-2001-32008 project "MolCoNet", CRDF-MRDA project, and BGP-II, Award No. MM2-3034.

This paper is a study of the switching mechanisms of molecular-genetic triggers (MGT) [4]. MGT play a key role in the processes of receiving, processing and transmitting of the information. MGT have two alternative functioning regimes (stable states) which can be switched from one stable state (activated/inactivated genes) to another one as a response to stimuli (e.g., temperature, UV radiation, pH, concentrations of specific molecules etc.).

Essentially, in MGT modelling it is important to adequately implement ways of interaction processes between regulatory proteins and RNA polymerase molecules with regulatory regions and promoters of genes. Interaction processes of proteins with DNA in prokaryote and eukaryote cells are modelled using the concept of symport/antiport P transducer (having only communication rules) [1]. Because a MGT system is not only reduced to interaction processes of different proteins with DNA sites, but also involves processes of proteins translation, interactions of enzymes with regulatory proteins (which ensure feedbacks), degradation processes of proteins, of genes copies, etc., it could be modelled by a P transducer where the computation is described by both communication and evolution rules.

We tried to model MGT systems using the concept of P transducers. We analyzed two cases of MGT systems:

- first, on the basis of the *lexA recA* genetic system, it is introduced a model of MGT in prokaryote cells; as control parameters one considers damaging factors (mutagen agents) which exert their effects amplifying the *recA* gene expression process;

- secondly, a regulatory mechanism of allelic gene expression of eukaryotic cells is modelled; this genetic system can translate external factors into proteins which determine dominant and recessive traits.

Experimentally, we have demonstrated that using external factors, such as mutagen agents (UV irradiation, chemical mutagens), temperature, the gene transcription process of *recA* gene can be controlled and directed. It is shown that the level of expression of *recA* gene correlates with the intensity/concentration of external control signals.

We introduce a discrete/continuous Timed Hybrid Petri Nets (THPN) models which are isomorphic to P transducer models of the MGT systems to simulate the gene switching mechanism in prokaryote and eukaryote cells. THPN comprise guard functions, a class of discrete/continuous locations, discrete/continuous transitions (taking into consideration rates, delay time), discrete/continuous test arcs, flow arcs, inhibitory arcs [5]. For every multiset of objects placed within each membrane of P transducer and for every rule associated to this membrane we put into correspondence a concrete discrete location and transition of *THPN*, respectively. Firing rates of transition fire in the *THPN* as functions of model parameters, reflecting actual (experimental) values of concentrations and rates of biochemical reactions.

The gene switching mechanisms of the *lexA recA* dependent recombination of *E. coli* and of allelic genes using Visual Hybrid Petri Nets (VHPN) software tool developed by employing the architecture of THPN are simulated. The VHPN simulation of the P transducer formal model of MGT permits us to analyze and verify the processing of objects (molecules) in living cells.

In the article the next topics are discussed. First, we give some details about

the operon model of gene regulation process in prokaryote and about the switching mechanism of MGT. Then we describe the results of a series of experiments destined to a deeper study of the switching mechanism of MGT which control the *recA* gene expression process. We continue with a P transducer model of MGT of the *lexA recA* genetic system; the VHPN simulation results of this P transducer model of MGT are then presented. We pass to a model of MGT of allelic genetic system, and end with screen snapshots of the VHPN simulation of the P transducer model of MGT of allelic gene expression.

References

- [1] Ciobanu G., Păun Gh., Ștefănescu Gh.: P transducers. *New Generation Computing*, to appear.
- [2] Jacob F., Monod J.: Gene activity regulation. In *Cellular regulatory mechanisms*, Cold Spring Harbor Symposia on Quantitative biology, v. XXVI, The biological Laboratory Cold Spring Harborg, L.I., New York, 1961, translated in Russian, ed. "Mir", Moscow, pp. 278–306.
- [3] Curtis H., Sue Barnes N.: *Biology*. Fifth edition, Worth Publishers, Inc., N.Y., 1989.
- [4] Kovarskii V.A., Profir A.V.: Recombination bistability on the basis of sigmoid kinetics of regulatory enzymes. *Biofizika*, 33 (1988), 758–762 (in Russian).
- [5] Guțuleac E., Reilean A., Boșhneaga C.: VPNP - software tool for modeling and performance evaluation using generalized stochastic Petri nets, In *Proc. of 6th International Conference on DAS2002*, Suceava, România, 2002, pp. 243–248.
- [6] Horii T., Ogawa T., Ogawa H.: Nucleotide sequence of the *lexA* gene of *E.coli*. *Cell*, 23 (1981), 689–697.
- [7] Bakhlanova I.V., Alexeyev A.A., Zaitzev E.N., Zaitzeva E.M., Lanzov V.A.: Comparative analysis of the structure and functions of *recA* gene from *Serratia marcescens* *S_b* and *Echerichia coli* *K-12*. *Molecular Genetics*, 26, 1 (1990), 3–11.
- [8] Lewin B.: *Genes*. Oxford University Press, 1997.
- [9] Priest F.G.: *Extracellular Enzymes*. Van Nestrand Reinhold (UK) Co.Ltd, 1984.
- [10] Kovarskii V.A., Profir A.V.: Trigger model of allelic gene expression. Dominance in transcription rate. *Mol. Biol.*, 31, 3 (1997), 377–380. Translated from *Molekulyarnaya Biologiya*, 31, 3 (1997), 454–457 (in Russian).
- [11] Knight A.W., Keenan P.O., Goddard N.J., Fielden P.R., Walmsley R.M.: A yeast based cytotoxicity and genotoxicity assay for environmental monitoring using novel portable instrumentation. *Journal of Environmental Monitoring*, 6 (2004), 71–79.