Strategic Initiative on
Multi-scale Biological Active matter
(SIMBA)

Executive Summary:

We propose to pursue a fundamental understanding of the structure and dynamics of multi-scale biological assemblies using a interdisciplinary approach that cuts across scientific and engineering methodologies with the goal of enabling control of function in vivo and aiding in the development of novel bio-inspired materials and devices.

Succinct definition of thematic area:

This area cuts across several themes 3 (Human Health), 7 (Information, Computational, and Data Sciences, and Engineering), 8 (Matter Science and Engineering: from theory to application) and 9 (Life Sciences). Our proposal is synergistic with several initiatives proposed from Physics, Chemistry and Chemical Biology, QSB, MSE and BEST.

Intellectual Components:

In nature, the whole is definitely greater than the sum of its parts. The hierarchical assembly of cellular and multicellular structures poses significant challenges for our understanding while also providing inspiration for new soft, adaptive materials. Many biomolecules have evolved to assemble into complexes that exhibit structure on all scales, from the nanometer scale of individual proteins to the full cellular scale of tens of micrometers, and even beyond to the scale of extracellular matrices and multicellular tissue. These assemblies are inherently "soft" and highly dynamic because their properties are determined by weak interactions on the scale of thermal energy at room temperature leading to large fluctuations and complex dynamics. These systems are also typically driven by active processes that consume energy leading to an intrinsically non-equilibrium situation. There are many rich examples of such complex assemblies at the molecular, cellular and multicellular scales that display functional structure and dynamics that are emergent from the interactions of the constituent elements and the active diving forces. These include self-assembled lipid membranes, protein assemblies involved in DNA replication and membrane channel gating, hierarchical assemblies of motors and filaments involved in chromosome segregation, cell division, cell migration and mechano-sensation, ciliary and flagellar propulsion in bacteria and multicellular assembly dynamics such as biofilm formation and cardiac tissue dynamics.

While our quantitative understanding of the individual building blocks of cells has increased tremendously over the last few years, e.g., as a result of new single-molecule

biophysical tools such as super-resolution fluorescence imaging, scanning-probe, and other microscopies, as well as advances in computational modeling, we are just beginning to learn about the basic principles that govern both the assembly and non-equilibrium collective properties at the larger scales.

Advances in this area require contributions from many different fields: biochemistry to understand molecular recognition and signaling mechanisms, soft matter physics and materials science and engineering to understand and characterize material properties, optical physics for cutting edge imaging and manipulation, bioengineering approaches for mechanical and electrical manipulation and multicellular tissue mechanics and biology and chemical biology to probe functional properties in vivo. Since a complete understanding of such hierarchically assembled systems requires the integration of interactions and dynamics across multiple scales, it is also critical to involve theory and computation from multiple fields including applied math, physics and chemistry.

Progress in this area will lead to not only a better fundamental understanding of the emergence of function in non-equilibrium, multiscale, biological assemblies but will also allow us to attain better control of their functional dynamics potentially leading to therapeutic improvements in human health. Along the same lines, understanding the design principles that lead to emergent function in these systems can allow us to design and optimize functional bio-inspired materials.

Research within this initiative will be loosely organized around three thrust areas based on the scales of the assemblies and processes involved.

a. *Nano-scale and sub-cellular assemblies*: Functional biological assemblies that span length scales from sub-nanometer/nanometer ranges of small protein complexes to several tens to hundreds of nanometers of large macromolecular complexes and assemblies will be the focus of this thrust. Areas of high interest in this general field at present and going forward include – functional assemblies of intrinsically disordered proteins; the aggregation of misfolded proteins; lipid rafts; DNA condensation and organization; the mechanics and dynamics of different chromosome segregation apparatus and the functioning of cell division machinery.

b. *Cellular-scale mechanics and dynamics*: This thrust will focus on phenomena that integrate multiple sub-cellular assemblies and processes to produce function at the scale of the whole cell. Areas with high activity and potential include active gels of cytoskeletal protein filaments and molecular motors, assembly and disassembly kinetics of viral capsids, cell wall synthesis and regulation in bacteria, cellular response to mechanical stimuli via the assembly of mechanosensitive filament complexes; bacterial propulsion in complex media and cell migration in 3D elastic matrices.

c. *Multicellular aggregates*: Cell-cell interactions and the structure of multicellular aggregates can give rise to novel functional collective phenomena. This thrust will focus on the mechanics and dynamics of multicellular aggregates including cardiac

tissue and bacterial biofilms; biological fluids and their interactions with cellular and multicellular structures including tumors and clots; collective migration of multicellular aggregates; developmental patterning and differentiation in tissue.

It is to be noted that though these themes have been listed distinctly, they are inextricably interconnected with one level of organization influencing the next, thus requiring a focused effort at all levels.

UCM's role in this theme

It is interesting to note that there have been several initiatives at various places across the country and internationally that emphasize, very broadly, the quantitative studies of biological systems. Most of these centers or institutes are formed with the realization that to truly make progress in this vast area, one needs to facilitate synergy between multiple approaches and foster interdisciplinary approaches. Examples include the Wyss institute for Bio-inspired Engineering at Harvard, the Institute for Biophysical Dynamics at the University of Chicago and the UC's very own California Institute for Quantitative Biosciences (QB3). While the missions of these institutions vary, they are primarily research driven. It is particularly interesting to note in this context that the Wyss institute started out as an initiative in response to the provost's challenge to the faculty to come up with an initiative for the future of bioengineering.

There are several factors that make our proposed initiative at UC Merced unique, distinctive and competitive.

The necessarily broad purview of the institutes mentioned above are a result of trying to minimize the considerable disciplinary boundaries that exist already and bring together as many people as possible to foster potential connections. This is not a critical barrier here at UC Merced, since we are quite interdisciplinary from the very outset and both our current size and structure make it much easier to focus our resources further on a specific and fairly unique theme – Multiscale Assemblies of Soft and Active Biological Matter – in which we already have considerable strength. A particular edge we have in this respect is the number of people who are comfortable working with soft matter (polymers, colloids, gels, liquid crystals, membranes) with a strong interest in biological problems across multiple units including mainly Physics, Applied Math, CCB, Bioengineering and MSE (see list below). Unlike other institutions where such "soft matter" expertise is splintered across multiple departments in far-away buildings, at UCM, multiple interdisciplinary collaborations already exist across these units that fall within this theme that are fostered by proximity and sharing space. The organized initiative can serve to add to this. Unlike some of the diffuse umbrella organizations cited above, our specific focus is, by its very nature, truly integrated across the thrust areas and will allow us to conduct tight-knit team science at a high level. This will be valuable in potentially leveraging our multi-disciplinary approach for center type grants as well as education and training grants down the line.

<u>Growth:</u>
Since we are still in a growth phase we have the opportunity to build a formidable team of

researchers in this specific theme at the interface of soft materials and biology with a potential for high impact and transformative science and technology. One of our major goals down the line is to leverage this initiative and establish an interdisciplinary Center for Soft Biological Matter (CSBM).

We are currently reasonably well represented in thrust (a) at the sub cellular scale but need additional strength at the multicellular scale (c) and especially at the cellular scale (b). Potential further areas of expansion that would be critical to bolstering our strength in these areas include – super-resolution imaging that will allow access to very high spatial and temporal resolution; mechanical force production and sensing at the cellular level including cytoskeletal mechanics; 3D cell migration; collective phenomena in multicellular and bacterial systems. It is to be noted that we are currently (this year-2014) in the process of hiring 3-4 people across physics, applied math and material science (including potential cross-unit hires) in bio fluids and whole cell membrane biophysics who would contribute significantly to these areas.

We currently number roughly about 18 FTEs (full list below) and to get to a critical mass (in terms of being competitive for center grants) of about 30 faculty members, we would need an additional 2-3 FTEs per year for the next 5-6 years. We intend to be proactive about leveraging the FTEs allocated to this initiative. We will form joint search committees including people from at least two of the most relevant (for the particular search) participating groups - bylaw units in SNS and grad groups in Engineering. The specific search area will also dictate the actual composition, in terms of faculty, of the committees. We will aggressively pursue high quality hires in this area with appointments either being joint between multiple units or residing wholly in one depending on what is most preferred and workable on a case-by-case basis.

Funding:
Research in this area has many potential avenues of funding with current faculty having obtained grants from the NSF (Materials Research, Physics, Bio), DARPA, American Heart Association, CIRM, DOE and NIH among others and we expect this trend to continue. As we approach a critical number of faculty members (~30) we anticipate applying for center grants from federal funding agencies including the NSF (MRSEC (Materials Research Science and Engineering Centers) or STC (Science and Technology Centers) type) and NIH (P series) among others.

Participation:

Below is a list of people from various bylaw units/graduate groups that would contribute significantly to this initiative in terms of their research interests.

Physics
Ajay Gopinathan (protein assemblies, bacterial mechanics, cell division)
Linda Hirst (cytoskeletal network structure, membranes, liquid crystals)
Jay Sharping (biophotonics, vesicles)
Jing Xu (Molecular motors, active transport)

Sayantani Ghosh (magnetic measurements in biofluids)
+2 potential hires (bacterial propulsion, membrane biophysics and self-assembly)

Bioengineering
Wei-Chun Chin (polymer gels in biology)
Ariel Escobar (cardiac tissue dynamics)
Kara McCloskey (mechanical cues in stem cell differentiation)
Victor Munoz (protein folding and dynamics)

MSE
Jennifer Lu (polymer mechanics and biocompatible materials)
Christopher Viney (biological materials, polymers, liquid crystals)

Mechanical Engineering
Sachin Goyal (biopolymer mechanics)
Yanbao Ma (bio-fluids)

Applied Math
Karin Leiderman (biofluid/structure dynamics)
Suzanne Sindi (protein aggregation dynamics)

CCB
Mike Colvin (disordered protein dynamics)
Christine Isborn (biomolecular dynamics)
Andy LiWang (structural biology of protein complexes)
Tao Ye (nanoscale biomolecular assemblies)

Requirements:
There are no particularly special requirements beyond what is required for such research normally – combinations of wet and dry lab space, computational resources, and improved shared facilities (microscopy, fabrication, machine shop).