



Final Project Report

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Project Title: Workshop on the Cell as a Machine:

Mechano-, Controls, Systems Engineering Approach to Cell/Molecular Biology

PI:

Professor K. Jimmy Hsia
Department of Mechanical Science and Engineering
University of Illinois at Urbana-Champaign

Co-PIs:

Professor Roger D. Kamm
Department of Mechanical Engineering and Department of Biological Engineering
Massachusetts Institute of Technology

Professor Michael P. Sheetz
Department of Biological Sciences
Columbia University

Professor Subra Suresh
Dean of Engineering and Department of Materials Science and Engineering
Massachusetts Institute of Technology

Website: <http://www.mechse.uiuc.edu/conferences/CellAsMachine/>

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I. Executive Summary

1.1 Workshop Goals

Understanding biological systems such as living cells, which are intrinsically complex in nature, requires a multidisciplinary approach. Engineering disciplines such as mechanics, control theory, and systems engineering can potentially make significant contributions to the fundamental understanding of the workings of biological systems.

The workshop aimed to identify the important issues in this emerging research area, to examine the appropriate platform/approaches for conducting such research, and to provide recommendations to the research communities and funding agencies for future activities and possible new initiatives. The invitation-only workshop drew more than 50 experts from academia, national labs, and federal agencies with diverse background in engineering, biology, and biophysics. In addition to short presentations to review the state of current research and education activities, a significant portion of the workshop was devoted to breakout sessions to brainstorm on the key workshop objectives, and to produce a report to guide future activities.

1.2 Summary of the Workshop Methodology and Findings

The workshop was held at NSF on December 20-21, 2007. Thirty-six experts from academia and 23 experts from several federal agencies participated in the workshop. The complete list of participants is given in Appendix A1.

The main activities of the workshop included: presentations to review the current state of knowledge and to provide opinions on critical issues in this field; brainstorming sessions to identify the critical issues and grand challenges; a general session to discuss recommendations to NSF in this area; and special presentations to provide perspectives on the future of engineering and funding opportunities. Several questions were asked throughout the workshop, including: i) What are the critical issues; ii) What are the grand challenges; iii) What are the most effective ways to foster BIO-ENG-MED collaborations; iv) What are the important tools; and v) What are the resources needed and barriers to progress.

The workshop participants unanimously agreed that studying “the cell as a machine” is an emerging, interdisciplinary area of cell/molecular biology and engineering systems. This area poses major challenges to the research and education communities, holds tremendous promises and opportunities in biological and engineering research and education, and may have significant impacts on many biological, medical, and engineering applications.

The workshop participants identified a wide range of issues that need to be addressed to achieve success in this area. The most important ones include: understanding cell behavior and functions in different environments, such as different stiffnesses of the extra cellular matrix (ECM); bridging the individual cell, cell population, and subcellular behavior; uncovering the complex behavior of cells through coupled biological signaling and mechanical stimuli; understanding the interactive and iterative communication between cells and the coupled biological, chemical, mechanical, electrical, and thermal stimuli; exploring the potential of using cells or “components” of a cell to build a “machine”; determining the controls and feedback systems for biological signaling and mechanotransduction in cells.

The workshop participants proposed three grand challenges: i) physical environmental control in cellular diversity, form, and functions; ii) 4D quantification:

bridging the cellular length and time scales; and iii) making cells work for you: engineering cellular systems to convert chemical/thermal energy to mechanical action or communication.

The workshop participants recommended that actions be taken to stimulate research and education in this area. They included, but are not limited to: pursuing the establishment of a multi-agency initiative focused in this area, possibly entitled “The Cell as a Machine”; promoting collaborations among engineers, biologists, physicists, and chemists by providing funding for interdisciplinary teams of two to four people; enhancing community awareness of this emergent field by holding special symposia, and special conferences/workshops with seed funding opportunities for the best ideas.

Furthermore, the workshop participants strongly recommended a coordinated educational effort be pursued in the area of “the Cell as a Machine.” The goals of the educational activities shall be to teach engineering researchers and graduate students the basic concepts, terminologies, and current state of understanding in biology; and to introduce the biological researchers and students to the physical science methodologies and tools for quantitative analysis. Participants suggested that several different types of educational activities be encouraged, including: coordinated courses co-taught by biologists and physical scientists; a series of summer schools for faculty members, postdocs and graduate students in ENG and BIO; and web-based teaching tools to educate a new generation of researchers in this area.

II. Agenda

Workshop Agenda

Day 1

7:45 – 8:30 **Breakfast and Registration**

8:30 – 8:50 **Opening Remarks**

Prof. Jimmy Hsia, University of Illinois at Urbana-Champaign

Prof. Roger Kamm, Massachusetts Institute of Technology

Dr. Clark Cooper, Program Director, CMMI, NSF

Dr. Adnan Akay, Division Director, CMMI, NSF

Session I: Current State of the Knowledge

Chair: **Prof. Muhammad Zaman**, University of Texas at Austin

8:50 – 9:10 **Prof. Michael Sheetz**, Columbia University
Much on Parts and Cells But Little on Meso-scale Functions

9:10 – 9:30 **Prof. Mary Boyce**, MIT
Mechanics of Cell Deformations: Constitutive Modeling of the Finite Deformation Behavior of Biological Networks and Membranes

9:30 – 9:50 **Prof. Paul Janmey**, University of Pennsylvania
Cell type-specific responses to substrate rigidity

9:50 – 10:10 **Prof. Metin Sitti**, Carnegie Mellon University
Cell and Bacteria Actuated Microobjects

10:10 – 10:30 **Prof. Jean Schwarzbauer**, Princeton University
Development of tissue mimetics based on natural extracellular matrices

10:30 – 10:50 **Coffee Break**

Session II: Critical Issues and Challenges

Chair: **Prof. Chwee Teck Lim**, National University of Singapore

- 10:50 – 11:10 **Prof. Dennis Discher**, University of Pennsylvania
Is Matricellular Elasticity felt by cells both in vitro & in vivo?
- 11:10 – 11:30 **Prof. Beth Pruitt**, Stanford University
Critical Issues and Challenges of Engineering Tissues from Cells
- 11:30 – 11:50 **Prof. Ravi Iyengar**, Mt. Sinai School of Medicine
Regulatory Networks Controlling Cell State Decisions
- 11:50 – 12:10 **Prof. Huajian Gao**, Brown University
Nanomechanics of biological systems – from single molecular bonds to continuum mechanics descriptions of cell adhesion
- 12:10 – 12:30 **Prof. Clare Waterman**, NIH/NHLBI
Animation of macromolecular ensembles: How do protein dynamics translate into higher order cellular properties?
- 12:30 – 1:30 **Lunch**
- 1:30 – 1:35 **Instruction to Participants on Brainstorming Session 1**
- 1:40 – 2:40 **Brainstorming Session 1: Critical Issues and Challenges**
- Group 1 (Room 555)
Leaders: **Prof. Taher Saif**, University of Illinois
Prof. Denis Wirtz, Johns Hopkins University
- Group 2 (Room 525)
Leaders: **Prof. Gang Bao**, Georgia Inst. of Technology
Prof. Richard Murray, California Inst. of Technology
- Group 3 (Room 535)
Leaders: **Prof. Victor Barocas**, University of Minnesota
Prof. Dan Hammer, University of Pennsylvania
- Group 4 (Room 545)
Leaders: **Prof. Phil LeDuc**, Carnegie Mellon University
Prof. Sasha Popel, Johns Hopkins University

Four breakout groups, each led by two co-chairs, will have in-depth discussion on the issues of 1) where the opportunities are; 2) how to identify the critical problems; 3) what the grand challenges and obstacles are; etc.

2:40 – 3:20 **Reporting from Brainstorming Session 1**

3:20 – 3:40 **Coffee Break**

Session III: General Discussion on Critical Issues

Moderators: **Prof. Ellen Arruda**, University of Michigan
Prof. Dan Fletcher, UC-Berkeley

3:40 – 4:10 Two moderators will be invited to conduct this session to further focus on the goals of the workshop, i.e., the critical issues facing the cell biology and engineering communities in this area. The objective of this session is to bring the critical issues and grand challenges raised by workshop participants to a sharper focus.

Session IV: Tools and Resources

Chair: **Prof. Michelle Oyen**, Cambridge University

4:10 – 4:30 **Prof. Roger Kamm**, MIT

Multi-Scale and Multi-Physics Computational Tools

4:30 – 4:50 **Prof. Jay Groves**, UC-Berkeley

Membrane mechanics and cellular signal transduction

4:50 – 5:10 **Prof. G. Ravichandran**, California Institute of Technology

Quantitative Characterization of 3-D Deformation in Soft BioMaterials and its Application to Cell Mechanics

5:10 – 5:30 **Prof. Sam Safran**, Weizmann Institute of Science, Isreal

Structure and function of biological cells: theoretical approaches from soft matter physics

5:30 – 5:50 **Prof. Harry Asada**, MIT

A Stochastic Approach to Dynamic Modeling and Control of Collective Cell Behavior

6:30 – 7:00 Cash Bar

7:00 – 9:30 **Dinner**

Dinner Presentation

Professor Subra Suresh, Dean of Engineering, MIT

Day 2

- 8:00 – 8:30 **Breakfast**
- 8:30 – 9:00 **Government Perspectives**
Dr. Richard Buckius, Assistant Director for Engineering, NSF
NSF, Engineering and Interdisciplinary Research
- 9:00 – 10:00 **Brainstorming Session 2: Opportunities in Collaborative Research between Mechanics, Controls, Systems Engineering and Cell Biology**
Four breakout groups, each led by two co-chairs, will have in-depth discussion on opportunities in collaborative research. The groups will focus on collaborations between mechanics and biology, control theory and biology, system engineering and biology, respectively. The groups will also discuss the impacts of such collaborative research, and potentials to bring about transformation in the way engineering and cell biology research is done.
- 10:00 – 10:15 **Coffee Break**
- 10:15 – 10:45 **Reporting from the Brainstorming Session 2**
- 10:45 – 11:45 **Brainstorming Session 3: Resources Needed, Format of Collaboration, and Recommendations**
Four breakout groups, each led by two co-chairs, will brainstorm to identify the preferred format for collaboration, the most effective way to nurture such collaboration, and the educational needs.
- 11:45 – 1:00 **Lunch**
- 1:00 – 1:30 **Reporting from the Brainstorming Session 3**
- 1:30 – 2:00 **General Discussion on the Recommendations of the Workshop**
- 2:00 – 2:30 **Concluding Remarks from NSF and Other Funding Agency Representatives**
- 2:30 – 4:30 **Special Session for Organizers, Group Leaders: Preparation of a coherent document containing workshop findings and recommendations. This document will be used by NSF PDs and other federal funding agencies to define the future funding policies in this area.**
- 4:30 **Adjourn**

III. Current State of the Knowledge and the Critical Issues in This Field

Recently, there have been major advances in our ability to analyze many aspects of biological systems: genomes are sequenced, many protein structures are known, proteomics, lipidomics and glycomics have provided important insights. In addition, mainly to the credit of biologists and, very recently, of some bioengineers, many tools have been developed to quantify cell physiological parameters. However, we lack a detailed understanding of many if not most cellular functions in an in vivo context. A useful analogy is that we are faced with a task of reverse-engineering that is similar to that of a naïve engineer trying to understand how automobiles work. At this time, the engineer has all of the parts of the automobile on the table and has some binary complexes. In addition, there are complete automobiles around to study as well. What is not known is how functional complexes in the automobile actually complete a task, e.g. how the windshield wipers, side window opening mechanisms, or even the engine works on a detailed level. These cellular functions and underlying mechanisms are affected by processes at different levels: subcellular signaling processes and response mechanisms, interactions of cells with extra-cellular matrix (ECM), cell-cell interactions in tissues, and many others.

At the Workshop, 15 experts from academia and national labs presented their views on the current state of the knowledge and their opinions on the critical issues in this field. The presentations covered a very wide range of topics, including: subcellular structures and their functions in cell motility; regulatory networks controlling cell state decisions; macromolecular ensembles and their correlations with cellular properties; theoretical physics approach to structure and function of biological cells; effects of substrate rigidity on cell behavior and differentiation; tissue engineering from cells; nanomechanics of cell adhesion; constitutive modeling of cell deformation; multi-scale and multi-physics computational tools for cells and biomolecules; 3D quantitative measurement of cell deformation; cells and bacteria as motors to move nano-objects; and stochastic modeling of cell dynamics and control of collective behavior of cells.

IV Grand Challenges

4.1 Methodology

The workshop participants were assigned to four breakout groups. Each group was led by two highly respected group leaders, one from the biology community and the other from the engineering community:

Group 1: **Prof. Taher Saif**, University of Illinois
Prof. Denis Wirtz, Johns Hopkins University

Group 2: **Prof. Gang Bao**, Georgia Inst. of Technology
Prof. Richard Murray, California Inst. of Technology

Group 3: **Prof. Victor Barocas**, University of Minnesota
Prof. Dan Hammer, University of Pennsylvania

Group 4: **Prof. Phil LeDuc**, Carnegie Mellon University
Prof. Sasha Popel, Johns Hopkins University

The breakout groups were asked to identify up to 3 grand challenges addressing each of the following:

1. Title of Grand Challenge
2. Provide a 1-2 sentence statement in lay terms of the grand challenge.
3. What is the transformative nature of the challenge?
4. What is the expected impact of addressing this challenge, both technical (discovery, new technology, new paradigm) and societal (national needs: e.g., energy, environment, sustainability)?
5. What is the multidisciplinary/interdisciplinary nature of the challenge? Be specific with regard to the NSF Directorates (ENG and BIO).
6. What are the basic research problems?

While the responses from the 4 working groups were extremely rich in variety, and numerous critically important issues were raised, there were several that repeatedly came up. Here we will provide a short overview of the findings and recommendations, but the individual sub-group reports are also provided at the end of this document.

Several grand challenges were identified, including:

1. To achieve mechanical control over cellular diversity, form and function. A first step is to achieve an integrative spatio-temporal quantitative understanding of cell function and interactions.
2. To design mechanically-based therapies for disease, injury, and aging by controlling the physical environment of cells. This might be viewed as a valuable outcome of achieving challenge #1.
3. To make cells work for us: engineering cellular systems to convert chemical/thermal energy to mechanical action or communication.
4. To develop new tools and methods (experimental and computational) for observation, analysis and prediction towards the design of cell-inspired therapeutics.

4.2 Individual Group Reports

Each break-out group prepared their own individual statement regarding the stated objectives of the Workshop. Below are the un-edited versions.

Group 1

(1) Title of grand challenge

Mechanical control in cellular diversity, form, and function

(2) Statement about grand challenge

Genetics creates the building blocks of cells and tissues (i.e. individual proteins, protein assemblies); it establishes the parts list of cells. Physical and chemical cues regulate how these building blocks organize to create functional tissues and organs and respond rapidly to environmental changes. For example, in the context of wound healing, new cells will take on the chemical and mechanical functions of dead cells. How

biochemical cues (i.e. chemical stimuli, matrix composition) regulate the building blocks of cells for their function and shape is becoming well understood. The diversity in shape and function of cells in the biological kingdom, which is crucial to the diversity of tissues and organs, depends as much on genes and chemical cues as on environmental forces and geometry. A grand scientific challenge is to understand the mechanisms by which physical cues, such as force and geometry, regulate cell shape and function. Engineering principles can help explain how the building blocks assemble and drive cell behavior.

(3) Transformative nature

Not merely recognize that force and geometry affect cell shape and function, but understand how. The chemical aspects of cell function have been studied extensively, but how physical cues are transformed into cellular responses and how biochemistry is coupled to mechanical environment.

(4) Impacts

Understanding how cells operate in and respond to their biophysical environment will allow us to rationally design tissues, bioreactors, organs, biomimetic materials for biological and non-biological applications. Will also establish the fundamental scientific principles for tissue engineering, as opposed to current empirical approaches.

(6) What are the basic research problems?

Multifunctional tools for cell mechanics. Need for the development of multifunctional tools for quantitative real-time, live-cell, high-resolution, subcellular sensing of localized mechanical/force measurements

Multiscale modeling for cell mechanics. Predictive multiscale modeling (over wide ranges of time and spatial scales) to understand at the subcellular and multi-cell scales how cells integrate mechanical and biochemical cues to perform cellular functions (i.e. mechanotransduction, cell motility, resistance/response to stress, cell differentiation, cell adhesion).

Group 2

Grand Challenge #1:

Title

Controlling physical environments for cells: designing mechanically-based therapies for disease, injury, aging.

Challenge Statement

We now understand that biological cells sense and respond to the physical forces (stiffness/softness and pushing/pulling) of their environment. Cell stiffness reflects the health of the cell, and the environment around the cell affects its behavior and function. Understanding this better can lead to new diagnoses and therapies such as cancer, heart attacks, nerve regeneration, wound healing.

- What is the transformative nature?
 - The notion of manipulating mechanical properties of the cell and tissue to improve outcome is entirely new.

- Manipulating cell function and behavior through the physical environment
- Molecular component: understanding the molecular mechanisms by which the physical environment is transduced and how it affects the cell, its behavior and morphology.
- What is the expected impact of this initiative, both technical (discovery, new tech, new paradigm) and societal (national needs: e.g., energy, environment, sustainability)?
 - New paradigm in medical treatments and improvements in health and quality of life.
 - New tools for biological studies
 - Extension of engineering approaches to the micro to nano-scale.
 - Enable engineers to understand new types of dynamic and adaptive machines and materials.
- What is the multidisciplinary/interdisciplinary nature of the challenge? Be specific with regard to the NSF Directorates (ENG and BIO).
 - ENG and BIO, Physical sciences and mathematics, computational modeling sciences.
- What are the basic research problems?
 - Molecular mechanisms of mechanical sensing and mechano-transduction
 - Understanding the physical principles of force transmission through living biological materials, across scales from molecular to cell to tissue.
 - How the mechanical signaling pathways integrate chemical signaling pathways
 - Improved tools, especially imaging tools. Multiscale imaging and modeling.

Grand Challenge #2:

Title

Making cells work for you: engineering cellular systems to convert chemical/thermal energy to mechanical action or communication

Challenge Statement

Nature has perfected cells to survive and perform specific functions using diverse fuels. Cells can sense, respond to, and transform their environment to tailor their tasks, such as moving, self-healing, transportation, communication, and growth. Our challenge is to harness these functions and adaptability to our needs.

- What is the transformative nature?
 - Providing more efficient and cheaper energy conversion and generation (e.g., producing energy directly from sugar)
 - Designing cells to do specific jobs at the micro and nano-scales.
 - Designing machines that use cells as part of their function.
- What is the expected impact of this initiative, both technical (discovery, new tech, new paradigm) and societal (national needs: e.g., energy, environment, sustainability)?
 - Sustainable energy
 - Environmental rehabilitation
 - Green technology

- Transforming engineering
- What is the multidisciplinary/interdisciplinary nature of the challenge? Be specific with regard to the NSF Directorates (ENG and BIO).
 - ENG, BIO
 - Biochemistry, mechanical engineering, control systems, chemical engineering, genetic engineering, metabolic engineering
- What are the basic research problems?
 - Interfacing biotic and abiotic systems
 - Understanding mechano-chemical coupling
 - Genetic engineering of cells: how to control cell function and behavior from a genetic level.
 - Modeling and control of stochastic and biological systems.
 - Understanding how cells use stochastic fluctuations and noise
 - Improved tools, especially imaging tools.
 - Multiscale imaging and modeling.
 - Building hybrid biotic-abiotic systems.

Group 3

Title

ENVIRONMENTAL CONTROL OF CELL FUNCTION

Challenge statement

Cells respond to their surroundings in complex ways. The grand challenge is to understand that response and use the local environment to guide cellular function via the underlying machinery of the cell.

Transformative nature

Although there are some successes, the vast potential of the cell remains largely untapped. Incomplete understanding of interactions between cells and their surroundings remains the major barrier to our attempts to harness the power of the cell. Meeting this challenge will allow us to control fundamental cell functions to achieve a wide range of societal goals.

Impact

Controlling the behavior of cells is essential to treatment of disease, such as cancer, inflammatory and infectious diseases, and also to the creation of biological technologies, such as tissue engineering. Predictive knowledge of the cell, its surroundings, and their interactions would pave the way for effective treatments based on control of cell behavior – to stop the spread of cancer, to promote the regeneration of damaged tissues, etc.

Further, cell-based devices, such as sensors and micromotors, could be developed and implemented taking advantage of the cellular machinery by means of appropriate environmental cues.

Multidisciplinary Nature

The task at hand requires the active participation of biologists, chemists, physicists, and engineers. A wealth of mathematical and biological tools, cell lines, and procedures for

molecular manipulation have been developed in biology over decades, and these tools are obviously essential for success. Many of the chemical methods of tracking and manipulating molecules inside and outside of cells have been developed by chemists, and further methods for precise manipulation of molecules need to be developed. Physicists and engineers can play essential role in the development of mathematical models that reveal fundamental rules governing the behavior of molecular assemblies that appear so unique to the control of biological behavior. Engineers increasingly familiar with biology have unique skills in developing tools and assays that allow for manipulation and observation of individual cell behavior or in an ensemble. In order to carry forth this vision, education will be extremely important. Students will need to be educated across the traditional boundaries of disciplines, and faculty will also need to become increasingly familiar with techniques and tools observed in other disciplines. Further, uniquely styled coursework and learning tools will need to be developed.

Basic Research Problems

The basic research problems that should be tackled in such an initiative are:

- How do cells assemble into multicellular structures and form functional tissues, and how can this be manipulated and coordinated?
- How can an extracellular environment be created to provide the necessary chemical and mechanical cues to obtain a desired cell function?
- How do cells differentiate? How do stem cells know when to differentiate into more mature cell lines, and how can we get stem cells to revert to pluripotent phenotypes?
- How do cells move from place to place, and how can they be manipulated to move faster or slower? What factors provide the force and direction for cell motion?
- What controls cell division and growth? Despite the wealth of information about growth factors and their receptors, what other factors control cell division?
- What level of detail in describing cell behavior is sufficient to achieve functional goals?
- How can cell-based devices, such as sensors, actuators, nanomotors, etc., be created and used, and how can such devices be interfaced with their surroundings in a useful way?

Group 4

1. title

4D Quantification: Bridging the cellular length and time scales

2. 1-2 sentence statement in lay terms of the grand challenge.

To understand the cell as a machine using engineering principles. To develop new tools for analysis and prediction towards the design of cell-inspired therapeutics.

3. Transformative nature:

The engineering-biology inspired transformation of bio-manufacturing: Integrative spatio-temporal understanding and regulation of cell function and cellular interactions with natural and artificial/synthetic microenvironments (biochemical and physical).

4. What is the expected impact of this initiative, both technical (discovery, new tech,

new paradigm) and societal (national needs: e.g., energy, environment, sustainability)?
Using the entire range of cellular processes from the level of the genome to tissue formation with the goal of understanding and intervening in disease states, cell-based therapies, tissue engineering, enabling improved drug testing, and pharmacological development.

5. What is the multidisciplinary/interdisciplinary nature of the challenge? Be specific with regard to the NSF Directorates (ENG and BIO).

This work crosses the domains of engineering (all fields), biology, materials, computer science, chemistry, and physics. ENG, BIO, MPS (DMR, Physics), and CIS.

6. What are the basic research problems?

- Engineering the 2D -> 3D -> 4D environment and mimicking *in-vivo* conditions
- Formulating general laws of cell function and structure that are predictive, flexible, reflecting the stochastic nature of the cell as a machine
- Understanding and designing biomaterials, biochemical, physical interactions, and cellular regulation and control

V. Recommendations

A special session on Mechanisms, Tools and Resources was attended by all participants. The goal of the session was to come up with recommendations to address the critical issues, to tackle the grand challenges, and to coordinate and effectively pursue the research in this field. Several questions were asked. The participants' opinions were recorded as follows.

Do you see the need to establish a new initiative? If yes, what should be the title of the initiative?

YES!!! The title of the initiative should be "The Cell as a Machine."

What are the preferred ways/mechanisms of collaborations?

- Promote culture of collaboration, but need ways to avoid more paperwork
- Model after the EFRI program, 2-4 investigators of focused teams
- Possible ERC-type centers; but caution about bureaucracy
- Possibility of multi-agency initiative
- Conferences, symposia focused in this area, e.g., Gordon Conferences, special symposia at ASCB
- Organize workshops/conferences with possible seed funding opportunities for participants

What are the tools needed to achieve success in this area?

- Technical: major components are covered in grand challenges identified by groups
- Educational (the participants feel strongly about this):
 - Revise undergraduate curricula.
 - require the biology major to take more mathematics
 - create a set of courses or multi-subject courses tailored toward educating biology student of engineering knowledge and vice versa
 - Enhance graduate student education.
 - Offer Woods Hole-type courses or other mechanism to educate them in area different from their major

- Encourage teamwork in education
- Require more usage of the web and other new technologies
- Combine multiple subjects to the single course
- Organize summer schools for faculty, postdocs, under- and graduate students with hands-on experiences

What are the resources needed?

Funding level: \$10M/yr to start the initiative

Infrastructure:

- An instrumentation grant attached to or independent of the research projects and made available to the entire research community
- World wide simulation web
- “Institute” to support these (educational and research) activities
- Techniques e-bay, i.e., mechanisms for exchange of experimental and computational techniques

Appendix A1 Participant List

Organizers

Professor K. Jimmy Hsia
Department of Mechanical Science &
Engineering
University of Illinois at Urbana-Champaign
Email: kjhsia@uiuc.edu

Professor Roger Kamm
Department of Mechanical Engineering &
Bioengineering
Massachusetts Institute of Technology
Email: rdkamm@mit.edu

Professor Michael Sheetz
Department of Biological Sciences
Columbia University
Email: ms2001@columbia.edu

Professor Subra Suresh
Dean of Engineering
Department of Materials Science &
Engineering
Massachusetts Institute of Technology
Email: ssuresh@mit.edu

Participants from Academia

Professor Ellen Arruda
Department of Mechanical Engineering
University of Michigan
Email: arruda@umich.edu

Professor Harry Asada
Department of Mechanical Engineering
Massachusetts Institute of Technology
Email: asada@mit.edu

Professor Gang Bao
Department of Biomedical Engineering
Georgia Institute of Technology
Email: gang.bao@bme.gatech.edu

Professor Victor Barocas
Department of Biomedical Engineering
University of Minnesota
Email: baroc001.umn.edu

Professor Ashraf Bastawros
Department of Mechanical Engineering
Iowa State University
Email: bastaw@iastate.edu

Professor Mary Boyce
Department of Mechanical Engineering
Massachusetts Institute of Technology
Email: mcboyece@mit.edu

Dr. Keng-Hwee Chiam
A*STAR Institute for High Performance

Computing, Singapore
Email: chiamkh@gmail.com

Dr. Ming Dao
Department of Materials Science and
Engineering
Massachusetts Institute of Technology
Email: mingdao@mit.edu

Professor Dennis Discher
Department of Chemical & Biomolecular &
Mechanical and Bioengineering
University of Pennsylvania
Email: discher@seas.upenn.edu

Professor Alison Flatau
Department of Aerospace Engineering
University of Maryland
Email: aflatau@umd.edu

Professor Dan Fletcher
Department of Bioengineering
University of California-Berkeley
Email: fletch@berkeley.edu

Professor Huajian Gao
Department of Biomechanics
Brown University
Email: Huajian_Gao@brown.edu

Professor Jay Groves
Department of Chemistry

University of California-Berkeley
Email: jtgroves@lbl.gov

Professor Dan Hammer
Department of Bioengineering and Chemical
Engineering
University of Pennsylvania
Email: hammer@seas.upenn.edu

Professor Ravi Iyengar
Department of Pharmacology and Systems
Therapeutics
Mt. Sinai School of Medicine
Email: ravi.iyengar@mssm.edu

Professor Paul Janmey
Department of Medicine and Engineering
University of Pennsylvania
Email: janmey@mail.med.upenn.edu

Professor Phil LeDuc
Department of Mechanical Engineering
Carnegie Mellon University
Email: prl@andres.cmu.edu

Professor C. T. Lim
Department of Biomedical Engineering
National University of Singapore
Email: ctlim@nus.edu.sg

Dr. George Lykotrafitis
Department of Materials Science and
Engineering
Massachusetts Institute of Technology
Email: gelyko@mit.edu

David Quinn
Department of Materials Science and
Engineering
Massachusetts Institute of Technology
Email: djquinn@mit.edu

Professor Richard Murray
Department of Controls and Dynamical
Systems
California Institute of Technology
Email: murray@cds.caltech.edu

Professor Michelle Oyen
Department of Biomechanics
Cambridge University
Email: mlo29@cam.ac.uk

Professor Sasha Popel
Department of Biomedical Engineering &
School of Medicine
Johns Hopkins University
Email: apopel@jhu.edu

Professor Beth Pruitt
Department of Mechanical Engineering
Stanford University
Email: Pruitt@stanford.edu

Professor Guruswami Ravichandran
Department of Aeronautics & Mechanical
Engineering
California Institute of Technology
Email: ravi@atlantis.caltech.edu

Professor Sam Safran
Department of Materials and Interfaces
Weizmann Institute of Science, Isreal
Email: sam.safran@weizmann.ad.il

Professor Taher Saif
Department of Mechanical Science &
Engineering
University of Illinois at Urbana-Champaign
Email: saif@uiuc.edu

Professor Jean Schwarzbauer
Department of Molecular Biology
Princeton University
Email: jschwarzbauer@princeton.edu

Professor Metin Sitti
Department of Mechanical Engineering
Carnegie Mellon University
Email: sitti@cmu.edu

Professor Clare Waterman-Storer
Department of Cell Biology

NIH/NHLBI
Email: watermancm@nhlbi.nih.gov

Professor Denis Wirtz
Department of Chemical & Biomolecular
Engineering
Johns Hopkins University

Email: wirtz@jhu.edu

Professor Muhammad Zaman
Department of Biomedical Engineering
University of Texas at Austin
Email: mhzaman@mail.utexas.edu

Participants from Federal Agencies

Dr. Adnan Akay
NSF-CMMI
Email: aakay@nsf.gov

Dr. Richard Aragon
NIH-NCI
Email: raragon@mail.nih.gov

Dr. Richard Baird
NIH-NIBIB
Email: bairdri@mail.nih.gov

Dr. Richard Buckius
NSF-ENG
Email: rbuckius@nsf.gov

Dr. Ken Chong
NSF-CMMI
Email: kchong@nsf.gov

Dr. Clark Cooper
NSF-CMMI
Email: ccooper@nsf.gov

Dr. Semahat Demir
NSF-CBET
Email: sdemir@nsf.gov

Dr. Yogesh Gianchandani
NSF-ECCS
Email: ygiancha@nsf.gov

Dr. Fred Heineken
NSF-CBET
Email: fheineke@nsf.gov

Dr. Suhada Jayasuriya

NSF-CMMI
Email: sjayasur@nsf.gov

Dr. Rajinder P. Khosla
NSF-ECCS
Email: rkhosia@nsf.gov

Dr. Bruce Kramer
NSF-EEC
Email: bkramer@nsf.gov

Dr. Jennie Larkin
NIH-NHLBI
Email: larkinj2@nhlbi.nih.gov

Dr. Jerry Lee
NIH-NCI
Email: leejerry@mail.nih.gov

Dr. S. Chi Liu
NSF-CMMI
Email: sliu@nsf.gov

Dr. Peter Lyster
NIH-NIGMS
Email: lysterpe@nigms.nih.gov

Dr. Eduardo Misawa
NSF-CMMI
Email: emisawa@nsf.gov

Dr. Larry Nagahara
NIH-NCI
Email: nagaharl@mail.nih.gov

Dr. Grace Peng
NIH-NIBIB
Email: penggr@mail.nih.gov

Dr. Lynn Preston
NSF-EEC

lpreston@nsf.gov

Dr. Sohi Rastegar

NSF-EFRI

Email: srastega@nsf.gov

Dr. Mike Roco

NSF-ENG

Email: mroco@nsf.gov

Assistants

Susan Bailey

Department of Mechanical Science and Engineering

University of Illinois at Urbana-Champaign

sjbailey@uiuc.edu

Tammy Smith

Department of Mechanical Science and Engineering

University of Illinois at Urbana-Champaign

tssmith1@uiuc.edu

Group Assignment

Group Leaders:

Group 1: Taher Saif, UIUC; Denis Wirtz, Johns Hopkins University

Group 2: Gang Bao, Georgia Tech; Richard Murray, Cal Tech

Group 3: Victor Barocas, University of Minnesota; Dan Hammer, UPenn

Group 4: Phil LeDuc, Carnegie Mellon University; Sasha Popel, Johns Hopkins University

Discussion Group Assignment (first 2 in each group are group leaders)

First Name	Last Name	Institution	Email
Group 1			
Taher	Saif	University of Illinois at Urbana-Champaign	saif@uiuc.edu
Denis	Wirtz	Johns Hopkins University	wirtz@jhu.edu
Dan	Fletcher	UC-Berkeley	fletch@berkeley.edu
Huajian	Gao	Brown U	Huajian_Gao@brown.edu
Paul	Janmey	U Penn	janmey@mail.med.upenn.edu
George	Lykotrafitis	MIT	gelyko@mit.edu
Michelle	Oyen	University of Cambridge	mlo29@cam.ac.uk
Michael	Sheetz	Columbia U	ms2001@columbia.edu
Metin	Sitti	Carnegie Mellon U	sitti@cmu.edu
Ken	Chong	NSF-CMMI	kchong@nsf.gov
Suhada	Jayasuriya	NSF-CMMI	sjayasur@nsf.gov
Yogesh	Gianchandani	NSF-ECCS	ygiancha@nsf.gov
Grace	Peng	NIH-NIBIB	penggr@mail.nih.gov
Jerry	Lee	NIH-NCI	leejerry@mail.nih.gov
Group 2			
Gang	Bao	Georgia Tech	gang.bao@bme.gatech.edu
Richard	Murray	CalTech	murray@cds.caltech.edu
Mary	Boyce	MIT	mcboyce@mit.edu
Keng-Hwee	Chiam	A*STAR Institute for High Performance Computing	chiamkh@gmail.com
Alison	Flatau	University of Maryland	aflatau@umd.edu
Jay	Groves	UC-Berkeley	jtgroves@lbl.gov
Roger	Kamm	MIT	rdkamm@mit.edu
Clare	Waterman-Storer	NIH/NHLBI	watermancm@nhlbi.nih.gov
Clark	Cooper	NSF-CMMI	ccooper@nsf.gov
Adnan	Akay	NSF-CMMI	aakay@nsf.gov
Lynn	Preston	NSF-EEC	lpreston@nsf.gov
Jennie	Larkin	NIH-NHLBI	larkinj2@nhlbi.nih.gov
Richard	Aragon	NIH-NCI	raragon@mail.nih.gov
Group 3			
Victor	Barocas	University of Minnesota	baroc001@umn.edu
Dan	Hammer	U Penn	hammer@seas.upenn.edu
Ellen	Arruda	University of Michigan	arruda@umich.edu

Harry	Asada	MIT	asada@mit.edu
Ashraf	Bastawros	Iowa State University	bastaw@iastate.edu
C. T.	Lim	National University of Singapore	ctlm@nus.edu.sg
David	Quinn	MIT	djquinn@mit.edu
Jean	Schwarzbauer	Princeton University	jschwarzbauer@princeton.edu
Subra	Suresh	MIT	ssuresh@mit.edu
Muhammad	Zaman	The University of Texas at Austin	mhzaman@mail.utexas.edu
Eduardo	Misawa	NSF-CMMI	emisawa@nsf.gov
Fred	Heineken	NSF-CBET	fheineke@nsf.gov
Sohi	Rastegar	NSF-EFRI	srastega@nsf.gov
Richard	Baird	NIH-NIBIB	bairdri@mail.nih.gov
Larry	Nagahara	NIH-NCI	nagaharl@mail.nih.gov
Group 4			
Phil	LeDuc	Carnegie Mellon U	prl@andrew.cmu.edu
Sasha	Popel	Johns Hopkins University	apopel@jhu.edu
Dennis	Discher	U Penn	discher@seas.upenn.edu
K. Jimmy	Hsia	UIUC	kjhsia@uiuc.edu
Ravi	Iyengar	Mt. Sinai School of Medicine	ravi.iyengar@mssm.edu
Ming	Dao	MIT	mingdao@mit.edu
Beth	Pruitt	Stanford University	pruitt@stanford.edu
Guruswami	Ravichandran	CalTech	ravi@atlantis.caltech.edu
Sam	Safran	Weizmann Institute of Science, Israel	sam.safran@weizmann.ac.il
S. Chi	Liu	NSF-CMMI	sliu@nsf.gov
Semahat	Demir	NSF-CBET	sdemir@nsf.gov
Peter	Lyster	NIH-NIGMS	lysterpe@nigms.nih.gov

Appendix A2 Abstracts of Presentations

Is Matricellular Elasticity felt by cells both in vitro & in vivo?

Professor Dennis Discher
Department of Chemical & Biomolecular & Mechanical and Bioengineering
University of Pennsylvania, Philadelphia, PA 19104

Most tissue cells must adhere to a solid for viability, and we have found that such aspects of microenvironment appear particularly important in stem cell differentiation. Mesenchymal stem cells specify lineage and commit to phenotypes with extreme sensitivity to tissue-level elasticity, at least when the matrix ligand is the most abundant mammalian protein, collagen-I. Soft matrices that mimic brain are neurogenic, stiffer matrices that mimic muscle are myogenic, and comparatively rigid matrices that mimic collagenous bone prove osteogenic. Inhibition of nonmuscle myosin II blocks all elasticity directed lineage specification. The results have significant implications for 'therapeutic' stem cells, and they also motivated development of a method to tag domains across the proteome that are mechano-responsive. However, a number of questions arise:

- (1) Do cells interacting with other cells or other matrix proteins yield similar 'cell on gel' responses as collagen-I coated matrices? (=GENERALIZABLE?)
 - (2) If matricellular elasticity is a key external signal, what are the relevant intracellular signalling pathways in sensing? (=MECHANISMS?)
 - (3) What are the implications for development, pharmacology, and tissue engineering? (=SIGNIFICANCE?)
-

Nanomechanics of biological systems – from single molecular bonds to continuum mechanics descriptions of cell adhesion

Professor Huajian Gao
Department of Engineering
Brown University, Providence, RI 02912

An important and interesting question is how animal cells control adhesion/deadhesion via cytoskeletal processes. Experiments have revealed that cell adhesion is localized to discrete focal adhesions that involve assemblies of more than 50 different proteins. Due to such complexity, there is currently little or no theoretical understanding on how cell adhesion is actively controlled through motors and other energy consuming processes. Inspired by various experimental observations on the mechanical behaviors and evolution of focal adhesions, we consider an idealized theoretical model on the lifetime and strength of an adhesive patch of molecular bonds between two dissimilar elastic media subject to an applied tensile load. In this model, the distribution of interfacial traction obeys classical elasticity equations in contact mechanics, while the rupture and rebinding of individual molecular

bonds are governed by stochastic equations in statistical mechanics. The effects of elastic moduli, adhesion size and bond rebinding rate on the cluster lifetime and strength are studied under strongly non-uniform distributions of interfacial traction. While overly simplified in a number of aspects, our model seems to give predictions that are broadly consistent with relevant experimental observations on focal adhesion.

Regulatory Networks Controlling Cell State Decisions

Professor Ravi Iyengar
Department of Pharmacology and Systems Therapeutics
Mount Sinai School of Medicine, New York, NY 10029

Mammalian cells undergo state change in response to extracellular signals. To understand the logic underlying decision making in the signaling network that controls cellular responses, we have studied how a G protein coupled receptor induces the outgrowth of neurites (the precursor to axons and dendrites) from a cultured neuronal cell line. For this receptor-stimulated transcription factor activity profiling was combined with network development and graph theory analysis. Using 23 activated transcription factors as seeds, an *in silico* signaling network was assembled from a database of known binary interactions. Statistical analysis of this network predicted new components and pathways regulating neurite outgrowth. These predictions have been experimentally verified. Combining pharmacological inhibitors of upstream kinases and transcription factor activity profiling with prior knowledge of upstream regulation reveals a network organization of OR gates to the kinases stacked above AND gates to transcription factors allowing for distributed decision making in receptor mediated triggering of neurite outgrowth. These studies highlight the need for complementary approaches to qualitatively define the regulatory landscape and quantitatively analyze the dynamics of the regulatory processes to develop predictive models of decision making in cells.

Cell type-specific responses to substrate rigidity.

Professor Paul Janmey
Department of Medicine and Engineering
University of Pennsylvania, Philadelphia, PA 19104

The mechanical properties of surfaces or three dimensional matrices on which or in which cells grow have a critical influence on the morphology, transcriptional program, and function of many cell types. Differences in rigidity, as quantified by the elastic modulus, lead to specific changes in function or preferential growth. For example hepatic stellate cells and astrocytes activate on surfaces of pathologically increased rigidity, whereas neurons extend processes with increased branching with *decreased* substrate rigidity. Some cell types such

as fibroblasts change their own stiffness to match that of the substrate to which they are bound. In some cases the magnitude of the mechanical effect can be modified by other factors such as the type of adhesion receptor involved or the amount and nature of chemical stimuli. One example of the interplay between substrate adhesivity and stiffness is seen in the differential ability of cells devoid of the actin crosslinker filamin A to spread on surfaces that engage different classes of integrins. The mechanism(s) by which cells sense stiffness are beginning to be clarified and appear to involve different signaling pathways in different contexts.

Multi-Scale and Multi-Physics Computational Tools

Professor Roger D. Kamm
Depts. of Mechanical Engineering and Biological Engineering
Massachusetts Institute of Technology, Cambridge, MA 02139

Numerous methods have been developed to address biological problems in control or mechanics. These techniques draw upon advances in numerical simulation from a variety of fields ranging from structural engineering (e.g., finite element methods) to computational chemistry (e.g., molecular dynamics). While there remains a need to further refine these tools and improve computational efficiency, many of the critical problems of the next decade will require that these methods be combined in ways that we are only beginning to recognize. One example can be found in the field of mechanobiology, where one can already envision problems that span from molecular to multi-cellular length scales, from nanoseconds to years in duration, and encompass issues that simultaneously involve mechanics, control theory, transport, signaling and chemistry. Some “grand challenges” will be discussed including mechanotransduction, tumor cell extravasation and intravasation, and coordinated cell population behavior such as organ regeneration or angiogenesis.

Critical Issues and Challenges of Engineering Tissues from Cells

Professor Beth Pruitt
Department of Mechanical Engineering
Stanford University, Stanford, CA 94305

Engineering functional tissues requires understanding of the functional cellular environment. Our research focuses on understanding the mechanical properties of cells and how they are related to the ways in which cells interact with their environment electrically, mechanically, and chemically. Issues include identifying critical in vitro factors for directed cell growth, differentiation and maintenance, reconstituting proper cellular function and structure in vitro, and the associated challenges of cross-disciplinary communication and teaming.

Quantitative Characterization of 3-D Deformation in Soft Biomaterials and its Application to Cell Mechanics

Professor Guruswami Ravichandran
Department of Engineering and Applied Science
California Institute of Technology, Pasadena, CA 91125

A three-dimensional (3-D) full-field measurement technique developed for measuring large deformations in optically transparent soft materials is presented. The technique utilizes a digital volume correlation (DVC) algorithm to track motions of sub-volumes within 3-D images obtained using fluorescence confocal microscopy. The measurement technique was used to measure large deformations in a transparent agarose gel sample embedded with fluorescent particles under uniaxial compression. The technique was validated by measuring non-uniform 3-D deformation fields near a hard spherical inclusion and an air bubble (void) under far-field uniaxial compression. The results show that the proposed technique is well-suited for investigating cell-extra cellular matrix mechanical interactions as well as for obtaining local constitutive properties of soft biomaterials in 3-D. Recent results from investigating the motility of a fibroblast cell on an artificial extracellular matrix (aECM) in a quasi 3-D system and its implications are discussed. Some perspectives on the use of quantitative tools for studying cell-aECM interactions on 3-D are presented.

Structure and function of biological cells: theoretical approaches from soft matter physics

Professor Sam Safran
Department of Materials and Interfaces
Weizmann Institute of Science, Rehovot, Isreal 76100

The large-scale structure, phase behavior and dynamics of artificial systems such colloidal dispersions, polymers, membranes and vesicles have been successfully elucidated in the last 30 years using approaches that focus on the collective behavior and “coarse grain” over the atomic or molecular details. Applying similar theoretical approaches to cells and biomaterials requires a major extension of these concepts since biological cells are not in thermal equilibrium. For example, an understanding their structure or mechanics must account for the internal forces generated by (energy consuming) acto-myosin contractility. To illustrate how such an approach may be useful in cell mechanics, we summarize a theoretical model we have proposed to predict the dynamical orientation of cells subject to applied stresses. Interest in the fundamental response of cells in an elastic medium is inspired by recent studies of the dependence of cell function and development on matrix elasticity as well as by tissue engineering. As a first step, we propose an explanation of the puzzling observation of parallel alignment of cells for static and quasi-static stresses and of nearly perpendicular alignment for dynamically varying stresses, using a “coarse grained” approach in which a

contractile cell is represented by a force dipole. An ensemble of interacting cells is treated using an elastic analogy of the dielectric constant. Current work focuses on how feedback within the cell can lead to spontaneous polarization of contractile, anisotropic cells, using ideas that derive from both soft matter science and the mechanics of inclusions in elastic media. An important, future goal is to synthesize the “coarse grained” approach to the entire cell with the properties of its components, such as focal adhesions and stress fibers. These components can also be treated at a macromolecular or coarse-grained scale with extensions of ideas from soft matter science.

Development of tissue mimetics based on natural extracellular matrices

Professor Jean E. Schwarzbauer
Department of Molecular Biology
Princeton University, Princeton, NJ 08544

The architecture of the extracellular matrix (ECM) determines cell morphology, movement, and growth rate within tissues. We are using natural fibronectin-based matrices, soft versus rigid substrates, and micropatterned surfaces to study the regulatory effects of the ECM on cell signaling and differentiation decisions. Fibronectin fibrils are a major component of connective tissues in vivo and of the ECM deposited by cells in culture. We have developed a three-dimensional fibrillar matrix culture system that supports migration of tumor cells and affects the differentiation of embryonic stem cells. A second type of matrix, the fibrin-fibronectin wound provisional matrix, is a protein network that polymerizes at sites of tissue injury in vivo but can also be generated from blood plasma or purified proteins in vitro. We manipulate the properties of these matrices by including enzymes, other ECM proteins, covalent crosslinkers, or surfaces of different rigidity in order to change fibril organization or matrix stiffness. Our results show that varying the properties of these matrices changes how they affect cell functions. We are analyzing cells on 2D micropatterns of fibronectin domains in order to learn how the positions and distributions of cell-binding sites within these complex 3D ECM networks contribute to cell functions.

We Know About Proteins and Cells But Little About Functions in Cells

Professor Michael P. Sheetz
Department of Biological Sciences
Columbia University, New York, NY 10027

There have been major advances in our ability to analyze many aspects of biological systems: genomes are sequenced, many protein structures are known, proteomics, lipidomics and glycomics have provided important insights. In addition, there are many tools to quantify

cell physiological parameters. However, we lack a detailed understanding of many if not most cellular functions in an in vivo context. A useful analogy is that we are faced with a task of reverse engineering similar to that of a naïve engineer trying to understand how automobiles work. At this time, the engineer has all of the parts of the automobile on the table and has some binary complexes. In addition, there are complete automobiles around to study as well. What is not known is how functional complexes in the automobile actually complete a task, e.g. how the windshield wipers, side window opening mechanisms, or even the engine works on a detailed level. These meso-scale functions are at the heart of many cellular functions and often occur in stereotypical ways. Tools of nanotechnology and several new light microscopic methods can enable us to start to address this intermediate level dynamically.

Cell and Bacteria Actuated Microobjects

Professor Metin Sitti
Department of Mechanical Engineering
Carnegie Mellon University, Pittsburg, PA 15212

Recent studies have shown the possibility of integrating biological microorganisms such as bacteria, muscle cells, and algae to microobjects to move them in liquid environments. Such a hybrid actuation concept could be an alternative method of building microscale miniature and efficient actuators where motility of microorganisms could be harvested to move the microobjects and actuation power source could come from the chemical energy inside the microorganism or the liquid environment. However, there are many challenges to achieve hybrid actuators such as adhesion of biotic and abiotic interfaces, sustainability of microorganisms, stochastic control of such actuators, and microorganism alignment and patterning. Examples from literature will be given and bacteria integrated swimming microobjects will be presented as a case study. *S. marcescens* bacteria are attached to 10 micron polystyrene beads. Randomly attached bacteria are shown to propel the beads at an average speed of 15 $\mu\text{m}/\text{sec}$ stochastically. Using chemical stimuli, bacteria flagellar propulsion is repeatedly on/off controlled. To improve the speed performance of the bacteria attached beads, beads are patterned, and half coated beads show speeds in average around 33 $\mu\text{m}/\text{sec}$. Moreover, to improve the motion directionality, microcylinders are patterned and bacteria are attached to only bottom side of the cylinders.

Appendix A3 Presentations

To be included in the report to the NSF.