NSF-CREST
Center for Cellular and Biomolecular Machines
University of California, Merced
5200 North Lake Road
Merced, California 95343
ccbm.ucmerced.edu

Updated 11/07/19

2019 CCBM Workshop on
Emerging Themes in Cellular and Biomolecular Machines

November 8-9, 2019

University of California, Merced and Yosemite National Park/Yosemite Valley Lodge

Invited Speakers:

David Bishop, Boston University: "Mending Broken Hearts, the CELL-MET ERC"

Steven M. Block, Stanford University, "Optical Tweezers: Biophysics in a New Light"

Hana El-Samad, UCSF: "Biological Feedback Control"

Hernan G. Garcia, UC Berkeley: "Dissecting Transcriptional Dynamics in Development One Burst at a Time"

Kerwyn Casey Huang, Stanford University: "Physics of Bacterial Growth"

Roger D. Kamm, MIT: "The Promise of Multi-cellular Engineered Living Systems"

Susan Marqusee, UC Berkeley: "Protein Folding On and Off the Ribosome"

Taher Saif, University of Illinois at Urbana-Champaign: "Emergent Living Machines"

Vivek Shenoy, University of Pennsylvania: "Cell-Matrix Interactions in Cancer: Multiscale Chemo-Mechanical Models"

Sara Vassmer, University of Missouri, "Broader Impacts: Best Practices, Tools, & Resources for Success"

Sponsors: Agilent Technologies, Inc., Thermo Fisher Scientific, Fisher Scientific

Thursday, November 7, 2019 in Merced, CA

Time	Event	Location / Details
6:00-8:00 pm	Dinner	Bear Creek Inn (575 W. North Bear Creek Dr., Merced, CA 95348; 209-723-3991) --Speakers and invited faculty/staff

Friday, November 8, 2019 at UC Merced

Talks and poster session are open to all.

Location: 5200 North Lake Road, Merced, CA 95343

25 minute talks, with 5 minutes Q&A.

Time	Event	Location / Details
8:00-8:45 am	Breakfast	California Room, Terrace Center --Open to all
8:45-9:15 am	Welcome and Introduction: Victor Muñoz, Ajay Gopinathan, and Carrie Kouadio	California Room, Terrace Center

Single Molecule Machines Session Chair – Victor Muñoz		
9:15-9:45 am	Susan Marqusee, UC Berkeley: "Protein Folding On and Off the Ribosome"	California Room, Terrace Center
9:45-10:15 am	Steven M. Block, Stanford University, "Optical Tweezers: Biophysics in a New Light"	California Room, Terrace Center
10:15-10:30 am	Break	California Room, Terrace Center
Biological Control Session Chair – Ajay Gopinathan		
10:30-11:00 am	Hana El-Samad, UCSF: "Biological Feedback Control"	California Room, Terrace Center
11:00-11:30 am	Hernan Garcia, UC Berkeley: "Dissecting Transcriptional Dynamics in Development One Burst at a Time"	California Room, Terrace Center
11:30 am-12:00 pm	Kerwyn Casey Huang, Stanford University: "Physics of Bacterial Growth"	California Room, Terrace Center
12:00-1:15 pm	Lunch	Pavilion 104 --Speakers and invited faculty/staff
Multicellular Mechanics Session Chair – Kara McCloskey		
1:15-1:45 pm	Vivek Shenoy, University of Pennsylvania: "Cell-Matrix Interactions in Cancer: Multiscale Chemo-Mechanical Models"	California Room, Terrace Center
1:45-2:15 pm	Taher Saif, University of Illinois at Urbana-Champaign: "Emergent Living Machines"	California Room, Terrace Center
Broader Impacts of Research Session Chair – Carrie Kouadio		
2:15-2:45 pm	Sara Vassmer, University of Missouri, "Broader Impacts: Best Practices, Tools, & Resources for Success"	California Room, Terrace Center
2:45-3:00 pm	Break	California Room, Terrace Center
3:00-4:00 pm	Sara Vassmer, Lead: Discussion on Broader Impacts	California Room, Terrace Center
4:15-5:30 pm	Poster Session / Reception	KL 355
5:45-7:15 pm	Dinner	Elizabeth's Garden / Yablokoff-Wallace Dining Center --Speakers and invited faculty/staff

Saturday, November 9, 2019 at Yosemite National Park
Speakers and by invitation only

Time	Event	Location / Details
8:00-10:15 am	Travel to Yosemite National Park (west entrance) Bus departs at 8:00 am.	Park at Le Grand Parking Lot / UC Merced (free parking, Nov. 9). Light breakfast available on bus.
10:15-10:45 am	Coffee and refreshments	Garden Terrace Room / Yosemite Valley Lodge
Designer Tissue for Biomedicine Session Chair – Victor Muñoz		
10:45-11:15 am	David Bishop, Boston University: "Mending Broken Hearts, the CELL-MET ERC"	Garden Terrace Room / Yosemite Valley Lodge
11:15-11:45 am	Roger D. Kamm, MIT: "The Promise of Multi-cellular Engineered Living Systems"	Garden Terrace Room / Yosemite Valley Lodge
11:45 am-12:30 pm	Lunch	Garden Terrace Room / Yosemite Valley Lodge
12:30-2:00 pm	Discussions	Garden Terrace Room / Yosemite Valley Lodge
2:00-5:30 pm	Free time / coordinated activities (hiking, bus trip, and exploration)	Yosemite Valley
5:30-7:00 pm	Reception and Dinner	Garden Terrace Room / Yosemite Valley Lodge
7:00-9:15 pm	Travel to Merced	Return to Le Grand Parking Lot

Option 2, If Weather Permits
***Earlier start time**

Time	Event	Location / Details
7:30-9:45 am	Travel to Yosemite National Park (south entrance) Bus departs at 7:30 am.	Park at Le Grand Parking Lot / UC Merced (free parking, Nov. 9). Light breakfast available on bus.
9:45-11:30 am	Hiking and exploration	Mariposa Grove of Giant Sequoias
11:30 am-12:30 pm	Drive to Yosemite Valley Lodge	
12:30-1:15 pm	Lunch	Garden Terrace Room / Yosemite Valley Lodge
Designer Tissue for Biomedicine Session Chair – Victor Muñoz		
1:15-1:45 pm	David Bishop, Boston University: "Mending Broken Hearts, the CELL-MET ERC"	Garden Terrace Room / Yosemite Valley Lodge
1:45-2:15 pm	Roger D. Kamm, MIT: "The Promise of Multi-cellular Engineered Living Systems"	Garden Terrace Room / Yosemite Valley Lodge
2:15-3:00 pm	Discussions	Garden Terrace Room / Yosemite Valley Lodge
3:00-5:30 pm	Free time / coordinated activities (hiking, bus trip, and exploration)	Yosemite Valley
5:30-7:00 pm	Reception and Dinner	Garden Terrace Room / Yosemite Valley Lodge
7:00-9:15 pm	Travel to Merced	Return to Le Grand Parking Lot

Meeting Information

- Presentations and poster session are open to all UC Merced, center, and community affiliates.
  UC Merced Parking Map Campus Maps

CCBM Executive Committee
Victor Muñoz, Co-Director (Bioengineering)
Ajay Gopinathan, Co-Director (Physics)
Sayantani Ghosh (Physics)
Kara McCloskey (Materials Science and Engineering)

CCBM Staff
Carrie Kouadio, CCBM Executive Director
David Quint, CCBM Project Scientist
Mourad Sadqi, CCBM Project Scientist

Center Staff/ Contact Information
Carrie Kouadio
CCBM Executive Director
Office: SE1, 396
ckouadio@ucmerced.edu
(217) 898-3522 (cell)
(209) 228-3608 (office)

University of California, Merced: Leadership
Internal Steering Committee (SC) Members/Executive Leadership, Academic:
Betsy Dumont, Dean of the School of Natural Sciences
Mark Matsumoto, Dean of the School of Engineering
Marjorie Zatz, Vice Provost and Dean of the Graduate Division
Executive Leadership, Academic:
Gregg Camfield, Provost and Executive Vice Chancellor
Executive Leadership, Administrative:
Samuel J. Traina, Vice Chancellor, Research and Economic Development

External Evaluator:
Ayesha Boyce, The University of North Carolina at Greensboro

External Advisory Board (EAB) Members:
Kent Carey, formerly Keysight Technologies, Inc.
Daniel Cox, University of California, Davis
Angel E. Garcia, Los Alamos National Laboratory
Martin Gruebele, University of Illinois at Urbana-Champaign
Eva Nogales, University of California, Berkeley

External Steering Committee (SC) Member:
Philip Pincus, University of California, Santa Barbara

Abstracts:

David Bishop, Boston University: "Mending Broken Hearts, the CELL-MET ERC"

Heart disease is the number one cause of death in the US and a leading cause worldwide, but current medicine cannot regenerate and or repair diseased human heart tissue. Today, there is no cure for a heart attack. The vision of Directed Multiscale Assembly of Cellular Metamaterials with Nanoscale Precision (CELL-MET) Nanosystems Engineering Research Center is to change this. CELL-MET will develop tissue-engineering principles to create scalable, low-cost technologies for growing clinically significant cardiac tissues from cell-level building blocks. The research approach is to adapt and advance novel nanomanufacturing techniques to integrate a variety of functional biological structures and elements into flexible polymer scaffolds that support and guide heart cells. The goal of this project is to create cardiac patches that will someday allow for the repair of hearts damaged by a heart attack or other diseases. In addition to their potential for repairing damaged hearts, artificial cardiac tissues will be used to test the effects of heart drugs or other drugs more realistically and efficiently than is currently possible. Broader impacts will include kindergarten to post-doctoral education and training programs that will produce a diverse, well-trained, world aware workforce to support the new billion dollar industries enabled by CELL-MET research. Industrial partners will work with CELL-MET to create these new industries, developing the business opportunities generated by the research breakthroughs.

Steven M. Block, Stanford University, "Optical Tweezers: Biophysics in a New Light"

Single-molecule techniques record characteristics that are obscured by traditional biochemical approaches, revealing the behaviors of individual biomolecules. Prominent among single molecule techniques is the laser-based optical trap, or 'optical tweezers,' which relies on radiation pressure to manipulate tiny objects. Optical traps can measure biomolecular properties with a precision down the atomic level—achieving a resolution of 1 angstrom over a bandwidth of 100 Hz—while exerting controlled forces in the piconewton range. Among the successes of optical traps have been measurements of the molecular steps made by motor proteins (for example, kinesin and myosin) and by processive nucleic-acid enzymes (for example, RNA polymerase), determinations of the strengths of noncovalent bonds, and studies of the energetics and kinetics of structure formation in proteins and nucleic acids. Optical trapping instruments have been particularly useful in mapping the energy landscapes of folding for structured RNAs. We're now able to follow the co-transcriptional folding of RNA in real time, revealing how folding can regulate downstream genes, mediated by elements called riboswitches. In recent developments, optical traps are being used in conjunction with single-molecule FRET (Förster Resonance Energy Transfer) to report simultaneously on the folding configurations and internal degrees of freedom of riboswitches.

Hana El-Samad, UCSF: "Biological Feedback Control"

Organisms are an evolutionary masterpiece of feedback control, featuring a mind-boggling capacity to self-correct. In this talk, we discuss our attempts to both understand feedback control in cells and to forward engineer it with de novo designed proteins.

Hernan G. Garcia, UC Berkeley: "Dissecting Transcriptional Dynamics in Development One Burst at a Time"

Over the last few decades *in vitro* and *in situ* approaches have revealed the identity of the molecular players driving transcription in eukaryotes. Yet, these studies are virtually silent on the precise timing of the recruitment of each of these players to the promoter, and on how this recruitment determines output transcriptional dynamics *in vivo*. Here, we present a new method for simultaneously measuring local input transcription factor concentration at target loci and the resulting output transcriptional activity of these loci in single living cells. Specifically, we study how the Dorsal activator, a key transcription factor in the

development of the fruit fly *Drosophila melanogaster*, is recruited to the promoter of its target gene *snail* in order to drive transcriptional bursting. We found that transient surges in Dorsal concentration coincide with, but do not precede, the onset of transcriptional bursts. Interestingly, these surges are not maintained throughout the duration of the bursts and subside before the promoter transitioned back into a transcriptionally inactive state. Instead, we discovered that the *amplitude* of the transient Dorsal concentration surges at the start of transcriptional burst, and not surge duration, dictates transcriptional burst duration. We speculate that Dorsal delivers a "package" of downstream players to the promoter (e.g., a cluster of RNA polymerase molecules) that sustains the transcriptional burst until this package is exhausted. Thus, our tool sets the stage for uncovering the precise timing and ordering of the diverse molecular players that drive the transcriptional process.

Kerwyn Casey Huang, Stanford University: "Physics of Bacterial Growth"

Bacterial cells constantly face complex environmental changes in their natural habitats. While steady-state cell size correlates with nutrient-determined growth rate, it remains unclear how cells regulate their morphology during rapid environmental changes. Here, we systematically quantified cellular dimensions throughout passage cycles of stationary-phase cells diluted into fresh medium and grown back to saturation, and found that cells exhibit characteristic dynamics in surface area to volume ratio (SA/V). SA/V dynamics were conserved across many genetic/chemical perturbations, as well as across species and growth temperatures. We developed a model with a single fitting parameter, the time delay between surface and volume synthesis, that quantitatively explained our SA/V observations, and showed that the time delay was indeed due to differential expression of volume and surface-related genes. The first division after dilution occurred at a tightly controlled SA/V, a previously unrecognized size-control mechanism highlighting the relevance of SA/V. Finally, our time-delay model successfully predicted the quantitative changes in SA/V dynamics due to altered surface area synthesis rates or time delays from translation inhibition. Our minimal model thus provides insight into how cells regulate their morphologies through differential regulation of surface area and volume synthesis and potentiates deep understanding of the connections between growth rate and cell shape in complex environments.

Roger D. Kamm, MIT: "The Promise of Multi-cellular Engineered Living Systems"

The capability to produce in vitro models of normal physiological function and disease is rapidly expanding, and it is now becoming clear that these microphysiological systems (MPS) will soon find their place in the multi-step process of identifying and validating new drugs, and testing for their potentially toxic side-effects. In order to gain acceptance by the pharma and biotech industries, however, these systems will need to be further developed, validated, and methods developed to fabricate them at high throughput and consistency. In this presentation, we focus on systems being developed to model neurological function, disease, and the process of transport of drugs across the tight blood-brain barrier (BBB) to treat neurological disorders and cancer. These MPS are each derived entirely from human cells, produced in microfluidic platforms of different design, and include models of the BBB, Alzheimer's Disease, and amyotrophic lateral sclerosis (ALS).

Susan Marqusee, UC Berkeley: "Protein Folding On and Off the Ribosome"

Understanding the structural and dynamic information encoded in the primary sequence of a protein is one of the most fundamental challenges in modern biology. The amino acid sequence of a protein encodes more than the native three-dimensional structure; it encodes the entire energy landscape – an ensemble of conformations whose energetics and dynamics are finely tuned for folding, binding and activity. Small variations in the sequence and environment modulate this landscape and can have effects that range from undetectable to pathological. I will present our recent results probing these sequence and environmental effects using a combination of single-molecule and ensemble-based studies.

Taher Saif, University of Illinois at Urbana-Champaign: "Emergent Living Machines"

Industrial revolution of the 19th century marked the onset of the era of machines that transformed societies. However, these machines cannot self assemble or heal themselves. On the other hand, since the discovery of genes, there is a considerable body of knowledge on engineering living cells. It is now possible to envision biohybrid machines with engineered living cells and scaffolds. These machines may self assemble and emerge from complex interactions between the cells and the scaffolds at various hierarchical levels. In this talk we will present two elementary biohybrid machines. They are both small scale swimmers. One of the swimmers is powered by primary rat cardiomyocytes. These cells are plated without any patterning on a scaffold which consists of a head and a tail. The cells self-orient to maximize scaffold deformation, and synchronize their beating. As a result, the tail deforms periodically and propels the swimmer forward. As a first step towards intelligence, the second machine consists of optogenetic neurons and muscle cells. It's scaffold consists of a head and two tails. The muscle cells self assemble into myotubes around the tails, while the neurons are hosted by the head. The neurons spontaneously send out long cables of axons preferentially towards the muscle forming functional neuro functional junctions. They also form a neural network within themselves. Upon shining light, the neurons fire synchronously in a periodic fashion. The muscle contracts and bends the tails to propel the swimmer. These swimmers pave the way towards intelligent biohybrid machines.

Vivek Shenoy, University of Pennsylvania: "Cell-Matrix Interactions in Cancer: Multiscale Chemo-Mechanical Models"

Cell invasion into the surrounding matrix from non-vascularized primary tumors is the main mechanism by which cancer cells migrate to nearby blood vessels and metastasize to eventually form secondary tumors. This process is mediated by an intricate coupling between intracellular and extracellular forces that depend on the stiffness of the surrounding stroma and the alignment of matrix fibers. A multiscale model is used to elucidate the two-way feedback loop between stress-dependent cell contractility and matrix fiber realignment and strain stiffening, which enables the cells to polarize and enhance their contractility to break free from the tumor and invade into the matrix. Importantly, our model can be used to explain how morphological and structural changes in the tumor microenvironment, such as elevated rigidity and fiber alignment prior to cell invasion, are prognostic of the malignant phenotype. The model also predicts how the alignment of matrix fibers can recruit macrophages, which are among the first responders of the innate immune system following organ injury and are crucial for repair, resolution, and re-establishing homeostasis of damaged tissue. I will discuss how the deformation of the nucleus during migration can lead to changes in the spatial organization of chromosomes and their intermingling which can result in genetic mutations and genomic instability.

Sara Vassmer, University of Missouri, "Broader Impacts: Best Practices, Tools, & Resources for Success"

The National Science Foundation (NSF OIA-1810732) awarded a $5.2 million grant to fund the Center for Advancing Research Impact in Society (ARIS), building upon the work completed through the National Alliance for Broader Impacts (NABI, MCB-1408736). ARIS works with scientists and engagement practitioners to build capacity, advance scholarship, grow partnerships and provide resources to help them engage with and demonstrate the impact of research in their communities and society. This short talk will highlight lessons learned, thoughts for the future, best practices, tools and resources for broader impacts support for researchers and practitioners.