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PHYSICS OF OPEN SYSTEMS: EFFECTS OF THE IMPACT OF CHEMICAL STRESSORS ON DIFFERENTIAL GENE EXPRESSION[1]

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Abstract. *The technologies of the physics of open systems are applied to generate the systemic knowledge about variations in gene activity under the impact of chemical stressors. The system knowledge is automatically generated based on the genomic data obtained by using the microarray technology. The system knowledge has been used for scientific understanding and rational explanation of regular changes in gene activity depending on the biomaterial sample, type of the chemical and its concentration, and time series of experiments.*

Keywords: *knowledge generation technologies, systemic knowledge, microarrays, gene expression.*

INTRODUCTION

The physics of open systems (POS) has proposed an approach to the analysis of open natural, humanitarian, and anthropogenic systems in the context of holism in their natural scales and real complexity [1, 2]. The ideas and methods of the POS are embodied in new information technologies of the generation of systemic knowledge.

Technologies of POS generate systemic knowledge based on empirical data and provide its application with the following purpose:

— rational explanation of the effects of impact of various chemical stressors;
— scientific understanding of the effects of impact of toxic substances on biological systems;
— detection of genetic markers of the adverse effect of poisons;
— identification of potential hazard;
— increase in the accuracy and efficiency of the estimates of risk health under chemical effects.

In the present paper, we apply POS methods to specific problems of genetic toxicology to obtain scientific reconstructions of gene expression profiles, which reveal natural correlations between gene expression and concentration of the chemical with regard for time parameter [3]. Reconstructions of gene expression profiles answer the following questions:

— what genes naturally vary their activity under chemical action?
— what genes and how (identically or differently) react to impact of different chemicals?
— what is the form of the profile of the expression of each active gene?
— what are gene expression patterns with regard for the concentration of the chemical and the moments of time series?
— what is the minimum dose of the chemical for gene to react to chemical impact?

The numerosity and variety of the effects of toxic stressors show the high heterogeneity of biosystems hidden in genomic data. The patterns revealed using the POS are determined by the uncovered and explained intrasystem mechanisms, which form the states of systems under study.

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1. COMPLEXITY OF GENOMIC DATA ANALYSIS

The answer of biosystems to chemical action is considered as a result of the coordination of multiple intrasystem processes influencing the variation of gene activity. These processes are implemented in each biological object in a different way and set the specific levels of gene activity. Different biological objects can react to the same dose of a chemical by different levels of activity of the same gene. Analyzing the aftereffects at the genomic level is an important problem of systems biology.

To reveal natural responses of biosystems to chemical actions, purposeful studies with the use of microarray technologies are conducted. The parameters of experiments in such studies are the type of the chemical, concentration of the chemical, and time series. Each study provides the measured values of the levels of expression of tens of thousands of genes. Repeated tests are conducted for the reproducibility of the results at the points of experiments. An analysis of such great amount of data from systemic positions is an important bioinformatic problem.

In the paper we consider the process of generation and application of systemic knowledge in two problems of the analysis of empirical data obtained based on genomic technologies.

Problem 1. Determining the variations in the activity of genes in human colon cancer cells after exposure to oxidizers (H_2O_2 or menadione).

The gene expression was investigated in the time series (0.08, 0.25, 0.5, 1, 2, 4, 8, 16, 24 hours). 72 hybridizations for two oxidizers, two biological replicas, two-color joint hybridization, nine time points were obtained (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE15327).

Problem 2. Analyzing the gene expression in epithelial cells of tracheobronchial tissues in healthy people before and after an impact of HOCl oxidizer.

The experimental data on gene expression were used (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE11630). The parameters of the experiment: chemical concentration (0, 0.4, 1, 4 mM), time of chemical exposure (2 hours; 6 hours). The extent of the study: 24 experiments for two time points, four doses of the chemical, and three replicas.

2. GENERATION OF SYSTEMIC KNOWLEDGE

The POS technologies generate systemic knowledge by using only the empirical description of the biosystem in its states through state indices, parameters of the experiment, and variables that characterize the external environment of the system. The observable variability of the indices of the state of the biosystem is determined by scaled intrasystem correlations. The POS technologies represent the system as an integrated unit in the external format of attributed structure of binary relations between all the indices of the empirical description of biological system.

The system ontology is revealed by detecting the characteristic symmetries of the structure of binary relations (symmetries of singlets, doublets, triplets, localities) and generation of the complete sets of constructive models of systemic knowledge: systemic models, models of interaction, models of reference states [4–6]. The understanding and explanation of all the observable states of the system, intrasystem mechanisms, evolution of states, and emergent properties of the system are attained through the reconstruction of all actual states of the biosystem based on the systems language and qualitology of systemic knowledge [7, 8].

The problem on gene expression under chemical impact on biological objects can be solved based on POS technologies as a result of serial execution of five stages of a highly-automated technological process. Each stage is implemented by a certain POS technology (Fig. 1).

Empirical contexts are initial representations of systems. The context formation technology represents each biosystem under study as a normatively arranged database. In the problem on the gene expression profile, representations of gene ontology are used to separate the systems. The set of genes is structured in three representations (http:// www.genetools.no), which map biological processes, molecular functions, and cellular components, respectively. In each representation, the ontology has hierarchical structure. GO-categories correspond to structure levels. Each GO-category includes certain gene set. In the present paper, the solution of Problem 1 is shown for three GO-categories: (i) GO:0031324, negative regulation of cellular metabolic process (biological processes), (ii) GO:0016879, ligase activity, forming carbon-nitrogen bonds (molecular functions), and (iii) GO:0016023, cytoplasmic membrane-bounded vesicle (cellular components). The solution of Problem 2 is illustrated by the results obtained for the following GO-categories: (i) GO:0006979, response to oxidative stress (biological processes), (ii) GO:0050662, coenzyme binding (molecular functions), and (iii) GO:0005813, centrosome (cellular components).

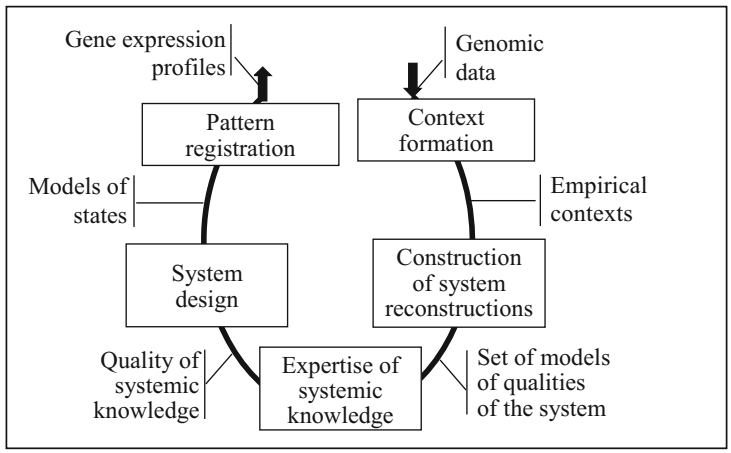

Fig. 1. Knowledge generation scheme.

TABLE 1. The Main Results of the Technology of Systemic Reconstruction

GO-category	Number				Quality evaluation of the reduction of complexity
	indices	binary relations	singlets	system models	
Problem 1					
GO:0031324	191	12029	3085	139	0.82
GO:0016879	100	3232	1728	80	0.97
GO:0016023	161	8573	3588	136	0.93
Problem 2					
GO:0006979	102	2409	1042	97	0.90
GO:0050662	165	6419	2211	157	0.79
GO:0005813	189	7701	2965	180	0.81

The effects obtained as a result of chemical actions are estimated as systemic responses of biological objects. Gene activities are revealed through internal systemic mechanisms. The patterns of variation of the activity of each gene obtain scientific explanation in the formal models of states of biosystems presented by GO-categories.

The technology of systemic reconstructions automatically derives systemic knowledge from empirical contexts. The objects of systemic knowledge are as follows:

— indices (they are characterized by systemic roles, semantic activity, involvement in the set of binary relations and structures of relations);

— system models (they are characterized by inhomogeneity carriers (singlets), structure, and morphology);

— models of reference states of the system (they are characterized by the structure and morphology, measures of the coordination of structures of relations, and measures of the variability of indices).

The set of objects of systemic knowledge forms the knowledge base about the mutual conditionality of genes and systemic effects of chemical action (Table 1).

The complexity inherent in each GO-category is uncovered through the reconstructive set of its system models. This fact is confirmed by rather high evaluations of the quality of reduction of the complexity inherent in the biosystems under study (it is characterized by the quantitative measure of overcoming the heterogeneity of genomic data).

The technology of system expertise evaluates the quality of the obtained knowledge. For all system models, objective complex indicators of quality (statefulness, homogeneity) are established. The share of high-quality models is used as a generalized characteristic of the completeness and perfection of the obtained systemic knowledge. System models generate models of reference states, which define the states in the qualitative-semantic world of the system. These models are mapped onto actual states of biological objects in the feature space of the system. The mapping quality is determined by the quality of the calculated mapping function (quality of a reference state) and by the quality of the verification of the model of reference state. The result of the mapping is models of the forms of embodiment of reference states of the system, which characterize the quality of the obtained knowledge about the states in the context of its applicability for detection, understanding, and explanation of the rules of formation of the systemic response to the chemical action. The results of systemic expertise are presented in Table 2.

TABLE 2. The Main Results of the Technology of Systemic Expertise

GO-category	Quality evaluations				Share of high-quality models
	Statefulness	Homogeneity	Reference	Verification of reference states	
Problem 1					
GO:0031324	0.86	0.92	0.72	0.98	0.74
GO:0016879	0.88	0.93	0.78	0.97	0.80
GO:0016023	0.89	0.94	0.76	0.96	0.91
Problem 2					
GO:0006979	0.76	0.98	0.66	0.92	1.00
GO:0050662	0.81	0.9	0.67	0.91	0.60
GO:0005813	0.55	0.75	0.64	0.92	0.97

TABLE 3. The Main Results of the Technology of Systemic Design

GO-category	Number of embodied references	Number of models of state	Average number of references per object	Share of explained indices	Share of indices with the level of values
Problem 1					
GO:0031324	3948	72	55	0.999	0.999
GO:0016879	1977	72	27	0.99	0.998
GO:0016023	3661	72	51	0.999	0.999
Problem 2					
GO:0006979	768	24	32	0.99	0.999
GO:0050662	1282	24	53	0.999	1
GO:0005813	1279	24	53	0.9996	0.9998

The objects of observation in their actual states are specified by the sets of values of indices. Each object is represented by its state in the feature space of the system. The scientific system reconstruction of actual states of biological objects are based on the models of forms of the embodiment of reference states. Any individual reconstruction is a scientific definition of the state of one specific biological object and is the formal quantitatively-semantic model of its state. The technology of system design solves all the problems of automatic generation of the reconstructions of states (Table 3).

The models of the reconstructions of actual states have revealed the complexity inherent in the system (the number of embodied references, average number of references per object), explained the variability of almost all indices, modeled the observable values of the indices by the levels of their values. The obtained systemic knowledge about the states of biological objects is a sufficient scientific basis to reveal and handle the rules that explain the effect of the chemical impact.

Problems of the analysis of differential gene expression can be solved as problems of revealing the rules of the form "chemical impact – variations in gene activity." The systemic knowledge about the reconstructions of the states of all biological objects explaining the variability of indices of their states was used in the problem solution. For the analysis of differential gene expression, the key attribute of the index in the reconstruction of states called value level is applied instead of the observable value of the index. This attribute is defined on the ordinal 17-step scale of the prevalence of levels, which envelopes the whole range of values of the index and characterizes the detailed structure of this range in the concepts of large, middle, and small values (Fig. 2).

The rule handling technology automatically obtains the solutions of specific-subject problems (Problem 1 and Problem 2) based on the systemic knowledge. Within the framework of this technology, problems are solved under the unified scheme: recovery of passes, aggregation of value levels, determination of active genes, and construction and typification of gene expression profiles.

The scale of the prevalence of levels models the value of indices by value levels on the basis of quantitatively-semantic models of the reconstructions of states. The value of each quantity in the reconstruction of states of the system is determined by the whole set of the backbone mechanisms that form these states. This property of reconstruction is used to recovery data passes by applying a special scale of recovery of values.

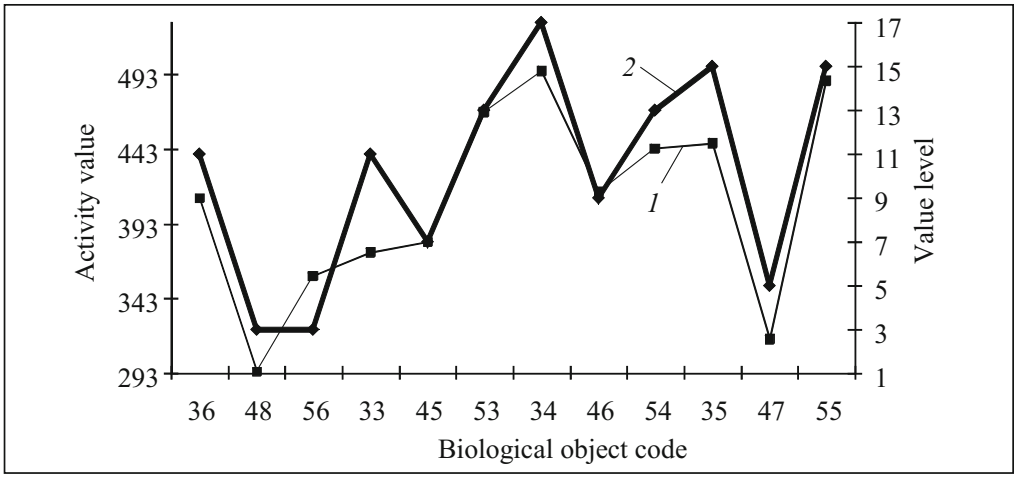

Fig. 2. Values of the activity (1) and levels of the values (2) for probe 1371123_at; W is concordance coefficient ($W = 0.96$).

Active genes are defined by applying statistical difference criteria (χ^2 criterion, Fisher's exact criterion, Mann–Whitney criterion, Wilcoxon criterion, Kraskel criterion, etc.) not to the values but to the value levels of the quantities.

Given multiply repeated experiments, the aggregated value levels of gene activity are determined for homogeneous data from the scale of aggregated levels and for inhomogeneous data from the scale of restored levels. The determinancy of the value levels of indices by system mechanisms allows evaluating the degree of data homogeneity at each point of the experiment and carrying out the aggregation with the evaluated reliability.

The gene expression profiles with respect to the parameters of the experiment are constructed for the aggregated value levels. The special features of the behavior of genes are revealed in profile typification.

3. DIFFERENTIAL GENE EXPRESSION UNDER THE ACTION OF OXIDIZERS

The key point of Problem 1 is to determine the set of genes whose activity is due to the effect of oxidizers (H_2O_2, menadione). To demonstrate the efficiency of the solution of this problem based on systemic knowledge, the data analyzed in [9] are used.

The data systems used to solve Problem 1 have passes of values of the observable indices. The reconstructions of the state of all the biological objects were constructed by POS methods. The value levels were defined with respect to the indices. For the overwhelming majority of the passed values of genes, value levels were recovered (97–99%) (Table 4).

The set of active genes is established according to the following rules. The differential expression under the action of chemicals at least at any one instant of time (if this condition is not satisfied, the gene is assumed to be inactive) is determined by the statistical method for each gene. For these instants of time, the value levels of gene activity are established on the scale of aggregated levels, separately for each chemical. The aggregated levels should belong to the ultimate domains of the scale (low or high levels), at least one of these domains should not be the domain values of the test group. If these conditions are satisfied, the gene is considered active; otherwise, it is low-active. Table 5 shows the distribution of the number of genes of GO-category with respect to the type of activity.

In comparison with the results presented in [9], the POS reveals a larger number of active genes and introduces a new gradation: low-active genes. The number of low-active genes in each GO-category exceeds the number of active genes.

The coincidence and difference of the sets of active genes obtained on the basis of POS and published in [9] can be specified on the example of GO:0016879: 41 active gene is revealed on the basis of POS and 23 active genes based on [9]. Both sets contain 15 genes with identical forms of activity; POS has not confirmed the activity of three genes presented in [9]; another result is obtained for five genes.

The activity of genes in [9] is established for each gene separately based on the given threshold of the difference with respect to a reference group at least at one point of time series. The activity of genes is established based on the POS from systemic positions:

TABLE 4. Data Quality Evaluation at the Stage of Rule Handling

GO-category	Recovered passes of values, %	Share of genes without level	Share of genes with the level of value on the scale	
			of aggregated levels	of restored levels
GO:0031324	99	0.07	0.81	0.12
GO:0016879	97	0.09	0.79	0.12
GO:0016023	99	0.07	0.79	0.13

TABLE 5. Distribution of the Number of Genes of GO-category by the Activity Type

Activity type	Number of genes for the category					
	GO:0031324		GO:0016879		GO:0016023	
	POS	[9]	POS	[9]	POS	[9]
Activity on H_2O_2	28	29	22	12	13	16
Activity on menadione	30	19	12	5	28	17
Activity on H_2O_2 and menadione	28	8	7	6	23	12
Low activity	97	—	49	—	90	—
No activity	6	133	8	75	5	114

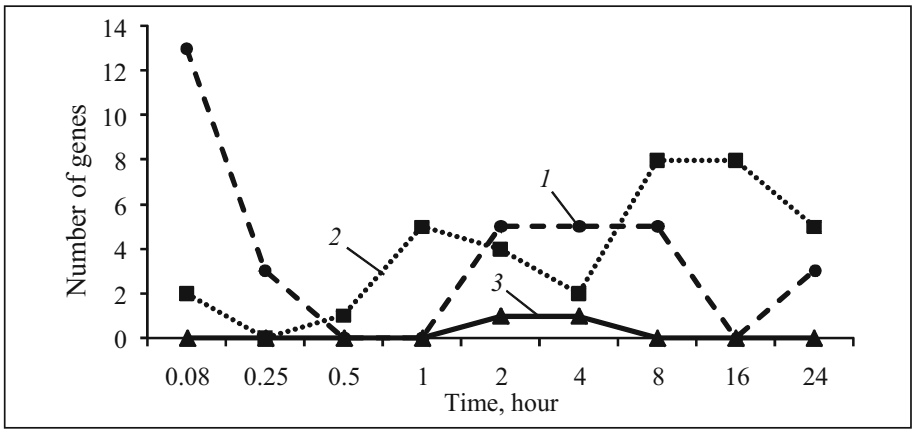

Fig. 3. Distribution of the number of POS-based active genes according to the types of chemicals (H_2O_2 (*1*), menadione (*2*), H_2O_2&menadione (*3*)) and time series (GO:0016879).

— the activity of genes in the biosystem is determined according to the holism principle and is an emergent property;

— intrasystem mechanisms of the determination of the level of each gene are revealed, understood, and have rational explanations;

— the level of each gene for each biological object is referred to the variability domain provided with system properties represented by the level prevalence scale;

— the aggregation of gene activity levels is carried out based on system properties of the levels, which allowed establishing the behavior (identical or different) of the variations of gene activity in different biological objects.

The differential gene expression varies in time and depends on the type of the chemical (Fig. 3).

The technology of handling of the rules constructs the gene expression profiles based on the aggregated levels of their values specified according to a special scale. This scale has five points: L (low level); $L-M$ (intermediate level between L and M); M (middle level); $H-M$ (intermediate level between H and M); H (high level). An analysis of the profiles has shown a substantial relation of the profile and gene response to the chemical at the first instant of time (Fig. 4). A characteristic feature of the profiles is the decrease in the activity level by the time $t = 0.5$, increase in the activity level at time $t = 4$ (for high level), $t = 2$ (for low level), return for $t = 24$ of the majority of genes to the initial activity level, and the loss of activity for the other genes.

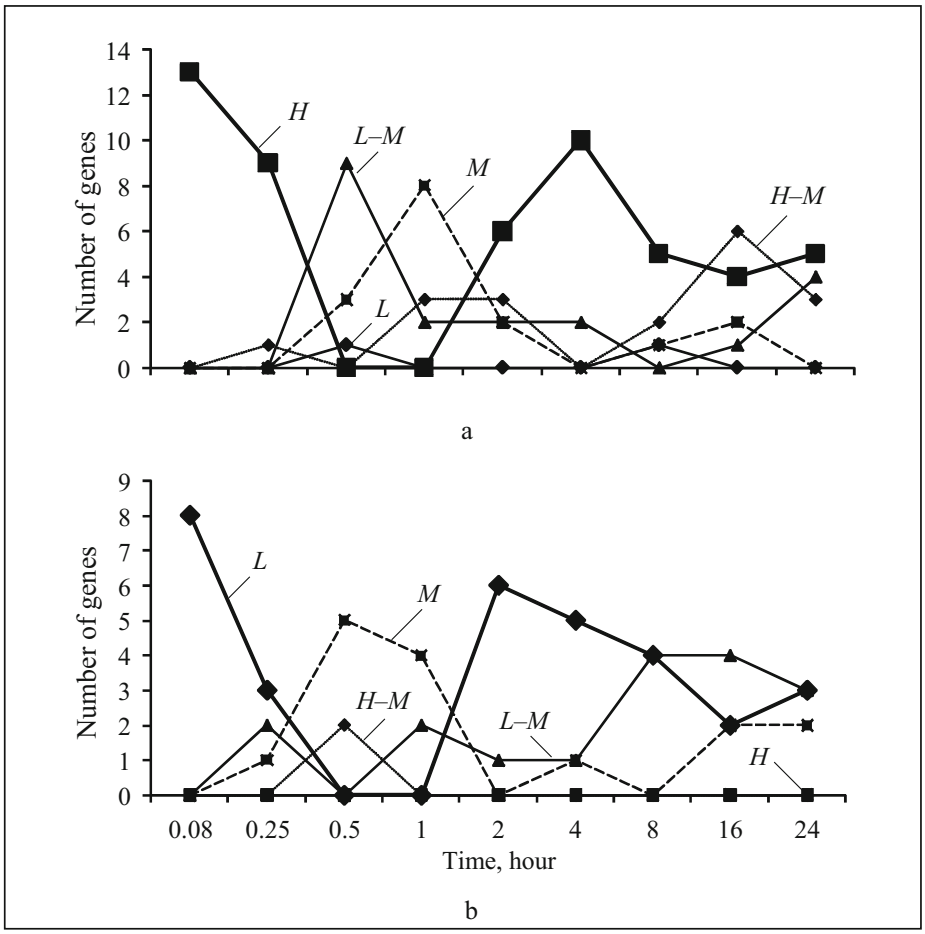

Fig. 4. Distribution, according to the instants of time of the time series, of the number of POS-based active genes exposed to H_2O_2, with high (a) and low (b) levels of value for $t = 0.08$ (GO:0016879).

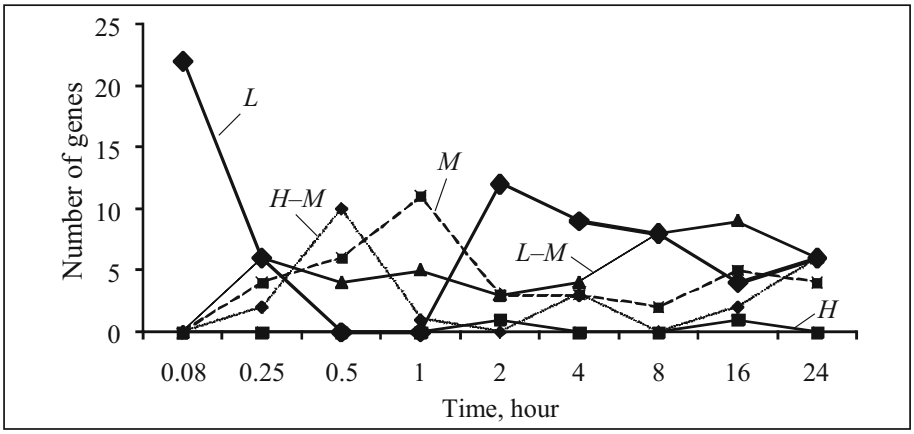

Fig. 5. Distribution, according to the instants of time of the time series, of the number of active and low-active genes exposed to H_2O_2, with low level of values for $t = 0.08$ (GO:0016879): decrease in the activity level for $t = 0.5$; increase in the activity level at time $t = 2$; return of the part of genes to the initial activity level to $t = 24$; the loss of activity for the other genes.

TABLE 6. The Number of Models within the Class

GO-category	The number of models in the class		
	1st class	2nd class	3rd class
GO:0006979	127	125	82
GO:0050662	221	192	126
GO:0005813	271	248	82

The type of the chemical and gene response for $t = 0.08$ restrict the gene activity range in the whole time series. Along with active genes, POS determines low-active genes. The distribution of the set of active and low-active genes is similar to the distribution of the set of active genes (Fig. 5).

The difference of genes in the activity is related only to the choice of the degree of expression of the effect of chemical action. The choice of such a measure is specified by objective research problems, and the result of the choice obtains a system explanation in any case.

4. ANALYSIS OF THE GENE EXPRESSION OF EPITHELIUM CELLS UNDER THE EFFECT OF HOCL OXIDIZER

The solution of Problem 2 is related to detecting genetic biomarkers to evaluate the risk of the adverse effect of HOCl-toxicant. To show the advantages of the solution of this problem based on systemic knowledge, the data analyzed in [10] are used.

The data systems representing GO-categories are characterized by a great number of indices and small presentability of their values (only 24 biological objects). The POS methods were used to construct the reconstructive sets of formal models, sufficient to obtain the models of states of all the biological objects and to determine the levels of values of almost all genes.

Based on the POS technologies, the models of forms of the embodiment of the references, with explicit specificity to the time parameter were obtained (Table 6). Each such model can be referred to one of the following three classes.

1st class. Models typical of the instant of time of 2 hours;

2nd class. Models typical of the instant of time of 6 hours;

3rd class. Models typical of both times.

Applying the classification of models of the forms of embodiment within the limits of variation of the other parameter of the experiment (chemical concentration) does not reveal explicit specific effect (Tables 7 and 8).

To determine the activity profile of each gene, the generalized results of repeated studies at each point of the experiment are used (Table 9).

For the majority of genes in each GO-category the level of values is obtained according to the aggregated scale. This fact suggests that the results of multiply repeated experiments for the groups of biological objects are close for these genes. For a great number of genes (~ 30 %) the response to the chemical effect is apparently ambiguous.

The set of active genes is specified according to the following rules. For each gene, the variation in its activity with respect to the reference group is determined by the statistical method for at least one concentration of the chemical for the given instant of time (if this condition is not satisfied, the gene is considered inactive). If the aggregated gene levels in the reference group and in the revealed exposed group belong to different domains on the special scale of levels, the gene is considered active. If this condition is not satisfied, i.e., there is no significant difference in the levels of values, the gene is considered low-active. The distribution of the number of genes according to the activity type is shown in Table 10.

For each GO-category, typical profiles of the expression of active genes with respect to the concentration of the chemical are constructed for the fixed value of the time parameter. Three classes of reference profiles of the variation in the gene activity are distinguished (Table 11):

— for low concentrations of the chemical (0.4 and 2 mM);

— for high concentrations of the chemical (4 mM);

— for different concentrations of the chemical.

The activity of genes in this study depends on both parameters of the experiment, exposure time and chemical concentration.

TABLE 7. Share of Models of the Forms of Embodiment of References

GO-category	Share of models of forms of the embodiment							
	1st class for chemical concentration				2nd class for chemical concentration			
	0	0.4 mM	1 mM	4 mM	0	0.4 mM	1 mM	4 mM
GO:0006979	0.16	0.26	0.24	0.33	0.26	0.27	0.28	0.18
GO:0050662	0.20	0.26	0.26	0.27	0.25	0.32	0.24	0.19
GO:0005813	0.18	0.27	0.27	0.28	0.33	0.26	0.22	0.19

TABLE 8. Share of Models of Forms of the Embodiment of References of 3rd Class

GO-category	Share of models of forms of the embodiment							
	for two hours for the concentration				for six hours for the concentration			
	0	0.4 mM	1 mM	4 mM	0	0.4 mM	1 mM	4 mM
GO:0006979	0.29	0.21	0.28	0.23	0.27	0.20	0.26	0.27
GO:0050662	0.25	0.27	0.25	0.22	0.22	0.23	0.27	0.28
GO:0005813	0.27	0.25	0.22	0.27	0.21	0.20	0.28	0.31

TABLE 9. Distribution of the Share of Genes by the Type of Scales of Levels and Time

Scale type	Share of genes in the category					
	GO:0006979		GO:0050662		GO:0005813	
	2 hours	6 hours	2 hours	6 hours	2 hours	6 hours
Aggregated levels	0.65	0.66	0.72	0.65	0.74	0.75
Restored levels	0.25	0.21	0.19	0.25	0.16	0.15
No level	0.11	0.13	0.09	0.09	0.10	0.10

TABLE 10. Distribution of the Number of Genes by the Type of Activity

Activity type	Number of genes in the category		
	GO:0006979	GO:0050662	GO:0005813
Activity for two hours	12	22	25
Activity for six hours	13	14	29
Activity for two and six hours	3	1	6
Low activity	33	50	93
No activity	42	77	40

TABLE 11. Distribution of the Number of Genes by the Form of Activity and Parameters of the Experiment

GO-category	Number of genes					
	active	low-active	active	low-active	active	low-active
	low concentration		high concentration		different concentrations	
for two hours						
GO:0006979	4	4	0	3	8	7
GO:0050662	10	9	5	5	7	6
GO:0005813	11	23	1	8	13	9
for six hours						
GO:0006979	4	7	7	7	2	5
GO:0050662	2	11	6	12	6	7
GO:0005813	4	17	11	23	14	13

The POS methods have overcome the heterogeneity of genomic data. Despite the small number of biological objects (24) in Problem 2 and a larger number of biological objects (72) in Problem 1, the number of the obtained system models in these problems is comparable. The number of active genes in Problem 2 is less than in Problem 1. This fact is manifested already at the stage of obtaining the aggregated levels of values. The system effects in the determination of the differential expression to the specific chemical effect in Problem 2 are more various than in Problem 1. The POS methods in each of these problems yield certain system answer.

CONCLUSIONS

Problems of systems biology related to reconstruction of gene networks, metabolic, regulatory systems of cells, tissues, organs, organisms based on the analysis of multiparameter heterogeneous experimental data obtained by genomic, transcriptomic, proteomic, and metabolomic methods are an important domain of application of POS technologies. The POS methods ensure the creation of the scientific base for the solution of these problems whose kernel is the systemic knowledge about the mechanisms, processes, and properties in complex biological systems. In the present paper, we have shown a unified scheme of the generation of systemic knowledge and its application for the scientific understanding and rational explanation of the effects of chemical stressors on biological systems, detection of genetic markers of the adverse effect of the chemicals, and identification of potential hazard.

The first stage of the considered scheme of the solution of the problem on the differential gene expression based on the POS is automatic generation of the system ontology of variations in the gene activity with respect to genomic data: knowledge about the system mechanisms that determine the levels of gene activity; reconstruction of the states of biological objects; and models of the activity of genes in the states. The second stage of the solution scheme is filling the system ontology with estimates: completeness and perfection of the systemic knowledge, the quality of the formal models of reference states; adequacy of the reconstructed states; and the quality of modeling of the value of gene activity. The third stage of the solution scheme is using the system ontology to reveal natural variations in gene activity with respect to the parameters of the experiment.

POS ensures the solution of problems of postgenomic studies on the basis of systemic knowledge. The POS methods overcome the heterogeneity of genomic data, reveal and explain the activity of genes due to the genome in the large, and eliminate the uncertainty of system responses.

REFERENCES

1. T. Kachanova and B. Fomin, “Physics of systems is a postcybernetic paradigm of systemology,” in: Proc. Intern. Symp. “Science 2.0 and Expansion of Science: S2ES” in the context of the 14th World Multi-Conference on Systemics, Cybernetics and Informatics WMSCI 2010, June 29 –July 2, 2010, Orlando, USA (2010), pp 244–249.
2. T. Kachanova and B. Fomin, “Physics of open systems: Generation of system knowledge,” J. Systemics, Cybernetics and Informatics, **11**, No. 2, 73–82 (2013).
3. V. Ageev, B. Fomin, O. Fomin, et al., “Physics of open systems: A new approach to use genomics data in risk assessment,” in: The Continuum of Health Risk Assessments, InTech (2012), pp. 135–160.
4. T. L. Kachanova and B. F. Fomin, Fundamentals of the Systemology Phenomenal [in Russian], Izd. SPbGETU LETI, St. Petersburg (1999).
5. T. L. Kachanova and B. F. Fomin, The Metatechnology of System Reconstructions [in Russian], Izd. SPbGETU LETI, St. Petersburg (2002).
6. T. L. Kachanova and B. F. Fomin, The Technology of System Reconstructions [in Russian], Politekhnika, St. Petersburg (2003).
7. T. L. Kachanova and B. F. Fomin, An Introduction to Systems Language [in Russian], Nauka, St. Petersburg (2009).
8. T. L. Kachanova and B. F. Fomin, Methods and Technologies for Generating a Systemic Knowledge: A Manual for Masters and Postgraduate Students [in Russian], Izd. SPbGETU LETI, St. Petersburg (2012).
9. J. Briede, J. Delfi, T. Kok, et al., “Global gene expression analysis reveals differences in cellular responses to hydroxyl and superoxide anion radical-induced oxidative stress in caco-2 cells,” Toxicolog. Sci., **114**, No. 2, 193–203 (2010).
10. L. Zhu, J. Pi, S. Wachi, et al., “Identification of Nrf2-dependent airway epithelial adaptive response to proinflammatory oxidant-hypochlorous acid challenge by transcription profiling,” Amer. J. Physiol. Lung Cell Mol. Physiol., **294**, No. 3, 469–477 (2008).