Summary of Articles

Paul Smolen, Douglas Baxter and John Byrne. Reduced Models of the Circadian Oscillators in Neurospora crassa and Drosphila melanogaster Illustrate Mechanistic Similarities.

We have developed a reduced model representing feedback loops of transcriptional regulation underlying circadian rhythms in *Neurospora crassa*. The model contains two delay differential equations that describe the dynamics of two core gene products, FRQ and WCC. In a negative feedback loop, FRQ protein represses *frq* transcription by binding the white-collar complex (WCC), which consists of the WC-1 and WC-2 proteins. In a positive feedback loop, WCC indirectly enhances its own formation. The model simulates circadian oscillations, light entrainment, and a phase-response curve (PRC) similar to experimental PRCs. The *Neurospora* model is virtually identical to a model describing *Drosophila* circadian rhythm generation, illustrating that rhythm generation in these divergent organisms shares important mechanistic elements. Significant dynamic differences were found when the parameter spaces of both models were explored to analyze changes in oscillations and bifurcations to steady states. Stochastic fluctuations in molecule numbers were simulated with the Gillespie algorithm. Circadian oscillations and entrainment to light were simulated with < 80 molecules of FRQ and WCC present on average. Simulations suggest that in both *Neurospora* and *Drosophila*, only the negative feedback loop is essential for circadian oscillations. Similar models may aid understanding of circadian mechanisms in mammals and other organisms.

Herbert Sauro, Michael Hucka, Andrew Finney, Cameron Wellock, Hamid Bolouri, John Doyle and Hiroaki Kitano. Next Generation Simulation Tools: The Systems Biology Workbench and BioSPICE Integration.

Researchers in quantitative systems biology make use of a large number of different software packages for modelling,analysis,visualization and general data manipulation. In this paper,we describe the Systems Biology Workbench (SBW),a software framework that allows heterogeneous application components written in diverse programming languages and running on different platforms to communicate and use each others capabilities via a fast binary encoded-message system.Our goal was to create a simple,high performance, open-source software infrastructure which is easy to implement and understand.SBW enables applications (potentially running on separate,distributed computers)to communicate via a simple network protocol.The interfaces to the system are encapsulated in client-side libraries that we provide for different programming languages.We describe in this paper the SBW architecture, a selection of current modules, including Jarnac, JDesigner and SBWMetatool, and the close integration of SBW into BioSPICE which enables both frameworks to share tools and compliment and strengthen each others capabilities.

Daniel Zak, Ronald Pearson, Rajanikanth Vadigepalli, Gregory Gonye, James Schwaber and Francis Doyle III. Continuous-time identification of gene expression models.

We have developed a bioinformatics tool named PAINT that automates the promoter analysis of a given set of genes for the presence of transcription factor binding sites. Based on coincidence of regulatory sites, this tool produces an interaction matrix that represents a candidate transcriptional regulatory network. This tool currently consists of: (1) a database of promoter sequences of known or predicted genes in the Ensembl annotated mouse genome database, (2) various modules that can retrieve and process the promoter sequences for binding sites of known transcription factors, and (3) modules for visualization and analysis of the resulting set of

candidate network connections. This information provides a substantially pruned list of genes and transcription factors that can be examined in detail in further experimental studies on gene regulation. Also, the candidate network can be incorporated into network identification methods in the form of constraints on feasible structures in order to render the algorithms tractable for large-scale systems. The tool can also produce output in various formats suitable for use in external visualization and analysis software. In this manuscript, PAINT is demonstrated in two case studies involving analysis of differentially regulated genes chosen from two microarray data sets. The first set is from a neuroblastoma N1E-115 cell differentiation experiment, and the second set is from neuroblastoma N1E-115 cells at different time intervals following exposure to neuropeptide angiotensin II. PAINT is available for use as an agent in BioSPICE simulation and analysis framework (http://www.biospice.org), and can also be accessed via a WWW interface at http://www.dbi.tju.edu/dbi/tools/paint/.

Daniel Forger, Dennis Dean, Katherine Gurdziel, Jean-Christrophe Leloup, Choogon Lee, Charlotte von Gall, Jean-Peirre Etchegaray, Richard Kronauer, Albert Goldbeter, Charles Peskin, Megan Jewett and David Weaver. Development and Validation of Computational Models for Mammalian Circadian Oscillators.

Circadian rhythms are endogenous rhythms with a cycle length of approximately 24 hours. Rhythmic production of specific proteins within pacemaker structures is the basis for these physiological and behavioral rhythms. Prior work on mathematical modeling of molecular circadian oscillators has focused on the fruit fly, *Drosophila melanogaster*. Recently, great advances have been made in our understanding of the molecular basis of circadian rhythms in mammals. Mathematical models of the mammalian circadian oscillator are needed to piece together diverse data, predict experimental results, and help us understand the clock as a whole. Our objectives are to develop mathematical models of the mammalian circadian oscillator, generate and test predictions from these models, gather information on the parameters needed for model development, integrate the molecular model with an existing model of the influence of light and rhythmicity on human performance, and make models available in BioSpice so that they can be easily used by the general community. Two new mammalian models have been developed, and experimental data are summarized. These studies have the potential to lead to new strategies for resetting the circadian clock. Manipulations of the circadian clock can be used to optimize performance by promoting alertness and physiological synchronization.

Stephanie Loranger, Gerald Higgins, Soham Sen and Henry Kelly. The Digital Human, Towards a Unified Ontology.

The exponential increase in biological data resulting from the latest automated experimental techniques and the accelerated availability of molecular sequences has provided an explosion of empirical data and analysis on the molecular foundations of biological structure and function. The complexity of this kind of analysis has grown to the point where biological systems can best be understood by using modern computers. Computers were essential for sequencing the human genome and will be even more important for understanding how genomes work by developing computer simulations of their functions. These tools can also make it possible to visualize the operation of complex systems – how cells assemble miniature machines or how defects in electrical networks degrade the performance of a heart – and allow one to “see” what happens when these system are altered with drugs, surgeries, or other therapies.

The ability to simulate biological systems will give us an extraordinary set of new tools that could increase economic productivity while reducing pollution and our need for natural resources. We have reached a critical juncture where model integration using diverse data derived from various biomedical domains can significantly enhance our understanding of complex phenomenon in normal human function and disease states. Integration of all of this data into a “*Digital Human*” will help biomedical researchers master the staggering complexity of their discoveries, physicians

make effective use of their discoveries to improve health, and engineers imitate biological mechanisms to achieve revolutionary change in computing, for the design of artificial organs, robots, and a variety of other applications.

Rasha Hammamieh, Shuguang Bi, Sachin Mani, Nabarun Chakraborty, Chanaka Mendis, Rina Das and Marti Jett. Genetic variation in peripheral blood mononuclear cells in piglets used as an animal model for staphylococcal enterotoxins exposures.

Piglets are easy to handle, easy to carry out vital measurements, inexpensive and more importantly, express remarkably similar pathological symptoms and responses to SE intoxication as human at comparable doses. All the above reasons made piglets an indispensable animal model for studying the toxic effects of staphylococcal enterotoxins (SEs). Microarray analyses were used to study the effect of many infections on gene expression profiles in peripheral blood mononuclear cells. This high throughput application offered detailed depiction of alterations at the molecular level. When using high throughput gene expression analysis for the tissues under study, there was a high possibility of finding genes, the expression levels of which might be inconsistent in expression even in control, healthy animals. Those variably expressed genes were critical to identify in order to recognize the altered expression level due to pathogen exposures. To evaluate the normal physiological variation in gene expression in vivo in piglets, we used cDNA microarray to measure gene expression levels in peripheral blood mononuclear cells from 10 normal, healthy Yorkshire piglets. We used analysis of variance to determine genes that showed statistically significant variations across piglets. Out of 1185 genes, 19 (1.6%) genes revealed statistically significant variance between RNA samples. Some of these varying genes are involved in stress response, immune-response and transcription. This study facilitates the characterization of gene expression base line needed for meaningful interpretation of microarray data.