BioSystems and Micromechanics

RESEARCH THEME

One organizing theme of research in the BioSyM program is that mechanical forces and interactions are critical regulators and indicators of molecular, cellular, and tissue functions. It is now widely recognized, for example, that mechanical signaling pathways operate in parallel with biochemical ones in regulating biological function. This mechanical/biochemical coupling in biology offers diverse opportunities to diagnose, intervene, and control biological outcomes from the molecular to tissue levels. The work of BioSyM will have broad impact on many pathophysiological states since there is ample evidence that many mechanical/biochemical coupling mechanisms are ubiquitous in biology. Our major goals are to develop novel imaging, manipulation, measurement and control platforms that are applicable from the molecular to the tissue levels; and to apply these platforms for fundamental studies relevant to tissue degenerative diseases, fibrosis and drug screening targets. The integrated research efforts will bridge key gaps between engineering and molecular/cell biology by bringing together technologists in micro- and nanofabrication; single-molecule and single-cell manipulation; 3D molecular, cell, and tissue imaging; and computational biology with engineers, biologists, and clinicians focused on developing new tissue-based disease models, diagnostics, and treatment modalities.

CORE RESEARCH PROJECTS

Single Molecule Sensors and Sequence Identification

- The aim of this effort is to develop and validate mechanical and optical sensors of intermolecular binding events at the single molecule level. Successful development of our approach – quantitative sensing of kinetic interactions among intra- and extracellular proteins and proteolytic enzymes – will be critical to the identification of drug targets that are implicated in cell/tissue disease or that significantly affect cell migration and tissue degeneration rates. The experimental and modeling capabilities explored herein will serve as the basis for a new class of mechano-diagnostic sensors. The aim is to engineer generalized sensor platforms to harness single molecule methods for detection and measurement of molecular and cellular interactions and measurements.

Micro/Nanofluidic and Optical Profiling of Cells and Molecules

- It is increasingly evident that the mechanics of biomolecule / cell interactions are critical in the normal operation of many biological systems. Recent scientific advances in cellular and molecular biomechanics revealed many different examples where biomechanical cues and interactions are indeed critically important to normal cell function and molecular / cellular recognition. In addition, such interactions and cellular / molecular mechanical properties could be utilized for diagnostic purposes. It is crucial to develop experimental tools allowing one to manipulate individual cells and molecules mechanically towards further development of this promising field. The aim is to develop platform technologies that provide mechanical, chemical, and immunological information about cells under study. Focus will be on cell-based biomechanical sorters / assay devices, and will be further expanded toward the molecular biomechanical problems.

Multi-Scale Image Informatics Investigation of Liver Fibrosis

- Many diseases have strong mechanical and structural components to their etiology, such as arteriosclerosis, cancer metastasis, and liver fibrosis. Liver fibrosis is particularly prevalent in a number of Asian countries. It arises from chronic insult to the liver with the accumulation of extracellular matrix (ECM) proteins, leading to cirrhosis, portal hypertension, liver failure and hepatocellular carcinoma. Although many molecular pathways are important for liver fibrosis progression, the complex interactions of individual pathways limit the development of effective pharmaceutical intervention. The system biology approach has emerged as an important approach to understand how complex pathway interactions regulate many different cellular biological processes. The specific aims are:
    - Develop biological models (engineered tissues and animals) and perturbation techniques for systems biology investigation of liver fibrosis.
    - Develop quantitative, high throughput technologies to characterize tissue molecular, biochemical, morphological and functional states.
    - Develop data analysis, synthesis, mining, and modeling algorithms for tissue bioinformatics data
    - Understand and model liver fibrosis progression processes with an emphasis on the effect of therapeutic agents on stellate cell activation and fibrogenesis.

Control of Cell population behaviour in tissue constructs using image analysis and stochastic modeling

- The potential now exists for controlling the growth of tissue constructs by tailored delivery of growth factors and cytokines in combination with controlled physical factors such as shear stress and matrix stiffness. The objective of this project is to advance our understanding of multiple cell interactions with a long term goal of actively controlling collective behavior of cell populations. We view the complex biological processes leading to capillary morphogenesis as a consequence of cell-level decisions that are based on global signals and environment conditions, limited near-neighbour communication, and stochastic decision making with various feedback loops. The aim is to develop both experimental and computational methods integrated into closed-loop control of cell population behavior. Stochastic cell decision models with state transition probabilities modulated by local and global signals will be developed. Micro-fluidic stations equipped with a suite of instrumentation, including state-of-the-art 3-D imaging systems and advanced control of comprehensive physical and biochemical factors, will be developed and used for verification of the stochastic model of cell population behavior. Based on the stochastic model, feedback control will be designed to drive the cell population towards a desired collective behavior.

Research Projects Catering to SMART BioSyM IRG Core Research

(November 9, 2009)

Viscoelastic behavior of cytoskeletal network

PI: Kamm (MIT) and Liao (NTU)

To study experimentally and through theoretical modeling, the viscoelastic behavior of cytoskeletal networks.

Experimental study and modeling of cell-substrate adhesion mechanisms and adhesion strength

PI: Kamm (MIT), Liao (NTU), Van Vliet (MIT)

To elucidate the interactions between cell and substrate (in terms of its stiffness and other parameters), using techniques such as TIRFM and force spectroscopy, and to model the adhesion behavior at nano- and micrometer scale.

Primary Human Neural Stem Cells

PI: Griffith (MIT), Kamm (MIT), Chan (NUS)

To re-examine the role of FGF and EGF gradients in maintaining stemness and self-renewal, to examine the role of Notch in the same, and using lineage specific markers to track directed differentiation in real time.

Endometriosis

PI: Griffith (MIT), Kamm (MIT), Chan (NUS)

Comparative growth and cell specification in either ectopic or orthopic endometrium The effect of inflammatory cytomines and derangement of growth, enzymes and metaplasia.

Micropatterned hydrogels for systems biology of mesenchyaml stem cell (MSC) growth and differentiation

PI: Hammond (MIT), Griffith (MIT), M.B.E.Chan (NTU)

Outstanding questions in the field of MSC biology revolve around the synergistic roles of autocrine and paracrine growth factors and extracellular matrix chemical composition and stiffness on growth, migration, and differentiation of stem cells. In this project, advanced 2D and 3D processing methods developed in the M.B.E.Chan/Hammond labs will be adapted to both existing hydrogel materials and new materials to create niches for MSC in the Griffith lab. An advantage of the approaches is the ability to pattern large areas with fidelity using robust processing methods.

Kinetics of adhesive ligand-receptor interactions under force

PI: Van Vliet (MIT), Kamm (MIT), Thiery (IMCB), Lim (NUS), and Raghunath (NUS)

This project will use molecular-scale experiments and simulations to predict the lifetime of key ligand-receptor complexes between cells and between cells and extracellular matrices.

Mesenchymal stem cell organization & migration as a function of applied stresses and matrix mechanics

PI: Van Vliet (MIT), Griffith (MIT), Han (MIT), and Lim (NUS)

This project will focus on mulitscale analysis of bone marrow-derived mesenchymal stem cells as a function of externally applied stresses and matrix/substrata properties such as mechanical stiffness.

Mesenchymal stem cell differentiation as a function of forced ligand-receptor interactions

PI: Van Vliet (MIT), Han (MIT), Griffith (MIT), Lim (NUS), and Raghunath (NUS)

This experiment-based project will focus on unique mechanical identification and sorting of stem cell state, particularly as a function of altered ligand-receptor binding kinetics.

Mesenchymal stem cell interactions with endothelial cells
PI: Griffith (MIT), Kamm (MIT), Chan (NUS)
Endothelial cells require other cell types to develop into a mature and stable vascular network. In this study, microfluidic cell culture methods are used to examine these multi-cell type interactions.

Studies of epithelial-mesenchymal transition (EMT) in microfluidic systems
PI: Kamm (MIT), Thiery (IMCB)
These studies have the aim of understanding the nature of EMT from an epithelial cell line and identifying the nature of the phenotypical changes that lead to resistance of metastatic cells to normal cancer therapies.

Single Molecule Sensors and Sequence Identification
PI: Doyle (MIT), Yan (NUS), Van der Maarel (NUS), Van Kan (NUS)
DNA Micromechanics: We will develop nanofluidic devices for the manipulation and mapping of single DNA molecules. another objective is to Interface optical and magnetic tweezers with fluidic devices to interrogate DNA-protein interactions.

Single-strand binding protein binding to single stranded DNA
PI: Lang (MIT) and Jie (NUS)
Such proteins are involved DNA replication and in DNA damage repairing process. This research aims to study the mechanical properties of DNA-SSB complexes. Two major experimental methods will be involved:

1. Magnetic tweezer manipulation of DNA-SSB co-polymer. The force-extension (FE) curve of the co-polymer will be measured and compared with the FE curves of a double-stranded DNA (dsDNA) and ssDNA.
2. AFM imaging of DNA-SSB co-polymers. From the high resolution imaging we may be able to obtain structural information of the co-polymer.

Cross-scale image quantification and informatics analysis of liver diseases
PI: Peter So (MIT), Hanry Yu (NUS), Jagath Rajapakse (NTU)
High throughput optical imaging capabilities will be developed to quantify molecular and cellular features in disease models in 3D tissue models, mice and rats; and correlate with data from clinical imaging modalities (MRI, ultrasound etc) to establish the biological basis of the diagnostic imaging of liver diseases (cancer, cirrhosis and fatty liver).

Microfluidic single cell sorting / detection
PI: Han (MIT), Lim (NUS)
In this project, we will employ advanced microfluidic cellular / molecular manipulation systems in order to identify and sort the cells of interest out of larger cell population, and their molecular signatures will be analyzed for advancing various detection / diagnostic modality.

Integrated waveguide based particle actuation and imaging
PI: Barbastathos (MIT), Sheppard (NUS)
A new concept for simultaneous manipulation and imaging of particles in an opto-fluidic platform. The main motivation is to enable cell and tissue manipulation and measurement functions while avoiding the mechanical complication of free-space optics surrounding the fluidic channel that plague traditional opto-fluidic systems. Our concept replaces the free space optics with a multimode waveguide where light localization for trapping and imaging is achieved through interference between field modes including reflections.

Manipulation of Stiffness Gradients in Extracellular Microenvironment through Stochastic Control of Magnetic-Particle Ensemble

PI: Peter Chen (NUS), Harry Asada (MIT), Roger Kamm (MIT)

The mechanical properties of microstructures that surround cells play an important role in determining the behavior of a cell population, including differentiation, proliferation, and apoptosis. The objective of this project is to develop engineering approaches to directly manipulate the extracellular microenvironment in order to produce desired changes in its stiffness.