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DARPA PREPROPOSAL (RA00-14)

TITLE: **Modeling, Measuring, Visualizing, and Manipulating Biochemical Networks for Health and Defense**

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Robert Johnson, Professor of Computer
Science and founder of nDV, LLC;
Richard Van Wagenen, Vice-President,
Protein Solutions, Inc.;
James Keener, Professor of Mathematics and
Adjunct Professor of Bioengineering.

This pre-proposal is submitted pursuant to the research announcement RA00-14 "Fundamental Research at the {Bio:Info:Micro} Interface", published in the Commerce Business Daily 23 December 1999

Importance and Novelty:

Life is a non-equilibrium state dependent on the constant flow and transduction of energy. Any significant disturbance or alteration in that energy flow results in a pathology or in death. Energy flow and transduction are controlled and regulated by a complex set of interacting biochemical networks, often called the biochemical and metabolic pathways (www.expasy.ch/cgi-bin/search-biochem-index). Biochemical networks involve literally thousands of different substrates, products, and enzymes -- all interdependent, interacting, and self regulating. Although many pieces and parts of the overall network have been studied and mapped (1), the network itself is not understood.

Rapid advances in mathematical modeling and simulation, coupled with today's inexpensive, high-speed computational capabilities and storage capacity, now make it possible to propose the modeling and simulation of complex biochemical networks (see www.ncgr.org then click on GEPASI).

We propose the simultaneous measurement of up to 1000 key metabolites in microliter volumes of blood, sweat, tears, saliva, and/or urine -- easily, cheaply, sensitively, and reliably (2).

We also propose to present such multivariate analytical information (3, 4) so as to visualize, understand, and manipulate the biochemical network which produced it.

Although we understand and appreciate the robustness of biochemical networks and their abilities to maintain a steady state -- a homeostasis -- we are also aware of their enormous individual diversities – our private biochemical individualities (5). The understanding of such biochemical uniqueness will permit the management and modification of our individual responses to diet, disease, environmental changes, toxins, chemical agents, and bio-pathogens.

These topics are highly responsive to **RA00-14**: **Bio** includes biochemistry, pharmacology, pharmaceutics, and biochemical networks; **Info** includes modeling, simulation, and visualization of large, complex networks and highly multi-dimensional data sets; and **Micro** includes microfabrication, microassembly, and enzyme/antibody assemblies for biosensors.

Disciplines/Investigators/Subcontracts (see also Cover Page):

Joseph Andrade, Principal Investigator, is professor and co-chair of the Department of Bioengineering and also holds appointments in Materials Science and Engineering and Pharmaceutics; 30% effort (see www.bioen.utah.edu/faculty/jda). Joe works on enzyme- and antibody-based biosensors and on the behavior and application of protein films.

Steven Kern is experienced in modeling, simulation, and clinical studies related to pharmacokinetics and pharmacodynamics; 15% effort.

James Herron is experienced in antibody biochemistry, immunoassay, and protein physical biochemistry; 15% effort (pceurp1.pharm.utah.edu/herron.html).

Bruno Frazier is an expert in micromachining and microfabrication. He, Andrade, and Van Wagenen have been collaborating on biosensors for patient applications; subcontract.

Jarmila Janatova is a protein biochemist experienced in protein production and characterization, including monoclonal antibody production; 50% effort.

James Wiskin is a computational mathematician applying non-linear methods to the modeling, control, and simulation of biochemical networks; he is a primary investigator in the Center for Inverse Problems, Imaging and Tomography at the University of Utah; 20% effort (www.bioen.utah.edu/faculty/wiskin).

Robert Johnson is the founder of n-DV (n-Dimensional Visualization), LLC, a corporate participant; his activities in n-DV (3, 4)will address a major objective of this program; his proprietary web-site is www.globalsvcs.com/ndv^ (**please treat this as proprietary information**); subcontract.

Richard Van Wagenen, corporate participant (www.proteinsolutions.com) has a Ph.D. in materials science and engineering and considerable experience in analytical instrument product design and development; subcontract.

In addition we will involve a number of the faculty in our biomathematics group, particularly **James Keener** (www.math.utah.edu/~keener); 35% effort among several biomathematics faculty.

We also propose to establish an Advisory Board of 5 to 7 experts to advise, critique, and review our activities; the Board would meet annually in Salt Lake City and quarterly via telephone and web conferencing.

Environment

The University of Utah has a long history and tradition of interdisciplinary and multidisciplinary research. There is very strong collaboration and interaction between the Colleges of Engineering, Science, and Pharmacy and the School of Medicine. Dr. R. Koehn, Vice President for Research; Dr. D. Pershing, Senior Vice President; and Dr. B. Machen, President; all have technical backgrounds and are highly supportive of inter- and multi-disciplinary research and related activities.

Several of the participants in this pre-proposal (Andrade, Kern, Van Wagenen) have been involved the past three years in a unique research program sponsored by the National Science Foundation and the Whitaker Foundation on Cost Reducing Health-Care Technologies. Our particular grant was titled and focused on Personal Sensors for the Management of Chronic Metabolic Disease (www.healthtechcost.med.utah.edu).

ProjectTasks:

--Model, simulate, and do virtual experiments on the complex biochemical networks involved in bioenergetics and metabolism.

A key goal is to identify metabolites and related molecules which can provide the most information with which to help characterize and test the local network. Methods of metabolic engineering (6) and metabolic control analysis (7) will be employed. We will apply established mathematical tools for network analysis and inverse problem methods for the analysis of complex biochemical networks.

--Select, design, engineer, test, and produce enzymes and antibodies.

A key goal is to significantly improve robustness/stability, activity/efficiency, and selectivity/sensitivity (8) (9) (10) of the enzymes and antibodies required using modern protein engineering and expression methods. The proteins expressed and produced include sequences and domains to facilitate immobilization and multi-enzyme complex formation (8) (9).

--Model, simulate, design, and fabricate a 50 channel ChemChip.

We will use microfabrication (11) and micro-reaction chamber concepts and technologies to design and prototype biosensors for amino acids, vitamins, carbohydrates, and important drugs and toxins. We expect to move on to 100 channels, and to even approach 1000 distinct channels as the project and technologies develop and mature. We will develop and apply luminescence and bioluminescence based enzyme and antibody assays for sensitive (sub micromolar), low volume (sub microliter), specific biochemical and enzyme analyses (2). Microscale technologies, including micro spray and stamping processes, will be used for reagent deposition and stabilization.

--Assess and evaluate nontraditional sample sources for biochemical measurements.

Sweat, saliva, tears, interstitial fluid, and human milk, as well as traditional blood and urine, will be studied, modeled, and evaluated. We also propose to develop simple means to collect and sample saliva, tears, and milk, which, because they are glandular secretions, provide unique analytes, providing information not available in traditional samples.

--Assess available means (and develop new means, if necessary) for multidimensional visualization of biochemical concentrations and related parameters.

We will use several geometric signature driven parallel coordinate methods applicable to large, multidimensional data sets, as well as several virtual reality modeling methods. The goal is to provide understandable, useful quantitative images and visualizations of the network and its various states which facilitate interpretation and understanding of drugs, toxins, and related chemical and biological agents – and point the way to the prevention, minimization, and/or treatment of their toxic effects.

Budget Estimate

We anticipate an annual budget in the range of $1.5 million in total costs; about $500K for personnel (including 4 post docs, 8 graduate students, and 2 technicians), $75K for major equipment, and about $200K for the 3 subcontracts.

Biographical Sketches (following pages):

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