BIOGRAPHICAL SKETCH

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NAME: Bahar, Ivet

eRA COMMONS USER NAME (credential, e.g., agency login): ivetbahar

POSITION TITLE: Distinguished Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Bogazici University, Istanbul	BS	6/1980	Chemical Engineering
Bogazici University, Istanbul	MS	6/1983	Chemical Engineering
Istanbul Technical University, Istanbul	PhD	2/1986	Chemistry

A. Personal Statement

As the Founding Chair of the Department of Computational and Systems Biology at the University of Pittsburgh, School of Medicine, and an Associate Director of the University of Pittsburgh Drug Discovery Institute, I am dedicated to initiating and establishing collaborative and interdisciplinary research and training activities in the areas of computational and systems biology. Our lab is currently developing models and methods for exploring the structure and dynamics of complex biological systems at multiple scales, from full atomic interactions to supramolecular machinery. We have made online accessible to the biomedical community a large number of broadly used software, servers, and databases. Our overarching goal is to bridge between molecular structure and biological function, and to fill the gap between current molecular simulations and systems-level mathematical models. To this aim, we have introduced coarse-grained models and methods with structural and/or spatiotemporal details at various levels of resolution which can efficiently and accurately explore mesoscopic scales.

B. Positions and Honors

Positions and Employment

Present Positions

2013 - Distinguished Professor, Department of Computational & Systems Biology (DCSB) University of Pittsburgh (Pitt), School of Medicine (SOM), Pittsburgh, PA
2010 - Professor and John K. Vries Chair, DCSB, SOM, Pitt
2011 - Associate Director, SOM, University of Pittsburgh Drug Discovery Institute
2010- Founding Chair, DCSB, SOM, Pitt.

Past Positions

2004 - 2010 Founding Chair, Department of Computational Biology, School SOM, Pitt
2005 - 2010 John K. Vries Chair, Department of Computational Biology, SOM, Pitt
2005 - 2009 Founding Director, PhD Program in Comp Biology, Joint Pitt and Carnegie Mellon U
2001 - 2004 Founding Director, Center for Computational Biology & Bioinformatics, SOM, Pitt
2001 - 2004 Professor, Department of Molecular Genetics & Biochemistry, SOM, Pitt
1993 - 2001 Professor, Chemical Engineering Department, Bogazici University
1987 - 1993 Associate Professor, Chemical Engineering Dept, Bogazici University
1986 - 1987 Assistant Prof, Associate Professor, Chemical Engineering Dept, Bogazici University
1992 - 2000 Director, Polymer Research Center, Bogazici University

Short-term visits

1992 - 2000 Fogarty Fellow/Visiting Scientist, Exp & Comp Biol Lab, Div of Basic Sci, NCI, NIH (*summers*)
1987 - 1991 UNESCO Fellow and Visiting Prof, U of Akron, Institute of Polymer Science (*summers*)
1989 - 1998 Visiting Scientist, Ecole Supérieure de Physique et Chimie (ESPCI), Laboratoire de Physicochimie Structurale et Macromoléculaire (PCSM), Paris, France (*1 month/year, for 10 years*)

Other Experience and Professional Memberships

2016 - 2020	NIH NLM Biomedical Library and Informatics Research Committee (BLIRC) Membership
2015	International Society for Computational Biology (ISCB) *Senior Member* Designation
2015	NIH NINDS Board of Scientific Counselors, *Ad-hoc* Member
2014	NIH Study Section Chair, Special Emphasis Panel for Library of Integrated Network Based Cell Signatures (LINCS): Perturbation-Induced Data & Signature Generation Centers (U54)
2010 - 2012	Executive Board Member (Elected), Biophysical Society
2008 - 2011	Council Member (Elected), Biophysical Society
2008 - 2012	Council Member (Elected), International Soc of Quantum Biology and Pharmacology

Honors

2014	Chancellor's Distinguished Research Award, University of Pittsburgh
2000	European Molecular Biology Organization (**EMBO**) Elected Member
1998	*Excellence in Research Award*, Bogazici University
1997	Turkish Academy of Sciences, Principal Member (Elected)
1995	*TUBITAK-TWAS Science* Prize
1991	*Sedat Simavi Physical Sciences* Prize (joint with B. Erman)
1990	*Chemistry Award* for Young Scientists from TUBITAK

C. Contribution to Science

1. **Demonstrating the significance of structure-encoded dynamics as a major determinant of biomolecular mechanisms of interaction, machinery and allostery.** Our hypothesis first introduced two decades ago has been the following: in the same way as sequence encodes structure, structure encodes dynamics, which defines the mechanisms of structural changes involved in biological function. Based on this hypothesis, accurate modeling of structural dynamics is essential to gaining insights into functional mechanisms. Our lab has been pursuing this goal by developing models (in particular elastic network modes (ENMs) for predicting cooperative changes in structure) and methods (graph theoretical and statistical mechanical), and extensive comparison with existing experimental data. The use of ENMs opened the way to efficient characterization of biomolecular systems dynamics, including supramolecular systems of tens of thousands of residues. We can now determine the spectrum of motions encoded by any structure as a unique analytical solution specific to the particular inter-residue contact topology. Applications to protein-protein[(c)] and protein- drug/inhibitor[(b)] interactions, to enzymes[(d)] and to supramolecular machines, have now shown consistently that the collective motions undergone by proteins during their biological function (e.g. ligand binding, allosteric signaling, substrate/ion channeling) are simply those uniquely defined by their architecture, which are predictable to a good approximation by analytical methods based on ENMs (for a review see [(a)]).

a. Bahar I, Lezon TR, Yang LW, Eyal E. Global dynamics of proteins: bridging between structure and function. *Annu Rev Biophys.* 2010;39:23-42. PubMed PMID: 20192781; PubMed Central PMCID: PMC2938190.
b. Bakan A, Bahar I. The intrinsic dynamics of enzymes plays a dominant role in determining the structural changes induced upon inhibitor binding. *Proc Natl Acad Sci U S A*. 2009 Aug 25;106(34):14349-54. PubMed PMID: 19706521; PubMed Central PMCID: PMC2728110.
c. Tobi D, Bahar I. Structural changes involved in protein binding correlate with intrinsic motions of proteins in the unbound state. *Proc Natl Acad Sci U S A*. 2005 Dec 27;102(52):18908-13. PubMed PMID: 16354836; PubMed Central PMCID: PMC1323175.
d. Yang LW, Bahar I. Coupling between catalytic site and collective dynamics: a requirement for mechanochemical activity of enzymes. *Structure.* 2005 Jun;13(6):893-904. PubMed PMID: 15939021; PubMed Central PMCID: PMC1489920.

2. **Unveiling the coupling between structural dynamics and sequence conservation and co-evolution patterns.** Evolutionary conservation patterns observed in proteins are often attributed to structural stability requirements (e.g. core contacts), or biochemical activities (e.g. catalysis); and it is broadly established that evolutionarily selected structures ought to be stable enough to tolerate mutations, or maintained by correlated mutations. Our studies showed, on the other hand, that conformational dynamics is equally important to achieving function, as determinant of biomolecular mechanics. Motions predicted by our ENM-based computations to be intrinsically favored by native fold often correlate with those observed during molecular machinery or allosteric cycles: opening/closing of an interdomain cleft for substrate binding; alternating between inward- and outward-facing states to enable substrate uptake and release; or global torsional motions to facilitate pore opening, suggesting that structures have evolved to favor functional dynamics, which led us to several studies [(b-d)] aiming at elucidating the significance of conformational dynamics in sequence and structure evolution. We have learned from these studies

that residues that play a key role in mediating the dynamics (e.g. hinge sites) ought to be conserved; global motions (that cooperatively embody the entire structure) are robust and conserved, and define the generic dynamics of families of proteins. Local motions, on the other hand, are versatile; they mediate the specific interactions of family members while retaining the global dynamics. We also learned that it is essential for native structures to strike a balance between stability and flexibility. The latter is a requirement to accomplish many biophysical activities including protein-protein recognition, often enabled via co-evolution of residue pairs or clusters, especially in complex systems where adaptability and promiscuity are key to functional diversity; see our recent review for more details and examples of studies in support of these fundamental concepts.[a] The new insights we acquired from combined analysis of structural dynamics and sequence evolution now open the way for designing intervention strategies that take account of structural dynamics.

a. Haliloglu T, Bahar I. Adaptability of protein structures to enable functional interactions and evolutionary implications. *Curr Opin Struct Biol*. 2015 Dec;35:17-23. PubMed PMID: 26254902; PubMed Central PMCID: PMC4688206.
b. Liu Y, Bahar I. Sequence evolution correlates with structural dynamics. *Mol Biol Evol*. 2012 Sep;29(9):2253-63. PubMed PMID: 22427707; PubMed Central PMCID: PMC3424413.
c. Liu Y, Gierasch LM, Bahar I. Role of Hsp70 ATPase domain intrinsic dynamics and sequence evolution in enabling its functional interactions with NEFs. *PLoS Comput Biol*. 2010 Sep 16;6(9)PubMed PMID: 20862304; PubMed Central PMCID: PMC2940730.
d. Liu Y, Eyal E, Bahar I. Analysis of correlated mutations in HIV-1 protease using spectral clustering. *Bioinformatics*. 2008 May 15;24(10):1243-50. PubMed PMID: 18375964; PubMed Central PMCID: PMC2373918.

3. **Development and applications of theory and methods for unraveling and establishing the molecular basis of complex cell signaling, regulation and transport processes.** Understanding complex systems behavior has been a major research topic in our lab since 1987, originally starting with the adoption of Markovian models to represent the conformational dynamics of polymers[d] until mid 1990s (reviewed in *Advances in Polymer Sciences*, in 1994), and continuing with that of biomolecular systems dynamics in the cell in the last 20 years. Notably, the ensemble perspective and master equation formalism established then for polymers proved useful in biological applications. We have contributed to understanding the molecular basis of a broad range of cellular processes including the regulation of apoptotic responses,[c] the mechanism of neurotransmitter transport[a-b] response to perturbing certain targets/pathways. We anticipate systems biology and polypharmacology approaches to gain importance in dealing with the networks of interactions and the promiscuity of proteins in the cell environment.

a. Cheng MH, Bahar I. Molecular Mechanism of Dopamine Transport by Human Dopamine Transporter. Structure. 2015 Nov 3;23(11):2171-81. PubMed PMID: 26481814; PubMed Central PMCID: PMC4635030.
b. Shrivastava IH, Jiang J, Amara SG, Bahar I. Time-resolved mechanism of extracellular gate opening and substrate binding in a glutamate transporter. *J Biol Chem*. 2008 Oct 17;283(42):28680-90. PubMed PMID: 18678877; PubMed Central PMCID: PMC2568915.
c. Bagci EZ, Vodovotz Y, Billiar TR, Ermentrout GB, Bahar I. Bistability in apoptosis: roles of Bax, Bcl-2, and mitochondrial permeability transition pores. *Biophys J*. 2006 Mar 1;90(5):1546-59. PubMed PMID: 16339882; PubMed Central PMCID: PMC1367306.
d. Bahar I. Stochastics of Rotational Isomeric Transitions in Polymer Chains. *J Chem Phys*. 1989; 91:6525.

4. **Introduction Elastic Network Models (ENMs) and Development of ENM-Based Methods for Bridging Structure and Function.** Our lab has been developing algorithms for full atomic simulations of macromolecules since the early 1990s. It became clear, early on, in these studies, that brute force MD simulations have limitations: they are limited to short time scales (e.g. up 100s of nanoseconds) or relatively small size systems (10^4-10^5 atoms) depending on the tradeoff between simulated system size and duration, or they suffer from sampling inaccuracies. To address the challenge of attaining time and length scales of biological interest, we focused since mid-1990s on the development, establishment and implementation of novel physics-based approaches. Our most significant contribution has been the introduction of models and methods based on elastic network models (ENMs), including the Gaussian Network Model (GNM),[d] and the anisotropic network model, ANM[c] for inferring functional motions from known structures. The use of ENMs has been a breakthrough in understanding and interpreting many experimental observations, as described above. We further developed hybrid methodologies that combine simulations at multiple resolution,(a) as well as spectral graph-theoretic methods for mapping allosteric signaling mechanisms.[b] Applications of ENM-based methodologies have helped elucidate the mechanism of function of many molecular machines; the significance of conformational flexibility in mediating ligand binding/unbinding (essential to designing new inhibitors), the role of global motions in enabling substrate transport via alternating access mechanism, the molecular origin of

the anisotropic response of proteins to external forces in AFM experiments, and the pre-disposition of allosteric proteins to undergo cooperative conformational-switches and transmit allosteric signals.

a. Gur M, Madura JD, Bahar I. Global transitions of proteins explored by a multiscale hybrid methodology: application to adenylate kinase. *Biophys J.* 2013 Oct 1;105(7):1643-52. PubMed PMID: 24094405; PubMed Central PMCID: PMC3791301.
b. Chennubhotla C, Bahar I. Markov propagation of allosteric effects in biomolecular systems: application to GroEL-GroES. *Mol Syst Biol.* 2006;2:36. PubMed PMID: 16820777; PubMed Central PMCID: PMC1681507.
c. Atilgan AR, Durell SR, Jernigan RL, Demirel MC, Keskin O, Bahar I. Anisotropy of fluctuation dynamics of proteins with an elastic network model. *Biophys J.* 2001 Jan;80(1):505-15. PubMed PMID: 11159421; PubMed Central PMCID: PMC1301252.
d. Bahar I, Atilgan AR, Demirel MC, Erman B. Vibrational dynamics of proteins: Significance of slow and fast modes in relation to function and stability. *Phys. Rev Lett.* 1998; 80:2733-2736.

5. **Implementation of Computational Technology for Predicting Biomolecular Systems Dynamics and the Mechanisms of Drug-Target interactions.** We have implemented several servers, databases and the application programming interfaces, including ProDy,[(d)] iGNM[(a)] and ANM[(b)] for enabling the efficient usage of the ENM-based methods and software by the broader community. ProDy became in less than 5 years a major resource for analyzing and predicting structural dynamics, with more than 400,000 downloads (recorded by *Google analytics*). A more recent technology we developed is the Balestra webserver[(c)] for the identification of potential drug-target interactions and repurposable drugs, using an advanced machine learning methodology that we applied to DrugBank (DB of known protein-drug interactions). The latter, recently extended to Stitch DB, is anticipated to serve as a resource for assessing potential protein-ligand interactions at the proteome scale.

a. Li H, Chang YY, Yang LW, Bahar I. iGNM 2.0: the Gaussian network model database for biomolecular structural dynamics. *Nucleic Acids Res*. 2016 Jan 4;44(D1):D415-22. PubMed PMID: 26582920; PubMed Central PMCID: PMC4702874.
b. Eyal E, Lum G, Bahar I. The anisotropic network model web server at 2015 (ANM 2.0). *Bioinformatics*. 2015 May 1;31(9):1487-9. PubMed PMID: 25568280; PubMed Central PMCID: PMC4410662.
c. Cobanoglu MC, Oltvai ZN, Taylor DL, Bahar I. BalestraWeb: efficient online evaluation of drug-target interactions. *Bioinformatics*. 2015 Jan 1;31(1):131-3. PubMed PMID: 25192741; PubMed Central PMCID: PMC4271144.
d. Bakan A, Meireles LM, Bahar I. ProDy: protein dynamics inferred from theory and experiments. *Bioinformatics*. 2011 Jun 1;27(11):1575-7. PubMed PMID: 21471012; PubMed Central PMCID: PMC3102222.

Complete List of Published Work in My Bibliography:
http://1.usa.gov/1U2e9L0 [H: index = 63 and Citations: 15,214, based on Google Scholar report of 7/21/16)

D. Research Support

Ongoing Research Support

P41 GM103712-04, NIGMS (PI: Bahar) 09/24/12-07/31/17
High Performance Computing for Multiscale Modeling of Biological Systems
This project aims at creating and establishing a National Biomedical Technology & Research Center (BTRC) on developing high performance computing tools for exploring the complex dynamics of biological systems at multiple scale, in collaboration with Carnegie Mellon University, the Pittsburgh Supercomputing Center (PSC) and the Salk Institute, in addition to other institutions involved in providing experimental data and leading five biomedical driving projects. The methods proposed will help build predictive models for investigating neurotransmission events at multiple levels, ranging from single molecule recognition, transport and signaling events, to complex dynamics of cellular systems involved in synaptic transmission, to morphological and organizational changes at the CNS cell and (brain) tissue levels.

R01 GM099738-04, NIGMS (PI: Bahar) 03/26/12-12/31/16
Continued Development of Protein Dynamics Software ProDy
In view of the growing recognition of the significance of protein dynamics in defining the mechanisms of biomolecular function, and the rapidly growing experimental data on protein structures in multiple forms, we propose herein to modernize and extend our protein dynamics software, ProDy, into an easily modifiable and integrative application programming interface (API). ProDy will not only evaluate protein dynamics using extensive experimental data and

analytical tools, but also offer the community a database of dominant motions and accessible conformers for well-studied protein families.

P30 DA035778-01A1 (PIs: Bahar, Xie, Xing) 08/01/14-07/31/19
NIDA Center of Excellence OF Computational Drug Abuse Research (CDAR)
Recent years have seen a significant increase in the number of structurally characterized membrane proteins, including those implicated in drug abuse and addiction. CB4DA (Core B) will take advantage of the rapidly accumulating structural data as well as advances in biocomputing technology to generate data and develop and disseminate software that will facilitate the design, discovery and development of structure-based computer-aided strategies against DA.

P01DK096990, NIH-NIDDK (PI: Perlmutter), 09/24/12-08/31/17
Drug- and Cell-Based Therapies for α1-Antitrypsin Deficiency (ATD)
The Bahar lab will lead the Computational Pharmacology Core of this Center and provide expertise in developing and applying computational tools for modeling protein-inhibitor interactions, and analyze high throughput and high content screening (HTS/HCS) data for assessing target proteins, identifying relevant pathways and networks, evaluate systems (poly) pharmacological effects of therapeutic strategies. (Role: Comp Pharmacology Core PI)

U54HG007934-01, NIH-NHGRI (PIs: Cooper/Bahar/Berg) 09/15/14-09/14/19
Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data
We will establish our Center for Causal Modeling and Discovery (CMD) of Biomedical Knowledge from Big Data as collaboration among the University of Pittsburgh (Pitt; lead institution), Carnegie Mellon University (CMU), and Yale University (Yale). The CMD Center will develop, validate, and disseminate methods, tools, and software based on Causal Bayesian Networks, which will enable the broader scientific community to effectively interrogate large imaging, genomic, and clinical (phenotype) data and derive knowledge on the causality of observed phenomena.

U19AI68021, NIH-NIAID (PI: Greenberger) 09/01/10-08/31/20
Mitochondrial Targeting Against Radiation Damage
Core F ("Chemo-Informatics", Ivet Bahar, Ph.D., Principal Investigator) carry out two critical roles: (1) assist in the design, screening, validation, and optimization of novel inhibitors using pharmacophores modeling, docking simulations and QSAR techniques, and screen and validate all project designed drugs for potential or expected side effects based on known structure and binding characteristics in close coordination with Core B, and (2) screen for predicted or expected drug effects and interactions as the "cocktail" of a multi-drug regimen is being formulated. (Role: Chemoinformatics Core PI)

Completed Research Support

R01 GM086238, NIH-NIGMS (PI: Bahar) 01/01/09-12/31/14
Structural Dynamics of Biomolecular Systems
We build on our previous work, to explore the supramolecular machinery and the structure -> dynamics -> function mapping of allosteric and/or multimeric proteins using physically-based and computationally efficient models, in collaboration with the NCBC Simbios at Stanford U.

5R01LM07994-07, NIH-NLM (PI: Bahar) 9/30/03-9/29/13
Bridging Sequence Patterns and Structural Dynamics (former title: Alignment-Independent Analysis of Sequence).
The goal of this project was to analyze sequence conservation and co-evolution patterns and the physical constraints imposed by structure. Our goal is to further our understanding of sequence-function relationships by investigating the couplings between sequence evolution and structural dynamics, with focus on widely studied systems such as molecular chaperones, selected enzyme families and membrane proteins, along with their multimerization, assembly and intermolecular interactions.