EPSRC Engineering and Physical Sciences Research Council

UNIVERSITY OF BIRMINGHAM

An international workshop on molecular network inference

Towards a Systems Biology approach to Ecotoxicology

19 January 2011 University of Birmingham, UK
Lucas House (Conference Park)

Funded by Bridging the Gap (BTG) program
(http://www.btg.bham.ac.uk)

The international **workshop on molecular network inference** aims to give to a broad audience an overview of the research ongoing in this area of Systems biology both from a methodological and application prospective. It is intended as a one-day workshop based on a series of talks from UK and international leaders in the area of **computational network inference**. We have contributions from both **method developers** and computationally minded **experimental biologists** that use such methodologies.

From an application prospective the workshop focuses on one of the most exciting new developments in the area of Systems Biology. This is the development of a Systems Biology based approach to predictive toxicology in an environmental context. This area poses a great challenge in terms of integrating laboratory-based experiments with information coming from field studies but at the same time represent an opportunity to develop a much needed mechanism-based biomarker discovery platform.

Registration

Attendance is **free** and includes **refreshments and lunch**, however the **number of places is limited**.

If you would like to register please email **Annette Evans** (a.evans@bham.ac.uk) as soon as possible and specify any special dietary requirements.

If you have any questions about this workshop, please email one of the **workshop organisers**.

Workshop Organizers

Francesco Falciani (f.falciani@bham.ac.uk)
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University of Birmingham, UK

Natalia Reyero (natalia@icnanotox.org)
Jackson State University

Workshop Program

19 January 2011

8:30 **Registration and Opening**

9:00 - 9:30 **Systems Biology, Adverse Outcome Pathways, and Ecotoxicology in the 21st Century**
Stephen Edwards, USA EPA

9:30 - 10:00 **Environmental Monitoring: Using Microarrays to Inform Field Investigations**
Nancy Denslow, University of Florida, Gainesville, FL

10:00 - 10:30 **Compendium of transcriptome effects of endocrine disrupting chemicals on the fathead minnow ovary.**
Natalia Reyero, Jackson State University

10:30 - 11:00 Coffee break

11:00 - 11:30 **Using metabolite signatures to predict whole organism traits of ecological importance**
Mark Viant, University of Birmingham

11:30 - 12:00 **Molecular toxicity identification evaluation in *D.magna***
Chris Vulpe, University of California, Berkeley

12:00 - 12:30 **A network biology approach to ecotoxicology: Can toxicant exposure and health outcomes be predicted?**
Tim Williams, University of Birmingham

12:30 – 14:00 Lunch Break

14:00 – 14:30 Peter Kille

14:30 - 15:00 **Extrapolation of mode of action for neurotoxicity across species using ion-channel homology and transcriptional network mapping.**
Edward Perkins, US Army ERDC, Environmental Laboratory

15:00 - 15:30 **Systems Biology of Reproductive Endocrine Disruption in Small Fish**
Daniel L. Villeneuve, USA EPA

15:30-16:00 **Coffee break**

16:00 – 16:30 **New methods for exploring ecotoxicogenomics data: nonlinear relationships and pathway tools**
Tim Ebbels, Imperial College, London

16:30 – 17:00 **Inference of Biological Regulatory Networks from High-Throughput Data: The State of the Field**
Ronald Taylor, Pacific Northwest National Laboratory

17:00 – 17:30 **Developing a Systems Toxicogenomics Approach in the Netherlands Toxicogenomics Centre (NTC)**
Eugene van Someren, Netherlands Toxicogenomics Centre (NTC)

ABSTRACTS

Systems Biology, Adverse Outcome Pathways, and Ecotoxicology in the 21st Century

***Stephen Edwards**, U.S. EPA,* Research Triangle Park, N.C. , USA

While many definitions of systems biology exist, the majority of these contain most (if not all) of the following elements: global measurements of biological molecules to the extent technically feasible, dynamic measurements of key biological molecules to establish quantitative relationships among them, and experimental designs which perturb the system in specific ways to determine these relationships. This presentation will discuss how these components can be used to develop a model for disease based on an interconnected network of molecular-, cellular-, and organism-level events. Such disease networks can serve as the framework for a network-based description of mode of action or adverse outcome pathway. Approaching the problem from this perspective provides a biologically-based mechanism for incorporating other factors affecting risk such as species relative susceptibility, life stage relative sensitivity, and other influences on the health of individuals or populations. Expanding this concept to include networks of populations, communities, and ecosystems potentially provides a framework for building multi-scale models to predict the effects of chemicals on the environment. It also enhances the ability of more traditional biological modeling approaches to lay the groundwork for toxicity pathway-based risk assessment in ecotoxicology. The approach will be illustrated by analysis of global transcriptional networks in response to endocrine disrupters in the fathead minnow (Pimephales promelas).
[This abstract does not necessarily reflect the views of the Environmental Protection Agency.]

Biographic note

Stephen Edwards is a Systems Biologist within the National Health and Environmental Effects Research Laboratory (NHEERL) in Research Triangle Park, N.C. NHEERL is the focal point for toxicological, clinical, epidemiological, and biogeographic research within EPA. Dr. Edwards is spearheading the development of a systems approach, integrating relationships and interactions at all levels of a biological system from the sub-cellular to whole organism to connect the effects of environmental pollutants to human health. The goal behind these efforts is to improve the scientific underpinnings of the Agency's risk assessments. With a combination of experimental and computational experience, Dr. Edwards also serves as a liaison with the EPA's National Center for Computational Toxicology (NCCT). Dr. Edwards received his bachelor of science in chemistry from the University of North Carolina at Chapel Hill and his doctorate in pharmacology from Vanderbilt University Medical Center. Before joining the EPA, he served as a senior research scientist and research fellow at Rosetta Inpharmatics (Merck & Co.), in Seattle, Washington, a recognized leader in computational and systems approaches to drug development.

Environmental Monitoring: Using Microarrays to Inform Field Investigations

Nancy Denslow, *University of Florida, Gainesville, FL, USA*

Microarray technology is a relatively novel tool that can be used as an aid to risk assessment for environmental monitoring. We have used the fathead minnow as a surrogate species to measure potential aquatic contamination from wastewater spray fields in Turkey Creek at the Eglin Air Force Base in Florida. The main interest is in understanding how environmental contaminants may play a role in the degradation of the habitat of the Okaloosa darter (*Etheostoma okaloosae)* which is found almost exclusively in streams in the Choctawhatchee Bay watershed of Florida located directly on the lands of the air force base. Portions of this limited habitat are threatened with erosion of soils, altered hydrology, and impaired water quality. The East Turkey Creek has demonstrated potential water quality problems including poor invertebrate bioassessment scores (IBI), uncharacteristically high conductivity values, and low numbers of Okaloosa darters. Water quality was assessed during a 30 day exposure using passive samplers for both non-polar and polar effluent parameters. Metal loading in the system was assessed via fish tissue burdens in resident *Pteronotropis hypseleotris*. Additionally, microarray analysis was performed on gonad and liver tissue from fathead minnows, *Pimephales promelas*, after 48 h exposures to water collected from the affected creek and another reference creek that appears not to be impacted. Gene expression changes were evident at the site below the influence of a wastewater spray field along East Turkey Creek, suggesting that anthropogenic compounds in the effluent waters are bioavailable and change gene expression in both liver and testis.

Biographic note

Nancy Denslow is a professor in the Department of Physiological Sciences and in the Center for Environmental and Human Toxicology at the University of Florida. She received her Ph.D. from the University of Florida in Biochemistry and Molecular Biology. Nancy has pioneered the use of molecular technologies for environmental toxicology especially focusing on endocrine disruption. She has developed estrogen receptor reporter assays to determine the molecular effects of environmental xenoestrogens. In addition, she has pioneered the use of microarray technology for non-model species, adapting technologies used for assessing toxicant effects on human health. She was awarded the University of Florida 2007 Pfizer Award for Research Excellence and was named the 2009-2011 University of Florida Research Professor. Nancy has over 150 peer-reviewed publications and is an inventor on four patents relating to protein factors, biomarkers for endocrine disruption and proteomics methodologies. She is a member of the Society of Toxicology (SOT, Councilor, 2009-2011), Society for Environmental Toxicology and Chemisty (SETAC), American Society for Biochemistry and Molecular Biology (ASBMB) and the Association of Biomolecular Research Facilities (ABRF, Executive board member 2004-2009).

A compendium of transcriptome effects of endocrine disrupting chemicals on the fathead minnow ovary

Natalia Reyero, *Jackson State University, USA*

Understanding potential hazards of chemicals released into environment is challenging not only due to the large and growing number of chemicals and materials needing to be screened, but also the diverse environments, bioavailability, exposure conditions, and species differences that dramatically effect risks posed by chemicals. One effective approach to screening large numbers of chemicals utilizes low content but high throughput in vitro assays to assess effects on very specific endpoints such as the ToxCast program. However this approach is limited to the "lightpost" that shines a light on well-characterized specific effects while still leaving many potential impacts in the dark. Examining effects on critical pathways resulting in adverse outcomes of interest such as reduced reproduction provides broader measure of potential hazards of a chemical. However, many of the biological pathways and key events that influence outcomes associated with chemical exposure are presently unknown or poorly defined. Gene expression approaches provide low throughput, high content transcriptome-wide data useful for assessment of chemical impacts. Transcriptome approaches using large chemical exposure sets are powerful in classifying chemical hazards, but are generally limited to known gene-function relationships. However, effective mining of complex relationships, effects and potential impacts can be gained through network analyses derived from expression data. The Hypothalamus-Pituitary-Gonadal (HPG) Axis is an evolutionarily conserved endocrine pathway principally responsible for control of reproduction (refs). Measuring impacts of chemicals on steroidogenesis in ovaries provides a functional measure of chemical reproductive hazards. Therefore, analysis of steroidogenesis and biological network elements controlling it in ovaries can be used to understand chemical effects and key events leading to adverse outcome reproductive outcomes. We have proposed the use of a network reverse engineering approach to help elucidate adverse outcome pathways effecting reproduction in fish. In this work, we used this reverse engineering approach to investigate the impacts of chemicals on the HPG reproductive adverse outcome pathway. Fathead minnows (*Pimephales promelas*) were exposed to known endocrine disruptors and impacts on ovaries were examined through network analysis of a large compendium of gene expression and hormone data sets. The compendium contains 1,472 arrays, each with 12,437 responsive gene-specific features. The microarray data included were generated in twenty-three different in vivo exposure experiments encompassing 13 different chemicals, 1 complex mixture, 5 ovary stages, multiple time points, and multiple chemicals doses.

Biographic note

Natalia Reyero received my BS in Biology from Universitat de Girona (Girona, Spain), and my MS in Biology from Universitat de Barcelona (Barcelona, Spain). I also did my PhD in Spain (CSIC, Barcelona, Spain), studying the presence of POPs and their endocrine-disrupting activity in European high mountain lakes. After that, I did a postdoc at the University of Florida (Gainesville, FL, USA). My research focused on the effects of endocrine disruptors on several fish species. Now I am a research Professor at Jackson State University (Jackson, MS), and I work with the Environmental Genomics Group at ERDC (USACE). My research focuses on

environmental pollutants and their effects on aquatic species while trying to elucidate their mechanisms of action using ecotoxicogenomics and a systems biology approach.

Using metabolite signatures to predict whole organism traits of ecological importance

Mark Viant, *University of Birmingham, Birmingham, UK*

Molecular biomarkers have considerable potential as diagnostic tools in environmental toxicology and ecological risk assessment. One of the greatest challenges in environmental biomarker research is discovering molecular markers that are truly predictive of whole animal fitness, such as growth, energetic status and reproductive output. We have measured both the physiological and metabolic responses (using metabolomics) to several toxicants, and these data were then analysed using multivariate regression techniques to create mathematical models that can predict the whole animal responses. Specifically, I will describe such studies in both marine mussels (*Mytilus edulis*) and water fleas (*Daphnia magna)*. For the mussels, metabolic signatures are derived that can predict scope for growth, an established measure of physiological energetics; and for the daphnids, metabolic signatures are determined that can predict their reproductive fitness. These findings highlight the genuine possibility that metabolomics can discover biomarkers that provide information on both molecular mode of toxicity as well as more ecologically relevant consequences for the whole organism.

Biographic note

Mark Viant is a Professor of Metabolomics in the School of Biosciences at the University of Birmingham, UK. He also serves as the Director of the Natural Environment Research Council's (NERC) Environmental Metabolomics Facility at Birmingham. He received his BSc in Chemistry and PhD in Chemical Physics at the University of Southampton, UK. Following postdoctoral research in chemistry at the University of California, Berkeley, he shifted his research interests into environmental toxicology, conducting further postdoctoral studies at the University of California, Davis. In 2003 he was awarded a NERC Advanced Fellowship and relocated to the University of Birmingham, where his research team now focuses on the development and application of both NMR spectroscopy and mass spectrometry in environmental metabolomics, specifically as tools for chemical risk assessment and environmental monitoring. His primary research interests include the molecular characterisation and understanding of stress responses in aquatic organisms, in particular to environmental pollution. In addition his team develops novel analytical and bioinformatic approaches for metabolomics. He has authored over 90 publications, including pioneering applications of metabolomics to environmental health issues in aquatic organisms.

Molecular toxicity identification evaluation in *D.magna*

Hun-Je Jo, Philipp Antczak, Don Pham, Seonock Woo, Candace Clark, Alex Loguinov, Francesco Falciani, ***Chris Vulpe***, Univ. of California, Berkeley

Current methods to identify the underlying cause of toxicity, or toxicology identification evaluation (TIE), are limited in their ability to rapidly, specifically, and cost-effectively identify toxic chemicals in an effluent. We describe our development of molecular TIE (mTIE) approaches that uses gene expression to identify the contaminant(s) to which an organism has been exposed. *Daphnia magna*, is ideal for this work because of its small size, easy culture, rapid generation time, and sensitivity to a diversity of contaminants. We have carried out gene expression profiling to 36 EPA priority pollutants at equitoxic concentrations using a new 15K *D.magna*, Agilent array developed by an international consortium of *D. magna* researchers. Each contaminant produces a distinct expression profile and we identified 2738 genes which are differentially expressed in at least one exposure. We will describe our utilization of computational approaches to robustly discriminate between each contaminant. For example, we utilized the Hierarchical Ordered Partitioning And Collapsing Hybrid (HOPACH) algorithm which is a hybrid of divisive and agglomerative methods with bootstrapping to assess cluster assignment as one approach. We are also investigating various classifier approaches including random forest for development of robust discriminators between exposures. We will also present the development of predictive models based on advanced machine learning methods which aims to identify predictive signatures based on the synergistic effects of small gene subsets. These methods have been already validated on a number of other systems and proved to have the potential to provide accurate mechanism based biomarkers.

Biographic note

Chris Vulpe is an Associate Professor at Univ. of California, Berkeley.
His group has been exploring the use of toxicogenomics to characterize the response of ecoindicator species to contaminants.
A primary goal is to develop practical tools that can be utilized in the field for identification of the sources of toxicity in aquatic ecosytems.

A network biology approach to ecotoxicology: Can toxicant exposure and health outcomes be predicted?

T.D. Williams, Birmingham University, Birmingham, UK

Omics techniques have previously been applied to study marine pollution, but hitherto linkage to health outcomes and prediction of the composition and molecular mechanisms of action of complex pollutant mixtures has been lacking. To address these challenges, we have used a network inference approach to integrate multi-level datasets derived from European flounder fish sampled at seven locations in the Irish Sea and North Sea. The adult male flounders were characterised at molecular and physiological levels using a broad and unprecedented set of assays including histopathology, standard biomarkers, microsatellite markers and hepatic transcriptomics and metabolomics. We show that the overall molecular state of the fish liver can be predictive of the profile of contaminants at different sites. With the purpose of identifying molecular pathways linked to adaptation and adverse outcome, we set out to develop an interpretative framework based on inference of a molecular network integrating the multi-level datasets. This approach allowed the identification of two sub-networks whose activity was predictive of environmental exposure and linked to morphometric indices such as hepatosomatic index. At the functional level these represented both known and candidate novel adverse outcome pathways. Novel pathways were representative of several aspects of human liver pathophysiology such as liver hyperplasia, fibrosis, and hepatocellular carcinoma. At the molecular level networks predictive of the differential response between sites involved pathways linked to TNF alpha, TGF beta, PDGF, AGT and VEGF signalling. Therefore we propose that network biology approaches can lead to the identification of health impacts of environmental pollutants upon non-model organisms and demonstrate the linkages between toxicants and histopathology via alterations in molecular signalling pathways and metabolism.

Biographic note

Dr. Tim Williams, BSc (Bath), PhD (Warwick) is a Research Fellow in the School of Biosciences at The University of Birmingham. He has 33 peer-reviewed publications focussing on gene expression and transcriptomics. His interests include the responses of aquatic organisms to model toxicants and to environmental stimuli, particularly in UK-relevant non-model species; the regulation of these responses including via epigenetics; and the mechanisms of environmental carcinogenesis.

Extrapolation of mode of action for neurotoxicity across species using ion channel homology and transcriptional network mapping.

Edward Perkins, *US Army ERDC, Environmental Laboratory, USA*

Abstract - At military training sites, a variety of pollutants may contaminate the area originating from used munitions. These contaminants, munitions constituents (MCs), include nitroaromatic compounds such as hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). RDX has been detected in the environment and several studies have reported toxicity to soil invertebrates at high doses. Studies investigating the mechanism of toxicity of RDX have shown that it affects the central nervous system causing seizures in humans and animals. Environmental pollutants such as RDX have the potential to affect many different species, as they can accumulate and be present in many environmental compartments, thus in a long term may also have evolutionary consequences. In relation to this it is important to establish first how phylogenetically distant species may respond to these types of emerging pollutants. Comparative toxicology and comparative genomics can be used to assess the effects of a contaminant on different species. We analyzed the effects of RDX on five different species to elucidate if it elicits effects via common pathways among the species examined. We used a genomics and network approach to compare and contrast the neurotoxic effects of RDX among five phylogenetically disparate species: rat (Sprague Dawley), fathead minnow (Pimephales promelas), earthworm (Eisenia fetida), Northern bobwhite quail (Colinus virginianus), and coral (Acropora formosa). Our results showed that RDX accumulated into the brain of rat, Northern bobwhite and the fathead minnows. RDX impacted neuronal function in rat, Northern bobwhite and earthworm, but apparently not in fathead minnows. Blood-related impacts were observed in most species. The comparison of Gene Ontology terms indicated several biological processes affected by RDX in all species, such as impacts on calcium signaling (involved in seizure response), effects on xenobiotic metabolism, electron transport, and cell signaling pathways. Overall, the meta-analysis using a neurotransmission transcriptional network of the effects of RDX on several species suggested a common and conserved mode of action of the chemical throughout phylogenetically remote organisms.

Biographic note

Dr. Perkins is a Senior Research Scientist (ST) in Environmental Networks and Genetic Toxicology in the US Army ERDC, Environmental Laboratory. In 1987, Dr. Perkins received his PhD in Genetics and Cell Biology from Washington State University studying the biodegradation of the herbicide 2, 4-D. Prior to joining ERDC, Dr Perkins worked in development of transgenic plants for phytoremediation and molecular measures of soil quality. Dr. Perkins joined the ERDC Environmental Laboratory in 1996 where he established a genetics research lab. His research focuses on using biological networks to understand how chemicals cause harmful effects in ecologically important organisms using toxicogenomics, the use of gene expression to monitor adverse environmental impacts, the use of environmental DNA to monitor invasive species, and the effect of military activities on genetic viability of threatened and endangered species on Department of Defense lands.

Systems Biology of Reproductive Endocrine Disruption in Small Fish

Daniel L. Villeneuve, US EPA, Mid-Continent Ecology Division, Duluth, MN, USA.

A variety of chemicals present in the environment and/or used in commerce are known or suspected to elicit adverse effects in humans and wildlife via their interaction with, or modulation of, endocrine signaling involved in the regulation of critical biological functions (e.g., development, reproduction, behavior). Among wildlife, effects of endocrine active chemicals (EACs) in fish have been particularly well documented. A variety of methods to screen chemicals for endocrine activity and/or monitor for endocrine disruption in the environment have been developed. However, there remains a need to further improve the efficiency and effectiveness of these methods. Additionally, to effectively predict and understand risks, there is a need to increase our understanding of the mechanisms of endocrine disruption as well as the capacity of organisms to resist or compensate for the effects of EACs. The aims of this presentation will be to provide workshop participants with 1) a general introduction to the issue of endocrine active chemicals in the environment, 2) a short overview of the reproductive endocrine system in fish, and 3) describe an on-going research program that employed a systems biology approach to study effects of a variety of EACs on fish reproduction, with a focus on developing linkages between dynamic molecular responses at the transcriptional and biochemical level and adverse outcomes traditionally considered relevant for risk assessment. A large compendium of toxicogenomics data from these studies will serve as a case study to explore the application of computational network inference and associated analytical approaches to the challenges of ecological risk assessment for EACs and other chemicals in the environment.

Biographic note

Dr. Dan Villeneuve is a Toxicologist at the US Environmental Protection Agency, Mid-Continent Ecology Division (MED). Dan received his BS in biology and water resources from the University of Wisconsin-Stevens Point, in 1995 and a Ph.D. in zoology/environmental toxicology from Michigan State University in 2000. After completing his Ph.D. Dr. Villeneuve did post-doctoral research at Michigan State University, Oregon State University, and the US EPA MED, before joining MED's permanent federal staff in September 2008. Dr. Villeneuve has authored or co-authored over 80 peer reviewed papers in the field of ecotoxicology. He is an associate editor of aquatic toxicology for Environmental Toxicology and Chemistry. He co-chaired a 2009 Society of Environmental Toxicology and Chemistry (SETAC)-sponsored international workshop on Predictive Ecotoxicology in the 21st Century and also serves as an expert advisor for the Organization for Economic Cooperation and Development (OECD) Advisory Group on Molecular Screening and Toxicogenomics. Dr. Villeneuve's current research is focused on the use of systems biology and ecotoxicogenomic approaches to extend fundamental understanding of the ways in which chemical stressors can interact with the hypothalamic-pituitary-gonadal (HPG)-axis to produce reproductive toxicity in fish and other vertebrates.

New methods for exploring ecotoxicogenomics data: nonlinear relationships and pathway tools

Tim Ebbels Imperial College, London

Post genomic technologies such as transcriptomics and proteomics are seeing increasing use in environmental research. However, while such techniques yield wide-ranging benefits such as a global overview of the system, the data they produce are hard to process and visualise. Through the NERC funded project 'Data Mining and Integration Tools for Ecotoxicogenomics' we have developed new tools to exploring metabolomic and transcriptomic data from environmental toxicology projects.

It is often said that biology is inherently nonlinear. However, most bioinformatics and statistical tools (e.g. Pearson correlation) assume linear relationships. We have adapted a statistical approach based on information theoretic tools to detect and visualise variables which exhibit nonlinear relationships with each other. This could be, for example, a transcript whose abundance varies nonlinearly with toxicant dose. I will demonstrate the approach using transcriptional and metabolomic data from ecotoxicology experiments.

A key difficulty in analysing data from ecotoxicogenomics projects is how to interpret data at the level of biological processes rather than individual genes or metabolites. One approach is to look for pathways which are enriched with differentially expressed or regulated genes/metabolites. We have developed a new approach to pathway analysis which looks at the differential expression of all entities in the pathway simultaneously. Using ROC analysis and permuted real data sets, the new method is compared with two conventional analyses and shown to perform better in terms of false positive and true positive rates.

It is hoped that a synthesis of bioinformatics techniques such as these, developed with environmental data in mind, will soon begin to yield new and exciting insights as omics methods become more common in the environmental arena.

Biographic note

Tim Ebbels obtained his PhD in astrophysics from the University of Cambridge and in 1998 moved into bioinformatics via postdoctoral work at Imperial College in the metabolic profiling group of Prof Jeremy Nicholson. He was a key post-doctoral member of the Consortium for Metabonomic Toxicology (COMET), a large academic-industry collaboration which developed expert systems for predicting adverse effects in pre-clinical toxicity studies via metabolic profiling. In 2003 he joined Prof David Jones' group at University College London to work on modelling and visualisation of gene transcriptomic data. In 2005 he returned to a lectureship at Imperial, within one of the world's largest metabolomics departments. Now a senior lecturer, his group focuses on the application of bioinformatic, machine learning and chemometric techniques to post-genomic data, with a particular emphasis on metabolic profiles. He is involved in projects ranging from NERC funded ecotoxicology, through NIH funded molecular epidemiology, to the development of *in vitro* omics based platforms to predict carcinogenicity funded by the EU. Much work focuses on detailed modelling of the analytical technologies used to obtain metabolic

profiles, but his group is also addressing problems of data integration, visualisation and time series analysis.

Inference of Biological Regulatory Networks from High-Throughput Data: The State of the Field

Ronald C. Taylor, Pacific Northwest National Laboratory, Richland, WA

The ground covered will include: (1) An introduction to the basic ideas behind algorithms for (and problems involved with) inference of regulatory connections using correlations in gene expression or protein abundance data. (2) Brief descriptions of some of the current state-of-the-art algorithms. (3) Information on the Dialogue for Reverse Engineering Assessments and Methods (DREAM) project (http://wiki.c2b2.columbia. edu/ dream/ index.php/The_DREAM_Project), its history, and the public DREAM network inference challenges. This will include a report on the new algorithms described at the 5th Annual DREAM reverse engineering challenge meeting held in November 2010 at Columbia University. Finally, some notes on the latest work in integrating inferred regulatory networks with control of metabolic pathways.

Biographic note

Ronald C. Taylor is a research scientist at the Pacific Northwest National Laboratory, Richland, WA. He has a PhD in Bioinformatics from George Mason University, and dual MS degrees in Computer Science and Biology, as well as a BS in Physics, from Case Western Reserve University. His current research interests and expertise are in development of algorithms for inference of regulatory and interaction networks, development of terabyte scale computational platforms for systems biology (Hadoop/HBase clusters), biological database and knowledgebase design, biological data transfer standards, and development of computational biology tools in general.

Developing a Systems Toxicogenomics Approach in the Netherlands Toxicogenomics Centre (NTC)

Eugene van Someren Netherlands Toxicogenomics Centre (NTC)

Current toxicological research concentrates on identifying hazards of chemical compounds and assessing risks of human exposure. These assessments are based on toxicological tests, most using animals as models for man. Despite decades of experience, this risk assessment is still hampered by uncertainties, such as extrapolation of data from animal to man and from short-term experiments in animals to long-term real-life exposure of man.

Toxicogenomics - the application of genomics-based technologies in toxicological research - may provide tools to tackle these uncertainties. It also offers the opportunity to develop tests that require fewer laboratory animals or cause them less inconvenience, and may eventually replace animal tests completely by in vitro assays using animal or human cells.

Consequently, the Netherlands Toxicogenomics Centre (NTC) aims to employ toxicogenomics to increase the basic understanding of toxicological mechanisms towards developing new and better test methods that also provide alternatives to animal testing, by developing highly predictive screens based on gene expression or protein/metabolite fingerprints, to be used for in depth evaluation of chemical safety for human health, thereby replacing/reducing/refining animal experiments, and thereby, for improving the scientific basis of chemical risk assessment.

NTC has been initiated by the Netherlands Genomics Initiative and represents a collaboration of the leading Netherlands institutions in the area of toxicogenomics: RIVM, RIKILT, TNO, Leiden University, Leiden Univeristy Medical Centre (LUMC) , Wageningen University, Erasmus MC and Maastricht University (coordinator).

NTC's current research projects focus on developing genomics approaches towards important toxicological endpoints e.g. carcinogenicity, immunotoxicity and reproduction toxicity, all major public health concerns. Various high throughput technologies will be evaluated as well. NTC's new 5-year research program involves evaluating the potential of combining microarray-based technologies with other -omics technologies such as proteomics and metabonomics.

Biographic note

Eugene van Someren has a background in genetic network reconstruction developed at the Delft University of Technology (TUD) and applied these techniques to discover the mechanisms behind mesenchymal stem cell development and lineage specification. During that time he worked at the Radboud University Nijmegen (RUN) and for the pharmaceutical company Organon, later Schering-Plough. Since November 2009, Eugene van Someren works as a researcher in Systems Biology and Toxicogenomics for the Dutch Organization for Applied Research (TNO). He coordinates the bioinformatics for the Netherlands Toxicogenomics Centre (NTC).