Институт проблем передачи информации РАН

Research and Training Center "*Bioinformatics*"

Head – Mikhail S. Gelfand, Dr.Sc. (Biol.), Ph.D. (Math.)
Phones: (095) 209-42-25, 8-916-609-29-71; E-mail: gelfand@iitp.ru

Leading researchers:

Dr.Sc. (Biol.), PhD. (Math.)	A.A. Mironov	PhD. (Biol.)	D.A. Rodionov
PhD. (Med.)	A.E. Kazakov	PhD. (Biol.)	A.B. Rakhmaninova

DIRECTIONS OF RESEARCH ACTIVITY:

- development and application of methods for functional annotation and metabolic reconstruction of bacterial genomes;
- study of evolution of regulatory systems;
- study of the structure, function and evolution of riboswitches;
- development of algorithms for prediction of functional pecificity of enzymes, transporters, and regulators from large protein families;
- development of algorithms and programs for gene recognition;
- study of function, regulation and evolution of alterantive splicing.

MAIN RESULTS

Metabolic reconstruction and comparative regulatory analysis was done for seven completely or draft-quality genomes of delta-proteobacteria. This is a poorly studied group of metal-reducing bacteria used for bioremediation of toxic waste. A number of key pathways involved in the biosynthesis of building blocks and cofactors, metal-ion homeostasis, stress response, and energy metabolism were analyzed using a combination of regulatory sequence detection and analysis of genomic context. We identified candidate binding sites for four regulators of known specificity (BirA, CooA, HrcA, sigma-32), four types of metabolite-binding riboswitches (RFN-, THI-, B12-elements and S-box), and new binding sites for the FUR, ModE, NikR, PerR, and ZUR transcription factors, as well as for the previously uncharacterized factors HcpR and LysX. After reconstruction of the corresponding metabolic pathways and regulatory interactions, we identified possible functions for a large number of previously uncharacterized genes covering a wide range of cellular functions. Phylogenetically diverse delta-proteobacteria were shown to have homologous regulatory components. This study for the first time demonstratef the adaptability of the comparative genomic approach to de novo reconstruction of a regulatory network in a poorly studied taxonomic group of bacteria.

The comparative genomics approach was used to analyse the KdgR regulon in completely sequenced genomes of eight enterobacteria, including plant pathogen Erwinia chrysanthemi, and two Vibrio species. KdgR is the main regulator of the pectinolysis pathway, a major virulence factor of plant pathogenes. Application of a signal recognition procedure complemented by operon structure and protein sequence analysis allowed identification of new candidate genes of the KdgR regulon. Most of these genes were found to be controlled by the cAMP-receptor protein, a global regulator of catabolic genes. At the next step, regulation of these genes in Erw. chrysanthemi was experimentally verified using in vivo transcriptional fusions and an attempt was made to

clarify the functional role of the predicted genes in pectin catabolism. It was found that the KdgR protein, previously known as a repressor, positively regulates expression of two new members of the regulon, phosphoenolpyruvate synthase gene ppsA and an adjacent gene, ydiA, of unknown function. Other predicted regulon members, namely chmX, dhfX, gntB, pykF, spiX, sotA, tpfX, yeeO and yjgK, were found to be subject to classical negative regulation by KdgR. Possible roles of newly identified members of the Erw. chrysanthemi KdgR regulon, chmX, dhfX, gntDBMNAC, spiX, tpfX, ydiA, yeeO, ygjV and yjgK, in pectin catabolism were characterized. Finally, complete reconstruction of the KdgR regulons in various gamma-proteobacteria yielded a metabolic map reflecting a globally conserved pathway for the catabolism of pectin and its derivatives with variability in transport and enzymic capabilities among species. In particular, possible non-orthologous substitutes of isomerase KduI and a new oligogalacturonide transporter in the Vibrio species were detected.

One more regulator of pectinolysis is PecS. It belongs to the MarR family, also controls the synthesis of various other virulence factors, such as cellulases and indigoidine. The PecS consensus-binding signal, CGANWTCGTATATTACGANNNCG was determined by computational analysis and confirmed in experiment. Candidate sites were detected in the regions involved in PecS of previously characterized target genes. Preliminary scanning of the E. chrysanthemi genome sequence with the derived signal revealed the presence of strong PecS-binding sites in the intergenic region between fliE and fliFGHIJKLMNOPQR which encode proteins involved in the biogenesis of flagellum. In subsequent experiment it was shown that PecS directly repressed fliE expression. Thus, PecS was shown to control the synthesis of virulence factors required for the key steps of plant infection

We characterized the methionine metabolic pathway and the methionine regulons in available genomes of Gram-positive bacteria. A large number of methionine-specific RNA regulatory elements were identified. S-boxes were shown to be widely distributed in Bacillales and Clostridia, whereas methionine-specific T-boxes occurred mostly in Lactobacillales. A candidate binding signal (MET-box) for a hypothetical methionine regulator, possibly MtaR, was identified in Streptococcaceae, the only family in the Bacillus/Clostridium group of Gram-positive bacteria having neither S-boxes, nor methionine-specific T-boxes. Positional analysis of methionine-specific regulatory sites complemented by genome context analysis lead to identification of new members of the methionine regulon, both enzymes and transporters, and reconstruction of the methionine metabolism in various bacterial genomes. In particular, we found candidate transporters for methionine (MetT) and methylthioribose (MtnABC), as well as new enzymes forming the S-adenosylmethionine recycling pathway. Methionine biosynthetic enzymes in various bacterial species are quite variable. In particular, Oceanobacillus iheyensis possibly uses a homolog of the betaine-homocysteine methyltransferase bhmT gene from vertebrates to substitute missing bacterial-type methionine synthases. Some of the predictions are now subject to experimental analysis in a collaborating laboratory.

Candidate attenuators were identified that regulate operons responsible for biosynthesis of branched amino acids, histidine, threonine, tryptophan, and phenylalanine in gamma- and alpha-proteobacteria, and in some cases in low-GC Gram-positive bacteria, Thermotogales and Bacteroidetes/Chlorobi. This allowed us not only to describe the evolutionary dynamics of regulation by attenuation of transcription, but also to annotate a number of hypothetical genes. In particular, orthologs of ygeA of Escherichia coli were assigned the branched chain amino acid racemase function. Three new families of histidine transporters were predicted, orthologs of yuiF and yvsH of Bacillus sub-

tilis, and lysQ of Lactococcus lactis. In Pasteurellales, the single bifunctional aspartate kinase/homoserine dehydrogenase gene thrA was predicted to be regulated not only by threonine and isoleucine, as in E. coli, but also by methionine. In alpha-proteobacteria, the single acetolactate synthase operon ilvIH was predicted to be regulated by branched amino acids-dependent attenuators. Histidine biosynthetic operons his were predicted to be regulated by histidine-dependent attenuators in Bacillus cereus and Clostridium difficile, and by histidine T-boxes in L. lactis and Streptococcus mutans.

In studying the sigma(32) and HrcA regulons in beta- and gamma-proteobacteria, we found some new potential participants in the heat shock response and proposed the protein disulfide isomerase function for one of them. We described the connection between the two regulons through cross-regulation of the HrcA repressor and sigma(32) in some beta-proteobacteria.

In collaboration with experimentalists we characterized a novel phytase PhyA from Obesumbacterium proteus. Phytases are enzymes with wide application in agriculture. The cleavage site of the PhyA signal peptide was predicted and experimentally proved. Based on protein sequence similarity of PhyA and its homologs, the phytases were shown to form a novel subclass of the histidine acid phosphatase family.

We developed an algorithm for identifying orthologous sets of genes that deviate from a clock-like model of evolution. The approach used is based on comparing the evolutionary distances within a set of orthologs to a standard intergenomic distance, which was defined as the median of the distribution of the distances between all one-to-one orthologs. Under the clock-like model, the points on a plot of intergenic distances versus intergenomic distances are expected to fit a straight line. A statistical technique to identify significant deviations from the clock-like behavior was developed. For several hundred analyzed orthologous sets representing three well-defined bacterial lineages, the alpha-Proteobacteria, the gamma-Proteobacteria, and the Bacillus-Clostridium group, were analyzed, and it was found that the clock-like null hypothesis could not be rejected for approximately 70% of the sets, whereas the rest showed substantial anomalies. Subsequent detailed phylogenetic analysis of the genes with the strongest deviations indicated that over one-half of these genes probably underwent a distinct form of horizontal gene transfer, xenologous gene displacement, in which a gene is displaced by an ortholog from a different lineage. The remaining deviations from the clock-like model could be explained by lineage-specific acceleration of evolution. The results indicate that although xenologous gene displacement is a major force in bacterial evolution, a significant majority of orthologous gene sets in three major bacterial lineages evolved in accordance with the clock-like model. The developed approach allows for rapid detection of deviations from this mode of evolution on the genome scale.

Alternative splicing of cancer/testis antigens (CT-antigens) was analyzed. These proteins are predominantly expressed in cancer and testis and thus are possible targets for immunotherapy. Most of them form large multigene families. The evolution of the MAGE-A family of CT-antigens was shown to be characterized by four processes: (1) gene duplications; (2) duplications of the initial exon; (3) point mutations and short insertions/deletions inactivating splicing sites or creating new sites; and (4) deletions removing sites and creating chimaeric exons. All this concerns the genomic regions upstream of the coding region, creating a wide diversity of isoforms with different 5'-untranslated regions. Many of these isoforms are gene-specific and have emerged due to point mutations in alternative and constitutive splicing sites. There are also examples of chimaeric mRNAs, likely produced by splicing of read-through transcripts. Since

there is consistent use of homologous sites for different genes and no random, indiscriminate use of pre-existing cryptic sites, it is likely that most observed isoforms are functional, and not result from relaxed control in transformed cells.

We tested the hypothesis that alternative splicing is correlated with contact regions of protein-protein interactions. Protein sequence spans involved in contacts with an interaction partner were delineated from atomic structures of transient interaction complexes and juxtaposed with the location of alternatively spliced regions detected by comparative genome analysis and spliced alignment. The total of 42 alternatively spliced isoforms were identified in 21 amino acid chains involved in biomolecular interactions. Using this limited dataset and a variety of sophisticated counting procedures we were not able to establish a statistically significant correlation between the positions of protein interaction sites and alternatively spliced regions.

We developed a method for automated selection of residues that determine the functional specificity of proteins with a common general function (the specificity-determining positions [SDP] prediction method). Such residues are assumed to be conserved within groups of orthologs (that may be assumed to have the same specificity) and to vary between paralogs. Thus, considering a multiple sequence alignment of a protein family divided into orthologous groups, one can select positions where the distribution of amino acids correlates with this division. Unlike previously published techniques, the introduced method directly takes into account nonuniformity of amino acid substitution frequencies. In addition, it does not require setting arbitrary thresholds. Instead, a formal procedure for threshold selection using the Bernoulli estimator is implemented. We tested the SDP prediction method on the LacI family of bacterial transcription factors and a sample of bacterial water and glycerol transporters belonging to the major intrinsic protein (MIP) family. In both cases, the comparison with available experimental and structural data strongly supported our predictions.The method was implemented in the SDPpred Internet server that is available at http://math.genebee.msu.ru/~psn/. The input of SDPpred is a multiple alignment of a protein family divided into a number of specificity groups, within which the interaction partner is believed to be the same. SDPpred does not require information about the secondary or three-dimensional structure of proteins. It produces a set of the alignment positions (specificity determining positions) that determine differences in functional specificity.

Invited talks at conferences:

– Scientific session of the Computer Science Division of RAS "Information technologies in biology (bioinformatics)" (Moscow, January 2004) – M.S. Gelfand, A.A. Mironov.
– 12th Int. Conf. "AIDS, Cancer and RelatedProblems" (St. Petersburg, May 2004) – M.S. Gelfand.
– 3rd Meeting of the Vavilov Society "Genetics in the XXI century: current state and development perspectives" (Moscow, June 2004) – M.S. Gelfand, A.A. Mironov.
– Meeting of HHMI International Research Scholars (Tallinn, Estonia, June 2004) – М.С. Гельфанд.
– 3rd Meeting of Russian Biophysicists (Voronezh, June 2004) – D.A. Ravcheev.
– Second International Conference "Genomics, Proteomics and Bioinformatics for Medicine" (Moscow, July 2004) – M.S. Gelfand.
– 4th International Conference "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Novosibirsk, July 2004) – M.S.Gelfand, A.A.Mironov, D.A. Ravcheev.

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– International BCB Workshop on Gene Annotation Analysis & Alternative Splicing (Berlin, Germany, December 2004) – M.S. Gelfand.

International trips and collaboration: Lawrence Berkeley National Laboratory, Berkeley, USA (D.A.Rodionov, A.E.Kazakov); Institute of Bioinformatics GSF, Munich, Germany (M.S.Gelfand, A.A.Mironov); Ludwig Institute of Cancer Research, London, UK (M.S.Gelfand); INRA, Paris, France (M.S.Gelfand); Institute Pasteur, Paris, France (M.S.Gelfand).

GRANTS:

- **Russian Academy of Sciences, program «Molecular and Cellular Biology».**
- **Russian Academy of Sciences, program «Origin and Evolution of the Biosphere»:** project «Early stages of evolution of bacterial and archaeal metabolic and regulatory networks».
- **Russian Fund of Basic Research (No. 04-04-49440):** «Comparative genomics of alternative splicing».
- **Russian Fund of Basic Research (No. 04-04-49361):** «Metabolic reconstruction of bacterial genomes».
- **Howard Hughes Medical Institute: grant 55000309.**
- **Ludwig Institute for Cancer Research:** project "Computer-aided Studying of Human Transcriptome".

TRAINING ACTIVITIES

- **Supervision of Ph.D. students**
  - E.D. Stavrovskaya (IITP RAS, A.A. Mironov).
  - D.A. Ravcheev (Department of Bioengineering and Bioinformatics, MSU; and IITP RAS, M.S. Gelfand).
  - E.O. Ermakova (Department of Bioengineering and Bioinformatics, MSU; and IITP RAS, M.S. Gelfand).
  - G.Yu. Kovaleva (Department of Bioengineering and Bioinformatics, MSU; and IITP RAS, M.S. Gelfand).
  - O.V. Kalinina (Department of Bioengineering and Bioinformatics, MSU, A.B. Rakhmaninova).
  - R.N. Nurtdinov (Department of Bioengineering and Bioinformatics, MSU, A.A. Mironov).
  - V. Boeva (Department of Bioengineering and Bioinformatics, MSU, A.A. Mironov).
  - A.V. Gerasimova (State Scientific Center GosNIIGenetika, M.S. Gelfand).
  - E. Kotelnikova (State Scientific Center GosNIIGenetika, M.S. Gelfand).
  - A. Neverov (State Scientific Center GosNIIGenetika, A.A. Mironov and M.S. Gelfand).
- **Lectures, seminars, and development of lecture courses for the Department of Bioengineering and Bioinformation of the Moscow State University**
  - Course «Primer in computers», 1st year, 1st semester (A.B. Rakhmaninova).
  - Course «Bioinformatics: comparison of amino acid sequences», 1st year, 2nd semester (A.B. Rakhmaninova).

- Lecture cycle «Introduction to molecular biology», 2nd year, 1st semester (M.S. Gelfand, A.A. Mironov).
- Course «Bioinformatics: nucleic acids», cycle «Phylogenetic trees», 2nd year, 1st semester (A.B. Rakhmaninova).
- Course «Bioinformatics», cycle «Gene recognition», 2nd year, 2nd semester (M.S. Gelfand).
- Course «Bioinformatics», cycle «Identification of regulatory signals», 2nd year, 2nd semester (D.A. Ravcheev, M.S. Gelfand).
- Course «Introduction to algorithms», 2nd year, 2nd semester (A.A. Mironov).
- Course «Algorithms of bioinformatics», 3rd year, 1st semester (A.A..Mironov).

- **Course work of students at the Department of Bioengineering and Bioinformation of the Moscow State University**

2nd year

- Ya. Voldgorn (I.I. Artamonova and M.S. Gelfand) «Evolution of genes from the PAGE family».
- S. Garushyants (D.A. Ravcheev, A.V. Gerasimova and M.S. Gelfand) «Computer anaalysis of the tryptophan biosynthesis operons in archaeal genomes».
- M. Tsyganova (D.A. Ravcheev, A.V. Gerasimova and M.S. Gelfand) «Regulation of nitrogen fixation in archaea».
- A. Zinin (A.A. Mironov) «Computer modeling of evolution of populations».
- S. Eremeev (O.V. Kalinina and A.B. Rakhmaninova) «Identification of positions determining specificity of malate and lactate dehydrogenases using SDPpred».
- A. Panchin (I. Merkeev and A.A. Mironov) «Genome-specific genes of Bacillus subtilis».
- O. Koborova (O.V. Kalinina and A.B. Rakhmaninova) «Analysis of residues determining functional specificity of guanylate and adenylate cyclases».
- I. Ignatovich (A. Golovin and A.B. Rakhmaninova) «Dynamic modeling of interactions of PurR and RbsR repressors with their operators».

3rd year

- L. Sycheva (E.Permina and M.S.Gelfand) «Reglation of SOS-ответа in eubacteria».

AWARDS

- D.A. Ravcheev: diploma of the International Conference of Students and Young Scientists "Lomonosov-2004".
- M.S. Gelfand: "Best Scientist of the Russian Academy of Sciences" award (Russian Science Support Fund).

PUBLICATIONS IN 2004

Published articles and book chapters

1. Гельфанд М.С. Вычислительная геномика: от пробирки к компьютеру и обратно // Biomediale: Современное общество и геномная культура. Под ред. Д. Булатова. Государственный центр современного искусства, Калининградский филиал. 2004. С. 28-39.
2. Гельфанд М.С. Эволюция альтернативного сплайсинга // Русский журнал ВИЧ/СПИД и родственные проблемы. 2004. Т. 8. № 2. С. 16.

3. Миронов А.А., Гельфанд М.С. Предсказание и компьютернай анализ экзон-интронной структуры генов человека // Молекулярная биология. 2004. Т. 38. № 1. С. 82-91.
4. Artamonova I.I., Gelfand M.S. Evolution of the exon-intron structure and alternative splicing of the MAGEA family of cancer/testis antigens // J. Molecular Evolution. 2004. V. 69. No. 5. P. 620-631.
5. Iarovaia O.V., Bystritskiy A., Ravcheev D., Hancock R., Razin S.V. Visualization of individual DNA loops and a map of loop domains in the human dystrophin gene // Nucleic Acids Res. 2004. V. 32. No. 7. P. 2079-2086.
6. Kalinina O.V., Mironov A.A., Gelfand M.S., Rakhmaninova A.B. Automated selection of positions determining functional specificity of proteins by comparative analysis of orthologous groups in protein families // Protein Science. 2004. V. 13. No. 2. P. 443-456.
7. Kalinina O.V., Novichkov P.S., Mironov A.A., Gelfand M.S., Rakhmaninova A.B. SDPpred: a tool for prediction of amino acid residues that determine differences in functional specificity of homologous proteins // Nucleic Acids Res.2004. V. 32. P. W424-W428.
8. Novichkov P.S., Omelchenko M.V., Gelfand M.S., Mironov A.A., Wolf Y.I., Koonin E.V. Genome-wide molecular clock and horizontal gene transfer in bacterial evolution // J. Bacteriology. 2004. V. 186. No. 19. P. 6575-6585.
9. Offman M., Nurtdinov R.N., Gelfand M.S., Frishman D. No statistical support for correlation between the positions of protein interaction sites and alternatively spliced regions // BMC Bioinformatics. 2004. V. 5. No. 1. P. 41.
10. Permina E.A., Gelfand M.S. Heat Shock (sigma32 and HrcA/CIRCE) regulons in beta-, gamma- and epsilon-proteobacteria // J. Mol. Microbiol. Biotechnol. 2004. V. 6. No. 3-4. P. 174-181.
11. Rodionov D.A., Dubchak I, Arkin A.P., Alm E., Gelfand M.S. Reconstruction of regulatory and metabolic pathways in metal-reducing delta-proteobacteria // Genome Biol. 2004. V. 5. No. 11. P. R90.
12. Rodionov D.A., Gelfand M.S., Hugouvieux-Cotte-Pattat N. Comparative genomics of the KdgR regulon in Erwinia chrysanthemi 3937 and other gamma-proteobacteria // Microbiology. 2004. V. 150. No. 11. P. 3571-3590.
13. Rodionov D.A., Vitreschak A.G., Mironov A.A, Gelfand M.S. Comparative genomics of the regulation of methionine metabolism in Gram-positive bacteria // Nucleic Acids Res. 2004. V. 32. No. 11. P. 3340-3353.
14. Rouanet C., Reverchon S., Rodionov D.A., Nasser W. Definition of a consensus DNA-binding site for PecS, a global regulator of virulence gene expression in Erwinia chrysanthemi and identification of new members of the PecS regulon // J. Biol. Chem. 2004. V. 279. No. 29. P. 30158-30167.
15. Vitreschak A.G., Lyubetskaya E.V., Shirshin M.A., Gelfand M.S., Lyubetsky V.A. Attenuation regulation of amino acid biosynthetic operons in proteobacteria: comparative genomics analysis // FEMS Microbiol. Lett. 2004. V. 234. No. 2. P. 357-370.
16. Vitreschak A.G., Rodionov D.A., Mironov A.A., Gelfand M.S. Riboswitches: the oldest mechanism for the regulation of gene expression? // Trends in Genetics. 2004. V. 20, No. 1, P. 44-50.
17. Zinin N.V., Serkina A.V., Gelfand M.S., Shevelev A.B., Sineokii S.P. Gene cloning, expression and characterization of novel phytase from Obesumbacterium proteus // FEMS Microbiol. Lett. 2004. V. 236. No. 2. P. 283-290.

In press

1. Витрещак А.Г., Гельфанд М.С., Герасимова А.В., Котельникова Е.А., Лайкова О.Н., Макеев В.Ю., Миронов А.А., Панина Е.М., Равчеев Д.А., Родионов Д.А. Сравнительная геномика и эволюция регуляторных систем бактерий // Вестник ВОГИС.
2. Gelfand M.S. Computational analysis of alternative splicing // Handbook on Computational Molecular Biology S. Alluru, ed. CRC Press.
3. Gelfand M.S., Kriventseva E.V. Alternative splicing: conservation and function // Encyclopedia of Genetics, Genomics, Proteomics and Bioinformatics. V. 2 (Genomics), P.F.R. Little, ed. Wiley Publ.
4. Kotelnikova E.A., Makeev V.Y., Gelfand M.S. Evolution of transcription factor DNA binding sites // Gene.
5. Neverov A.D., Mironov A.A., Gelfand M.S. Similarity-based gene recognition splicing // Handbook on Computational Molecular Biology S. Alluru, ed. CRC Press.
6. Rakhmaninova A.B., Kalinina O., Minin A.A. Discriminative sites in the conserved core of various annexin families from vertebrates // Annexins.

Conference abstracts

1. Калинина О.В., Гельфанд М.С., Миронов А.А., Рахманинова А.Б. Аминокислотные остатки, образующие специфические контакты между субъединицами при образовании тетрамера мембранного канала GlpF // Международная научная конференция студентов, аспирантов и молодых учёных «Ломоносов-2004» (Москва, апрель 2004). С. 17.
2. Ковалева Г.Ю., Макеев В.Ю., Гельфанд М.С. Компьютерный анализ GCN4-регулона дрожжей Saccharomyces cerevisiae и Candida albicans // Международная научная конференция студентов, аспирантов и молодых учёных «Ломоносов-2004» (Москва, апрель 2004). С. 18.
3. Равчеев Д.А., Рахманинова А.Б. Исследование регуляции нитрат-нитритного дыхания протеобактерий методами сравнительной геномики // Международная научная конференция студентов, аспирантов и молодых учёных «Ломоносов-2004» (Москва, апрель 2004). С. 27.
4. Denisov S.V., Gelfand M.S. Conservation of alterantive splicing regulatory signal UGCAUG in mouse and human genomes. // 4th Int. Conf. "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Новосибирск, июль 2004). V. 1. P. 54-57.
5. Favorov A.V., Gelfand M.S., Gerasimova A. V., Mironov A.A., Makeev V.J. Gibbs sampler for identification of symmetrically structured, spaced DNA motifs with improved estimation of the signal length and its validation on the ArcA binding sites // 4th Int. Conf. "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Новосибирск, июль 2004). V. 2. P. 269-272.
6. Gelfand M.S. Comparative genomics of bacterial regulatory systems and its medical applications // Second International Conference "Genomics, Proteomics and Bioinformatics for Medicine" (Москва, июль 2004). С. 6.5.
7. Gelfand M.S. Evolution of alternative splicing // International BCB Workshop on Gene Annotation Analysis & Alternative Splicing (Berlin, Germany, December 2004). P. 6.
8. Gelfand M.S. Evolution of bacterial regulatory systems. // 4th Int. Conf. "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Новосибирск, июль 2004). V. 2. P. 193-194.
9. Gelfand M.S., Gerasimova A.V., Kazakov A.E., Kotelnikova E.A., Laikova O.N., Mironov A.A., Permina E.A., Ravcheev D.A., Rodionov D.A., Vitreschak A.G. Com-

parative genomics, metabolic reconstruction, and analysis of regulation in bacterial genomes // Meeting of HHMI International Research Scholars (Tallinn, Estonia, June 2004). P. 45.

10. Gerasimova A.V., Ravcheev D.A., Rakhmaninova A.B., Gelfand M.S. Computer analysis of aerobic-anaerobic regulation in gamma-proteobacteria // 12th Int. Conf. on Intelligent Systems for Molecular Biology ISMB'2004 (Glasgow, UK, August 2004). P. 111.
11. Gerasimova A.V., Ravcheyev D.A., Gelfand M.S., Rakhmaninova A.B. Complex analysis of respiration switch in gamma-proteobacteria. // 4th Int. Conf. "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Новосибирск, июль 2004). V. 2. P. 195-198.
12. Kalinina O.V., Novichkov P.S., Mironov A.A., Gelfand M.S., Rakhmaninova A.B. SDPPRED: A method for prediction of amino acid residues that determine differences in functional specificity of homologous proteins // 4th Int. Conf. "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Новосибирск, июль 2004). V. 1. P. 274-277.
13. Kalinina O.V., Novichkov P.S., Mironov A.A., Gelfand M.S., Rakhmaninova A.B. SDPpred: a method for prediction of amino acid residues that determine differences in functiona lspecificity of homologous proteins // 12th Int. Conf. on Intelligent Systems for Molecular Biology ISMB'2004 (Glasgow, UK, August 2004). P. 177.
14. Kazakov A.E., Kalinina O.V., Permina E.A., Gelfand M.G. Bacterial metal resistance systems regulated by transcription regulators of the MerR family // 4th Int. Conf. "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Новосибирск, июль 2004). V. 1. P. 91-94.
15. Kovaleva G.Y., Mironov A.A., Gelfand M.S. The conservation of transcription factor-binding sites in *Saccharomyces* genomes // 4th Int. Conf. "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Новосибирск, июль 2004). V. 2. P. 210-213.
16. Rakhmaninova A.B., Kalinina O.V., Minin A.A. Discriminative sites in conserved core of diferent annexin subfamilies of vertebrates // 8th Meeting of the European Calcium Society (Cambridge, UK, July 2004). P. 46.
17. Stavrovskaya E.D., Mironov A.A. Binary tree for clustering of regulatory signals // 4th Int. Conf. "Bioinformatics of Genome Regulation and Structure" BGRS'2004 (Новосибирск, июль 2004). V. 1. P. 195-199.