



Laboratory for Interdisciplinary Breakthrough Science

Machine learning is increasingly seen as a method with which to attempt difficult problems in a range of fundamental science areas. Over a period of a decade, dramatic developments in ML architectures and the availability of fast computing has allowed us to overcome many of the limitations associated with standard scientific methodologies. Additionally, some of the most significant contributions have been made by research divisions in commercial enterprises. This has led TIFR as whole to seek to build an industry-academia consortium to take on significant disciplinary challenges using ML techniques in collaboration with industry partners. This day-long discussion meeting brings together interested faculty from all TIFR centres and ML scientists in industry to develop a scientific collaboration plan.

25 May 2022
Madhava Lecture Hall
ICTS, Bengaluru

Organiser
Shravan Hanasoge (TIFR, India)

✉ program@icts.res.in
🌐 <https://www.icts.res.in/discussion-meeting/lib2022>

Protein Folding and Design for Making Mechanically-Robust Protein-Based Materials

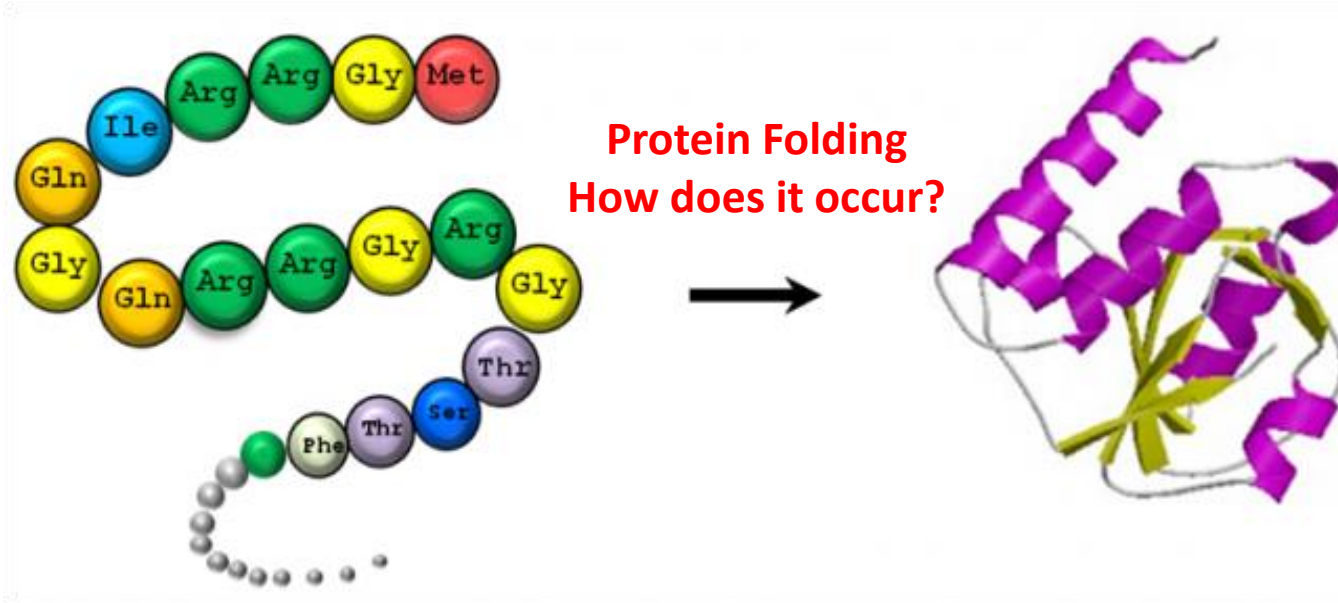
Prof. Sri Rama Koti Ainavarapu

Dept. of Chemical Sciences
TIFR, Mumbai



Proteins – Natural molecular (nano)machines

Proteins are biopolymers



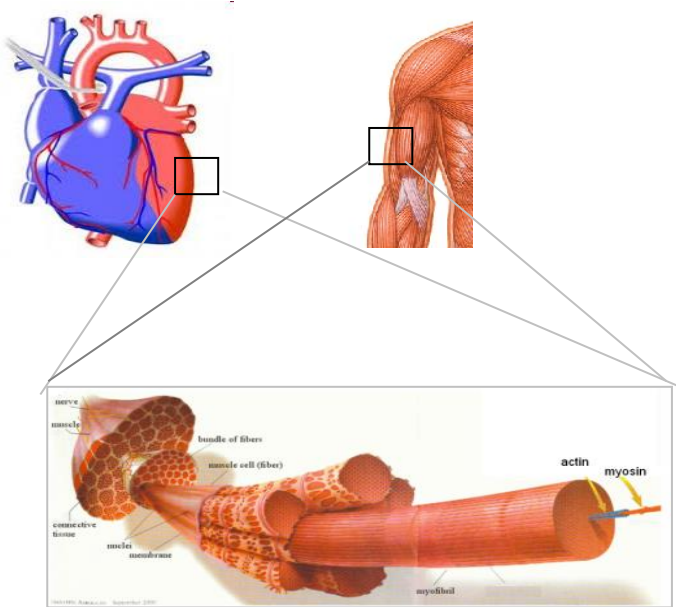
String of amino acids
(Unstructured)

Native (*Functional*) state
(Folded structure)
(AlphaFold 2 can predict the 3D structure)

Sidechains:
Ionic (+ve, -ve), Polar,
Hydrophobic, H-bonding, etc.

Natural World: Proteins have the ultimate molecular strength

Muscle Proteins



Spider silk (web)

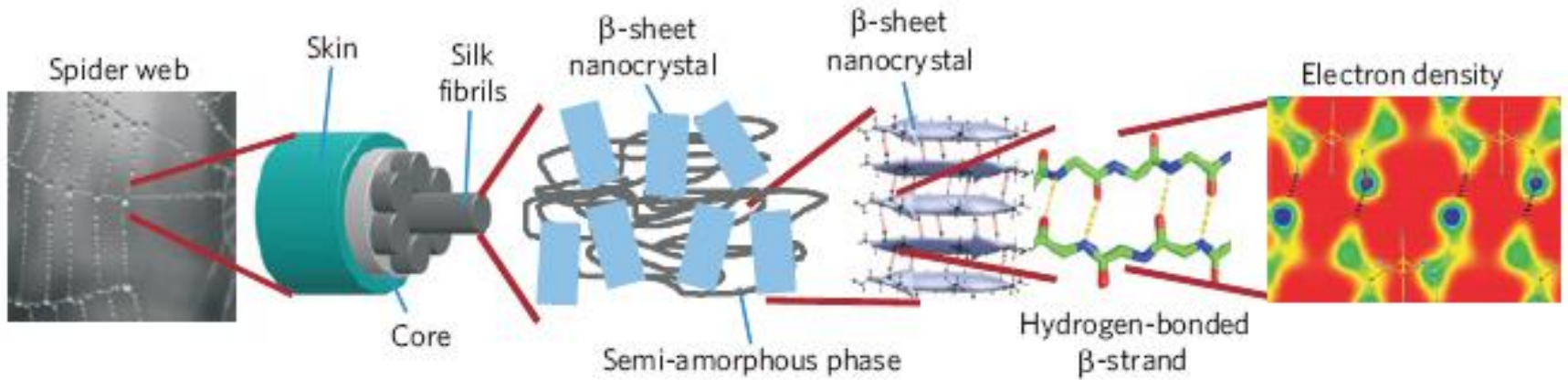


~ 1000 times thinner than a human hair
~ 5 times stronger than steel!

Proteins are molecular springs!

Muscle and Spider silk:
Both contain **organized protein networks**
which impart mechanical properties

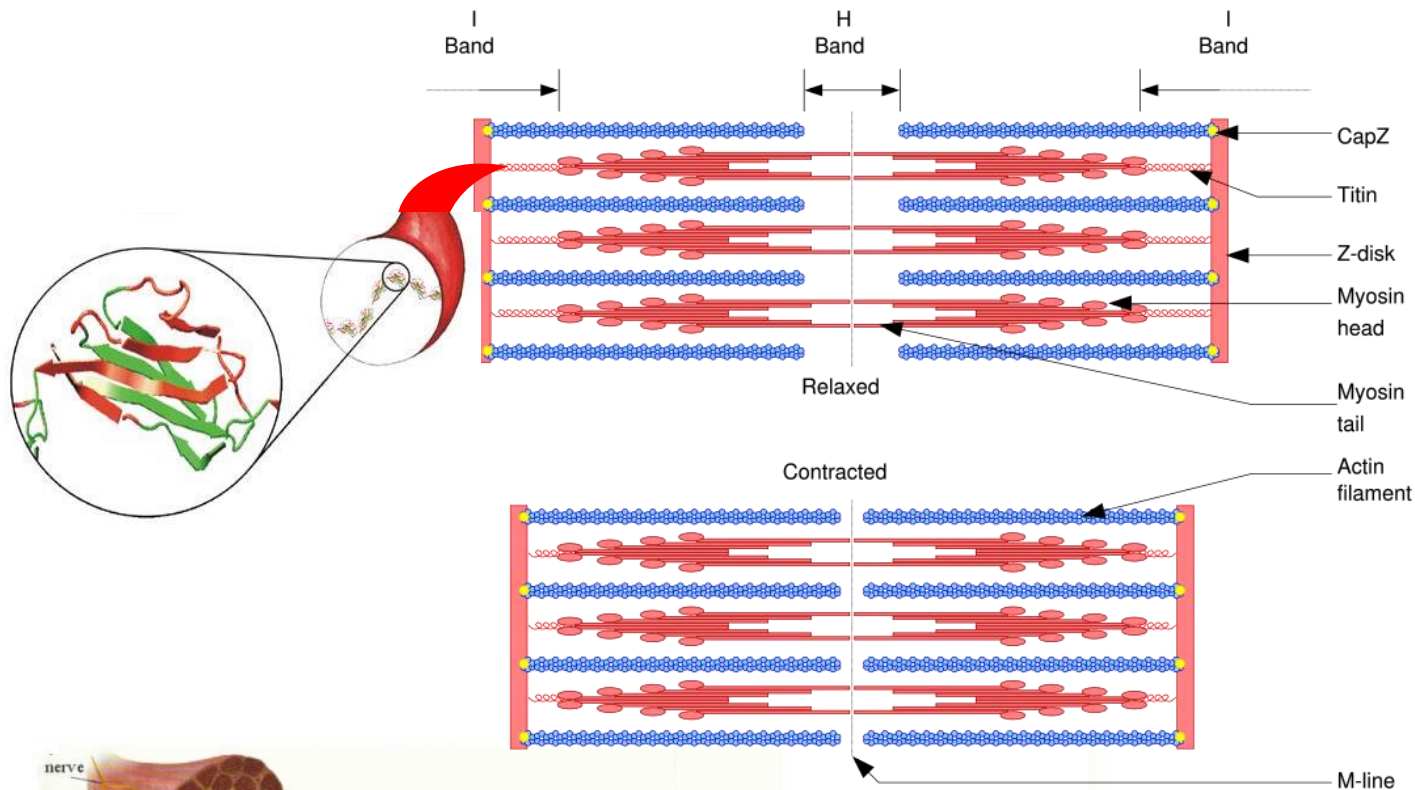
Spider silk (complex) protein network



Titin and tension: molecular spring in skeletal muscle

Titin:

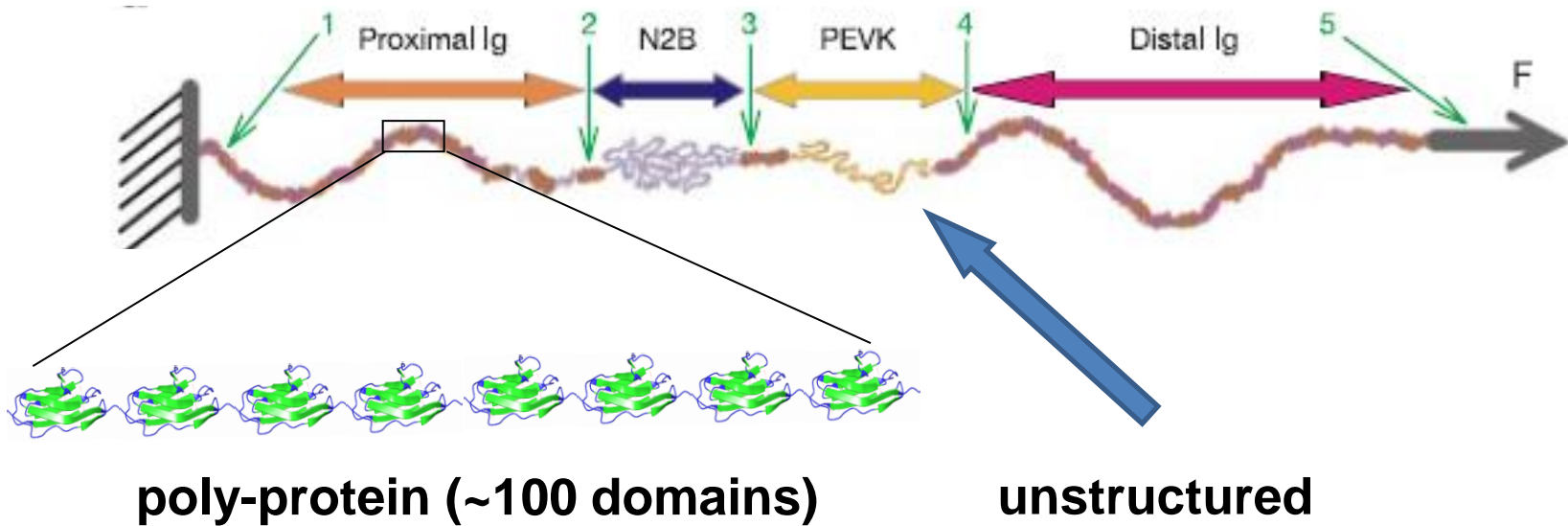
- Giant elastomeric protein (~1 μm)



**Skeletal muscle:
40% body mass**

Muscle protein (complex) architecture

Molecular Force sensor



Titin:

- Giant elastomeric protein (~1 μ m)

What We do? And How do we do?

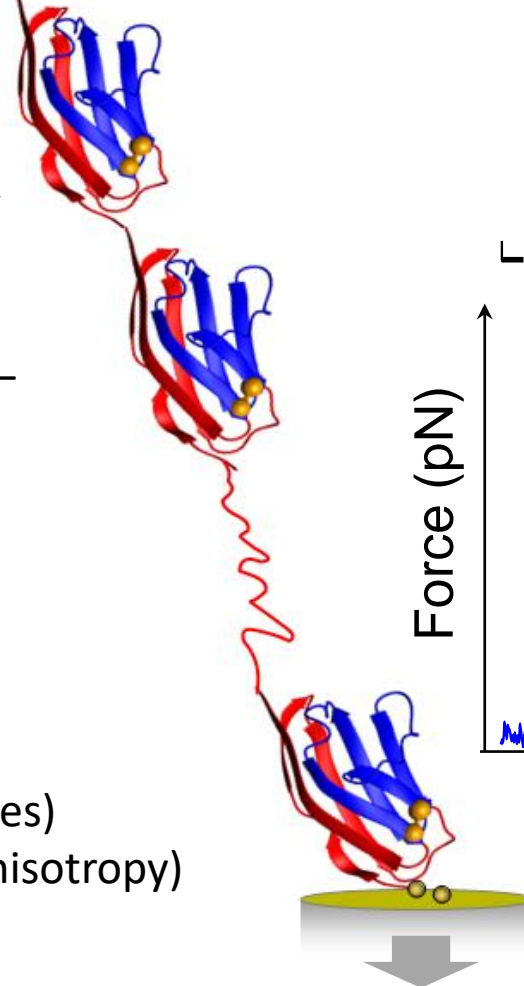
Stretching protein (**single**) molecules one at a time using AFM and MagTweezers

Importance:

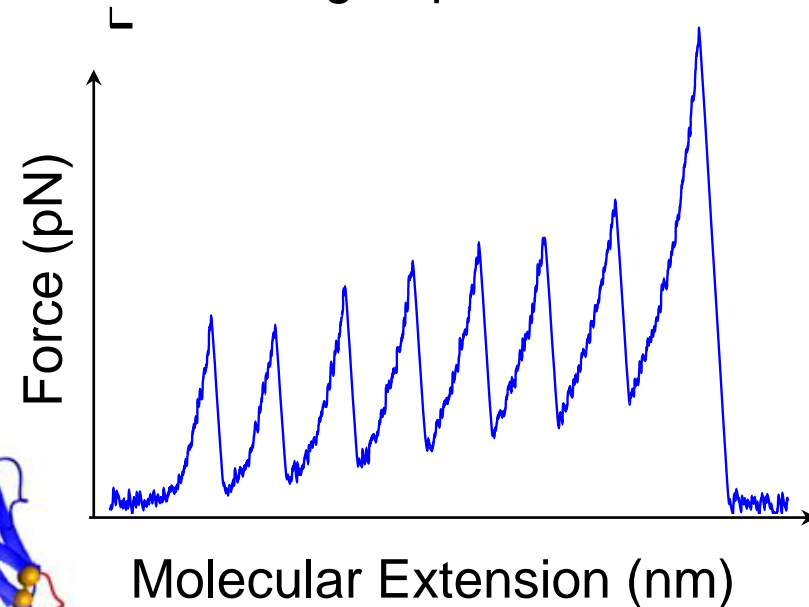
- Fundamental understanding on the origin of mechanical stability
- Sequence-structure-(mechanical stability)
- Correlation between Mutations – diseases
- Multiple scales: Nanoscale to whole organism
- Etc.

Limitations:

- Low-throughput (single-molecules)
- Difficult problem (mechanical anisotropy)

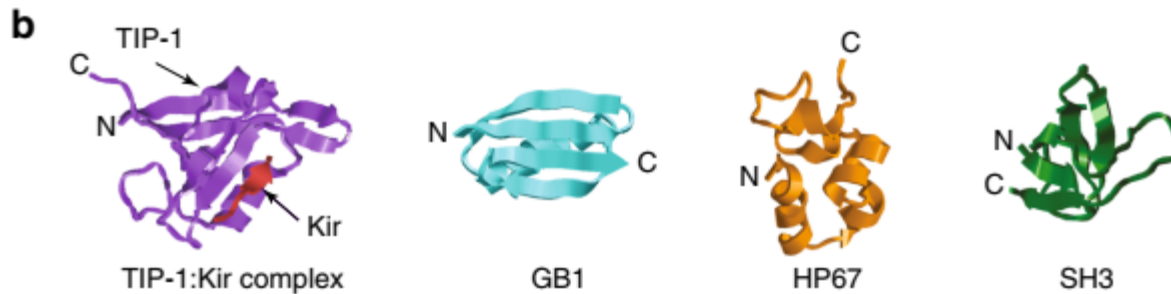
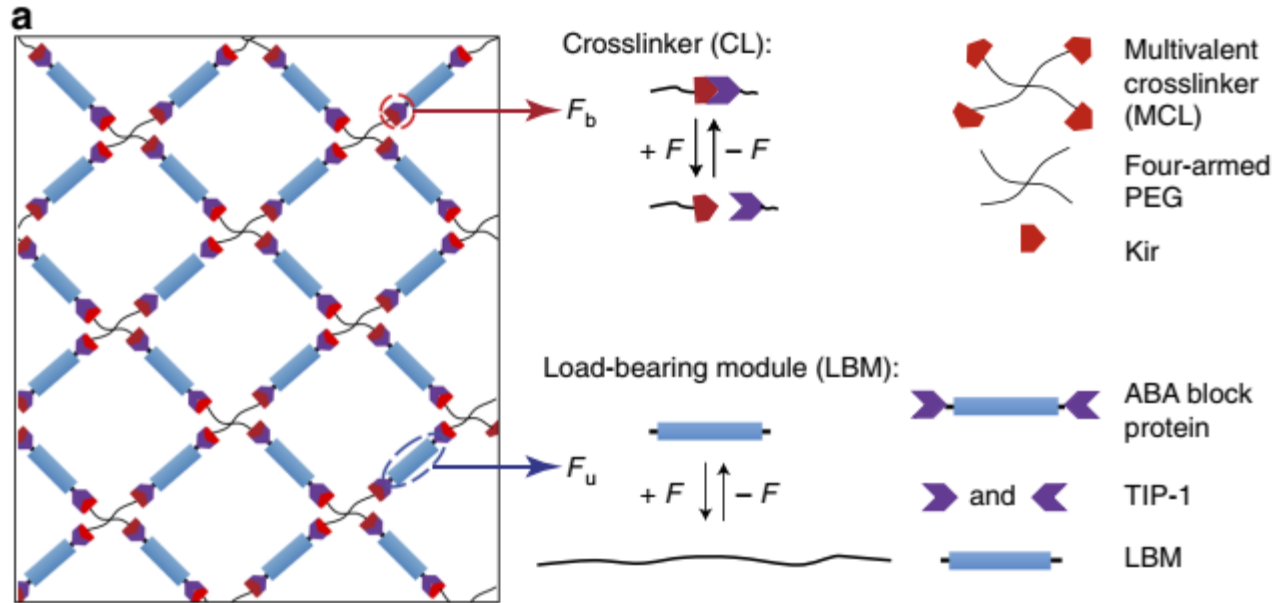


A Pulling Experiment

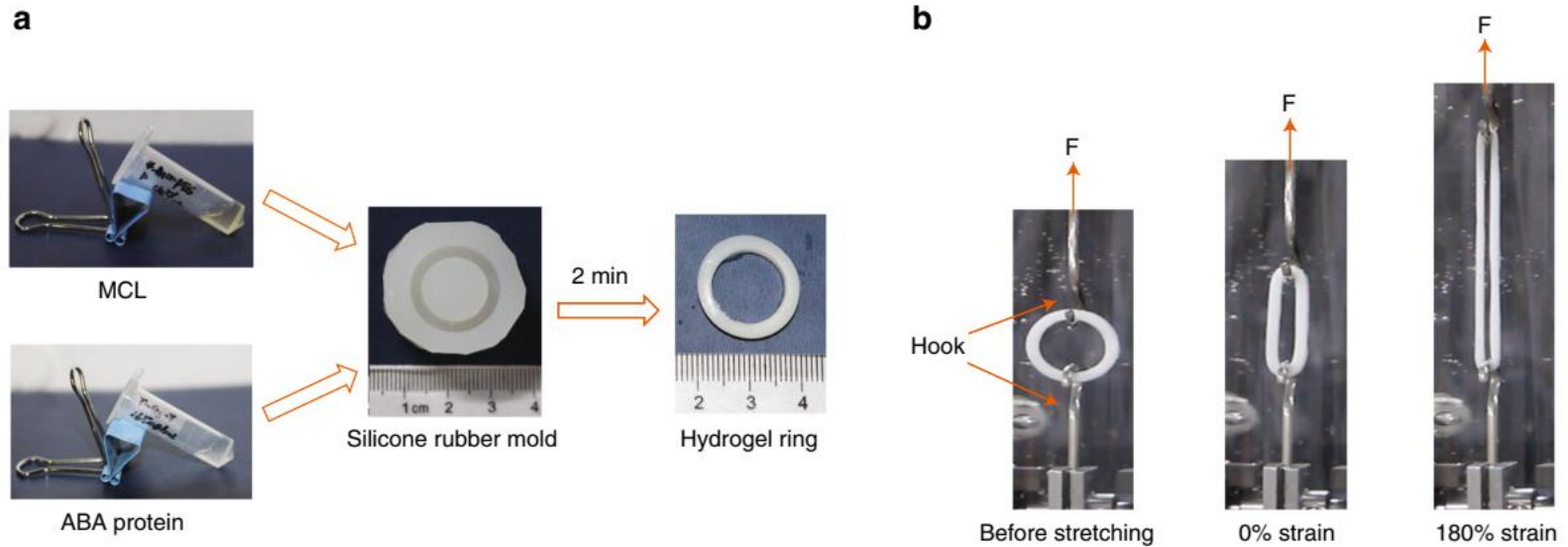


Rational design

Protein-based hydrogels with predictable mechanical properties



Protein-based bulk-material with tailor-made mechanical properties



- Applications in: (1) Protein-based, **self-repair materials**
(2) Protein-based hydrogels for **biomedical applications**

How Machine Learning (ML)/ Deep Learning (DL) Will Benefit This Field?

- Use the existing dataset of mechanical stability information from *many* different proteins (they vary in size, structure, topology, function, organisms, etc.)
- Protein descriptors (?) (use the strategies from 'directed evolution of protein design' known in enzyme catalysis)
- Identify the substructures of proteins in complex large proteins
- Sequence comparison across similar topology (homologous proteins)
- Combine (elastic) Network Model
- Design new proteins (à la Alpha-fold) and test them for mechanical stability
- Etc.
- ??

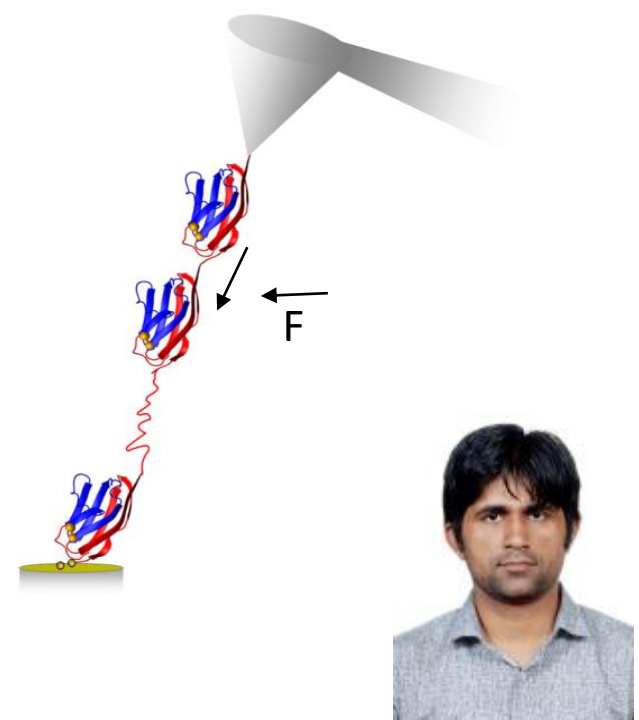
Acknowledgements



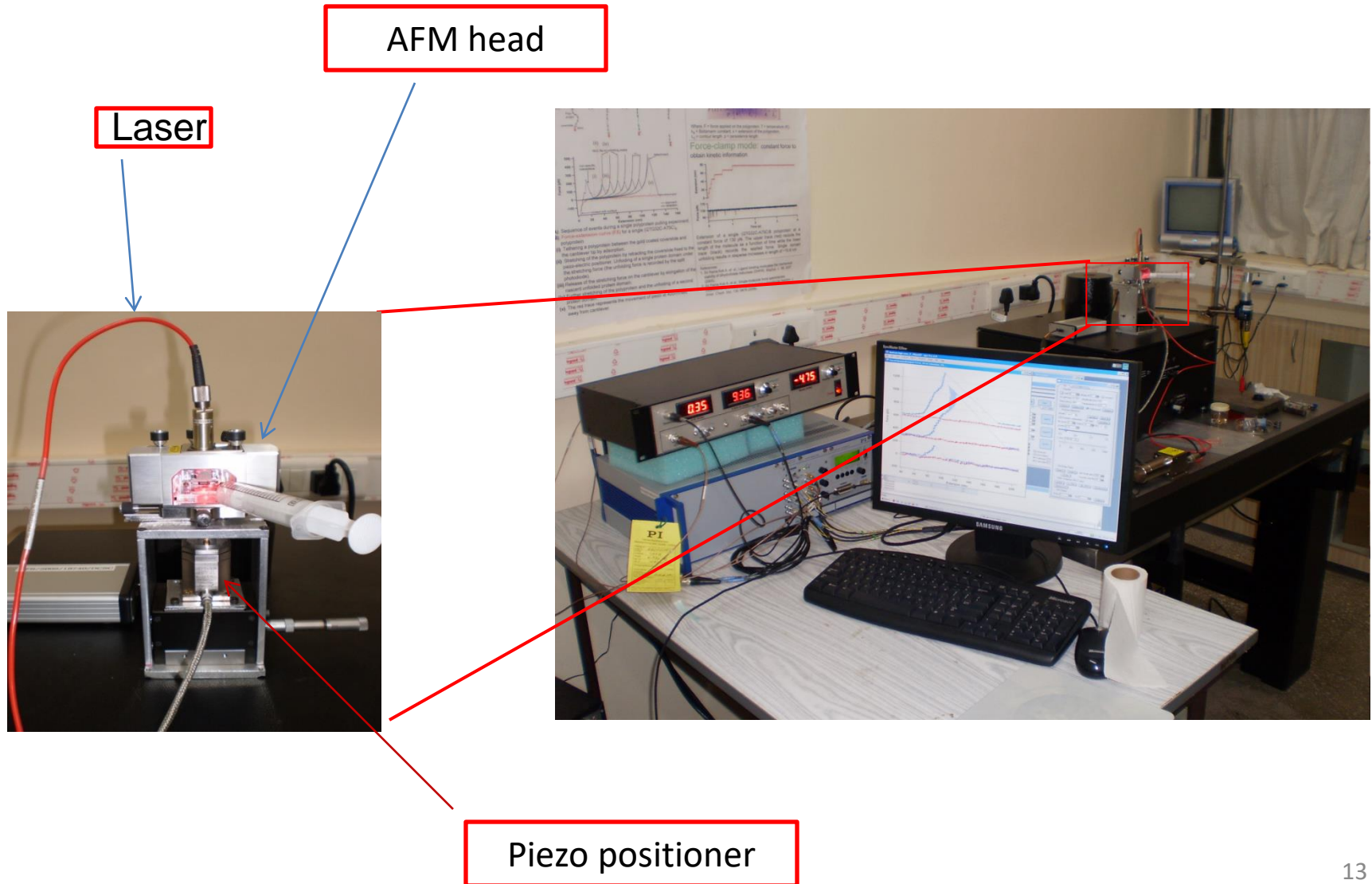
Thank You!

Department of Chemical Sciences

Lab members, Collaborators, and Funding Agencies



Custom-built AFM for single-molecule pulling



Current Research Theme in Our Laboratory:

Probing (Mechano)chemical and (Mechano)biological processes

Chemical bonds to biological cells

