UVA Diabetes and Endocrine Research Center – Integrated Data Management Core

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Objective

The objective of the Integrated Data Management (IDM) Core is to create and maintain a shared facility that will support cutting-edge biomedical research with a hierarchically integrated database and data analysis/modeling kernel, development of new customized computational tools, and training/dissemination program. Ultimately, this will result in a fusion creating a new field of interdisciplinary studies: Computational Diabetes and Endocrinology. The goal is to cover the problem spectrum of diabetes from a molecular/sub-cellular level, through animal physiology and hormone interactions, to human glycemic control and self-treatment behavior. For the first time, genetics, physiology, pathology, and treatment of diabetes, will be assessed from a computational perspective as an interconnected coherent system.

Specific Objectives of the IDM Core

1) Provide advanced quantitative support to diabetes/endocrine research projects that would benefit significantly from high-end computing and nonstandard modeling/analytical solutions to their problems. This will be achieved through interfacing diabetes/endocrine projects and high-throughput computing systems, available at the University of Virginia (UVA), via a data management facility. The following elements will make this facility unique:

    a. An integrated research database that will be organized hierarchically to encompass the consecutive levels of diabetes/endocrine data acquisition from molecular, through hormonal and endocrine-network, to human self-treatment behavior. This structure will facilitate discovery of connections between the bio-system levels, such as understanding of genetic mechanisms driving physiology, or interactions between physiology and behavior;

    b. A new approach to vertical database integration based on hierarchical aggregation of processes and definition of unified information-exchange units. At all levels, the data processing will follow the unified scheme of:

        i. Data pre-processing/normalization prior to inclusion into the database;
        ii. Partitioning of database information into functionally-relevant classifications;
        iii. Data reduction (extracting principal factors from static data, or process aggregation of dynamic data);
        iv. Pattern recognition/identification including classification of unknown cases, and prognosis;
        v. Linking of characteristics between disparate database subsets including unified information exchange.

    c. A data processing environment consisting of an array of computational tools that includes standard data analysis, as well as innovative non-standard computing/modeling. When developed, this environment will provide diabetes/endocrine projects with capabilities to actually utilize high-end computing;

    d. Continuous quantitative expert assistance to biomedical projects – a major difference between this Core and a traditional statistical consulting group will be the continuity of the collaboration between biomathematicians and biomedical researchers, and the level of their involvement.

2) Execute planned modeling/analytical studies, based on experiments from ongoing research projects at UVA, that hold greatest promise for advancement of science through interdisciplinary research. Specifically:

   a. At a sub-cellular/cellular level we will use cutting-edge gene expression analysis methods and will develop new methods for analysis of temporal gene expression patterns and predictive algorithms to study transcriptional regulation directing the differentiation of insulin-producing beta-cells of the pancreatic islets of Langerhans;

   b. At a hormonal-pattern level we will study key disturbances in hormonal rhythms resulting from insulin over-treatment in animal models using a combination of: (i) new and existing computational tools for assessment of cyclic or episodically pulsatile hormone secretion; (ii) new physiology-based differential-equation networks that simulate hormone systems, and (iii) model-independent methods that analyze coupled hormone time series;

   c. At an endocrine-network level, structural and dynamic modeling and simulation will be used to quantitatively understand functional mechanisms of insulin transport within the vasculature and insulin-glucose interaction. This level has numerous potential applications ranging from assessment of insulin resistance to automated insulin/carbohydrate control algorithms (the artificial pancreas of the future);

   d. At a human macro-level, we will study patterns of glycemia and behaviors occurring in patients' natural environments and resulting in an increased risk for hypoglycemia. We will set the formal framework for a new integrated bio-behavioral-monitoring procedure that would help improve the prevention of hypoglycemia without compromising patients' metabolic control. For that purpose we will use our methods for risk analysis of blood glucose (BG) data and will develop new stochastic models that will integrate self-monitoring and behavioral data.

3) Create a training environment and initiate a research-oriented interdisciplinary educational program at graduate and post-graduate levels. This program will follow the established template of the UVA Multidisciplinary Training Program in Clinical Investigation. A parallel dissemination effort will ensure the proliferation to other institutions of training modules, algorithms, software and data analysis tools. In addition to our traditional workshops on specific topics of computational diabetes/endocrinology, we anticipate building an interactive Internet portal that will be a major resource for these dissemination efforts.

Training

We will create a training model that supports transitions both from fundamental mathematics to applications in the life sciences, and from a biomedical education to computing sophistication. We will coordinate our activities with the established UVA Multi-disciplinary Training Program in Clinical Investigation directed by Dr. Bill Evans. The goals are: (i) to involve trainees from mathematics, statistics, computing, and engineering in mentored biomedical research, and (ii) to enhance the understanding of biomedical trainees of computational techniques applicable to their disciplines.

The IDM Core will support 2 workshops annually: 1) Hormone Pulsatility, and 2) Quantitative Methods for Diabetes Research. The established Hormone Pulsatility workshop is delivered by Drs. Johnson, Straume, and Evans. This annual three-day workshop is structured such that participants are provided a well-rounded pedagogical experience wherein presentation and discussion consider: (i) biomedically-based introductions to pathophysiologies assessable by quantitative analytical solutions; (ii) detailed consideration of concepts, their quantitative and computational implementation, and considerations important for formation of valid interpretive conclusions from output generated during analytical sessions; and (iii) practical, hands-on experience with demonstrative synthetic and real data using representative software solutions developed by the course instructors. This workshop is intensive in that covered in three days time are topics ranging from general introductions to (i) data structures and formatting, (ii) parameter optimization strategies, and (iii) measurement error and its consequences, to specific strategies for detailed quantitative assessments of (i) hormone pulsatility, (ii) deconvolution of secretory rate profiles, (iii) copulsatility statistics, (iv) patterning complexity in temporal profiles, and (v) robust methods for extracting rhythmic information from heavily confounded time series data. Using a similar format, we plan to create and deliver a new 3-day annual workshop on Quantitative Methods for Diabetes Research, delivered by Drs. Kovatchev and Cox.

Dissemination

As we presented above, the IDM Core will accumulate and organize a substantial volume of data at all diabetes/endocrine levels, a large array of corresponding computational tools, as well as training modules for their implementation. We plan to make special efforts to disseminate this potentially valuable information to researchers and clinicians. Our workshops will be advertised and open to everybody. Hundreds of copies of our hormone pulse analysis software have been distributed free of charge to UVA and non-UVA researchers. When the database structure and the data processing environment are established, we plan to build a comprehensive Internet portal that will allow for remote download of data, software and training modules, and will provide interactive training on selected topics.

Participants

Dr. Boris Kovatchev will serve as the director of the IDM Core with primary responsibility for development and implementation of the proposed array of computer-based and modeling solutions to the broad diversity of research problems expected to require the services of the IDM Core. In particular, Kovatchev will be responsible for data management at the highest levels of the diabetes endocrine system, network modeling to human behavior. Dr. Kovatchev is Associate Professor of Psychiatric Medicine and Health Evaluation Sciences, has a Ph.D. in Probability & Statistics, and 10 years experience in biomathematics. He has continuous NIH funding since 1996. His new study "Bio-behavioral Monitoring and Control of IDDM," RO1 DK 51562, was rated "outstanding" by its reviewers, received a percentile of 1%, began in 2001, and is one of few NIDDK studies exclusively dedicated to development of new monitoring, data processing, and modeling techniques for diabetes. Dr. Kovatchev's previous studies: (i) introduced the Low BG Index, the best predictor of severe hypoglycemia known to date; (ii) created the theory of risk analysis of BG data; (iii) developed new computational tools for assessment of behavioral irregularity associated with T1DM and for assessment of long-term diabetes control, and (iv) modeled insulin-glucose dynamics revealing a new dynamic dimension of the counterregulatory impairment related to recurrent severe hypoglycemia - a slower counterregulatory response at its onset. Two inventions based on these theories were filed with the UVA Patent Foundation, and have been licensed by industry leaders such as Lifescan, Inc. (Milpitas, CA).

Dr. Michael Johnson will apply his pioneering expertise in analysis of hormone time series to support studies of hormone patterns in animal models and studies of hormonal networks at both the model-free analytical level and the network-dynamics simulation level. In addition, Johnson will be the prime mover behind the training/dissemination initiatives of the IDM Core, a task consistent with his track record of Hormone Pulsatility workshops. Dr. Johnson is Professor of Pharmacology and Internal Medicine (Division of Endocrinology and Metabolism) who has a Ph.D. in biophysics with a specialty in modeling of biological processes. Johnson has written more than 280 publications and edited 8 books, the majority of which involve mathematical modeling of various biological processes. For example, Methods in Enzymology volumes 210, 240, and 321 are on “Numerical Computer Methods,” and Methods in Neuroscience 28 is on “Quantitative Neuroendocrinology." Johnson is the biomathematician for the UVA General Clinical Research Center, the only biomathematician on the staff of any of the NIH General Clinical Research Centers.

Dr. Martin Straume will be primarily responsible for supervision of the building of the integrated research database proposed by this project. This task is consistent with his expertise in mining and analysis of large data volumes, gene expression data in particular. The latter predetermines Straume’s predominant involvement with projects concerning the lowest sub-cellular/cellular levels of the diabetes/endocrine system. Dr. Straume is Associate Professor of Research in the Division of Endocrinology and Metabolism, Department of Internal Medicine and the biomathematician of the NSF Center for Biological Timing at UVA. He has a decade of experience with biomathematics applied to circadian rhythms research, as well as with clinical and basic research in epilepsy and cancer therapy. Straume currently is participating in a project for intelligent data processing and analysis of gene chip data (together with Steve Kay and colleagues at the Scripps Research Institute in La Jolla, CA), and has worked closely with Kovatchev on BG prediction and control in diabetes. With Johnson, Straume collaborates on analysis of hormone pulsatility, network dynamics and regulation, and endocrine decline with aging and disease.