

Dr. Evgeni V. Nikolaev

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BACKGROUND

Applied mathematics with major fields of expertise in the theory of bifurcations with symmetry, differential equations, nonlinear dynamics, singular perturbations, and numerical analysis. Mathematical modeling with focus on systems biology, genome-scale metabolic pathways and networks analysis. Additional experience includes development of algorithms and modeling technologies.

EDUCATION

Ph.D. <i>in physics and mathematics</i> (with speciality in differential equations): Lobachevsky Nizhegorod State University, Nizhnii Novgorod, Russia	1995
M.S. <i>in applied mathematics (with distinction)</i> : Moscow Engineering Physics Institute	1986

POSTDOCTORAL STUDIES

The Pennsylvania State University, University Park, U.S.A.	October 2002 – present
University of Leeds, Leeds, England	February 1996 – July 1997

PROFESSIONAL EXPERIENCE

Integrated Genomics (IG), Inc., Chicago, U.S.A.: <i>project leader</i>	July 1999 – August 2002
Institute for Mathematical Problems in Biology (IMPB RAS), Russian Academy of Sciences, Pushchino, Moscow Region:	
– <i>senior research scientist</i>	since 2002
– <i>research scientist</i>	1993 – 2002
– <i>junior research scientist</i>	1988 – 1993
– <i>research assistant</i>	1986 – 1988

TEACHING AND SUPERVISION EXPERIENCE

- *lectureship in mathematics*, School of Natural Sciences, Pushchino, Russia
- *co-advising graduate students*:
 - Anthony P. Burgard, The Pennsylvania State University, U.S.A.
 - Gennady S. Cymbalyuk, IMPB RAS, Pushchino, Russia
- *supervision of a team of programmers*, Integrated Genomics, Inc., Chicago, U.S.A.:
 - Yuri Grechkin, Mark Martin (Ph.D.), Sergey Kireev, Sergey Rudakov, and Alexander Tolstov

HONORS AND AWARDS

Soros Scholarship in Mathematics, International Science Foundation in Washington	1993
Soros Grant in Mathematical Modeling, International Science Foundation in Washington	1993

MEMBERSHIP

Scientific Council of IMPB RAS – elected member	1998 – 2003
Moscow Mathematical Society – elected member	since 2003

REVIEWER OF SCIENTIFIC JOURNALS

Bioinformatics – since 2003

Nonlinearity – since 2003

COMPUTER SKILLS

Languages: C/C++, OOP in C++ STL, Perl, and Fortran

Operating systems: Linux (RedHat), Unix, and Windows NT/Me/2000/XP

Software used: Auto, Content, Lindo API, LocBif, L^AT_EX, Maple, Matlab, Numerical Recipes in C, and VMware**ACCOMPLISHMENTS**PROJECT #9: “Modeling genome-scale metabolic networks”*Department of Chemical Engineering, Penn State, University Park, U.S.A. October 2002 – present*

Analyzed genome-scale metabolic networks, including location of subsets of coherently regulated enzymes and metabolic genes, and pools of metabolites shearing common conserved moieties. Showed that distributions of subsets of directionally regulated enzymes and genes are scale-free. Suggested a novel algorithm to predict operons based on genome-scale metabolic reconstructions (patented by Penn State). Studied genome-wide metabolic network reconstructions of prokaryotic and eukaryotic microorganisms, *Escherichia coli*, *Helicobacter pylori*, and *Saccharomyces cerevisiae*.

PROJECT #8: “Development of stoichiometric pathway modeling tools”*Integrated Genomics, Inc., Chicago, U.S.A.**July 1999 – August 2002*

Led a team of five programmers to develop MetaCell, a Web-based metabolic pathways modeling tool, including a remote PostgreSQL database computational server and graphical “client side” Java-based pathway editor. Carried out a genome-scale modeling of *Bacillus Subtilis* for optimization of biosynthesis of lysine, folate, methanol, and uridine, *Corynebacterium Glutamicum* for optimization of biosynthesis of diacetyl, lysine, threonine, and valine, *Escherichia coli*, and *Methylobacillus flagellatus*.

PROJECT #7: “Bifurcations of steady states in ODEs with finite symmetries”*Institute for Mathematical Problems in Biology, Pushchino, Russia**August 1997 – June 1999*

Studied bifurcations of symmetric equilibria, associated with double pairs of purely imaginary eigenvalues (Andronov-Hopf bifurcation). Analyzed all possible bifurcation scenarios 1) the representation of the symmetry group on a four-dimensional central eigenspace is *not absolutely* irreducible and 2) the representation splits into two *isomorphic* and *absolutely* irreducible representations. In the first case a three-dimensional sphere with a complicated dynamics emanates from the critical equilibria, and in the second case a pair of limit cycles and two-dimensional torus appear through the bifurcation. By using an appropriate Liapunov function a complete investigation of the phase space in the small neighborhood of a critical equilibrium, which does not depend on a bifurcation parameter, was done. This study has completed a long history in the analysis of the symmetric version of the famous Andronov-Hopf bifurcation.

PROJECT #6: “Simulation of suppression of heart arrhythmias by low-voltage resonance defibrillation”*School of Biomedical Sciences, University of Leeds, Leeds, England**February 1996 – July 1997*

Applied the Poincaré normal form and central manifold theories to study resonance and non-resonance bifurcations of uniformly rotating spiral waves in reaction-diffusion systems (partial differential equations) on the whole **2D**-plane. Factorized the center manifold with respect to Euclidean symmetry of rotations and translations in the plane to study local bifurcations in the underlying distributed system with the goal to understand resonance phenomena related to meandering spiral waves causing arrhythmia and fibrillation of the heart. Applied the theory of parametric resonance to the modeling of elimination of meandering spiral waves from active **2D** circular domains.

Institute for Mathematical Problems in Biology, Pushchino, Russia *May 1986 – January 1996*

PROJECT #5: “Bifurcations of periodic solutions in ODEs with finite symmetry groups,” Ph.D. thesis
Studied bifurcations of periodic solutions with discrete spatial-temporal symmetries. In 1985 while a graduate student, modeling populations of identical cells, independently revealed a new fundamental property of the Poincaré map P of a symmetric limit cycle: The n -th root can be extracted from P , $P = Q^n$, if a symmetric cycle has a cyclic symmetry of order n . Built a general theory of local bifurcations of limit cycles in systems with symmetry.

PROJECT #4: “Mathematical modeling of two electrically coupled neurons”

Studied a model of two electrically coupled oscillatory neurons. Considered the case of a weak coupling between the neurons and used a functional approach in the space of smooth periodic functions to obtain an analytical asymptotic equation to control the phase shift in the neurons. Suggested a new approach to control transitions between in-phase and anti-phase self-oscillations in the neurons using weak polarizing currents.

PROJECT #3: “Mathematical modeling of ion transport accompanied with chemical reactions”

Studied ionic transport, coupled with fast reactions, through synthetic membranes with applications in medicine (artificial kidney), pharmacology and food industry (purification of substances). Shown that even simple reactions like $\text{H}_2\text{O} = \text{H}^+ + \text{OH}^-$ can generate sharp gradients of electric fields within thin interior reaction layers that play a crucial role in overall electro-diffusion processes in such electro-diffusion distributed systems. Suggested a new technology to separate ions by moving electro-diffusion reaction layers between membrane boundaries, varying concentration of transported substances outside the membrane.

PROJECT #2: “Continuation of solutions to nonlinear problems depending on parameters”

Developed BEETLE, a numerical algorithm, and Fortran code to compute solutions of arbitrary nonlinear equations, depending on a parameter. BEETLE is a basic continuation techniques used in an interactive computational and graphical environment LocBif, Local Bifurcation Analyzer, developed to study local bifurcations of steady states and periodic solutions in ODEs, and fixed points of iterated maps. Both LocBif and its core computational engine have been used worldwide to analyze nonlinear bifurcation phenomena arising in many fields of science and technology – the LocBif *Physica D* paper has been cited more than 100 times. At present, LocBif’s core routines are used in DBSolve, a biological modeling benchmark developed at GlaxoSmithKline, a transnational pharmaceutical corporation.

PROJECT #1: “Mathematical modeling of non-growing cell populations,” M.S. thesis

Studied synchronization in mathematical models of cellular populations to provide a theoretical framework for efficient ways of synchronization in cellular cultures.

PRESENTATIONS, CONFERENCES AND VISITS

2002 Department of Pathology and Cell Biology, Thomas Jefferson University, Philadelphia, U.S.A.

2002 Institute for Mathematical Problems in Biology, Pushchino, Russia, one hour talk

1995 University of Groningen, the Netherlands. Dynamical Systems Conference in Honor of Johann Bernoulli, one hour talk.

1993 University of Groningen, the Netherlands. Staff Colloquium, one hour talk.

1993 Centre de Recherche Mathématiques, Université de Montréal, Canada. Fall Special Semester on Spatial and Temporal Dynamics, two two-hours talks.

1993 Institute for Applied Mathematics and Cybernetics, Lobachevsky Nizhegorod State University, Nizhnii Novgorod, Russia. L.P.Shilnikov Dynamical Systems Seminar, one hour talk.

1992 Department of Mathematics and Mechanics, Lomonosov State University, Moscow, Russia. Yu.S.Ilyashenko Seminar on “Analytical Theory of Ordinary Differential Equations,” one hour talk.

1992 Samarkand State University, Samarkand, Republic of Uzbekistan, The 8th CIS Conference on

Qualitative Theory of Differential Equations, one hour talk.

1988 A. V. Dumansky Institute of Colloid and Water Chemistry, Kiev, Ukraine, one hour talk

MANUSCRIPTS IN PREPARATION

[1] **Nikolaev, E.V.**, Burgard, A.P., and Maranas, C.D. [2003], The structural analysis of metabolic pools inferred from genome-scale metabolic reconstructions

PAPERS IN PEER REVIEWED JOURNALS¹

[2] Burgard*, A.P., **Nikolaev***, E.V., Schilling, C.H., and Maranas, C.D. [2003], Flux Coupling Analysis of Genome Scale Metabolic Network Reconstructions, *Genome Research* (*accepted*)

[3] Pharkya, P., **Nikolaev, E.V.**, and Maranas, C.D. [2003], Review of the Brenda Enzymes Database, *Metabolic Engineering* **5**, 71-73

[4] **Nikolaev E.V.**, Biktashev, V.N., and Holden A.V. [1999], "Bifurcations of spiral waves in the plane," *International Journal of Bifurcation and Chaos* **9**(8), 1501-1516

[5] Shnol E.E. and **Nikolaev E.V.** [1998], "Bifurcations of equilibria in systems of differential equations with a finite symmetry group," *Sbornik: Mathematics* **190**(9), (translated from *Matematicheskii Sbornik* **190**(9), 127-150)

[6] **Nikolaev E.V.** and Shnol E.E. [1998], "Bifurcations of cycles in systems of differential equations with a finite symmetry group I," *Journal of Dynamical and Control Systems* **4**(3), 315-342

[7] **Nikolaev E.V.** and Shnol E.E. [1998], "Bifurcations of cycles in systems of differential equations with a finite symmetry group II," *Journal of Dynamical and Control Systems* **4**(3), 343-364.

[8] **Nikolaev E.V.**, Biktashev V.N., and Holden, A.V. [1998], "On feedback resonant drift and interaction with the boundaries in circular and annular excitable media," *Chaos, Solitons and Fractals* **9**(3), 363-376

[9] Biktashev V.N., Holden A.V., and **Nikolaev E.V.** [1996], "Spiral wave meander and symmetry of the plane," *International Journal of Bifurcation and Chaos* **6**(12), 2433-40

[10] **Nikolaev E.V.** [1995] "Bifurcations of limit cycles of differential equations admitting an involutive symmetry," *Sbornik: Mathematics* **186**(4), 611-627 (translated from *Matematicheskii Sbornik* **186**(4), 143-160)

[11] Cymbalyuk G.S., **Nikolaev E.V.**, and Borisyyuk R.M. [1994], "In-phase and anti-phase self-oscillations in a model of two electrically coupled pacemakers," *Journal of Biological Cybernetics* **71**, 153-160

[12] Khibnik A.I., Kuznetsov Yu.A., Levitin V.V., and **Nikolaev E.V.** [1993], "Continuation techniques and interactive software for bifurcation analysis of ODEs and iterated maps," *Physica D* **62**, 360-371

[13] Denisov G.A., Kalyuta V.K., **Nikolaev E.V.**, Tischenko G.A., and Shataeva L.K. [1993], "Modeling of coupled transport of ions and zwitterions across porous ion exchange membranes," *Journal of Membrane Science* **79**, 211-226

[14] Denisov G.A., Kalyuta V.K., and **Nikolaev E.V.** [1990], "Formation of an electric-potential jump in a weakly dissociating ion-exchange membrane located between acidic and basic electrolytes," Plenum Publishing Corporation, translated from *Doklady Akademii Nauk USSR* **315**(1), 132-136

CONTRIBUTIONS TO BOOKS

[15] Denisov G.A., Kalyuta V.K., **Nikolaev E.V.**, Tischenko G.A., and Shataeva L.K. [1991], Modeling of coupled transport across artificial and biological membranes, in V.N.Buravtsev, G.A.Denisov and V.M.Starov, eds., 'Transport Across Artificial and Biological Membranes,' Pushchino, Moscow Region, 1-24 (*in Russian*)

PROCEEDINGS OF CONFERENCES

¹* equal authorship

- [16] Burgard, A.P., **Nikolaev, E.V.**, and Maranas, C.D. [2003], Optimization based strategies for analyzing the topological features of genome-scale metabolic models, 2003 Annual Meeting, American Institute for Chemical Engineers, November 16-21, San Francisco, Hilton & Towers San Francisco, CA, U.S.A.
- [17] Selkov, E.E., Selkov, G., Karpeev, D., DeHorn, D., Minkoff, M., **Nikolaev, E.V.**, and Poluektova, Yu. [2003], Metabolic theory of the cell clock and its experimental verification with sequenced cyanobacteria, Plant Biology 2003, Meeting of American Society of Plant Biologists, July 25-30, Honolulu, Hawaii, U.S.A.
- [18] Burgard, A.P., **Nikolaev, E.V.**, and Maranas, C.D. [2003], Optimization-Based Analysis of Topological Features of Genome-Scale Metabolic Networks, Biochemical Engineering (XIII) 2003, Biochemical Engineering in the Era of Genomics, Systems Biology, Genetic Medicine & Nanotechnologies, July 19-23, Boulder, Colorado, USA
- [19] **Nikolaev E.V.** and Shnol E.E. [1996], Bifurcations of limit cycles and symmetry *in* "Proceedings of ICND-96 Conference on Nonlinear Dynamics and Chaos. Applications in Physics, Biology and Medicine," Saratov State University, Saratov, Russia
- [20] **Nikolaev E.V.** [1992], On bifurcations of periodic solutions in the presence of the simplest symmetry, *in* "Proceedings of the 8th CIS Conference on Qualitative Theory of Differential Equations," Samarkand State University, Samarkand, Republic of Uzbekistan
- [21] Denisov G.A., Lazarev P.I., and **Nikolaev E.V.** [1987], Formation of a spatial charge located in a thin interior layer which separates two electrolytes reacting upon each other, *in* "Proceedings of the 2nd USSR Conference on Mathematical and Computational Methods in Biology," Pushchino, Moscow Region (*in Russian*)

PREPRINTS (*issued by Scientific Publishing House of Pushchino Research Center*)

- [22] **Nikolaev E.V.** [1994], "Periodic motions in systems with a finite symmetry group," Institute for Mathematical Problems in Biology, Russian Academy of Sciences, Pushchino, Moscow Region, 1-29
- [23] **Nikolaev E.V.** [1993], "Geometrical features of a vector field with built-in an involution and bifurcations of symmetric limit cycles," Institute for Mathematical Problems in Biology, Russian Academy of Sciences, Pushchino, Moscow Region, 1-15
- [24] **Nikolaev E.V.** [1992], "On bifurcations of closed orbits in the presence of involutory symmetry," Institute for Mathematical Problems in Biology, Russian Academy of Sciences, Pushchino, Moscow Region, 1-35
- [25] **Nikolaev E.V.** [1989], "Validity of the electro-neutrality condition for electro-diffusion systems," Research Computing Centre, USSR Academy of Sciences, Pushchino, Moscow Region (*in Russian*)
- [26] **Nikolaev E.V.** [1989], "Existence of solutions of two point boundary value problems for electro-diffusion systems," Research Computing Centre, USSR Academy of Sciences, Pushchino, Moscow Region (*in Russian*), 1-12
- [27] Denisov G.A., Lazarev P.I., and **Nikolaev E.V.** [1987], "The influence of chemical reactions on the profile of the diffusion potential in a membrane located between electrolytes," Research Computing Centre, USSR Academy of Sciences, Pushchino, Moscow Region (*in Russian*), 1-30

MANUALS

- [28] Khibnik A.I., Kuznetsov Yu.A., Levitin V.V. and **Nikolaev E.V.** [1993], LocBif, version 2: Interactive LOCAL BIFurcation Analyzer, CAN Expertise Centre, Amsterdam, 1-148

MANUSCRIPTS

- [29] Nazarenko V.G., **Nikolaev E.V.**, Selkov E.E., and Shnol E.E. [1986], "Mathematical modeling of self-synchronization of cell clocks in non-growing cell populations," *Deposited in VINITI*, Moscow, 1-68 (*in Russian*)

References

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