Doctoral Dissertation Defense Announcement

“Computational Modeling of Physiologic and Pathologic Systems”

Christopher E. Monti
Candidate for Doctor of Philosophy
Microbiology & Immunology
School of Graduate Studies
Medical College of Wisconsin

Committee in Charge:
Scott S. Terhune, PhD (Mentor)
Ranjan K. Dash, PhD (Co-Mentor)
Nathan A. Ledeboer, PhD
Amy Hudson, PhD
Joseph T. Barbieri, PhD (Committee Chairperson)

Date: Monday, April 1, 2024
Time: 11:00 AM (CST)
Defense Location: Bolger Auditorium

Zoom: https://mcw-edu.zoom.us/j/96029985598?pwd=ZjRVQzhtK1B5Vnl5ZzJKSWhzNWgzUT09
Meeting ID: 960 2998 5598 Passcode: qr4MdVMV
**Graduate Studies:**

Reading and Research

Doctoral Dissertation

Ethics & Integrity in Science

Research Ethics Discussion Series

Techniques in Molecular & Cell Biology

Foundations in Biomedical Science III

Immunology Journal Club

Microbiology & Immunology Seminar Course

Modeling & Simulation of Integrated Cellular Systems (audit)

Independent Study in Biomedical Engineering Topics in Mathematical Biology: Computational Virology
“Computational Modeling of Physiologic and Pathologic Systems”

Computational modeling is a tool that can be used to integrate extant knowledge about a system, discover emergent properties of a system, and develop hypotheses that would otherwise be obfuscated by a system’s complexity. In this dissertation, I apply computational modeling to two systems relevant to the translational field of transplant surgery and post-transplant care. Generally, this dissertation demonstrates the applicability of computational modeling to biological and clinical sciences.

The first system investigated is in vitro human cytomegalovirus (HCMV) infection. HCMV is a ubiquitous herpesvirus which can lead to pathologies ranging from retinitis to sepsis, particularly in immunosuppressed transplant patients. HCMV has a DNA-based genome and undergoes a 96-hour lytic replication cycle in diverse cell types. Post-transplant antivirals targeting viral DNA (vDNA) replication prevent lytic replication; however, their singular target is a risk for resistance and side-effects are often undesirable. A better understanding of the underlying mechanisms of the HCMV lifecycle outside the mechanisms targeted by extant antivirals is crucial for developing novel therapies to improve post-transplant care.

To this end, I developed an empiric vDNA replication model that drives a mechanistic model of virion assembly and egress (late lytic replication), which was fit to time-course measurements of two viral proteins and output viral titers measured at three multiplicities of infection (MOIs). These studies yielded two findings: 1) There is a range of MOIs leading to optimal vDNA replication and cell-free virus production and 2) Viral protein degradation rates increase with increasing vDNA. While these studies provided quantitative understanding of late
lytic replication, the data used for fitting were limited to fibroblast cells. To assess its generalizability, I applied the model to similar kinetic data obtained by infecting epithelial cells with HCMV generated from fibroblast (TB40Fb) and epithelial (TB40Epi) sources. Despite similar vDNA kinetic parameters, viral pp28 protein accumulation and output viral titers were higher in TB40Epi than in TB40Fb when infecting epithelial cells at comparable MOIs. This finding corresponds with a larger synthesis constant for pp28 in TB40Epi suggesting that viral source impacts replication efficiency.

The second system investigated is the pathophysiology of ischemia-reperfusion injury (IRI) occurring during liver transplant assessed by changes in the kinetics of biliary sodium fluorescein (SF) excretion. IRI is inevitable during liver transplant arising from ligation of major vessels. Qualitative guidelines to mitigate IRI exist; however, a mechanistic understanding of IRI pathophysiology is lacking, despite its contribution to transplant failure and paucity of donor organs. To investigate the effect of IRI on hepatic transplants, I developed a “liver-centric” model of SF clearance parameterized using in situ SF biliary excretion data from rats without IRI. I simulated IRI by altering relevant model parameters and found that the model was most sensitive to decreases in the activity of the MRP2 protein ($V_{\text{max,3, SF}}$), which is associated with transporting SF from hepatocytes into bile. To assess the effect of IRI on ex vivo machine perfusion (MP), a novel organ preservation technique, I fit the model to rat biliary SF excretion MP data with varying degrees of IRI. By fitting to individual biological replicates, I was able to show that all model parameters were similar across IRI conditions, except for
\( V_{\text{max,3.3F}} \), which showed a statistically significant decrease with 30 minutes of warm ischemia time (an IRI proxy).

In this dissertation, I applied a computational approach to two systems related to transplant surgery and post-surgical care. Whether it is the development of a new model (i.e., HCMV late lytic replication or liver-centric models) or application of an established model to new datasets (i.e., viral source differences or MP), this dissertation has demonstrated the versatility and predictive power of computational modeling.
March 2024
Christopher E. Monti
CURRICULUM VITAE
cmonti@mcw.edu

EDUCATION

<table>
<thead>
<tr>
<th>Degree</th>
<th>Institution</th>
<th>Honors</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.D.</td>
<td>Medical College of Wisconsin</td>
<td></td>
<td>June 2026</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(anticipated)</td>
</tr>
<tr>
<td>Ph.D.</td>
<td>Medical College of Wisconsin</td>
<td></td>
<td>April 2024</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(anticipated)</td>
</tr>
<tr>
<td>Bachelor of Science in</td>
<td>Duke University</td>
<td>Magna Cum Laude</td>
<td>June 2017</td>
</tr>
<tr>
<td>Chemistry with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distinction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Medical</td>
<td>College of Lake County</td>
<td></td>
<td>August 2014</td>
</tr>
<tr>
<td>Technician – Basic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School Diploma</td>
<td>Elgin Academy</td>
<td>Valedictorian</td>
<td>June 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EMPLOYMENT AND TRAINING

2024                      | Visiting Scholar. Jackson Laboratories, Bar Harbor, ME (Supervisor: Brian Hoffmann) |
2018-2026                 | Medical Scientist Training Program (MSTP) Student. Medical College of Wisconsin, Milwaukee, WI |
2017-2018                 | Intramural Research Training Award (IRTA) Fellowship under the supervision of Drs. Anand Swaroop and Samantha Papal at the National Institutes of Health - National Eye Institute, Bethesda, Maryland |
2015 (Summer)             | Laboratory assistant in the Bernhardt Laboratory (Supervisor: Stephen Anderson) |

PROFESSIONAL CERTIFICATES AND LICENCES

2022-2024                 | Basic Life Support (#225412297290) |
2020-                     | Private Pilot Certificate (#4409159) |
2016-2024                 | Illinois Department of Public Health - Emergency Medical Technician #060623139 |
2014-2019 National Registry of Emergency Medical Technicians
#E3152327

PROFESSIONAL MEMBERSHIP

2017-present Phi Beta Kappa Society (Member)

LEADERSHIP

2023-2024 Microbiology and Immunology Graduate Qualifying Exam and Proposal Defense Preparation Committee

2022-2023 MSTP Student Council, G3 Class representative

PUBLICATIONS


ORAL PRESENTATIONS

International


POSTER PRESENTATIONS

International

dependent on source of virus production. *International Herpesvirus Workshop*. 2023. Missoula, MT


**National**


**Regional**


**GRANTS**

2023-2027  **NIAID F30AI179084**: “Bottom-up and top-down computational modeling approaches to study CMV retinitis"

2017 (Fall) Undergraduate Research Support Independent Study Award: “Collagen concentrations across the human heel pad.”
2016 (Spring)  URS Independent Study Award: “Analysis of collagen protein in the tissue samples from heel pads of human and gorilla cadavers.”

HONORS AND AWARDS

2023  Open Finalist Student Paper Competition 45th Annual International Conference of the IEEE Engineering in Medicine and Biology Society

Raj and Prem Goyal Translational Research Award of the Gastrointestinal & Liver Section

2013-2017  Magna Cum Laude (Spring, 2017)

Duke University Dean’s List with Distinction (Spring, 2016; Spring, 2017)

Duke University Dean’s List (Spring, 2014; Spring, 2015; Fall, 2015; Fall, 2016)

Honors Thesis in Chemistry

Duke University Sophomore Outdoor Leadership Experience (2014)

Atlantic Coast Conference Honor Roll (2014; 2015)

NCAA Division 1 Fencing All-American (2014)

NCAA Division 1 Fencing Championship Contestant (2014; 2015)

JOURNAL REVIEWER

2023  Journal of Clinical Microbiology. Ad hoc reviewer.


COMMUNITY ENGAGEMENT

2024  Medical College of Wisconsin. SUPREMES Student (Eiman Mir) Mentor. Supervisor: Ranjan Dash

2023  Medical College of Wisconsin. Summer Student (Krisna Parab) Mentor. Supervisor: Ranjan Dash
<table>
<thead>
<tr>
<th>Year</th>
<th>Role</th>
<th>Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2022</td>
<td>Medical College of Wisconsin. Rotation Student (Lauren Prochniak) Mentor.</td>
<td>Scott Terhune</td>
</tr>
<tr>
<td>2020-2021</td>
<td>Medical College of Wisconsin. Step 1 Tutor.</td>
<td>Molly Falk-Steinmetz</td>
</tr>
<tr>
<td>2018-2019</td>
<td>Greater Milwaukee Free Clinic. MSTP student volunteer.</td>
<td>Joe Barbieri</td>
</tr>
<tr>
<td>2018-2019</td>
<td>Medical Student Saturday Free Clinic. Student volunteer.</td>
<td>Jakara Griffin</td>
</tr>
<tr>
<td>2018-2019</td>
<td>Student Emergency Medicine Association School Outreach.</td>
<td>Diwante Shuford</td>
</tr>
<tr>
<td>2016-2018</td>
<td>American Red Cross Disaster Health Services Team Volunteer, Chicago, Illinois.</td>
<td>Giustina Johnston</td>
</tr>
<tr>
<td>2016-2017</td>
<td>Treasurer, Windsor House Council, Duke University</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>Playworks Physical Education Volunteer,</td>
<td>China Duff</td>
</tr>
<tr>
<td>2014</td>
<td>Companion Animal Specialty and Emergency Hospital, Crystal Lake, Illinois.</td>
<td>Mike Hochman</td>
</tr>
</tbody>
</table>