INTERFACE OF MATHEMATICAL MODELS AND EXPERIMENTAL BIOLOGY: ROLE OF THE MICROVASCULATURE

PROGRAM BOOK

american physiological society

SCOTTSDALE, ARIZ.
SEPTEMBER 11–14, 2019

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american physiological society

> “APS meetings [...] are the best way to keep up with what is going on in my field.”
>
> —Eleanor Lederer, MD, APS Member
> University of Louisville

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CONNECTIONS

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2019 APS Interface of Mathematical Models and Experimental Biology: Role of the Microvasculature

September 11–14, 2019

Scottsdale, Arizona

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Julia Arciero
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Anita Layton
Tim Secomb

Acknowledgements:

The conference organizers and the American Physiological Society gratefully recognize the generous support from the following exhibitor:

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American Physiological Society Annual Meeting

at Experimental Biology

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New look.
New website.
What's next for APS?

NEW LOOK

This year we revealed a new brand for the Society, including new themes and messaging. The new brand presents a dynamic image that represents the process of scientific discovery itself, how idea leads to idea and discovery leads to discovery.

NEW WEBSITE

Our new state-of-the-art website reflects APS' commitment to provide our members and community with exceptional experiences.

MYAPS FEATURE NOW LIVE

Our new website now features the MyAPS dashboard where you can update your membership information, stay in touch with your fellow members and view the latest Society news.

THE PHYSIOLOGIST MAGAZINE

Our new member magazine has a journalistic style that dives deeper into what our members do, the conversations they're having in the lab and the interesting stories and experiences that set our membership apart from the rest.

FUNCTION

Function, a new, high-profile journal that will provide a home for physiology-focused papers that might otherwise have been published in other top-tier, high-impact journals, is in development and scheduled to launch in 2020.

APS ANNUAL MEETING 2023

Recently announced, the APS Council unanimously voted to part ways with Experimental Biology following the 2022 meeting. Join us as we begin the process of building a new, world-class APS Annual Meeting.

MORE INITIATIVES

Look out for more on developing Society initiatives geared toward strengthening our membership, our community and the discipline.

"We will increasingly be putting the spotlight on you, our members, on your work, and on the ways in which you are changing the world. So stay tuned for more exciting changes."

Scott Steen, CAE, FASAE
Executive Director of the American Physiological Society

2019 APS Interface of Mathematical Models and Experimental Biology: Role of the Microvasculature
September 11–14, 2019
Scottsdale, Arizona

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General Information

Location:

The 2019 APS Interface of Mathematical Models and Experimental Biology: Role of the Microvasculature is held at the Scottsdale Plaza Resort, 7200 N. Scottsdale Road, Paradise Valley, AZ 85253. Phone: (480) 948-5000.

Conference Registration Hours:

Wed., September 11.....3:00 p.m.–8:00 p.m.
Thurs., September 12.....7:00 a.m.–7:00 p.m.
Fri., September 13.....7:00 a.m.–7:00 p.m.
Sat., September 14.....7:00 a.m.–10:00 a.m.

Student Registration:

Any student member or regularly matriculated student working toward a degree in one of the biomedical sciences is eligible to register at the student fee. Nonmember postdoctoral fellows, hospital residents and interns, and laboratory technicians do not qualify as students. Non-member students who register on-site must provide a valid university student ID card. APS student members should present their current APS membership card indicating their student category status.

Postdoctoral Registration:

Any person who has received a PhD degree in physiology or related field within five years of the conference start date, as attested to by their department head, is eligible to register at the postdoctoral fee. **A statement signed by the department head must accompany the registration form and remittance when registering.**

Included in your Registration:

Your registration to this conference includes entry into all oral and poster scientific sessions; opening reception; lunch, morning and afternoon breaks during the conference; and a program book which serves as the conference proceedings.

Registration is nontransferable. You must pay the entire fee regardless of the number of sessions/events you attend. Guests of attendees are not permitted in the oral scientific sessions, poster sessions, opening reception, meals, conference breaks or social events.

Press Registration:

Press badges will be issued at the Conference Registration Desk to working members of the press and freelance writers bearing a letter of assignment from an editor. Representatives of allied fields (public relations, public affairs, etc.) must register as nonmembers.

Photograph/Video Recording:

Photo or video capture of any scientific presentation, whether an oral or poster presentation in whole or in part, is expressly prohibited. Recording or taking photography of another person without their explicit permission is prohibited.

Individuals observed photographing or videotaping any presentation, in whole or in part, will be asked to leave the conference immediately, forfeiting the registration fee.

Social Media Policy:

APS encourages the use of social media during our conferences and conferences as a way of connecting with other attendees and expanding the reach of science being presented. If you plan on using social media to discuss the conference, please use the official APS conference hashtag, #PhysiologyConf.

Sharing of specific research presentations, poster or slides is prohibited without the express permission of the presenter.

Code of Conduct:

APS is committed to providing a safe, productive and welcoming environment for all conference participants and staff. All participants including, but not limited to, attendees, speakers, volunteers, APS staff, hotel staff, service providers and others are expected to abide by the APS Conference Code of Conduct which maintains that all individuals should:

- Be treated with respect and consideration, valuing a diversity of views and opinions;
- Be considerate, respectful and collaborative;
- Communicate openly and with respect, critiquing ideas rather than individuals; avoid personal attacks;
- Be mindful of your surroundings and fellow participants; and,
- Be respectful of the rules and the conference venue.

Contact the APS staff at the Conference Registration Desk if you notice a dangerous situation or someone in distress or in violation of this Code of Conduct.

Additional information on APS' Conference Policies can be found on our website: https://www.the-aps.org/conferences-awards/conferences/conference-events/control-of-renal-function/Code-of-Conduct?SSO=Y

Program Objective:

Attendees of this conference should expect to gain both a greater appreciation and understanding of the collaborations between experimental physiologists and theoretical investigators who are indispensable in advancing the study of complex physiological systems. To do so, the focus is:

- How investigators integrate mathematical models with experimental approaches in an effort to understand the roles of microcirculation and hemodynamics in a variety of organs
- Present largely unpublished data, state-of-the-art computational approaches and their innovative, multiscale applications in understanding microcirculation in various organs
- To inspire and promote early-career investigators and trainees to develop new research programs that take advantage of mathematical modeling insights

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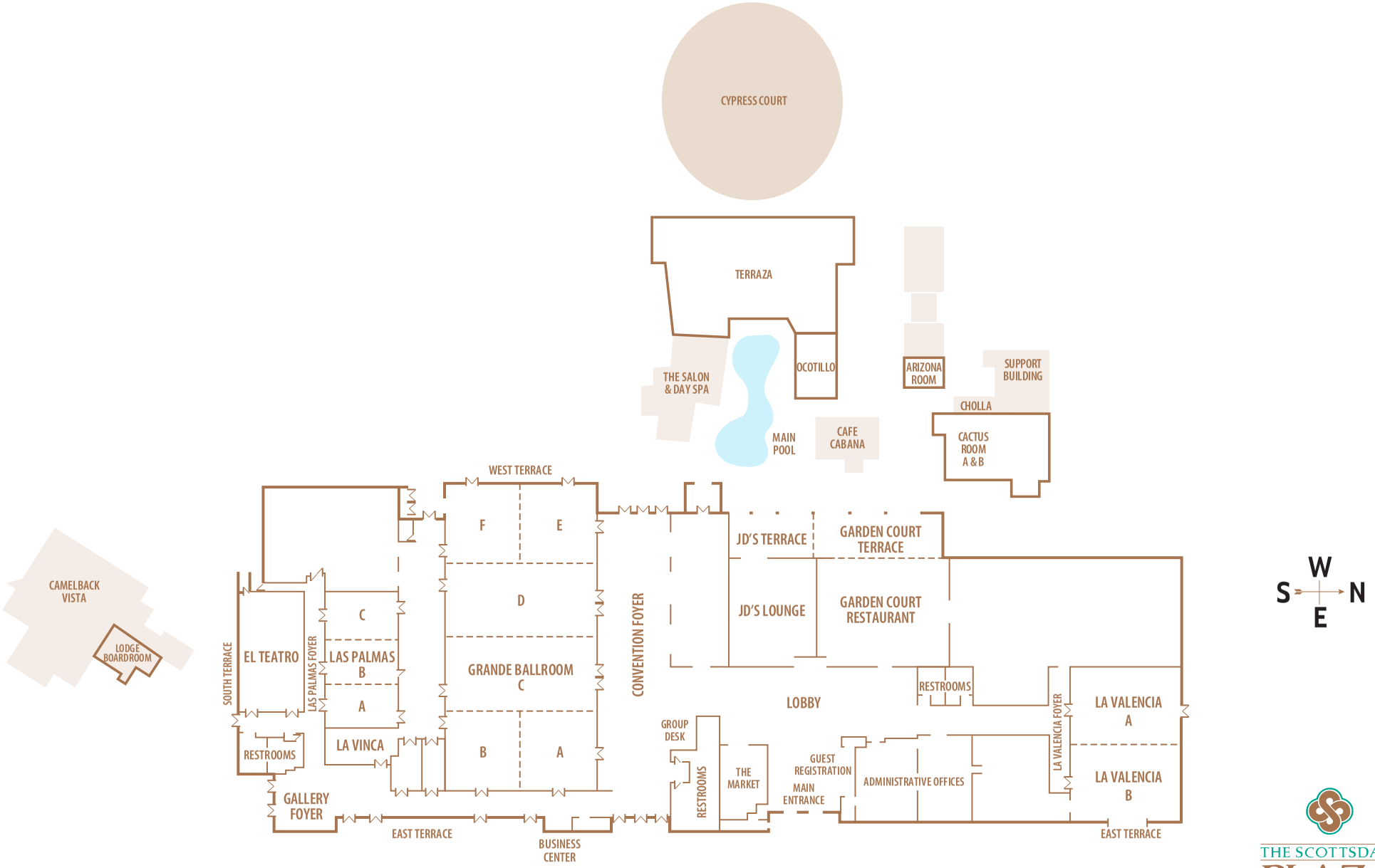
TIME	Wednesday, September 11	Thursday, September 12	Friday, September 13	Saturday, September 14
8:00 a.m. - 7:00 p.m.		Registration	Registration	
8:00 a.m.- 10:00 a.m.				Registration
8:00 a.m.- 10:00 a.m.		**Symposium 1:** Flow in microvascular networks	**Symposium 4:** Structural adaptation and angiogenesis in microcirculatory pathways	**Symposium 7:** Retinal microcirculation
10:00 a.m.- 10:15 a.m.		Break	Break	Awards Ceremony
10:15 a.m.- 10:30 a.m.				Break
10:15 a.m.- 12:15 p.m.		**Symposium 2:** Oxygen transport tissue	**Symposium 5:** Cancer tissue microcirculation	
10:30 a.m.- 12:30 p.m.				**Symposium 8:** Brain microcirculation
12:15 p.m.- 1:30 p.m.		Lunch (provided)	Lunch (provided)	
12:30 p.m.- 12:45 p.m.				Concluding Statements

TIME	Wednesday, September 11	Thursday, September 12	Friday, September 13	Saturday, September 14
2:00 p.m.-4:00 p.m.		**Symposium 3:** Myocardial microcirculation	**Symposium 6:** Renal microcirculation	
3:00 p.m.-8:30 p.m.	Registration			
4:00 p.m.-5:00 p.m.		**Trainee Career Workshop:** Careers in theoretical modeling and quantitative analysis of physiological systems		
5:15 p.m. – 6:30 p.m.		**Poster Session 1 & Social Activity**	**Poster Session 2 & Social Activity**	
6:00 p.m. - 6:15 p.m.	Welcome & Opening Comments			
6:15 p.m.-7:15 p.m.	Keynote Lecture			
7:15 p.m.-8:30 p.m.	Opening Reception			

CONFERENCE CENTER MAP



THE SCOTTSDALE PLAZA RESORT

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WEDNESDAY, SEPTEMBER 11, 2019

6:00 p.m. – 6:15 p.m.	1.0	Welcome **Alan Weinstein**, *Weill Cornell Medicine*
6:15 p.m. – 7:15 p.m.	**2.0**	**Keynote Lecture** **Grand Ballroom A/B**
	2.1	Using mathematical models to understanding what we observe: from the microscope to the telescope **FitzRoy Curry**, *Univ. of California, Davis*
7:15 p.m. – 8:30 p.m.		Opening Reception **Grand Ballroom C**

THURSDAY, SEPTEMBER 12, 2019

7:00 a.m. – 8:00 a.m.		Breakfast Grand Ballroom C
8:00 a.m. – 10:00 a.m.	**3.0**	**Symposium 1:** **Flow in microvascular networks** **Grand Ballroom A/B**
	Chair:	**Tim Secomb**, *Univ. of Arizona*
8:00 a.m. – 8:30 a.m.	**3.1**	Nonlinearity in microvessel networks: multiple solutions and spontaneous oscillations **Russell Carr**, *Univ. of New Hampshire*
8:30 a.m. – 9:00.m.	**3.2**	Developing anatomical models of the coronary circulation network **Nicholas Smith**, *Univ. of Auckland*
9:00 a.m. – 9:30 a.m.	**3.3**	High-fidelity computational modeling of blood flow in physiologically realistic microvascular networks with fully resolved erythrocyte deformation **Prosenjit Bagchi**, *Rutgers Univ.*
9:30 a.m. – 10:00 a.m.	**3.4**	One size fails to fit all: knowledge of structure and function are required to appropriately model flux from microvascular networks **Virginia Huxley**, *Univ. of Missouri*
10:00 a.m. – 10:15 a.m.		Coffee Break Grand Ballroom Foyer
10:15 a.m. – 12:15 p.m.	**4.0**	**Symposium 2:** **Oxygen transport tissue** **Grand Ballroom A/B**
	Chairs:	**Jefferson Frisbee**, *Western Univ.* **Andrew Marquis**, *Univ. of Michigan*

10:15 a.m. – 10:45 a.m.	**4.1**	Multi-scale modeling of skeletal muscle oxygen transport using arteriolar and venular networks reconstructed from experimental data **Daniel Goldman**, *Western Univ.*
10:45 a.m. – 11:15 a.m.	**4.2**	Effect of pulmonary flow heterogeneity on oxygen uptake and delivery **Tuhin Roy**, *Mayo Clinic*
11:15 a.m. – 11:45 a.m.	**4.3**	A multi-scale computational model of rat ventilation-perfusion matching **Andrew Marquis**, *Univ. of Michigan*
11:45 a.m. – 12:15 p.m.	**4.4**	Muscle oxygen transport in health and disease: innovative approaches, novel insights **Daniel Hirai**, *Purdue Univ.*
12:15 p.m. – 1:30 p.m.		Lunch Grand Ballroom C
2:00 p.m. – 4:00 p.m.	**5.0**	**Symposium 3:** **Myocardial microcirculation** **Grand Ballroom A/B** **Chairs: Dan Beard,** *Univ. of Michigan* **Christine Lauren Sy,** *The Univ. of Auckland*
2:00 p.m. – 2:30 p.m.	**5.1**	Supply-demand matching of oxygen across the myocardium at rest and during exercise **Brian Carlson**, *Univ. of Michigan*
2:30 p.m. – 3:00 p.m.	**5.2**	Towards a coronary microscope: insights into the microvasculature through the lens of macro-hemodynamics **Jonathan Mynard**, *Murdoch Children's Research Institute*
3:00 p.m. – 3:30 p.m.	**5.3**	Imaging coronary vasculature in cleared rat ventricle **Christine Lauren Sy**, *The Univ. of Auckland*
3:30 p.m. – 4:00 p.m.	**5.4**	Endothelium-dependent vasodilation in the human microcirculation: a switch in mechanism with disease or stress **David Gutterman**, *Medical College of Wisconsin*
4:00 p.m. – 5:00 p.m.	**6.0**	**Trainee Career Workshop: Careers in theoretical modeling and quantitative analysis of physiological systems** **Grand Ballroom A/B** **Chair: Paola Causin**, *Univ. of Milan*
4:00 p.m. – 4:20 p.m.	**6.1**	Navigating biological research as an early-career mathematician **Marissa Renardy**, *Univ. of Michigan*

4:20 p.m. – 4:40 p.m. **6.2** Microvasculature and how I got here
Adebowale Adebiyi, *The Univ. of Tennessee Health Science Center*

5:15 p.m. – 6:30 p.m. **7.0** **Poster Session 1 & Social Activity**
Grand Ballroom A/B

Board #

1 **7.1** The role of microvascular permeability on the dynamics of biomarker exhalation
Anastasios Angelopoulos, Jonathan Bernstein, Reza Shekarriz, *Univ. of Cincinnati; Univ. of Cincinnati; Exhalix, LLC*

3 **7.2** Hydrogen sulfide diffusion through animal and human tissue
Reza Shekarriz, Debra Friedrichsen, Elani Fourie Wiest, Bill Brooks, Grayson Silaski, Nancy Kanagy, Anastasios Angelopoulos, *Exhalix, LLC; Univ. of New Mexico; Exhalix, LLC; Exhalix, LLC; Exhalix, LLC; Univ. of New Mexico; Univ. of Cincinnati*

5 **7.3** Interactions between pairs of red blood cells in microvascular flows
Jared Barber, Carlson Triebold, Maryam Amran, *Indiana Univ.-Purdue Univ. Indianapolis; Indiana Univ.-Purdue Univ. Indianapolis; Univ. of California, Irvine*

7 **7.4** Structural analysis of coronary microcirculation in healthy and diseased hearts
Vibujithan Vigneshwaran, Christine Lauren Sy, Gregory Sands, Bruce Smaill, Nicolas Smith, *The Univ. of Auckland; The Univ. of Auckland; The Univ. of Auckland; The Univ. of Auckland; The Univ. of Auckland*

9 **7.5** Oxygen permeability of red blood cells: insights from mathematical modeling
Rossana Occhipinti, Pan Zhao, R. Ryan Geyer, Fraser J. Moss, Walter F. Boron, *Case Western Reserve Univ.; Case Western Reserve Univ.; Case Western Reserve Univ.; Case Western Reserve Univ.; Case Western Reserve Univ.*

11 **7.6** Organismal systems modeling (OSyM) research coordination network
Kendra J. Greenlee, Dianna Padilla, *North Dakota State Univ.; Stony Brook Univ.*

FRIDAY, SEPTEMBER 13, 2019

7:00 a.m. – 8:00 a.m. Breakfast
Grand Ballroom C

8:00 a.m. – 10:00 a.m. **8.0** **Symposium 4:**
Structural adaptation and angiogenesis in microcirculatory pathways
Grand Ballroom A/B
Chairs: **Shayn Pierce-Cottler**, *Univ. of Virginia*
Owen Richfield, *Tulane Univ.*

8:00 a.m. – 8:30 a.m. **8.1** Agent-based modeling of multi-cell niches in health and disease
Shayn Peirce-Cottler, *Univ. of Virginia*

8:30 a.m. – 9:00 a.m.	**8.2**	Glomerular capillary shear stress and hoop stress are significantly elevated in 5/6-nephrectomy: a modeling study **Owen Richfield**, *Tulane Univ.*
9:00 a.m. – 9:30 a.m.	**8.3**	Mathematical models of non-drug therapies in angiogenesis **Feilim Mac Gabhann,** *Johns Hopkins Univ.*
9:30 a.m. – 10:00 a.m.	**8.4**	A systems biology view for discovering cell dynamics during microvascular network growth **Walter Murfee**, *Univ. of Florida*
10:00 a.m. – 10:15 a.m.		Coffee Break Grand Ballroom Foyer
10:15 a.m.- 12:15 p.m.	**9.0**	**Symposium 5:** **Cancer tissue microcirculation** **Grand Ballroom A/B**
	Chair:	**Daniel Heller**, *Weill Cornell Medicine*
10:15 a.m. – 10:45 a.m.	9.1	Multiscale modeling of blood flow in the human vasculature **Peter Balogh,** *Duke Univ.*
10:45 a.m. – 11:15 a.m.	**9.2**	Emerging mechanistic biomarkers of cancer chemo-radiation and immunotherapy from mathematical biophysics **Vittorio Cristini**, *Houston Methodist Research Institute*
11:15 a.m. – 11:45 a.m.	**9.3**	Image-based systems biology of the microvasculature in cancer **Arvind Pathak,** *Johns Hopkins Univ.*
11:45 a.m. – 12:15 p.m.	**9.4**	Mechanobiological control of vascular function **Lance Munn**, *Harvard Medical School*
12:15 p.m. – 1:30 p.m.		Lunch Grand Ballroom C
2:00 p.m. – 4:00 p.m.	**10.0**	**Symposium 6:** **Renal microcirculation** **Grand Ballroom A/B**
	Chair:	**Anita Layton**, *Univ. of Waterloo*
2:00 p.m. – 2:30 p.m.	**10.1**	Renal oxygenation during diuresis **Bruce Gardiner**, *Murdoch Univ.*
2:30 p.m. – 3:00 p.m.	**10.2**	Determining risk factors for triple whammy AKI using computational models of long-term blood pressure regulation **Jessica Leete**, *Duke Univ.*

3:00 p.m. – 3:30 p.m. **10.3** Renal microcirculation: from the arterial network topology to the blood flow dynamics and synchronization.
Dmitry D. Postnov, *Boston Univ.*

3:30 p.m. – 4:00 p.m. **10.4** Pericytes protect against renal ischemia-reperfusion injury, via sex-specific mechanism
Jennifer Sullivan, *Augusta Univ.*

5:15 p.m. – 6:30 p.m. **11.0** **Poster Session 2 & Social Activity**
Grand Ballroom A/B

Board #

2 **11.1** Computational modeling of oxygen exchange between a urine bolus and the ureter wall
Chang-Joon Lee, Bruce Gardiner, Roger Evans, David Smith, *Murdoch Univ.; Murdoch Univ.; Monash Univ.; Univ. of Western Australia*

4 **11.2** Modeling intraglomerular transport in diabetic kidney disease
Ashlee N. Ford Versypt, Minu R. Pilvankar, Ashlea D. Sartin, Claire Streeter, Steve M. Ruggiero, *Oklahoma State Univ.; Oklahoma State Univ.; Oklahoma State Univ.; Oklahoma State Univ.; Oklahoma State Univ.*

6 **11.3** Investigation of the potential components signals of renal natriuresis: a mathematical modeling analysis
Hongtao Yu, Melissa Hallow, *Univ. of Georgia; Univ. of Georgia*

8 **11.4** *A multicontrast 3D imaging pipeline for image-based computational modeling of cancer tissue microcirculation*
Akanksha Bhargava, Benjy Monteagudo, Priyanka Kushwaha , Qihong Wang, Ryan Riddle, Manisha Aggarwal, Aleksander Popel, Arvind Pathak*, Johns Hopkins Univ.; Johns Hopkins Univ.; Johns Hopkins Univ.; Johns Hopkins Univ.; Johns Hopkins Univ.; Johns Hopkins Univ.; Johns Hopkins Univ.; Johns Hopkins Univ.*

10 **11.5** Modeling of blood flow and oxygen transport in the cerebral microcirculation
Timothy W. Secomb, Jose T. Celaya-Alcala, Jeffrey S. Lee, Bohan Li, Sava Sakadzic, David A. Boas, Univ. of Arizona; Brown Univ.; Univ. of Arizona; Univ. of Arizona; Massachusetts General Hospital; Boston Univ.

SATURDAY, SEPTEMBER 14, 2019

7:00 a.m. – 8:00 a.m. Breakfast
Grand Ballroom C

8:00 a.m. – 10:00 a.m. **12.0** **Symposium 7:**
Retinal microcirculation
Grand Ballroom A/B
Chairs: **Julia Arciero**, *Indiana Univ.-Purdue Univ. Indianapolis*
Lucia Carichino, *Rochester Institute of Technology*

8:00 a.m. – 8:30 a.m.	**12.1**	Ocular blood flow: a delicate balance of pressures **Giovanna Guidoboni**, *Univ. of Missouri*
8:30 a.m. – 9:00 a.m.	**12.2**	Modeling blood flow regulation and oxygen transport in the retinal microcirculation **Brendan Fry**, *Metropolitan State Univ. of Denver*
9:00 a.m. – 9:30 a.m.	**12.3**	Modeling the effect of retinal microvasculature on ocular hemodynamics **Lucia Carichino**, *Rochester Institute of Technology*
9:30 a.m. – 10:00 a.m.	**12.4**	Recent advancements in imaging technologies allow us to visualize and quantify hemodynamic and vascular parameters within the eye **Alon Harris**, *Indiana Univ. School of Medicine*
10:00 a.m. – 10:15 a.m.		**Awards Ceremony** **Grand Ballroom A/B**
10:15 a.m. – 10:30 a.m.		Coffee Break Grand Ballroom Foyer
10:30 a.m. – 12:30 p.m.	**13.0** **Chair:**	**Symposium 8:** **Brain microcirculation** **Grand Ballroom A/B** **Fabrice Dabertrand**, *Univ. of Colorado*
10:30 a.m. – 11:00 a.m.	**13.1**	Decoding the brain microvasculature by blood flow modeling in realistic microvascular networks **Franca Schmid**, *Univ. of Zurich*
11:00 a.m. – 11:30 a.m.	**13.2**	Modeling cerebral blood flow control: an integrated framework for linking macroscale changes in blood perfusion and oxygenation to cell level signaling. **Nikolaos Tsoukias**, *Florida International Univ.*
11:30 a.m. – 12:00 p.m.	**13.3**	Restoration of neurovascular coupling by exogenous phosphatidylinositol 4,5-bisphosphate (PIP2) application in small vessel disease of the brain **Fabrice Dabertrand**, *Univ. of Colorado Denver*
12:00 p.m. – 12:30 p.m.	**13.4**	Imaging cerebral microvascular structure, oxygen concentration and blood flow in animal models **Sava Sakadzic,** *Harvard Univ.*
12:30 p.m. – 12:45 p.m.		**Conference Concluding Statements** **Grand Ballroom A/B** **Thomas Pannabecker,** *Univ. of Arizona* **Alan Weinstein,** *Weill Cornell Medicine* **Tim Secomb**, *Univ. of Arizona*
12:45 p.m.		Box lunches available upon departure Grand Ballroom Foyer

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This program is the official conference proceedings of the 2019 APS Interface of Mathematical Models and Experimental Biology: Role of the Microvasculature.
Find the program at: www.the-aps.org/conferenceproceedings.

To cite your abstract, use the format listed below:
Curry F. Using mathematical models to understanding what we observe: from the microscope to the telescope (Abstract). *APS Conference: Interface of Mathematical Models and Experimental Biology: Role of the Microvasculature, Scottsdale, AZ, 11-14 September 2019, p. A2.1*

2: KEYNOTE LECTURE

2.1

Using mathematical models to understanding what we observe: from the microscope to the telescope

FitzRoy Curry[1]
[1]Biomedical Engineering and Physiology and Membrane Biology, Univ. of California, Davis

I am fascinated by the parallels between the study of astronomy and the microcirculation. With the human eye, telescope and microscope as tools, both areas have progressed by the cycle of observation, theory and modeling, followed by new observations. The astronomy examples are classic; to name just a few: the retrograde motion of the planets and Copernicus' heliocentric model; Tyco Brahe's observations of planetary motion and Kepler's elliptical orbits, the orbit of Mercury and Newtonian mechanics v Einstein's general relativity. In the microcirculation much of the material in this conference builds on classical observations and subsequent models: Poiseuille's observations of blood flow and the plasma sleeve in the frog mesentery leading to experiments in small glass tubes and the fourth power law; Krogh's observation of the number and distribution of perfused capillaries in muscle leading to the Krogh-Erlang-cylinder model of tissue oxygen diffusion; Starling's observation of hematocrit after saline infusion leading to measurements of colloid osmotic pressure, and the Starling Principle of fluid exchange; Landis' observation of the leakage of colored dyes of different molecular weight leading to the models of diffusion through porous membranes. What are the lessons we take from parallels in astronomy and microcirculation research? Both areas depend on the continued development of imaging tools. Spectacular progress continues in astronomy (imaging a black hole, and gravitational waves). In the microcirculation, new applications of electron microscopy, multifocal microscopy, and high resolution imaging methods provide a bridge between observations made at the molecular, cellular and whole organ level and integrate multiple cellular functions into a more physiologically relevant whole. These methods also reveal heterogeneity in cellular function, even within a single microvessel, that challenges assumptions about the characteristic parameters to be used in a model. The sheer volume of data can limit the capacity of a single investigator's laboratory to manage the project. Just compare the author list on modern astronomy papers, sometimes many hundreds, with the list currently considered acceptable on microvascular papers. Both areas can wander off course when the limitations of experimental approaches are ignored. Examples include improper instrument calibration, poor signal to noise, and optical artifacts in imaging. Critical microvascular functions can be compromised in microvascular preparations exposed to poorly controlled perfusion or superfusion conditions. Different limitations arise from cultured endothelial cell monolayers. It is easy to bias the predictions of a well formulated model by choice of over-simplified initial conditions and the wrong boundary conditions. Finally, there are important contrasts between the ways our knowledge from astronomy and microcirculation studies are applied. Misconceptions in astronomy may not affect human health (at least not over time scales we are currently working with), but those from microcirculatory studies certainly can. Incorrect assumptions about the way high molecular weight cancer drugs or nanoparticles distribute from plasma into tumor tissue result in poor delivery and ineffective treatment and textbook dogma describing the way fluid is distributed across microvessel walls limits the adoption of new strategies in perioperative fluid management. Curry,F.E. Mechanics and thermodynamics of transcapillary exchange. pp.309-374, Section2, Vol.IV, Part1,In: E.M.Renkin and C.C.Michel,(Eds.),"HandbookofPhysiology:Microcirculation, American Physiological Society,1984. Curry FR, Adamson RH.Vascular permeability modulation at the cell, microvessel, or whole organ level: towards closing gaps in our knowledge. Cardiovasc. Res. 87:218-29. 2010 Adamson,R.H. et al Oncotic pressures opposing filtration across non-fenestrated rat microvessels. JPhysiol. (London), 557(3): 889-907.

3: SYMPOSIUM 1: FLOW IN MICROVASCULAR NETWORKS

3.1

Nonlinearity in microvessel networks: multiple solutions and spontaneous oscillations

Russell Carr[1]
[1]Chemical Engineering, Univ. of New Hampshire

Our model of blood flow in microvessel networks includes the following concepts -Network topology and geometry (nodal interconnections and branch lengths and diameters) - Red cell and total blood material balances (plasma skimming and mixing at branch points) - Momentum balances (blood viscosity is a function of local hematocrit)These concepts generate a nonlinear system when combined together. The nonlinearity occurs because the flow distribution depends on the local viscosity, which depends on the local hematocrit which depends on plasma skimming at diverging branch points which depends again on the flow distribution. In mathematical language, $Q=\varphi(Q)$, where $\varphi(Q)$ is a nonlinear function. Our objective is to study the dynamics of this nonlinear network flow system. The analysis begins with finding the fixed points or "steady states" of the system. As is common with nonlinear systems, multiple solutions are possible. For the model to be related to the physical flow system on which it is based, at least one solution should exist. Additional solutions often arise by means of what nonlinear mathematics calls "saddle node bifurcations." Saddle node bifurcations lead to hysteresis where a system jumps from one solution branch to another when a parameter (e.g. vessel diameter) is adjusted. Numerical investigation shows that this hysteresis phenomenon is due to differences in fluid viscosity in different inlet branches along with network parameters and does not directly depend on plasma skimming. This interpretation has been verified in scaled up model experiments. Network flow problems having multiple solutions which are connected by hysteresis have interesting physiological implications. For example, jumping from one solution branch to another when a network parameter is perturbed can result in a change in flow direction or an apparent, sudden reduction in oxygen delivery due to drastic reduction of blood flow through a portion of the network. The dynamics of microvessel network blood flow can be approximated by a set of one dimensional, nonlinear convection equations. This set of partial differential equations can be linearized about the "steady states" previously identified and converted into a time delay integral equation. The stability of the "steady states" in response to small disturbances can be determined by computing the eigen values from the characteristic equation of the time delay integral equation. These eigen values may be real, imaginary or complex. If at least one of the eigen values has a positive real part, then the steady state is repulsive and unstable. If all eigen values have negative real parts, then the steady state is attractive and stable. The long term trajectory of the dynamics for a system with a locally unstable steady state can be determined by numerical solution of the model convection equations. Such numerical experiments show that a wide variety of dynamics are possible in relatively simple microvessel networks. Stable steady states, damped oscillations, super critical, as well as subcritical, Hopf bifurcations leading to limit cycles and spontaneous chaotic oscillations have all been discovered. Inspired by the modeling results, experiments were conducted with red blood cell suspensions flowing through a simple three node network with branch diameters of 50 μm. These experiments provide video evidence of sustained oscillations. Video image analysis techniques indicate that these oscillations have more structure than is readily apparent during visual observation. Blood flow in microvessel networks is an example of nonlinearity. This nonlinearity was identified through mathematical modeling. The modeling activities provided direction for experiments that demonstrate the existence of both multiple solutions and spontaneous oscillations as predicted. Funding support: NIH (R01 HL67789) and Univ. of New Hampshire.

3.2

Developing anatomical models of the coronary circulation network

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The maintenance of coronary blood flow to cardiac tissue is not only critical for heart function, it is also remarkable. Specifically it is extraordinary that blood flow is maintained given that coronary vessels are embedded within muscular walls that compress with every heartbeat. Highly organised layers of muscle fibres form these walls. Our preliminary observations that coronary vessels are highly aligned to these muscle layers in the healthy heart suggests this arrangement may be fundamental for ensuring

protection from this compression. Interestingly, this hypothesis is further supported by the observation that in Heart Failure changes in the structure of the muscle layers in the heart wall are highly correlated with a reduction in coronary flow. We have recently developed technologies to test this hypothesis. Our imaging platform enables simultaneous observation of both the muscle layers of the heart and coronary vessels at their smallest scale. Applying our novel imaging process to this data we have been able to fully reconstruct microcirculatory vascular beds and simultaneously characterise vessel alignment within the heart's muscle layers . Specifically, these models have been built using confocal image data collected from hearts with induced Heart Failure and aged matched normals. Using our purpose built imaging system we have visualised the three-dimensional arrangement of muscle tissue and blood vessels at sub-micron spatial resolution within blocks of tissue from the cardiac left ventricle. From these data, applying our segmentation algorithms, we have been able to quantify the arrangement of both cardiac muscle cells and for the first time complete coronary networks. These extracted networks underpin the application of anatomically based models of coronary blood flow, which in turn provide the ability for advancing our understanding of adaptation and deterioration in health and disease respectively. This work is supported by the Marsden funding administered by the Royal Society of New Zealand, grant number UOA1620.

3.3

High-fidelity computational modeling of blood flow in physiologically realistic microvascular networks with fully-resolved erythrocyte deformation

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Microvascular networks represent geometrically complex networks of blood vessels that are often very tortuous, and continuously bifurcating and merging with other vessels. Most existing computational models of network blood flow suffer from major limitations in terms of representing actual blood vessels, and resolving the true microvascular hemodynamics. A major drawback of these models is that they treat each blood vessel as a 1D straight segment, ignoring the variation of blood velocity, hematocrit etc over the cross-section of a vessel, and the tortuosity of vessels [1-3]. Thus, these models do not faithfully retain the important architectural details of microvascular networks. Furthermore, these models use empirical correlations to model blood rheology, and hematocrit distribution at vascular bifurcations. Therefore, such models lack the ability to resolve the cellular-scale details that are important in understanding pathophysiology of microcirculation. We have recently developed a high-fidelity, 3D computational model of blood flow in complex microvascular networks resembling the in vivo-like architecture with fully resolved deformation of blood cells [4-8]. The vascular networks are designed following in vivo images and are comprised of bifurcating, merging, and tortuous vessels. Unlike 1-D network models, our model accurately resolves deformation and dynamics of each individual red blood cell (RBC), while simultaneously retaining complex geometric details of the vascular architecture. Our model is versatile, and can consider networks irrespective of topological/geometrical complexities. Flow can be driven by either pressure or flow boundary conditions of physiological values. Extreme deformation and a wide range of RBC shapes are observed that are in agreement with in vivo observations. Quantitative comparisons were made with in vivo data using hemodynamic quantities such as flow resistance, wall shear stress, cell-free layer, etc., and good agreement was observed. The model provides a full 3D quantification of hemodynamic quantities with unprecedented details that are not available in the existing 1D network models. For example, the model provides full 3D and time-dependent map of wall shear stress (WSS) and its gradient (WSSG). It shows high WSS at bifurcations, which the earlier 1D models fail to predict. It also shows highly 3D and heterogeneous distribution of WSSG, which the 1D models cannot predict. Our model also predicts strong but differential variations in axial versus circumferential WSSG. We predict that the WSS increases significantly in presence of RBCs, and the increase is more in venous sides, and also at capillary bifurcations. Similarly WSSG is predicted to be higher in presence of RBCs. These results cannot be obtained by the 1D network models, and they imply that the effect of RBCs on WSS is more enhanced at specific locations in a microvascular network. In conclusion, we have developed a high-fidelity 3D computational model that, for the first time, resolves flow dynamics and deformation of every blood cells, while simultaneously retaining the geometric complexities of a microvascular network, and does not have the major limitations of the widely-used 1D network models. Our model can be readily used to better understand diverse pathophysiological conditions in the microcirculation when cellular-scale

details and vascular architectures both are important, such as, angiogenesis, and drug delivery. The model can also consider white blood cells and platelets, and receptor-mediated adhesion between vascular wall and cells. [1] Secomb et al , Microcirculation, 2000. [2] Pries and Secomb (2008), Handbook of Physiol. [3] Fry et al, Microcirculation, 2012. [4] Balogh & Bagchi, Biophysical J., v-113 (2017). [5] Balogh & Bagchi, Physics of Fluids, v-30 (2018). [6] Balogh & Bagchi, J. Fluid Mech., v-864 (2019). [7] Balogh & Bagchi, J. Computational Phys. (2017). [8] Balogh & Bagchi, Physiological Reports, (2019).

3.4

One size fails to fit all: knowledge of structure and function are required to appropriately model flux from microvascular networks

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Successful design of experiments to investigate complex physiological systems relies on insights gained from mathematical models. The setting of boundary conditions and choice of values included in the model are critical components in this process. In the case of transvascular fluid movement, especially, given that we now know the barrier separating circulating blood from metabolizing tissue is a dynamic, not passive, component, it is necessary to go beyond the use of single values for the transport parameters. For example, in the case of the relatively simple planar microvascular network geometry of the frog mesentery, calculated net volume flux can vary by as much as 60-fold. On analyzing mesenteric microvascular networks data it became evident that the anatomical variables of vessel diameter and segment length were of particular importance given their influence on the surface area for exchange. The next most important component is the choice of the value of hydraulic conductivity (Lp). Assuming Lp is represented adequately by the average value for all elements, volume flux from the network is predicted to be 8-fold higher than a model that allows for Lp to be distributed by position within the network. While the relationship between Lp and microvascular anatomy has not been studied, our simple analysis demonstrates the critical nature of obtaining these data to design appropriate models of volume flux at the network level. It has been shown that parameters such as Lp and permeability to proteins, change in response to relevant vasoactive substances such as atrial natriuretic peptide. Modeling these interactions and the influence of fluid distribution within the network are only recently being considered. Further, the distributions of Lp and permeability to solute not only differ by organ but also by sex, age, as well as by season. While study of these variables is in its infancy, mathematical modeling helps us to focus on the study of the most critical components. The ability to integrate data obtained at the level of individual microvessel segments to predict whole organ function is requires consideration of these functional interactions in addition to understanding network architecture and its ability to remodel in health and disease. Supported by NIH R01 DK095501 (VHH) and NSF DMS-1853222/1853303 (GG)

4: SYMPOSIUM 2: OXYGEN TRANSPORT TISSUE

4.1

Multi-scale modeling of skeletal muscle oxygen transport using arteriolar and venular networks reconstructed from experimental data

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Delivering oxygen to tissue is one of the principal roles of the microcirculation, and is especially important in highly metabolic tissues such as skeletal muscle. Although sufficient bulk blood flow is essential to supply skeletal muscles with oxygen, it is also necessary for blood flow to be properly distributed within microvascular networks to ensure local matching of oxygen supply with metabolic demand. Therefore, given that arterioles are the main site of microvascular flow regulation, it is important to consider arteriolar network structure in studying local regulation of oxygen delivery. The corresponding venular network structure is also believed to be important in determining the overall blood flow and hence oxygen distribution within the microcirculation. We have recently described methods for using intravital videomicroscopy (IVVM) to reconstruct arteriolar and venular networks in the rat gluteus maximus muscle (GM) and to quantify blood flow and red blood cell (RBC) distribution in these networks [Refs. 1, 2]. We have also developed methods for approximating the resistance of smaller vessels (arterioles, capillaries and venules) not captured by our experimental measurements in order to perform

accurate simulations of blood flow distribution in these networks. The objectives of the current work are to determine how relatively large-scale arteriolar and venular networks are connected via blood flow to capillary beds and to develop a computational model of diffusive oxygen transport between reconstructed arteriolar/venular networks and surrounding capillary-perfused tissue. Since even a relatively small muscle such as the GM contains millions of discrete capillaries and their detailed structure is difficult to determine, we are using a "tissue model" containing continuously distributed capillaries. We will describe our current discrete/continuous models of microvascular blood flow and oxygen transport, and present results from numerical simulations of intravascular and tissue oxygen distributions in and around a sample arteriolar/venular network. These transport models will be used in future studies aimed at developing a model of blood flow and oxygen delivery regulation in the rat GM. This work is supported by Natural Sciences and Engineering Research Council of Canada (NSERC) grants R4081A03 (DG) and R4218A03 (DNJ).

4.2

Effect of pulmonary flow heterogeneity on oxygen uptake and delivery

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A critical determinant of functional capacity is the diffusing capacity of the lung for oxygen, which determines the rate of oxygen uptake into the bloodstream. This rate is affected by the transport characteristics of the alveolar-capillary membrane as well as heterogeneity of pulmonary blood flow. We have previously showed that under resting conditions the healthy lung has a high degree of tolerance for pulmonary flow heterogeneity, but that under conditions of exercise such flow heterogeneity can preclude the high levels of oxygen uptake necessary to meet tissue demand. The goal of the present study is to assess the extent to which flow regulation mechanisms such as hypoxic pulmonary vasoconstriction (HPV) mitigate flow heterogeneity and enable adequate oxygen transport levels in the lung to meet tissue needs under conditions of physiologic stress such as exercise. Investigating the interaction of pulmonary oxygen uptake and peripheral oxygen delivery and utilization necessitates the use of a coupled pulmonary and systemic model for oxygen transport, and is conducted as follows. In the pulmonary compartment, flow heterogeneity is simulated by considering parallel capillaries with the same entering venous oxygen content but an initial lognormal distribution of flows as characterized by a coefficient of variation (CV). Since vessels with higher flows may reach lower arterial saturation values and such vessels are disproportionally represented in the flow-weighted average, a high degree of flow heterogeneity may significantly decrease the oxygen content of blood exiting the lung. This blood then enters the systemic circulation, where oxygen consumption is modeled using Michaelis-Menten kinetics, which accounts for the fact that oxygen consumption is delivery-dependent and may be significantly less than oxygen demand under extreme conditions. Values of arterial and venous oxygen content are then iterated to convergence. This combined model is then used to assess how arteriovenous values of oxygen content are affected by pulmonary flow regulation in the form of HPV. To simulate HPV, pulmonary capillary resistances (and therefore flows) are adjusted by using HPV response models that depend on the capillary oxygen tension (approximated as the mean of the venous and arterial values in each capillary). Preliminary results show reductions in the effective CV from a baseline of approximately 3 to 2.5 under normoxic conditions and to values less than 0.5 in the case of exercise with hypoxia. The stronger reduction in heterogeneity under conditions of hypoxia and exercise corresponds to the need for greater flow regulation to minimize heterogeneity under conditions of physiologic stress. The predicted level of heterogeneity in exercise is in general agreement with our previous prediction of the upper limit of CV consistent with the levels of oxygen uptake in literature data for exercising humans. The results demonstrate the essential role of HPV to regulate flow and minimize heterogeneity under conditions of exercise and highlight the need for a functional pulmonary flow regulation mechanism under stressful or pathophysiological conditions. Support or Funding Information Supported by NIH U01 HL133362.

4.3

A multi-scale computational model of rat ventilation-perfusion matching

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Ventilation-perfusion (V/Q) matching is a fundamental determinant of gas exchange efficiency in the

pulmonary circulation. V/Q mismatching and subsequent secondary blood gas derangement is a common occurrence in patients with vaso-occlusive diseases such as pulmonary embolism. Despite the physiological importance of V/Q matching, there are gaps in our knowledge of the regulatory mechanisms that maintain adequate gas exchange under normal conditions and in pathology. Here we present a multi-physics multi-scale computational model of the rat pulmonary microcirculation and oxygen transport as an in silico platform to test hypotheses regarding the regulation of V/Q matching. Our model recapitulates many experimental observations of the pulmonary circulation including: (1) regional capillary pressure and flow distributions; (2) oxygenation is inversely proportional to the capillary flow rate; (3) recruitment of microvascular volume with increasing cardiac output; and (4) the dynamic consequences of breathing on regional V/Q ratio distribution. We show that in the absence of pathological insult (vascular occlusions or tissue remodeling), the pulmonary circulation can facilitate efficient oxygen transport when challenged with extreme V/Q mismatching. Our results demonstrate how the fractal-like redundancy of the lung anatomy can maintain systemic arterial oxygen levels within a homeostatic range without active vasoregulation to optimize regional V/Q ratios. However, inclusion of a local feedback mechanism, such as hypoxic pulmonary vasoconstriction, is required to obtain physiologically realistic transit time distributions and observed V/Q ratio distributions. We anticipate that our computational model will be a starting point for dynamic and integrative analysis of various diseases such as pulmonary emboli and fibrotic remodeling of the airway. Moreover, our model predictions suggest that under healthy conditions hypoxic pulmonary vasoconstriction is not essential to optimize the transport of oxygen into the bloodstream, but does operate to homogenize the distribution of mechanical stresses throughout the pulmonary vascular network.

4.4

Muscle oxygen transport in health and disease: innovative approaches, novel insights

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The oxygen transport pathway from atmospheric air down to cell mitochondria involves a series of transfer steps within closely integrated systems (i.e., pulmonary, cardiovascular and tissue metabolic). Small and finite O2 stores in most mammalian species mandate exquisitely controlled changes in O2 flux rates to support elevated ATP turnover. This is particularly true for the contracting skeletal muscle where O2 demand may increase two orders of magnitude above rest. The current work focuses on the mechanistic bases of microvascular blood-myocyte O2 flux ($\dot{V}O2$) during transitions in metabolic demand. Within the skeletal muscle microcirculation, O2 transport across the capillary wall is dictated by Fick's law of diffusion: $\dot{V}O2=DO2*\Delta PO2$; where $\dot{V}O2$ is the rate of O2 flux, DO2 is the diffusing capacity (determined primarily by the aggregate number of red blood cells within capillaries adjacent to the myocyte at any given moment), and $\Delta PO2$ is the O2 partial pressure gradient between the microvascular and interstitial spaces (PO2mv and PO2is, respectively). This relationship establishes that alterations in O2 flux ($\dot{V}O2$) imposed by metabolic transitions (rest-contractions-recovery) require corresponding changes in effective diffusing capacity (DO2) and/or driving force (i.e., $\Delta PO2=PO2mv-PO2is$) to adequately support oxidative phosphorylation. While previous evidence indicates that increased DO2 helps modulate contracting muscle O2 flux, the role of the dynamic $\Delta PO2$ across the capillary wall has only recently been explored. Dual-probe phosphorescence quenching techniques targeting both microvascular and novel interstitial PO2 kinetics in health have resolved an important step in the O2 transport cascade between the capillary and myocyte. Specifically, the significant transcapillary $\Delta PO2$ observed at rest was largely sustained (as opposed to increased) during submaximal muscle contractions. These findings support that the short diffusion path between the red blood cell and sarcolemma (also known as the 'carrier-free region') is the site of considerable resistance to transcapillary O2 flux. Moreover, based on Fick's law, elevated O2 flux ($\dot{V}O2$) with contractions must be achieved via corresponding changes in effective DO2 (mainly red blood cell hemodynamics and distribution) in the face of preserved $\Delta PO2$. Evaluation of the O2 transport pathway close to muscle mitochondria is fundamental for identifying disease mechanisms and, therefore, to the design of effective therapies aiming to improve exercise tolerance and reduce morbidity and mortality in disease. Funding: This work was supported in part by a Post-doctoral Fellowship from the College of Human Ecology, Kansas State Univ.; and National Heart, Lung and Blood Institute Grant HL-2-108328.

5: SYMPOSIUM 3: MYOCARDIAL MICROCIRCULATION

5.1

Supply-demand matching of oxygen across the myocardium at rest and during exercise

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At rest, myocardial oxygen consumption (MVO2) is met through the extraction of 80% of the oxygen delivered to the coronary vasculature leaving little room for additional extraction during exercise. Therefore, coronary flow is intimately matched to any exercise induced increase in MVO2. We have employed a mechanistic multi-scale model to represent left anterior descending (LAD) flow and oxygen delivery to understand the regulation of blood flow during exercise to match MVO2. In the Tune lab, healthy Ossabaw adult swine were instrumented to provide simultaneous left ventricular and aortic pressures along with blood flow in the LAD at rest and at two levels of exercise. In the Beard lab, a recent model by Mynard and Smolich was modified simulating blood flow in the LAD where each terminal branch in the network feeds into a three-compartment lumped parameter model representing the subepicardial, midmyocardial and subendocardial flow. At rest, parameter values for the epicardial segments were directly from Mynard and Smolich while some of the parameters for the myocardial flow portion of the model were adjusted to match the mean LAD flow data and give an endo/epi flow ratio of 1.14. We then used this model exactly as parameterized at rest and drove it with the exercise level 2 aortic and LV pressures to see how well it matched the exercise level 2 LAD flow data. Simulation results employing a graded vasodilation across the subepicardial to subendocardial regions produces an endo/epi flow ratio to about 0.85 which match experimental values for endo/epi flow ratios during exercise in a review by Duncker and Bache. Overlaying a simple model of oxygen delivery and consumption on this model of blood flow shows that the subendocardium is at the highest risk for oxygen deficit and graded vasodilation across the vascular beds mitigates this risk. This multi-scale model is currently being made available in CellML and Modelica for wider dissemination. Upon publication of this work the original data will be available on the PhysioNet repository.

5.2

Towards a coronary microscope: insights into the microvasculature through the lens of macro-hemodynamics

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In vivo assessment of coronary microvascular properties is challenging due to the major impact of time-varying extravascular forces on blood flow patterns in the large epicardial conduit arteries ('macro-hemodynamics'). Coronary wave intensity analysis quantifies forward- and backward-running waves in the conduit arteries and is increasingly being utilised in clinical research to investigate mechanisms underlying observed changes in hemodynamics. However, recent work using a combination of computational modelling and experimental data has shown that the origins of the observed waves are more complex than previously thought [1]. In particular, waves that are actively generated by variations in aortic 'driving' pressure proximally and intramyocardial pressure distally undergo non-linear superposition with waves that are passively reflected at the coronary ostium and in the coronary microcirculation. With the aid of computational modelling [2], a comprehensive explanation of the origins and relative amplitudes of coronary waves becomes possible and it is shown that, with a few reasonable assumptions and additional measurement of aortic flow, active and passive coronary waves can be disentangled. A key result is that the reflection coefficient of the coronary microcirculation appears to be relatively stable during the period spanning the major coronary waves. Using experimental data from adult sheep, it is shown that changes in coronary resistance induced by inhibition of NO synthesis produce marked increases in coronary reflection coefficient that can be measured via wave intensity analysis. Although dependent on high fidelity signals, these techniques provide a promising avenue for gaining insights into active forces on and passive properties of the coronary microvasculature in health and disease.

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5.3

Imaging coronary vasculature in cleared rat ventricle

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Obtaining detailed and precise morphology of the coronary vasculature is an important requirement for generating physiologically accurate mathematical models of cardiac coronary flow. Despite many efforts to develop three-dimensional imaging and experimental techniques to capture such data, the resulting datasets have, to date, been limited due to the innate size and complexity of the coronary network. In this study, we have combined optical tissue clearing, fluorescent labelling, and extended-volume confocal imaging to acquire high-resolution 3D images of rat coronary networks in the left ventricle. Optical clearing has been widely used for nervous tissue, such as the brain, but has seen only limited use in cardiac tissue. In this study we have adapted the existing optical clearing technique CUBIC1 to clear rat ventricles, and demonstrate its compatibility with fluorescent labels for vasculature and myocytes. All experimental work was approved by the Animal Ethics Committee of the Univ. of Auckland (Ref: 001119) and conforms to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23). Hearts were extracted and mounted on a Langendorff apparatus, and cleared via perfusion, which substantially reduces the time required for clearing while maintaining transparency and the ability for fluorescent labeling. We applied this technique to clear both Wistar-Kyoto (WKY) normal rat hearts, and 18-month-old spontaneously hypertensive rat (SHR) hearts, followed by labelling of the coronary vasculature with Tomato Lectin (Vector Labs, DL-1178) and the cardiac myocytes with Phalloidin (Biotium, BIT00044). Using a novel extended-volume confocal imaging system developed at the Auckland Bioengineering Institute, we acquired three-dimensional anatomical geometries of the coronary network from cleared WKY and SHR left ventricle, at a resolution of 1 µm, over dimensions of tens of mm. The results are unique 3D datasets of healthy and diseased coronary anatomy. This work is supported by the Marsden Fund Council from New Zealand Government funding, managed by the Royal Society Te Aparangi, grant number UOA1620. 1 Susaki, E. A. et al. (2014). Whole-Brain Imaging with Single-Cell Resolution Using Chemical Cocktails and Computational Analysis. Cell, 157(3), 726–739. https://doi.org/10.1016/j.cell.2014.03.042.

5.4

Endothelium-dependent vasodilation in the human microcirculation: a switch in mechanism with disease or stress

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Shear stress in arterioles normally stimulates, through mechanotransduction, the production of nitric oxide (NO) to elicit vasodilation and to maintain quiescence of the vessel wall and underlying parenchymal cells. In human subjects with conduit coronary artery disease (CAD), shear also elicits vasodilation but the mediator is switched from NO to hydrogen peroxide. Hydrogen peroxide is an effective dilator but is also known to exert deleterious effects including upregulation of endothelial adhesion molecules, stimulation of pro-inflammatory and proliferative changes in the vessel wall, and stimulation of pro-oxidant pathways. How this switch occurs and identifying ways to reverse it are the focus of this presentation. We have examined the pathways of shear-induced dilation in human arterioles in health and disease. Resistance arterioles (50-150 microns internal diameter) are isolated from human atrial appendages or adipose tissue obtained at the time of surgery. Vessels are mounted on glass pipettes, pressurized, and maintained in warmed buffer. Endothelium-dependent dilation to shear or acetylcholine and endothelium-independent dilation to papaverine or nitroprusside are assessed before and after interventions. Key findings include identifying a critical role for the endothelial cytoskeleton, and demonstrating TRPV4 channels as playing a key role in mediating FMD during disease. We have also determined the source of hydrogen peroxide as originating from the mitochondrial electron transport chain. Hydrogen peroxide is released from the mitochondria and acts on the underlying smooth muscle by dimerizing PKG1-alpha which opens large conductance calcium-activated potassium channels (BK) to elicit dilation. This production of mitochondrial ROS can be ablated by mitochondrial-targeted antioxidants. Recent findings implicate extra-nuclear telomerase, ceramide, and

autophagy as key players in the pathological mechanism of shear-induced dilation. Translocation of telomerase reverse transcriptase (TERT) from nucleus to the cytosol and mitochondria during stress inhibits mitochondrial ROS production and restores NO formation in response to shear in patients with CAD. Key roles have been identified for ceramide, lysophosphatidic acid, PGC1-alpha, and autophagy have been demonstrated in this switch in mediator of dilation. New data will be presented exploring whether these seemingly pathways are linked or distinct in their modulation of microvascular endothelium-dependent dilation. Supported by grants from NHLBI and from the Northwestern Mutual Endowment.

6: TRAINEE CAREER WORKSHOP: CAREERS IN THEORETICAL MODELING AND QUANTITATIVE ANALYSIS OF PHYSIOLOGICAL SYSTEMS

6.1

Navigating biological research as an early-career mathematician

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Collaboration between mathematicians and biologists is crucial for developing and interpreting mathematical models that represent biological systems. This type of collaboration can bring about great opportunities for progress as well as, potentially, great difficulties in communication. In this talk, I will describe my experiences through graduate school and postdoctoral training as a mathematician studying biological systems. I will outline the various opportunities that benefited me along the way as well as the various projects I have worked on, which include models of cell polarization, cancer, and tuberculosis.

6.2

Microvasculature and how I got here

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Microcirculation, a key determinant of vascular resistance is regulated by several factors, including smooth muscle reactivity, endothelium-derived vasoactive mediators, and neurotransmitters. These factors participate in integrating vasodilator and vasoconstrictor stimuli via signal transduction mechanisms that are mediated by ion channels and G-protein-coupled receptors (GPCRs). My current research focuses on the function and regulation of ion channels and GPCRs in microvessels and cells that impinge on them. The underlying theme of the trainee career workshop is “careers in theoretical modeling and quantitative analysis of physiological systems.” Hence, my talk will primarily address trainees that investigate or that are interested in the physiological systems of microcirculation. I will briefly share how my career path progressed, including predoctoral research on uterine smooth muscle reactivity, a postdoctoral fellowship in vascular ion channels, and independent research in physiology and pathophysiology of microcirculation. The goal of my presentation is to convey critical personal experiences that brought me to my current career stage; the career-defining moments and the significance of networking, deviating from original research interests, creating a niche, and finding/having good mentors. I hope that, by sharing the specific experience that I have garnered so far, trainees will obtain some helpful guidance or strategy to get ahead in their career pursuits.

7: POSTER SESSION 1 & SOCIAL ACTIVITY

7.1

The role of microvascular permeability on the dynamics of biomarker exhalation

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Non-invasive measurement of blood-based biomarkers detected through the breath is widely gaining popularity for early diagnosis of chronic disease including cancer detection. This is due to the promise of this more rapid and less expensive approach than currently available standard blood analysis or other invasive diagnostic techniques. Current analysis methods rely on the accumulation of breath over a period of time in a sample holder such as a bag or cartridge. Breath biomarker concentration is retrieved utilizing the known (constant) volumetric exhalation rate and collection time. However, this approach presumes that biomarker concentration in the breath remains constant. In preliminary clinical trials, we have observed that the rate at which biomarker accumulates varies with collection time, suggesting that the exhaled biomarker concentration is time-dependent. This data was obtained utilizing a novel polymeric membrane-catalyst approach to chemical sensing capable of sub-second time resolution. Such

rapid measurement is essential to capturing dynamic data in-situ over a typical exhalation time of 30 seconds and it cannot presently be achieved by other methods. In this presentation, we discuss theoretical modeling of time-dependence gas exchange that introduces biomarker molecules of distinctly different microvascular permeability characteristics into breath samples and simultaneous exhalation of these molecules. Heuristically, permeability is a measure of how quickly a molecule, for example acetone, crosses the lung vasculature walls during each breath cycle. The timescale required for equilibrium to occur between the blood levels of a gas and the gas concentration in the lung airways is dictated by microvascular permeability and, consistent with clinical data, is determined to be much longer than the 30 seconds that are typical of a breath cycle. Our model provides an understanding of the interplay between dynamic measurements of breath biomolecule concentration and microvascular permeability.

7.2

Hydrogen sulfide diffusion through animal and human tissue

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Peripheral artery disease (PAD) is a narrowing of large peripheral arteries caused by atherosclerotic plaque and blood vessel inflammation, while small vessel disease (SVD) is damage to the microvasculature and impaired local perfusion. Both are preceded by endothelial dysfunction and lead to vascular stenosis and limb ischemia. Within the vascular wall, hydrogen sulfide (H2S) is produced by cysthathionine γ-lyase (CSE) in endothelial cells. In diabetic patients, the loss of H2S production impairs vasodilation that results in irreversible vascular disease and the ensuing diabetic complications. In human and animal models of type 2 diabetes, it is increasingly apparent that both obesity and hyperglycemia decrease vascular production of H2S and that this decreased production contributes to endothelial dysfunction and diabetic tissue damage. Thus, H2S detection provides the means to diagnose early stage vascular disease, monitor progression of endothelial disease, and explore novel therapeutic paths. Current diagnostic methods are expensive and technically difficult to implement for wide-spread use. A miniature, highly sensitive device named TAGS has been used to transdermally measure H2S permeated through the skin and its correlation to superficial blood perfusion. The diffusion of H2S, produced locally and systemically is affected by a number of parameters including water solubility. In this paper, we present the results of a transient one-dimensional model of H2S permeation rate that affects the TAGS measurements, followed by experimental measurements in the laboratory on both model animals and volunteer human subjects. In Sprague Dawley rats, it was found that transdermal levels of hydrogen sulfide decrease after administration of a hydrogen sulfide suppressing agent PAG. The results of measurements in healthy human volunteers indicate that after adjustment for age, measurements from TAGS are comparable to those of laser speckle contrast imaging (LSCI), the gold standard for monitoring skin blood flow ($r=0.5717$, $p=0.0132$ $n=18$). These results indicate that TAGS is not inferior to LSCI in healthy individuals using a non-inferiority margin of 5 ($p=0.0394$). When extended to simultaneous diffusion of two molecules such as H2S and acetone with dramatically different water solubility, the model provides details of tissue permeability characteristics that can be measured using a modified version of TAGS.

7.3

Interactions between pairs of red blood cells in microvascular flows

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The hematocrit distribution across a vessel depends on a balance between cell-wall interactions and cell-cell interactions. Cell-wall interactions tend to push red blood cells away from the vessel walls while cell-cell interactions tend to push red blood cells away from each other and towards vessel walls. To better understand these interactions, a two-dimensional model of red blood cell interactions has been used to consider pairs of cells in approximately infinite linear shear flow, linear shear flow near a wall, and Poiseuille flow. Initial results have allowed classification of three types of behavior including a passing interaction where a faster moving cell overtakes and passes by a slower moving cell, a swapping interaction where the faster cell and slower cell swap roles by moving in opposite directions transversely across streamlines, and a dancing interaction where cells circle around each other multiple times. In addition, results have also

suggested that when near a wall, interaction magnitudes depend on the distance to that wall. Finally, we show our initial results regarding the presence of another cell on the tendency for a cell near the wall to tumble, swing, and tank-tread.

7.4

Structural analysis of coronary microcirculation in healthy and diseased hearts

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The purpose of this study was to identify the structural relationship between the coronary microcirculation and muscle fibers in healthy and diseased rat hearts. High-resolution extended-volume 3D images of the coronary network along with myocytes, from 10 rats including 5 spontaneous hypertensive rats (SHR), were acquired using a confocal microscope and a custom-built fluorescent microscope. An automatic image processing pipeline was developed to enhance, segment, skeletonize, and quantify the corresponding image data. In each processed sub-block, we calculated vessel properties such as radius, variation in directions, and alignment with myocytes. These measurements were used to compare coronary network structure in SHR hearts to normal rat hearts. This work is supported by the Marsden funding administered by the Royal Society of New Zealand, grant number UOA1620.

7.5

Oxygen permeability of red blood cells: insights from mathematical modeling

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Red blood cells (RBCs) play a central role in life by carrying O2 from lungs to tissues, and CO2 in the opposite direction. A crucial step in the transport of these gases within the body is their movement across cell membranes-including the plasma membrane (PM) of RBCs-that these gases encounter along their journey in and out of the body. The traditional view on gas transport across cell membranes has been based on the solubility-diffusion theory, which states that all gases move across all membranes by dissolving in and diffusing through the lipid phase of the membrane. However, the discoveries of the first CO2-impermeable membrane (Waisbren et al, 1994 Nature) and of the first membrane protein, aquaporin-1 (AQP1), that can conduct CO2 (Nakhoul et al, 1998 AJP, Cooper & Boron, 1998 AJP) challenged this view and pointed towards the role of integral membrane proteins in augmenting membrane permeability to gases. In human RBCs, Endeward and coworkers (Endeward et al, 2006 FASEB J, Endeward et al, 2008 FASEB J) showed that AQP1 and the RhAG protein of the Rhesus family mediate ~90% of membrane CO2 permeability (PM,CO2) and that the amino-reactive agent 4,4'-diisothiocyanatostilbene-2,2'-disulfonate (DIDS) decreases PM,CO2. Recently, Zhao and colleagues (Zhao et al, 2016 FASEB J) used stopped-flow (SF) analysis of hemoglobin (Hb) absorbance spectra-during O2 efflux, in the presence of an extracellular O2 scavenger-to determine the effect of DIDS and p-chloromercuribenzenesulfonate (pCMBS) on the rate constant of Hb deoxygenation (kHbO2). These authors found that, in mouse WT RBCs, DIDS reduces kHbO2 by ~49%, and pCMBS by ~64%. Because these two agents are excluded from cytosol, and likely target membrane proteins rather than membrane lipids, Zhao et al hypothesized that O2 can traverse the PM of RBCs via known integral membrane proteins. By performing SF experiments on mouse RBCs genetically deficient in AQP1, RhAG, or both (dKO), they found that kHbO2 falls by (i) 9% in mouse RBCs genetically deficient in AQP1, (ii) 17% in mouse RBCs genetically deficient in RhAG, and (iii) 31% in mouse RBCs from dKO. Moreover, pCMBS reduces kHbO2 by ~79% in dKO. To investigate whether decreases in kHbO2 can be explained by small changes in RBC geometry and [Hb], we developed a reaction-diffusion model of a spherical RBC-with diameter equal to the thickness of the RBC-to describe the dynamics of oxyhemoglobin [HbO2], [Hb], and [O2] as O2 diffuses from the RBC cytosol, through the PM and extracellular unconvected fluid (EUF), and to the bulk extracellular fluid. Informed by flow cytometry and hematology data, the model predicts that the observed decreases in kHbO2 cannot be explained by changes in RBC size and [Hb]. We employed the model to predict membrane O2 permeability (PM,O2) and found that the observed decreases in kHbO2 correspond to decreases in PM,O2 of 22% for AQP1–/–, 37% for RhAG–/–, 57% for dKO, 74% for WT+DIDS, 84% for WT+pCMBS, 81% for dKO+DIDS, and 92% for dKO+pCMBS. We explored the predicted sensitivity of kHbO2 to seven key kinetic and geometric parameters (i.e., intracellular diffusion constant (D) of HbO2 and Hb, intracellular and extracellular DO2, rate constant of HbO2 deoxygenation, EUF

thickness, and cell diameter) and found that no reasonable changes in any parameter can explain the kHbO2 data. Finally, contrary to common belief, the model predicts that the PM represents >20% of total resistance to O2 diffusion, even for a WT mouse. Supported by NIH K01-DK107787 to RO and NIH R01-DK113197, ONR N00014-15-1-2060, ONR N00014-16-1-2535 to WFB.

7.6

Organismal systems modeling (OSyM) research coordination network

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Animals are complex systems of interconnected elements (modules) operating at multiple spatial and temporal scales. Discovering systems-level attributes that make animals resilient or robust, or conversely sensitive or fragile, to change presents a grand challenge for biology. Knowledge of these attributes and the underlying mechanisms controlling them is necessary for predicting how animals will respond to short- and long-term changes in internal and external environments. But, traditional approaches in biology are inadequate for the task. Significant advances can be made by incorporating tools from other disciplines, particularly applied mathematics, engineering, and modelling. However, to successfully incorporate these tools into organismal biology, mechanisms are needed for cross-training and facilitating collaborations at all professional levels among these diverse scientific fields. The creation of the Organismal Systems-type Modeling (OSyM) Network will: 1) Provide mechanisms to build and broaden the community of organismal biologists, mathematicians, modellers, computer scientists, and engineers using integrative, systems-level approaches to investigate stability and change in organismal animal systems and 2) Facilitate development of effective collaborations and the exchange of approaches, skills, and ideas among members of this community.

8: SYMPOSIUM 4: STRUCTURAL ADAPTATION AND ANGIOGENESIS IN MICROCIRCULATORY PATHWAYS

8.1

Agent-based modeling of multi-cell niches in health and disease

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Whether a tissue successfully repairs itself following an injury, scars over, or succumbs to disease is largely based on cell-to-cell and cell-to-environment signals that form feedback loops within the local niches where cells reside. Traditional approaches use reductionist experimental designs to isolate key variables, but cause-and-effect relationships are difficult to infer when there exists a multitude of interacting drivers. The objective of our work is to develop new computational modeling approaches, in conjunction with experiments, to study the multi-cell interactions that give rise to changes in tissue structures over time. We combine agent-based computational modeling with other modeling approaches and dynamic intravital microscopy of living tissues to predict how stimuli, such as acute and chronic inflammation, affect microvascular remodeling and tissue regeneration. Our computational models necessarily bridge across spatial and temporal scales. With agent-based modeling serving as the backbone of our simulation framework, we integrate network models of intracellular signaling and models of tissue-level mechanics to span biological phenomena from gene-to-tissue. Thus, our computational models serve as test beds for exploring how biochemical and biomechanical signals drive cell behaviors, and predict how targeted interventions might alter outcomes.

8.2

Glomerular capillary shear stress and hoop stress are significantly elevated in 5/6-nephrectomy: a modeling study

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Loss of kidney mass leads to hypertrophy of and increased blood flow and filtration in the remaining nephrons. An experimental model to study the consequences of renal mass reduction is the 5/6-nephrectomy (5/6 Nx) rat model which has been shown to have increased glomerular pressure (ΔP) and afferent plasma flow (Qa) in the remaining glomeruli. These hemodynamic consequences of

reduced renal mass are assumed to increase glomerular capillary circumferential hoop stress (HS) and shear stress (SS), respectively. The actual magnitudes of these mechanical forces in the entire network of glomerular capillaries remain uncertain in 5/6-Nx and are of significance due to the sensitivity of endothelial cells to SS and podocytes to HS. Hypertrophy of the glomerular capillaries characteristic of 5/6-Nx may mitigate the increase in SS but in turn will increase HS. Due to a lack of anatomically-accurate mathematical models of the glomerulus, it remains unknown how these anatomical changes affect the mechanics in the glomerular capillaries. We developed a mathematical model of blood flow through an anatomically-accurate rat glomerular capillary network to estimate the magnitudes of SS and HS on the glomerular capillary walls in 5/6-Nx. Individual filtration rates, wall HS and wall SS were calculated for each capillary segment of the network based on values of Qa, ΔP and single nephron GFR (SNGFR) obtained from a micropuncture study using normal rats and rats with 5/6-Nx (Kasiske, Bertram L., et al. Circ. Res. 62.2: 367-374. (1988)). In this study, 5/6-Nx increased Qa and ΔP by 174.8% and 19.0%, respectively and increased the filtration coefficient (Kf) such that filtration fraction (FF) was maintained. Using these data, the Young-Laplace equation was used to calculate HS in each capillary, and SS was calculated assuming Poiseuille flow with blood viscosity scaled based on vessel diameter and hematocrit. To validate mechanical predictions of our model, we compared our calculated SS magnitudes to results from intravital imaging studies of blood flow in rat glomeruli (Ferrell, Nicholas, et al. Am. J. of Phys-Renal 308.6: F588-F593. (2015)). To simulate glomerular capillary hypertrophy in 5/6-Nx, the capillary diameteSrs were all increased by 16.1%. Our model's calculated mean glomerular capillary wall SS was approximately 51.7% larger than the SS predicted using intravital imaging in control conditions. Taking into account an increase in diameter of the glomerular capillaries, the model predicted mean SS values of 48.1 dynes/cm2 in control and 79.4 dynes/cm2 in 5/6-Nx. The increase in diameter of the glomerular capillaries was not substantial enough to control the SS, contrary to experimental findings which showed a normalization of SS in 5/6-Nx. Additionally, the increase in glomerular capillary diameter increased HS by 38.2%. This study demonstrates that the increase in diameter in 5/6-Nx reduces but fails to normalize SS in 5/6-Nx and contributes to a significantly increased HS. These increased mechanical stresses on the glomerular capillaries may play a causative role in the progression of glomerular injury in 5/6-Nx thus leading to chronic kidney failure.

8.3

Mathematical models of non-drug therapies in angiogenesis

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8.4

A systems biology view for discovering cell dynamics during microvascular network growth

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Systems Biology can be characterized by the application of experimental and computational approaches for integrating interactions of the key elements across scales. What happens, however, when the interactions are unknown? Basic science discovery is needed to inform computational rules, inputs, and these dependent relationships. This presentation will highlight the impact of an integrated perspective on the discovery of cell dynamics during microvascular growth. Specifically, novel observations made possible by biomimetic model development will motivate paradigm creating questions related to lymphatic-blood vessel plasticity, pericyte recruitment, and the vasculogenic potential for stem cell populations.

9: SYMPOSIUM 5: CANCER TISSUE MICROCIRCULATION

9.1

Multiscale modeling of blood flow in the human vasculature

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Building a detailed, realistic model of human blood flow, is a formidable mathematical and computational challenge. The models must incorporate the motion of fluid, intricate geometry of the blood vessels, continual pulse-driven changes in flow and pressure, and the behavior of suspended bodies such as red blood cells. In this talk, I will discuss the development of HARVEY, a parallel fluid dynamics application designed to model hemodynamics in patient-specific

geometries. I will focus on the recent introduction of a scalable fluid-structure-interaction model and the techniques introduced to enable efficient scaling on over one million cores. This code relies on the lattice Boltzmann method to capture the underlying fluid flow and the immersed boundary method to couple the fluid with the cell model. Within this framework, we are able to investigate the role of different biophysical properties in influencing a cell's trajectory through the vasculature and explore the impact of inter-cellular interactions. The computational framework's parallel performance in this setting as well as validation against in vitro experiments are evaluated and future development lessons will be discussed.

9.2

Emerging mechanistic biomarkers of cancer chemo-radiation and immunotherapy from mathematical biophysics

Vittorio Cristini[1]
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We have formed a multidisciplinary, multi-institution team in deploying systems cancer biology and immunology platforms to enable predictive modeling of therapeutic interventions. We have developed from first principles and validated, through pre-clinical models and retrospective analysis of clinical trials, first-of-their-kind mechanistic mathematical models of chemo-radiation and immunotherapy response, which describe the complex coupling of physical and biological processes and have identified novel, early biomarkers of patient response. Our work shows that this model can accurately predict response to anti-CTLA4 and anti-PD1/PDL1 therapies, and a set of model parameters were found to act as mathematical markers of patient response and of patient survival. Our long-term vision is to design personalized therapy plans, which optimize immune system and tumor microenvironment biomarkers for maximum therapeutic efficacy.

9.3

Image-based systems biology of the microvasculature in cancer

Arvind Pathak[1]
[1]*Johns Hopkins Univ.*

9.4

Mechanobiological control of vascular function

Lance Munn[1]
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The lymphatic system is responsible for fluid homeostasis, immune cell trafficking and regulation of the immune response, and it is often dysfunctional in and around solid tumors. Fluid and cells from tissue enter lymphatic capillaries, and then pass through collecting lymphatic vessels, which actively contract to pump the lymph back to the systemic circulation. Unfortunately, the mechanobiological mechanisms that regulate lymphatic cell contractions are poorly understood, so no pharmacological treatments are available for lymphatic pathologies. The ability of cells to sense and respond to physical forces has been recognized for decades, but researchers are only beginning to appreciate the fundamental importance of mechanical signals in biology. At the larger scale, there has been increased interest in the collective organization of cells and their ability to produce complex, “emergent” behaviors. Often, these complex behaviors result in tissue-level control mechanisms that manifest as biological oscillators, such as observed in fireflies, heartbeats and circadian rhythms. In many cases, these complex, collective behaviors are controlled-at least in part-by physical forces imposed on the tissue or created by the cells. Using mathematical simulations, we discovered that two complementary mechanobiological oscillators are sufficient to control fluid transport in the lymphatic system: Ca++ - mediated contractions can be triggered by vessel stretch, while nitric oxide produced in response to the resulting fluid shear stress causes the lymphatic vessel to relax locally. The model demonstrates how Ca++ and nitric oxide (NO) levels alternate spatiotemporally, establishing complementary feedback loops, and that the resulting phasic contractions drive lymph flow. This mechanism is self-regulating and robust over a range of fluid pressure environments, allowing the lymphatic vessels to provide pumping when needed but remain open when flow can be driven by tissue pressure or gravity. The model accurately reproduce the responses to pressure challenges and signaling pathway manipulations observed experimentally, providing an integrated, conceptual framework for lymphatic function.

10: SYMPOSIUM 6: RENAL MICROCIRCULATION

10.1

Renal oxygenation during diuresis

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Study objective: We have previously developed a set of oxygen transport models for the renal cortex and the medulla based on the adult rat kidney that can accurately predict normal and abnormal oxygen states within the kidney, in terms of tissue oxygen tension (PO2). The objective of this study was to use the model to investigate how renal oxygenation changes during diuresis, specifically saline diuresis (induced by excess sodium intake) and water diuresis (induced by excess water intake). Methods: The renal cortex model consists of pseudo-three-dimensional (3D) 25 multiscale systems that represent various branch levels of the pre- and post-glomerular vessels and capillaries [1, 2]. The model calculates the spatial average cortical tissue PO2 and blood PO2 at various cortical levels using the equations of advection, diffusion and oxygen-hemoglobin dissociation. The renal medulla was modeled as multiscale model based on a realistic 3D renal medulla geometry, consisting of macroscale (top-level) models and microscale (low-scale) models [3]. The top-level models represent the axial blood flow and the oxygen transport throughout the whole medulla, and the low-scale models represent the distribution of oxygen in two spatial dimensions across the renal tissue of different medullary levels. The renal cortex and the renal medulla models work in tandem: the renal cortex model first calculates the cortical tissue PO2 and the corticomedullary junction PO2, and the renal medulla model calculates the medullary tissue PO2 based on the corticomedullary junction PO2. Five key input parameters were altered to describe the changes in the kidney during diuresis: (1) renal blood flow (RBF); (2) oxygen consumption (VO2); (3) local fraction of blood flowing to the medulla (fRBF); (4) local fraction of oxygen consumed in the medulla (fVO2,M); and (5) hematocrit level (Hct). The changes in these parameters were based on experimental and clinical data found in the literature. Results: Our model predicts that under normal physiological condition, the average tissue PO2 for the cortex is ~43 mmHg. The average tissue PO2 for the whole medulla is ~30 mmHg, with the lowest tissue PO2 of ~24 mmHg in the outer stripe of the outer medulla (OSOM). Our parametric study shows that medullary oxygenation is more sensitive to reduction in blood flow than in increase in oxygen consumption. We also show how the normal renal oxygenation changes as the input parameters change during saline and water diuresis. Conclusion: The renal cortex model and the renal medulla model are robust and able to accurately capture the behavior of renal oxygenation in both normal state and during diuresis. The use of a realistic 3D geometry potentially opens the door to image-based patient-specific modeling of human kidneys.

10.2

Determining risk factors for triple whammy AKI using computational models of long-term blood pressure regulation

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Concurrent use of diuretics, angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), and nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of acute kidney injury (AKI). AKI resulting from use of all three drugs is referred to as “triple whammy”. Diuretics and ACEI/ARB are often prescribed in tandem for the treatment of hypertension while some NSAIDs, such as ibuprofen, are available over the counter. As such, concurrent treatment with all three drugs is common. To address the critical need to better understand the mechanisms behind the increased risk of AKI and to identify potential risk factors, we use computational models of long-term blood pressure regulation we developed previously. We hypothesize that individual variations in tubuloglomerular feedback, the myogenic effect, and renal sympathetic nervous activity will determine whether or not triple whammy patients develop AKI. Other circumstances that we hypothesize to influence AKI development include hypertension and genetic polymorphisms in enzymes (ACE) or receptors (angiotensin type 1). The computational models used include variables describing the heart and circulation, kidney function, sodium and water reabsorption in the nephron, and the renin angiotensin system (RAS) and is fit separately for male and female humans. This research was supported by the Canada 150 Research

Chair program and by the National Institutes of Health via National Institute of Diabetes and Digestive and Kidney Diseases, grant R01DK106102.

10.3

Renal microcirculation: from the arterial network topology to the blood flow dynamics and synchronization

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By maintaining the volume and composition of the body fluids within narrow ranges, and by producing a set of hormones that affect the blood vessels, the kidneys provide important long-term regulation of blood pressure. Disturbances of kidney function can cause hypertension and related cardiovascular diseases - the major cause of death worldwide. The kidneys protect their own function against short-term variations in blood pressure. At the level of the individual functional unit (the nephron), it involves two different mechanisms that both produce oscillations in the blood flow and pressure: myogenic mechanism and tubuloglomerular feedback (TGF). Over the years it has become clear that nephrons interact trough hemodynamical and electrical signaling which is mediated through the arterial network of the kidney. Simultaneous micropuncture recordings in 2-3 nephrons have shown that this interaction can lead to synchronization of TGF and myogenic activity in adjacent nephrons [1]. Due to the technique being restricted to a small number of nephrons, however, the question of the extent and functional consequences of such interaction was left unanswered. Recent advances in imaging technologies allowed us to come closer to the answer by analyzing both renal vascular structure ex-vivo and blood flow dynamics in-vivo: Ex-vivo: we apply fluorescence microscopy and micro-computed tomography to study the topology of the rat renal arterial network at high resolution allowing us to identify patterns and features that are specific to the kidney and are likely to play a role in the interaction between nephrons[2,3]. In-vivo: we have improved methodology of renal laser speckle contrast imaging and applied it image blood flow dynamics simultaneously in multiple arterioles close to the renal surface of a rat. Analysis of the blood flow dynamics, including phase and frequency locking, and show persistent clusters of more than 20 vessels during Ang II infusion and significantly ($p<0.05$) reduced clustering in the vasodilated state. Furthermore, we show the dynamic evolution of clusters and the presence of the phase waves, which are often observed in active media such as neural networks in the brain. We combine in-vivo and ex-vivo imaging results to predict the scale of the three-dimensional synchronization field and discuss a potential role of the synchronization in pathological conditions. D.D. Postnov research was supported by grant NNF17OC0025224 awarded by Novo Nordisk Foundation, Denmark. 1. Holstein-Rathlou NH. Synchronization of proximal intratubular pressure oscillations: evidence for interaction between nephrons. Pflügers Archiv. 1987 May 1;408(5):438-43. 2. Marsh DJ, Postnov DD, Rowland DJ, Wexler AS, Sosnovtseva OV, Holstein-Rathlou NH. Architecture of the rat nephron-arterial network: analysis with micro-computed tomography. American Journal of Physiology-Renal Physiology. 2017 Apr 19;313(2):F351-60. 3. Postnov DD, Marsh DJ, Postnov DE, Braunstein TH, Holstein-Rathlou NH, Martens EA, Sosnovtseva O. Modeling of kidney hemodynamics: probability-based topology of an arterial network. PLoS computational biology. 2016 Jul 22;12(7):e1004922.

10.4

Pericytes protect against renal ischemia-reperfusion injury, via sex-specific mechanism

Jennifer Sullivan[1]

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11: POSTER SESSION 2 & SOCIAL ACTIVITY

11.1

Computational modeling of oxygen exchange between a urine bolus and tshe ureter wall

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Study objective: Renal hypoxia is postulated to be a leading cause of acute kidney injury (AKI) during cardiopulmonary bypass (CPB) surgery. Currently it is not possible to directly monitor the oxygen level in the kidney real-time during surgery and respond to signs of hypoxic injury in a patient. A possible solution is to monitor bladder urine oxygen tension

(PO2). In this study, we have developed a computational model of a urine bolus traveling along the ureter, to investigate how much oxygen in the urine bolus is lost or gained from the surrounding ureter wall (and associated blood vessels) to assess whether the bladder urinary PO2 can be a viable biomarker for hypoxia-associated AKI during CPB. Methods: We modeled the urine bolus and the surrounding ureter wall as a two-dimensional (2D) axisymmetric geometry based on the rabbit and human ureters. Instead of modeling a moving bolus traveling the whole length of the ureter, we treated the bolus as stationary and the fluid and the oxygen in the surrounding ureter wall move past the stationary bolus by setting the model's frame of reference to move with the bolus rather than fixed at the ureter wall. This approach simplifies the modeling and so greatly reduces the computational burden. The model consists of two components: (1) several porous media 'Darcy flow' modules representing axial and radial advective blood flow through the vasculature of the ureter wall and, (2) advection-diffusion modules representing the oxygen transport within the ureter wall, and between the bolus and the ureteral tissue. Results: The model was successfully validated against experimentally measured bladder urinary PO2 for a wide range of pelvic PO2 and urine flow rates. We then simulated a normal physiological condition for the rabbit ureter and the human ureter and compared the difference in bladder urinary PO2 in rabbits and humans. In both species, the initial pelvic PO2 was around 10 mmHg and the ureteral tissue PO2 was around 30 mmHg. In the rabbit ureter, the bladder urinary PO2 increased by ~ 11 mmHg (final PO2 of 21 mmHg) after the transit time of 11.5 s. In comparison, the bladder urinary PO2 in the human ureter increased only by ~5 mmHg (final PO2 of 15 mmHg) after transit time of 15 s. A parametric study of pelvic PO2 showed that bladder urinary PO2 increased linearly with pelvic PO2. Conclusion: Our simulation results for human ureter supports the bladder urinary PO2 as a viable biomarker for AKI during CPB. The model also suggests that it may be possible to predict the bladder urine PO2 for a given pelvic PO2 using a simple linear relationship.

11.2

Modeling intraglomerular transport in diabetic kidney disease

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Diabetic kidney disease (DKD) is among the severe complications of diabetes and is the primary cause for end-stage kidney failure. Hyperglycemia is the condition of excess glucose that can lead to diabetic complications and contribute to the loss of kidney function. Each kidney includes thousands of glomeruli that are comprised of a network of capillaries through which blood is filtered. The glomerular filtration barrier is a highly specialized microvascular interface made up of glomerular endothelial cells, basement membrane, and podocytes. Podocytes are terminally differentiated epithelial cells that form the outermost layer of the glomerular filtration barrier and normally prevent leakage of protein, such as albumin into the urine. Mesangial cells form the central stalk of the glomerulus and are known to interact closely with other cells including podocytes. Podocyte depletion and damaging structural changes around the mesangial cells are key predictors of DKD progression. There is evidence suggesting that the tissue damage is caused by signaling pathways and interactions between podocytes and mesangial cells. However, these are several interconnected pathways, and the tissue damage is not immediately detectable with non-invasive clinical methods until after proteinuria develops. Hence, a quantitative approach is used to understand and predict and design therapies to slow the progression of DKD before significant podocyte damage occurs. The objective of this study is to model the transport of glucose from the glomerular microvasculature to the cells that comprise the tissue as well as the transport of key biochemicals that respond to glucose in glomerular injury. We focus specifically on the roles of angiotension II (ANG II) and transforming growth factor beta 1 (TGF-–β) on effects in podocytes and mesangial cells within a glomerulus. Elevated ANG II levels have been associated with several deleterious effects on podocytes. We developed an ODE-based model of glucose-stimulated ANG II dynamics in podocytes. TGF- β increases in hyperglycemic conditions via a mechanism mediated by ANG II and has been shown to play a key role overexpression of extracellular matrix proteins in the mesangial space and thickening of the glomerular basement

membrane, eventually leading to podocyte loss. We extended our podocyte ANG II model to predict the downstream effects of glucose and ANG II on TGF- β production and tissue damaging behaviors. The model accounts for the production of TGF- β by glucose and ANG II that is synthesized by glucose-dependent as well as glucose-independent mechanisms. We combined the reaction network model with transport equations to study the movement of albumin and glucose through different layers of the filtration barrier. Small molecules can travel directly through the filtration barrier or indirectly through the mesangium and then into the filtration barrier. Macromolecules such as albumin cannot travel through the filtration barrier until significant damage occurs that modifies the permeability of the barrier to macromolecules. The model shows how high glucose affects the mesangial cells as glucose moves through and stimulates various biochemical networks in a glomerulus and how the structure of the tissue is damaged gradually over time.

11.3

Investigation of the potential components signals of renal natriuresis: a mathematical modeling analysis

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Background: Renal excretory mechanisms regulating fluid homeostasis and blood pressure continue to be debated, and are potentially driven through alterations of renal interstitial hydrostatic pressure (RIHP), interstitial fluid volume (IFV), renal blood flow (RBF), or neurohumoral activity. Changes in renal perfusion pressure (RPP) or RBF alter sodium excretion, but sodium excretion can also be altered without changes in perfusion pressure or RBF - e.g. during volume expansion. Renal venous congestion, which increases RIHP, has opposite effects on sodium excretion in volume expansion vs. hydropenia [1]. The complexity of renal function make it difficult to experimentally determine relative magnitudes and ranges of potential regulatory mechanism. Mathematical modeling provides a tool for integrating known physiology and data across experiments to provide insights into renal regulation. Methods: A previously proposed cardiorenal model was used to evaluate possible physiological signals modulating the renal natriuretic response [2,3]. The model describes renal hemodynamics and Na+/water filtration/reabsorption, whole body fluid/electrolyte distribution, and cardiac cycle dynamics, as well as the renin-angiotensin-aldosterone system (RAAS). It was coupled with a previously published experimental study [1], in which RIHP, RBF, fractional sodium excretion (FENA), and other variables were measured in volume expanded or hydropenic dogs during incremental renal vein constriction. Three different cases were established: 1) RIHP-driven natriuresis, 2) RBF-driven natriuresis, and 3) RIHP-RBF-driven natriuresis. RIHP was approximated from the starling's forces equation for the peritubular capillaries. RIHP also depends on interstitial fluid volume (IFV), such that as IFV increases, both the value of RIHP and the slope of the RIHP-RPP relationship increases. Different functional forms and parameter ranges were also evaluated for each case. Simulation results were compared against experimental measurements of RIHP, FENA, GFR, and RBF under various levels of renal vein constrictions, during volume expansion or hydropenia. Results: The RIHP-RBF-driven case is capable of capturing the changing trends in RIHP, FENA, GFR, and RBF observed in the experimental study, and other test cases failed to reproduce the experimental data especially for the changes in FENA. Our simulations indicate that RIHP-driven natriuresis dominates in the absence of volume expansion and when RBF is well-regulation, but the RIHP effect may become saturated as RIHP increases in volume expansion or venous congestion, while the RBF-driven natriuresis may take effect when the RBF autoregulatory capacity of the kidney is surpassed. Conclusion: Coupling mathematical modeling with experimental data, this analysis demonstrates that while RIHP and RBF may both serve as signals for natriuresis, RBF dominates in volume expansion and natriuresis. This has particular implications for cardiorenal function in states of heart failure.

References: 1. BurnettJC, et al. Am J Physiol Renal Physiol. 1980. 238(4):279-282.2. Hallow KM et al. AJP -Regula Int Comp Phys. 2014. 306(9):647-62.3. Bovendeerd PH et al. Annals of Biomed Eng. 2006. 34(12):1833-45.

11.4

A multicontrast 3D imaging pipeline for image-based computational modeling of cancer tissue microcirculation

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The role of microcirculation is a critical tumor microenvironmental (TME) factor in cancer progression, metastasis and response to therapy1-3. To elucidate this role, a powerful new 'image-based computational modeling' paradigm is emerging that integrates whole-tumor vascular imaging data into mathematical models of fluid transport4-6. Traditional image-based approaches primarily employ ex vivo high-resolution tumor vascular data5,6 or in vivo blood flow measurements to model tumor transport6. However, there are a number of other factors within the TME such as extracellular matrix remodeling, cellular density, white matter fiber distribution (for brain tumors) etc. that can complement image-based simulation data. Thus, a new imaging approach is urgently needed that facilitates the integration of complementary imaging data from different TME elements to better elucidate intra-and extravascular transport mechanisms in intact whole-tumor samples. A logical starting point is to image and integrate whole-tumor data across ex vivo imaging techniques such as magnetic resonance microscopy (MRM), computed tomography (CT) and optical imaging. However, multimodality data integration has remained a challenge due to inherent differences in imaging contrast mechanisms, spatial resolution, sample preparation requirements and issues with image co-registration. Therefore, to facilitate image co-registration across multiple imaging modalities and spatial resolutions, we developed a "multicontrast" vascular contrast agent. This agent is water-soluble, radio-opaque, MR-visible and fluorescent. Moreover, as we shall demonstrate, it does not interfere with other contrast mechanisms. We employed it for multiscale imaging of the TME in an orthotopic breast cancer xenograft using MRM (40µm), micro-CT (7.5µm) and lightsheet-microscopy (1µm). First, the vascular contrast agent labeled the entire blood vessel lumen including small vessels enabling the visualization of microvascular networks at high-resolution for image-based hemodynamic modeling. Moreover, this multicontrast imaging approach facilitated image registration and data integration across spatial scales ranging from cells to whole-tissue via the presence of internal "vascular landmarks or fiducials". Second, since the vascular contrast agent did not interfere with conventional contrast mechanisms for each imaging modality, one could visualize the microvascular morphology, complementary soft tissue contrasts (e.g. 3D diffusion directions, anatomical structure) and the spatial distributions of fluorescent moieties, all within a single tissue in 3D. For example, we successfully imaged the vasculature using T1-relaxation in combination with diffusion weighted MRI; bone and vascular contrast from micro-CT; and performed immunofluorescent staining of whole-mount optically cleared tissues with antibodies targeted to collagen type IV and laminin for lightsheet-microscopy. Finally, we used image-based mathematical modeling to simulate tumor hemodynamics and intravascular oxygenation5. The results of this novel 3D imaging pipeline collectively demonstrate the feasibility of integrating multiple imaging contrasts from MRI, CT and optical-imaging of tumors via a single trimodality vascular contrast agent. We expect that the development of this multicontrast vascular imaging platform will help establish: (i) a freely downloadable, multimodality atlas for cancer systems biology investigators and novel in silico applications; (ii) an in silico platform for testing novel therapeutics that can circumvent antiangiogenic resistance in breast cancer. NCI 1RO1CA196701-01 1. G. Follain et al., Dev Cell 45, 33-52 e12 (2018). 2. M. W. Dewhirst, T. W. Secomb, Nat Rev Cancer 17, 738-750 (2017). 3. J. D. Martin, G. Seano, R. K. Jain, Annu Rev Physiol 81, 505-534 (2019). 4. E. Kim et al., Ann Biomed Eng 40, 2425-2441 (2012). 5. S. K. Stamatelos, A. Bhargava, E. Kim, A. S. Popel, A. P. Pathak, Sci Rep 9, 5276 (2019). 6. A. d'Esposito et al., Nat Biomed Eng 2, 773-787 (2018).

11.5

Modeling of blood flow and oxygen transport in the cerebral microcirculation

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Advances in imaging techniques have provided information on the three-dimensional structures of

microvascular networks in cerebral cortex containing many thousands of vessel segments. However, the interpretation of such data with regard to tissue perfusion and oxygen delivery presents multiple challenges. Here, modeling and computational approaches to address these challenges are outlined. (i) Image enhancement and network mapping. For simulation of blood flow and oxygen transport, network structures must be relatively complete and free of artifacts such as blind ends and spurious connections. These structures are typically derived from optical image stacks, which approach resolution limits for micron-scale structures. We have developed a suite of GPU-based image enhancement techniques including percentile filtering, “vesselness” filtering and “fill-in” filtering to improve segmentation of both small and large vessels. When applied to image stacks from brain microvasculature prior to segmentation, these techniques result in networks with improved continuity and fewer spurious structures. (ii) Blood flow modeling. A challenge in estimating flow rates in a microvascular network is that flow conditions on boundary segments of the network are generally unknown. We previously developed algorithms for flow estimation with incomplete boundary conditions, based on information about distributions of pressure and shear stress in microvessel networks. For large networks, these algorithms require multiple solutions of large systems of linear equations and we have developed more efficient methods that greatly decrease computational time. (iii) Oxygen transport modeling. We previously developed a Green’s function method for rapid computation of the oxygen distribution in tissue supplied by a network of microvessels. A remaining challenge is to establish boundary conditions on the oxygen content of inflowing boundary segments, depending on the oxygen supply and demand in the tissue. Here, a method is proposed for estimating oxygen levels in all inflowing vessels, given information on flow in all vessels and oxygen levels in inflowing arterioles. All vessels crossing the region boundary are classified as arterioles, capillaries or venules. Oxygen levels in inflowing capillaries are assigned based on values in outflowing capillaries, and similarly for venules. Assigning boundary conditions by this method reduces artifacts in the simulated oxygen field associated with region boundaries. These methods provide a basis for the development of multiscale theoretical models to gain improved quantitative understanding of blood flow and oxygen transport to the brain. This work has applications to normal physiology and to conditions in which oxygen transport to tissue is impaired, including stroke, brain injury and neurodegenerative diseases. Supported by NIH U01 HL133362.

12: SYMPOSIUM 7: RETINAL MICROCIRCULATION

12.1

Ocular blood flow: a delicate balance of pressures

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The eye is the only place in the human body where vascular and hemodynamic features can be observed and measured easily and non-invasively down to the capillary level. Numerous clinical studies have shown correlations between alterations in ocular blood flow and ocular diseases (e.g. glaucoma, age-related macular degeneration, diabetic retinopathy), neurodegenerative diseases (e.g. Alzheimer’s disease, Parkinson’s disease) and other systemic diseases (e.g. hypertension, diabetes). Thus, deciphering the mechanisms governing ocular blood flow could be the key to the use of eye examinations as a non-invasive approach to the diagnosis and continuous monitoring for many patients. However, many factors influence ocular hemodynamics, including arterial blood pressure, intraocular pressure, cerebrospinal fluid pressure and blood flow regulation, and it is extremely challenging to single out their individual contributions during clinical and animal studies. In the recent years, we have been developing mathematical models and computational methods to aid the interpretation of clinical data and provide new insights in ocular physiology in health and disease. In this talk, we will review how these mathematical models have helped elucidate the mechanisms governing the interaction between ocular biomechanics, hemodynamics, solute transport and delivery in health and disease. We will also present a web-based interface that allows the user to run and utilize these models independently, without the need of advanced software expertise.

12.2

Modeling blood flow regulation and oxygen transport in the retinal microcirculation

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Dysfunctional blood flow regulation and impaired oxygenation of the retina have been identified as potential factors contributing to glaucomatous optic neuropathy. Here, a theoretical model is used to simulate flow regulation in a heterogeneous retinal arteriolar network obtained from confocal microscopy images. Blood flow regulation is modeled using the length-tension characteristics of vascular smooth muscle that are assumed to depend on myogenic, shear-dependent, and conducted metabolic responses. Oxygen transport is simulated in the vasculature and surrounding tissue using a Green's function model that allows for a non-uniform network structure. The impact of the regulatory mechanisms is assessed by simulating responses independently and in combination. Simulations for a moderate level of tissue oxygen demand predict similar average tissue PO2 values regardless of including the myogenic response; however, the tissue hypoxic fraction (% of tissue < 1 mmHg) is more than three times as high when the myogenic response is included. These results suggest that mean tissue PO2 may be a poor indicator of oxygenation and that the myogenic response may be leading to an increase in hypoxic tissue regions. In addition, the difference in tissue oxygenation with and without the myogenic response is predicted to grow as the contribution of the metabolic response decreases, indicating that a stronger metabolic response to hypoxia may mitigate the detrimental effects of the myogenic response on flow regulation predicted by the model. Overall, this model allows for spatial predictions of tissue oxygenation in the retina, which is an important feature for identifying hypoxic regions in a realistic, heterogeneous retinal vascular network and for providing insight into glaucoma risk factors.

12.3

Modeling the effect of retinal microvasculature on ocular hemodynamics

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Elevated intraocular pressure is a primary risk factor for glaucoma, the second cause of blindness worldwide. Clinical observations show significant correlations between alterations in retinal hemodynamics and vision impairment. However, the mechanisms giving rise to these correlations are not yet fully understood. We developed a reduced-order fluid-structure interaction mathematical model that describes the hemodynamics in the central retinal artery and vein, which nourish and drain the retina, respectively. The central retinal vessels hemodynamics is coupled to the retinal microvasculature and to the ocular structure deformation. The model can be used to interpret clinical data. In particular, results suggest that the nonlinear compliant effect of the retinal venues might be relevant in explaining the changes in retinal hemodynamics as the intraocular pressure varies. In order to expand the model to account for real geometries of the central retinal vessels, multiscale coupling between distributed and lumped fluid flow models arise. We propose a novel algorithm, based on operator splitting, for the time discretization of these multiscale fluid flow problems. The algorithm allows for solving separately and sequentially the distributed and lumped models, without the need of sub-iterations. The novelty of this approach is that it ensures that the energy of the semi-discrete problem mirrors the behavior of the energy of the fully coupled problem, providing unconditional stability. Numerical examples have been derived and tested to support the theoretical analysis.

12.4

Recent advancements in imaging technologies allow us to visualize and quantify hemodynamic and vascular parameters within the eye

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These technologies have generated much data and these data have generated questions on how to

interpret the data from the clinical viewpoint, such as whether vascular changes are primary or secondary to the disease process and what the relationship between vascular, structural, and functional changes is. In this talk, we will review the importance of ocular perfusion pressure and blood flow in many diseases of the eye and beyond. Individual susceptibility with various comorbidities can complicate risk assessment, but mathematical models might help understand and identify risk factors. A successful example of how mathematical modeling can help disentangle and identify risk factors is provided by the recent findings of the Singapore Epidemiology of Eye Diseases study, which will be discussed in this talk.

13: SYMPOSIUM 8: BRAIN MICROCIRCULATION

13.1

Decoding the brain microvasculature by blood flow modeling in realistic microvascular networks

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The cortical vasculature consists of different vessel types, which differ topologically and which fulfill distinct functional tasks. Capillaries are the most frequent vessel type and highly relevant for oxygen supply. Besides their relevance, our knowledge of the topology of the cortical capillary bed is limited and their role in neurovascular coupling remains highly debated. Our goal is to improve our understanding of structural and functional properties of the brain microvasculature with focus on the capillary bed. We use blood flow simulations in realistic microvascular networks (MVN) [1] to jointly study topology and perfusion of the capillary bed as well as the impact of capillary diameter changes on the flow field. Our numerical model has the unique feature to track individual RBCs, which is in contrast to other commonly used blood flow models. This approach enables us to minimize the number of empirical functions required and to resolve fluctuations resulting from varying RBC concentrations. In a recent study we investigate the impact of RBC dynamics on the flow field at capillary bifurcations [2]. Based on in vivo and in silico experiments we show that the impact of RBCs reduces the difference in outflow velocities at divergent capillary bifurcations. Moreover, our blood flow simulations provide evidence that capillary dilation locally alters the flow field and the RBC distribution. Taken together, our results suggest that the bi-phasic nature of blood is an important intrinsic feature of microvascular flow, which increases the robustness of perfusion and is relevant for small-scale regulation. On the larger scale, our results reveal that the pressure drop in the capillary bed decreases with cortical depth and that red blood cells (RBCs) enter and leave the capillary bed at approximately the same cortical depth [1]. However, it remains unknown how these flow patterns are enforced by the cortical vasculature. To address this question we computed the flow resistance between two points of the capillary bed. The average flow resistance between descending arterioles (i.e. capillary start point) and ascending venules (i.e. capillary end point) reaches its minimum in cortical layer V. Comparison of the average flow resistance between randomly chosen points [3] and between start and end points in the capillary bed reveals that random point selection overestimates the flow resistance by a factor of ~2. Therewith, the average flow resistance of the capillary bed is only twice as large as the resistance of the descending arterioles. Our results reveal significant differences in perfusion and topology over cortical depth. We conjecture that these differences are relevant for nutrient supply and blood flow regulation during baseline and during neuronal activation. Indeed, we postulate that different regulation mechanisms might be in place depending on cortical depth. References: [1] Schmid et al., PLOS Computational Biology, 2017, doi: 10.1371/journal.pcbi.1005392 [2] Schmid et al., 2019 (under revision) [3] Blinder et al., Nature Neuroscience, 2013, doi: 10.1038/nn.3426

13.2

Modeling cerebral blood flow control: an integrated framework for linking macroscale changes in blood perfusion and oxygenation to cell level signaling.

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The on-demand delivery of oxygen (O2) and other nutrients is critical for proper functioning of the brain and its impairment is associated with pathological conditions including Alzheimer's disease, stroke and aging (Phillips, et al., JCBFM, 2016). The exact mechanism for signaling neuronal activity to the vasculature (i.e. Neurovascular coupling, NVC) is not completely understood, but recent experimental evidence supports the idea that capillaries in the brain act as networks that sense neural activity, and initiate electrical signals that dilate upstream arterioles, causing an increase in local blood supply

to the region of neural activity (Longden, et al., Nature, 2017). In this study, we propose an integrative modeling approach to model microcirculatory responses to NVC mediators and their effect on the regulation of blood flow, tissue perfusion, and oxygenation. Single cell models of endothelial cells (ECs) and smooth muscle cells (SMCs) that captures membrane electrophysiology and Ca2+ dynamics are coupled through gap junctions to form branched capillary networks connected to PAs to examine capillary to arteriole communication. Hemodynamic responses are governed by conservation of flow, Fåhræus–Lindqvist effect, and the phase separation effect (Pries, Secomb, AJPHAP, 2005). Oxygen simulations provide PO2 within vessels and in the tissue. Simulations are extended to a macroscale level by incorporating reconstructed brain vascular network data from (Blinder, et al., Nature, 2013). The model predicts changes in tissue perfusion and oxygen distribution in response to neuronal activity. The model accounts for dynamic regulation of arteriolar diameters by NVC mediators and propagating electrical signals from connected capillary beds. Simulations suggest an important role of capillary-level NVC in regulating functional hyperemia. The theoretical framework presented allows for testing proposed NVC mechanisms and assisting in the interpretation of macroscale functional imaging responses in health and in disease.

13.3

Restoration of neurovascular coupling by exogenous phosphatidylinositol 4,5-bisphosphate (PIP2) application in small vessel disease of the brain

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary form of small vessel disease of the brain caused by dominant mutations in the NOTCH3 gene, expressed predominantly by smooth muscles and pericytes. Recent studies in patients and in a genetic mouse model have revealed an impairment of neurovascular coupling (NVC), which matches local cerebral blood flow to increased neuronal activity, at an early stage of the disease. However, the mechanism of disruption is not known. During normal NVC, increases in extracellular [K+]o concentration, resulting from neuronal activity, activate inward-rectifier K+ (Kir2.1) channels on capillary endothelial cell (cEC) to produce a rapidly propagating retrograde hyperpolarization that causes upstream arteriolar dilation, increasing blood flow into the capillary bed. Using conventional whole cell patch clamp, we measured a 50% reduction in Kir2.1 current in cECs from CADASIL mice. Computational modeling determined that small increases in [K+]o can exert a powerful hyperpolarizing effect on cECs as a result of a bifurcation when a threshold [K+]o is crossed. Simulations predicted that contrary to physiological conditions, decreasing Kir2.1 activity by 50% would desensitize cEC to [K+]o increase from 3 to 10 mM. Accordingly, stimulation of capillaries with 10 mM [K+]o failed to trigger upstream arteriolar dilation in an innovative ex vivo capillary-parenchymal arteriole preparation and did not increase RBC flux measured in vivo using two-photon laser-scanning microscopy in CADASIL mouse. We previously identified phosphatidylinositol 4,5-bisphosphate (PIP2) as a necessary requirement for capillary-to-arteriole Kir2.1-mediated electrical signaling, so we hypothesized that lower PIP2 level in cECs was responsible for crippled NVC in CADASIL mouse. We found that addition of diC16-PIP2, a soluble form of the phospholipid, to the bath solution in patch clamp experiments restored Kir2.1 current density to control levels. Addition of soluble PIP2 also restored electrical signaling in capillary-parenchymal arteriole preparation from CADASIL mouse as evidenced by the upstream arteriolar dilation in response to capillary stimulation with 10 mM K+. This dilation was inhibited by the specific Kir2 blocker Ba2+ (30 μM), and exogenous PIP2 had no effect on control animals and endothelial-specific Kir2.1-knockout mice. In conclusion, our study supports the concept that exogenous PIP2 restores Kir2.1-mediated currents and capillary-to-arteriole electrical signaling in CADASIL mouse model.

13.4

Imaging cerebral microvascular structure, oxygen concentration and blood flow in animal models

Sava Sakadzic[1]
[1]*Harvard Univ.*

*Indicates Invited Speaker

NOTES:

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Research reported in this publication was supported by the National Institute Of Biomedical Imaging And Bioengineering of the National Institutes of Health under Award Number R13EB028680. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Program Updates:

Thursday, September 12, 2019

4:00 p.m. – 5:00 p.m. **6.0** **Trainee Career Workshop: Careers in theoretical modeling and quantitative analysis of physiological systems**
Grand Ballroom A/B
Chair: TBA

Friday, September 13, 2019

10:45 a.m. – 11:15 a.m. **9.2** Emerging mechanistic biomarkers of cancer chemo-radiation and immunotherapy from mathematical biophysics
Joseph Butner, *Houston Methodist Research Institute*
Replacing **Vittorio Cristini**, *Houston Methodist Research Institute*