Integrative Systems Biology

The 21st Century Challenge to Biological, Biomedical and Biotechnological Research in Canada

Briefing Paper and Working Recommendations

Contents:

The spectacular successes of the Human Genome Project and subsequent technological advancements have radically transformed the strategies and visions of biological, biomedical and biotechnological research. While only a decade ago, scientists were largely restricted to studying parts of the biological whole in isolation, advances in information technology, biotechnology and nanotechnology now enable more holistic approaches to biology. The direct outcome of these new capacities is the emergence and increased significance of a scientific discipline termed *Integrative* or *Systems Biology.*

Systems Biology offers concrete opportunities for the advancement of science and technology and the field is widely recognized in academia and industry as a driver of innovation in 21st century bioscience. The extent of this recognition is witnessed by substantial new investments made to develop Systems Biology internationally and in the number of Systems Biology initiatives, ranging from environmental science and plant biotechnology to stem cell research and cancer biology, launched across the globe over the past few years.

In this report[1], we give an overview of Systems Biology, its potential socio-economic impact and the existing strengths that provide Canada a unique opportunity to become a key international contributor to innovation in this emerging field. We also discuss the challenges facing Systems Biology in Canada and make recommendations on how to address them. These recommendations are compatible with measures implemented in most other world-leading nations. In brief, past investments in genomics, proteomics and bioinformatics have provided Canada with the technological and intellectual capacity needed for Systems Biology to flourish. However, this capacity and opportunity is at risk of not being efficiently harnessed without investing in Systems Biology research and education. To ensure that Canadian industries remain competitive internationally and that Canadians continue to reap the socio-economic benefits of an internationally competitive biomedical research enterprise, Canada should make a dedicated and substantial long-term investment to nurture and develop a far-reaching and comprehensive Systems Biology research environment.

[1] The present document aims at facilitating further discussions within the scientific community. Please send comments and suggestions to mkaern@uottawa.ca or visit the Canadian Society for Systems Biology http://www.sysbiosociety.ca.

Introduction

Past investments in technology development have made it possible for scientists to systematically identify and characterize the molecules and molecular interactions that define cellular pathways, cells and cellular interactions, tissues, organs and organisms. Combined with more traditional approaches, such systems-level experimentation allows researchers to gather many of the essential pieces of information that make up the puzzle of life. The next challenge is to put the pieces together and make sense of the puzzle. To achieve this goal, it will be necessary to accumulate and evaluate data spanning multiple biological levels and traditionally disconnected fields. Recognizing this need, scientists from diverse disciplines have joined forces under the banner of Systems Biology[2] in a determined effort to pursue the elusive grail of the biological whole.

Systems Biology is a new frontier in bioscience research that promises to provide a comprehensive understanding of biological systems as more than the sum of their parts. The need for such an integrative perspective is most clearly exemplified by the Human Genome Project. The completion of this project was expected to rapidly accelerate the understanding of illnesses by identifying disease-causing gene variants. While the Human Genome Project was extraordinarily successful, it did not deliver on this promise. Unfortunately, simple gene variation is not sufficient to explain the occurrence of many common serious illnesses such as cancer, diabetes, asthma, heart and neurodegenerative disease. It is now clear that understanding these complex diseases will require the ability to obtain, integrate and analyze staggering amounts of biomolecular data, and link the resulting integrative model of the disease back to human biology. A scientific strategy that strives to understand the biological whole by combining these four steps represents the essence and a definition of Systems Biology research.

Systems Biology is experimental biology. However, the complexity of biological systems makes it very difficult to develop a

[2] The concept of "Systems Biology" emerged in the mid-1900 in the context of Cybernetics and Systems Science. One of the first examples of its use in a modern context is a 1998 meeting abstract by Hood entitled "Systems Biology: New opportunities arising from genomics, proteomics and beyond" published in the journal *Experimental Hematology*. Although some scientists differentiate between Integrative and Systems Biology, we use here the term Systems Biology in its broadest definition, which includes Integrative Biology and other areas such as Functional Genomics.

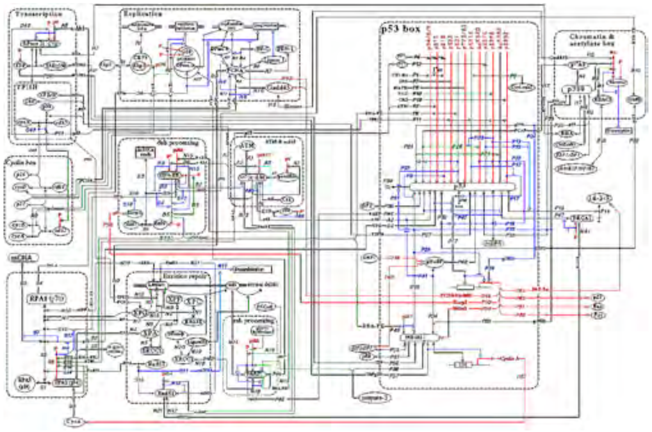

Figure 1. The p53 regulatory network. Source: *Molecular Interaction Map of the Mammalian Cell Cycle Control and DNA Repair Systems* by Kohn.[5]

holistic perspective from experimental facts alone. This is because biological systems are composed of a very large number of interacting components that strongly influence each other. A case in point is a protein involved in many cancers called p53. In 1999, Kurt Kohn developed a map, shown in Figure 1, capturing the biological facts known at the time about the p53 regulatory network[3]. Although the Kohn map does not incorporate the data from over 20,000 scientific studies on p53 published since its completion[4], it is still so complex that intuition and qualitative arguments fail to generate new knowledge about the function and the dynamics of the system as a whole[5]. However, scientists with appropriate training in bioinformatics and computational biology are able to gain such systems-level insights by converting molecular interaction data and other biological information into quantitative computational models. Consequently, modelling plays a critical role in Systems Biology research[6] as a tool for systems simulation, systems analysis and hypothesis generation.

Systems Biology and society

The emergence of a scientific discipline can have enormous and lasting societal impact. The establishment of Molecular Biology in the late 1930's led to the discovery of the structure of DNA in the 1950's, Genetic Engineering in the 1970's, and the introduction of Genomics and Bioinformatics in the 1990's. In addition to firmly establishing the molecular basis of life, these scientific milestones transformed the biological, biomedical and biotechnological sciences and laid the foundation for the development of new industrial sectors that now generate global revenues measured in trillions of dollars.

Systems Biology represents the next step in the chain of scientific advancements that started with the emergence of Molecular Biology. While it is difficult to predict the outcomes of future scientific advancements and discoveries, Systems Biology offers a clear potential for significant and lasting impact on society. Below we provide a brief summation of how Systems Biology in the future could facilitate advancements in science, health and the economy.

Science: Understanding the biological whole has always been a vision and a driving force of biological research. Indeed, many prominent scientists, particularly in physiology and neuroscience, have long relied on systems-level integrative approaches. This has, for example, provided us with a deep understanding of the heart[7] that could not be have obtained by studying system components, such as individual genes and cardiac muscle cells, in isolation. In this and other areas, a key to success is a combination of readily available experimental data and the use of quantitative modelling tools in the analysis of system function and behaviour.

The circumstances that have led to the emergence of Systems Biology from molecular and cellular biology are reminiscent of those that have allowed the systems-level and quantitative perspectives to be successfully integrated into other bioscience fields such as structural biology, pharmacology, physiology, epidemiology, neuroscience and ecology. Immense information on molecular entities and their interactions can now be obtained through systems-level experimentation and is readily available, often with the click on a mouse, through online databases. Moreover, our knowledge about the molecular processes that take place within living cells has reached a level where it makes sense to broadly apply quantitative modelling in the analysis of system function and behaviour. This is, among others, evident from the launch of several new journals, including *Molecular Systems Biology*[8], *In Silico Biology*[9]*, Synthetic and Systems Biology*[10]*, Systems Biology*[11], *Journal on Bioinformatics & Systems Biology*[12] and *Transactions on Computational Systems Biology*[13] dedicated to Systems Biology.

The development of a comprehensive Systems Biology discipline in Canada will allow significant progress in our knowledge of the fundamental principles that governs cellular dynamics and regulation, as well as provide a more complete understanding of the biological whole. Two key goals of Systems Biology are to provide a quantitative and predictive understanding of cellular processes in model animals, and to make sense of the majority of the human genome. In the long term, the progression of the field will enable an integral understanding of more complex biological systems, including human physiology and disease, in terms of their components and their interactions. With appropriate levels of abstraction, the resulting models will span all levels of biological organisation, from genes and molecular pathways, to cells, organs, organisms and ecosystems. In fact, the development of computational

[3] Kohn. Molecular Interaction Map of the Mammalian Cell Cycle Control and DNA Repair Systems. *Mol. Biol. Cell* **10**, 2703 (1999).
[4] Out of the 35,463 publications in the PubMed database (www.ncbi.nim.nih.gov) containing p53 in the title or abstract on June 25, 2006, 21,556 were published after the Kohn map was published in August 1999.
[5] An example of the complex dynamics is given in Geva-Zatorsky *et al.* Oscillations and Variability in the p53 System. *Mol. Syst. Biol.,* **2**, 0033 (2006).
[6] The consensus opinion obtained in an international survey commissioned by the European Union in the context of the 6th Framework Program: "The Take-off of European Systems Biology (EUSYSBIO)"

[7] Noble "Systems Biology and the Heart". *Biosystems* **83**, 75 (2002).
[8] http://www.nature.com/msb/
[9] http://www.bioinfo.de/isb/
[10] http://www.ssbjournal.com/
[11] http://www.iee.org/Publish/Journals/ProfJourn/Proc/SYB/
[12] http://www.hindawi.com/GetJournal.aspx?journal=BSB
[13] http://www.science.unitn.it/~priami/TCSB.html

frameworks for simulating whole cells[14] and organisms, including virtual patients[15], are already well underway. Moreover, quantitative modelling is already being used as a tool to better understand metabolism and enhance crop performance through metabolic engineering.

Health: Systems Biology has enormous long term potential in the area of health. There can be little doubt that the development of tools to accurately predict biological activities at the molecular, cellular and organ levels will have significant impact on the future development of drugs as well as diagnostic and prognostic tools. There are also short-term implications and benefits, including the application of Systems Biology strategies in studies of metabolic disorders[16]. Systems Biology is also likely to facilitate future opportunities for more dynamic and personalized treatment and prevention of illness by promoting a more comprehensive perspective on disease[17]. This could result from the adaptation of Systems Biology tools in the analysis of complex health data to improve public health decisions[18]. For example, many otherwise effective drugs are currently unavailable because of a few cases of adverse side effects that potentially could be predicted. Systems Biology-based personalized medicine could assist in identifying individuals with predisposition for adverse side effects and thus increase the number of available drugs and treatment options for patient groups without these predispositions.

Another research area important to human health is environmental science. The environmental problems facing our society are so complex that it will require interdisciplinary approaches to address them. Consequently, many environmental scientists have adopted Systems Biology approaches in their research[19]. This includes the development of tools to predict damage to organisms and ecosystems caused by exposure to environmental contaminants; to recognize early warning signs of ecosystem stress and damage; and the development of strategies for waste-site cleanup and bioremediation. Additionally, Systems Biology strategies are being employed to study the impact of man-made pollutants in the atmosphere on respiratory health, and to develop methods for the detection and mitigation of outbreaks such as severe acute respiratory syndrome (SARS), avian influenza (bird flu) and bovine spongiform encephalopathy (mad-cow disease).

Economy: Systems Biology has broad applicability in industry (Figure 2) and the potential of applying Systems Biology methods to advance economic growth is widely accepted in industry (see Appendix I). The economic impact of Systems Biology on the health, pharmaceutical, biotechnological and agricultural

[14] http://www.projectcybercell.ca/
[15] http://www.canhealth.com/News143.html
[16] This is exemplified by GlaskoSmithKline partnering with Beyond Genomics to apply Systems Biology for the purpose of drug discovery and development in metabolic diseases. http://www.bg-medicine.com/pdf/gsk_partnership(Sv4).pdf
[17] See e.g., the essays by Ahn *et al.*, "The Limits of Reductionism in Medicine: Could Systems Biology Offer an Alternative?" and "The Clinical Applications of a Systems Approach" in the June 2006 issue of *PLoS Medicine*
[18] http://dir.niehs.nih.gov/dirlt/portier.htm
[19] An example of a Canadian initiative is the Centre for Advance Research in Environmental Genomics. http://www.careg.uottawa.ca/

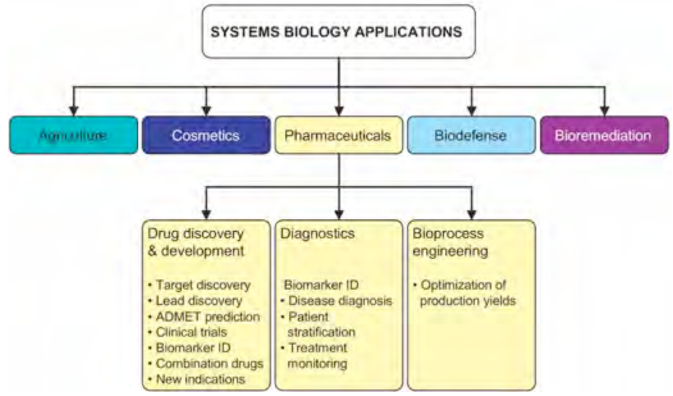

Figure 2. Examples of industrial applications of Systems Biology. Source: *The Future of Systems Biology: Emerging technologies and their impact on drug discovery, development and diagnostics.*[6]

sectors is expected to be substantial[20,21]. For example, the biological information technology (Bio-IT) market is estimated at $38 billion[22] with revenues from Systems Biology products and services in this one niche expected to grow at an annual compound rate of 66% to $785 million by 2008[23].

In the pharmaceutical industry, Systems Biology strategies are already being used to improve decision-making during development and to identify targets during drug discovery[24]. For example, F. Hoffmann-La Roche uses *in silico* technologies[25] in approximately 50% of its projects, mostly drugs in Phase II and Phase III clinical trials[26]. Companies in the pharmaceutical sector are also investing directly in the development of academic Systems Biology research. Novartis and AstraZeneca both sponsor Systems Biology professorships at Harvard University and the University of Manchester, respectively. In Canada, Merck-Frosst is funding Systems Biology-related research on Alzheimer's disease[27] and Invitrogen is, among others, a scientific partner of the Canada-led International Regulome Consortium (IRC)[28] focussing on the Systems Biology of gene regulatory networks in stem cells.

Recent years have also seen the emergence of numerous small and mid-sized companies commercializing Systems Biology. Examples of Canadian companies include GenoLogics[29] (Victoria, BC), Phenomenome Discoveries[30] (Saskatoon, SK) Caprion Pharmaceuticals[31] (Montreal, QC) and Biosystemix[32] (Sydenham, ON). These companies operate in different areas

[20] See reports by Frost & Sullivan (http://www.the-infoshop.com), Navigant Consulting http://www.mindbranch.com), Research and Markets (http://www.researchandmarkets.com), and Strategic Directions International (http://www.strategic-directions.com).
[21] Market analysis report by Business Insights (http://www.globalbusinessinsights.com/report.asp?id=rbdd0005)
[22] http://www.idc.ca/media/pressReleases/pressReleaseMar11-1_2002.html
[23] http://www.researchandmarkets.com/reportinfo.asp?report_id=42935
[24] See e.g., Butcher, Berg and Kunkel *Nature Biotechnology* **22**, 1253 (2004), van der Greef and McBurney *Nature Reviews Drug Discovery* **4**, 961 (2005).
[25] The term *in silico* refers to computational modelling and analysis.
[26] http://www.globalbusinessinsights.com/content/rbdd0005m.pdf
[27] http://www.math.ubc.ca/~keshet/MITACS/AchievementsSummary.htm
[28] http://www.internationalregulomeconsortium.ca/
[29] http://www.genologics.com
[30] http://www.phenomenome.com/
[31] http://www.caprion.com/
[32] http://www.biosystemix.com/

of the Systems Biology market. GenoLogics offer commercial computational tools for the management, integration and analysis of scientific data generated in life science and pharmaceutical laboratories. Phenomenome Discoveries markets a technology platform that can be used to measure and identify metabolites and pathways. Caprion Pharmaceuticals is a clinical stage biotechnology company focusing on the use of proteomics technologies in oncology and infectious diseases. Biosystemix provide analysis solutions, including data mining and predictive modelling services, for personalized medicine and genomics.

While the Bio-IT and pharmaceutical sectors are expected to dominate the Systems Biology market, the applications of Systems Biology extend further. Among others, the integration and incorporation of multi-scale biological data into bioprocess design, development, operation and optimization will benefit Canadian industries through reduced production cost. For example, the global ethanol production capacity was 24 billion litres in 2005. Increasing this capacity by merely one percent will result in tens of millions of dollars in profit. In the context of the fuel alcohol industry, researchers in Canada and abroad are turning to Systems Biology to alleviate the adverse effects resulting from inhibition of ethanol synthesis under industrial conditions. Moreover, the future competitiveness in the global economy of the Canadian agri-food industry, which is the country's third largest employer and generates roughly $100 billion in sales and retail activity annually, depends heavily on improving the yield and performance of major crops as well as developing new traits in crops[33]. Similar to the trends in the fuel alcohol industry, agri-food researchers are increasingly relying on Systems Biology approaches when developing metabolic and process-engineering strategies.

Canadian strengths and challenges

Canada is in a favourable position to be a major international player in Systems Biology due to investments in building cutting-edge research capacity by the Federal Government (i.e., Genome Canada, the Canada Research Chairs program and the Canada Foundation for Innovation), as well as the Provincial Governments and medical, academic and governmental research institutions. As a result of these investments, Canada is a world-leader in the experimental technologies that fuel Systems Biology, particularly genomics, proteomics and metabolomics. Canada also has significant capacity in relevant areas of computer science and engineering and has recently significantly bolstered its capacity in bioinformatics, computational, theoretical and mathematical biology by aggressive hiring of international experts in these fields.

There are currently a number of initiatives in Systems Biology underway across the country, some of which are described in Appendix III. These initiatives have arisen due to a combination of strategic investments and the determination of individual scientists to be at the cutting-edge of this new and significant field. This widespread enthusiasm among many Canadian scientists, particularly in the younger generation, is a key advantage that could lead to rapid progress of the field. Nevertheless, despite availability of core technological and intellectual capacity, Systems Biology is presently underdeveloped in Canada compared to other countries.

There are several factors that impede the development of Systems Biology in Canada. We have identified three specific challenges should be addressed for Systems Biology research in Canada to achieve its full potential and to ensure optimal use of capacity generated by past investments:

- Systems Biology projects often require a combination of funding-intensive high-throughput experimentation across multiple technology platforms and substantial expertise in data management, integration and analysis. Such projects are difficult to establish and maintain in the current funding environment. Specifically, the operational funding dedicated to interdisciplinary and integrative biological research is limited and existing funding mechanisms are not designed to evaluate Systems Biology applications. Moreover, Genome Canada, which presently funds several Systems Biology and Systems Biology-related projects, only supports large-scale projects and is not clearly sustainable.
- Lack of communication across the boundaries of scientific disciplines represents a serious obstacle to the future success of Systems Biology in Canada. Mathematical, statistical and computational modelling and analysis is vitally important for Systems Biology. The absence of quantitative methodologies in biological and biomedical training curricula makes it a challenge to establish interdisciplinary interactions and collaborations, particularly across the interfaces between science and medicine and between experiments and theory.
- The training of highly qualified Systems Biology personnel is virtually non-existent. As discussed in a recent Special Feature in *Science* magazine devoted to careers in Systems Biology[34], traditional training programs are not ideal for the education and training of highly qualified personnel with expertise in Systems Biology. This is also true in Canada where the existing research environments are not able to train a sufficient number of highly qualified personnel with the broad skill base required to meet the present and anticipated future demand in academia and industry.

Facing the Systems Biology challenge

The development of Systems Biology in Canada will require adjustment to a new scientific reality at multiple levels. It is clear that the biosciences have entered a period where researchers with different expertises must work in close collaboration to address increasingly complex biological, technological and medical problems. Researchers, institutions and federal and provincial governments should take concrete steps to ensure that the Canadian public and economy benefit optimally from this new opportunity by facilitating and promoting the transition of Canadian research into the Systems Biology era.

[33] http://ghi-igs.nrc-cnrc.gc.ca/enhancedcrop_e.html

[34] http://www.sciencemag.org/content/vol311/issue5765/

Researchers should actively acquire the knowledge outside of their field of specialty required to efficiently exchange ideas with experts from other disciplines and engage in larger research teams and projects. To assist researchers in addressing this challenge, for example through workshops, site visits and exchange programs, the formative process of establishing a Canadian Society for Systems Biology[35] was initiated by the scientific community in late 2005.

Institutions and provincial governments should actively promote and encourage interdisciplinary and collaborative research endeavours and educational programs. This integration and migration of scientific knowledge is a cornerstone in the formation of cohesive Systems Biology research groups, centres and institutes. The new reality of the molecular-based biosciences will continue to affect virtually all biological and biomedical disciplines and there is a clear need for developing integrated cross-disciplinary educational programs. Individual institutions should make substantial commitments specifically for Systems Biology in ter ms of capital investments that can bring scientists from different disciplines together, in resource management and in interdisciplinary education. Additionally, to encourage and support the younger generation of Systems Biology researchers, institutions should develop clear career paths in collaborative and integrative science.

The Government of Canada should implement appropriate measures to support Systems Biology research and education. To bring Canada to an internationally competitive level, the Canadian funding agencies and the Government of Canada should provide new funding in four key areas:

- The characterisation of the components, the interactions and the dynamics of complex biological systems through genome- and systems-scale analysis and experimentation.
- The development of accessible Systems Biology technology platforms, including technologies for automated high throughput and quantitative experimentation, biological sample and data repositories, cross-platform data integration and analysis, and systems-level simulations.
- The exploration and elucidation of the fundamental principles that govern information processing and dynamics at different levels of biological organization and across their boundaries.
- The education and training of highly qualified personnel to enhance the capacity for innovation in academia and industry, and provide the next generation of Systems Biology researchers.

Because faculty development and capital investments in these areas depend on institutional priorities, there is a clear need for institutional incentives to engage in long-term initiatives. A strong commitment in terms of operational funding from the Government of Canada could provide such an incentive.

Recommendations

A determined and significant commitment should be made to Systems Biology for Canada to maintain and improve its competitiveness in science and technology innovation and to build

35 http://www.sysbiosociety.ca

Table 1. Proposed Funding Envelope

1-2 Team Grants	$10.0 M
4-6 Group Grants	$5.00 M
8-12 Individual Grants	$2.50 M
4-6 High risk Grants	$1.00 M
Training and Education	$1.50 M
Total amount awarded annually	**$20.0 M**

capacity that can attract industrial investments and foster new commercial enterprises. Specifically, investing in Systems Biology provides a clear opportunity for economic diversification into a market that is expected to show significant growth over the next few years. For this purpose, it is recommended that the Canadian funding agencies and the Government of Canada in collaboration with scientists should develop a new mechanism and funding envelope for Systems Biology. This funding envelope is needed to fuel the capacity generated by past investments, to ensure the sustainability of a core constituency of cutting-edge scientists and to develop educational initiatives to train the next generation of academic, medical and industry researchers.

The establishment of a comprehensive and world-leading Systems Biology research environment in Canada will require at least $100 million in new annual operating funding with $20 million being awarded annually (Table 1). This envelope, which is a preliminary estimate, is quite substantial; we note that this funding must not detract from increased and sustained funding for the Federal Granting Councils (CIHR, NSERC, SSHRC) since these agencies provide the essential foundation for all strategic research initiatives in Canada. The size of the program reflects the need for large-scale systematic experimentation (see below), which requires larger than normal operational funding. The benefit is that such data, when made publicly available, provides an invaluable and lasting research tool for the scientific community and an ongoing source of intellectual property and knowledge generation.

The proposed envelope should award funding on a peer-reviewed competitive basis in four categories:

- Team grants in the range of $2-10 million annually to support clearly integrated groups conducting collaborative systems-level and integrative research on a biological problem of particular importance to the economy or health. The research supported in this category would involve systematic high-throughput experimentation across multiple levels, the integration and analysis of the generated data as well as mathematical, statistical and computational modelling. The data generated should be accessible to the general scientific community.
- Operating grants up to $2 million. A portion of the research supported in this category would be similar to that supported in the Team grant category but at a smaller scale. Additionally, the Operating grant category would support Systems Biology research by interdisciplinary groups and individuals[36].

36 It is in this context noted that interdisciplinary research does not necessarily involve investigators with appointments in different departments or faculties.

- Training grants to support graduate and post-graduate education and programs. To encourage collaboration between industry and academia, this category could also include funding for industry internships, temporary positions for industry-based researchers, as well as commercialization and technology transfer workshops.
- Short-term high-risk grants for the development of new technologies, or the launch of new initiatives with the potential of being funded in the Team or the Operating grant category within two to three years.

The new operational resources are envisioned to fund innovative research groups and projects that will promote and foster Canadian Systems Biology in areas that have the greatest potential (see Appendix III). However, the program should support both basic and applied research. While the promise of Systems Biology will be realized short-term by applying existing technology platforms, further developments in basic research and instrumentation is needed to foster scientific advancements with long-term impact. It is, for example, essential to develop new and improved methods to accurately describe and simulate multi-scale systems, such as organs and ecosystems, based on molecular-level information. Moreover, biological research is largely driven by technological innovation enabling new depths of experimental inquiry. There is a clear need to further support nanotechnology and the development of new experimental tools in the context of Systems Biology.

Initiatives supported by the proposed program should be awarded solely on scientific merit. Requiring fund matching or industrial co-sponsorship would negatively impact the international competitiveness of Canadian Systems Biology as funding mechanisms have been implemented abroad without such restrictions. Moreover, future commercial innovation and success in the biotechnology and health sectors will require the development of a strong academic basis in Systems Biology. Investing in Systems Biology in an academic context will provide Canada with the know-how and intellectual property that will facilitate the emergence of new companies, as well as foster regional clusters of expertise that can attract industrial investments. Industrial partnerships and the potential for commercialization should be considered when a scientific review panel evaluates the societal impact of a proposed project.

To foster a true integration of the physical and applied sciences with life and medical sciences, it is recommended that the new funding envelope be administered through collaboration between CIHR and NSERC. Dual-agency involvement is needed because the funding administration and the peer-review panels for Systems Biology should reflect and be able to evaluate the highly interdisciplinary research envisioned to be funded. Systems Biology is also a logical research area for future investment by Genome Canada, since initiatives are likely to evolve from capacities put in place by this agency.

Outlook

Systems Biology has been broadly accepted as the next wave in the evolution of the biosciences. This emerging scientific field will be a key component of innovation and development in 21st century biotechnology and biomedicine. The novelty, strength and potential of Systems Biology come from the integration of concepts and methodologies from traditionally disconnected fields. As such, Systems Biology can be viewed as an approach that expands on existing research capacity by providing researchers with new tools and strategies to address biological and medical questions of fundamental importance. The complexity of these questions requires interdisciplinary research and the coordinated expertise of multidisciplinary teams where biologists and clinicians are engaged in collaborative work with experts from other disciplines. The successful creation of such teams across Canada, together with the necessary support infrastructure and teaching facilities is one of the proposed program's most important first goals and successful early outcomes.

Significant investments have already been made worldwide to develop Systems Biology in academic and industrial contexts. The absence of support in Canada that can compare to that seen in other countries puts Canada and Canadian industries at serious risk in terms of international competitiveness. Moreover, without new operational funding for Systems Biology research, there is a real possibility that the full benefits of the substantial past investments in research capacity and technology will not be realized. These investments have placed Canada in a unique position to take advantage of the opportunities offered by Systems Biology - this is the right time, and Canada is the right place, for Systems Biology to flourish. Investments dedicated to interdisciplinary Systems Biology research and education will ensure that Canada maintains a leading role in science and technology innovation, and that Canadian bioscience and biotechnology sectors can improve and maintain competitiveness and opportunities for growth.

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This report is the outcome of the "Organisational Meeting for Systems Biology in Canada" held at University of Toronto's Terrence Donnelly Centre for Cellular & Biomolecular Research in February 2006, and subsequent discussions with representative scientists.

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Normand Voyer. Université Laval
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Edwin Wang. National Research Council
Elizabeth Weretilnyk. McMaster University
John Wilkins. University of Manitoba
David Wishart. University of Alberta
Jim Woodgett. University of Toronto
Gerry Wright. McMaster University
Xihua Xia. University of Ottawa

Appendix I: Systems Biology in industry

The potential of Systems Biology for advancing innovation in biomedical applications, medical instrumentation and bio-information technology have been recognized broadly in industry[37]. For example, one of the world's leading pharmaceutical companies, Eli Lilly and Company, has established Lilly Systems Biology in Singapore[38]. Additionally, GlaxoSmithKline has invested directly in Systems Biology through its Scientific Computing and Mathematical Modelling Group. Merck has established an Applied Computer and Mathematics Department and is funding theoretical work on Alzheimer's disease in Canada[39]. Novartis is viewing Systems Biology as a necessary next step in drug discovery[40] and sponsors a Professorship of Systems Biology at Harvard Medical School. AstraZeneca is employing Systems Biology methodologies in their Pathway Analysis Program[41] and is supporting a Senior Research Associateship in Systems Biology at the University of Cambridge[42].

In addition to investments by larger international corporations, numerous emergent biotech and Bio-IT companies, including BG Medicine, BioSeek, CellZome AG, Entelos, Genomatica, Gene Network Sciences, GeneGo, Genstruct, Incora, InSilico Biosciences, Panomics and Optimata have been founded based on Systems Biology technology platforms that are used primarily in drug discovery and in the development of products for medical and industrial biotechnology. The industrial aspects of Systems Biology, current market trends, emergent companies and future potential is further described and discussed in Bio-IT World's *Briefing on Systems Biology* (available from www.bio-itworld.com), and in two reports: *Systems Biology - Key to unlocking the value within the omics revolution* by Drug & Market Development Publications and *The Future of Systems Biology: Emerging technologies and their impact on drug discovery, development and diagnostics* by Business Insights (both are available to purchase at www.researchandmarkets.com).

Appendix II: Systems Biology internationally

The United States, Japan, the United Kingdom, Switzerland and the countries of the European Union have all implemented mechanisms to fund Systems Biology research with the United States and Japan being viewed as most progressive due to the early recognition of the field and substantial early investments. In fact, initiatives launched in the United States and in Japan are viewed as the main thrust behind the emergence of Systems Biology as a formal discipline. Central milestones include the founding in the US of the Molecular Sciences Institute[43] in 1996 and the Institute of Systems Biology[44] in 2000, and the launch in Japan of the E-Cell Project[45] in 1996 and the Kitano Symbiotic Systems Project in 1998[46].

In order to recognize the context in which Canadian Systems Biology has to operate and compete, the sections below provide brief summaries of some of the major System Biology and Systems Biology-related initiatives in the United States and selected European countries. It is noted that the review is not exhaustive and only highlights a few of the most representative initiatives. Additional information is provided by *Science* magazine[47] and the World Technology Evaluation Centre[48].

The United States of America

The US government has made massive investments to establish, develop and sustain systems-oriented and integrative research, and the major universities have made substantial commitments. For example, Harvard University has established a Department of Systems Biology[49], its first new academic unit in 40 years, with is own Ph.D. program and an expected size of 20-25 faculty members. Other noticeable interdisciplinary centres include the NIH-funded Institute of Systems Biology in Seattle[25], the Computational and Systems Biology Initiative at the Massachusetts Institute of Technology[50], the Bio-X program at Stanford University[51] and the Center for Quantitative Biology at Princeton University[52]. In addition, the Broad Institute, which is a research collaboration of the Massachusetts Institute of Technology, Harvard University and its affiliated hospitals and the Whitehead Institute, was founded to bridge the gap between genomics and medicine by hosting scientific programs in diverse areas such as Cancer, Medical and Population Genetics, Genome Biology and Cell Circuits, Chemical Biology, Metabolic Disease as well as Computational Biology and Bioinformatics. These and other initiatives are supported through programs launched by the National Institutes of Health, the National Science Foundation, the Department of Defence, the Army Research Office, and the Department of Energy.

The National Institutes of Health (NIH) has a Roadmap for Medical Research[53] that contains several Systems Biology-related strategic areas of development, including the US$300 million Molecular Libraries Initiative, which includes the NIH Chemical Genomics Center, a national network of molecular screening centres, and the development and expansion of computational and predictive modelling. The NIH is in this context supporting seven Roadmap National Centers for Biomedical Computing[54]. The National Institute of General Medical

[37] A more detailed discussion is provided by the Bio-IT World Briefing on Systems Biology
[38] http://www.lsb.lilly.com.sg
[39] http://www.math.ubc.ca/~keshet/MITACS/index.htm
[40] This view was expressed by P. L. Herrling, Head of Corporate Research, Novartis International AG in his Nov. 15, 2004 presentation "Systems Biology: a necessary next step in drug discovery" (http://www.bsse.ethz.ch/press/Herrling_Media_15.11.2004.pdf)
[41] http://www.astrazeneca.com/article/504804.aspx
[42] http://subversive.gen.cam.ac.uk/~danielle/www-ccbi/particulars.pdf
[43] http://www.molsci.org
[44] http://www.systemsbiology.org
[45] http://www.e-cell.org/
[46] http://www.symbio.jst.go.jp/symbio2/
[47] http://sciencecareers.sciencemag.org/career_development/previous_issues/articles/2006_03_03/systems_biology_initiatives/
[48] http://www.wtec.org/sysbio/welcome.htm
[49] http://sysbio.med.harvard.edu/
[50] http://csbi.mit.edu/
[51] http://biox.stanford.edu/
[52] http://quantbio.princeton.edu/
[53] http://nihroadmap.nih.gov/
[54] http://www.bisti.nih.gov/ncbc/

Sciences (NIGMS) has a dedicated Systems Biology Initiative[55] that funds centres, research projects and education programs. The specific objective of the initiative is to attract investigators trained in the mathematically based disciplines to the study of biomedical problems. The NIGMS currently supports centres at Case Western Reserve University, Harvard University, Massachusetts Institute of Technology, Princeton University and the University of Washington. Additionally, the National Heart, Lung, and Blood Institute has currently an open Request for Applications[56] to apply Systems Biology approaches to innovative, high-risk, high-impact research by multidisciplinary teams of investigators.

The National Science Foundation has an Integrative Organismal Biology program[57] that supports research aimed at integrative understanding, through advanced computational techniques and interdisciplinary perspectives, from the molecular through the ecosystem levels.

The Defence Advanced Research Projects Agency (DARPA) under the Department of Defence (DOD) has supported Systems Biology research, including $5.3 million US for Stanford's Bio-X program[58] and two computational technology platforms, the Systems Biology Mark-up Language[59] and the Bio-Spice software[60], for the simulation of complex biological systems.

The Army Research Office is funding Systems Biology-related biotechnology development through, for example, its five-year US$50 million award to the establishment of the Institute of Collaborative Biotechnology[61] as a partnership between University of California, Santa Barbara, the Massachusetts Institute of Technology, the California Institute of Technology and six industrial partners that will develop the technologies created in the university laboratories.

The Department of Energy (DOE) launched a major Systems Biology initiative, the Genomics: GTL (Genomes to Life) program, in 2002[62]. The initial phase of the 25-year program seeks to facilitate and accelerate the transition from genomics to Systems Biology with an emphasis on microbiology. It sponsors seven major research initiatives, three Institutes for the Advancement of Computational Biology Research & Education as well as principal investigator-based projects. The DOE budget for 2007 includes roughly $160 million for the Genomics: GTL program[63]. It is interesting to note this is significantly higher than that requested for the Human Genome project, highlighting the seriousness of the commitment to develop Systems Biology.

[55] http://www.nigms.nih.gov/Initiatives/SysBio/
[56] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-004.html
[57] http://www.nsf.gov/bio/iob/about.jsp
[58] http://news-service.stanford.edu/news/2000/september27/darpa-927.html
[59] http://sbml.org/ SMBL receives funding from multiple agencies
[60] http://biospice.lbl.gov/
[61] http://www.engineering.ucsb.edu/Announce/icb.html
[62] http://doegenomestolife.org/
[63] http://www.aau.edu/budget/07DOEOverview.pdf

Europe

A recent European Science Foundation Policy Briefing[64] outlined several national and trans-national Systems Biology funding programs recently launched in European Union member states. Most European countries have long traditions of Systems Biology-related research and have numerous local clusters of expertise that are gradually evolving into Systems Biology groups and centres. The sections below provide a brief description of some of the national Systems Biology initiatives in Germany, Switzerland and the United Kingdom as well as pan-European projects supported by the European Commission. Additional noteworthy initiatives include the $3.7 million Systems Biology initiative at the Hamilton Institute in Ireland[65], and the French Agence Nationale de la Recherche new funding program "Biologie Systémique (BIOSYS)", which had its first call for applications in February 2006[66].

Germany is among the leading European Systems Biology nations and has made substantial investments and commitments. For example, the Federal German Government has a "Systems to Life – Systems Biology" funding priority program[67], and has committed $152 million to a Systems Biology project studying the liver[68].

Switzerland supports Systems Biology through initiatives such as the SystemsX[69] program founded by ETH Zurich, University of Basel and University of Zurich. The initiative, which is funded by pharmaceutical giant F. Hoffmann-La Roche (Roche), receives support amounting to $8.7 million (10 million Swiss Francs) from the Swiss Federal Institute of Technology in 2006 and 2007. An additional $17.4 million is provided by the local government to construct a new Center of Biosystems and Engineering in Basel[70]. Additionally, the Department of Biology at the ETH Zurich founded the Institute of Molecular Systems Biology in 2005[71].

The United Kingdom provides direct support for Centres for Integrative and Systems Biology through the Biotechnology and Biological Sciences Research Council. These centres are intended to possess the vision, breadth of intellectual leadership and research resources to integrate traditionally separate disciplines, such as biology, chemistry, computer science, engineering, mathematics and physics, into quantitative and predictive Systems Biology programs. Each centre may request up to $14 million with an additional $3 million dedicated to the building of multidisciplinary teams through the engagement of physical scientists and mathematicians.

[64] www.esf.org/publication/212/SPB25SystemsBiology.pdf
[65] http://www.hamilton.ie/systemsbiology/
[66] http://www.agence-nationale-recherche.fr/templates/appel-a-projet.php? NodId=17&lngAAPId=69, http://www.sg.cnrs.fr/usar/projets-2006/bio-sys.htm
[67] http://www.bmbf.de/en/1140.php
[68] http://www.systembiologie.de/en/ http://sciencecareers.sciencemag.org/career_development/previous_issues/articles/2006_03_03/systems_biology_initiatives/(parent)/106;
[69] http://www.systemsx.ch/
[70] http://www.bsse.ethz.ch/press/eth_systemsx_25.06.04.pdf
[71] http://www.imsb.ethz.ch/

The European Commission is providing strong support for Integrative and Systems Biology that augments the national initiatives. Examples of Systems Biology-oriented transnational funding and research programs supported by the European Commission are EUSYSBIO, focusing on the training of young scientists and international networking; ERASysBio, a long-term initiative to coordinate research activities and to create a European Research Area for Systems Biology[72]; the Yeast Systems Biology Network, which uses yeast as a model system to study the rules governing the dynamic operation of cellular systems[73]; BIOSIM, a Network of Excellence for the development and use of simulation techniques[74]; QUASI, a program employing multidisciplinary approaches to decipher basic mechanisms underlying signal transduction, intracellular communication and transcriptional activation[75]; COMBIO, aiming at bringing computational biology to the bench through an integrative approach to cellular signalling and control processes[76]; EMI-CD, a modelling initiative for the development of software platforms for combating complex diseases[77]; and the COSBICS program aiming to establish and apply a novel computational framework in which to investigate dynamic interactions of molecules within cells[78].

Appendix III: Assessment of Systems Biology potential in Canada[79]

While a national Systems Biology funding strategy is yet to be developed, Canadian researchers have been active in launching Systems Biology-related initiatives both nationally and internationally. An example of international leadership in Systems Biology is the Canada-led International Regulome Consortium (IRC). Noticeably, the Canadian component of the IRC, in contrast to the international partners, the Welcome Trust Sanger Institute, the Erasmus Medical Center and Genomics Institute of Singapore and other research institutions in continental Europe and Australia, has yet to secure funding. In addition, investments made through the Genome Canada program have created significant Systems Biology-related research capacity, particularly in infrastructure supporting genomics and proteomics research. If utilized appropriately, this infrastructure provides Canada with the potential to become one of the world-leading Systems Biology nations. In the sections below, we provide further evidence for the potential of Systems Biology in Canada by highlighting existing initiatives across the country.

Atlantic Canada has several initiatives under development to promote integrative and systems level understanding of biological phenomena and biomedical conditions. The North Atlantic Resource for Molecular, Cellular, Integrative and Network Sciences (NARIS) is expected to provide a major addition to high-throughput experimental and computational capacity in Newfoundland, and act as a hub for Systems Biology-related research in this region. Additionally, Dalhousie University recently started a graduate program in Bioinformatics and Computational Biology based on a tradition of strength in the area of evolutionary biology. Dalhousie researchers are spearheading one of this country's oldest interdisciplinary Systems Biology-related initiatives, the Canadian Institute of Advanced Research's program in Evolutionary Biology, which aims at providing new understanding of organisms and ecosystems by combining molecular biology, genetics, population biology, bacteriology, protozoology, botany, zoology, chemistry, biochemistry, mathematics, and computer science.

Quebec has a long tradition of integrative and quantitative research and has held a strong international position for many years through the interdisciplinary, multi-university Centre for Nonlinear Dynamics in Physiology and Disease (CND) hosted by McGill University. The CND runs a summer school entitled "Systems Biology: from Genes to Organisms". In addition to this international flagship for Systems Biology and interdisciplinary education, McGill University's Department of Anatomy and Cell Biology will soon introduce a graduate track in Human Systems Biology. Moreover, the University of Montreal's Institute for Research in Immunology and Cancer (IRIC) is at the first step in setting up a new Systems Biology graduate training program, and the Institut de recherches cliniques de Montréal (IRCM) have made significant effort towards the implementation of Systems Biology as a new research theme. École Polytechnique de Montréal also has numerous Systems Biology-related initiatives in the areas of functional genomics, metabolomics and biological pathway analysis and the opening of a new Genomics Centre in Québec City is expected to accelerate the formation of a virtual Systems Biology group with participation from Montreal, Québec City and Sherbrooke. Additionally, Genome Québec has made significant investments to improve genomics and proteomics infrastructure through the McGill University and Genome Québec Innovation Centre, and is sponsoring Systems Biology-related research programs, such as, for example, the multi-university project "Regulatory Networks in Gene Expression: From the Genome to the Organism" and the "Montreal Network for Pharmaco-Proteomics and Structural Genomics".

Ontario has several emerging Systems Biology-specific initiatives that include the establishment of the Centre of Cellular and Biomolecular Research at the University of Toronto to stimulate unconventional interactions among disciplines; the founding, by the University of Ottawa and the National Research Council, of the Ottawa Institute of Systems Biology; and the launch of a program in Integrated Systems Biology and of the Sun Centre of Excellence in Systems Biology at Mount Sinai Hospital's Samuel Lunenfeld Research Institute in Toronto. Additionally, the Centre for Computational Biology at Toronto's Hospital for Sick Children is dedicated to the advancement of Systems Biology research and the University of Toronto has

[72] http://europa.eu.int/comm/research/health/genomics/newsletter/issue5/newprojects_en.htm
[73] http://www.ysbn.org
[74] http://chaos.fys.dtu.dk/biosim/
[75] http://www.idp.mdh.se/quasi/
[76] http://www.pdg.cnb.uam.es/COMBIO/
[77] http://pybios.molgen.mpg.de/EMICD/index_html
[78] http://www.sbi.uni-rostock.de/cosbics/index.html
[79] The information in this section is obtained from individual investigators, Federal and Provincial Funding Agencies, and other public domain sources. It was not possible at the time of the writing to include full references.

recently launched a new Department of Cellular and Systems Biology. Another example of a Systems Biology-related initiative in Ontario is the University of Ottawa's recently established Centre for Advanced Research in Environmental Genomics (CAREG), which seeks to integrate the fields of eco-toxicology, genetics, physiology and bioinformatics to develop novel genomics-based solutions to environmental problems. Genome Canada, through the Ontario Genomics Institute, has made significant investments in genomics and proteomics infrastructure as well as Systems Biology-related research programs such as the Stem Cell Genomics Project, the Biomolecular Interaction Network Database project, the Proteomics and Functional Genomics: An Integrated Approach program, and the Dynactome Project seeking to map spatio-temporal dynamic systems in humans.

The Prairie Provinces host several interdisciplinary research centres, including the Manitoba Centre for Proteomics and Systems Biology, dedicated to the promotion and practice of Systems Biology and Proteomics, and the Institute for Biocomplexity and Informatics at the University of Calgary, which, in collaboration with the Alberta Ingenuity Centre for Machine Learning, focuses on the structure, dynamics and evolution of genetic regulatory networks and their behaviours. In addition, the Institute for Biomolecular Design at the University of Alberta, which is an interdisciplinary research and platform technology centre, is an international contributor to *in silico* technology innovation through its Project CyberCell. Genome Prairie is also supporting Systems Biology-related research programs, such as the development of an integrated and distributed bioinformatics platform, and the Sun Centre of Excellence for Visual Genomics at the University of Calgary. In addition, the University of Manitoba's Mammalian Functional Genomics program is involved in Systems Biology-related research, for example, through the Genome Canada funded NorCOMM project and the International Knockout Mouse Project. Genome Canada also supports the Human Metabolome Project at the University of Alberta. University of Alberta also has a Centre for Mathematical Biology that is active in the area of Systems Biology.

British Columbia has a strong presence in Systems Biology through a formal affiliation of the world-leading Institute of Systems Biology in Seattle with the University of British Columbia. Significant existing strengths, particularly in genomics, proteomics, bioinformatics and mathematical biology, provide a solid foundation for further developments. For example, in proteomics, the University of British Columbia recently launched a new life science institute, the Canadian Laboratories in Integrated Proteolysis. Moreover, the nationally and internationally renowned Bioinformatics Training Program for Health Research, offered through a partnership between Simon Fraser University, the University of British Columbia, and the BC Cancer Agency, and the Canadian Genetic Disease Network's Canadian Bioinformatics Workshop series housed at the bioinformatics.ca resource, which is the portal to bioinformatics activities in Canada, are some of the examples of the strong capacity and expertise in Systems Biology-related research. Additionally, the University of British Columbia has a pan-Canada program in Biomedical Models of Cellular and Physiological Systems and Disease, which is a full project under the auspices of the Mathematics of Information Technology and Complex Systems Network of Centres of Excellence housed at Simon Fraser University. This project is focussed on industry-relevant mathematical analysis of human diseases, with current projects related to type 1 diabetes and Alzheimer's disease, among others.

The National Research Council is traditionally strong in integrative multi-disciplinary research and technology development and transfer. Its investments through the Genomics and Health Initiative (GHI) have lead to a significant genomic and proteomic infrastructure in several regions across the country. The GHI, established in 1999 in order to bring the benefits of genome and health sciences to all Canadians, funds focused inter-disciplinary programs combining elements of genomics, proteomics, bioinformatics and convergence technologies to address health-related issues in a Systems Biology-related manner. Examples of NRC-based Systems Biology-related programs include Cancer Genomics; Genomics for Enhanced Crop Performance; Human Pathogens and their Host Interactions; and Systems Biology of Brain Cell Interactions. The NRC also has considerable expertise and strength in Information Technology and has developed a number of tools for data mining of large datasets and the integration of diverse datasets. Additionally, the program in Genomics-Based Approach to Enhancing Bioremediation through Microbial Identification and Community Profiling could provide a cornerstone for the development of Environmental Systems Biology in Canada. Innovation and expertise in instrumentation is critical for Systems Biology and the NRC could become an important partner in Canadian Systems Biology by developing and providing cutting-edge technology platforms and facilitating interactions among scientific and industry communities.