ABSTRACT

High-throughput next-generation DNA sequencing has evolved rapidly over the past 20 years. The Human Genome Project published its first draft of the human genome in 2000 at an enormous cost of 3 billion dollars, and was an international collaborative effort that spanned more than a decade. Subsequent technological innovations have decreased that cost by six orders of magnitude down to a thousand dollars, while throughput has increased by over 100 times to a current delivery of gigabase of data per run. In bioinformatics, significant efforts to capitalize on the new capacities have produced software for the identification of deviations from the reference sequence, including single nucleotide variants, short insertion/deletions, and more complex chromosomal characteristics such as copy number variations and translocations. Clinically, hospitals are starting to incorporate sequencing technology as part of exploratory projects to discover underlying causes of diseases with suspected genetic etiology, and to provide personalized clinical decision support based on patients' genetic predispositions. As with any new large-scale data, a need has emerged for mechanisms to translate knowledge from computationally oriented informatics specialists to the clinically oriented users who interact with it.

In the genomics field, the complexity of the data, combined with the gap in perspectives and skills between computational biologists and clinicians, present an unsolved grand challenge for bioinformaticians to translate patient genomic information to facilitate clinical decision-making. This doctoral thesis focuses on a comparative design analysis of clinical decision support systems and prototypes interacting with patient genomes under various sectors of healthcare to ultimately improve the treatment and well-being of patients. Through a combination of usability methodologies across multiple distinct clinical user groups, the thesis highlights reoccurring domain-specific challenges and introduces ways to overcome the roadblocks for translation of next-generation sequencing from research laboratory to a multidisciplinary hospital environment. To improve the interpretation efficiency of patient genomes and informed by the design analysis findings, a novel computational approach to prioritize exome variants based on automated appraisal of patient phenotypes is introduced. Finally, the thesis research incorporates applied genome analysis via clinical collaborations to inform interface design and enable mastery of genome analysis.

BIOGRAPHICAL NOTES

Place of Birth:	Taipei, Taiwan
Academic Studies:	B. Sc. (Hons. Co-op) University of British Columbia, 201
Current Position:	Systems Analyst at Fraser Health Authority

GRADUATE STUDIES

Field of Study:	Bioinformatics: Development and Evaluation of Software Interface for Applied Clinical Genomics

Courses		**Instructors**
CPSC 540	Machine Learning	Dr. N. de Freitas
MEDG520	Advanced Human molecular Genetics	Dr. M. Lorincz
BIOF 520	Problem-Based Learning in Bioinformatics	Dr. S. Jones
STAT540	Statistical Methods for High Dimensional Biology	Dr. P. Pavlidis
CPSC545	Algorithms for Bioinformatics	Dr. I. M. Meyer

AWARDS

Doctoral Award: Frederick Banting and Charles Best Canada Graduate Scholarships (CGS-D)

Canadian Institutes of Health Research (CIHR) / Michael Smith Foundation for Health Research (MSFHR) Bioinformatics Graduate Trainee Award

NSERC Alexander Graham Bell CGSM Scholarship

Four Year Fellowships (FYF) For PhD Students & Four Year Fellowships (4YF) Tuition Award

CFRI Trainee Award & CFRI Trainee Travel Grant

1st place for presentation, 2nd place for poster competition at 2012 BTP/IOP Retreat

College for Interdisciplinary Studies Graduate Award

SELECTED PUBLICATIONS

C. Shyr, A. Kushniruk, W.W. Wasserman, 2014, "Usability study of clinical exome analysis software: Top lessons learned and recommendations", *Journal of Biomedical Informatics*, 51, 129-136.

C.Shyr, C.D.M. van Karnebeek, A. Kushniruk, W.W. Wasserman, “Dynamic software design for clinical exome and genome analyses: insights from bioinformaticians, clinical geneticists and genetic counselors”, JAMIA, 2015 Jun 27.

C. Shyr, M. Tarailo-Graovac, M. Gottlieb, J.J.Y. Lee, C. van Karnebeek and W.W. Wasserman, 2014, “FLAGS, Frequently Mutated Genes in Public Exomes”, *BMC Medical Genomics*, 7, 64.

C.D. van Karnebeek, W.S. Sly, C.J. Ross, R. Salvarinova, J. Yaplito-Lee, S. Santra**,** **C. Shyr**, et. al., 2014, “Mitochondrial carbonic anhydrase VA deficiency due to CA5A alterations presents with hyperammonemia in early childhood”, *American Journal of Human Genetics*, 94, 453-461.

SELECTED PRESENTATIONS

Poster presentations:
Cold Spring Harbor Laboratory: Meeting-Precision Medicine: Personal Genomes & Pharmacogenomics 2013

Cold Spring Harbor Laboratory: Biological Data Science 2014

Talk presentations:
AMIA Joint Summits on Translational Science 2012

Pacific Northwest Genetics Exchange 2013

Pediatric Neurology Division Rounds at BC Children’s Hospital 2013

Garrod Symposium– Metabolic in Motion 2015

SUPERVISORY COMMITTEE

Primary supervisor:
Dr. Wyeth W. Wasserman

Co-supervisor:
Dr. Andre Kushniruk

Committee members:
Dr. Jehannine Austin
Dr. Bruce Carleton
Dr. Sohrab Shah

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

Graduate and Postdoctoral Studies

PROGRAMME

The Final Oral Examination
For the Degree of

DOCTOR OF PHILOSOPHY
(Bioinformatics)

CASPER SHYR

B. Sc. (Hons., Co-op), University of British Columbia, 2010

Thursday, April 21, 2016, 9:00 AM
Room 203, Graduate Student Centre
Latecomers will not be admitted

“Development and Evaluation of Software Interface for Applied Clinical Genomics”

EXAMINING COMMITTEE

Chair:
Dr. Robert Rohling (Electrical and Computer Engineering)

Supervisory Committee:
Dr. Wyeth W. Wasserman, Research Supervisor (Medical Genetics)
Dr. Jehannine Austin (Medical Genetics)

University Examiners:
Dr. Aly Karsan (Pathology and Laboratory Medicine)
Dr. Martin Dawes (Family Practice)

External Examiner:
Dr. Russ Altman
Department of Bioengineering, Genetics and Medicine
Stanford University
Menlo Park, California
United States