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 | 2016/09/30 |

| Type of Award | Reference No. |
|---|---|
| PGS D | 396157246 |

| 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<br>Montreal, QC<br>CANADA H2M 1S2 | 11 Reighley Close<br>Red Deer, AB<br>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 — Indicate date of landing as stated on official immigration document

[ ] Other — 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.

Version française disponible

Canada

**PROTECTED B WHEN COMPLETED**

**Not Completed**

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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 | 4 / 2017 |

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|---|---|---|---|
| Cassidy | Tyler | TT | 439027 |

### 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) |
|---|---|---|---|
| Teaching Assistant - Part Time<br>Teaching assistant for calculus for management students | McGill University<br>Mathematics and Statistics | Dr. Sidney Trudeau | 9/2016 - 12/2016 |
| Research Assistant - Full Time<br>NSERC USRA research assistant | University of Alberta<br>Mathematics and Statistics | Dr. Hassan Safouhi | 5/2015 - 9/2015 |
| Research Assistant - Full Time<br>NSERC USRA research assistant | University of Alberta<br>Mathematics and Statistics | Dr. Hassan Safouhi | 5/2014 - 9/2014 |
| Teaching Assistant - Part Time<br>Teaching assistant for Calculus I,II and linear algebra I courses. | University of Alberta<br>Campus Saint-Jean | Dr. Sarah Pelleteir | 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 | 2017/01 |

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

Title of proposed research
Mathematical Modelling of the Immune System

List ten (10) key words that describe your proposed research.
Mathematical Modelling, Mathematical Physiology, Mathematical Biology, Dynamical Systems,

**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 and Michael Mackey |

Are any of your proposed programs of study:

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

16 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.**

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

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

☒ 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    ☒ 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

Natural Sciences and Engineering Research Council of Canada
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| PGS D | **Valid** 439027 | Cassidy, Tyler TT |

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

| Name of Award | Value (CDN$) | Level<br>Institutional, Provincial, National, International | Type<br>Academic, Research, Leadership, Communication | Location of tenure | Period held (yyyy/mm - yyyy/mm) |
|---|---|---|---|---|---|
| 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 | Institutional | Research | McGill University | 2016/09 - 2017/09 |
| James Lougheed Award of | 15,000 | Provincial | Research | McGill University | 2015/09 - 2016/09 |
| Graduate Excellence Fellowship | 3,500 | Institutional | Academic | 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 |
| Bourse Roger Mahé | 2,500 | Provincial | Academic | University of Alberta | 2012/09 - 2013/09 |
| Academic Excellence | 3,000 | Institutional | Academic | University of Alberta | 2011/09 - 2012/09 |

| Type of Award | Personal identification no.(PIN) | Family name, given name and initial(s) of applicant |
|---|---|---|
| PGS D | **Valid** 439027 | Cassidy, Tyler TT |

**THESIS COMPLETED OR IN PROGRESS**

| 1. Degree | Supervisor | Date degree requirements completed |
|---|---|---|
| Master's of Science | Antony Humphries and Michael Mackey | 04/2017 |

Title of thesis
Mathematical Modelling of Cyclical Neutropenia

| 2. Degree | Supervisor | Date degree requirements completed |
|---|---|---|
| | | |

Title of thesis

**SUMMARY OF THESIS MOST RECENTLY COMPLETED OR IN PROGRESS**

Do not reproduce abstract of thesis.

Cyclical neutropenia is a dynamical disease that results in oscillations in the number of circulating neutrophil cells. Mathematical models have attempted to model this behavior since the 1970s with varying degrees of success. One of the main difficulties in modelling the disease is the lack of useful data for patients suffering from the disease. Available data is typically very sparse and highly oscillatory and is thus ill-suited to typical parameter fitting routines. In this work, we define a novel error functional that is well suited to sparse and oscillatory data.
Starting from the neutrophil model presented by Craig, Humphries and Mackey in 2016, we apply our parameter fitting routine to model cyclical neutropenia. We produce a mathematical model that reproduces the qualitative characteristics of the disease. We also model G-CSF treatment of cyclical neutropenia. Finally, we produce a hypothesis for the origins of cyclical neutropenia in humans.

Mathematical Modelling of Immune Response to Bacterial Infection

The hematopoietic (blood production) system is comprised of cells with lifespans varying from 24 hours to 120 days. The hematopoietic system is constantly producing new blood cells and produces the human body's own weight in blood cells roughly every 10 years. Homeostasis is maintained via a complicated chain of positive and negative feedback loops that involve a legion of cytokines and hormones. Beyond maintaining homeostasis, the hematopoietic system must also respond to blood loss and fungal, viral, and bacterial infections.

Bacterial infections lead to interactions between the immune system and the hematopoietic system. These interactions are controlled by a number of complex mechanisms and via crosstalk relationships inherent to the immuno-hematological system. A critical cytokine, granulocyte colony stimulating factor (G-CSF), links the immune and hematopoietic systems and is amplified following infection. G-CSF induces increased white blood cell production and the release of mature white blood cells into the bloodstream [1, 2, 3]. After responding to the infection, the immune system decreases G-CSF production to signal the hematopoietic system to arrest emergency production of white blood cells and return blood populations to homeostasis.

Historically, most mathematical models of the hematopoietic system have not explicitly modelled the effect of G-CSF, instead using circulating white blood cells as a cipher for G-CSF concentration. This assumption is not valid when G-CSF is administered exogenously or is present at high levels during infection, when high populations of G-CSF and white blood cell occur concurrently. In [4], the authors model G-CSF concentration separately from white blood cell populations to account for exogenous administration following chemotherapy.

Experimental work has been primarily focused on pairwise interactions between the cytokines governing the immuno-hematologic interaction as the sheer number of cytokines involved renders large scale experiments intractable. Therefore, mathematical modelling is required to provide a systems level characterization of the immuno-hematological response.

My doctoral research will focus on mathematically modelling the immuno-hematopoietic response to bacterial infection. I will characterize the interaction between the bacterial infection and the resulting immune response by extending the delay differential equation model given in [4] to include white blood cell production driven by the resulting increased G-CSF production.

An accurate model for the bacterial infection will be constructed, including the intrinsic bacterial growth and white blood cell and T-cell instigated death. As G-CSF production is dependent on the type and severity of infection [5], I will introduce a variable G-CSF production term to the model and will use the bacterial model to drive G-CSF production and the resulting white blood cell production. By tying G-CSF production to bacterial load, we will understand how bacterial infections influence the production and release of white blood cells. This mathematical modelling project will combine techniques from dynamical systems and numerical analysis as well as parameter estimation techniques.

Combining the bacterial, G-CSF and white blood cell models will yield a realistic representation of the interaction between the immune and hematopoietic systems. The goal of my work is to provide a more accurate picture of the body's response to infection by elucidating the mechanisms and interactions that characterize the immuno-hematopoietic chain. Ultimately, this work will have a variety of applications, including improving our understanding of auto-immune diseases, like rheumatoid arthritis, and is critical to the refinement of current work at the experimental and clinical levels.

[1] Roberts, A. (2005) *Growth Factors* **23(1)**, 33–41.
[2] Riether, C., Schürch, C., and Ochsenbein, A. (2014) *Cell Death and Differentiation* **22**, 1–12.
[3] Panopoulos, A. and Watowich, S. (2008) *Cyokine* **42(3)**, 277–288.
[4] Craig, M., Humphries, A., and Mackey, M. (2016) *Bulletin of Mathematical Biology*.
[5] Kawakami, M., Tsutsumi, H., Kumakawa, T., Hirai, M., Kurosawa, S., Mori, M., and Fukushima, M. (1990) *Blood* **76(10)**, 1962–1964.

**I Contributions to research and development**

**b) Articles submitted to peer-reviewed journals**

1)**Tyler Cassidy**, Philippe Gaudreau and Hassan Safouhi, On the Computation of Eigenvalues of the Anharmonic Coulombic Potential (2016), Journal of Mathematical Chemistry, JOMC-D-16-00316 (B.Sc work)

**d) Non-peer-reviewed contributions**

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

2) **Tyler Cassidy***, Antony R. Humphries and Michael C. Mackey, Mathematical Modelling of Cyclical Neutropenia, SIAM General Meeting 2016 ( International Poster),2016 (M.Sc work)

3) **Tyler Cassidy***, Antony R. Humphries and Michael C. Mackey, Mathematical Modelling of Cyclical Neutropenia, PIMS Young Researchers Conference (National Oral Presentation), 2016 (M.Sc work)

4) **Tyler Cassidy***, Philippe Gaudreau and Hassan Safouhi, 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) **Tyler Cassidy*** and Hassan Safouhi, The Importance of Delays in a Mathematical Model of Cyclical Neutropenia (Institutional Oral Presentation), Apprentis Chercheurs- University of Alberta, 2015 (B.Sc work)

6) **Tyler Cassidy**,Philippe Gaudreau and Hassan Safouhi, Efficient Computation of Eigenvalues for Potentials having $n$ Order Singularities (Technical Report), 2015, (B.Sc work)

7) **Tyler Cassidy***, Philippe Gaudreau and Hassan Safouhi, The Use of the DESCM to Produce Numerical Solutions to the Schrödinger Equation (Provincial Oral Presentation), Undergraduate Research in Science Conference of Alberta, 2015 (B.Sc work)

8) **Tyler Cassidy***, Philippe Gaudreau and Hassan Safouhi, La résolution de l'équation de Schrödinger utilisant des fonctions SINC, (Institutional Oral Presentaion), Apprentis Chercheurs - University of Alberta, 2014, (B.Sc work)

**II Most significant contributions to research and development**

1) During my undergraduate, I worked as a research assistant in numerical analysis for two summers. During this work, I performed asymptotic analysis of solutions to the Schrödinger equation with a potential involving singularities of arbitrary order. I used the approximate wavefunction to construct an adaptation to the Sinc collocation method that results in exponential convergence to the energy eigenvalues of the potential. I wrote MATLAB code that implements the numerical method. The singularities present in the potential lead to numerical instability when calculating higher order energy eigenvalues. I introduced a numerical scaling and proved the existence of an interval where the scaling will increase convergence speed. This numerical scaling also increased stability of the algorithm, allowing for arbitrary energy level eigenvalues to be found 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 is currently under review.

2) During my master's work, I utilized the delay differential equation model for neutrophil production presented by Craig et al. (Craig 2016) to model a dynamical haematological disease, cyclical neutropenia. I utilized physiological explanations for the origins of cyclical neutropenia to find a Hopf-bifurcation in the model that corresponds to physiological explanations of the disease and reproduces the quantitative behaviour of the disease. Typical data from patients with cyclical neutropenia is sparse in time and highly oscillatory and therefore ill-suited to typical parameter fitting routines. I utilized Lomb periodograms and

sparse data analysis techniques to extract characterizing details of the data. I defined an error functional and parameter fitting routine that reproduces the defining characteristics of cyclical neutropenia without relying on high data quality. Utilizing the parameter fitting routine reproduces the dynamical behaviour of the disease and provides a mathematical model of the disease.

Following the successful modelling of the disease, I incorporated G-CSF treatment into the model. The necessary mathematical changes to the model to reproduce the impact of treatment are consistent with the current understanding of the disease, and also raise possible avenues of further experimental work.

**Part III Applicant's statement**

**Research experience**

During my bachelors degree, I performed research in numerical analysis during two summers. I learned Matlab, Maple and C++ coding languages as well as how to prepare scientific reports in LaTeX. I also learned to analyse solutions to differential equations via their asymptotic behavior. This work led to multiple poster and oral presentations in English and French where I learned the importance of tailoring presentation content to audience level. I presented to audiences varying from the general scientific public to numerical analysis experts.

My final year project during undergraduate introduced me to delay differential equations and the theory regarding their stability. This project led to oral presentations in French and in English. The project served as an introduction to my current area of interest, mathematical biology. I have attended two summer schools in mathematical biology where I have learned to apply mathematical methods to biological problems.

My graduate research experience has involved sparse data analysis techniques, dynamical systems for infinite dimensional systems and delay differential equations.

**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. My responsibilities included preparing and leading tutorial sessions, giving office hours and marking exams and assignments. At McGill, I am the teaching assistant for Calculus for Management, with the same responsibilities to a class of over 240 students.

**Organizational**: I organized a series of undergraduate research summer seminars at the University of Alberta-Campus Saint Jean during my final summer of research. I obtained funding for weekly lunches and organized to have undergraduate researchers present their work to a multi-disciplinary audience during lunch. The seminar series also included professional development presentations and social activities to promote interdisciplinary communication.

At McGill, I co-organized a Montreal wide student's only mathematical biology seminar. The seminar is geared towards a scientific audience, and is chalk talk format. We obtained funding to host social events as well as weekly informal research presentation. We will organize professional development workshops throughout the summer.

**Volunteer**: I was elected to the board of governors for the Francophone Sport Association of Alberta from 2012 to 2014. During my tenure on the board, we started a recreational sports league for francophone seniors and re-configured the provincial games. I volunteered as a *Chef de Mission* at the provincial games from 2012-2014 as well as an assistant track and field coach at the Canadian Francophone games (2014,2017). In Edmonton, I volunteered with Alberta Sport and Recreation for the Blind. I organized training sessions and seasonal training plans for blind athletes. This included tracking the training and being an athletes guide-runner I also organized nutritionist and motivational speakers for the training group. I was a member of the Canadian Ski Patrol from 2014-2015.