ANNUAL REPORT

Award Period September 2004 - August 2005

A. SPECIFIC AIMS

Computational. The specific aims continue to be the development of computational tools and methodologies at molecular and supramolecular (Aim 1A), microphysiological or subcellular (Aim 1B) and cellular systems (Aim 1C). Specific aims 2 (integration of these methods) and 3 (development and implementation of tools for dissemination & visualization) remain unchanged.
Biomedical. The Biomedical Aims of the 3 developmental projects (DP1-3) remain unchanged, as dynamics of apoptosis and effect of NO (DP1), DNA damage recognition and signaling (DP2), and ligand interactions with signaling molecules (DP3). A number of new collaborative efforts have also been launched, on neurotransmitter release as described in section D.

B. STUDIES AND RESULTS

Specific Aim 1A. We have made significant progresses in developing and implementing methods based on elastic network models (or Gaussian Network Model, GNM) for examining the structure and dynamics of biomolecular systems as recently reviewed (Bahar & Rader, 2005). Notable extensions of the methodology to supramolecular systems include the examination of the dynamics of HK97 bacteriophage capsid (Rader et al., 2005); the elucidation of ribosomal machinery (Wang et al., 2004). We have also developed a new algorithm for switching between different levels of resolution in protein models (Lyman & Zuckerman, 2005). The approach, termed "Resolution Exchange," generalizes the widely-used replica exchange approach by allowing configuration swaps between simulations at different levels of resolution.

Specific Aim 1B. MCell and DReAMM (www.mcell.psc.edu) were originally designed to simulate and visualize the 3-D reaction/diffusion aspects of neurotransmission, and a continuing aim is expansion of both to encompass more general signaling pathways such as those of the DPs. Since early 2005, new versions (v.3.0) of both have been in heavy alpha testing. As originally proposed, new MCell testing and use focuses on reaction network motifs such as single and coupled autocatalytic feedback loops (e.g., the Lotka-Volterra reaction, the Repressilator circuit, and the Oregonator version of the Belousov-Zhabotinski reaction). Our recent studies have illustrated surprising quantitative and qualitative differences between MCell simulations and ODE-based simulations of the same networks. Reports on spatially realistic modeling (Stiles et al, 2004) and Grid computation with MCell 2.5 (Casanova et al, 2004) have also appeared.

Specific Aim 1C. We have made major developments in our software for a logical network model of apoptosis (Ta'asan lab, CMU) so as to include stochastic modeling and ODEs, on top of agent based architecture that we have. We have attempted to connect between existing modeling approaches such as ODEs and Stochastic differential equations and the Logical Modeling approach. This has led us to examine different implementations which were derived from the law of mass action with certain assumptions of discreteness. Our recent implementation of logical models can be viewed as a coarse graining of stochastic models. Our current BioLogic software platform can simulate arbitrary hierarchy of objects with arbitrary compartment structure. A new version of XPPAUT (version 5.91) has been made available on the internet by the lab of Dr. Ermentrout (Pitt, Math), which also includes an SBML to ODE file converter.

Specific Aim 2. With recent developments in the elastic network models and methods, it is now possible to examine the collective dynamics of large structures at residue-level. The extension of molecular models by Bahar's lab to systems comprised of 10^5 residues or 10^6 atoms (e.g. Rader et al., 2005) and the elucidation of the functional dynamics of supramolecular systems by efficient computational methods is an important advance in the field towards filling the gap between molecular and microphysiological simulations. Another effort launched towards bridging across these two scales is the collaboration between molecular and subcellular simulation groups for exchange of output/input, e.g. the use of on- and off- rates for ligand binding, or associated free

energy changes, or the diffusion coefficients predicted by molecular simulations, as input parameters for microphysiological simulations.

Specific Aim 3. For continued improvements to microphysiological model building and visualization, DReAMM v.3 (see Aim 1B) has been expanded dramatically. We have made extensive improvements to OpenDX (www.opendx.org, originally from IBM) hardware and software rendering routines (corrected shading and lighting so that images match), as well as user interface design modules. Another database/server recently implemented by Bahar's lab is the iGNM server (Yang et al., 2005). The mathematical modeling site XPPAUT maintained by Ermentrout has continued to be extensively used for cell modeling and simulations.

Developmental Project 1 (DP1). Previously, we increased the realism of the model of apoptosis originally reported by Fussenegger et al. (2000) by including Bid/tBid interactions as proposed in the DP1. We also created the first-generation model of the reaction pathways of NO, and coupled it to our apoptosis model. This mathematical model reproduced our previous experimental results on the differential effect of NO on apoptosis observed in different cellular environment (Vodovotz et al., 2004). We have shown that Hill-type cooperativity in the formation of apoptosome complex is instrumental in leading to a bistable response (Bagci et al., 2005, submitted). Bistability could explain the effects of excessive mitochondrial transmembrane pore (MPTP) formation and excessive iron-nitrosyl nitric oxide species on cellular fate. Excessive MPTP formation may cause pathological cell death (Green and Kromer, 2004) and excessive iron-nitrosyl NO species produced in hepatocytes may render these cells very resistant to apoptosis (Kim et al., 2000). We showed that if the modulators exceed some critical values, the bistable responses may convert to a monostable response (either cell survival or cell death). The model suggests that a passage from bistable to monostable response may be induced by changes in Bax and Bcl-2 synthesis and degradation rates (Bagci et al., submitted).

Developmental Project 2 (DP2). We modeled the structure of the DNA polymerase domain of POLQ, as described in the collaborative manuscript published by Dr. Wood and Dr. Bahar's labs (Seki et al, 2004). Importantly, the collaborative efforts between the labs of Drs. Wood, Bahar and Stiles within the scope of the pre-NPEBC DP2 *have led to an NIH Nanomedicine Center proposal.* A concept development memo was submitted to NIH in an open competition, in July 2004. Of 86 such memos submitted, ours was one of 20 approved for planning for a nanomedicine center application. A "concept development plan" was submitted in February, 2005. This project stemmed from discussions of DP2, initiated by the pre-NPEBC grant. Thus, the pre-NPEBC funding has been valuable in stimulating a collaborative effort for specific applications for future funding from the NIH.

Developmental Project 3 (DP3). Substantial progress has been made in free energy methods of potential use in computing protein-ligand affinities (Ytreberg & Zuckerman, 2005) and protein-protein docked conformations (Tobi & Bahar). The new approaches allow free energy differences to be computed between configurational ensembles. Following a general strategy championed by H. Meirovitch, a new protocol accurately calculates absolute free energies in molecular systems, and has been successfully applied to peptides. Another noteworthy development is the productive collaboration between Bahar's lab and Lazo's lab in the prediction of the binding affinity and geometries of lead compounds that potentially inhibit dual specificity phosphatases (Brisson et al., 2004). Two other important publications appeared from Bahar's lab, which aim at improving our understanding of the mechanism of enzyme inhibition (Sluis-Kremer et al., 2004; Yang & Bahar, 2005).

C. SIGNIFICANCE. As mentioned above, supramolecular systems have been modeled for the first time at the residue-level resolution, and advanced models and methods have been implemented in iGNM and MCell for improving the ability and extending the applicability of both software. The collaboration with experimental groups started to be extremely productive, as evidenced by the large number and high quality of collaborative publications described above. Many joint publications appeared for the first time between team members (e.g. co-authored by Bahar & Wood, by Bahar & Lazo, by Billiar, Ermentrout, Vodovotz and Bahar, by Sluis-Cremer &

Bahar) indicative of the utility and effectiveness of multidisciplinary collaborations launched within the scope of the pre-NPEBC between experimental and computational groups.

D. PLANS

Given the large number of involved labs and limited funds in the pre-NPEBC budget, and the considerable progresses made in both the computationally driven and the developmental (pilot) projects, it can be anticipated that efforts will now be focused on seeking additional funds for pursuing the collaborative studies that have been launched in the last two years. A large number of investigators have indeed submitted proposals in small groups (to NIH, NSF or other agencies) and succeeded in finding support for their lab members that have effectively contributed to the research and educational goals of the pre-NPEBC. In line with the overall goal of the pre-Center, our overarching goal in the coming year will be to continue to conduct interdisciplinary research and integrate the models and methods developed/used by different groups towards gaining a deeper understanding of the molecular basis of cell signaling and regulation processes. Below is a more specific summary of the planned activities, both research and educational.

Specific Aim 1. We will continue to develop models and methods at multiple scales. With regard to GNM/ANM, the goal is to extent the ability of the methodology at both lower and higher scales, by incorporating amino acid specificity, on the one hand, and adopting hierarchically coarse-grained representations at higher scales, on the other. Hybrid models that explore a system at different resolutions will be constructed, and simulations based on the resolution exchange method described above will be conducted. At the microphysiological level simulations, a preliminary report on MCell v.3 has appeared (Kerr et al, 2004) and in the coming year, this version will be in the final stages of testing for accuracy and optimized execution before more generalized release to the Computational Biology and Neuroscience communities. At the higher level (mathematical models), reactions will be implemented using logical modeling, while extensions to include ODEs as well as stochastic differential equations will be developed to allow us to perform multiscale computations in the same framework. Notably, XPPAUT started to support SBML as of May 2005, which will enable users to use/share tools/models more efficiently.

Specific Aim 2. The integration of the different tools for multiscale modeling remains a challenging task despite the progress made in exploring intermediate scales (between molecular and cellular) that were beyond reach using conventional molecular models or classical chemical kinetics-based mathematical models. More efforts will be concentrated towards further advancing the models and methods for exploring multiscale dynamics.

Specific Aim 3. The new codes/routines of DReAMM v.3 will be released to users in source code form as PSCDX. DReAMM presently supports direct import of surface and volume meshes from CAD and VRML files as well as simulation output from MCell. We will also improve the streamlined handling of MCell3 datasets that can include thousands of mesh objects, mesh regions, and fixed and diffusing molecular species, and the mesh editing pipeline with preliminary mesh region annotation that allows direct export of MCell MDL (Model Description Language) files for simulations (Stiles et al, 2004).

DP1-3. With respect to DP1, we are planning to couple this model with pathways involving nitric oxide (NO) that we presented before (Vodovotz et al., 2004). We will change the parameters of the model that are obtained from the literature where possible to account for different environments in different cell types. This will be a generic model that might explain the dichotomous effects of NO. We will then examine the pivotal role of superoxide anion in directing the effect of NO (Wink et al., 1999). These results will be tested *in vitro* by incubating hepatocyte cultures with different concentrations of NO and superoxide donors, as well as using NO donors that release NO with different kinetics, to examine the response of cells to apoptotic stimuli. These studies will greatly enhance our understanding NO as a modulator of apoptosis.

As an extension of the research studies initiated within the scope of DP2, we are currently organizing a concept development application for the nanomedicine center, to be submitted in July 2005. The concept development centers around the examination of the mechanism of nucleotide excision repair of DNA and its future manipulation in nanomedicine. In the coming year, our efforts in this field will be intensified, with the addition of new team members (Drs. Camacho and Benos at the Dept of Comp Bio, SOM, Pitt and Dr. Sanford Leuba at Cell Biol & Physiology, SOM, Pitt). Finally, the efforts on understanding protein-protein and protein-inhibitor interactions within the scope of DP3 are expected to be conducted more efficiently in the coming term, building on the computational accumulation in Bahar's and Madura's labs, and on the productive collaboration that has already started between experimental and theoretical labs.

Other DPs. (1) *Calcium imaging and neurotransmitter release.* These ongoing experimental and applied mathematical studies, undertaken by J. Stiles in collaboration with S. Meriney (Neuroscience, Pitt), focus on determination of the number and opening probability of voltage-gated calcium channels in active zones of the frog neuromuscular junction. A publication from the previous grant period (Wachman et al., 2004, J. Neurosci. 24:2877) reported values averaged across multiple entire active zones, and current work focuses on subregions of single active zones (Luo et al, 2005, in press). **(2)** *Monte Carlo simulations of presynaptic calcium dynamics and neurotransmitter release*, directed by J. Stiles and carried out by John Pattillo, a post-doc in Stiles's lab. These computational studies are directly coupled to experimental inputs and tests from the preceding project. Based on those and other experimental constraints, our model directly predicts recent evidence for up to 8 SNARE complexes and 40 Ca^{2+} binding sites per synaptic vesicle, and possible cooperativity of synaptotagmin binding to trigger fusion. It also makes novel predictions for the spatial relationships and stoichiometry of channels and vesicles during exocytosis (Pattillo et al, 2004; *ibid* 2005, submitted). These presynaptic simulations are complemented by postsynaptic simulations of quantal variability arising from normal or ectopic sites of neurotransmitter release at a reconstructed central synapse, carried out by Stiles and collaborators at the Salk Institute (Coggan et al, 2005, in press).

Other Significant Collaborations: One outcome of the collaborative research efforts of the Pre-NPEBC has been the newly established Center for Inflammation and Regenerative Modeling (CIRM) within the McGowan Institute for Regenerative Medicine. The CIRM, directed by Y. Vodovotz (Surgery, Pitt) with G. Bard Ermentrout (Math, Pitt) as the co-director of the Simulation Core, aims at understanding the molecular basis of inflammation in the initial stages of injury, healing and eventually tissue regeneration. Details can be found at www.mirm.pitt.edu/cirm.

Another outcome, as mentioned earlier, is the NIH Nanomedicine Center (section B, DP2). This is a collaborative effort between the experimental group of R. Wood supported by the computational research group of I. Bahar, and focuses on the mechanism of nucleotide excision repair of DNA and its future manipulation in nanomedicine. A "concept development application" is planned for submission in July 2005.

E. PUBLICATIONS. Publications related to this grant are presented in Appendix I. A total of 23 publications (21 papers + 2 book chapter) are listed, of which **16 are published/accepted**, 5 submitted, and 2 are currently in preparation. Electronic copies of most of the published/accepted papers are made accessible in the pre-NPEBC website http://www.health.pitt.edu/pcbc.

F. SPECIAL REQUIREMENTS

F.1. Description of activities. Research activities have been described above. Educational activities are described in F.4.

F.2. Organizational activities.

1. *External Advisory Committee.* Douglas Lauffenberger (MIT), who accepted our invitation to serve on the EAC, visited Pittsburgh on October 5, 2004. During his visit, he presented a seminar

and also discussed the current and future plans of the Pre-NPEBC with Dr. Bahar and other members involved with research and organizational activities of the award.

2. *The second Pre-NPEBC workshop*, titled "Computational Methodology in Modeling Complex Biological Systems", was held on October 13, 2004 at the Pittsburgh Supercomputing Center, and was attended by a large number of researchers (PIs, postdoctoral fellows, and students) from all the participating institutions (Pitt, CMU, PSC, and Duquesne). The goal of this workshop was to focus on "computational models and methods" developed and used by researchers in the Pittsburgh area for investigating complex biological systems at molecular, supramolecular, and subcellular/cellular levels, and the integration of these methods. An outline of the workshop program can be found in Appendix III.

3. *New pre-NPEBC Investigators*. New Faculty that joined pre-NPEBC activities are C. Camacho (Comp Bio, Pitt SOM), I. Maly (Comp Bio, Pitt SOM), and D. Swigon (Math, Pitt). All three have already contributed to this project using their start-up funds and we plan to provide partial support from the pre-NPEBC award from the next granting period (7% for Camacho, none for others).

4. *Formation of a new Department of Computational Biology at Pitt SOM.* A new Department of Computational Biology (CB), chaired by Dr. Bahar, was approved and established at Pitt SOM in October 2004. The department is amongst the first in the nation, and currently has 7 full-time Faculty with interests in computational structural biology, systems biology, and genomics (bioinformatics), and we anticipate recruiting additional faculty to the department. The Pre-NPEBC award is now administered by this new department allowing for dedicated financial and administrative resources for the development and implementation of computational tools and methodologies in collaboration with experimental groups at the participating institutions. Furthermore, this department is also the administrative center of a new PhD-granting program in computational biology jointly offered by CMU (see F.4.1)

F.3. DPs that have been initiated and progress made in each of them. See the paragraphs DP1, DP2 and DP3 in Section **B** (Studies and Results), and DP1-3 and Other DPs in Section **D**.

F.4. Progress toward developing educational opportunities in biomedical computing.
1. CMU-Pitt Joint PhD Program in Computational Biology (JPCB). A cross-campus PhD program in computational biology between Pitt and CMU has been newly proposed by Drs. Ivet Bahar (Program Director, Comp Bio, Pitt) and Robert Murphy (Biol Sci, CMU), and approved by both universities (www.compbio.cmu.edu). Students have been admitted to the new program for the 2004-2005 academic year, starting in the Fall 2005. The program aims to provide intensive interdisciplinary education to enable outstanding students to become leaders in identifying and solving tomorrow's biological problems using computational and/or mathematical methods and fundamental principles of life and physical sciences. Currently, the program offers five areas of specialization, consistent with the goals of the Pre-NPEBC: computational genomics, comp structural biology, cellular and systems modeling, bioimage informatics, and comp neurobiology. The program currently includes 67 Faculty from physical, life, computer and mathematical sciences at both universities.

2. *Biomedical and Bioinformatics Summer Institute (BBSI)*. The BBSI is an NSF/NIH funded program offering a 10-week summer program to undergraduate (junior and senior) and $1^{st}/2^{nd}$ year graduate students. The major theme of the program is '**Multiscale Modeling'** in line with the pre-NPEBC goals. Six PIs playing a key role in the pre-NPEBC (Bahar, Stiles, Coalson, Madura, Ermentrout and Meirovitch) also serve as instructors and co-PIs in the BBSI. Additionally, 17 Faculty from Pitt, CMU, PSC and Duquesne serve as research mentors. A manuscript on BBSI has been recently submitted to *Biotechnology Progress* (Munshi et al., 2005; invited article).

3. *Other programs and courses*. A PhD program in Molecular Biophysics, with a strong component in Comp Bio, started in the Fall 2004. In addition to the molecular biophysics basics, first-year classes introduce concepts of modeling at different scales. CMU started a new course

"Modeling and Simulation of Biological Systems" for undergrad students (taught by Dr. Ta'asan).

4. *Several postdoctoral fellows and students* funded by other (NIH or NSF) sources are involved in, and benefit from, collaborative multidisciplinary activities conducted within the scope of the pre-NPEBC (see Appendix IV).

Appendix I: Publications by pre-NPEBC investigators

(The pre-NPEBC participants (Faculty) and their postdocs/students are written in boldface. The publications labeled as (*) refer to developmental projects DP1-DP3 and the other DPs)

1. **Bagci ,E.Z., Vodovotz, Y., Billiar,T.R., Ermentrout, G.B., Bahar,** I. Roles of cooperativity and nitric oxide in regulating apoptotic response. (submitted**).(*)**

2. **Bagci, E.Z., Ermentrout, G.B., Billiar, T.R., Vodovotz, Y., Bahar,** I. Bistability in mitochondria dependent apoptotic pathways: Role of cooperative apoptosome formation. (submitted)**. (*)**

3. **Bahar, I. & Rader, AJ.** "Coarse-Grained Normal mode analysis in Structural Biology" *Curr Opin Struct Biol* 2005, submitted (as invited review).

4. **Brisson, M**., Theresa Nguyen, Andreas Vogt, Jack Yalowich, Angela Giorgianni, **DrorTobi, Ivet Bahar**, Corey R. J. Stephenson, Peter Wipf, and **John S. Lazo**. "Discovery and characterization of novel small molecule inhibitors of human Cdc25B dual specificity phosphatase" *Mol Pharm*, Oct. 2004, 66(4): 824-833. **(*)**

5. Casanova, H, Bartol, T, Berman, F, Birnbaum, A, Dongarra, J, Ellisman, M, Faerman, M, Gokcay, E, Miller, M, Obertelli, G, Pomerantz, S, Sejnowski, T, **Stiles, J**, and Wolski, R. (2004) The Virtual Instrument: Support for Grid-enabled MCell Simulations. *Intern. J. High Performance Computing Applications* 18:3-18.

6. Coggan, JS, Bartol, TM, Esquenazi, E, **Stiles, JR,** Lamont, S, Maryann E. Martone, ME, Berg, DK, Ellisman, MH, and Sejnowski, TJ. "Evidence for ectopic neurotransmission at a neuronal synapse" *Science* 2005, in press.

7. **Gandlin, R.** and **Ta'asan, S**. Modeling and analysis of interacting heterogeneous populations. (manuscript in preparation).

8. Kerr, R, Bartol, TM, **Stiles, JR**, Kennedy, MB, and Sejnowski, TJ. (2004) MCell3: A next-generation simulator of cellular microphysiology. *Soc. Neurosci. Abst.*

9. Luo, F, **Stiles, JR**, and Meriney, SD. (2005, in press) Variance analysis of action-potential-evoked calcium influx reveals low opening probability of presynaptic calcium channels at the frog neuromuscular junction. *Soc. Neurosci. Abst.*

10. **Lyman, E**. and **Zuckerman, DM.** Simulation of biomolecules by resolution exchange. (manuscript in preparation)

11. **Munshi, R**., **Coalson, R., Ermentrout, GB., Stiles, JR, Madura, J; Meirovitch, H. and Bahar, I**. "An introduction to simulation and visualization of biological systems at multiple scale: A summer training program for interdisciplinary research" *Biotechnology Progress*, submitted (invited article).

12. **Pattillo, JM**, Meriney, SD, and **Stiles, JR**. (2004) Spatially realistic Monte Carlo simulations predict calcium dynamics underlying transmitter release at a neuromuscular active zone. *Soc. Neurosci. Abst.*

13. **Pattillo, JM**, Meriney, SD, and **Stiles, JR**. (2005, submitted) Design principles of neurotransmitter exocytosis predicted by spatially realistic Monte Carlo simulations. *Nature Neurosci.*

14. Ramaswamy, A. Ivet Bahar and Ilya Ioshikhes. "Structural Dynamics of Nucleosome Core Particle: Comparison with Nucleosomes Containing Histone Variants" *Proteins: Structure, Function and Bioinformatics*, 58:683-696, 2005.**(*)**

15. **Rader, AJ., Daniel Vlad and Ivet Bahar** "Maturation Dynamics of Bacteriophage HK97 Capsid". Structure (Camb), 2005 Mar;13(3):413-21.

16. Seki, M., C. Masutani, **LW Yang,** A Schuffert, S Iwai, **I Bahar** and **R Wood**. (2004) High efficiency bypass of DNA damage by a single human DNA polymerase, *EMBO J.,* 23:4484 **(*)**

17. Sluis-Cremer, N.., N. A. Temiz and I. Bahar. "Conformational changes in HIV-1 reverse transcriptase induced by nonnucleoside reverse transcriptase inhibitor binding." *Current HIV Research*, 2004 Oct; 2 (4): 323-32. **(*)**

18. **Stiles, JR**, Ford, WC, **Pattillo, JM**, Deerinck, TE, Ellisman, MH, Bartol, TM, and Sejnowski, TJ. (2004) Spatially realistic computational physiology: past, present, and future. In: *Parallel Computing: Software Technology, Algorithms, Architectures & Applications*, ed. Joubert, G, et al. Elsevier, Amsterdam, pp. 685-694.

19. Vodovotz,Y., Kim,P.K., **Bagci,E.Z., Ermentrout,G.B.**, **Chow,C.C**., **Bahar,I**., **Billiar,T.R**. "Inflammatory Modulation of Hepatocyte Apoptosis by Nitric Oxide: In Vivo, In Vitro, and In Silico Studies." *Current Molecular Medicine* 4, 753-762 (2004).**(*)**

20. Wang, Y. **Rader, AJ, Bahar, I.** And Jernigan, RL. "Global Ribosome Motions Revealed with Elastic Network Model", *J. Struct Biol*, Sept. 2004, 147(3): 302-314.

21. **Yang, L.W., Ivet Bahar**. "Coupling between Catalytic Site and Collective Dynamics: A requirement for Mechanochemical Activity of Enzymes." *Structure* (in press)

22. **Yang, L. W., Xiong Liu, Christopher Jon Jursa, Mark Holliman, Hassan Karimi, Ivet Bahar.** "iGNM: A Database of Protein Functional Motions Based on Gaussian Network Model" *Bioinformatics* (in press)

23. **Ytreberg, FM**; **Zuckerman, DM**. Peptide Conformational Equilibria Computed via a Single-Stage Shifting Protocol J. Phys. Chem. B.,109; 9096-9103 (2005).

Other papers cited in the report:

M Fussenegger, JE Bailey, and J Varner. (2000). A mathematical model of caspase function in apoptosis. *Nature Biotechnology* **18**, 768-774.

Seki, M., F. Marini, and R.D. Wood (2003) POLQ (Pol theta), a DNA polymerase and DNA-dependent ATPase in human cells. *Nucleic Acids Res.* **31**:6117-6126.

Wink,D.A., Feelisch,M., Vodovotz,Y., Fukuto,J., & Grisham,M.B. The Chemical Biology of Nitric Oxide in *Reactive Oxygen Species in Biological Systems: An Interdisciplinary approach* (eds. Colton,C.A. & Gilbert,D.L.) 245-291 (Kluwer Academic / Plenum Publishing, New York, 1999).

Kim,Y.M., Chung,H.T., Simmons,R.L., Billiar,T.R. Cellular non-heme iron content is a determinant of nitric oxide-mediated apoptosis, necrosis, and caspase inhibition. *Journal of Biological Chemistry* **275**, 10954-10961 (2000)

Green,D.R. and Kromer,G. The pathophysiology of mitochondrial cell death. *Science* **305**, 626-629 (2004)

Appendix II: Pre-NPEBC Seminar Series

Date	Speaker	Presentation Title
October 5, 2004	Douglas Lauffenberger MIT Biological Engineering Division, Dept of Biology and Chem Engg	Cue-Signal-Response Analysis of Cell Decision Processes
November 4, 2004	Jianpeng Ma Baylor College of Medicine Rice University	Simulating, Refining and Modeling Protein Structures at Multi-resolution and Multi-length Scales
January 21, 2005	Matt Jacobson Dept. of Pharmaceutical Chemistry UCSF	Computational Investigations of Protein Regulation by Post Transitional Phosphorylation.
February, 24 2005	Brian Shoichet Dept. of Pharmaceutical Chemistry UCSF	Model Systems for Virtual Screening
March 15, 2005	Eran Eyal Dept. of Plant Science Weizmann Institute of Science, Israel	Modeling side chain conformations and structural analysis of mutants using contact surface areas
March 28, 2005	Alex Mogilner Dept. of Math & Center for Genetics & Development Univ. of California	A Ran GTP gradient facilitates the “Search-and-Capture” of Chromosomes
April 14, 2005	Eivind Almaas Department of Physics University of Notre Dame	The Plasticity and Structure of Metabolic Networks
May 5, 2005	Richard Lathrop Dept. of Information and Comp Sci University of California, Irvine	Computationally Optimized DNA Assembly

Appendix III: Pre-NPEBC Worskhop, October 13, 2005.

TIME	TOPIC, SPEAKER
9 – 9.10 am	Registration
9.10 – 9.15 am	**Introduction** Dr. Ivet Bahar (CCBB, Pitt)
9.15 – 10.15 am	**SESSION I: Molecular Simulations** Chair: Dr. Carlos Camacho (CCBB, Pitt)
9.15 – 9.30 am	Dr. Christopher Langmead (CS, Biol Sci, CMU) *Chemical Shift Prediction and Dynamics Regime Classification: Applications of Probabilistic and Geometric Reasoning in NMR*
9.30 – 9.45 am	Dr. Daniel Zuckerman (CCBB, Pitt) *Free Energy Calculations: The Slow, The Fast, and The Abrupt*
9.45 – 10.00 am	Dr. Carlos Camacho (CCBB, Pitt) *From Recognition to Docking: Predicting Protein-Protein Interactions*
10.00 – 10.15 am	Discussion
10.25 – 11.25 am	**Session II: Supramolecular Simulations** Chair: Dr. Joel Stiles (PSC/CMU)
10.25 – 10.40 am	Dr. A. J. Rader (CCBB, Pitt) *Simulating Viral Capsid Maturation Using Elastic Network Models*
10.40 – 10.55 am	Dr. Russell Schwartz (Biol Sci, CMU) *Efficient Discrete Event Modeling of Molecular Self-Assembly*
10.55 – 11.10 am	Dr. David Swigon (Math, Pitt) *Mesoscale Modeling of Nucleo-Protein Assemblies*
11.10 – 11.25 am	Discussion
11.35 am – 12.45 pm	**SESSION III: Subcellular / Cellular Simulations** Chair: Dr. Ivan Maly (CCBB, Pitt)
11.35 – 11.50 am	Dr. Alan Wells (Pathology, Pitt) *Decision Tree Analysis of Cell Motility*
11.50 – 12.05 pm	Dr. Shlomo Ta'asan (Math, CMU) *A Framework for Logical Modeling of Cellular and Subcellular Systems*
12.05 pm – 12.20 pm	Dr. John Pattillo (PSC) *Spatially Realistic Monte Carlo Simulations Predict Calcium Dynamics Underlying Transmitter Release at a Neuromuscular Active Zone*
12.20 pm – 12.35 pm	Dr. Ivan Maly (CCBB, Pitt) *Reaction-Diffusion Models of Signaling Networks, From Cells to Tissues*
12.35 – 12.50 pm	Discussion
12.50 – 1 pm	**Concluding Remarks** Dr. Joel Stiles (PSC/CMU)
1 pm	**LUNCH (Mellon Institute Social Room)**

Appendix IV: Postdocs and students who participated in pre-NPEBC activities (*)

Name	Position	PI	Support Source
Anes Aref	Undergraduate Student	Klein-Seetharaman	NIH-NSF BBSI
Z. Bagci (*)	PhD Student	Bahar	Pre-NPEBC
Julie Blackwood	Undergraduate Student	Ta'asan	NIH-NSF BBSI
J. Chang	Scientific programmer	Stiles	NIH
C. Chennubhotla	Postdoc	Bahar	Dept of Comp Bio, SOM
Mark Connell	Undergraduate Student	Benos	NIH-NSF BBSI
Jason Funt	Undergraduate Student	Meirovitch	NIH-NSF BBSI
R. Gandhlin	Postdoc	Ta'asan	Center for Nonlinear Analysis, Math, CMU
Holliman, Mark	MS student	Karimi	Dept of Comp Bio, SOM
B. Isin	PhD Student	Bahar	NSF ITR
Alexandre Ismail	Undergraduate Student	Evanseck	NIH-NSF BBSI
Andrew Kohlway	Undergraduate Student	Madura	NIH-NSF BBSI
Liu, Xiong	PhD student (SIS)	Karimi	School of Information Sci, Pitt
Ed Lyman	Postdoc	Zuckerman	NIH
Nicholas Morsillo	Undergraduate Student	Stiles	NIH-NSF BBSI
R. Munshi	Postdoc	Bahar	Dept Comp Biol/ NIH-NSF BBSI
Deanna Nachreiner	Undergraduate Student	Stiles	NIH-NSF BBSI
Jerome Nilmeir	PhD Student (UCSF)	Bahar	NIH-NSF BBSI
J. Patillo	Postdoc	Stiles	NIH
A. J. Rader	Postdoc	Bahar	Dept of Comp Bio, SOM
A. Ramaswamy	Postdoc	Bahar	Dept of Comp Bio, SOM
Tristan Richards	Undergraduate Student	Day	NIH-NSF BBSI
M. Seki	Postdoc	Wood	UPCI and NIH
Indira Shrivastava	Postdoc	Bahar	Dept of Comp Bio, SOM
Jay Shukla	Undergraduate Student	Nicholas	NIH-NSF BBSI
Kate Stafford	Undergraduate Student	Wymore	NIH-NSF BBSI
N. A. Temiz	PhD Student	Bahar	Dept of Comp Bio, SOM
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