An Introduction to Simulation and Visualization of Biological Systems at Multiple Scales: A Summer Training Program for Interdisciplinary Research

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Advances in biomedical research require a new generation of researchers having a strong background in both the life and physical sciences and a knowledge of computational, mathematical, and engineering tools for tackling biological problems. The NIH−NSF Bioengineering and Bioinformatics Summer Institute at the University of Pittsburgh (BBSI @ Pitt; www.ccbb.pitt.edu/bbsi) is a multi-institutional 10-week summer program hosted by the University of Pittsburgh, Duquesne University, the Pittsburgh Supercomputing Center, and Carnegie Mellon University, and is one of nine Institutes throughout the nation currently participating in the NIH−NSF program. Each BBSI focuses on a different area; the BBSI @ Pitt, entitled "Simulation and Computer Visualization of Biological Systems at Multiple Scales", focuses on computational and mathematical approaches to understanding the complex machinery of molecular-to-cellular systems at three levels, namely, molecular, subcellular (microphysiological), and cellular. We present here an overview of the BBSI @ Pitt, the objectives and focus of the program, and a description of the didactic training activities that distinguish it from other traditional summer research programs. Furthermore, we also report several challenges that have been identified in implementing such an interdisciplinary program that brings together students from diverse academic programs for a limited period of time. These challenges notwithstanding, presenting an integrative view of molecular-to-system analytical models has introduced these students to the field of computational biology and has allowed them to make an informed decision regarding their future career prospects.

Introduction

There have been fundamental changes in biological and biomedical research methodology and topics in recent years. New initiatives are now taking shape in the form of structural genomics, functional genomics, or proteomics. There is now a shift in emphasis: from sequence to structure, from genes to proteins and their complexes, and from interacting pairs to interaction networks. There is also a change in the scale of the explored processes, from atomic/molecular to supramolecular, cellular, and systems levels. This field, broadly (and interchangeably) referred to as "computational biology" or "bioinformatics", encompasses a wide range of topics, from molecular modeling and protein dynamics to large-scale analysis of genome/proteome data. To successfully train a new generation of interdisciplinary investigators in this field, learning opportunities must be provided to individuals wishing to develop and implement theories, methods, and tools. These opportunities will allow new researchers to better create, evaluate, and employ computational, mathematical, and engineering tools for tackling biological problems (*1*).

Due to this emergence of interdisciplinary research, boundaries between traditional fields are gradually disappearing, especially at the level of graduate education. This is shown by the large number of multidepartmental graduate programs in biomedical science that have been established over the past several years. However, similar undergraduate programs are quite rare, even though the need to introduce interdisciplinary curricula, particularly in undergraduate biology programs, has been well documented and acknowledged (*2, 3*).

Undergraduate research, such as summer Research Experience for Undergraduates (REU) programs, offers students the opportunity to prepare for and pursue careers in science (*4*). In addition to improving and strengthening coursework fundamentals (*5, 6*), students who participate in these programs demonstrate a greater interest in careers in science, engineering, and mathematics (*7*). These programs have been shown to expand a student's educational potential and pave the way for students wishing to pursue graduate education (*8*) and to develop better research and communications skills (*9*). Furthermore, undergraduate research also contributes to retention of students from underrepresented minority groups and increases the rate of graduate education in this pool of students (*10*).

As important as traditional REU programs are, they have two limitations: (i) Student participants begin a research project with minimal preparatory training. Thus, knowledge acquired during the program is often "project-specific". (ii) For the most part,

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Table 1. NIH−NSF Bioengineering and Bioinformatics Summer Institutes (BBSI)

institution(s)	BBSI focus
University of Pittsburgh (lead), Pittsburgh Supercomputing Center, Duquesne University, Carnegie Mellon University	Computational Biology
California State University at Los Angeles	Bioinformatics
The Pennsylvania State University	Biomaterials and Bionanotechnology
Clemson University	Biomaterials Science and Engineering
Harvard University−Massachusetts Institute of Technology	Biomedical Optics
University of Minnesota	Bioinformatics
New Jersey Institute of Technology	BioMEMS (micro-electro-mechanical systems)
Virginia Commonwealth University	Bioinformatics and Bioengineering
Iowa State University	Bioinformatics and Computational Biology

only those students who already possess an appropriate background can join and successfully complete a research project. In other words, chemistry REU programs typically attract students majoring in chemistry; similarly, mathematics majors are generally drawn to mathematics REU programs. These issues notwithstanding, REU programs are a valuable educational tool for students and researchers alike.

Computational biology and bioinformatics are relatively new fields, with degree-granting programs being offered only recently. Due to the inherent nature of these new disciplines, they draw heavily upon the physical and biological sciences and also on mathematics, engineering, and computer science. We report here a new interdisciplinary summer research program for undergraduate and graduate students, which attempts to address both of the aforementioned issues. This program is the Bioengineering and Bioinformatics Summer Institute (BBSI), one of nine such BBSI programs nationally with joint NIH−NSF sponsorship and each with a specific research concentration (Table 1). The primary focus of the BBSI described herein (BBSI @ Pitt) is computational biology. Entitled "Simulation and Computer Visualization of Biological Systems at Multiple Scales", it is a joint program offered by the University of Pittsburgh (lead institution), the Pittsburgh Supercomputing Center, Duquesne University, and Carnegie Mellon University.

Program Details

Overview. The BBSI at the University of Pittsburgh (BBSI @ Pitt) is a 10-week interdisciplinary program organized into coursework, laboratory research, and student presentations. Students receive intensive didactic training in the form of comprehensive coursework that covers the theoretical and computational aspects of computational biology as applied to investigating molecular-to-cellular systems dynamics. At the same time, students conduct research in a laboratory of choice for the duration of the program. A major goal of this program is to identify talented students, increase their awareness of the quantitative and computer science methods in life sciences, and encourage them to consider career opportunities in the field of biomedical computing by providing them with an integrative team-based hands-on research experience at an early stage of their studies. Furthermore, the program strongly emphasizes professional development in the form of weekly research or career seminars, an ethics forum, career workshops, and student presentations.

Focus, Intellectual Merit, and Objectives. The program focuses on current computational and mathematical approaches to understand molecular and cellular systems dynamics and thereby function, using molecular and cellular structure, biological pathways, and other biochemical data. Undergraduate students typically are unaware of recent developments in these fields, and the BBSI @ Pitt (i) provides students with an overview of existing models, methods, and tools for exploring the dynamics of biological processes; (ii) presents an integrative

view of molecular-to-system analytical models and the fundamental physicochemical, statistical mechanical, and kinetic principles required for predictive theoretical and computational research; and (iii) stimulates student interest in the newly evolving field of computational biology and thus motivates them to pursue career opportunities in the field. An additional aim is also to enhance communication and interaction between the participating institutions and faculty, which is expected to have a synergistic effect on collaborative research activities.

Targeted Students. Consistent with the goals and desired impact of the program, student participants are selected from a diverse academic pool that includes basic life sciences or physical sciences, mathematics, computer science, or engineering. To attract students from all of these disciplines, program announcements are mailed to ∼1000 institutions on lists obtained from departments within the participating universities offering traditional REU programs. Program announcements are also distributed through electronic mailing lists developed by the Pittsburgh Supercomputing Center for their national biomedical workshops and a computational cell biology community. Last, the program announcement is also distributed to professional colleagues of the Core Instructors and Research Mentors. Due to the comprehensive coursework designed for the program, students must have completed their sophomore or junior year and should have demonstrated a strong interest in cross-disciplinary studies through coursework outside of their major field. Although a majority of the participants are undergraduates, the program also provides an opportunity for first or second year graduate students to participate. Furthermore, special emphasis is given to recruiting students from underrepresented groups and from institutions where research programs are limited. In accordance with NIH and NSF guidelines, undergraduate students receive a stipend of $300/week (total $3,000), and graduate students receive $500/week (total $5,000).

Organizational Structure. The overall organization is designed to maximize the interaction between the students and the faculty and to integrate the education and research activities. A group of six faculty members from the participating institutions form the Core Instructors of this program and also serve as Research Mentors for the students. In addition, 17 other faculty from the participating institutions are also available as Research Mentors during the research component of the program. Before and during each summer, a Program Coordinator oversees organization to ensure satisfactory implementation of the goals and vision. Following each summer, student evaluations are reviewed by the Core Instructors and the Program Coordinator in preparation for the following year. All decisions and changes are approved unanimously prior to implementation.

Didactic Training. *Coursework.* A distinguishing feature of the BBSI program is comprehensive coursework covering theoretical and computational aspects of computational biology as applied to molecular-to-cellular systems dynamics. This

Table 2. Organization of BBSI @ Pitt Coursework Sessions

session	general topic	inclusive topics	hours[a]
1	Review of Mathematical and Biochemistry Concepts	Linear Algebra	3
		Differential Equations	3
		Probability and Stochastics	3
		Biochemistry Review	4.5
2	Computer Visualization	Data Visualization	4.5
		Molecular Visualization	4.5
	Fundamentals of Computational Biology	Thermodynamics and Statistical Mechanics	3
		Kinetics: Theory and Methods	3
		Protein Folding	3
3	Multiscale Simulations	Molecular	6
		Subcellular	4.5
		Cellular	6

[a] Total: 48 h of coursework and 36 h of computer laboratory sessions over a 4-week period.

coursework, taught by the Core Instructors, is divided into three sessions (Table 2) and is briefly summarized below. A detailed description of the coursework is outlined in the Appendix.

Knowledge of a number of fundamental topics is required to understand the computational and mathematical models and algorithms applied to the dynamics of complex biological systems. In Session I, a summary of basic mathematical, numerical, and probabilistic methods is presented, along with a brief review of biochemistry, cell biology, and protein structure. Since the program brings together students from diverse academic backgrounds, this session is necessary to bring participants to a common level. Session II teaches visualization tools and fundamental concepts of statistical mechanics and kinetics, and in conjunction with Session I provides the necessary interdisciplinary theoretical background for the simulations of biological molecules and systems. Session III introduces the current problems and trends in computational biology, and models and methods are described for simulations at three different scales, namely, biomolecular, subcellular (microphysiological), and cellular. Students thus see the applications of the concepts and methods discussed in Session II to the multiscale simulations.

Computer Laboratory Sessions. Computer laboratory sessions complement the lectures described above. These sessions introduce students to the software applications related to the topics covered in lectures and allow students to obtain hands-on experience. Computer laboratory sessions are taught by the Core Instructors, who are often assisted by teaching assistants already familiar with the applications.

Research Experience. A positive research experience is the endpoint of the program and is clearly the most important aspect of the BBSI @ Pitt. It is critical that students be trained to identify, address, and solve a biologically significant question in a logical and organized manner. Based on their interests, students choose their research mentors and are matched to a laboratory by the Program Coordinator. After discussion of their research project with their mentors, all students are required to submit a written proposal that outlines their research goals during the program, the hypothesis that will be proposed and the methodologies that will be used to test the hypothesis, and the interpretation and significance of potential results. While research activity may be limited during the coursework component of the program, students are engaged in full-time research thereafter until the conclusion of the program.

Seminars. Three types of seminars are organized for this program: research, career, and an ethics forum. Research seminars expose students to state-of-the-art research opportunities and challenges and provide them with a variety of perspectives by active researchers in the field. Examples of topics include: characterization of allosteric effects in bio-

molecular complexes; mathematical modeling of cell cycle regulation; signaling/regulatory networks of apoptosis; simulation of microphysiological processes such as calcium dynamics; microarrays or gene expression profile analyses; sensor technology in medicine, etc. Career seminars expose students to career opportunities, helping them to make cognizant decisions at graduation. These seminars present options in academia as well as prospects in industry. Ethical issues are an important aspect of research, and a mentored team-based ethics forum is organized every year for students in the program. This allows the students to evaluate and discuss the implications of ethical choices they may be presented with during their career.

Professional Development. *Student Presentations.* All students are required to give a Journal Club presentation related to their research project after consultation with their Research Mentor. Every student also gives an oral presentation of their research project to the other students and faculty and also presents a poster at the Annual Undergraduate Research Symposium hosted by Duquesne University.

Team-Based Activities. Students are assigned to groups for the preparation of the Journal Club research articles and for the ethics forum. The objective of this is 2-fold: (i) it provides a foundation for team-based activities, and (ii) it allows students from different academic backgrounds to complement lack of coursework in a certain area.

Career Workshops. Two career workshops are organized with current graduate students and postdoctoral fellows during which program participants have the opportunity to discuss the basis of selection of graduate schools, the application process, and career options following graduation.

Dissemination. All course material, including lecture notes, assignments, and solutions to assignments, are made accessible on the Internet via a dedicated website at www.ccbb.pitt.edu/bbsi. This also includes student presentations and written proposals. This type of information is useful both for future applicants and other Institutes that are (or plan to be) engaged in similar efforts.

Program Assessment. At the conclusion of each summer, the program is carefully evaluated by the students and the faculty. Students participate in a discussion session on their experience and complete a detailed 65-question online feedback form. This information is assessed along with feedback from all participating faculty prior to any program changes. Furthermore, the progress and impact of the program is discussed at an annual awardees' meeting that is attended by NIH and NSF officials and the Program Directors of all BBSI programs. This provides an opportunity for different programs to share ideas and approaches and thus strengthen the entire BBSI endeavor.

Tracking of Program Alumni. One responsibility of the Program Coordinator is to maintain contact with past students,

Table 3. Distribution of Academic Majors for BBSI @ Pitt Student Participants, 2003−2005[a]

academic major	no.
Biological Sciences (total)	20
Biochemistry	3
Bioinformatics	6
Biology	7
Biophysics	3
Computational Biology	1
Chemistry	2
Computer Science	6
Engineering (total)	10
Bioengineering	5
Biomedical Engineering	4
Computer Engineering	1
Mathematics (total)	4
Applied Mathematics	3
Mathematics	1*

[a] A total of 42 students were accepted (14 students per year). While our recruiting efforts equally included departments of physics across the nation, only one dual Mathematics-Physics major (*) has participated in the program thus far.

track their progress and career achievements, and document how the BBSI @ Pitt has influenced their decisions. Although not every student will pursue a career in a related field, our goals are to continue to support this career path for those who remain interested and offer advice and encouragement to those who are undecided and seek additional guidance regarding graduate studies.

Observations and Challenges

Consistent with the interdisciplinary nature of the field, the BBSI @ Pitt has accepted student participants from very diverse academic majors since the program's first year in 2003 (Table 3). Although applications to the program were received from universities and colleges throughout the nation, a majority of these were from institutions in the Northeast and the Midwest, most likely due to their proximity to Pittsburgh. Applicants are evaluated on academic performance (GPA), completed relevant coursework, a personal essay describing their reasons for attending such a program, and any prior research experience. As seen in Figure 1A, the participating student pool has been well represented by entering juniors and seniors, indicating that there is strong interest at a very early stage to identify a potential career path and obtain experience in it. More importantly, these students are eager to apply knowledge acquired in traditional disciplines such as chemistry, mathematics, engineering, and computer science toward a biological question using nontraditional methodologies. Furthermore, the students are represented nearly equally by both genders (Figure 1B), suggesting a lack of gender-specific preference for the field of computational biology and bioinformatics. While we have been successful in recruiting underrepresented minority groups to our program (Figure 1C), our goal is to increase that fraction within the next few years.

Challenges. During the 3 years that this interdisciplinary training program has been offered, we have identified four aspects/characteristics that distinguish it from traditional summer REU programs:

(1) Group Heterogeneity. Due to the interdisciplinary nature of the field and the program, all program participants do not belong to the same academic major (Table 3). This results in a very diverse group of individuals with varied academic training and research interests. Thus, the BBSI is faced with the task of building a coherent learning environment among students from vastly differing academic philosophies. This necessitates a teaching approach that is effective for biologists and engineers and requires a higher degree of coursework preparation.

(2) Academic Curriculum. The program includes wide-ranging lectures and computer laboratory sessions, thereby broadening the student's view of post-genomic computational and mathematical research in molecular, cellular, and systems biology. A major challenge in developing an academic curriculum for such a diverse group is the ability of program participants to effectively understand the material at the desired level. We have found it necessary to include review sessions in mathematics and biochemistry to ensure that a lack of coursework in these fields does not limit understanding of advanced concepts in computational biology. Furthermore, the extent of coursework that can be covered is dependent to a great degree on the participant pool each year. Even though BBSI @ Pitt participants are academically excellent, we recognize that group diversity may hinder the ability of the faculty to cover the desired coursework (see Appendix) in the time period assigned (see next point), thereby permitting only summary coverage of certain topics. As the number of undergraduate programs in computational biology continues to increase and as newer outside curricula include more related material, we anticipate that our curriculum will be more familiar to a larger fraction of incoming students, and thus more detailed coverage will be possible.

(3) Time Constraint. One of the major challenges faced by the Core Instructors is the time constraint in covering all planned didactic activities. Though the participating students are academically strong and eager to develop skills in computational biology theory and methodology, the breadth of this discipline precludes exhaustive coverage of every topic in the time available. Furthermore, varying interests within the student group may even make this undesirable. Thus, for the faculty preparing the lecture material for a particular topic, finding the right balance between necessary coursework and appropriate coursework can often take several years of teaching in such a program.

(4) Balance between Coursework and Research. While coursework is undoubtedly necessary for a strong foundation in any field, especially for a relatively new discipline such as computational biology, the distribution of research and lecture time is critical. This is even more significant for summer training programs due to the limited time during which an entire research project must be completed. Coursework must not only provide an appreciation of the potential of the field but also provide the knowledge to effectively conduct research. Thus, it is key to find a compromise between fundamentals and application. Indeed, our student feedback has indicated that maximized research time is highly desirable because substantial contribution to a research project is important and rewarding. Thus, emphasizing coursework over research, or vice versa, could lead to an unsatisfactory training experience.

In an effort to address the challenges and to improve the program, we have evaluated detailed online feedback surveys and personal discussions with students. Although certain challenges, such as group heterogeneity and time constraints, are inherently part of such an interdisciplinary program, other challenges can be addressed effectively. As mentioned earlier, we have included additional review sessions in biochemistry at the suggestion of our students. We have also condensed lectures into 4 rather than 6 weeks (as initially planned), to allow additional uninterrupted research time. Based on feedback from faculty, we have also included a computer laboratory session
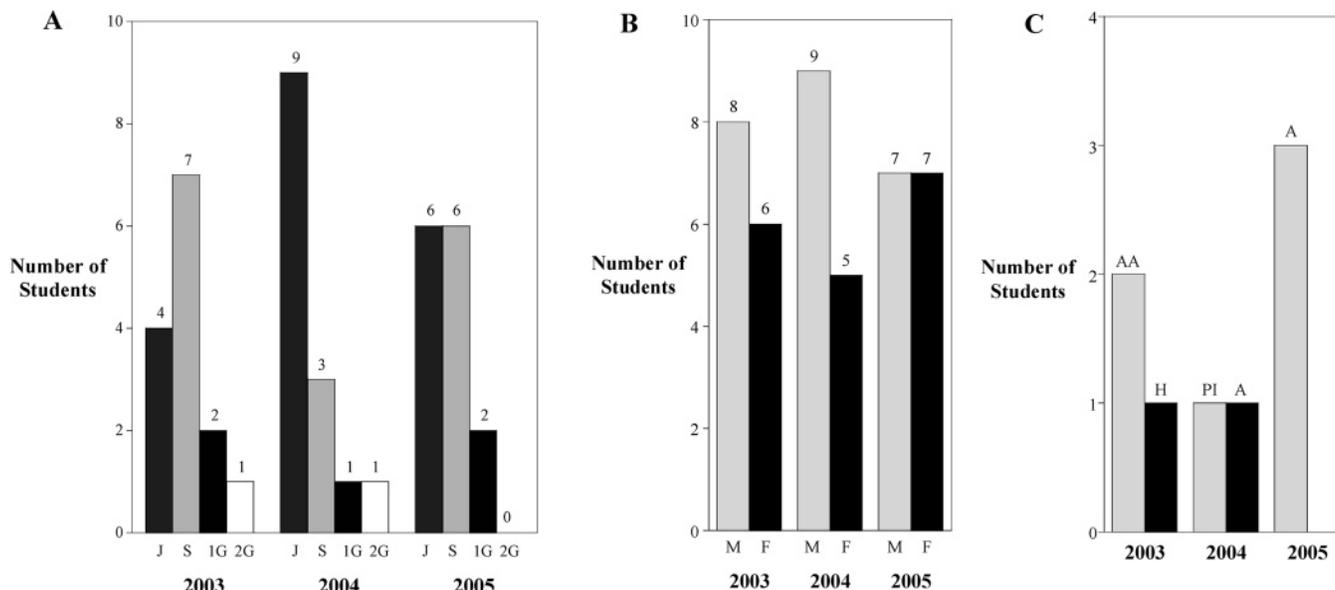
Figure 1. Demographic distribution of BBSI @ Pitt participants, 2003−2005 (14 students were accepted per year). (A) Academic year: J, entering junior year; S, entering senior year; 1G, entering first-year graduate school; 2G, entering second-year graduate school. (B) Gender: M, male students; F, female students. *(*C) Minority participation: AA, African American; H, Hispanic; PI, Pacific Islander; A, Asian.

that reviews the basics of research computing for students who are not familiar with relevant tools such as a command line-based interface to the operating system, both with Windows and especially UNIX. This session was specifically included on the recommendation of the Core Instructors and reflects a continuing lack of such training in many undergraduate science and engineering programs.

Discussion

In recent years, a considerable amount of attention has been directed toward support for interdisciplinary research, especially in biology programs (*2, 11*). A change in teaching principles has accompanied this interest, where active learning strategies have been shown to improve the learning process (*12*). We present here a novel summer research training program, the BBSI @ Pitt, which educates and prepares students for research in a relatively new field and initiates the development of talented young scientists with the necessary skills to make an impact in the fields of computational biology and bioinformatics, as outlined in the NIH Roadmap Initiatives (http://nihroadmap.nih.gov).

In a survey of students who completed at least some undergraduate research (*4*), 38.3% of the respondents indicated that they wished to pursue graduate education (Ph.D. or M.D./Ph.D.) in a biology-related discipline, while an additional 14.2% indicated a desire to complete a Ph.D. in the physical sciences. The goal of the BBSI program is to offer such students the opportunity to consider a career in computational biology, bioengineering, and bioinformatics by providing them with guidance and training at an appropriate time of their education. Although a majority of students (56.5%) do not change their plans for graduate education following a research experience, such an experience does confirm or alter plans for 30.5% of the students surveyed (*4*). This indicates that novel summer research training programs, such as the BBSI @ Pitt, can indeed be effective in retaining and/or increasing the number of individuals wishing to pursue a career in this field.

The critical question is "How effective has the BBSI @ Pitt been in providing a career path in computational biology?" Although we have yet to establish and confirm the career paths

of our student participants, primarily due to the infancy of the program, there already are identifiable trends: (i) 31% of our students have indicated confidently that computational biology is the career choice for them. However, several of these students were entering their junior year at the time of this declaration. (ii) An equal number of students (31%) said that they would likely or possibly continue in this field. (iii) Of the remaining 38%, 12% indicated that this was an unlikely career choice, while 26% stated with conviction that computational biology or bioinformatics was not a career option. This distribution is encouraging, and we believe that presenting an integrative view of molecular-to-system analytical models has been instrumental in introducing students from diverse academic backgrounds to the fields of bioengineering, computational biology, and bioinformatics and has allowed them to make an informed decision regarding their career prospects.

Program Outcomes

In addition to providing students with a potentially new and exciting career choice, the BBSI @ Pitt has offered students the option to continue their summer research at their home institution in the form of senior year and thesis projects. Additionally, graduate students serving as teaching assistants during the computer laboratory sessions have the opportunity to share their knowledge as instructors in a semiformal environment. Postdoctoral research associates, who mentor students in preparing for the ethics forum, also gain valuable and rewarding teaching experience.

Furthermore, the BBSI @ Pitt program has increased awareness of computational biology among investigators at the participating institutions. Indeed, two recent related developments are (i) the establishment of a new Department of Computational Biology at the University of Pittsburgh School of Medicine, and (ii) the initiation of a joint Ph.D. Program in Computational Biology offered by the University of Pittsburgh and Carnegie Mellon University (www.compbio.cmu.edu). The new joint Ph.D. program admitted its first class in Fall 2005, and combines the biomedical strength at the University of Pittsburgh with the expertise in computer science at Carnegie Mellon University.

Innovative experimental research initiatives are now taking shape in structural genomics, functional genomics, and proteomics, along with new initiatives in biomedical computation. As fresh academic programs are developed to train interdisciplinary researchers, experiences and results from the BBSI @ Pitt can be used to help develop novel curricula that promote a broad understanding of these disciplines. Thus, researchers with thorough interdisciplinary training will be available to meet the next wave of scientific challenges and thereby propagate scientific advances and breakthroughs.

Appendix: BBSI @ Pitt Course Descriptions

Biochemistry Review (4.5 h). A knowledge of protein structure is essential to a deeper understanding of protein dynamics and molecular motions. This review describes amino acid structure, peptide bond formation, the hierarchy of protein structure (primary, secondary, tertiary, quarternary), and Ramachandran plots. In addition, basic principles of cell signaling pathways are covered, including secondary messenger formation, signal amplification, and signal transduction. Finally, microarray technology is discussed, including cDNA microarrays and oligonucleotide arrays.

Linear Algebra (3 h). This review covers basic concepts from linear algebra used in modeling and simulations, including a description of matrix notation and matrix multiplication, solving systems of linear equations using manipulations of matrices, introduction of eigenvalues and eigenvectors, and Taylor series and linearization of equations. Laboratory sessions include demonstration of programs such as MatLab and use of simple commands for solving equations and finding eigenvalues.

Differential Equations (3 h). Ordinary differential equations play a pivotal role in cellular modeling and simulation. Starting with nonlinear differential equations, equilibria in general are discussed. The behavior near equilibrium is determined by solving the linearized system of equations. This requires knowledge of the eigenvalues of an associated matrix. For differential equations that cannot be solved explicitly, several simple numerical methods such as Euler and Runge–Kutta are discussed. Related software is demonstrated and used in the laboratory component.

Probability and Stochastics (3 h). Fundamental concepts of probability and stochastics are introduced, such as elementary probability spaces, permutations, combinations, random variable, expectation value, variance, probability density, stationary and nonstationary processes, stochastic differential equations, time averages and correlations, ergodicity, and thermal noise. Brownian movements are presented as an important physical application of stochastic processes. Finally, Markov processes and transition probabilities are covered. In the laboratory session, simple problems from classical comprehensive textbooks (*13, 14*) are solved, and all of this material is related to subsequent lecture and lab work on microphysiological simulations based on Monte Carlo algorithms (Table 1, Sessions II and III).

Data Visualization (4.5 h). Issues such as data structure design and organization, data flow and manipulation, grid design and data point (string, scalar, vector, tensor, matrix, etc.) representation are introduced, using the open source package OpenDX (www.opendx.org). OpenDX includes a visual programming environment, software and hardware rendering engines, and extensive tutorials and documentation. In addition, this material serves as groundwork for more specialized visualization covered in Session II and III coursework.

Molecular Visualization (4.5 h). Topics covered include importing and exporting coordinates, various rendering modes, visualizing and mapping various properties, and manipulation of the structures. Software introduced includes InsightII, MOE (www.chemcomp.com), Cerius2, RasMol, WebLab Viewer, Swiss-Pdb Viewer, Molscript, UCSF Chimera, and Ribbons. In the laboratory sessions, students gain experience with common web-based search and retrieval systems.

Thermodynamics and Statistical Mechanics (3 h). First, the difference between mechanical and thermodynamic systems and the relation between statistical mechanics and classical thermodynamics are presented. The canonical partition function is defined, discussed, and solved for an ideal gas. The concept of configurational partition function is introduced, followed by a discussion of the statistical nature of statistical mechanics. Finally, problems at the introductory level (*15*) are solved in the problem sessions to illustrate these theoretical concepts.

Kinetics (3 h). Kinetics includes both physical (structural change and/or diffusion) and chemical (reaction) kinetics. Elementary concepts of molecular mobilities, conformation and velocity distributions, changes (or fluxes) driven in the direction of decreasing potential (or concentration), and diffusion laws are introduced within the scope of physical kinetics. Chemical kinetics topics include the definition and applications of differential and integrated rate laws, the concepts of rate-controlling steps, steady-state approximation, transition states, and Michealis–Menten mechanism of enzyme reactions. From a different perspective, both the classical (simple mass-action) and modern (energy landscape) theories of kinetics applied to biochemical and biophysical changes are introduced. The master equation formalism is presented as a tool for exploring macromolecular motions (*16*), protein folding (*17*), and subcellular or cellular interaction dynamics (*18–20*). In addition, stochastic interactions are covered together with Monte Carlo algorithms for 3D-reaction/diffusion problems (*21*).

Molecular Simulations (6 h). Molecular simulations require the definition of two essential features, geometry and energetics, of the investigated structure. Accordingly, models commonly used for representing molecular geometry and the energy functions used for describing intra- and intermolecular interactions are introduced. The fundamental principles of molecular simulations are described, such as the numerical solution of Newton's equation of motion or the evaluation of molecular forces as the negative gradient of potential. Simple algorithms for molecular dynamics (MD), Brownian dynamics (BD), and Monte Carlo (MC) simulations coupled with the Metropolis algorithm are presented. Students are referred to the comprehensive books by Allen and Tildesley (*22*) and Leach (*23*). The utility of adopting low resolution (or reduced) models as a means of proceeding to longer time or larger scale dynamics is emphasized and illustrated in the laboratory sessions. The students thus acquire a basic understanding of the methodology of MD, BD, and MC simulations and have access to related software and databases. Finally, the use of the mathematical methods presented in the first week (e.g., eigenvalue decomposition and correlation analysis) for analyzing MD or MC trajectories are illustrated in the problem sessions.

Subcellular Simulations (6 h). Models for various components in the cell are presented. Applications such as simple ion pumps and molecular motors that participate in cell motility (*24*) are introduced. Recent engineered gene networks are discussed in the context of building simple "computational devices". Methods for characterizing the structure and function of protein channels (or pores) and the transport of simple ions (e.g., Na^+, Cl^-) and biopolymers (DNA, proteins) through these pores are illustrated in the lectures and laboratory sessions. The techniques for studying nonequilibrium dynamics, which play an essential role

in the operation of living systems (e.g., energy storage and conversion, signal transduction, etc.), are discussed. Finally, the software *MCell* (*21*, *25*), developed for quantitative simulations of synaptic physiology, is presented as an example of a simulator of cellular physiological processes. Students have access to the software and see its applications in the laboratory sessions.

Cellular Simulations (6 h). In this section, models describing cellular-level interactions are described, analyzed, and simulated. Topics discussed are the cell cycle models of Tyson and collaborators (*26*) and the model for apoptosis recently developed by Fussenegger et al. (*27*), as well as our own extension of it to incorporate the effects of nitric oxide. Another topic is DNA damage and repair (*28*). Models for metabolic pathways (e.g., glycolysis and the associated oscillations) are also introduced. Recent models for the MinD/MinE system in bacteria are used to illustrate some partial-differential equations and pattern formation ideas. Both in lectures and lab sessions, software packages such as *XXPAUT* (www.math.pitt.edu/∼bard/xpp/spp.html) for simulating, animating, and analyzing dynamical systems (*29*), VCell (www.nrcam.uchc.edu), *MCell* (www.mcell.psu.edu), E-cell (www.e-cell.org), and Gepasi (www.gepasi.org) are introduced.

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