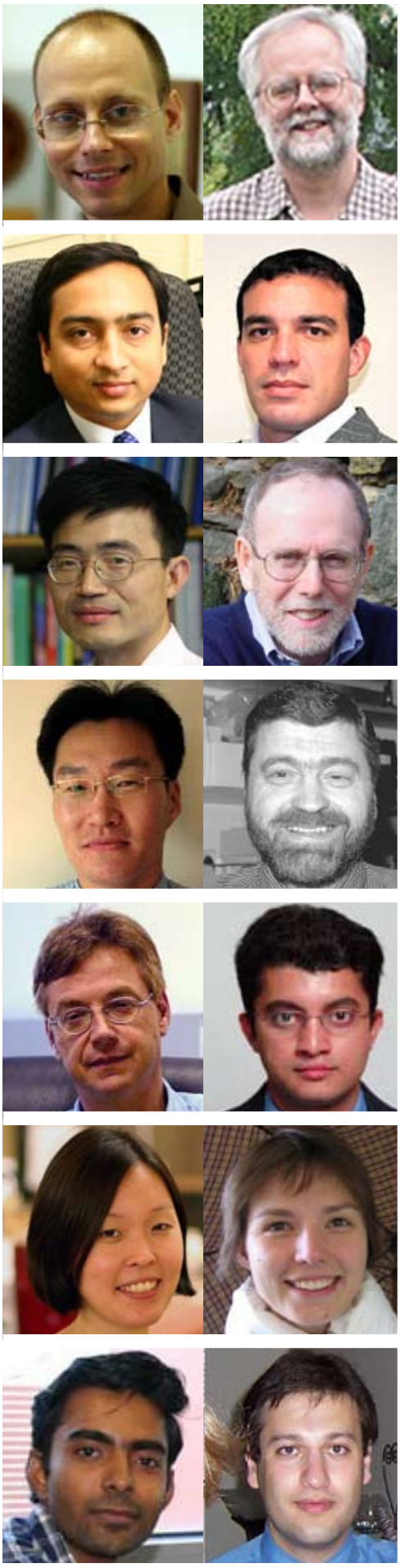

THE FIRST ROUND OF NYU-POLY SEED GRANTS

March 2009

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THE FIRST ROUND OF
NYU-POLY
SEED GRANTS

March 2009

Single Molecule Force Spectroscopy of Fluorinated Proteins

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Abstract

In this proposal, we aim to understand how the structure and topology of a protein affects its resilience to external forces by introducing artificial noncovalent interactions into the hydrophobic core of the native protein. These interactions play an important role in molecular assembly and stability. Fluorinated amino acids are of particular interest due to their chemical inertness and increased hydrophobicity. Specifically, fluorinated amino acids have been used in protein design to modulate stability, protease resistance, alter the surface properties, and mediate protein-protein assembly. To explore how fluorination influences mechanical stability, we propose to incorporate fluorinated amino acids into the polyprotein ubiquitin, which has been extensively studied in its native form. While the effect of fluorination has been examined in terms of thermodynamic stability and structural changes in other proteins, this will be the first study to investigate how the mechanical properties are influenced by fluorination. Moreover, following the rupture of the folded protein, we intend to study the refolding of the fully extended polypeptide, which is initially driven by the hydrophobic collapse. Therefore, the presence of fluorinated amino acids may significantly alter the folding pathways and timescales, as well as the resulting architecture of the molecule.

Project Description

It is a question of fundamental importance to understand the response of proteins to a stretching force, as it characterizes their mechanical architecture. Fluorination introduces non-native interactions, which influence the structure and stability of the resulting protein fold. Thus, by comparing the mechanical response of ubiquitin, with and without the fluorine modification, we will determine the key molecular interactions between the amino acids that drive the protein folding process.

This proposal brings together two complementary expertise, novel molecular biology techniques and single molecule force spectroscopy, to probe the fundamental interactions that drive the molecular assembly of proteins. We propose the forthcoming tasks for the one-year project to achieve this goal are:

- Express the native poly-ubiquitin construct from the plasmid available in the literature and then synthesize the fluorinated polyprotein.

- Characterize the proteins for incorporation of fluorinated amino acids.

- Use the AFM set-up, which we have recently custom-built, to stretch the novel proteins at different constant forces and probe the kinetics of their unfolding in the range between 50 - 400pN.

- Examine the breadth of each distribution of unfolding times to probe the complexity of the underlying energy landscape as a function of force. The force-dependence of the characteristic unfolding timescale for each protein will serve as a test of its mechanical resilience.

- Compare the native and non-native proteins' mechanical responses to reveal the importance of hydrophobic interactions within the folded core.

- Probe the importance of hydrophobicity in the folding trajectories by varying the amino acids and positions of fluorination.

We anticipate that the fluorinated polymeric ubiquitin will likely require a larger external force to pull apart, since the presence of fluorine increases the hydrophobic interactions. On the other hand, if the stronger interactions are introduced outside the folded core, this may prevent the correct folding of the protein. Lessons learned from these experiments will provide insight into designing mechanically stable molecular assemblies derived from proteins.

Nucleotide-directed Materials Assembly

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Abstract

Under NYU-POLY SGCR seed support Canary (NYU), Levicky (POLY), and Seeman (NYU) groups will lay groundwork for advanced materials synthesis based on nucleotide-derived interactions. The canonical example is that of materials assembly facilitated by the base-sequence specific interactions of nucleic acids (typically DNA). This approach has its limitations, however. Thermodynamics of nucleic acid hybridization are subject to temperature, salt concentration, and other environmental factors. This sensitivity renders DNA-directed materials assembly ineffective under certain conditions; e.g. under low ionic strengths or in non-aqueous environments. The proposed work will expand the functionality and range of conditions suitable for nucleotide-directed materials assembly by considering a redesign of the DNA backbone. Specifically, by rendering the backbone uncharged, nucleotide-directed assembly, for example of colloidal structures, should be enabled even at low ionic strengths and possibly also in non-aqueous environments. Two synthetic DNA analogues will be developed and preliminarily characterized for such applications: (i) Morpholinos (MOs) and (ii) nylon ribonucleosides (NRs). MOs and NRs are both synthetic molecules with programmable specificity of interactions derived from a nucleic base sequence, but along an uncharged backbone.

Project Description

Progress in fundamental understanding of kinetics and thermodynamics of hierarchical-assembly of complex structures, spanning from biological to synthetic systems, requires control over interactions between system components at the level of both specificity and affinity. Such control is essential to the study of general phenomena of defect formation and annealing, glassiness, and impact of local and global thermodynamic minima on material organization and properties. DNA-DNA hybridization, which is highly programmable, has been widely used as a flexible tool for organizing nonbiological components. However, DNA solubility limits this approach to aqueous conditions and, because of the high charge density of DNA, renders it sensitive to salt or other charged species. The capacity of DNA for strong charge-charge interactions can be a significant complicating factor, for example, if the components to be assembled are also charged. As an alternative to

nucleotide-directed materials assembly based on DNA as the parent molecule, this project will prepare and evaluate two uncharged, DNA nucleotides: Morpholinos (MOs) and nylon ribonucleosides (NRs). MOs and, it is expected, NRs, complex with DNA according to the usual base pairing rules, yielding DNA-MO and DNA-NR hybrids. Moreover, their self-complexation should also be possible; i.e., formation of sequence-specific MO-MO and NR-NR "bonds". If these interactions retain the sequence specificity of nucleic acids they would provide similarly outstanding versatility with regard to customization of strength and selectivity (complementarity) of their bonding. Stability of MO-MO and NR-NR bonds at low ionic strengths could be of paramount importance for organizing precursors, such as colloidal particles, that may require maintenance of electrostatic stabilization and hence be incompatible with elevated salt concentrations. Additionally, this approach may open up prospects for staged materials synthesis via triggering of distinct stages of assembly (e.g. from simpler to higher level structures) through changes in ionic strength and appropriate combinations of always "on" (e.g. MO-MO, NR-NR) and conditionally "on" (e.g. DNA-DNA) interactions. The synthetic origin of MOs and NRs also renders them resistant to enzymatic degradation.

The NYU-POLY SGCR seed program will pursue the following goals:

First, we will obtain sequence-dependent thermodynamic information on MO-MO, MO-DNA, NR-DNA, NR-MO, and NR-NR interactions, and develop predictive models from these measurements. Thermal denaturation as well as calorimetric methods will be used to determine solution association thermodynamics. Electrochemical methods will characterize molecular associations at solid-liquid interfaces, as typically encountered in materials synthesis applications. It will be especially interesting to contrast behavior of MO-DNA or NR-DNA systems with entirely neutral scenarios such as MO-MO or NR-NR bonding.

Second, we will synthesize modified phosphoramidite reagents for the preparation of NR oligomers containing dA and dG, and we will prepare longer oligomers that exhibit melting transitions at higher temperatures. As they are prepared synthetically at NYU, NRs are may be readily tailored for optimization of properties (e.g. improved solubility) that could be realized through additional modifications to the molecular backbone or side chains.

Third, an important issue involving both MOs and NRs is their helical repeat in complexes with other strands. This issue has been explored with peptide nucleic acid (PNA) DNA complexes, in an assay based on atomic force microscopy. A 2D DNA sheet is assembled with two tiles, one containing conventional DNA strands, and the second containing the nucleic acid variant. The tile structure is varied to offset the helicity mismatch from the DNA analog. This approach will be used to initially determine the helicity of MO-DNA complexes.

Blast and Impact Loading of Bones and Tissues: Deformation and Damage Mechanisms

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Abstract

Injuries under impulsive loading conditions are of great interest to the U.S. Army and many other agencies due to the threats presented by stress waves in ballistic and blast loading conditions. While armor and other materials may stop projectiles from penetrating the structure, propagation of stress waves through the medium still presents severe threats to soldiers and equipment. There is an urgent need to develop a quantitative understanding of propagation of stress waves in living tissue and biological materials and use this knowledge in designing advanced armor systems, treatment planning and procedures, biomedical device designing, and potential long-term effects of such loading conditions. A collaborative team from the NYU College of Dentistry and the Mechanical and Aerospace Engineering Department at Polytechnic Institute of NYU plans to study the effect of blast and impact loading on bones and tissue specimens. This arm of research is a current priority of the Department of Defense (DoD) for studying injuries and developing improved armor. The proposed project for a seed grant is aimed at generating preliminary results in order to facilitate future submission of well founded, highly competitive grant proposals to the NIH and to the Department of Defense (DoD), specifically for the Army. The seed grant will help in building interdepartamental collaboration through joint research, student advising, presentations at conferences, and publications in peer reviewed journals.

Project Description

Most blast tests have been conducted in the field on full-scale or scaled-down structures and are largely limited to examining the failure of the specimens. However, the acquisition of data under controlled laboratory experiments provides better opportunities for understanding the mechanics and physics of structural response to applied loads. Such data can then be used in understanding the origin of damage, propagation pattern, and final fracture to design new materials that effectively mitigate those and similar loads. A shock tube-based instrumentation, with integrated data acquisition system specifically designed for materials testing (developed by the Poly-PI Gupta) and an in-house

developed high-strain rate test equipment (split-Hopkinson pressure bar) will provide the basis for our experimental studies. In our shock test method, load-displacement data is obtained using dynamic pressure transducers and strain gauges. High-strain rate test setup is also capable of obtaining load-displacement curves.

There is almost no data available on the shock response of living tissues, especially mineralized tissues (bone, enamel, dentin). The lack of knowledge in this area is mainly attributed to absence of a method that can provide scientific data during testing. Our test instrumentation and method are intended to address this area of critical need by providing both mechanical simulation and laboratory testing. Existing studies on high-strain rate testing (at strain rates of 103-105 s-1) of materials such as aluminum and polymer matrix composites show that materials behave differently at high-strain rate. Elastic modulus is observed to be higher for most materials, especially of cellular materials, under higher strain rate loading. The strain-rate sensitivity of these materials is attributed to their microstructure, where buckling of cell walls is suppressed and shear failure becomes dominant. Inertial effects also play an important role in some materials in determining their high-strain rate properties. The proposed research plan will build on these observations available for cellular materials and develop a strong knowledge base for bone tissue.

The research plan is based on the current needs of the Army as specified in the open Broad Agency Announcement (BAA) and is focused to address their immediate needs. The following tasks have been identified in our proposed seed grant proposal:

1. Characterization of bone and muscular tissues morphology, and acquisition of its real geometry for modeling through imaging techniques.
2. Testing of compressive and flexural properties of laboratory animal femur and tibia bones and tensile testing of muscles.
3. Testing of bones under high-strain rate loading conditions.
4. Testing of bones and muscles under shock loading conditions.
5. Post-test microscopic characterization
6. Computer simulation utilizing the mechanical testing acquired mechanical properties on real specimen geometry acquired through imaging techniques.

Task 1: Extensive microscopy carried out at Poly on the rabbit and dog bones will be provided by the PI Coelho. The rabbit bones will be retrieved from animals being sacrificed for other research purposes. The tibia and femur bones have cellular structure. Thus, characterization of cell size, cell wall thickness, and cell morphology through imaging techniques such as microcomputerized tomography is required to understand their mechanical behavior.

Task 2: The bone specimens will be sectioned perpendicular and along their long axes and tested in compression. The testing will be carried out on several sections along the length of the bones to understand the effect of cellular structure on their mechanical properties. Muscles will be tested for tensile properties using a nano-precision translation stage and a high-resolution load cell set up (like a miniature Instron universal testing machine).

Tasks 3 and 4: Our in-house developed instrumentation will be used for conducting shock and high-strain rate testing.

Task 5: Included in tasks 2, 3, and 4.

Task 6: The 3D spatial geometry obtained from bone and muscular tissue through suitable imaging techniques will be imported into a 3D CAD software, and properties acquired through laboratory testing assigned to the specimen geometry. Static and dynamic finite element analysis will be developed to determine simulation parameters that replicate mechanical testing failure regions.

Fault-tolerant User-centric Security Services

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Abstract

Cryptography is the foundation for building secure systems and applications. One crucial assumption cryptography is based on is the availability and secrecy of cryptographic keys. For example, to digitally sign a message, one must have access to one's private keys and at the same time, the private key must be kept secret from an adversary in order to prevent signature forgery. However, in practice, the assumption on availability and secrecy of keys is often invalid. Traditionally, the keys are typically stored centrally (e.g., on a single server or a networked device), leading to a single point of failure (violating the assumption on availability of keys) as well as attacks (violating the assumption on secrecy of keys).

Threshold cryptography is a tool that allows for distribution of keys (or any secret information for that matter) and cryptographic operations or functions among multiple nodes, providing improved availability and secrecy. The primary motivation for this proposal is the realization of threshold cryptography in practice. We observe that the research focus on threshold cryptography thus far has mostly been limited to the application domain of critical security services (such as online certification). In contrast, the focus of this proposal will be on the protection of user-centric services, which we argue is equally, if not more important, and which has not received much attention so far. In addition to user-centric cryptographic services, we also consider protection of another important security service, which we call the password remembering service.

Project Description

We propose to utilize threshold cryptography towards protecting user-centric security services. A main challenge in adopting threshold cryptography in this setting is that unlike critical security services, users do not have access to an infrastructure of replicated servers over which cryptographic keys and functions can be distributed. To address this challenge, our idea is to exploit users' real-world trust relationships over the so called social networks, such as Facebook – the keys/passwords and cryptographic operations are distributed across a set of a user's friends or social relations. Assuming that a large fraction of the user's friends are trustworthy and their machines are uncorrupted, such a mechanism of distributing keys/passwords offers a high level of protection. In case a user has access to a number of personal devices (such as a desktop, a laptop, a cell-phone/PDA), a similar idea applies—distributing the keys/passwords among the user's own devices will also provide some level of protection.

We propose to extend existing threshold and proactive cryptographic algorithms for the above setting where the trust is to be distributed between a user's (primary) device and a set of user's friends' devices or a set of user's own devices. For ease of notation, we will call user's device to be protected as the primary device and other devices as servers. In particular, we aim at designing and evaluating protocols which can be realized into a system as a whole, allowing for efficient (preferably distributed)

system set-up, distributed addition of a new server (node admission), removal of a malicious server (node revocation) and proactive share updates. Towards this end, we plan to address a number of technical challenges of both fundamental as well as applied nature.

One challenge in designing such schemes is that the primary device might itself be corrupted by an adversary and therefore the control (e.g., to trigger a threshold signing protocol) should not be given to this device, but instead to the user herself. This can be achieved by making use of password authentication, similar in spirit to the so called "two-party" protocols, which provide control into the hands of the user by making use of password authentication between the user and the primary device. In addition to making use of password authentication, in our distributed setting, we need to make use of a hybrid secret sharing: first the secret key x (to be protected) is split into two parts xU and xS; the user's primary device stores xU, while xS is further split using an appropriate secret sharing, and each server is provided with its respective secret share. To invoke a service (such as signing) using a key x, the user simply types in a password on the primary device, which then connects to the servers to trigger the respective threshold protocol (such as threshold signing) and acquire the signature zS with the key xS. zS is then combined with the primary device's signature zU using the key xU to yield the final signature. Such an approach will remain secure, even if the user's primary device is corrupted, under off-line dictionary attacks and also to online dictionary attacks as long as only a certain threshold of servers are corrupted or are malicious.

Today's computer users have already started, and future users are expected to avail a wide variety of cryptographic services using their personal devices. In addition to user-centric cryptographic services, we also consider protection of the password remembering service, whereby the list of saved user's passwords is stored on the user's trusted servers and shared passwords are recalled with the help of a master password. Our goal is to protect all these services by adopting them to the above-mentioned distributed setting based on hybrid secret sharing. In this process, we have to make sure that keys are (preferably) never stored at a central device and that the user possesses the complete authority to control and manage her servers. To this end, we propose to build a modular system that provides (not just) the following functionalities and to resolve the underlying open questions. This system will be developed as a Facebook application.

Server Management: How can a user manage the set of its designated servers over a social network? This would involve (1) adding a new friend's server to the existing set, which can be achieved by adapting the distributed node admission protocols to the hybrid setting, and (2) revoking a particular friend's server (such as when a friend turns to, or "becomes" an enemy!), which can be achieved by adapting the proactive share update protocols.

Secret Reconstruction: To protect "password remembering service", the passwords would be distributed among a set of user-designated servers. At the time of recalling a particular password, the user would need to trigger the reconstruction of the distributed password. Can the existing secret reconstruction protocols be applied to achieve this functionality?

Signatures: Can traditional public-key based signatures be adopted to the hybrid setting? Can the "identity-based signatures" be adopted to the hybrid setting?

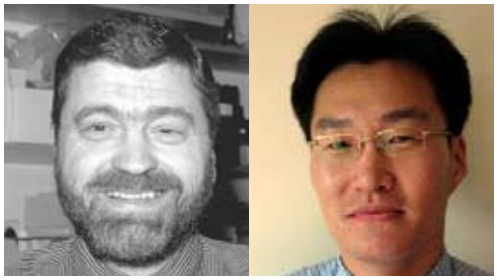
Public Key Encryption: Can public-key based encryption be adopted to the hybrid setting? Can "identity-based encryption" be adopted to the hybrid setting?

Key Agreement: A networked device often needs to establish shared secrets with remote servers (e.g., to establish SSL connection). Can two devices perform an authenticated key exchange, in a fault-tolerant manner when the role of one of the devices has been distributed among a set of servers? The desired keys should neither be generated nor stored at a central device/server. Can the same be extended to a setting where the user's device is involved in a group-wide communication over a network?

Symmetric-Key Encryption and Message Authentication: The user's device might be involved in an encrypted/authenticated communication with a remote server, with whom it shares a symmetric key. Can the symmetric key operations be adopted to the hybrid setting?

Group Signatures: Can the signing in a "group signature scheme" be distributed using the hybrid setting?

Peptide Design for Modulation and Detection of Brain Amyloid Aggregation and Toxicity



Jorge Ghiso[1] and Jin Ryoun Kim[2]

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Abstract

Aggregation of amyloid beta (Aβ) into fibrils is implicated in the pathology of Alzheimer's disease, the leading cause of dementia in the elderly. The process generates conformational rearrangements and intermediate oligomeric species that exert toxic effects on neuronal and vascular cells which, in turn, translate in cognitive decline, ischemic and hemorrhagic strokes or a combination thereof. Amyloidogenic aggregation occurs in many other neurodegenerative disorders and is highly dependent on the content of β-sheet structures of the amyloid subunit. In the case of Aβ, hydrophobic interactions between β-strands interconnected through a linker region seem to stabilize intermediate and fibrillar structures. Thus, development of a robust strategy to control and detect these molecular assemblies would greatly contribute to the understanding and modulation of the oligomerization process. To this end, we propose to engineer the linker region of Aβ to create an *in situ* molecular probe for rapid amyloid detection as well as a conformational catalyst for modulation of Aβ aggregation and toxicity.

Project Description

Molecular assembly of soluble proteins into high order β-sheet rich fibrillar structures is implicated in the pathogenesis of protein-folding disorders, including sporadic and familial Alzheimer's disease. In the case of Aβ fibrils, available data indicate that the N-terminus of the molecule is likely structurally disordered while the rest of the sequence forms a β-strand – loop – β-strand motif that is generated by conformational changes in the two existent anti-parallel β-sheets connected through a linker region. Interestingly, many of the Aβ mutations exhibiting enhanced fibrillogenesis and known to be associated with dementia and cerebral hemorrhage are located in the linker region.

We hypothesize that variations in the conformation, length and flexibility of the linker region will lead to alterations in the relative alignment and orientation of β-strand backbones, hydrogen bonding network and

cross-side chain interactions which, in turn, will affect the aggregation state and cellular toxicity.

In order to achieve these goals:

- A variety of peptides will be rationally designed, synthesized by solid-phase chemistry and tested using a comprehensive battery of biochemical, biophysical and biological assays.

- Modifications in toxicity of the engineered peptides will be assessed through the use of neuronal cell cultures in vitro.

- Their application as an *in situ* molecular probe for rapid amyloid detection will be verified via immunohistochemical analysis of tissue sections from Alzheimer cases and transgenic models of the disease.

The successful completion of the proposed research will offer an elegant tool for rapid *in situ* determination of aggregation profiles and will provide a better understanding of the structural role of a local linker region in the amyloidogenic assembly processes and products, as well as in their cellular toxicity. Lessons learned from these probe peptides will serve as the basis for the design of novel therapeutic strategies.

The Economics of User-generated Content in Online Social Media

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Abstract

The Internet has brought about a fundamental change in the way users generate and obtain content. The emergence of social media sites—such as Facebook, MySpace, and YouTube—highlights the direct social aspect of many online activities. Online social media forums provide means for maintaining social relationships, for finding users with similar interests, and for sharing user-generated content (for example, blogs, product reviews, podcasts, photos, and videos) with other users. They allow users to exchange ideas, help each other, act together, and in general engage in community-forging activities. Firms are increasingly looking for ways to monetize this content through online advertising. In this project, we propose to explore the economics of user-generated content, and in particular of user-generated text and video content on the Internet, and examine the linkages between user-generated content and its monetization through online advertising.

Project Description

Several key issues related to incentives and monetization of content emerge in these networks which are yet to be adequately addressed in prior work. Specifically, we aim to answer the following questions in this project:

How can content creators be incentivized to improve content quality?
- Specifically, what incentive mechanisms (monetary or otherwise) will lead to creation of an abundance of high-quality user-generated content?

How can user-generated content be monetized?
- How can advertising be done in a user-generated content site (such as YouTube)?
- Should the ads be text ads or video ads embedded in the content themselves?

- Should advertising revenues be shared with the content creators, and if so, how?

How can we design rigorous mathematical models to predict click-through and conversion rates for different monetization schemes?

- What are the appropriate probabilistic, statistical, econometric, and data-mining tools for this new paradigm of media economics?

The PIs in this project are Professor Vasant Dhar and Professor Anindya Ghose from NYU Stern and Professor Keith Ross from Poly's Computer Science and Engineering department.

Nanoparticle Dynamics in the Whispering Gallery Mode Carousel

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Abstract

Light fields exert forces on microscopic objects that are governed by gradients in the light's intensity and phase. Illuminated objects, in turn, exert a measurable influence on the light, creating richly structured scattering patterns and shifting the light's wavelength. This program exploits the properties of light skimming the circumference of spherical glass resonators, so-called whispering gallery modes, to gather up virus-sized microparticles, to send them circulating around the resonator, and thus to measure their properties with a resolution not possible with any other technique.

Project Description

This program will use the forces exerted by specially crafted light fields to probe the interactions and dynamics of microscopic objects dispersed in fluid media. Information derived from these measurements will address fundamental problems in statistical physics and also will have immediate applications in such areas as medical diagnostics.

Beams of light carry momentum that can be transferred to the objects they illuminate. The resulting forces are utterly negligible for macroscopic objects, but can govern the motions of microscopic objects, particularly those comparable in size to viruses. Gradients in the light's intensity give rise to forces that can be used to gather up microscopic objects and hold them in place. Gradients in the light's phase, akin to the inclination of water waves approaching a beach, give rise to complementary forces that can cause trapped particles to move along prescribed paths. Both come into play in the light fields that can be established in microscopic optical resonators created from tiny spheres of glass. These forces can draw minuscule fluid-borne objects near to the surface of the resonator and cause them to follow the wave around its circumference. This phenomenon is the whispering gallery mode carousel. The trapped particle, in turn, scatters light out of the evanescent wave and ever so slightly shifts the wavelength of the light in the resonator. Both effects can be

used to measure a circulating particle's size, its position, and its distance from the resonator's surface. This information can be used both to characterize the object, and also to measure the forces by which it interacts with the surface. This program will use this information to probe particle-surface interactions on a fundamental level, and to develop assays for disease-causing viruses based on viral interactions with functionalized surfaces.

The first phase of this program will focus on perfecting the protocols for measuring colloidal interactions in whispering gallery mode carousels. These measurements will take advantage of specially functionalized colloidal spheres and specially formulated supporting fluids whose properties are designed to cast light specifically on each of the basic physical mechanisms believed to be important for viral binding. Principal among these are electrostatic interactions based on surface charge, the valence of the charged surface groups, and the concentration and valence of salt ions in the surrounding fluid medium. Viral docking also may be affected by the population of other microscopic objects dispersed in the fluid through so-called entropic interactions. These too can be mimicked by adding polymers and nanostructured colloids to the suspending fluid. Still greater complexity and specificity can be expected when both the particle and the surface display polymers and polyelectrolytes on their surfaces. This final round of biomimetic models will set the stage for ongoing measurements on viral interactions with functionalized surfaces, which are likely to involve all of these mechanisms.

A successful conclusion to this pilot program would provide new and valuable insights into the mechanisms of colloidal particles' interactions with surfaces. This is an area with great economic value because colloidal particles play a fundamental role in virtually every major industry, including food, cosmetics, printing, surface coatings, petrochemicals, and pharmaceuticals. The whispering gallery mode carousel promises rapid advances in a well studied field because it provides information with far finer resolution than previously attained, and yields its information far more rapidly. This also is an area of substantial fundamental interest because colloidal interactions inherently involve a contributions at all scales ranging from nanometers up to micrometers and beyond. Such multi-scale many-body problems constitute an important frontier in statistical physics. The long-term goal of developing a diagnostic tool for rapidly identifying viruses could potentially revolutionize a major branch of medical diagnostics and biomedical research.

Structural Characterization and Structure-based Engineering of Cutinases

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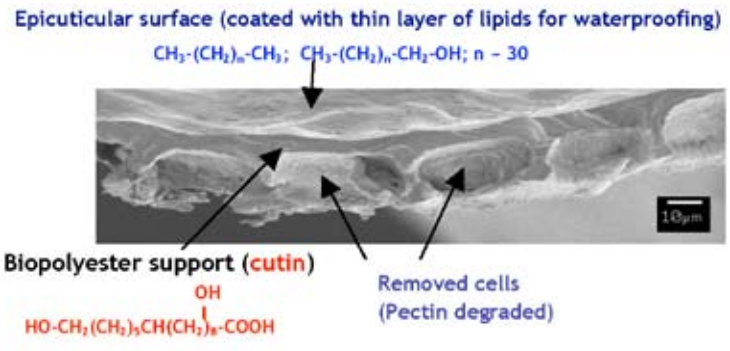
Abstract

With rising environmental concerns due to waste build up and limited supplies of petroleum feedstocks, the identification of enzymatic or greener approaches to perform efficient chemical reactions and degradation is in demand. Several enzymes have been exploited to not only perform stereo and regioselective chemical transformations on small molecules but also to breakdown or modify synthetic polymers. This proposal addresses these concerns by focusing on a promising family of enzymes known as cutinases that, thus far, have received disproportionally low attention than other related ester hydrolase enzymes. This program will conduct fundamental studies to explore cutinase sequence-structure-activity relationships. Knowledge gained during the course of this program will be applied towards the following scientific and technical challenges: i) surface modification of industrially important materials to tailor their physico-chemical properties by mild-processes and ii) improve the efficiency of biomass conversions to chemical feedstocks.

The intellectual merit of this proposal is that it seeks to provide insight into the sequence-structure-activity relationship of a set of 5 cutinases for its natural cutin and non-natural polymer substrates. The lessons gleaned from this work will provide an understanding of cutinase to assist in plant infection by attacking plant cell wall structures and raises important questions as to how it might function in enzymatic processes for conversion of biomass for production of chemicals, fuels, and specialized materials.



The broad societal impact of this research relies on the potential of this cutinase to be exploited in complex biomass conversion processes where the goal is efficient biomass conversion to chemicals, fuels and other specialized materials. Moreover, insight gleaned from the kinetics and mechanism of heterogeneous reactions with synthetic polymer substrates may be used to develop 'environmentally friendly' routes to tailor material surface chemical and physical properties.

Project Description

1) **Enzyme synthesis, purification and initial characterization:** Cutinases from *Humicola insolens* (HiC), *Alternaria brassicicola* (AbC), *Aspergillus fumigatus* (AfC) and *Aspergillus oryzae* (AoC) were selected based on their genetic diversity while exhibiting a sequence identity of between 45 and 65% relative to *Fusarium solanii* cutinase (FsC) over a minimum overlap of 175 amino acids. These cutinases have already been PCR assembled from synthetic oligonucleotides and cloned into the methanol inducible expression system pPICZalphaA (Invitrogen) using the restriction sites XhoI and XbaI and transformed in the intermediate host, *Escherichia coli*. The resulting plasmid was sequenced and then transformed into *P. pastoris* where it was integrated into the *Pichia* AOX1 (for alcohol oxidase) chromosomal gene. To further the studies proposed below, it will be necessary to improve the volumetric yield of protein produced. Thus, work will be performed to determine induction conditions, growth media and fermentation conditions that will improve enzyme production. Since the cutinases bear C-terminal hexa-histidine tags, purification of HiC, AbC, AfC, AoC and FsC will be performed on a VISION™ Workstation (Applied Biosystems Co.). Hydrolysis of *p*-nitrophenylbuytrate will be used to establish optimal temperature and pH conditions for each enzyme.

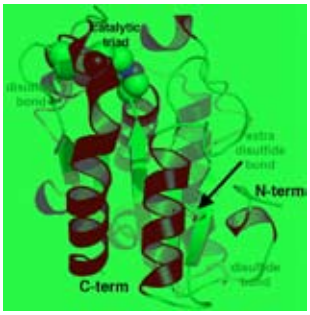


Figure 2. Crystal structure of A. oryzae cutinase (AoC) at 1.8Å resolution.

2) **Cutinase activity:** Cutinase activity for degradation of various natural cutin and synthetic cutin polyester analogues will be assayed using a pH-stat apparatus (Titrando 842, Metrohm). Using data from pH-stat studies, Michaelis-Menton rate constants will be determined. Enzyme concentrations will be optimized to allow for a linear slope or velocity. The velocities will then be plotted as a function of substrate concentration and fit to the M-M equation to determine k_{cat} and K_m. If the data can be fit by M-M kinetics, the specificity constant k_{cat}/K_m will also be determined and ratios of substrate specificities will be analyzed. The specificity observed by various cutinases will then be compared to the specificity of the FsC. However, to fit experimental data and determine kinetic parameters, other kinetic models may be needed that account for heterogeneity.

3) **Crystallize and determine atomic structures of selected cutinases and mutants by protein crystallography.** Cutinases will be crystallized by mixing equal volumes of concentrated protein solution with mother liquor, using the hanging drop vapor diffusion method. Conditions for crystallization will be adjusted as needed to obtain the desired results. X-ray diffraction data of cutinase crystals will be obtained at beamline X4A using the synchrotron light source at the Brookhaven National Synchrotron Light Source (NSLS) in collaboration with Dr. Vivian Stojanoff. The cutinase structures will be determined using a molecular replacement method. Structures obtained for AbC, AfC and HiC will be compared to FsC and the recently solved AoC structure. Overlays will be made of each cutinase relative to *F. solani*; similarities and differences will be documented. In particular, we plan to (1) determine deviations from existing structures in terms of catalytic residues and oxyanion hole; (2) identify regions with high B-factors that indicate flexibility; and (3) explore the hydrophobic and electrostatic surface characterization of the enzymes. The insight gained from structural analysis will then be used to help understand the functional data we've obtained in preliminary results.

4) **Carry out bioinformatics analysis and computer modeling to understand the sequence-structure-activity relationship of cutinase and to propose modifications for higher thermal stability and catalytic efficiency.** Structural modeling can suggest additional modifications that may further improve the activity and stability of cutinases. For example, an additional disulfide bond can be created between the very C-terminal and the second beta strand. We will therefore carry out a systematic bioinformatics investigation of cutinase structures. This includes: a) sequence analysis to examine conserved functional motifs; b) structural analysis to compare the topology of the active sites (catalytic triad, oxyanion hole, and hydrophobic cleft), and disulfide bond positions; c) docking substrate mimics or inhibitors to the binding site of different cutinases and their mutants; and d) in silico mutation to examine the hydrogen bond network and the possibility of forming additional disulphide bonds.

Equipment Failure Prediction with Machine Learning Methods

Yann LeCun[1] and Dariusz Czarkowski[2]

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[2] Dept. of Electrical and Computer Engineering, Polytechnic Institute of NYU

Abstract

The investigators will use Relational Regression Models developed by Prof. LeCun to predict which units of a large sample of industrial equipment should be serviced first to avoid failures. Distribution transformers of the Consolidated Edison of New York, Inc., will serve as such a sample. There are several factors that contribute to a transformer failure (corrosion, overload, insulation defects, gasses in oil, type and manufacturer) and relationships among all the contributing factors are not well understood. Also, the data on the transformers history and current state is far from complete and reliable. Such working conditions of equipment and the status of its database are quite typical in many industries. A machine learning approach is needed to handle prediction of failure under such circumstances.

Project Description

A group of researchers from Polytechnic Institute of NYU currently conducts a second phase of study on Network Transformer Failure Analysis and Root Cause Determination for Consolidated Edison of New York. The group includes Profs. F. de Leon, Z. Zabar, and D. Czarkowski from Electrical and Computer Engineering, E. Pearce and W. Zurawsky from Chemical and Biological Engineering, G. Vradis from Mechanical Engineering, M. Ghandehari from Civil Engineering, and M. Schooman from Computer Science and Engineering departments. The group is lacking, however, machine learning expertise which could be invaluable in providing Con Edison with a computer tool that could result in increased safety, reliability, and long-term savings for the company and its customers. The problem is that Con Ed is servicing about 25 000 distribution transformers and a few tens of them fail yearly, and some violently (explosions). The investigators propose to use Relational Regression Models developed by Prof. LeCun to handle the prediction of which transformers are about to fail, hence, require immediate servicing.

The work will be performed in four tasks:

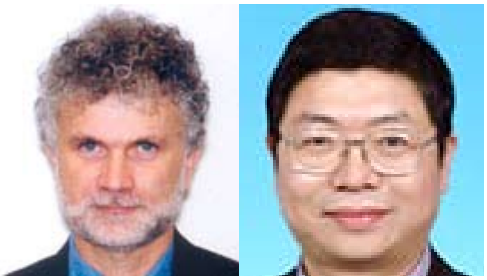
Task 1: Review of historical data
Historical data for the last 20 years concerning faulty network transformers will be collected from existing files of the Con Edison electronic library and reviewed. That data might include: active service time; load profiles; top oil temperatures; number of short-circuit faults on the load side (that caused tripping of the main circuit-breakers); number of inrush-current events; number of inspections; number of oil replacements; results of analysis of dissolved gases in oil; and corrosion conditions.

Task 2: Selection of the learning architecture for data estimation
Learning architectures for temporal time series prediction with hidden variables come in many different shapes and forms. Preliminary experiments will determine the degree to which the problem is non-linear, and whether the data needs to be pre-processed, perhaps using unsupervised machine learning methods, such as dimensionality reduction and automatic feature selection. Subsequent experiments will select the best architecture for the problem, as well as assess such parameters as the size of the temporal window and the number of hidden variables and trainable parameters.

Task 3: Investigation on historical data needed for reliable prediction
Needs of the selected machine learning algorithm in terms of types and amount of data needed for reliable prediction will be evaluated. The selected training data will be grouped by level of importance, such as years in service, normalized load conditions, rusting status, etc.

Task 4: Recommendation for future data collection
The process of future collection of historical data will be proposed. This will include sensors and communications means, data validation and storage, and software scripts for automated data processing. This will require interaction with Con Edison engineers for assessment of economical and technical viability of collection of particular data types.

Novel Medical Device for Preventing Epileptic Seizures



Nandor Ludvig[1] and H. Jonathan Chao[2]

[1] Dept. of Neurology, Comprehensive Epilepsy Center, NYU School of Medicine
[2] Dept. of Electrical and Computer Engineering, Polytechnic Institute of NYU

Abstract

This project will involve making several key steps toward the completion of a fully implantable device, the subdural Hybrid Neuroprosthesis (HNP), for the treatment of severe cerebral cortical epilepsy. This form of epilepsy, affecting about 150,000 people in US, is resistant to all available antiepileptic drugs, while also unsuitable for traditional surgical interventions. When completed, the HNP will record the electrical discharge of neurons in the epileptogenic cerebral cortical area, recognize the abnormal discharge patterns leading to an epileptic seizure, and, whenever such discharge patterns appear, deliver an antiepileptic drug directly into the epileptogenic area to prevent seizure generation. This idea is based on our previous experimental observations and theoretical considerations. The first step this project will make is to develop the basic algorithm for the HNP software, so that the device can recognize the neuronal discharge patterns that lead to seizures. Since no computer simulation can mimic the complex, ever-changing discharge patterns of cerebral cortical neurons in real life, and since no tissue slice or tissue culture preparations can faithfully reproduce the manifestations of an epileptic seizure, we will rely on animal experiments. Thus, brief seizure episodes will be induced in the animals, and the discharge patterns of cerebral cortical neurons before seizure generation will be analyzed to develop the algorithm for the HNP software. The computationally expensive nature of such algorithms makes it necessary to move to the next step of this project, namely, to develop hardware that allows the periodic recharging of the HNP battery through the skin, via magnetic induction. The third step will be to complete the radio frequency (RF) communication module of the HNP, so that the implanted device can receive command signals from outside of the body for function modification, if needed, while also transmitting a status report on its own function to an external monitoring system. Finally, the software will be adapted to a microprocessor, and the power supply and the RF module will be coupled to our already developed drug-delivery mini-pump. All of these components will be integrated into a single device, ready for testing its performance in animals. Reaching this phase will mark the end of this project and set the stage for the safety tests that may, ultimately, open the way for the clinical trials in epilepsy patients.

Project Description

In modern neurology and psychiatry, the horizon of traditional behavioral, pharmacological and surgical treatments has been broadened by the recent introduction of implantable therapeutic devices, called as “neuroprostheses”, such as the Vagus Nerve Stimulator (VNS) or various Deep Brain Stimulator (DBS) devices. The subdural HNP (Fig. 1) is the product of this

new intellectual current in neurology and psychiatry, while it also differs from all currently available neuroprostheses in four crucial aspects. First, the subdural HNP uses not only EEG recording, but also multi-neuron recording to receive feedback from the treated brain area. Second, the subdural HNP uses drugs, and not electrical stimulation, to correct abnormal brain functions. Third, the subdural HNP delivers the therapeutic drug solution into the cerebral cortex via the subdural/subarachnoid space, avoiding damage in the underlying brain tissue. Fourth, the subdural HNP, as it can incorporate multiple recording/drug delivery units placed bilaterally and over large cerebral cortical areas, can treat diseases with extensive neocortical pathology.

In the recent years, we have made progress in developing the subdural recording – drug delivery unit. In collaboration with Richard Rizzolo, DocXS Biomedical (Ukiah, CA). Our colleague at NYU, Geza Medveczky, successfully developed the minipump component of the HNP. We have also identified muscimol, as the primary choice for the seizure-preventing compound, and proved the therapeutic viability of the subdural HNP concept in rats and monkeys, as well as in a limited study in epileptic patients in neurosurgical setting (Ludvig et al., 2008, cited above; Madhavan et al., 2008, Epilepsy Res. 78:235-239). However, the software of the device and two of its key hardware components have yet to be developed, and it is this task the present project will undertake with the joint forces of neuroscientists and engineers.

Specifically, the project will accomplish the following four objectives:

1. **Development of the basic algorithm for recognizing pre-seizure multi-neuron discharge patterns.** This will be accomplished by the off-line analysis of a database comprising pre-seizure multi-neuron data collected in rats and monkeys before and during acetylcholine-induced focal neocortical seizures. Human data cannot be used, because multi-neuron recording technology allowing long-term monitoring of neuronal discharges in epilepsy patients has yet to be developed. A portion of the rat and monkey database has already been compiled in our laboratory, but new data will also be generated while the project unfolds.
2. **Development of the transcutaneously rechargeable power supply.** We will evaluate various rechargeable batteries for parameters such as power capacity, number of recharge cycles, medical safety, dimensions and weight. We will also evaluate and test commercially available power supply chip sets. Furthermore, a high-efficiency stable power supply circuit will be designed, optimizing the circuit for the selected battery. Small, lightweight coils will also be constructed specifically for providing power to the battery-charging circuit without posing health risk. The completed parts will be integrated, and the transcutaneous power-transfer performance of this integrated module will be tested, using porcine tissue to model human skin.
3. **Development of the two-way RF communication module.** The RF module should be able to transmit at least 640 kbps in order to accommodate the transmission of 4 channels of multi-neuron signals, while consuming minimum (<5 mA) power. The Medical Implant Communications Service (MICS) is the mobile radio service for data transmission with implanted medical devices standardized by the Federal Communication Commission (FCC) and European Telecommunications Standards Institute (ETSI). Thus, MICS-based design will be used. We will also evaluate the usefulness of data compression before transmission.
4. **Adaptation of the multi-neuron data analysis software to a microprocessor, integration of this processor, the power supply, the RF module, and the minipump into a single HNP prototype, and implantation of this apparatus into monkeys for testing its function.** This will be done by: (a) delivering a seizure-inducing acetylcholine solution into the neocortex via the minipump, (b) acquiring and recognizing the pre-seizure multi-neuron signals with the microprocessor software, (c) transmitting the pre-seizure recordings via the RF module, and (d) recharging the battery, periodically, with the magnetic induction/power transfer apparatus.

Dr. Sertac Artan (Polytechnic Institute of NYU) will play a key role in the engineering components of this research program, while Dr. Hai M. Tang and Shirn L. Baptiste (School of Medicine) will be responsible for generating the animal experimental data. Importantly, this project will be executed with continuous feedback from such renowned epileptologists and neurosurgeons at the NYU Comprehensive Epilepsy Center as Dr. Orrin Devinsky, Dr. Ruben I. Kuzniecky, Dr. Jacqueline French and Dr. Werner K. Doyle. We think this project will lay the groundwork for a novel medical implant that, with proper modifications, might also be used for the treatment of other brain disorders with predominant cerebral cortical pathology, while, by the mere virtue of its ability to transmit neuronal/cellular data from the human cortex in natural conditions, it may well open a completely new way to obtain insight into how the mind works.

CRISSP: CenteR for Interdisciplinary Studies in Security and Privacy

Helen Nissenbaum[1] and Nasir Memon[2]

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Abstract

The objective of this project is to create a center focusing on interdisciplinary aspects of information security. The long-term goal of this center is to build new approaches to security and privacy that recognize that technology alone cannot provide complete solutions, and to nurture and develop the next generation of security researchers with interdisciplinary expertise. The center will greatly bring together complementary expertise, faculty innovation, and student enthusiasm to enhance the state of knowledge and practical application of security and privacy

Project Description

Maintaining an orderly, peaceful, safe, and productive society will increasingly depend on maintaining trust in information systems. However, trust cannot be realized by technology alone. The notion of trust extends far beyond the narrow technical realms of information security. Engineering trustworthy systems requires an understanding of human psychology. It requires effective public policies and laws and must work within those policies and laws. It requires the right business models and incentives. And often, one needs all of these elements working in harmony. But the reality we witness today is different. Engineers work primarily with technical specifications to build information systems, and their success is often measured by purely technical metrics. This approach, by itself, does not address the broader issues that contribute to trust. To build a successful technology-enabled society, the entire cyber security paradigm must be re-examined and integrated with broader issues.

In this project we will form a Center for Interdisciplinary Studies in Security and Privacy (CRISSP) to combine NYU-Poly's security technology strengths by collaborating with experts in psychology, law, public policy, and business from NYU. The goal of this center is to build new approaches to security and privacy that recognize that technology alone cannot provide the information security and privacy needed in today's

interconnected world. The center will be led by Prof. Nasir Memon and Prof. Helen Nissenbaum, the two PI's of this proposal. In the long term, we expect to have a fully funded and self-supporting center with a full-time director and other personnel needed to support its research and education activities.

As a first step towards attainment of our long-term goals, we will initiate three different activities i) Seed Projects ii) a Distinguished Seminar Series and iii) an Annual Workshop. Below we briefly describe the goals of each of these activities:

SISSP: Seed projects for Interdisciplinary Studies in Security and Privacy: We will initiate a few exemplar seed projects that establish a precedence and culture of collaborative research among the stakeholders in the center. We expect many such projects eventually thriving under the umbrella of the center. In the first stage, we have chosen the following two projects that we will initiate as part of this proposal:

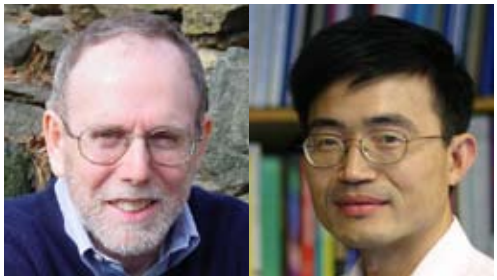
Privacy as contextual integrity; Ethics/Politics/Law (Nissenbaum) and Technology (R. Karri).
Critical Infrastructure Policy and Information Security; Policy (Zimmerman, Restrepo) Technology (Memon).

DISSP: Distinguished seminar series in Interdisciplinary Studies in Security and Privacy: We will institute a seminar series to bring well-known interdisciplinary researchers with a security mindset from outside to discuss research on all aspects of information security and privacy. The speakers will be invited for a two- or three-day period at a time to ensure that meaningful interactions of significant depth will take place beyond the seminar between the speakers and interested parties at NYU-Poly and NYU. CRISSP stakeholders will then be able to interact with these creative thinkers informally beyond the seminar. We will capture video of these seminars and record, archive, and disseminate them via the CRISSP web portal whenever possible.

WISSP:Workshop on Interdisciplinary Studies in Security and Privacy: In order to make progress towards defining a research and education agenda for CRISSP that will transcend the study of specific disciplines, the PI and Co-PI's of this proposal organized a one-day invited workshop titled "Workshop on Interdisciplinary Studies in Security and Privacy (WISSP)" in summer of 2008. The agenda for the workshop and the outcomes of the different panels can be seen at http://isis.poly.edu/wissp08. The objective of WISSP was to explore how different disciplines can come together to improve security and privacy. We propose to continue holding this workshop and make it the leading forum on interdisciplinary thinking in security and privacy.

Longer-Term Outcomes: The merger of Polytechnic University and NYU provides a perfect opportunity to build a Center for Interdisciplinary Studies in Security and Privacy. Such a center would bring together faculty and students in the fields of computer science, psychology, business/finance, risk analysis, public policy, and law to work on joint research projects. The research conducted by the center will result in significant advances in the theory and practice of information security. The center would enhance graduate education by facilitating intellectual collaborations that transcend disciplinary boundaries and lead to the development of a future cadre of security engineers and scientists who will be able to translate the foundational principles of security and privacy into information security technologies based on a deep understanding of social, economic, behavioral and public policy implications.

Physiological Control Mechanisms



Charles Peskin[1] and Zhong-Ping Jiang[2]

[1] Courant Institute of Mathematical Sciences, New York University
[2] Dept. of Electrical and Computer Engineering, Polytechnic Institute of NYU

Abstract

In this project, we propose to integrate our knowledge and expertise to address some challenging problems at the interface of physiology and feedback control theory. The main objectives of the project are twofold. First, we will derive biologically inspired new control-theoretical tools for two physiological systems, i.e., the circulation of the blood and the regulation of the NaCl and water content of the extracellular fluid. These new principles of control mechanisms will be tested in simulations and studied analytically. Then we plan to compare the predicted responses of the controlled systems to existing experimental data. The successful collaboration should lead to a new research direction in "Systems Physiology."

Project Description

Physiological systems employ feedback loops which maintain some variables nearly constant despite changes in the environment, while at the same time allowing other variables to respond to environmental changes and/or to the changing needs of the body. In the study of such controlled physiological systems, an important first step is to model the uncontrolled system. Indeed, the uncontrolled system is often governed primarily by physical principles, which simplify the task of formulating a mathematical model.

Control mechanisms, on the other hand, are less easily deduced from first principles, and the properties of physiological controllers are often difficult to measure. The engineering paradigm of opening feedback loops in order to determine the properties of a controller can only be applied biologically in certain cases, and this approach is complicated in most cases by the confounding effects of multiple feedback loops, all regulating the same or overlapping sets of variables simultaneously.

We propose to escape from the above difficulty by making use of the engineering design viewpoint. Given a mathematical model of an uncontrolled physiological system, our approach will be to design a controller for it that will be optimal in some sense. Having designed an optimal controller, we can then predict the response of the controlled system to various perturbations. If such predictions are confirmed experimentally, this will show that the controller we have designed resembles the physiological controller that has evolved by natural

selection. Such agreement is to be expected if we guess correctly what design problem (objective function and constraints) is being solved by evolution, and not otherwise.

A key hypothesis to be tested in this project is that physiological control systems are optimized for steady-state performance, subject to the constraint that the controlled system be stable. Because of this emphasis on the steady state, we begin by considering a static control problem. Dynamics will be introduced later, when we consider the stability problem.

In the proposed project, our research will be developed in the following ways.

First, we plan to apply the above-mentioned approach to two physiological systems: the circulation of the blood, and the regulation of the NaCl and water content of the extracellular fluid. These two systems are, in fact, related, as is well known from the effect of NaCl on blood pressure in salt-sensitive individuals.

In the case of the circulation, the controlled variables are the systemic arterial blood pressure and the stroke volume, the variables used to control them are the heart rate and the reserve vascular volume (both of which are under the control of the nervous system), and the disturbances involve such variables as the total blood volume (which changes during traumatic blood loss) and the peripheral resistance to blood flow (which changes during exercise).

In the case of the extracellular fluid, the controlled variables are the extracellular fluid volume and its NaCl concentration, the variables used to control them are the circulating levels of antidiuretic hormone and aldosterone, and the principal disturbances involve such variables as the rates of ingestion of NaCl and water.

In both of the above applications, we plan to use dynamic models of the uncontrolled system together with the static controller based on the steady-state behavior, and to study the stability of the resulting controlled system both analytically and numerically. We also plan to compare the predicted responses of the controlled systems to existing experimental data.

On the theoretical side, we plan to investigate the question of stability in a systematic way, by embedding the steady-state model of the uncontrolled system into a general dynamic model that, in particular, involves more state variables besides the variables that are to be held as nearly constant as possible. Preliminary investigation shows that this realistic feature makes the stability problem much more difficult than the elementary case in which the controlled variables constitute a complete description of the state of the system.

Finally, in order to accommodate a large class of physiological systems, the above-stated biological control strategy needs to be extended in various directions:

1. How to develop robust control laws when the physiological system in question is subject to unknown/changing parameters or uncertain dynamics.

2. How to depart from the above “linear” thinking based upon Jacobian linearization and develop nonlinear versus linear control laws which can guarantee global stability for the physiological system in question.

3. What are the other objective functions and constraints that we may use to better reflect the neural control mechanism evolved by natural selection?

4. How to address transient performance when the dynamic model is available and utilized for controller design as opposed to the steady-state model.

RESEARCH INSTALLATION:
EMOTIVE ASSOCIATION IN MULTIMEDIA

The Play of Association of Color, Movement, and Sound: from a Current Folksonomy to a Next-generation Taxonomy for Integrated Media

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[1] Music Technology, Steinhardt School, New York University
[2] Brooklyn Experimental Media Center, Polytechnic Institute of NYU

Abstract

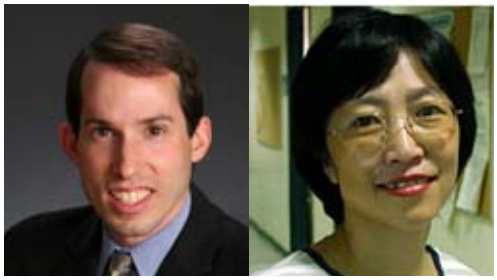
In this project, we will undertake a joint creative/research initiative about "emotive association," by which we mean affective coherence between images and sounds. Through the construction of an interactive public installation designed to store and analyze user input, we will develop a new unified lexicon for their description. This new taxonomy will be used to inform the design and use of new foundation courses geared to multimedia studio programs, to update, formalize, and integrate the language used to teach in interdisciplinary media programs.

Project Description

Graphic and acoustic phenomena generate qualitative impressions—some by literal association, some through form, filtered through audiences' cognitive and cultural characteristics. We would like to study this phenomenon through a carefully constructed public installation that facilitates audience participation in "mood setting" through interaction with sound and graphics in an immersive installation set up in or next to a well-trafficked public space. Members of the Institute's community would be invited to alter the installation's graphics and sound environment via a graphic interface, and to "tag" their changes with keywords of their own choosing.

The installation will be configured to invite participants into the casual exploration of associations, and will function as an empirical instrument for presenting and recording the associative responses of participants. Emotive qualities such as sad, vibrant, or depressing, often function as invisible matrices in film, media art, and design practice. The inability to address these qualities from an empirical standpoint enforces aesthetic decision-making by a small number of artists who are often powerless to discuss the motivations and rationale behind their practice. We propose to research these associations by involving an installation audience in producing them. Given the emotive quality "sad," how would visitors pull images and sounds from a library to produce their own combination? Given a combination, visitors can further rate the association in terms of its effectiveness for communicating sadness. Both the combination of images and sound chosen by visitors, as well as their subjective impression of its emotive strength, will be recorded for analysis.

Rapid Volumetric Imaging of Cardiac Perfusion with Compressive Sensing and Parallel MRI



Daniel K. Sodickson[1] and Yao Wang[2]

[1] Dept. of Radiology, School of Medicine, New York University
[2] Dept. of Electrical and Computer Engineering, Polytechnic Institute of NYU

Abstract

The proposed project will bring together the complementary expertise of investigators in the Center for Biomedical Imaging at the NYU School of Medicine and colleagues in the Department of Electrical and Computer Engineering at Polytechnic Institute of NYU to overcome current limitations of myocardial perfusion MRI – a technique which monitors the delivery of blood to the heart and which is a sensitive tool for evaluating heart disease.

Developments in the hardware and software of magnetic resonance image acquisition will be coupled with state-of-the-art tools derived from nonlinear image representation to achieve heretofore inaccessible imaging speed, spatial resolution and volumetric coverage for clinical perfusion datasets.

Beyond immediate applications in perfusion imaging, this partnership of investigators is expected to result in ongoing advances in the area of rapid diagnostic imaging, in which many seminal discoveries have resulted from the interaction of physics, engineering, and medicine.

Project Description

Given the broad prevalence and profound individual and public health impact of cardiovascular disease, noninvasive assessment of cardiac structure and function has long been a target for a wide range of imaging modalities. Clinical assessment of cardiac perfusion in particular plays a key role in the diagnosis and management of patients with ischemic heart disease. Myocardial perfusion imaging by magnetic resonance (MR), in which uptake of an injected MR contrast agent into the myocardium is monitored over time, has shown great promise as an alternative to traditional and in many ways limited techniques such as SPECT.

However, perfusion MR suffers in a particularly acute fashion from competing constraints of spatial

and temporal resolution which underlie most cardiac imaging techniques. In order to satisfy these stringent constraints, most cardiac perfusion MR studies have acquired images at only a small number of locations through the heart, and at comparatively coarse spatial resolution.

Traditional constraints on MR imaging speed may be circumvented by use of parallel imaging techniques. Parallel MRI, which was first developed by some of the NYU project team, uses arrays of radio frequency detector coils to generate multiple image components simultaneously rather than in a traditional sequential order. Parallel MRI allows many-fold accelerations of image acquisition, and it is now used in a substantial fraction of all MR examinations worldwide, with a particularly vigorous application in the area of cardiac imaging.

Another approach to accelerated imaging which has received increasing attention in recent times is compressive sensing. Compressive sensing techniques, which have a rich history in engineering and signal processing disciplines, but which have only recently been making their way into the MR field, represent a kind of prospective alternative to image compression (an area in which members of the Poly project team are recognized leaders). Rather than determining the sparsity of image content after the fact and truncating image representations accordingly, compressive sensing applies the fact that an image is typically sparse under an appropriate representation basis to design tailored image acquisitions and reconstructions which preserve image content despite a substantial degree of undersampling.

In this project, we will combine the complementary approaches of parallel imaging and compressive sensing in novel ways, with the goal of generating cardiac perfusion imaging studies at heretofore inaccessible combinations of spatial resolution, temporal resolution, and volumetric coverage. Indeed, our concrete target will be the acquisition of high-resolution, whole-heart image volumes in every cardiac cycle during the first pass of an injected contrast agent. We will also explore fundamental principles underlying the design of MR detector hardware, image acquisition, and image reconstruction for optimal combinations of parallel imaging with compressive sensing. These explorations will serve as the basis for ongoing basic and applied investigations to come.

The senior members of the project team are:
Daniel Sodickson, MD, PhD (Dept. of Radiology, NYU School of Medicine)
Yao Wang, PhD (Dept. of Electrical and Computer Engineering, Polytechnic Institute of NYU)
Leon Axel, MD, PhD (Dept. of Radiology, NYU School of Medicine)
Ivan Selesnik, PhD (Dept. of Electrical and Computer Engineering, Polytechnic Institute of NYU)
Ricardo Otazo, PhD (Dept. of Radiology, NYU School of Medicine)

Graduate students will also participate in the project under the supervision of these team members.

Biocompatible Materials Containing Stable Complexes of TSG-6 and HA

Hans-Georg Wisniewski[1] and Mary Cowman[2]

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[2] Dept. of Chemical and Biological Sciences, Polytechnic Institute of NYU

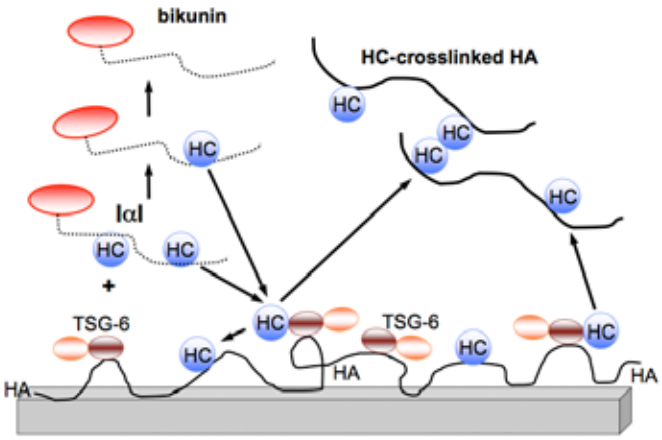
Abstract

The goal of this project is to produce functional prototypes for a new class of biomaterials that combine the potent anti-inflammatory and tissue-protective effects of TSG-6 protein with the biomechanical and anti-adhesive properties of the polysaccharide hyaluronan (HA). The prototypes planned include HA gels, a solid biocompatible material coated with HA, and soluble HA, all containing stable HA-TSG-6 complexes. Potential applications for these materials include intra-articular treatment for arthritis, use as wound fillers, anti-adhesion surgical aids, solid implantable materials, e.g., for use in catheters, and a liquid composition for use as an anti-inflammatory solution. The functionality of these biomaterials will be tested in vitro by determining their ability to transfer subunits of the serine protease inhibitor inter-α-inhibitor to free, surface-tethered, or cell-associated HA.

Project Description

The use of the polysaccharide hyaluronan (HA) and its derivatives for therapeutic intervention is long-established and successful in medical practice. It is widely used in eye surgery, for the treatment of arthritic disease, to control post-surgical adhesions, and for tissue augmentation and engineering. HA is present in most tissues and is therefore noninflammatory and non-antigenic. Its unique viscoelasticity provides for anti-adhesive and biomechanical properties that make it an ideal lubricant, e.g., in joints (1). TSG-6 protein (encoded by TNF-Stimulated Gene 6) is a more recently discovered molecule that is part of the TNF-mediated innate immune response (2). TSG-6 protein has consistently demonstrated anti-inflammatory and chondroprotective activities in experimental models of arthritis and acute inflammation (3-5). The potential medical uses of TSG-6 overlap with the current and proposed uses of HA. TSG-6 and HA interact physically and functionally in inflammation. We found that, under the proper conditions, a stable complex between HA and TSG-6 can be formed that retains the biological activities of both TSG-6 and HA (6). TSG-6 protein, free

or in a stable complex with HA, catalyzes the transfer of the heavy chain (HC) subunits of inter-α-inhibitor (IαI), a serine protease inhibitor, to HA, forming a covalent HAHC complex (7). IαI, present in blood, enters inflammatory sites due to increased vascular permeability. The interactions between TSG-6, IαI, and HA during inflammation result in the deposition of both HCs and TSG-6 in the extracellular matrix. The resulting stabilization of the extracellular matrix may be the basis of the protection of cartilage by TSG-6. Simultaneously, bikunin, a protease inhibitor with anti-inflammatory activities, is released from IαI. The Figure below is a simplified depiction of the major interactions of bioactive HATSG-6 complexes with IαI, the formation of intermediary complexes (HA-TSG-6-HC), the final transfer of HCs to HA, resulting in its structural stabilization, and the local release of bikunin.



Interactions of bioactive HA-TSG-6 complex with Iαl and HA

Stable HA-TSG-6 complexes represent an entirely new biocompatible material that enables the anti-adhesive and biomechanical properties of existing HA biomaterials to be combined with the anti-inflammatory activities of TSG-6. It can be specifically formulated for local administration and prolonged therapeutic activity.

The potential medical applications of this material include:

- intra-articular treatment of arthritic diseases
- wound fillers and dressings
- anti-inflammatory solutions
- coatings for solid biomaterials
- internal dressings for controlling post-surgical adhesions
- tissue augmentation.

A patent application has been filed by the inventors H.-G. Wisniewski (NYU School of Medicine), Mary Cowman of Polytechnic Institute of NYU and Philip Band of NYU School of Medicine, and jointly assigned to NYU Langone Medical Center and NYU Polytechnic Institute, to protect the intellectual property associated with this project.

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