

Emil Alexov

NAME: Emil Alexov	POSITION TITLE: Professor		
eRA COMMONS USER NAME: ealexov			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Sofia University, Bulgaria	MS	1979 –1984	Physics
Sofia University, Bulgaria	PhD	1986 - 1990	Physics
City College of New York	Post-Doc	1995 - 2000	Molecular Biophysics
Columbia University, New York	Senior Scientist	2000 - 2005	Molecular Biophysics

A. PERSONAL STATEMENT

This proposal aims to investigate the molecular effects caused by missense mutations in MeCP2 protein and their association with autism, and then to find small molecules which, upon binding to the malfunctioning mutant protein, reduce or eliminate the effects of disease-causing mutations. Such an investigation is along the lines of our previous and current research, namely to develop computational methods and approaches to map genetic variations or rare mutations onto the structure of the corresponding protein and then to reveal the effect of mutations on the protein's stability, flexibility, and interactions. As a result, we have successfully revealed the molecular mechanism behind various mental disorders and a case of Alzheimer disease. In terms of method development, we have reported an approach, termed scaled molecular mechanics Generalized Born (sMMGB) method, which performs better than other existing solutions as reported in a benchmarking test of more than thousand experimentally determined folding free energy changes due to point mutations in various proteins. With this proposal, which focuses on MeCP2 protein only, we will enhance our modeling by applying the Free Energy Perturbation (FEP) method, which is more rigorous than the Linear Interaction Energy (LIE) methods which we have been using in the past.

In addition, the lab is currently exploring various approaches for *in silico* screening for small molecules and we have established a dual PhD program with Molécules Thérapeutiques In Silico at Université Paris Diderot, France. One of our students has already completed his training for utilizing the two most popular software packages for *in silico* screening, Surflex and AutoDock Vina, and these packages are already installed locally and are fully functional. Recently we reported (see Ref. (2)) partial success of using small molecules to increase the activity of malfunctioning spermine synthase mutant causing Snyder-Robison syndrome.

B. POSITIONS AND HONORS

Positions and Employment

2005 – now	Professor of Physics, Clemson University
2005 – 2012	Associate Professor of Physics, Clemson University
2000 - 2005	Senior Scientist, Howard Hughes Medical Institute and Columbia University, NY
1997 - 2005	Adjunct Assistant, Professor Bronx Community College, New York
1995 – 2000	Research Associate, City College of New York
1994 - 1995	Visiting Scientist, The Institute of Physical and Chemical Research (RIKEN), Japan
1992 - 1994	Researcher, Bulgarian Academy of Sciences
1991 - 1992	Assistant Professor, Medical Academy, Bulgaria

1990 - 1991 Assistant Professor, Sofia University, Bulgaria

Other Experience and Professional Memberships

Awards: Science and Technology Agency Award (STA Fellowship), Japan, 2004-2005

Organizer: "Modeling electrostatics in Molecular Biology", Clemson, April 4-6, 2011.

Co-organizer: Gordon Research Conference "Human Single Nucleotide Polymorphisms & Disease", 2014, Aug 3-8, Stonehill College, MA; MBI "Emphasis Year on Mathematical Molecular Biosciences", 2015, Columbus, OH; ACS 2013 Annual meeting "Electrostatics in Molecular Biophysics: in silico, in vitro and in vivo approaches"; Indianapolis; IN, ACS 2012 Annual meeting "Continuum Solvation Modeling in Biological Systems: Developments and Applications", Philadelphia, PA.

Member: American Physical Society, American Chemical Society and Biophysical Society

Guest Editor: Journal of Molecular Biology (2013), International Journal of Molecular Sciences (2014), Communications in Computational Physics (2011, 2013), Journal of Theoretical and Computational Chemistry (2013), Curr Pharm Biotechnol. (2008).

Editor: Computational and Mathematical Methods in Medicine, Journal of Theoretical and Computational Chemistry, International Journal of Molecular Sciences

Editorial Board Member: Molecular Based Mathematical Biology; Computational Biology and Chemistry: Advances and Applications; The Open Chemical and Biomedical Methods Journal; The Open Bioinformatics Journal

Reviewer: Journal of Molecular Biology, Journal of Physical Chemistry, Proteins, Bioinformatics, Protein Science, Journal of Molecular Graphics, Computational Biology, Biophysical Journal, European Biophysical Journal, European Biochemistry Journal, Biochemistry, Journal of Computational Chemistry, PNAS, Protein Engineering, PLoS Comp. Biology, BMC Bioinformatics, Bioinformatics, NAR, Nucleic Acids, and more.

C. PEER-REVIEWED PUBLICATIONS

1) Emil Alexov; "Advances in Human Biology: Combining Genetics and Molecular Biophysics to Pave the Way for Personalized Diagnostics and Medicine"; Advances in Biology Volume 2014 (2014); Article ID 471836, 16 pages

2) Bohua Wu, Julia Eggert, Emil Alexov; "Molecular Mechanisms Underlying Pathogenic Missense Mutations"; eLS. John Wiley & Sons, Ltd: Chichester.; DOI: 10.1002/9780470015902.a0025698

3) Taylor Kimmett, Nicholas Smith, Shawn Witham, Marharyta Petukh, Subhra Sarkar, Emil Alexov; "ProBLM Web Server: Protein and Membrane Placement and Orientation Package"; Comp Math Meth Med.; Volume 2014 (2014), Article ID 838259

4) Li L, Li C, Alexov E.; "On the Modeling of Polar Component of Solvation Energy using Smooth Gaussian-Based Dielectric Function."; J Theor Comput Chem. 2014 May;13(3). doi: 10.1142/S0219633614400021.; PMID:25018579

5) Kucukkal TG, Yang Y, Chapman SC, Cao W, Alexov E.; "Computational and experimental approaches to reveal the effects of single nucleotide polymorphisms with respect to disease diagnostics."; Int J Mol Sci. 2014 May 30;15(6):9670-717. doi: 10.3390/ijms15069670. PMID:24886813

6) Minghui Li, Marharyta Petukh, Emil Alexov and Anna R. Panchenko. "Predicting the Impact of Missense Mutations on Protein-Protein Binding Affinity", J. Chem. Theory Comput., 10(4):1770-1780 (2014).

- 7) Dolzhanskaya N, Gonzalez MA, Sperziani F, Stefl S, Messing J, Wen GY, Alexov E, Zuchner S, Velinov M. "A novel p.Leu(381)Phe mutation in presenilin 1 is associated with very early onset and unusually fast progressing dementia as well as lysosomal inclusions typically seen in Kufs disease", *J Alzheimers Dis.* 2014;39(1):23-7.
- 8) Boccuto L, Aoki K, Flanagan-Steet H, Chen CF, Fan X, Bartel F, Petukh M, Pittman A, Saul R, Chaubey A, Alexov E, Tiemeyer M, Steet R, Schwartz CE. "A mutation in a ganglioside biosynthetic enzyme, ST3GAL5, results in salt & pepper syndrome, a neurocutaneous disorder with altered glycolipid and glycoprotein glycosylation", *Hum Mol Genet.* 2014 Jan 15;23(2):418-33
- 9) Alexov E, Sternberg M. "Understanding molecular effects of naturally occurring genetic differences", *J Mol Biol.* 2013 Nov 1;425(21):3911-3.
- 10) Onufriev AV, Alexov E. "Protonation and pK changes in protein-ligand binding", *Q Rev Biophys.* 2013 May;46(2):181-209.
- 11) Stefl S, Nishi H, Petukh M, Panchenko AR, Alexov E. "Molecular mechanisms of disease-causing missense mutations", *J Mol Biol.* 2013 Nov 1;425(21):3919-36.
- 12) Nishi H, Tyagi M, Teng S, Shoemaker BA, Hashimoto K, Alexov E, Wuchty S, Panchenko AR. "Cancer missense mutations alter binding properties of proteins and their interaction networks", *PLoS One.* 2013 Jun 14;8(6):e66273.
- 13) Li C, Petukh M, Li L, Alexov E. "Continuous development of schemes for parallel computing of the electrostatics in biological systems: Implementation in DelPhi", *J Comput Chem.* 2013 Jun 4. doi: 10.1002/jcc.23340.
- 14) Zhang Z, Norris J, Kalscheuer V, Wood T, Wang L, Schwartz C, Alexov E, Van Esch H. "A Y328C missense mutation in spermine synthase causes a mild form of Snyder-Robinson syndrome", *Hum Mol Genet.* 2013 May 31.
- 15) Chuan Li, Lin Li, Marharyta Petukh and Emil Alexov; "Progress in developing Poisson-Boltzmann equation solvers"; *Molecular Based Mathematical Biology.* 2013, Volume 1, Pages 42-62.
- 16) Li L, Li C, Zhang Z, Alexov E.; "On the Dielectric "Constant" of Proteins: Smooth Dielectric Function for Macromolecular Modeling and Its Implementation in DelPhi"; *J Chem Theory Comput.* 2013 Apr 9;9(4):2126-2136.
- 17) Zhang Z, Zheng Y, Petukh M, Pegg A, Ikeguchi Y, Alexov E. "Enhancing human spermine synthase activity by engineered mutations." *PLoS Comput Biol.* 2013 Feb;9(2):e1002924. doi:10.1371/journal.pcbi.1002924. Epub 2013 Feb 28. Figure 2 of the manuscript is taken for the cover page of the journal
- 18) Zhang Z, Witham S, Petukh M, Moroy G, Miteva M, Ikeguchi Y, Alexov E. "A rational free energy-based approach to understanding and targeting disease-causing missense mutations." *J Am Med Inform Assoc.* 2013 Feb 13. [Epub ahead of print]
- 19) Petukh M, Kimmet T, Alexov E. "BION web server: predicting non-specifically bound surface ions." *Bioinformatics.* 2013 Mar 15;29(6):805-6
- 20) Smith N, Campbell B, Li L, Li C, Alexov E. "Protein Nano-Object Integrator (ProNOI) for generating atomic style objects for molecular modeling." *BMC Struct Biol.* 2012 Dec 5;12:31. doi:10.1186/1472-6807-12-31.
- 21) Petukh M, Stefl S, Alexov E "The Role of Protonation States in Ligand Receptor Recognition and Binding." *Curr Pharm Des.* 2012 Nov 20. [Epub ahead of print]
- 22) Takano K, Lieu D, Tarpey P, Gallant E, Lam A, Witham S, Alexov E, Chaubey A, Stevenson RE, Schwartz CE, Board PG, Dulhunty AF "An X-linked Channelopathy with cardiomegaly due to a CLIC2

mutation enhancing ryanodine receptor channel activity", *Hum Mol Genet.* 2012 Aug Oct 15;21(20):4497-507. Epub 2012 Jul 19.

23) Petukh M, Zhenirovskyy M, Li C, Li L, Wang L, Alexov E. "Predicting nonspecific ion binding using DelPhi", *Biophys J.* 2012 Jun 20, 102(12)

24) Subhra Sarkar, Shawn Witham, Jie Zhang, Maxim Zhenirovskyy, Walter Rocchia and Emil Alexov "DelPhi Web Server: A comprehensive online suite for electrostatic calculations of biological macromolecules and their complexes", *Comm. Comp. Phys.*, (2013), 13, 269-84

25) Lin Wang, Shawn Witham, Zhe Zhang, Lin Li, Michael Hodsdon and Emil Alexov "In silico investigation of pH-dependence of prolactin and human growth hormone binding to human prolactin receptor", *Comm. Comp. Phys.*, (2013), 13, 207-222

26) Lin Wang, Zhe Zhang, Walter Rocchia and Emil Alexov "Using DelPhi capabilities to mimic protein's conformational reorganization with amino acid specific dielectric constants", *Comm. Comp. Phys.*, (2013), 13, 13-30

27) Sergio Decherchi, Jos'e Colmenares, Chiara Eva Catalano, Michela Spagnuolo, Emil Alexov, and Walter Rocchia "Between algorithm and model: different Molecular Surface definitions for the Poisson-Boltzmann based electrostatic characterization of biomolecules in solution", *Comm. Comp. Phys.*, (2013), 13, 61-89

28) Li C, Li L, Zhang J, Alexov E., "Highly efficient and exact method for parallelization of grid-based algorithms and its implementation in DelPhi.", *J Comput Chem.* 2012 Sep 15;33(24):1960-6. doi: 10.1002/jcc.23033. Epub 2012 Jun 4.; Figure 3 of the manuscript is the cover page of the journal: *J Comput Chem.* 2012 Sep 15;33(24):iii-iv. doi:10.1002/jcc.22080

29) Zhe Zhang, Maria A. Miteva, Lin Wang and Emil Alexov "Analyzing Effects of Naturally Occurring Missense Mutations" *Computational and Mathematical Methods in Medicine*, Volume 2012 (2012), Article ID 805827, doi:10.1155/2012/805827

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- 40) Mitra, R., Zhang. Zhe and Alexov, E, "In silico modeling of pH-optimum of protein-protein binding", *Proteins* (2011), **171**, 285-289.
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Model Building, and Energetic Analysis in Fold Recognition and Homology Modeling" *Proteins* (2003), 53, 430-435.

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