Department of Biological Sciences

Preface: Rationale for Biological Computing in the IT Initiative

Spurred on by developments linked to the human genome project, biology today is undergoing a massive change in the way research is conducted. Technological innovation is producing larger and larger quantities of data for biologists of all kinds to analyze and interpret. Because of this, biological computation and informatics is playing a more important and expanding role in development of biological research innovations. Recognizing this situation, the Department of Biological Sciences at LSU has recently been making strategic hires to enhance our capabilities in the area of biological computation. Thus, the IT Initiative to enhance biological computation is timely and in line with the department's current strategic plan. Research goals in Biological Sciences are to build, expand and/or establish nationally and internationally recognized programs, and to produce research results of both basic and applied value. We aim to serve as a resource for the state and nation and provide economic development via the active transfer of biological research findings into practice. Currently, department members hold more patents than any other group on campus.

In this proposal we identify three core areas where biological computation is making a large impact, and which complement current research strengths in our department. We propose that the IT Initiative should fund the hiring of a senior professor with a strong reputation in each of these three areas, along with one or two assistant professors in each area over the next few years. We will seek to hire individuals with biological goals and background, but with high-level interdisciplinary skills in computational areas including computer science, mathematics, statistics, and related areas of chemistry and physics. These hires should include substantial startup packages sufficient to attract the best researchers in these fields, along with funding of support positions needed to conduct basic research in biological computation. Together with the basic research expertise already in existence in our department, this funding strategy will develop LSU into an internationally recognized center of excellence in biological computation.

Biological Sciences is particularly well poised to participate in the IT Initiative due to the interdisciplinary nature inherent in this department, which spans biochemistry, molecular and cellular biology, integrative biology, and ecology and evolution. Our breadth prepares us for the kinds of inter-departmental interactions with e.g., Computer Science, Statistics, Applied Mathematics, Chemistry, and Physics, that are required for the success of the IT initiative. It is anticipated that these positions will be able to advantageously interact with the newly formed Biological Computation and Visualization Center in the Departments of Physics and Biological Sciences, which has state of the art facilities for cpu-intensive computational analyses on massively parallel architectures as well as immersive and interactive three dimensional visualization facilities.

Summarized below are three fundamental areas of modern biology that rely critically on intensive computation, that build on existing strengths within our department, and offer clear

opportunities to interface with other units outside of Biological Sciences: (a) evolutionary and comparative genomics, (b) cell signaling, and (c) proteomics. As explained below, we feel this cluster of hires will increase interdisciplinary research on campus and facilitate strong centers of excellence involving multiple academic units. It is appropriate to note that this proposal carries the endorsement of the 56-member faculty of Biological Sciences and was prepared by the Biological Sciences IT Committee: Mark Batzer (Chair), Richard Bruch, John Caprio, Mark Hafner, Steve Hand, Vince LiCata, Tom Moore and David Pollock.

Evolutionary and comparative genomics

This focus area centers around computational approaches to evolutionary and comparative genomics. Broadly defined, this area includes fields that compare diverse genomes, large genomic sequences and genome organization in order to understand gene function, gene/allele origin, and the underlying genetic basis of pathological genetic variants. This area is at the core of the functional and comparative genomics enterprise, which attempts to understand the basic function of genes, intergenic regions, gene regulation, and genome organization. As such, overlaps at its boundaries with structure prediction and proteomics (another proposed focus area in Biological Sciences), and with microarray based whole genome analyses. Our faculty apply evolutionary genomic approaches to phylogeny estimation, studies of comparative genome architecture or biochemistry, epidemiology, and population and quantitative genetics, and future applications may include ecological genomics and genomic biodiversity.

Each of the fields outlined above currently produces large quantities of genomic data that require heavy contributions from computational biology and mathematical biology to make biological inferences. In addition, they all rely on many of the same computational techniques, and there is a strong potential for beneficial cross-communication between researchers in these areas. For the same reason, the addition of new faculty hires in this area would enhance the newly emerging evolutionary/comparative genomics research cluster at LSU that has recently been bolstered with the hires of Drs. Hellberg, Noor, Pollock, Hand, and Batzer. These recent focused faculty hires demonstrate the institutional commitment of LSU to this research area, and they also add critical mass to the pre-existing strengths in the Biological Sciences Department and the Museum of Natural Science in the fields of systematics and evolution. The additional strengthening of our base of computational biologists in comparative/evolutionary genomics will allow us to develop a critical mass sufficient to give us national/international recognition as a center of excellence in this area.

Researchers in evolutionary genomics will also have extensive interactions with other departments and centers at LSU. In particular, they will work closely with applied mathematicians on theoretical aspects, computer scientists on algorithm development and enhancement, statisticians on modified statistical approaches, and will benefit from the visualization/modeling expertise and concurrent computing facility located in the Physics Department at LSU through interactions with Drs. Rajiv Kalia, Aiichiro Nakano and Priya

Vashishta. These faculty members are also quite likely to also have extensive interaction with the Dr. Steve Soper in the Department of Chemistry at LSU involving structural analyses of large macromolecules and the microfabrication center.

The importance of the Human Genome Project, and of the functional genomics effort in defining gene function, is tremendous. In the short-term these fields are heavily funded by federal agencies, and hires in them will immediately generate additional extramural research funds for the university. There are likely to also be long-term financial benefits and interactions with pharmaceutical companies, as well as the potential to generate independent bioinformatics companies here in Louisiana.

Cell signaling

From the first cell division onwards, cells continually interact with their environment to establish and maintain a functional organism. These interactions are collectively referred to as "cell signaling" and involve the detection, processing and generation of cellular responses to biologically relevant stimuli. It is these operations that allow organisms to develop and to survive in a complex environment. Moreover, defects in cell signaling pathways result in the pathogenesis of numerous human diseases including cancer, diabetes, cardiovascular disease, Alzheimer's disease and obesity.

Signaling pathways are conserved within many cell types across phyla, but can also be specialized for the detection of unique signals. For example, sensory receptor cells of the vertebrate retina are specialized to detect and process photic energy, whereas cells that respond to hormones detect and process chemical information. Because of the broad implications of understanding cell signaling across many cell types, comprehension of the underlying mechanisms requires a multidisciplinary approach. Relevant research areas include neurobiology, endocrinology, cellular biophysics, cell biology, immunology, developmental biology, biochemistry, and molecular and structural biology. Accordingly, the departmental strategic plan has emphasized our growth into this research arena.   Recent departmental hires (Drs. Belanger, Donze, Gleason, Grove, Hand, Hart, Larkin, Newcomer, Stephens and Waldrop), in addition to many pre-existing faculty, give us broad strength in the general area of cell signaling.

While historically, biochemistry has dominated research in signaling processes and continues to play a significant role (see proteomics below), our understanding of cellular responses has been revolutionized by remarkable advances in imaging technology. Techniques, such as FISH (fluorescent in situ hybridization), calcium imaging, pH and membrane voltage measurements using functional probes, are performed in living single cells and tissues. These methods are capable of both static and "real-time" imaging. The enhanced microscopy techniques for deconvolution and confocal imaging of signaling processes will generate massive data sets for analysis. The analysis of the tens to hundreds of megabytes of image data is contingent upon advanced computing power and algorithm development. Gathering the data requires key technology, including state of the art specimen preparation, digital imaging,

advanced microscopes and optical benches (e.g., deconvolution, confocal, two-photon, and multiphoton technology). These capabilities, supported by experienced technicians, will significantly enhance the research productivity of faculty and students. Faculty in other campus units, such as the School of Veterinary Science, the Departments of Psychology, Chemistry, and Physics and Astronomy, will be attracted to the Biological Sciences Microscopy Core Facility that will house the instrumentation, and their respective research programs will benefit. Research within the core facility will promote faculty interaction both within and across campus units substantially enhancing LSU's competitiveness in the federal R&D marketplace. Access to state-of-the-art digital imaging technology will significantly improve the ability of LSU to attract and maintain nationally and internationally prominent faculty and to attract and educate high quality undergraduate and graduate students in the various disciplines encompassed by cell signaling.

Proteomics

One of the consequences of the current large scale genomics efforts is that not all proteins have been identified, and that simple gene regulation does not account for many aspects cellular development and activity. In order for our department to make significant contributions to understanding how biological organisms grow and develop, we feel that a significant thrust should be made to understand the structure, function and interactions of proteins. This focus area is Proteomics. Within this focus area, and for the reasons described, we propose to emphasize the following two research domains.

Computational Biophysics
This research domain includes, but is not limited to:
de novo protein folding and modeling
electrostatics, molecular dynamics, and computational surface modeling
binding site and molecular interaction modeling

Researchers in these areas have, for example, begun efforts to design zinc fingers that can bind defined sequences of DNA. One can easily imagine using such zinc fingers to block transcription of specific genes that are involved in human diseases from the common cold to AIDS. Research in these areas leads not only to new principles of predictive protein design, but involve extensive new software development. It is anticipated that these positions will be able to advantageously interact with faculty such as Drs. Rajiv Kalia, Aiichiro Nakano and Priya Vashishta in the Department of Physics through the newly formed Biological Computation and Visualization Center, which has state of the art facilities for computer intensive computational analyses on massively parallel architectures as well as immersive and interactive three dimensional visualization facilities.

Proteomics/Metabolomics
This research domain includes the analysis of patterns of protein expression during development, in various diseased states, etc., using techniques such as protein chips and

microarray analysis. A complete understanding of even a simple signaling pathway must involve analysis of the proteins and their products that are involved in the pathway. Researchers in this field are measuring whole pathway or overall metabolic changes in an organism during development or in response to the environment. Since many proteins affect changes in metabolic pools and, conversely, metabolite pools can have significant effects on activity and function of many proteins, a complete understanding of an organism will come only with knowledge of these interactions. These efforts will involve utilization of computers to handle large quantities of data and build models. Recent developments in mass spectrometry, and especially the recent use of nano-electrospray ionization tandem mass spectrometry have been pivotal in the development of proteomics/metabolomics. Hires in these areas would thus interact with already existing mass spectrophotometric faculty in the Chemistry Department.

Researchers in these two areas would be appropriate hires for the IT initiative and would form a cluster in Proteomics. In addition, they would strengthen the research efforts of many of our current faculty who are working on many different aspects of protein structure and function. The biochemistry faculty in our department, like those in most biochemistry departments, are predominantly experimental biochemists. Departments where significant clusters of computational biochemists exist (e.g. Scripps, Johns Hopkins) have been able to take advantage of the advantageous synergy that occurs between experimental and computational biochemists to advance their research programs and significantly enhance their national reputation, along with enhancing their subsequent ability to attract new, high quality experimentalists. Faculty hires in this area will also have collaboratively overlap with faculty in chemistry, computer science, physics, and some departments in the vet school and/or agriculture. In addition, these new positions, because of their focus, will foster interactions with the pharmaceutical and biotechnology industries.

Summary

The three proposed focus areas in computational biology (evolutionary comparative genomics, cell signaling, proteomics) are critical to modern biology and complement each other well, and the proposed hires will accelerate our rise to national and international prominence in these areas. This, in turn, will attract students and build a core program in computational biology that can spin off to local private industry, creating jobs for our graduates here in Louisiana. Each of these areas will enhance research foci that have recently expanded in our department. Interdisciplinary research can enhance scientific discovery by bringing powerful and diverse problem-solving capabilities to bear on basic research questions and can yield significant rewards in the pace and quality of scientific discovery. These additional faculty hires will increase interactions with other academic units and thus strengthen interdisciplinary research at LSU.