Biomedical Informatics Training at the University of Wisconsin-Madison

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Introduction

A plethora of approaches support biomedical informatics training at the University of Wisconsin-Madison, all of which share a strong focus on interdisciplinary coursework and research. There are three primary approaches to training 1) The Computation & Informatics in Biology & Medicine Training Program, 2) formal biomedical informatics offered by various campus departments, and 3) individualized programs. Training at UW-Madison embodies the features of effective biomedical informatics training recommended by the American College of Medical Informatics as delineated as: 1) curricula that integrate experiences among computational sciences and application domains, 2) individualized and interdisciplinary cross-training among a diverse cadre of trainees to develop key competencies that he or she does not initially possess, 3) participation in research and development activities, and 4) exposure to a range of basic informational and computational sciences. The following description of biomedical informatics training at UW-Madison illustrates that these elements form the foundation for productive and integrated training across a spectrum of biomedical informatics application domains.

Computation & Informatics in Biology & Medicine Training Program

The Computation & Informatics in Biology & Medicine (CIBM) Training Program is a bioinformatics training program for pre-doctoral and post-doctoral trainees, funded by the National Library of Medicine (NLM) since 2002. CIBM’s mission is to provide modern training for a new generation of researchers wishing to solve biomedical problems requiring strengths in both computational and biological science.
Faculty & Trainees

The 41 CIBM faculty span 15 different departments and five colleges at the University of Wisconsin-Madison, and include several at the Marshfield Clinic Research Foundation, as well. The research foci of CIBM faculty are available on the CIBM Program website at www.cibm.wisc.edu. The management team includes George Phillips (Professor of Biochemistry and of Computer Sciences) as the Program Director, David Page (Associate Professor of Biostatistics & Medical Informatics and of Computer Sciences) and Jude Shavlik (Professor of Computer Sciences and of Biostatistics & Medical Informatics) as Co-directors, and a Management Committee that consists of Frederick Blattner (Oliver Smithies Professor of Genetics), Patricia Flatley Brennan (Moehlman Bascom Professor of Nursing, Industrial & Systems Engineering, and of Biostatistics & Medical Informatics), Mark Craven (Associate Professor of Biostatistics & Medical Informatics and of Computer Sciences), David DeMets (Professor and Chair of Biostatistics & Medical Informatics and Professor of Statistics), and Justin Starren (Director of the Biomedical Informatics Research Center, Marshfield Clinic Research Foundation).

The departmental homes of CIBM trainers who have served as primary mentors for CIBM trainees and CIBM trainees are summarized in Table 1. The percentages of trainees and faculty trainers differ because many faculty have joint appointments, and the Biostatistics & Medical Informatics Department does not directly accept graduate students. Joint appointments among faculty facilitate integrated training. Pre and postdoctoral trainees select a primary and a secondary mentor that reflect their primary and cross-training foci respectively. Several students have constructed a special multidisciplinary bioinformatics PhD degree.

Additional CIBM faculty trainers are in the Departments of Electrical and Computer Engineering, Oncology, and Statistics. Many are members of the Genome Center of Wisconsin, which administers the CIBM Training Program. Two CIBM faculty are affiliated with the Marshfield Clinic. The Marshfield Clinic is located in 41 centers throughout northern, central and western Wisconsin. Its research division, the Marshfield Clinic Research Foundation, conducts research on healthcare and public health. Areas of focus include clinical research, rural and agricultural health and safety, human genetics, epidemiology and biomedical informatics.

CIBM Curriculum

The CIBM program is not a degree granting program but designed to foster interdisciplinary training. CIBM trainees become well versed in a common language of concepts from computer science, statistics, and biology. Students can use the required CIBM classes to satisfy their PhD minor requirement in their respective home departments. The CIBM Program’s curriculum for pre-doctoral trainees (see Table 2) has three components:

- **Interdisciplinary bioinformatics core courses**: All pre-doctoral students are required to take an introductory class in biostatistics, an essential skill in an increasingly “data driven” world, as well as *Introduction to Bioinformatics*. The third course in this group can be chosen from a set of advanced biomedical informatics courses.

- **Molecular-biology training triad**: Students choose three classes from a set of genetics, genomics, and biochemistry courses that best match their research goals to provide education in the basics of molecular biology.

- **Basics of computer science**: All students are expected to take *Introduction to Data Structures*. The other classes address different aspects of computation that play key research roles in bioinformatics and scientific computation in general.

All CIBM trainees participate in a
Biomedical Informatics Training at the University of Wisconsin-Madison

### Table 2: CIBM Curriculum

<table>
<thead>
<tr>
<th>Course</th>
<th>Description</th>
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<tr>
<td>Stat 571</td>
<td>General Genetics: Genetics in eukaryotes and prokaryotes.</td>
</tr>
<tr>
<td>BMI 576</td>
<td>General Genetics: Molecular basis of bacterial physiology and genetics with emphasis on molecular mechanisms.</td>
</tr>
<tr>
<td>BMI 776</td>
<td>General Genetics: Chemistry, nutrition, and metabolism of biological systems.</td>
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<tr>
<td>ChE 782</td>
<td>General Genetics: Equilibrium thermodynamics, chemical kinetics and transport properties, with emphasis on solution behavior and application to noncovalent interactions of biological macromolecules in solution.</td>
</tr>
<tr>
<td>ISyE 617</td>
<td>General Genetics: Equilibrium thermodynamics, chemical kinetics and transport properties, with emphasis on solution behavior and application to noncovalent interactions of biological macromolecules in solution.</td>
</tr>
<tr>
<td>Gen 677</td>
<td>General Genetics: Provides knowledge of basics of genomic science and introduce students to cutting edge topics. Basics will be covered in both the physical and biological sciences.</td>
</tr>
<tr>
<td>AHABS 375/875</td>
<td>General Genetics: Introduction to genomics with an emphasis on microbial model organisms and agents of infectious disease.</td>
</tr>
<tr>
<td>CS 367</td>
<td>Intro. to Data Structures: Study of data structures (including stacks, queues, trees, graphs, and hash tables) and their applications. Analysis of efficient data structures and algorithms.</td>
</tr>
<tr>
<td>CS 540</td>
<td>Intro. to Artificial Intelligence: Principles of knowledge-based search techniques; automatic deduction; knowledge representation using predicate logic, machine learning, semantic networks, connectionist networks, etc.</td>
</tr>
<tr>
<td>CS 564</td>
<td>Database Management Systems: Database management systems; different data models for structuring the logical view of the database: relational, hierarchical, and network. Implementation techniques.</td>
</tr>
<tr>
<td>CS 577</td>
<td>Intro. to Algorithms: Survey of important and useful algorithms for sorting, searching, pattern-matching, graph manipulation, geometry, and cryptography. Paradigms for algorithm design.</td>
</tr>
<tr>
<td>CS 635</td>
<td>Tools &amp; Environments for Optimization: Formulation and modeling of applications from computer sciences, operations research, business, science and engineering involving optimization and equilibrium models. Survey and appropriate usage of software tools for solving such problems.</td>
</tr>
<tr>
<td>BMI 915</td>
<td>CIBM Seminar: Weekly seminar series; cross-disciplinary exposure to current research in computer science, biostatistics, engineering, biological sciences and biomedical research problems related to bioinformatics and computational biology.</td>
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</table>
weekly seminar during fall and spring semesters that brings trainees, trainers, and other interested faculty and students together for cross-disciplinary exposure to current research in computer science, biostatistics, engineering, biological sciences and biomedical research problems related to bioinformatics and computational biology. Presentations are designed to communicate across disciplines and are provided by CIBM trainees, UW-Madison faculty, and faculty from other institutions. The seminar is open to students, faculty, and others interested in bioinformatics. Another excellent training opportunity is the annual CIBM Program fall retreat, which features poster sessions where trainees as well as others in biomedical informatics share their research. Presentations include featured speakers by national and campus informatics scholars. Each year, one of the featured speakers is a UW bioinformatics alum.

### Research Training

The driving forces for the research training opportunities arise from health and life sciences phenomenon. In many cases these questions demand new approaches and technologies. The weaving of cultures from computer sciences, biological sciences, and health sciences are illustrated in short descriptions of a sampling of the many wide-ranging multidisciplinary projects on campus (see Table 3). These projects on campus (see Table 3). These

<table>
<thead>
<tr>
<th>Topic</th>
<th>¹Trainers, ²Trainees, &amp; ³Others</th>
<th>Focus</th>
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<tbody>
<tr>
<td>Whole-Genome Multiple Alignment</td>
<td>¹Perna, ²Darling</td>
<td>Computing whole-genome multiple alignments in the presence of large-scale evolutionary events. Developed algorithm for multiple-genome alignment called Mauve (<a href="http://gel.ababs.wisc.edu/mauve/">http://gel.ababs.wisc.edu/mauve/</a>).</td>
</tr>
<tr>
<td>Inducing Models of Regulatory Networks</td>
<td>¹Blatter, Craven, Page, ²Bockhorst, Durfee, McFarlin, Noto, Ong</td>
<td>Developing novel machine-learning algorithms for uncovering gene-regulatory networks. Current and future research directions include a) integrating regulatory-network with metabolic-network models, b) developing methods that are able to exploit all relevant sources of data, including the scientific literature, and c) applying the methods to aid in the understanding of disease-related data sets.</td>
</tr>
<tr>
<td>Structural Bioinformatics</td>
<td>¹Phillips, Shuvik, ²Dimaio, Soni, ³Cui, Phillips</td>
<td>Developing new algorithms for automatically interpreting electron density maps based on pictorial structures and matching. Future directions include employing fully connected Bayesian networks, using machine learning to recognize individual amino acids in electron density maps, scaling up to larger proteins, and handling poorer quality electron density maps.</td>
</tr>
<tr>
<td>Simulations of Biomolecular Information Processing</td>
<td>¹Yin, ²Haselme, Souchers, ³Gourse (Bacteriology), ⁴Rawlings (Chemical &amp; Biological Engineering)</td>
<td>Write and solve mass-action kinetic models with a focus on simulating the intracellular/viral responses to nutrient shifts. They have pioneered genome-to-organism dynamic models for diverse viruses. Fundamental advances include identifying protein synthesis as the limiting resource for virus growth, quantifying how interactions among genes contribute to virus fitness and robustness, and identifying conditions under which wild-type genome designs are optimal.</td>
</tr>
<tr>
<td>Statistical-Relational Learning Methods Applied to Mammography</td>
<td>¹Burnside, Page, Shuvik, ²Dav</td>
<td>Develop novel statistical relational learning (SRL) algorithms and apply them to the task of creating an expert system for mammography. They have shown that SRL algorithms can benefit from the ability to define new data views that can enhance the accuracy of predicting important fields in the original database.</td>
</tr>
<tr>
<td>Informatics for Clinical and Operational Support</td>
<td>¹Brennan, ²Haight, Hsieh, Siewertson, Zayas-Gaban, ³Kash, Cayon, Robinson (Industrial and Systems Engineering)</td>
<td>Research in the Brennan lab is aimed at supporting informed decisions at multiple levels within the healthcare system. The HeartCare II project developed, deployed and is evaluating the impact of technology enhanced nursing practice in home care settings. A recently established, Robert Wood Johnson-supported national coordinating center for personal health records brings academic and industry partners together to solve the challenge of creating a seamless link across all health information related to a given person. Mathematical modeling projects include employing Markov models for optimal treatment sequencing decisions, quality engineering and forecasting models to improve access to care for people who need treatment for substance abuse, stochastic simulation and real options models to the challenge of pricing health information exchange alliances.</td>
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</table>

Table 3: Examples of Interdisciplinary Research with CIBM Faculty and Trainees

1 CIBM Faculty Trainers, 2 CIBM Trainees, 3 Other Faculty

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examples illustrate the CIBM culture of research that generates productive interdisciplinary research training. A key focus of research at UW-Madison is the development of novel bioinformatics algorithms to analyze molecular data, genome sequences, proteins (levels, interactions, structures), and regulatory pathways. These advances are only possible when computer scientists understand enough about the problems to design usable tools and when bioscientists understand what is possible using computational and information technologies. The CIBM Program has established a culture of research that supports the development of these state-of-the-art bioinformatics algorithms. Trainees and faculty have published papers in the leading bioinformatics venues on such critical topics as multiple genome alignment [2], identification of regulatory structures in a genome [3], and analysis of high-throughput biological data [4] including expression data from microarrays [5], single-nucleotide polymorphism data [6], and structural bioinformatics [7 - 13].

As bioinformatics algorithms contribute more to our understanding of biology at a molecular level, there is a need for these algorithms to have a more direct impact on medical diagnostic and treatment processes. The CIBM Program recently added a unique translational medicine component through a collaboration with the Marshfield Clinic expanding its focus to span from molecular data to disease prediction and prevention.

An example project in the translational medicine component focuses on the design and deployment of machine learning algorithms to predict responses to a particular treatment from combined single-nucleotide polymorphism (SNP) data and clinical history data. This “Molecules to Bedside” component (see Figure 1) complements CIBM’s tradition of bioinformatics research and expands it - giving trainees the opportunity to apply their bioinformatics algorithms directly to clinical data. The Marshfield Clinic has an electronic medical record that dates back to the 1960s and a new personalized medicine program that already has collected DNA for nearly 20,000 of its patients for genotyping [14]. The clinic is the sole health care provider for many people in central Wisconsin including these 20,000. The Marshfield Clinic’s database is a rare resource of detailed clinical and growing genetic data on patients [15].

### Informatics Training within UW-Madison Departments

In addition to the CIBM Program, UW-Madison students have multiple options for pursuing biomedical informatics training. Options include a degree minor, certificate programs, research training programs in various informatics areas, and courses that provide an informatics component within graduate programs. Many of the faculty that provide biomedical informatics training within these departments are CIBM faculty thus providing an integration between these training programs. Formal courses that provide the foundation for academic training in biomedical informatics are housed in various departments, we next provide an overview of the biomedical informatics components within these departments.

#### Department of Biostatistics and Medical Informatics

The Department of Biostatistics and Medical Informatics, within the School of Medicine and Public Health, serves as a resource for clinical, population and basic sciences investigators. A major goal of the Department faculty and staff is to collaborate in the design, conduct, and analyses of laboratory, clinical, and epidemiologic studies in a variety of biomedical disciplines and departments. Faculty conduct research in statistical methodology and computational methods and participate in three graduate and postdoctoral training programs - one of these is a program in medical informatics. Medical informatics training is offered via 1) a degree minor from this department that can be satisfied by courses in the CIBM Program’s curriculum, 2) MS and PhD programs in Computer Sciences, 3) a Graduate Certificate program for students cur-
rently enrolled in medical science or biological science graduate programs, and 4) a Capstone Certificate program for post-doctoral fellows and employees of local companies working in molecular biology. Biomedical informatics research, offered in three main areas, illustrates how computation is integrated with medical applications in this department. Professors Craven, Kendzierski, Newton, Page, and Shavlik offer research projects in genetics/genomics. Projects include characterization of the genetic factors involved in susceptibility and resistance to cancer growth, mapping gene locations, analyzing genomic sequence data, analysis of mutagenesis experiments, analyzing gene-expression array data, optical mapping of genomes, predicting genomic regulatory elements, algorithms for analysis of mass spectrometry data, and novel gene-expression measurement technology. Collaborators include the UW Comprehensive Cancer Center, McArdle Laboratory for Cancer Research, Computer Sciences, Pharmacy, Genetics, and Biochemistry. Professors Craven, Page, Shavlik, Burnside and DeMets offer research projects in clinical informatics and bioinformatics. Collaborative projects include computational diagnosis of breast cancer including the determination of which mammogram abnormalities require biopsy, automated methods for extracting information from the biomedical literature, automated interpretation of images from x-ray crystallography, and automated pharmacophore discovery to help guide drug design. Collaborators include the UW Comprehensive Cancer Center, McArdle Laboratory for Cancer Research, Computer Sciences, Pharmacy, Genetics, Biochemistry, and the General Clinical Research Center.

Professors Chung and Dyer are developing algorithms for analyzing MRI images of the brain, where the algorithms perform segmentation, co-registration, and description. Collaborations exist with the Keck Lab (brain imaging), the Department of Ophthalmology and Visual Sciences, the Fundus Photograph Reading Center, Medical Physics, Mechanical Engineering, Waisman Center (speech kinematics), and the Department of Radiology (diagnostic and functional MRI). The Department of Computer Sciences. The Department of Computer Sciences is consistently ranked as one of the top ten computer science departments in the country. Most of UW’s formal biomedical informatics courses are offered through this department. In particular, the department has internationally recognized research programs in Artificial Intelligence (primarily Computer Vision and Machine Learning), Computational Biology, Computer Architecture and VLSI (Very Large Scale Integration), Computer Graphics, Computer Networks, Computer Security, Database Systems, Numerical Analysis, Operating Systems, Optimization, Performance Analysis, Programming Languages and Compilers, and Theoretical Computer Science – all of which have relevance to biomedical informatics applications.

A recent project, relevant to both biomedical and public health science, is a collaboration between Professors DeWitt and Shavlik (Computer Science), Hanrahan (Chief Epidemiologist, State of Wisconsin), and Trentham-Dietz (Population Health Sciences) to simultaneously develop algorithms for anonymizing data along with machine-learning algorithms capable of extracting useful information from anonymized data. Maximizing the tradeoff between these two conflicting goals will allow significant scientific knowledge to be extracted from biomedical data-sets while guarding patient privacy.

Health Systems. Clinical informatics training occurs in a unique environmental spanning the Department of Industrial and Systems Engineering and the School of Nursing. Professor Brennan teaches graduate level health informatics classes in the Department of Industrial and Systems Engineering and the School of Nursing. Training within these departments is primarily in the area of clinical informatics within the health care system. Curricula consist of established courses (for example, Health Systems Design) and special courses. For example, she recently partnered with faculty from three other universities that have a nursing informatics program to offer a cross campus course in Nursing Informatics. This endeavor was under the umbrella of the Committee on Institutional Cooperation (CIC) among ten leading Mid-west universities known as the Big Ten. Her multidisciplinary research, summarized in Table 2, is aimed toward developing informatics solutions that support informed decisions across the health care spectrum – from personal health to RHIO (Regional Health Information Organization) networks. The Brennan Health Systems Lab, comprised of trainees in Industrial and Systems Engineering and Nursing, offers a unique mix of perspectives that bring engineering knowledge to patient care, and the human care dimension to engineering approaches that make a distinctive contribution to the biomedical informatics literature [16 – 17]. A hallmark of training with the Brennan lab is that each trainee develops and executes his or her own research. In some cases it directly interfaces with funded lab research, in other cases it has conceptual relevance but is in a different area.

Dr. Brennan also provides informatics training that falls outside of a traditional curriculum. For example, trainees in the
nursing program participate in a video conference-mediated bi-monthly CIC Nursing Informatics Journal Club with participants from Nursing Informatics Training programs at four of the Big Ten universities: Indiana University, University of Iowa, Michigan State University, and University of Minnesota. Participants take turns selecting the topic, literature, and leading the discussion. She is also providing training to UW-Madison and UW-System Clinical Nurse Instructors for incorporating informatics and genomics content into nursing curriculum. These non-traditional training initiatives provide a mechanism for building collegial relationships and scholarship among nursing informatics researchers, and for translating clinical genomics into nursing practice via a train-the-trainer approach.

Health systems informatics research is supported by several center programs that allow trainees to participate in informatics research with various health care applications. The Center for Productivity and Quality Improvement, housed in the Department of Industrial and Systems Engineering, applies human factors solutions to health information systems implementation. Current projects evaluate the effect of computerized-provider order entry systems on clinical outcomes and examine the impact of bar code technology on safe medication administration. This group also benchmarks technology acceptance patterns among health care workers and patients. The Trace Research and Development Center develops and deploys adaptive technologies to insure that people with all levels of abilities are able to effectively use electronic health care resources. The Center for Health Systems Research and Analysis houses a national repository for quality assessment in long term care.

Informatics Training via Individual Fellowships, Traineeships and Mentorships

Biomedical informatics training at UW-Madison is also supported via individual training fellowships. Two informatics fellows funded by the NLM are from the Brennan lab. In one exemplary program, a doctoral candidate at the School of Nursing constructed a secondary emphasis in nursing informatics through intra and extra-mural training. She has a minor in Computer Sciences and took five courses in this department that support her interest in developing computable representations that accurately characterize concepts relevant to nursing practice. Informatics expertise that is represented on her dissertation committee include Dr. Brennan and faculty members from the UW-Madison School of Library and Information Studies as well as Stanford Medical Informatics. She participated in genomics training offered by the Jackson Laboratory in Bar Harbor and works with Dr. Brennan and Clinical Faculty at UW-Madison to incorporate informatics and genomics into the undergraduate nursing curriculum. An NLM-funded postdoctoral fellow works with Brennan’s HeartCare II research team. She is applying Brennan’s model of technology enhanced nursing practice toward developing informatics resources to support a model of integrated care for adolescents in the area of mental health. A NLM-funded career fellow in the Department of Biochemistry, and former CIBM postdoctoral fellow, is conducting research that will accelerate understanding proteins and their structures through the development of tools aimed to significantly speed up understanding of protein structures by building a probabilistic framework that integrates informatics and physical models. These examples show how biomedical informatics training can occur outside of a structured informatics program and can meet training needs over the course of one’s career.

Conclusions

Biomedical informatics training at UW-Madison is provided across a range of disciplines and is available at different training stages. The CIBM program illustrates how a cross-training program can support highly productive biomedical informatics research training outside of a degree granting biomedical informatics department. This program fosters a creative synergy that advances biomedical informatics across multiple fronts and prepares trainees to participate in an evolving and multidisciplinary field. Biomedical informatics training offered within established departments adheres to a similar model of immersing students in multidisciplinary training and education that is supported by faculty trainers that are conducting collaborative research across departments. The health systems informatics training complements the bioscience focus of the other programs and fosters the application of biomedical informatics to health care. Individual fellowships support the development of biomedical informatics expertise through individualized training programs. UW-Madison, with multiple departments across biological, computational and health fields, provides a rich biomedical informatics training environment that has been harnessed to create productive biomedical training programs.

Acknowledgements

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References