MCW
GRADUATE SCHOOL

Doctoral Dissertation Defense Announcement

"Computational Modeling of Physiologic and Pathologic Systems"

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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=ZjRVQzhTK1B5VnI5ZzJKSWhzNWgzUT09

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

Dissertation

"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 ($TB40_{Fb}$) and epithelial ($TB40_{Epi}$) sources. Despite similar vDNA kinetic parameters, viral pp28 protein accumulation and output viral titers were higher in $TB40_{Epi}$ than in $TB40_{Fb}$ when infecting epithelial cells at comparable MOIs. This finding corresponds with a larger synthesis constant for pp28 in $TB40_{Epi}$ 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 ($V_{max,3,SF}$), 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

$V_{max,3,SF}$, 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

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EDUCATION

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

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
2015-2017	Teaching assistant (Calculus), Department of Mathematics, Duke University (Supervisor: Rann Bar-On for Math 105, Supervisor: Emily Braley for Math 111L and 112L).
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

1. **Monti CE**, Hong SK, Audi SH, Joshi A, Terhune SS, Kim J, Dash RK. Assessing the Degree of Hepatic Ischemia-Reperfusion Injury Using PBPK Modeling of Sodium Fluorescein Disposition in *Ex Vivo* Machine-Perfused Livers. 2024 American Journal of Physiology–Gastrointestinal and Liver Physiology. *Submitted for publication*.
2. **Monti CE**, Audi SH, Womack J, Hong SK, Yang Y, Kim J, and Dash RK. Physiologically-Based Pharmacokinetic Modeling of Blood Clearance of Liver Fluorescent Markers for the Assessment of the Degree of Hepatic Ischemia-Reperfusion Injury. 2023 45th Annual International Conference of the IEEE Engineering in Medicine and Biology Society.
3. **Monti CE***, Mokry RL*, Schumacher ML, Dash RK#, and Terhune SS#. Computational Modeling of Protracted HCMV Replication using Genome Substrates and Protein Temporal Profiles. Proceedings of the National Academy of Sciences, 2022. PMID: 35994667 [#Equal Contribution for Senior Authorship; *Equal Contribution for First Authorship].
4. Papal, S., **Monti, CE**, Tennison, M. E., Swaroop, A. Molecular dissection of cone photoreceptor-enriched genes encoding transmembrane and secretory proteins. Journal Neuroscience Research, PMID: 30260491

ORAL PRESENTATIONS

International

1. Monti, C.E., Audi, S., Womack, J., Hong, S.K., Yang, Y., Kim, J., Dash, R. Physiologically-Based Pharmacokinetic Modeling of Blood Clearance of Liver Fluorescent Markers for the Assessment of the Degree of Hepatic Ischemia Reperfusion Injury. *45th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. 2023. Sydney, Australia.

POSTER PRESENTATIONS

International

1. Monti, C.E., Mokry, R.L., Rosas-Rogers, S., Schumacher, M.L., Dash, R.K., Terhune, S.S. Replication efficiencies of HCMV-infected ARPE19 cells are

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

2. Monti, C.E., Mokry, R., Schumacher M., Dash, R.K., Terhune S.S. Mathematical Modeling of Protracted HCMV Replication using Genome Substrates and Protein Temporal Profiles. *Experimental Biology Conference*. 2022. Philadelphia, PA.

National

1. Monti, C.E., Mokry, R.L., Rosas-Rogers, S., Schumacher, M.L., Dash, R.K., Terhune, S.S. Computational modeling of replication efficiency and late protein synthesis variabilities in HCMV-infected ARPE19 cells. *Biomedical Engineering Society 2023 Annual Meeting*. 2023. Seattle, WA
2. Monti, C.E., Mokry, R.L., Rosas-Rogers, S., Schumacher, M.L., Dash, R.K., Terhune, S.S. Computational modeling of virus-source dependent replication variability in HCMV-infected ARPE19 cells. *38th Annual M.D./Ph.D. National Student Conference*. 2023. Copper Mountain, CO.
3. Monti, C.E., Womack, J., Audi, S., Hong, S.K., Yang, Y., Kim, J., Dash, R. Physiologically-based pharmacokinetic (PBPK) modeling of sodium fluorescein (SF) blood clearance for assessing hepatic ischemia-reperfusion injury (IRI). *American Physiology Summit*. 2023. Long Beach, CA.
4. Monti, C.E., Mokry, R., Schumacher M., Dash, R.K., Terhune S.S. Computational Modeling of Protracted HCMV Replication using Genome Substrates and Protein Temporal Profiles. *American Society of Virology Conference*. 2022. Madison, WI.

Regional

1. Monti, C.E., Womack, J., Audi, S., Hong, S.K., Yang, Y., Kim, J., Dash, R. Physiologically-based pharmacokinetic modeling of blood clearance of liver fluorescent markers for assessment of the degree of hepatic ischemia-reperfusion injury. *Graduate School Research Poster Session*. 2022. Milwaukee, WI.
2. Monti, C.E., Mokry, R., Schumacher M., Dash, R.K., Terhune S.S. Computational Modeling of Protracted HCMV Replication using Genome Substrates and Protein Temporal Profiles. *5th Annual Graduate Student Association Symposium*. 2022. Milwaukee, WI.
3. Monti, C.E., Mokry, R., Schumacher M., Dash R.K., Terhune S.S. A predictive mathematical model describing the kinetics of human cytomegalovirus lytic replication. *30th Annual Graduate School Research Poster Session*. 2021. Milwaukee, WI.

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.
2023	2023 45th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. *Ad hoc* reviewer.
2022	2022 44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. *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

2022	Medical College of Wisconsin. Rotation Student (Lauren Prochniak) Mentor. Supervisor: Scott Terhune
2020-2021	Medical College of Wisconsin. Step 1 Tutor. Supervisor: Molly Falk-Steinmetz
2018-2019	Greater Milwaukee Free Clinic. MSTP student volunteer. Supervisor: Joe Barbieri
2018-2019	Medical Student Saturday Free Clinic. Student volunteer. Supervisor: Jakara Griffin
2018-2019	Student Emergency Medicine Association School Outreach. Supervisor: Diwante Shuford
2016-2017	Duke Cancer Center Volunteer. Supervisor: Holly Vincitorio.
2016-2018	American Red Cross Disaster Health Services Team Volunteer, Chicago, Illinois. Supervisor: Giustina Johnston
2016-2017	Treasurer, Windsor House Council, Duke University
2014	Playworks Physical Education Volunteer, Supervisor: China Duff
2014	Companion Animal Specialty and Emergency Hospital, Crystal Lake, Illinois. Supervisor: Mike Hochman