## ABSTRACT

Acute myeloid leukemia (AML) is a high grade malignancy of non-lymphoid cells of the hematopoietic system. AML is a heterogeneous disease, and numerous attempts have been made to risk-stratify AML so that appropriate treatment can be offered. Single cell analysis methods could provide insights into the biology of AML leading to risk-stratified and functionally tailored treatments and hence improved outcomes. Recent advances in flow cytometry allow the simultaneous measurement of up to 17 antibody markers per cell for up to millions of cells, and it is performed routinely during AML clinical workup. However, despite vast amounts of flow cytometry data being gathered, comprehensive, objective and automated studies of this data have not been undertaken. Another method, strand-seq, elucidates template strand inheritance in single cells, with a range of potential applications, none of which had been automated when this thesis work commenced. I have developed bioinformatic methods enabling research into AML using both these types of data.

I present flowBin, a method for faithfully recombining multitube flow cytometry data. I present flowType-DP, a new version of flowType, able to process flow cytometry and other single cell data having more than 12 markers (including flowBin output). I demonstrate the application of flowBin to AML data, for digitally isolating abnormal cells, and classifying AML patients. I also use flowBin in conjunction with flowType to find cell types associated with clinically relevant gene mutations in AML.

I present BAIT, a software package for accurately detecting sister chromatid exchanges in strand-seq data. I present functionality to place unbridged contigs in late-build genomes into their correct location, and have, with collaborators, published the corrected locations of more than half the unplaced contigs in the current build of the mouse genome. I present contiBAIT, a software package for assembling early-build genomes which consist entirely of unanchored, unbridged contigs. ContiBAIT has the potential to dramatically improve the quality of many model organism genomes at low cost.

These developments enable rapid, automated, objective and reproducible deep profiling of AML flow cytometry data, subclonal cell analysis of AML cytogenetics, and improvements to model organisms used in AML research.


## BIOGRAPHICAL NOTES

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| Place of Birth: | Pietermaritzburg, South Africa |
| Academic Studies: | B.Sc. University of Natal, 2002<br>B.Sc. (Hons) University of KwaZulu-Natal, 2004<br>M.Sc. University of KwaZulu-Natal, 2008 |

## GRADUATE STUDIES

| | |
|---|---|
| Field of Study: | Bioinformatics of flow cytometry and other high-throughput single cell methods. |

## SELECTED PUBLICATIONS

**Kieran O'Neill**, Adrin Jalali, Nima Aghaeepour, Holger Hoos, Ryan Brinkman (2013) Enhanced flowType/RchyOptimyx: A Bioconductor pipeline for discovery in high-dimensional cytometry data; Bioinformatics: 2014 May 1;30(9):1329-30

**Kieran O'Neill**, Nima Aghaeepour, Josef Špidlen, Ryan Brinkman (2013) Flow Cytometry Bioinformatic; PLOS Computational Biology 9 (12)

Mark Hills, **Kieran O'Neill**, Esther Falconer, Ryan Brinkman, Pieter Lansdorp (2013) BAIT: Organizing genomes and mapping rearrangements in single cells; Genome Medicine 5 (9), 1-17

## PRESENTATIONS

Deep Phenotyping of Multitube Flow Cytometry Data Reveals New Cell Types Associated with NPM1 Mutation in AML, Vancouver Bioinformatics User Group, September 2012

Automated Prediction of Clinically Relevant AML Genotypes from Bone Marrow Immunophenotype, Vancouver Bioinformatics User Group, April 2010

## SUPERVISORY COMMITTEE

Dr Ryan Brinkman (Medical Genetics)
Dr Paul Pavlidis (Psychiatry)
Dr Jenny Bryan (Statistics)
Dr Bakul Dalal (Pathology and Laboratory Medicine)

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THE UNIVERSITY OF BRITISH COLUMBIA

Graduate and Postdoctoral Studies

**PROGRAMME**

The Final Oral Examination
For the Degree of

DOCTOR OF PHILOSOPHY
(Bioinformatics)

# KIERAN O'NEILL

B.Sc. University of Natal, 2002
B.Sc. (Hons) University of KwaZulu-Natal, 2004
M.Sc. University of KwaZulu-Natal, 2008

Wednesday, 8 October, 2014, 12:30 pm
Room 200, Graduate Student Centre
*Latecomers will not be admitted*

**"Automated Analysis of Single Cell Leukemia Data"**

**EXAMINING COMMITTEE**

Chair:
Dr. Thibault Mayor (Biochemistry and Molecular Biology)

Supervisory Committee:
Dr. Paul Pavlidis (Psychiatry)
Dr. Ryan Brinkman (Medical Genetics)

University Examiners:
Dr. Victor Ling (Pathology & Laboratory Medicine)
Dr. Robert Holt (Molecular Biology & Biochemistry)

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