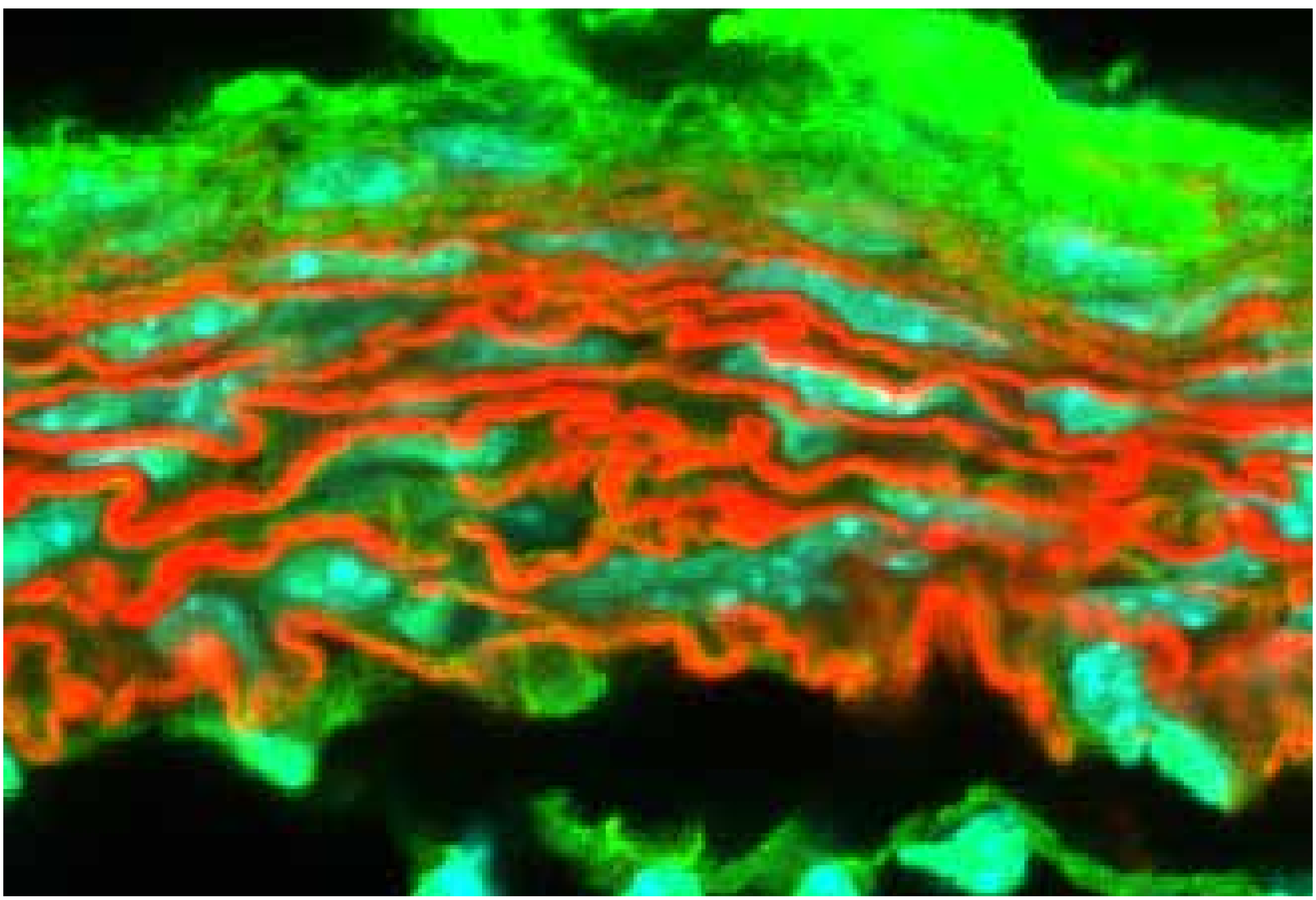
WASHINGTON UNIVERSITY MCKELVEY SCHOOL OF ENGINEERING

STRATEGIC PLAN TO ACHIEVE LEADERSHIP THROUGH EXCELLENCE

RESEARCH

Mechanobiology



RESEARCH

Mechanobiology

Executive Summary

Impacting Biology Through Applied Physics

Mechanobiology is broadly defined as the study of how biological systems sense, generate, and respond to physical forces. Mechanical force is a critical component of all biological systems, providing cues to sculpt morphogenesis of plants and animals, to enable cells to migrate or differentiate in response to physical changes in their environment, and to modulate the function of single molecules. Tools and technologies have advanced in the past decade so that force and the resulting changes in form, function, composition, and biochemical and genetic signaling can be measured across length and time scales from a tissue inside the body to an isolated DNA molecule.

Much of the necessary infrastructure, personnel, and intellectual capital in mechanobiology already exist at the School of Engineering & Applied Science (SEAS) and within other schools at Washington University. These aspects make SEAS well poised to make significant advances in mechanobiology, with a focus on key areas within development, injury/healing, and disease.

The proposed strategic initiative in mechanobiology will focus on attracting and retaining outstanding faculty and students. With the recruitment of six to eight new faculty members in mechanobiology, in MEMS and BME, Washington University can become a top choice for students and postdoctoral fellows. We should invest resources in PhD students and postdoctoral fellows to expand our influence in mechanobiology in the national and global landscape. A new graduate program is not needed, but the proposed PhD in biophysics would be highly synergistic with a mechanobiology focus. Shared equipment and pooled resources and staff to maintain and manage the equipment would decrease startup costs for many faculty hires and consolidate interactions among faculty and students.

Mechanobiology

Washington University McKelvey School of Engineering

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1. Overview

1.1 Definition and scope

Mechanical force is a critical component of all biological systems, providing cues to sculpt morphogenesis of plants and animals, to enable cells to migrate, proliferate, or differentiate in response to physical changes in their environment, and to modulate the function of single molecules. Mechanobiology is broadly defined as the study of how biological systems sense, generate, and respond to physical forces. Biological systems include whole organisms, tissues, groups of cells and their matrix, individual cells, subcellular structures, proteins, and molecules. Tools and technologies have advanced in the past decade so that force and the resulting changes in form, function, composition, and biochemical and genetic signaling can be measured across length and time scales from a tissue inside the body to an isolated DNA molecule.

1.2 Importance to the School of Engineering, WashU, and society

Mechanical factors play a major role in living tissue growth and the response to aging, injury, or disease and capacity for healing. Development, injury/healing, and disease are three key areas in which sensing, generating, and responding to mechanical forces are critical. Examples of these areas are given below:

A. Development

1. Force generation - Forces caused by differential growth of cells can lead to the formation of necessary folds in the developing brain.
2. Force response - Forces applied during growth can make plant fibers better for making useful materials.

B. Injury/healing

1. Traumatic brain injury - Large or repeated forces on the brain lead to traumatic brain injury and cognitive impairment.
2. Orthopedic injury/healing - Ligaments, tendons, and cartilage tear or wear down due to mechanical loading and are slow to heal and difficult to repair.

C. Disease

1. Fibrosis - Aging and pathology associated scarring of the heart, lungs, and liver, causing changes in mechanical properties of the tissue and compromising function.
2. Cancer - Aberrant changes in physical environment can alter cell motility and allow cancer cells to leave a tumor and metastasize to other parts of the body.

In the examples above, the mechanisms involved in sensing or generating the physical force and the pathways leading to the resulting collective response are largely unknown. Research on the force sensing, generating, and response mechanisms in biologic systems cuts across all three key areas and will require interdisciplinary teams to make significant progress. Measuring and manipulating mechanical forces are traditionally associated with engineering, while morphogenesis, cell behavior, and molecular functions are traditionally associated with biology and medicine. WashU mechanobiology strengths are well positioned to make advances in novel instrumentation and recording for force and morphology measurement, as well as development of imaging probes (e.g., molecular beacons, FRET constructs), and biological reporter constructs specific to conserved mechanobiological processes. Thus we can leverage WashU's strength in medical research, plant biology, computational modeling, imaging, and nanoscale materials technologies to create a world-class research and engineering enterprise within SEAS.

2. Unique advantages to pursuing mechanobiology within SEAS

Much of the necessary infrastructure, personnel, and intellectual capital in mechanobiology already exist at SEAS and within other schools at WashU. These aspects make SEAS well-poised to make significant advances in mechanobiology, with a focus on key areas within development, injury/healing, and disease.

2.1 Existing facilities

WashU has existing individual and shared facilities that will provide the equipment and technical knowledge necessary for advancing mechanobiology research. Facilities available within SEAS and the Institute of Materials Science & Engineering include confocal microscopes, Raman microscopes, fluorescence correlation microscopy system, atomic force microscopes, electron microscopes, ultrasound imaging system, rheometer, mechanical testing equipment, micro- and nano-fabrication equipment and state-of-the art animal facilities. Facilities available within the School of Medicine include the Center for Cellular Imaging, Genome Technology Access Center, zebrafish facility, flow cytometry and fluorescence activated cell sorting, tissue and fluid harvest cores, and histology cores. Facilities in the broader St. Louis area that enhance mechanobiology research include the Donald Danforth Plant Science Center for applications in plants and the Cortex Innovation Community to translate and commercialize discoveries.

2.2 Current faculty and programs

WashU is recognized for the strength and talent of individual research programs in mechanobiology. Established groups in SEAS with significant grant support include senior investigators (Bayly, Cui, Genin, Nehorai, Setton, Shao, Taber, Wagenseil) as well as relatively new faculty (Foston, Lake, Pathak) on upward trajectories. Notable recent developments include:

A. NSF Science and Technology Center for Engineering Mechano-Biology (CEMB): a collaborative center, funded by NSF, co-directed by Guy Genin.

B. T32 training grant Interdisciplinary Training in Mechanobiology from nm to cm: funded by NIH NIBIB, directed by Philip Bayly.

C. Physical Sciences Oncology Center: a collaborative center, funded by NIH, co-directed by Gregory Longmore.

D. Center for Biological Systems Engineering: a collaborative center, broadly funded, led by Rohit Pappu.

Key collaborators outside of SEAS include highly productive and respected researchers such as Farshid Guilak, Simon Tang, and Matthew Silva (Orthopaedics); Robert Mecham (Cell Biology & Physiology); Lila Solnica-Krezel (Developmental Biology); Barbara Pickard, Elizabeth Haswell, Ram Dixit, and Lucia Strader (Biology); Elliot Elson, Michael Greenberg, and Eric Galburt (Biochemistry & Molecular Biophysics); Gretchen Meyer (Physical Therapy); and the entire WashU imaging core. In general, the size, scope, and quality of the quantitative life science research enterprise at WashU are exceptional.

2.3 Reputation and intellectual capital

The combined group at WashU encompasses strengths in multi-scale modeling and simulation, advanced imaging techniques, fundamental mechanics, plant biology, and the nanoscale technologies that are pushing the envelope of mechanobiological measurement. The imaging capabilities of the WashU Center for Cellular Imaging also provide capabilities matched by few other institutions. Recent hires at WashU at both junior (Foston, Lake, Pathak) and senior (Guilak, Setton) levels demonstrate the ability to attract promising new investigators and established leaders in the field. Guilak is the president of the Orthopedic Research Society and Editor of the Journal of Biomechanics. Setton is the president of the Biomedical Engineering Society. The active research and training programs allow recruitment of very good PhD students and postdoctoral fellows. Overall, mechanobiology is an area of research in which WashU is already excellent and can compete among the handful of top institutions with mechanobiology programs worldwide, holding our own with places like Penn, National University of Singapore, UCSB, Georgia Tech and Duke.

2.4 Areas of interest

There are particular opportunities in tackling challenges of mechanobiology in development, injury/healing, and disease in plants and animals. New research within these broad areas should be synergistic with and extend current research. For example, understanding physical forces in cell division, cell motility, tissue extension, and tissue elongation in common developmental processes is critical for understanding birth defects, tissue regeneration, and plant growth. With existing strengths in understanding mechanobiology of the extracellular matrix and cytoskeleton in cancer, musculoskeletal systems and cardiovascular systems, we see identifying conserved processes in plant, nonmammalian organisms, neural, gastrointestinal, and pulmonary processes as being highly fertile areas for expansion. Major advances in mechanobiology arise from novel technologies for manipulation and characterization of forces from the nm to the cm length scale. We believe that progress requires bolstering WashU's strengths in instrumentation and recording, imaging and probe development, design of biological reporter elements.

3. Investments needed to achieve global leadership in mechanobiology

3.1 Human resources

Strategic investment in mechanobiology will ultimately focus on attracting and retaining outstanding faculty and students. The mechanobiology initiative will clearly strengthen interactions with the School of Medicine in many departments, and will strengthen interactions with Biology and Physics in Arts & Sciences. Current funding is already vital with many collaborative proposals across many Schools and divisions. Within SEAS, the initiative will particularly strengthen BME and MEMS, but also involves faculty from EECE and ESE.

3.1.1. Faculty

Mechanobiology researchers must represent a balance of expertise in new technologies for imaging and characterization and expertise in applications of mechanobiology. They must also be synergistic with and extend current research areas. With six to eight new faculty in mechanobiology, in MEMS and BME, WashU can become a top choice for students and postdoctoral fellows. We envision approximately half of the new faculty would be junior hires and half would be senior hires.

3.1.2 Staff

To have effective common and shared facilities, the School requires a group of technical experts and senior scientists to maintain equipment and to train students and postdoctoral fellows. Investment in staff to maintain shared facilities would reduce the startup costs for many hires and consolidate interactions among faculty.

3.1.3 Students and postdoctoral fellows

We should invest in PhD students and postdoctoral fellows to expand our influence in mechanobiology in the national and global landscape. Mechanisms include providing matching slots for PhD students in the existing training and center grants and subsidizing training slots for postdoctoral fellows in mechanobiology. We envision WashU as the preeminent training ground for future academicians seeking postdoctoral positions and faculty positions in mechanobiology. We could have a seminal conference or instructional short course in this area.

3.2 Infrastructure

3.2.1 Physical plant. To accomplish this growth we should create a branded physical space for mechanobiology researchers on the connecting levels of Whitaker and Jubel Halls. This grouping, which already exists in current Whitaker labs and planned Jubel space, will facilitate sharing of ideas, equipment, people, and supplies.

3.2.2 Shared equipment. Much shared equipment already exists at SEAS and the School of Medicine. We do not have pooled resources for maintenance or staffing, however, for most of the equipment at SEAS. Pooled resources for staffing and maintenance would ensure that the equipment serves its intended purpose and allow faculty and students to focus on acquiring new data. Some critical equipment is available only at the School of Medicine. Duplication of resources is to be avoided, although dedicated equipment in SEAS is essential for experiments involving the study of living systems over long durations (e.g, time-lapse imaging) or where transport is prohibitive for experimental success (e.g., moving in-ground plants or living animals). Examples of equipment at SEAS that would advance research in the field include a two-photon microscopy live cell imaging system, an in vivo imaging system, an intravital microscopy imaging system, and a biological atomic force microscope.

3.2.3 Graduate programs. A new graduate program is not necessary, but the proposed PhD in Biophysics would be highly synergistic with a mechanobiology research focus. PhD students in mechanobiology could earn PhDs in ME, BME, or Biophysics.

4. Responsibility and metrics for success

The current faculty form part of an initial SEAS mechanobiology steering committee: Nehorai, Foston, Lake, Pathak, Genin, Bayly, Wagenseil, Setton, and Taber. Additional faculty with strong mechanobiology interest and successes include Cui, Elson, and Pickard. Jessica Wagenseil is proposed as the chair of this steering committee. The steering committee will be updated to include new hires, and faculty will rotate off. Mechanobiology currently benefits from an advisory board with industry, alumni, and peer members that serve as mentors to our students and guide development of our program through the T32 training grant mechanism.

BME and MEMS have the most current research interest in mechanobiology within SEAS. The BME (to be determined) and MEMS (Philip Bayly) department chairs will identify faculty slots, support searches, and provide space and resources to attract talented and productive mechanobiology faculty to WashU. Guy Genin as co-director of the WashU-Penn CEMB, will seek opportunities to make the CEMB visible and enhance its impact on SEAS.

The success of the strategic plan can be judged by increases in the following metrics over the three-to-five year period:

1. New mechanobiology faculty recruited
2. Impact of papers and citations from faculty in mechanobiology
3. Funding for mechanobiology faculty
4. Program project or center grant in mechanobiology to complement existing T32 and NSF grants
5. Patents and commercialization of mechanobiology technology
6. PhD student dissertations
7. Placement of PhD and postdoctoral graduates
8. Visibility of mechanobiology faculty, trainees, and students at conferences