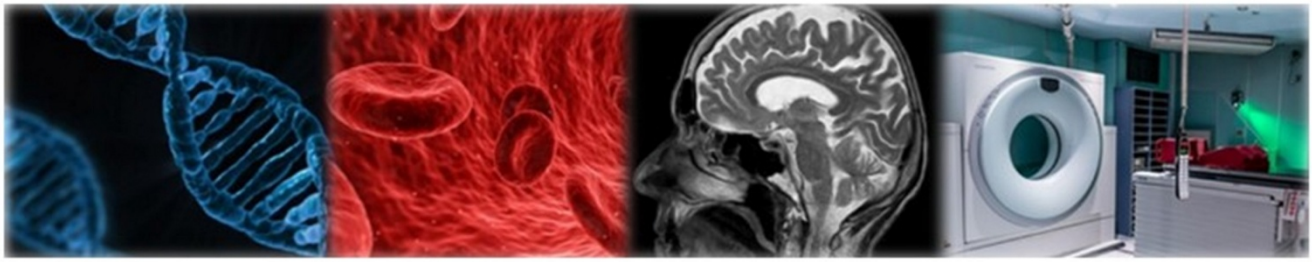
Division of Physics in Medicine and Biology
Canadian Association of Physicists



In this issue of DPMB Newsletter

Website: http://dpmb.physics.umanitoba.ca/
Contact Email: flin@physics.umanitoba.ca

Greetings from the Chair

Dear members and friends of DPMB,

On behalf of the 2018-2019 executive team of DPMB, I'd like to send our warmest greetings and welcome to the members and friends of our division. In the past year (2017-2018), there have been some very exciting happenings for our division including the birth of the first division external website (http://dpmb.physics.umanitoba.ca/), the creation of the first division logo *(see it in the first page of this newsletter and also in the front page of the division external website),* and a very rich DPMB program in the 2018 CAP Congress at Dalhousie University *(see the summary by the division Past Chair Luc Beaulieu along with more details in the later sections of this newsletter and also in the division external website).* I want to thank the 2017-2018 DPMB executive members, particularly, Luc Beaulieu for his excellent leadership in the past year, who now moved to the DPMB Past Chair; Christopher Bergevin for his leadership, hard work and many great initiatives during his term with the DPMB executive team; and Melanie Campbell for her great inputs to many DPMB matters. Special thanks also go to the past executives of DPMB, the local colleagues at Dalhousie University and all the DPMB participants at the 2018 CAP Congress. Of course, the support from the CAP and all the members and friends of DPMB is invaluable. So a big **Thank You** to all of you!

For 2018-2019, I'd like to first welcome Emily Heath from Carleton as the new DPMB Vice Chair. We look forward to the continued growth of DPMB, enhancing the excellent traditions and making progress toward implementing some exciting new initiatives. Toward this direction, we have started to plan for the DPMB program in the 2019 CAP Congress at Simon Fraser University, following up on existing collaborations and partnerships and initiating new ones. The idea of starting a DPMB newsletter resulted from the very productive discussion during the DPMB Get-Together session at the 2018 CAP Congress. In this very first issue, in addition to the information of the DPMB events at the 2018 CAP Congress, you will also find the stories of some featured DPMB members, upcoming events and funding opportunities. Your feedback will be highly appreciated that will help us develop future newsletters. With your continued support to DPMB, I am confident that our division will continue to play critical roles in promoting the research and education in medical physics and biophysics in Canada. I feel privileged to be a part of this community and to contribute at my role.

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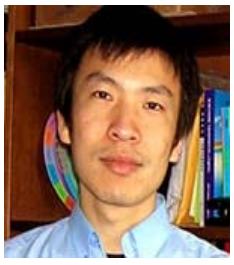
Francis Lin, DPMB Chair

DPMB Executives, 2018-19



Chair
Francis Lin
Univ. of Manitoba

Vice Chair
Emily Heath
Carleton Univ.

Treasurer
Melanie Campbell
Univ. of Waterloo

Past Chair
Luc Beaulieu
Université Laval

Message from the Past Chair

The 2018 CAP annual meeting was the home of a few firsts for the division. We saw the first edition of a DPMB 101 session to open the meeting. Based on a proposal by former division Chair Christopher Bergevin, these are meant as introductory talks, accessible to any physicists, to promote concepts used in biophysics and medical physics. This year Chris discussed random walks and electrodiffusion while Philippe Després introduced us to computed tomography imaging, looking into the historical perspective, recent advances and an overview of where the field is going. Another first was the get-together event at the University Club (pub!), where numerous ideas to help further the standing and activities of the division were discussed over a beer. A few of these ideas look promising and will be further explored by the executives in planning the 2019 meeting in Simon Fraser.

Apart from the DPMB 101 session, the division organized 11 more sessions which saw 16 invited speakers and 27 contributed talks, many of which were students, presenting the latest work in the field. We had two excellent symposiums, one on translational research in medical physics and one on soft matter. Both were of very high level symposiums and received praise by those attending. We further had a very well attended and extremely informative plenary session by Prof. Anne Martel (Sunnybrook Research Institute and Department of Medical Biophysics at the University of Toronto) on Machine Learning and Deep Learning. Prof Martel has been involved in that field for over 20 years and was able to present strengths and weaknesses of these methods for medical image analysis and predictive power of image textures and features.

We certainly want to underline the winner of this year's competition for best student presentations. Kyla Smith from the University of Manitoba won 1st place for her wonderful oral presentation. Michael Hupman from Dalhousie University and Yanitza Trosel of Memorial University of Newfoundland won 1st and 2nd place, respectively, for their poster presentations. The details of each winner and his/her presentation can be found in the later section of this newsletter.

Overall a big thank you and congratulations to the local DPMB team in Dalhousie: Andrew Rutenberg, Laurent Kreplak, Timmothy Bardouille, James Robar, Steven Beyea, Keven Hewitt, and all of their students who helped during the meeting.

In closing, I would like to highlight the work done by Christopher Bergevin over the past three years. Chris is now leaving the executive but he is still very much engaged in helping develop the division activities. As I moved to Past Chair, Francis Lin (University of Manitoba) took the lead role over the next year and Melanie Campbell (University of Waterloo) is staying with us as treasurer. We welcome Emily Heath from Carleton as the new Vice Chair of the division.

Luc Beaulieu, **DPMB Past Chair**

DPMB at the 2018 CAP Congress

DPMB events

June 11, Monday

M1-6: Biophysics, Microscopy and Diseases (11:15am-12:30pm)
Chair: Laurent Kreplak
Location: SUB 303

M2-4: DPMB "101" (1:30-3pm)
Chair: Luc Beaulieu and Francis Lin
Location: SUB 224

M3-1: Stochastic Biology (4:15-6pm)
Chair: Andrew Rutenberg
Location: SUB 302

June 12, Tuesday

T1-6: Topics in Medical Physics and Biophysics (8-9am)
Chair: Luc Beaulieu
Location: SUB 302

T2-4: Medical Imaging 1 (11:30am-12:30pm)
Chair: Philippe Després
Location: McCain 2016

DPMB Business Meeting (12:30-1:30pm)
Chair: Luc Beaulieu
Location: McCain 2017

T4-7: Physics of Biosensing (3:30-4:45pm)
Chair: Francis Lin
Location: SUB 224

DPMB Poster session (6-8pm)
Location: SUB McInnes Hall

June 13, Wednesday

W1-4: Translational Research in Medical Physics Symposium (joint with DAPI) (8-9:45am)
Chair: Tim Bardouille and Luc Beaulieu
Location: SUB 303

W2-5: COMP Special Session (11:30am-12:30pm)
Chair: Luc Beaulieu
Location: SUB 307

W3-4: Soft Matter and Molecular Dynamics (joint with DCMMP) (1:30-3pm)
Chair: Francis Lin
Location: SUB 302

W4-4: DPMB Get Together (3:30-4:45pm)
Location: University Club pub (http://daluclub.ca/the-pub/)

Plenary Talk by Dr. Anne Martel (5:00-5:45pm)
Location: McCain Ondaatji Hall

June 14, Thursday

R1-2: Medical Imaging 2 (8-9am)
Chair: Magdalena Bazalova-Carter
Location: McCain 2016

R2-4: Theoretical and Computational Biophysics (11:30am-12:30pm)
Chair: Christopher Bergevin
Location: SUB 224

R3-5: Multimodal and Nonlinear Imaging in Biological Systems (1:30-3pm)
Chair: Laurent Kreplak
Location: Dunn 101

CAP Best Student Presentations Final Competition (15:30-17:30)
Location: McCain Ondaatji Hall

Student Awards Ceremony (18:15-19:00)
Location: McCain Ondaatji Hall

DPMB at the 2018 CAP Congress

DPMB invited speakers

Dr. Anne Martel (plenary speaker)
Sunnybrook Research Institute
Title of the talk: *Machine Learning for Medical Image Analysis*

Dr. Grace Parraga
Western University
Title of the talk: *Seeing is Believing: Imaging Physics for a Better Asthma Outcomes*

Dr. Philippe Després
Université Laval; Researcher, CRCHU de Québec
Title of the talk: *The past, present and future of X-ray Computed Tomography*

Dr. Francois Legare
Institut National de la Recherche Scientifique, Centre Energie, Materiaux, et Telecommunications
Titel of the talk: *Interferometric Second Harmonic Generation Microscopy and applications.*

Dr. Drew Marquardt (jointy invited by DPMB and DCMMP)
University of Windsor
Title of the talk: *Physical properties of model membranes: From membrane asymmetry to vitamin E*

Dr. Magdalena Bazalova Carter
University of Victoria
Title of the talk: *CT imaging in small animal research: Have we reached the limit?*

Dr. Steven D. Beyea
Dalhousie University
Title of the talk: *Automated Optimization of Dynamic MRI Data Acquisition and Reconstruction Parameters using Image Quality Metrics*

Dr. Tim Bardouille
Dalhousie University
Title of the talk: *Machine Learning Applications in Functional Neuroimaging Data*

Dr. Victor Malkov (COMP Speaker)
Carleton University
Title of the talk: Monte Carlo simulations for magnetic resonance guided radiation therapy dosimetry

Dr. Michelle Svatos
Celestial Medical; University of Wisconsin Madison
Title of the talk: *Creating Research that Translates to Widespread Clinical Use*

Dr. Leyla Soleymani
McMaster University
Title of the talk: *Materials innovations for enhancing the limit-of-detection of biosensors*

Dr. Kevin Hewitt
Dalhousie University
Title of the talk: *First demonstration of surface-enhanced stimulated Raman spectroscopy using cw sources*

Dr. Andreas Hilfinger
University of Toronto
Title of the talk: *Constraining complex stochastic systems in biology*

Dr. Christopher Bergevin
York University
Title of the talk: *Random walkers & electrodiffusion: A primer*

Dr. Mads Kaern
Ottawa Institute of Systems Biology
Title of the talk: *Spontaneous development of drug resistance caused by a common gene regulatory network*

Dr. Claudiu Gradinaru
University of Toronto
Title of the talk: *Scaling Laws and Global Dimensions of Disordered Proteins: Single-molecule Data and Polymer Physics Theory*

Spencer Farrell
Dalhousie University
Title of the talk: *Probing the network structure of health deficits in human aging*

DPMB at the 2018 CAP Congress

DPMB student presentation winners

DPMB Division Student Oral Presentation Winner

1st Place: Kyla Smith, University of Manitoba
Title: Laplacian-Inspired Design of a Highly-Homogeneous, RF Shielded Magnet for Low-Field TRASE MRI

CAP Overall Student Oral Presentation Honourable Mention

Kyla Smith, University of Manitoba
Title: Laplacian-Inspired Design of a Highly-Homogeneous, RF Shielded Magnet for Low-Field TRASE MRI

DPMB Division Student Poster Presentation Winners

1st Place: Michael Hupman, Dalhousie University
Title: Response of an Organic Photodiode to a Kilovoltage Photon Beam under Different Bias Conditions

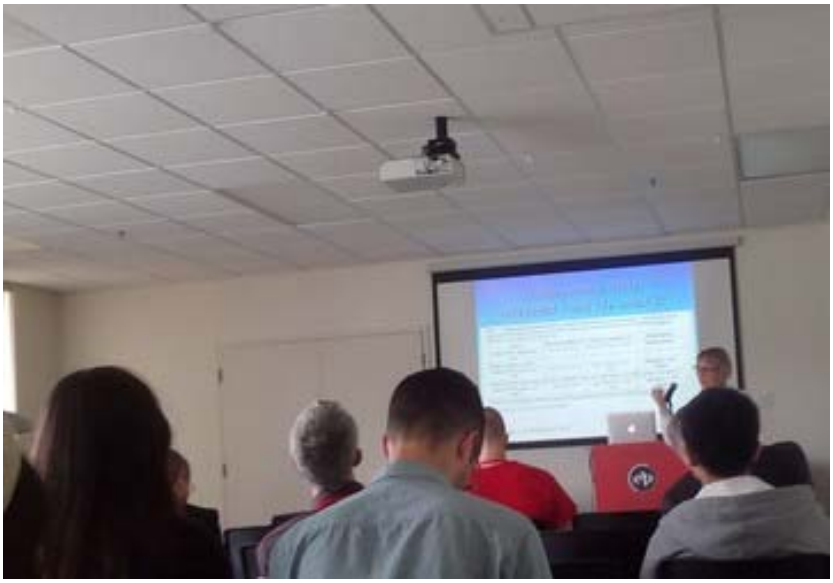
2nd Place: Yanitza Trosel, Memorial University of Newfoundland
Title: Effect of diffusion of cell lysate in a model polymer, via pulse gradient NMR

CAP Overall Student Poster Presentation Honourable Mention

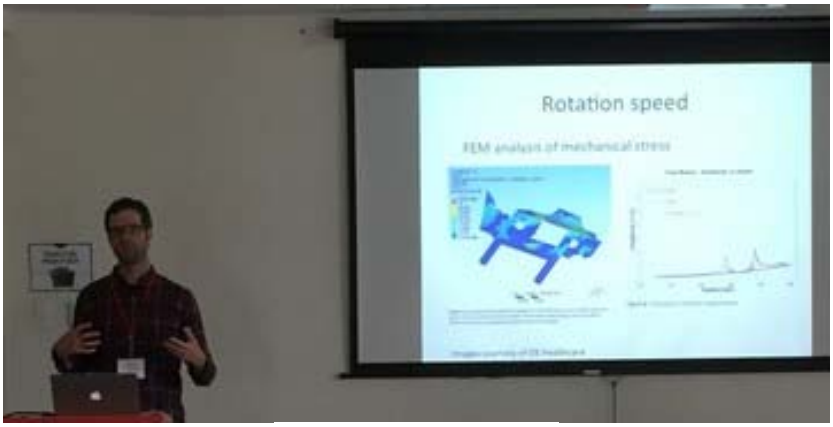
Michael Hupman, Dalhousie University
Title: Response of an Organic Photodiode to a Kilovoltage Photon Beam under Different Bias Conditions

DPMB at the 2018 CAP Congress

Photo gallery

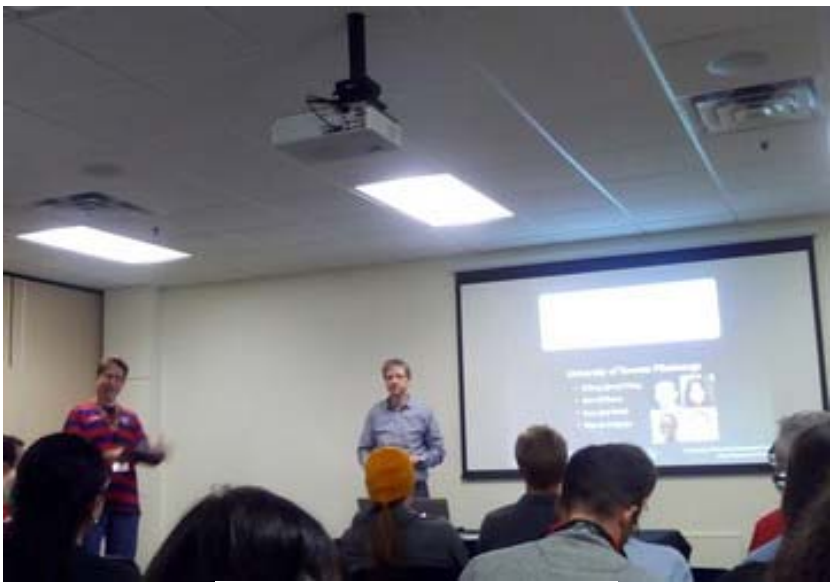


Biophysics, microscopy and diseases session



DPMB-101 session

DPMB-101 session



Stochastic biology session

Translational medical physics research symposium

COMP special session

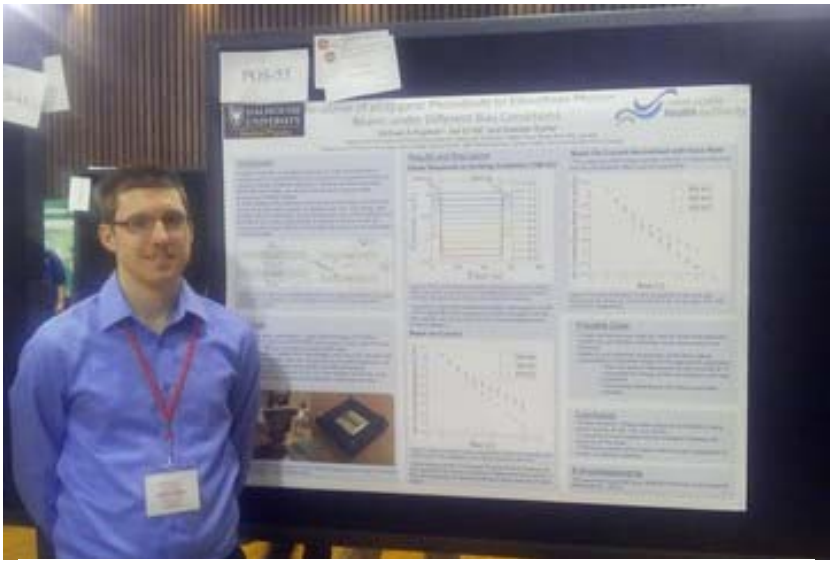
DPMB get-together at the University Club

DPMB sponsored plenary talk by Dr. Anne Martel

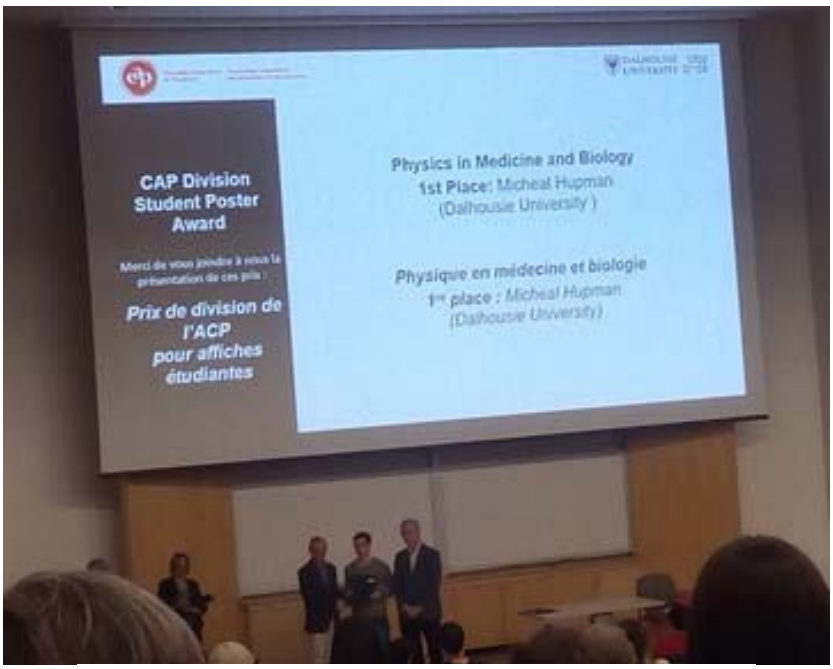
Theoretical and computational biophysics session

Bioimaging session

After the last DPMB session



Michael Hupman (DPMB poster competition winner)



Michael Hupman receiving the poster award

Kyla Smith receiving the oral presentation award

Featured DPMB members

Dr. James Gräfe, PhD, MCCPM

Assistant Professor
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james.grafe@ryerson.ca
https://www.physics.ryerson.ca/people/faculty/grafe

Background

I did a BSc is Physics at the University of Guelph. A second year course on radiation in the environment got me interested in real world applications of physics so I continued on and did a PhD in Medical Physics and Applied Radiation Sciences at McMaster University. I had the time of my life at McMaster using their proton beamlines, neutron sources, gamma sources, and nuclear reactor. After my PhD, I developed a sense of adventure and traded Ontario for the mountains for a few years and trained as a Radiation Oncology Physics resident at the University of Calgary Tom Baker Cancer Centre in their CAMPEP accredited program and worked for a year as a clinical medical physicist. I became certified as a member of the CCPM in the spring of 2015 and was hired as an Assistant Professor in the Department of Physics at Ryerson University. I felt a connection to Ryerson since it was where both my dad and uncle completed engineering degrees when it was a polytechnic institute.

Above photo: Image of Dr. Gräfe setting up equipment for spectroscopic measurements on a S250 Mevion proton therapy unit. We are investigating if we can detect gadolinium during proton therapy for tumor detection. A senior physicist once told me that the best experiments are the ones that use a bit of duct tape to piece them together. I've never forgot that!

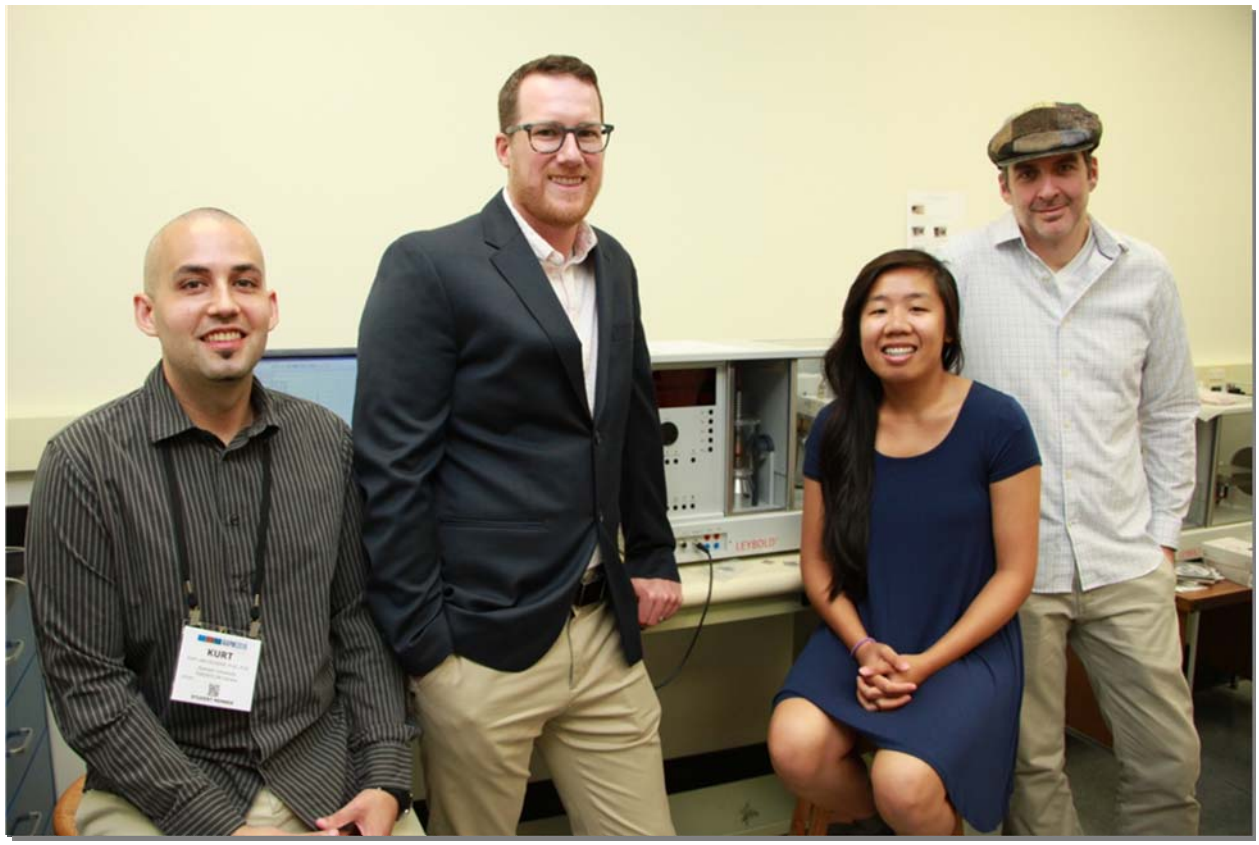
Research Description

The research conducted in my lab borders on two streams: applied nuclear medicine and radiation therapy. My NSERC DG program titled 'Utilizing the characteristic atomic and nuclear signatures of rare earth metals for detection and quantification' focuses on using the atomic or nuclear signals from rare-earth elements for either tumor detection or for detection of residual amounts of rare-earth metals from administration of certain pharmaceutical drugs. In my applied nuclear medicine work we are looking to determine the link between trace metal concentration and biological effect. In my work in radiation therapy I am currently investigating whether we can verify tumor position through nuclear and atomic interactions with gadolinium during proton therapy. This is sort of a spin-off to prompt gamma-ray imaging that has become popular in recent years. I am currently supervising 4 PhD students and 1 MSc student. I am also starting a

new project in the fall that I am very excited about on dose enhancement and sensitization. We are aiming to tackle the pancreatic cancer problem, a disease that drastically needs improvement in treatment methods and one that recently took my grandmother. We will be applying ultrasound microbubbles, gold nanoparticles and radiation in a combined therapy approach to a pancreatic cancer cell line. My PhD student will also work on modelling this through Monte Carlo simulation.

Collaborative potential

It is great to be a new member of the CAP DPMB community and I am always open to new collaborations with researchers. I enjoy both experimental and simulation studies. I am currently collaborating with Dr. Dave Howarth, a pathologist at Mt. Sinai on bone research, and Dr. Rao Khan at Washington University School of Medicine on dual energy IMRT. I am also looking for clinicians interested in lanthanum retention in bone, an element in which we have developed an i*n vivo* X-ray fluorescence system that can measure parts per million levels. In addition, aspiring graduate students are welcome to contact me at any time to discuss potential MSc and PhD projects.



Gräfe lab group photo (left to right): Kurt Van Delinder (PhD student), Dr. James Gräfe, Joanna Nguyen (PhD Candidate), Daniel Crawford (MSc student). Photo Credit: Graham Pearson

Featured DPMB members

Stefan Wallin, Ph.D.

Assistant Professor
Department of Physics and Physical Oceanography, Memorial University
swallin@mun.ca
https://www.physics.mun.ca/~stefan/

Biography

Stefan Wallin received his PhD degree in Theoretical Physics in 2003 from Lund University. Thereafter he held a postdoc position at the University of Toronto (2003-2005) and another at Harvard (2006-2008). From 2008-2015, he was an Assistant Professor at Lund University. He joined Memorial University of Newfoundland in 2015.

Simulating proteins with coarse-grained models and alternative sampling methods: folding, fold switching and conformational disorder

My research focuses on the development of methods for biomolecular simulations and their application to biologically relevant systems. To this end, I use techniques from various fields of physics, especially computational and statistical physics. In particular, my focus is on the folding, interaction and evolution of proteins. While much progress has been made towards an understanding of protein folding through advances in both experimental and computational techniques, there are fundamental questions that remain unresolved (see e.g. Dill and MacCallum, Science 338 1042, 2012).

Since joining Memorial University in 2015, I have worked on one of these unresolved questions, namely how variations in the amino acid sequence impact the folding process. I have also investigated the biophysical properties of so-called “metamorphic” proteins, which are proteins that exhibit a remarkable ability to reversibly switch between alternative native folds. In terms of method development, I have worked on the problem of how to interpret low-resolution electron density maps from cryogenic electron microscopy. The method we developed was used to characterize the structure of high-density lipoproteins.

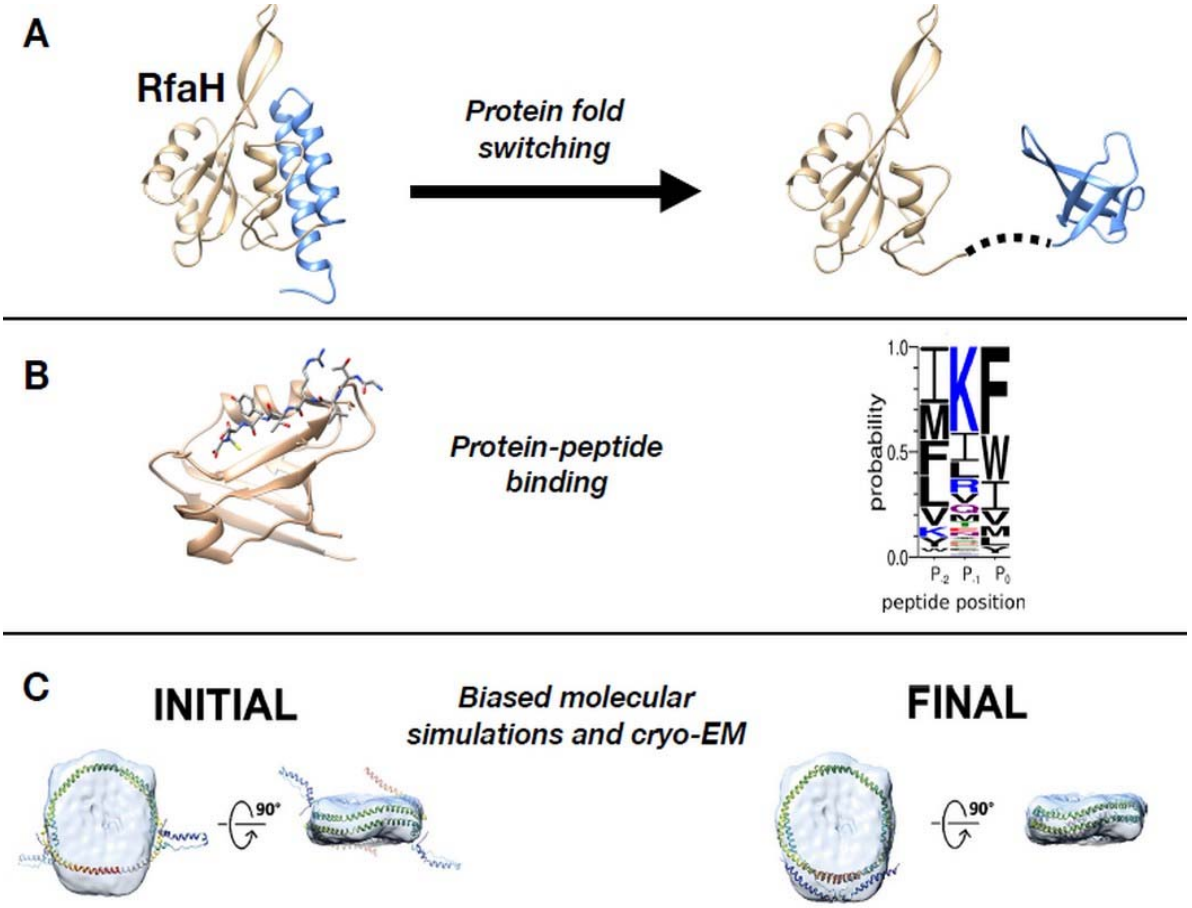
Proteins are generally challenging targets for molecular simulation methods because of their relatively large size, conformationally specific behavior and range of timescales involved. Typical folding times of small, single domain proteins alone span microseconds to seconds. To make things more difficult (as well as more exciting), current biophysical experiments on proteins increasingly emphasize the role of large-scale conformational transitions for how functions are carried out, such as the coupled folding-binding processes of intrinsically disordered proteins.

A substantial part of my research is therefore devoted to the computational challenges of biomolecular simulations. I tackle these in two ways. On the one hand, by developing models at various levels of resolution, acknowledging that coarse-grained models sometimes have limited transferability across different systems due to the diverse behaviors of proteins. On the other hand, by developing alternative methods for conformational sampling. I focus in particular on advanced Monte Carlo-based techniques, which can speed up the calculation of equilibrium properties of biological molecules and systems, such as folding free energy surfaces, by circumventing the inherent time-dependence of traditional molecular dynamics simulations. Recently, I have developed a generalized-ensemble method for efficient exploration of the equilibrium behavior of

multiple amino acid sequences, which can be used to study sequence effects in either binding or folding.

What are "metamorphic" proteins?

An interesting new development in the protein folding field has been the discovery of an increasing number of natural and engineered proteins that are able to reversibly switch between different three-dimensional structures. Because these transitions involve major changes in secondary structure content, hydrophobic core packing and overall shape, these proteins have been termed "metamorphic" (Murzin A G, Science 320, 1725-1726 2008). Their behavior is entirely in contrast to the traditional view of proteins, which holds that proteins have a unique native structure. Fold switching is typically triggered by an external signal such as ligand binding, a change of pH or – as in evolution – by mutational changes. We are interested in understanding the biophysical properties of these large-scale conformational transitions: What factors control the (delicate) free energy balance between different folded states? Why is fold switch so abrupt? How can different types of mutational changes drive proteins to switch folds? An example of a partial but dramatic fold switch is given by the Escherichia coli protein RfaH (see figure). The C terminal domain of this protein transitions from an α-helix bundle to a β-barrel, triggered by the separation of this domain from the rest of the protein. A graduate student in my group, Adekunle Aina, investigated conformational and stability properties of this protein. From simulations of the various



Three current areas of research. *(A) The C-terminal domain (blue) of the protein RfaH undergoes a spontaneous and reversible fold switch from an α-helical bundle to a β-barrel. (B) The peptide binding specificity of the protein GRIP1 PDZ7 determined using our computational peptide screening algorithm. (C) A model 3D-structure of discoidal high-density lipoprotein (HDL) obtained from low-resolution cryo-EM data and biased molecular simulations.*

structural forms of RfaH, including fragments and the full-length protein, Adekunle found a markedly reduced stability of the fold-switching region of RfaH. In particular, this suggests a way to search for as-of-yet undiscovered metamorphic proteins based on structural information. In his MSc project, he also applied a coarse-grained model to systematically study the folding properties of sequences in the space "in between" different protein folds. In order to make this computationally possible, he developed and studied a novel simulation algorithm that allows the equilibrium behavior of multiple sequences to be determined in a single simulation trajectory.

Disordered protein and peptide-protein interactions

Another major interest in my group is so-called intrinsically disordered proteins (IDPs). These proteins are special in that they persist as a dynamic ensemble of interconverting conformations even under native conditions, and yet they are fully functional. Somewhat counterintuitively, IDPs are often involved in molecular recognition, i.e., making specific interactions with other biomolecules. In these situations, IDPs typically undergo a folding transition as they bind their target molecule. We have found, however, along with other computational groups, that IDPs can exhibit substantial structural heterogeneity even in their final bound complexes. This behavior has major implications for how IDPs realize specific interactions. It also has practical implications for binding free energies calculations, as conformational entropy can be an important factor to binding.

We have also developed an algorithm that characterizes the specificity of a given peptide-binding pocket through molecular simulations. The algorithm works such that sequences s can be generated according to a Boltzmann weight, i.e., $P(s) \propto \exp(-\Delta F(s)/RT)$ where ΔF is the binding free energy at temperature T. This way strongly binding peptide sequences are frequently generated while poor binders are supressed. Importantly, this allows the specificity of peptide-binding sites to be explored even as conformational entropy factors are taken into account. We are currently exploring the possibility of adapting our algorithm for the discovery of unknown peptide-binding sites on protein structures.

A computational method for interpreting data from cryo-electron microscopy

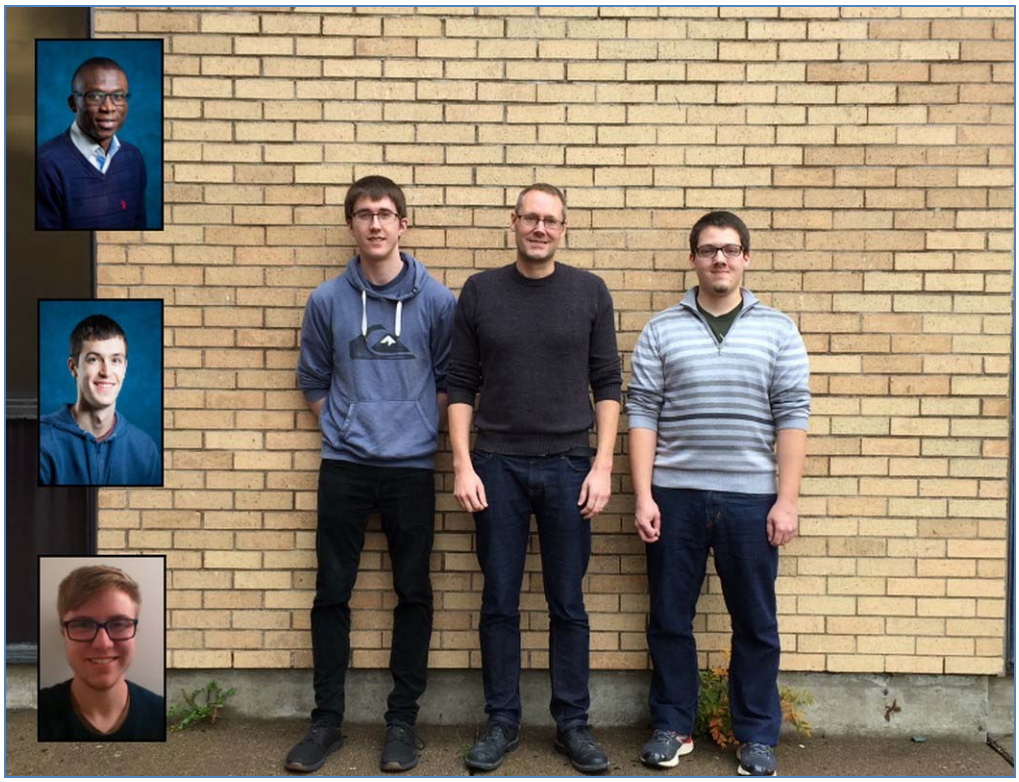
In a collaborative project with Karolinska Institute (Caroline Jegerschöld), and Lund University (Jens Lagerstedt), we developed a computational method for structural interpretation of data from cryogenic electron microscopy (cryo-EM). The determination of biomolecular structures has for a long time been dominated by X-ray crystallography and nuclear magnetic resonance spectroscopy. However, single-molecule cryo-EM is emerging as a rivalling technique (see Ewen Callaway Nature 525 2015). In this technique, biomolecular assemblies are flash-frozen in a thin film of vitreous ice and imaged at different angles. Many low-resolution images are combined into one or a few three-dimensional electron density maps, which must be interpreted through molecular modeling.

In this project, an undergraduate student in my group, Peter Gysberg, developed a method that combines our all-atom Monte Carlo framework for protein simulations with an auxiliary energy term that scores the correlation between experimental and calculated electron densities, thereby steering simulations toward structures that fit the underlying data. We applied this method to cryo-EM data on high-density lipoproteins (HDL), obtained from our collaborators. HDL is a blood plasma particle involved in lipid and cholesterol transport. Because its abundance in the blood is inversely correlated with the risk of cardiovascular disease, HDL is sometimes referred to as the "good" cholesterol. The large size and high conformational flexibility of HDL makes it challenging for structural studies and its structure is debated. By combining our simulation results with other data from in the literature, we recently reported new structural models for this particle (see figure).

Key publications:

1. Aina A, and Wallin S. Multisequence algorithm for coarse-grained biomolecular simulations: exploring the sequence-structure relationship of proteins. Journal of Chemical Physics 147 095102 (2017).
2. Staneva I, Huang Y, Liu Z, and Wallin S. Binding of two intrinsically disordered peptides to a multi-specific protein: A combined Monte Carlo and Molecular Dynamics study. PLoS Computational Biololy 8, e1002682 (2012).
3. Bhattacherjee A, and Wallin S. Exploring protein-peptide binding specificity through computational peptide screening. PLOS Computational Biology 9, e1003277 (2013).
4. Zhu L, Petrlova J, Gysbers P, Hebert H, Wallin S, Jegerschöld, C J and Lagerstedt J O. Structures of Apolipoprotein A-I in High Density Lipoprotein generated by Electron Microscopy and Biased Simulations. Biochem Biophys Acta — General Subjects 1861 2726-2738 (2017).

My group at Memorial University



From left to right: Nicholas Robichaud (summer, honors projects), Stefan Wallin, Aidan Tremblett (MSc). Insets from top to bottom (previous members): Adekunle Aina (MSc; now at UBC), Peter Gysbers (summer project; now at UBC), Daniel Trotter (summer, honours projects; now at UOttawa). Not shown: Ryan Wilkins (summer, honours projects; now at UOGuelph).

Future events

- **2019 Biophysical Society Meeting at Baltimore** (March 2-6)
  https://www.biophysics.org/2019meeting

- **2019 APS March Meeting at Boston** (March 4-8)
  https://www.aps.org/meetings/meeting.cfm?name=mar19

- **2019 Biophysical Society of Canada Annual Meeting at Toronto** (May 28-31)
  https://biophysicalsociety.ca/bsc-annual-meetings/

- **2019 CAP Congress at Simon Fraser University** (June 3-7)
  https://www.cap.ca/congress-conference/congress-2019/

Funding opportunities

- **BWF Collaborative Research Travel Grant**

  Deadline: Feb. 1, 2019

  The Collaborative Research Travel Grant (CRTG) program provides up to $15,000 in support for relatively unrestricted travel funds to academic scientists (faculty and postdocs) at U.S. or Canadian degree-granting institutions. Grants must be used for domestic or international travel to another lab to learn new research techniques or begin or continue a collaboration to address biomedical questions. All proposals must be cross-disciplinary. Applicants with a doctoral degree in the physical, mathematical, or engineering sciences working on a biological problem are encouraged to apply. Conversely, proposals from biological scientists who desire to collaborate with a physical scientist, mathematician, or engineer are also encouraged to apply.

  https://www.bwfund.org/grant-programs/biomedical-sciences/collaborative-research-travel-grants

Acknowledgements

https://www.bruker.com/ http://www.nikoninstruments.com/

BRUKER Nikon

https://www.mdpi.com/journal/micromachines

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