Natural Sciences and Engineering Research Council of Canada | Conseil de recherches en sciences naturelles et en génie du Canada

Application for a Postgraduate Scholarship or Postdoctoral Fellowship (FORM 201)

AID	
CTTEE	
Date	2017/09/29

Type of Award	Reference No.
PGS D	401226308

Family name of applicant	Given name	Initial(s) of all given names	Personal identification no. (PIN)
Cassidy	Tyler	TT	**Valid** 439027

ADDRESSES. Changes to any of the information below must be sent to schol@nserc-crsng.gc.ca.

Current mailing address	Permanent address (if different from current mailing address)
6- 9230 Rue Lajeunesse Montreal, QC CANADA H2M 1S2	11 Reighley Close Red Deer, AB CANADA T4P 3V7
If current mailing address is temporary, indicate leaving date	Telephone number at permanent address

Telephone number	Facsimile number	E-mail address (NSERC will use this information as the initial point of contact.)
11 (403) 8726089		tyler.cassidy@mail.mcgill.ca

CITIZENSHIP

[X] Canadian citizen [ ] Permanent resident of Canada [ ] Other

Indicate date of landing as stated on official immigration document

Indicate country of citizenship

LANGUAGE OF CORRESPONDENCE

I wish to receive my correspondence in:

[X] English [ ] French

University responsible for the internal selection process (Not applicable for PGS applications submitted directly and PDF applications.)

McGill

Mathematics and Statistics

Personal information collected on this form and appendices will be stored in the Personal Information Bank for the appropriate program.

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ACADEMIC BACKGROUND (include only current and past degree programs)

Degree	Name of discipline	Department, institution and country	Month and year started	Month and year awarded/expected
Bachelor's	Honors Applied Mathematics	Science, Faculty of Alberta, CANADA	9 / 2011	4 / 2015
Master's	Applied Mathematics	Mathematics and Statistics McGill, CANADA	9 / 2015	Transferred to Ph.D.
Doctorate	Applied Mathematics	Mathematics and Statistics McGill, CANADA	1 / 2017	9 / 2020

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ACADEMIC, RESEARCH AND OTHER RELEVANT WORK EXPERIENCE

Position held and nature of work (begin with current) Full Time - Part Time	Organization and department	Supervisor	Period (mm/yyyy-mm/yyyy)
Dynamical Systems Modeller - Full Time Quantitative systems biology scientist in the internal medicine research unit.	Pfizer Inc Internal Medicine Research Unit	Dr. Cynthia J. Musante	6/2017 - 9/2017
Teaching Assistant - Part Time Teaching assistant for Calculus for Management, Calculus II	McGill University Mathematics and Statistics	Dr. Sidney Trudeau	9/2016 - 12/2017
Research Assistant - Full Time NSERC USRA research assistant	University of Alberta Mathematics and Statistics	Dr. Hassan Safouhi	5/2015 - 9/2015
Research Assistant - Full Time NSERC USRA research assistant	University of Alberta Mathematics and Statistics	Dr. Hassan Safouhi	5/2014 - 9/2014
Teaching Assistant - Part Time Teaching assistant for Statistics I, Calculus I,II and linear algebra I courses.	University of Alberta Campus Saint-Jean	Dr. Sarah Pelletier	1/2013 - 4/2015

Personal identification no. (PIN)	Family name, given name and initial(s) of applicant
Valid 439027	Cassidy, Tyler TT

AWARD APPLIED FOR

Type of award	Proposed starting date of award
Postgraduate Scholarships - PGS D	2018/09

Proposed degree program (e.g. Masters, Doctorate)	Proposed field of study/research	Research subject code
Doctorate	APPLIED MATHEMATICS	2950

Title of proposed research

Quantitative Systems Biology Approach to Immunohematopoeitic Regulation

List ten (10) key words that describe your proposed research.

Quantitative systems biology, Mathematical physiology, Mathematical modelling, Computational biology, Mechanistic modelling, Immune Response Model,

PROPOSED LOCATION(S) OF TENURE (in order of preference)

Institution/organization	Department	Program of study	Proposed supervisor
McGill,	Mathematics and Statistics	Applied Mathematics	Antony Humphries, Michael Mackey

Are any of your proposed programs of study:

Clinically-oriented? [ ] Yes [X] No Joint programs with a professional degree (e.g., MD/PhD)? [ ] Yes [X] No

SECTION TO BE COMPLETED BY PGS APPLICANTS ONLY

Indicate the total number of months of graduate studies (master's and doctoral) you have completed as of December 31 of the year of application in the natural sciences and engineering.

25 months of full-time studies 0 months of part-time studies

Indicate the number of months of studies you have completed, as of December 31 of the year of application, **in the program for which you are requesting funding.**

5 months of full-time studies 0 months of part-time studies

Indicate if you are attending university at the time of application.

[X] Attending full time [ ] Attending part time [ ] Not attending

If you are offered an award, do you plan to take it up at a foreign university?

[ ] Yes [X] No

If you answered yes to the previous question, do you still want to be considered for an Alexander Graham Bell Canada Graduate Scholarship which is **tenable only in Canada?**

[ ] Yes [ ] No

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SCHOLARSHIPS AND OTHER AWARDS OFFERED (start with most recent and include NSERC awards)

Name of Award	Value (CDN$)	Level (Institutional, Provincial, National, International)	Type (Academic, Research, Leadership, Communication)	Location of tenure	Period held (yyyy/mm - yyyy/mm)
CRM Applied Math	5,000	Provincial	Research	McGill University	2017/09 - 2018/09
CAMBAM Fellowship	5,000	Provincial	Research	McGill University	2017/09 - 2018/09
Graduate Excellence Fellowship	5,812	Institutional	Academic	McGill University	2017/09 - 2018/09
CRM Applied Math	5,000	Provincial	Research	McGill University	2016/09 - 2017/09
Graduate Excellence Fellowship	6,866	Institutional	Academic	McGill University	2016/09 - 2017/09
CAMBAM Fellowship	7,500	Provincial	Research	McGill University	2016/09 - 2017/09
James Lougheed Award of	15,000	Provincial	Research	McGill University	2015/09 - 2016/09
NSERC USRA	7,500	Institutional	Research	University of Alberta	2015/05 - 2015/09
NSERC USRA	7,500	Institutional	Research	University of Alberta	2014/05 - 2014/09

Type of Award	Personal identification no.(PIN)	Family name, given name and initial(s) of applicant
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THESIS COMPLETED OR IN PROGRESS

1. Degree	Supervisor	Date degree requirements completed
Doctor of Philosophy	Antony Humphries and Michael Mackey	12/2019

Title of thesis
A Systems Biology Study of Immunity to Quantify Hematological Response

2. Degree	Supervisor	Date degree requirements completed
		01/2018

Title of thesis

SUMMARY OF THESIS MOST RECENTLY COMPLETED OR IN PROGRESS

Do not reproduce abstract of thesis.

In this work, I extend the quantitative system biology model of granulopoiesis derived by Craig et al. to include the immune response to bacterial infection. The physiology based model includes neutrophil recruitment to infected tissue, monocyte production, recruitment to infected tissue and differentiation into macrophages. The model reproduces the different time scales of immune response and can be used to understand local and systemic infection and to explore the pathology of chronic inflammation.

The hematopoietic (blood production) system is comprised of cells with lifespans varying from hours to years. The system creates new blood cells at a rate that reproduces the human body's own weight roughly every 10 years [1]. Homeostasis is maintained via complicated chains of positive and negative feedback loops that involve a legion of cytokines and hormones. Beyond maintaining homeostasis, the hematopoietic system must also respond to emergencies including blood loss and fungal, viral, and bacterial infections.

Bacterial infections lead to interactions between the immune and the hematopoietic systems. These interactions are controlled by a number of crosstalk relationships inherent to the immunohematological axis. Critical cytokines, including granulocyte colony stimulating factor (G-CSF), link the immune and hematopoietic systems and are amplified during infection. G-CSF induces white blood cell production and increases the release of mature white blood cells into the bloodstream [2]. Following resolution of the infection, the immune system decreases G-CSF production to signal the hematopoietic system to arrest the emergency production of white blood cells and return blood concentrations to homeostatic levels.

Experimental work has primarily focused on pairwise interactions between the cytokines governing immunohematologic interactions, as the number of cytokines involved in hematopoesis renders systems level experiments intractable. Therefore, mathematical modelling offers an unparalleled opportunity for systems level characterization of the immunohematological response and to understand how systemic defects result in acute inflammation.

Previous mathematical models have focused on characterizing the interaction between immune and bacterial cells [4, 5]. Existing work accurately reproduces murine data by accounting for the staggered arrival of neutrophils and macrophages without explicitly modelling the complex physiology leading to immune cell production. However, without explicitly accounting for the precise bacterial-immune cell interactions that engender increased cytokine production and the physiological differences in neutrophil and macrophage production that account for their staggered arrival, the potential of mathematical models in immunoregulation remains unfulfilled.

My doctoral research will focus on mathematically modelling the immunohematopoietic response to bacterial infection. I will extend the mechanistic state dependent delay differential equation (DDE) model of granulopoiesis given by Craig et al. [3] to include the innate immunohematopoeitic pathways.

I will construct a mechansitic mathematical model of bacterial infection by including bacteria proliferation and phagocyte mediated death. As G-CSF production is dependent on the severity of infection, I will introduce a bacteria-dependent G-CSF production rate. Linking G-CSF production to bacterial load will quantify how bacteria inoculum initiates immune response. I will derive a delay differential equation for monocyte production using partial differential equations, and I will model the evolution of circulating monocytes into macrophages during immune stress. Finally, I will use infection driven cytokine production to govern immune cell migration into infected tissues. The accumulation of immune and dead cells in infected tissue will then be used as a cipher for immune mediated inflammation.

To calibrate the resulting mathematical model, I will use sophisticated parameter estimation techniques and global sensitivity analysis. Analysis of the resulting model will combine techniques from infinite dimension dynamical systems and numerical analysis.

Extending Craig et al.'s mechanistic model of granulopoiesis [3] to include the innate immune response will allow for quantification of the interaction between the immune and hematopoietic systems. The goal of my work is to elucidate the mechanisms and interactions that characterize the immunohematopoietic chain. Beyond acute infection, this work is critical to understanding the mechanisms behind immunoregulation and how flaws in the immunohematopoietic chain lead to chronic inflammatory diseases, like rheumatoid arthritis and atherosclerosis, and will improve both clinical and experimental investigations of acute infections and chronic inflammation.

[1] Dale, D.C. and Mackey, M.C. (2015) *Bull. Math. Biol* **77(5)**, 739–757.
[2] Roberts, A. (2005) *Growth Factors* **23(1)**, 33–41.
[3] Craig, M., Humphries, A., and Mackey, M. (2016) *Bull. Math. Biol.* **78(12)**, 2304-2357
[4] Smith, A., McCullers, J., and Adler, F. (2011) *J. Theor. Biol.* **276(1)**, 106–116.
[5] Schirm, S., Ahnert, P., Wienhold, S., Mueller-Redetzky, H., Nouailles-Kursar, G., Loeffler, M., Witzenrath, M., and Scholz, M. (2016) *PLoS One* **11(5)**, 1–22.

I Contributions to research and development

a) Articles published or accepted in peer-reviewed journals

1) **Cassidy, T.**, Gaudreau, P. and Safouhi, H.,(2017) On the Computation of Eigenvalues of the Anharmonic Coulombic Potential, Journal of Mathematical Chemistry, DOI 10.1007/s10910-017-0801-5 (B.Sc work)

b) Articles submitted to peer-reviewed journals

1) De Souza, D.C, Craig, M., **Cassidy, T**., Li,J.,0 Nekka, F., Humphries, A.R., Transit and lifespan in neutrophil production: implications for drug intervention, Journal of Pharmacokinetics and Pharmacodynamics, JOPA-D-17-00062. Submitted 05/22/2017. (Ph.D Work)

d) Non-peer-reviewed contributions

1) **Cassidy, T.,***, Humphries, A.R., and Mackey, M.C, Mathematical Modelling of Cyclic Neutropenia, CAMBAM Seminar (National Oral Presentation), 2017 (M.Sc work)

2) **Cassidy, T.,***, Humphries, A.R., and Mackey, M.C, Understanding, Treating and Avoiding Hematological Disease: Better Medicine Through Mathematics, SIAM Life Sciences Meeting 2016 (International Oral Presentation), 2016 (M.Sc Work)

3) **Cassidy, T.,***, Humphries, A.R., and Mackey, M.C, Mathematical Modelling of Cyclic Neutropenia, SIAM General Meeting 2016 (International Poster), 2016 (M.Sc work)

4) **Cassidy, T.,**, Gaudreau, P., and Safouhi, H., The Use of the DESCM to Produce Numerical Solutions to the Schrödinger Equation (National Oral Presentation), PIMS Young Researchers Conference, 2015 (B.Sc work)

5) **Cassidy,T.,*** and Safouhi, H. The Importance of Delays in a Mathematical Model of Cyclical Neutropenia (Institutional Oral Presentation), Apprentis Chercheurs- University of Alberta, 2015 (B.Sc work)

6) **Cassidy, T.,**, Gaudreau, P., and Safouhi, H., Efficient Computation of Schrödinger Energy Eigenvalues for Potentials having nth Order Singularities (Technical Report), 2015, (B.Sc work)

f) Contributions resulting from your participation in industrially relevant RD activities

1) **Cassidy,T.,***, Rieger, T. and Baraldi, R., Modelling Lipoprotein Dynamics during PCSK-9 Inhibition, Pfizer Internal Medicine Research Unit Quantitative Research Group Seminar (Institutional Oral Presentation and technical report), 2017

II Most significant contributions to research and development

1) During my undergraduate, I worked as a research assistant in numerical analysis during two summers. I performed asymptotic analysis of solutions to the Schrödinger equation with a potential involving singularities of arbitrary order. I constructed an adaptation to the Sinc collocation method (SCM) that convergences exponentially to the energy eigenvalues of the potential. I wrote MATLAB code implementing this numerical method. I introduced a numerical scaling technique that increases numerical stability of the algorithm and proved the existence of a maximal scaling factor that increases convergence speed. The combination of the scaling factor and the SCM is capable of finding arbitrarily high energy eigenvalues to machine precision. I co-wrote the article detailing the application of the algorithm to the Coulombic potential with Philippe Gaudreau as well as a technical report detailing the general case. The resulting article was published in the *Journal of Mathematical Chemistry* in 2017.

2) During my M.Sc, I utilized the delay differential equation model for neutrophil production presented by Craig et al. (Craig 2016) to model a dynamical haematological disease, cyclic neutropenia. I identified a Hopf-bifurcation in the model that reproduces the quantitative behaviour of the disease. Translating the position of the Hopf bifurcation to mechanistic changes confirms one of the two accepted explanation for the origins of cyclic neutropenia. Typical data from patients with cyclic neutropenia is sparse in time, highly oscillatory and therefore ill-suited to typical parameter fitting routines. I utilized Lomb

periodograms and sparse data analysis techniques to extract useful details from the data. I defined an error functional and parameter fitting technique that reproduces the defining characteristics of cyclic neutropenia independently of data quality. Utilizing the parameter fitting routine reproduces the dynamical behaviour of the disease and provides a mathematical model of the disease. I incorporated the standard treatment technique into the model. Successfully reproducing the impact of treatment raised possible avenues of further experimental work to optimize treatment strategies.

3) During a summer internship at Pfizer Inc. I extended a mechanistic model of circulating lipoprotein dynamics to include liver production and internalization of blood lipoproteins and triglycerides. The extension of the model included modelling the production of lipoprotein receptors on the liver and the receptor antagonist. This model was capable of reproducing healthy dynamics and pathologies resulting from mechanistic defects, including familial cholesterolaemia. Finally, we explicitly modelled a monoclonal antibody and statin treatment to understand the mechanism leading to their synergistic function and impact on familial cholesteroalaemia. The model's predictions agreed with published clinical trials.

Part III Applicant's statement

Research experience

During my B.Sc, I performed research in numerical analysis and learned to analyse solutions to differential equations via their asymptotic behaviour. This work led to multiple presentations in English and French and a publication in the *Journal of Mathematical Chemistry*.

My senior year project introduced me to delay differential equations and the theory regarding their stability by studying the importance of delays in a mathematical model of hematopoiesis. I attended two summer schools in mathematical biology where I learned to apply mathematical methods to biological problems.

My graduate research has involved sparse data analysis techniques, analytic and numerical methods for dynamical systems for infinite dimensional systems and mechanistic modelling of the immune system using delay differential equations. During a research internship at Pfizer, I developed a physiology based model of a monoclonal antibody. The model reproduced published antibody mono-and combination therapy data. I performed global sensitivity analysis to understand interpatient treatment response variability.

Relevant activities

Teaching: I was the teaching assistant for *Calcul élémentaire I* (2013), *Calcul élémentaire* (2013,2014), *Calcul élémentaire* II (2013,2014), *Algebre linéaire* I (2012,2013,2014) and *Statistiques* I (2012) at the University of Alberta. These tutorials were given in French. At McGill, I was the teaching assistant for Calculus for Management and Calculus II. My responsibilities include preparing and leading tutorial sessions, giving office hours and marking exams and assignments.

Organizational: I organized a series of undergraduate research seminars at the University of Alberta-Campus Saint Jean. Undergraduate researchers presented their work to a multi-disciplinary audience during lunch. The seminar series included professional development presentations and social activities to promote interdisciplinary communication.

At McGill, I organize a Montreal wide student's only computational biology seminar. The seminar is geared towards a scientific audience and involves presentations from a variety of quantitative biology sub-fields. We host weekly research presentations and social events.

Volunteer: I was elected to the McGill mathematics graduate student government (2017). I was a governor of the Francophone Sport Association of Alberta (2012-2014). I was a *Chef de Mission* at the provincial francophone games (2012-2014) and an track and field coach at the Canadian Francophone games (2014,2017). I organized training sessions and seasonal training plans for blind athletes through Alberta Sport and Recreation for the Blind (2013-2015). I was a member of the Canadian Ski Patrol(2014-2015).