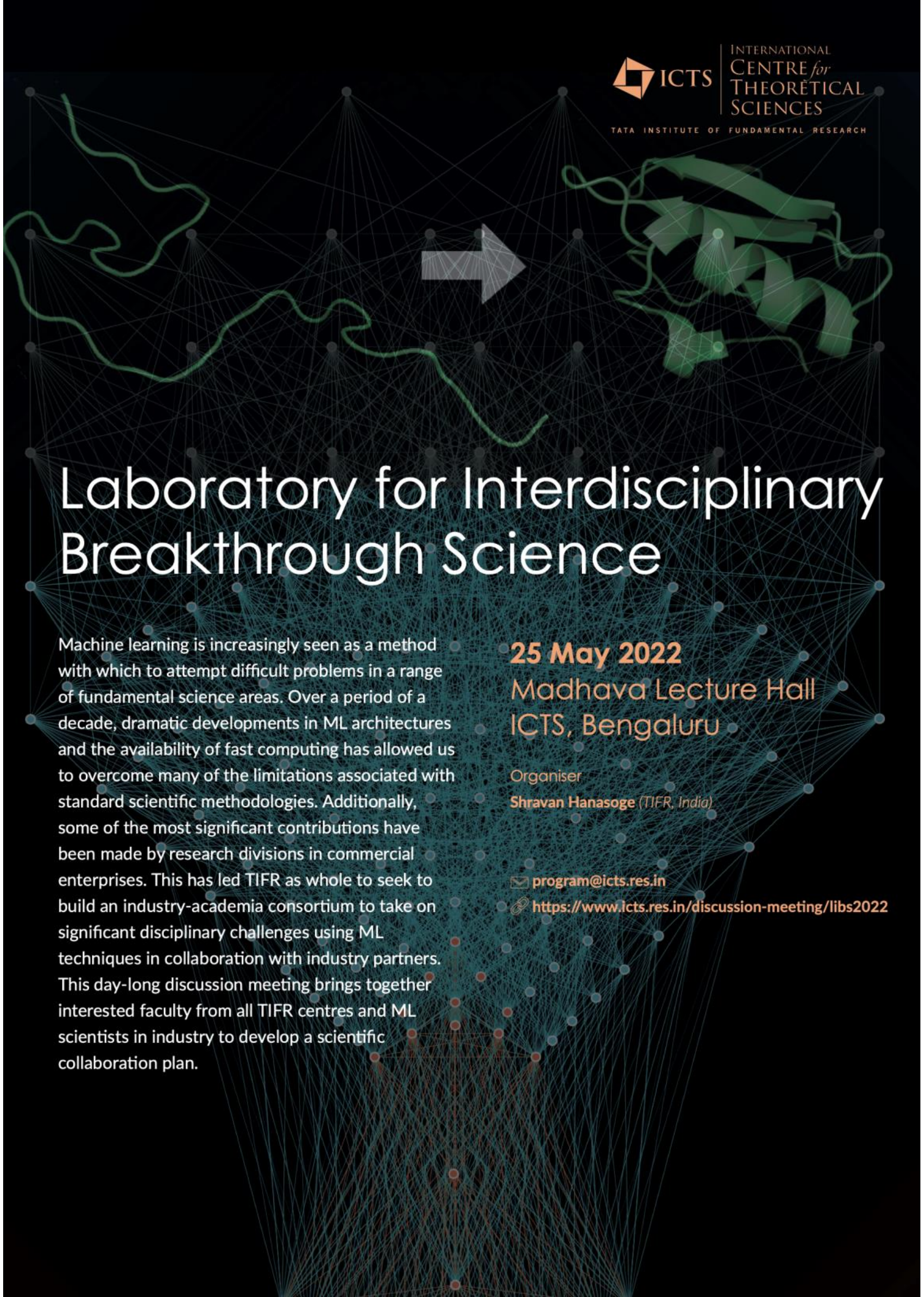

Protein Folding and Design for Making Mechanically-Robust Protein-Based Materials

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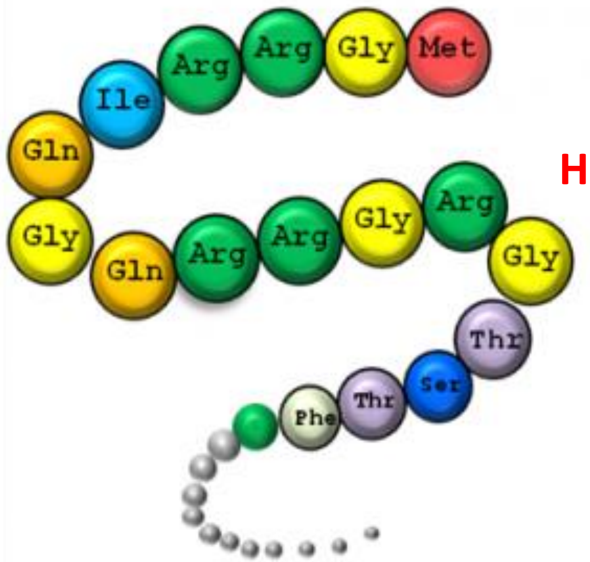
Proteins – Natural molecular (nano)machines

Proteins are biopolymers



Protein Folding
How does it occur?

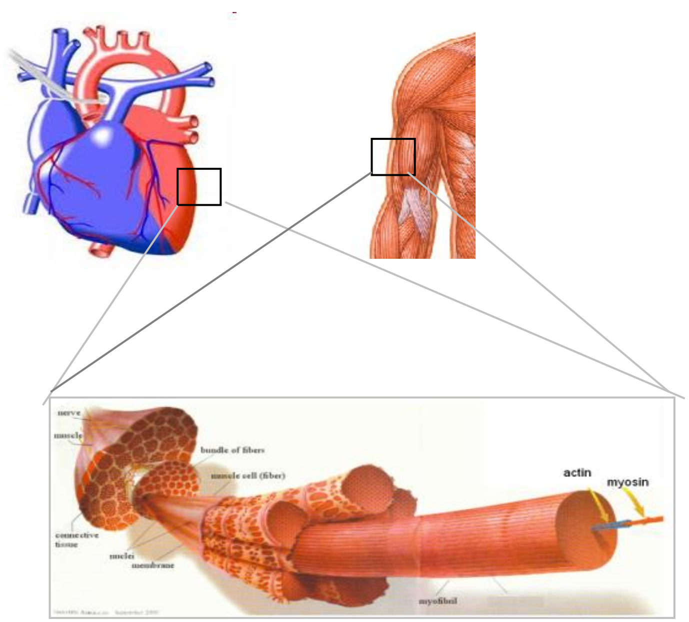
String of amino acids
(Unstructured)

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



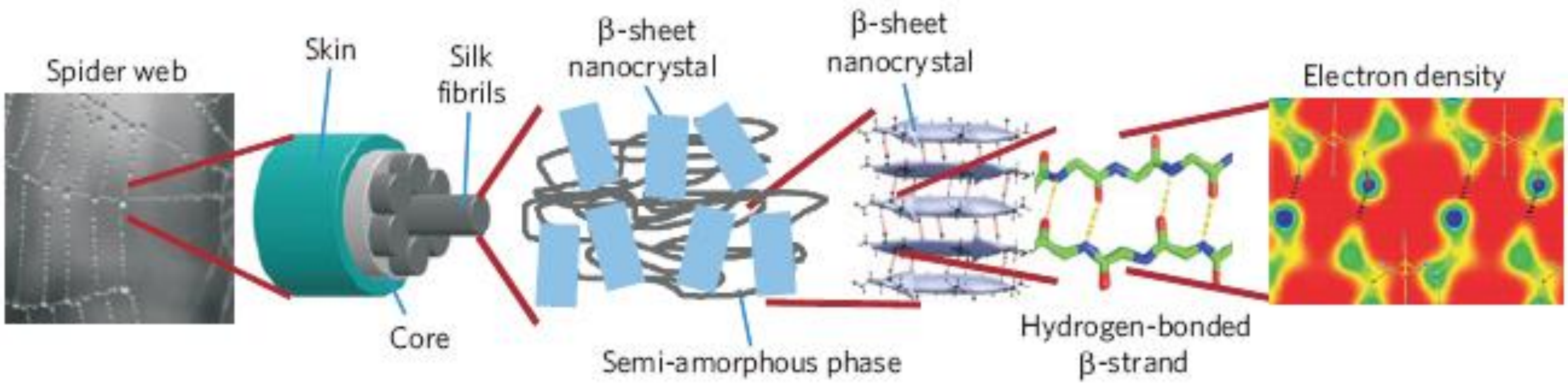
Spider silk (web)

~ 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

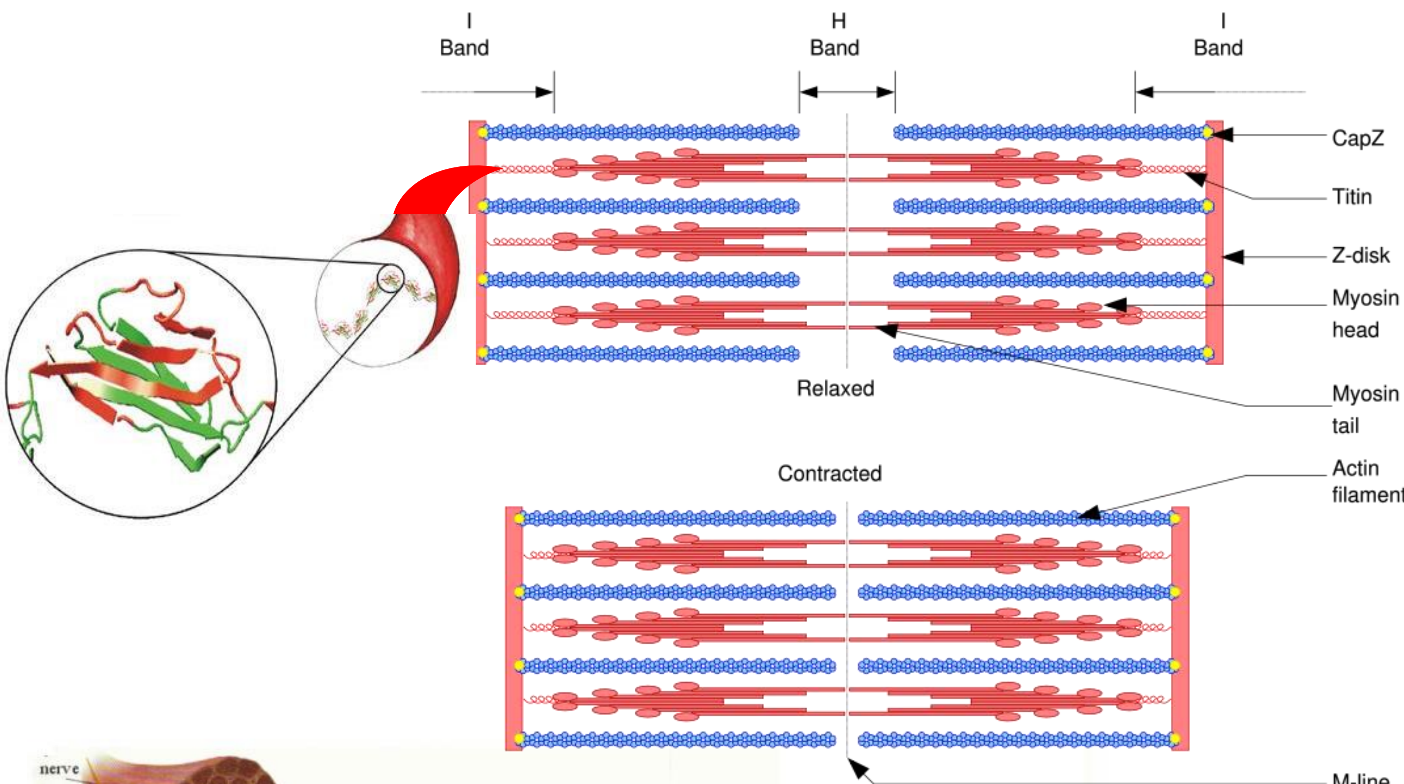
Spider silk (complex) protein network



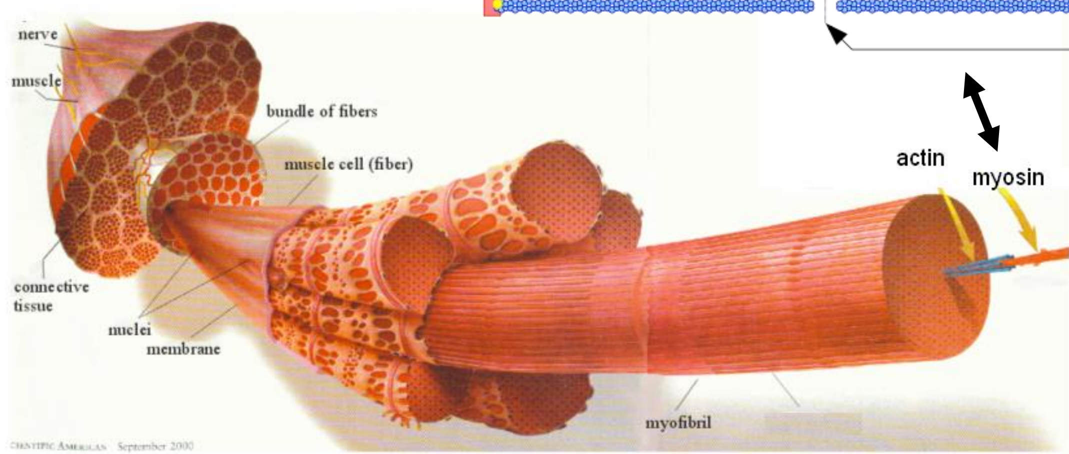
Ketan et al., Nat Mat (2010)9,359-367

Titin and tension: molecular spring in skeletal muscle

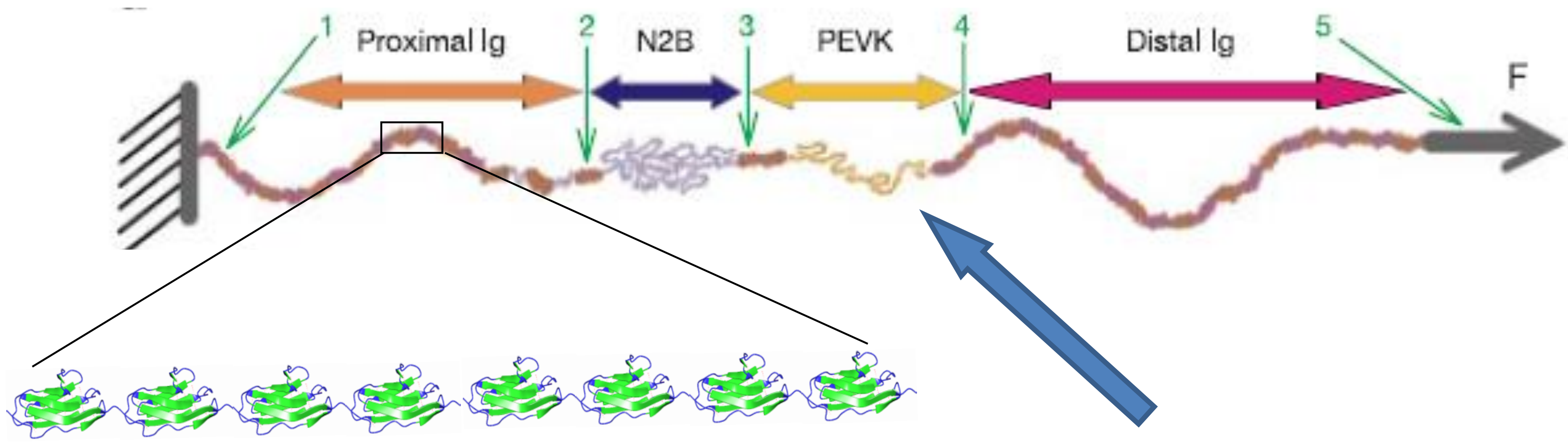
Titin:
- Giant elastomeric protein (~1μm)



Skeletel muscle: 40% body mass



Mulscle protein (complex) architecture
Molecular Force sensor



poly-protein (~100 domains) **unstructured**

Titin:
- Giant elastomeric protein (~1μm)

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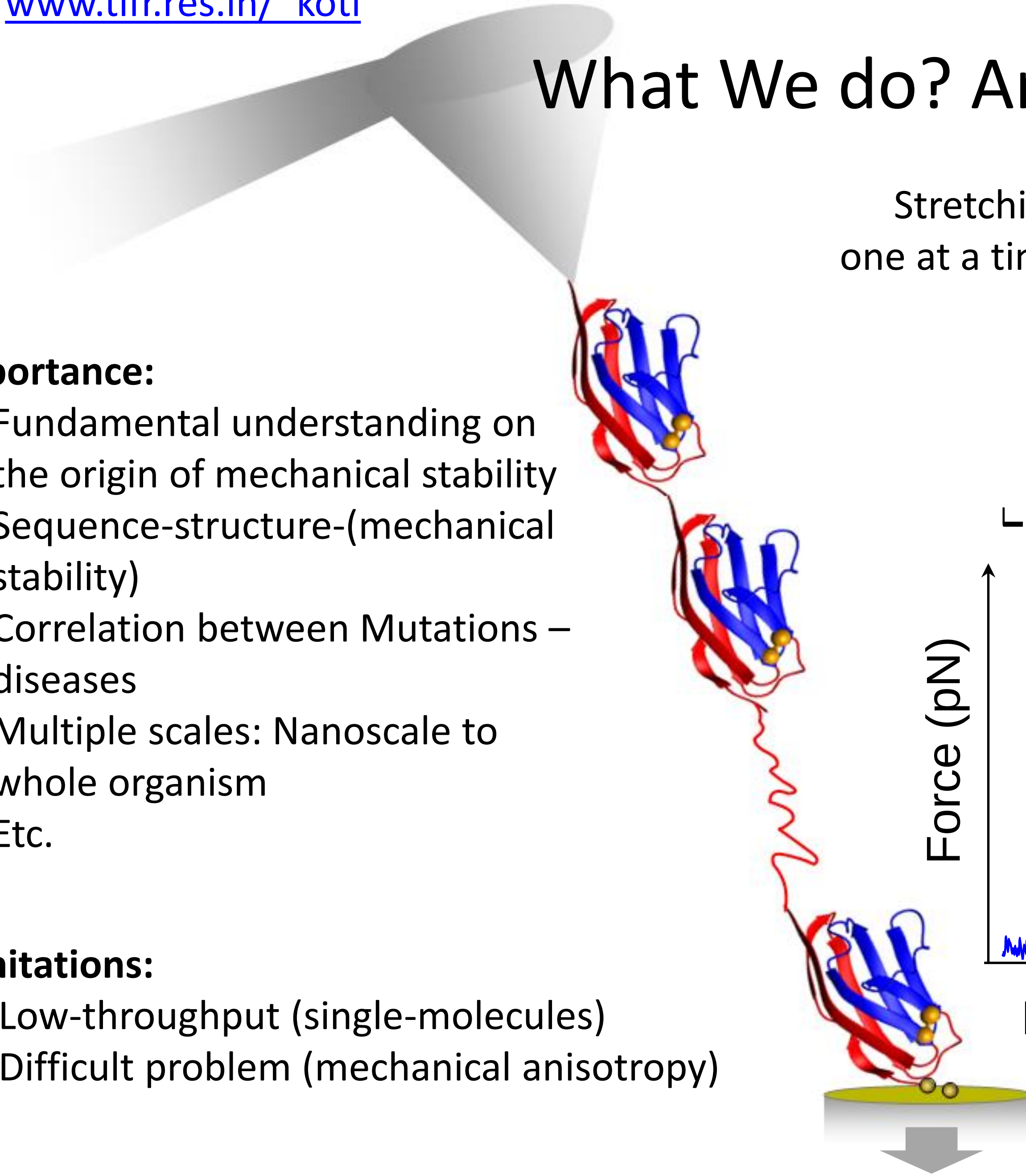
Our lab @ TIFR, Mumbai

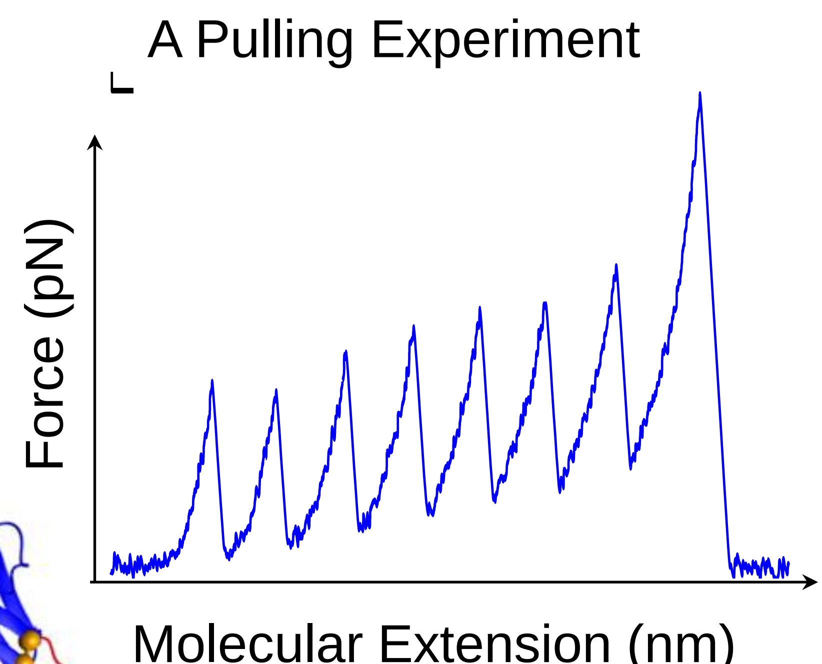
What We do? And How do we do?

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.

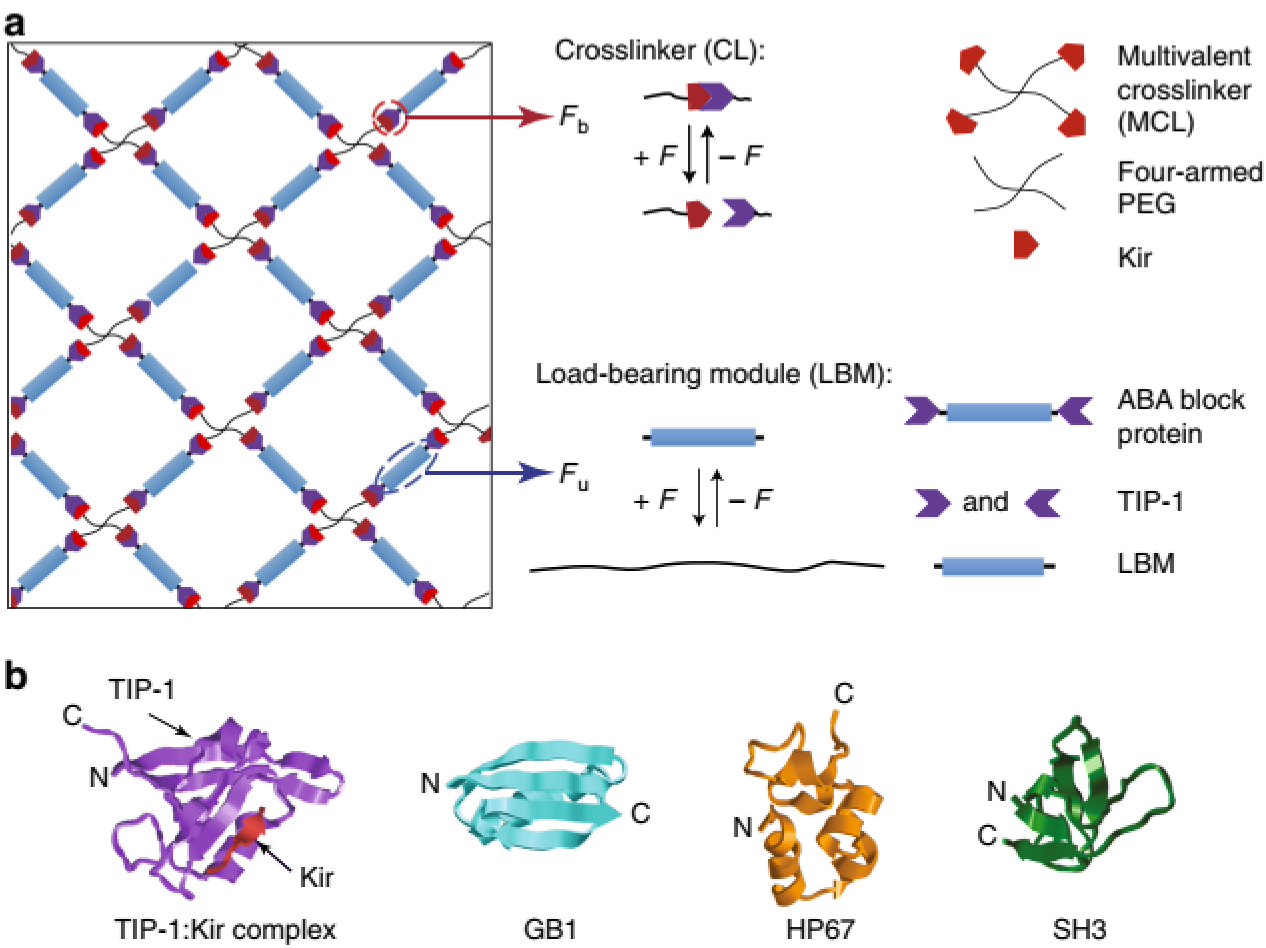


Limitations:

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

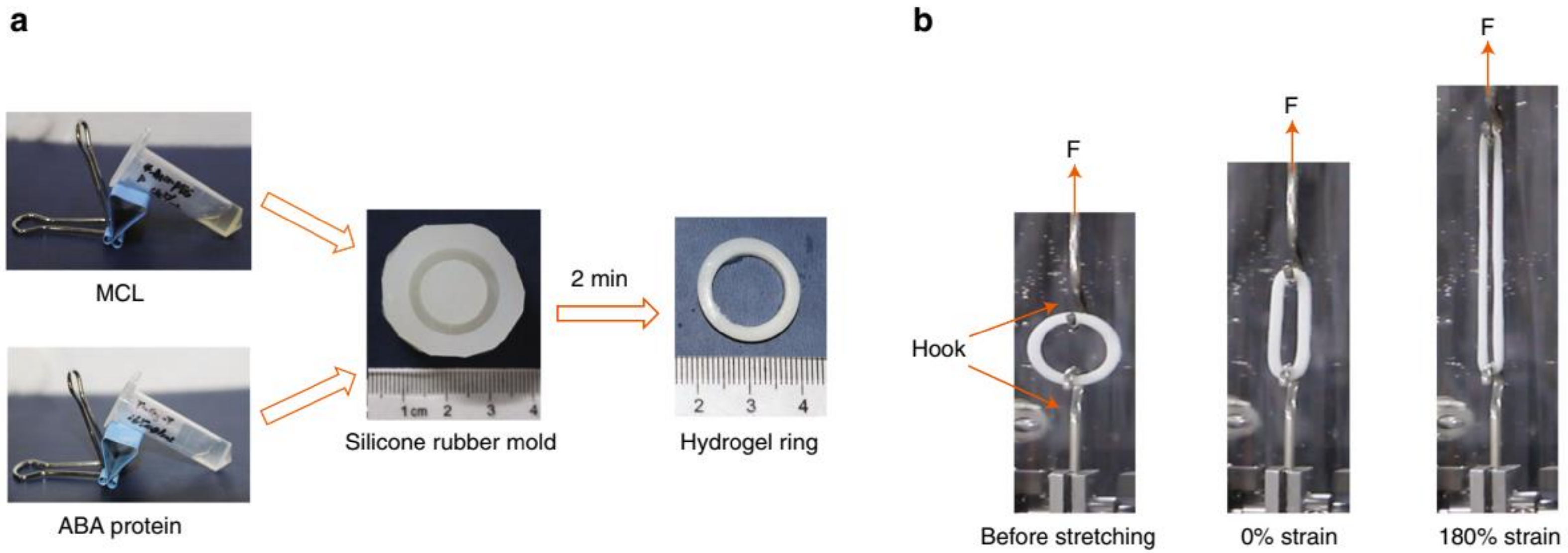
Rational design

Protein-based hydrogels with predictable mechanical properties



Wu et al, Nat Comm (2018) 9:260

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



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

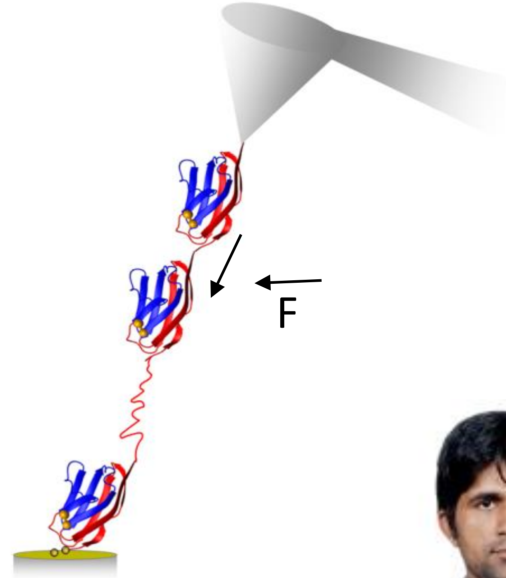
Wu et al, Nat Comm (2018) 9:260

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

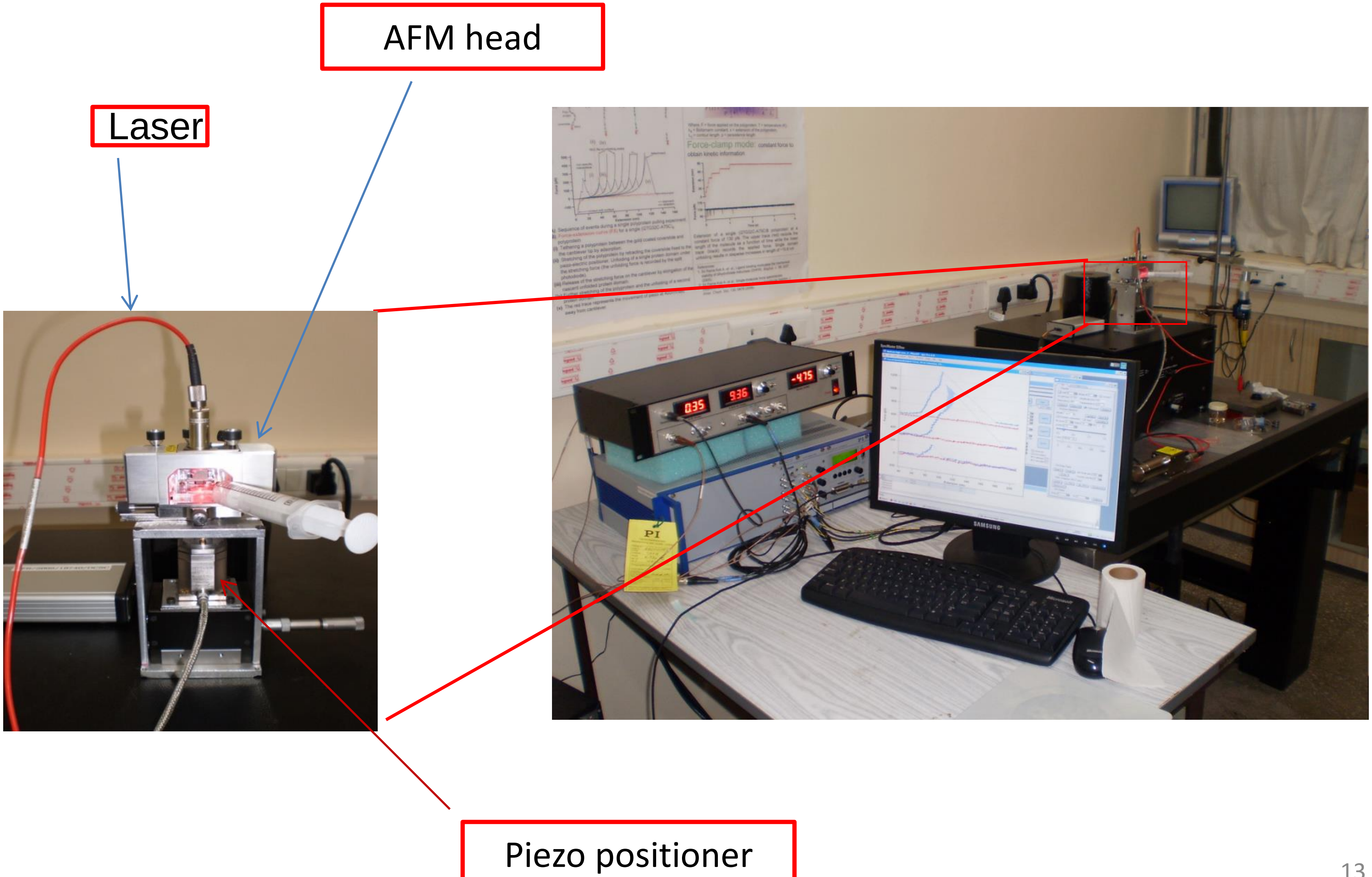


Thank You!

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