Physical Principles in Biology
Biology 3550
Spring 2024

Lecture 35

Protein Structure Prediction, Optical Tweezers and Introduction to Molecular Motors

Wednesday, 10 April 2024

©David P. Goldenberg
University of Utah
goldenberg@biology.utah.edu

Announcements

- Problem Set 5:
  - Due Monday, 15 April at 11:59 PM
  - Submit pdf file on Gradescope
- Quiz 5:
  - Friday, 12 April
  - 25 min, second half of class
- Review Session:
  - 5:15 PM, Thursday, 11 April
  - HEB 2002
  - Come with questions!

Some Approaches to Predicting Protein Structures

- Hierarchical approach:
  - Determine propensities of different amino acids to form α-helices and β-strands.
  - Use propensities to predict segments of polypeptide chain that will form α-helices and β-strands.
  - Assemble secondary-structure elements into overall fold.
  - Doesn't really work!
- Template-based modeling:
  - Works pretty well when the template structure is 50% or more identical to the unknown structure, but accuracy is limited.
- Physics-based modeling:
  - Build a computer model of the polypeptide chain.
  - Simulate process of sampling conformations to find those with minimum energies.
  - Now feasible with very small proteins, but with high computational cost.

Lindorff-Larsen, K., Piana, S., Dror, R. O. & Shaw, D. E. (2011). How fast-folding proteins fold. *Science*, 334, 517–520. http://dx.doi.org/10.1126/science.1208351

Inferring Residue-Residue Contacts from Co-evolution

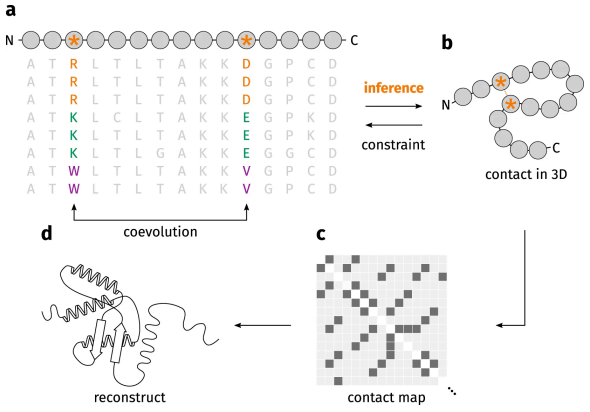


Figure from: Bittrich, S., Schroeder, M. & Labudde, D. (2019). StructureDistiller: Structural relevance scoring identifies the most informative entries of a contact map. *Scientific Reports*, 9, 18517.
https://www.nature.com/articles/s41598-019-55047-4

Göbel, U., Sander, C., Schneider, R. & Valencia, A. (1994). Correlated mutations and residue contacts in proteins. *Proteins: Struct. Funct. Bioinf.*, 18, 309–317.
https://doi.org/10.1002/prot.340180402

A Deep-learning Neural Network

Figure 1.6. Deep representations learned by a digit-classification model

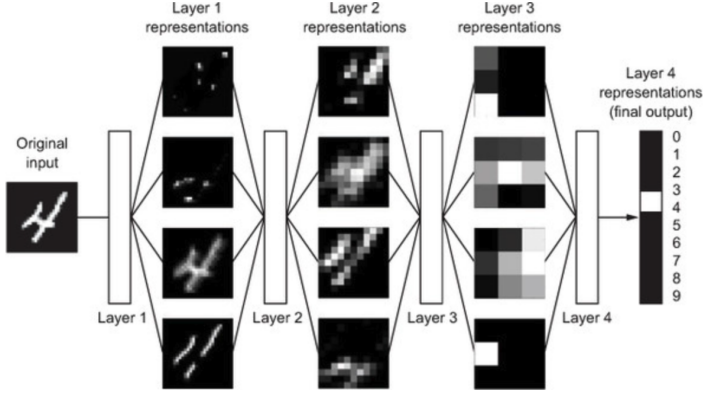
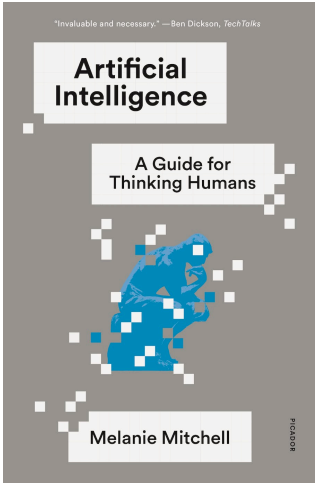
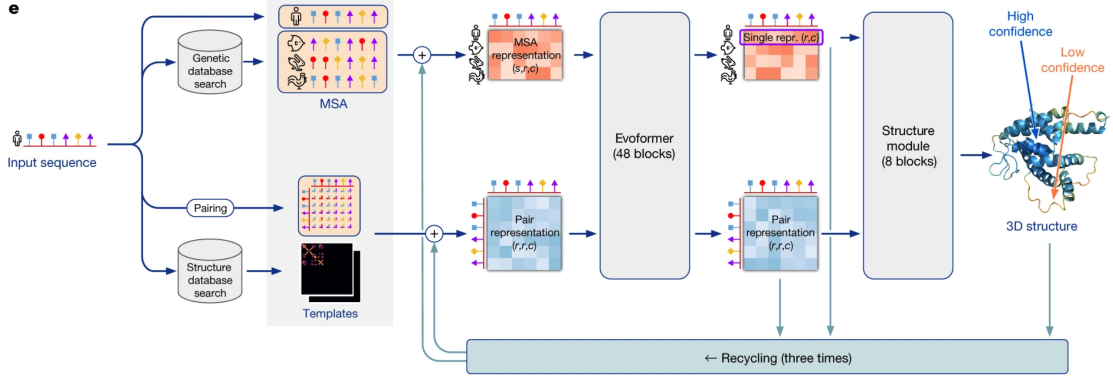


Figure from: Chollet, F. (2018). *Deep Learning with Python*. Manning.

A Recommended Book

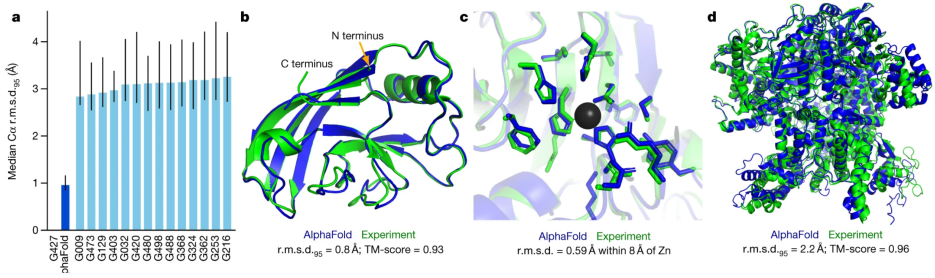


AlphaFold: Protein Structure Prediction Using Deep Learning



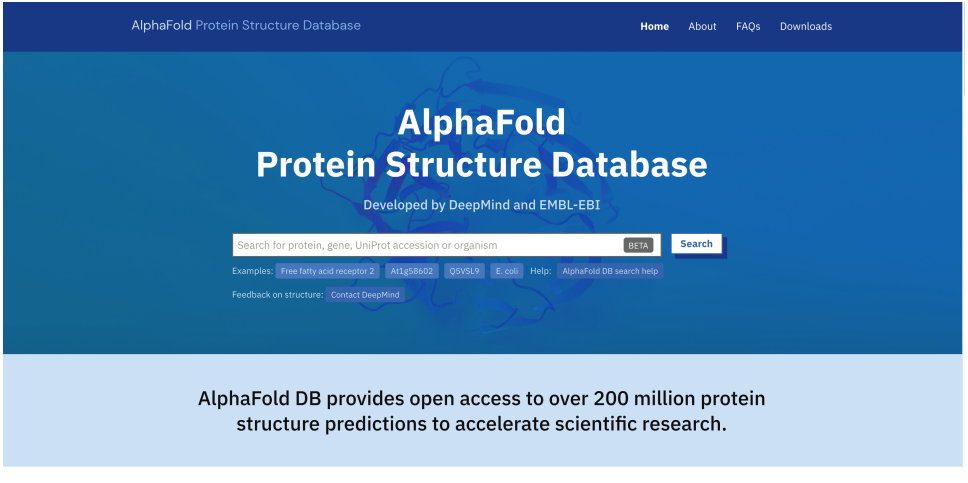
Jumper, J., *et al.* (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, 596, 583–589. https://doi.org/10.1038/s41586-021-03819-2

AlphaFold Results



Jumper, J., *et al.* (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, 596, 583–589. https://doi.org/10.1038/s41586-021-03819-2

Kryshtafovych, A., Schwede, T., Topf, M., Fidelis, K. & Moult, J. (2019). Critical assessment of methods of protein structure prediction (CASP)–Round XIII. *Proteins: Struct. Funct. Bioinf.*, 87, 1011–1020. https://doi.org/10.1002/prot.25823

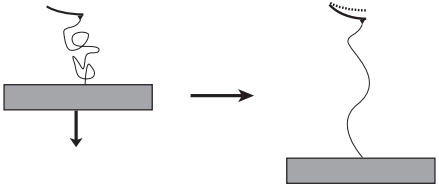

AlphaFold Protein Structure Database
Home
About
FAQs
Downloads
AlphaFold
Protein Structure Database
Developed by DeepMind and EMBL-EBI
Search for protein, gene, UniProt accession or organism
BETA
Search
Examples:
Free fatty acid receptor 2
A1g58602
Q5VSL9
E. coli
Help:
AlphaFold DB search help
Feedback on structure:
Contact DeepMind
AlphaFold DB provides open access to over 200 million protein structure predictions to accelerate scientific research.

Warning!

Direction Change

Optical Tweezers for Measuring Molecular Forces

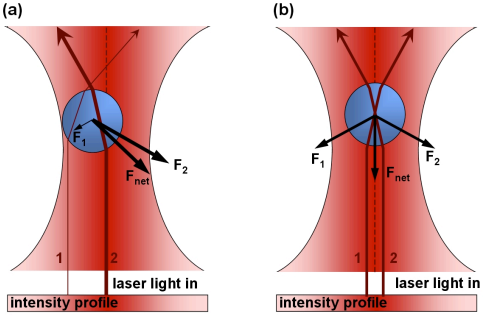
Stretching an Unfolded Protein with AFM



- Stage is moved very slowly, as deflection of cantilever is monitored.
- Deflection represents force as a function of distance.
- Force integrated over distance gives w_{rev}.
- $\Delta S_{\text{conf}} = -w_{\text{rev}}/T$

Thompson, J. B., Hansma, H. G., Hansma, P. K. & Plaxco, K. W. (2002). *J. Mol. Biol.*, 322, 645–652.
http://dx.doi.org/10.1016/S0022-2836(02)00801-X

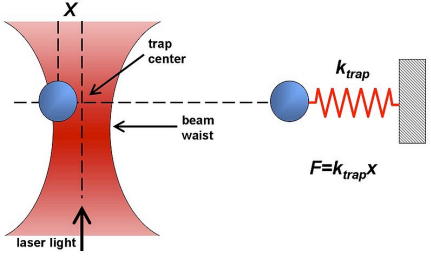
Another Tool for Studying Molecular Forces: Optical Tweezers



- Glass or silica beads ($\sim 1\,\mu$m diameter) placed in a narrowly focused beam of light.
- Light is refracted (bent) by the bead, resulting in an opposite force on the bead.
- If the bead is outside of the beam center, where the light is most intense, there is a net force that pushes it to the center.
- At the center of the beam, lateral forces on bead are balanced.

Figure from: https://en.wikipedia.org/wiki/Optical_tweezers

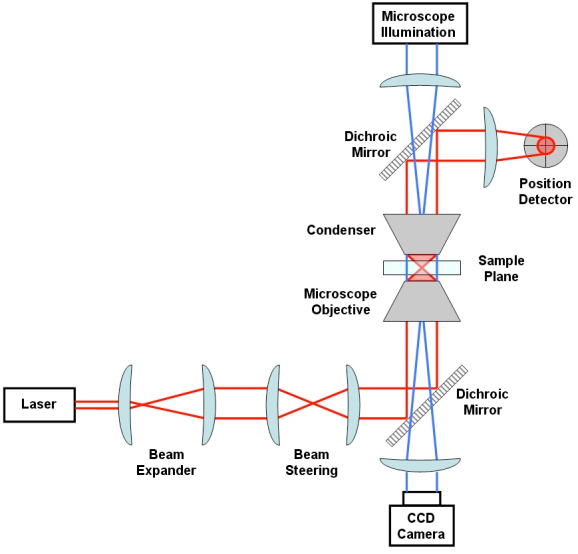
A Tool for Studying Molecular Forces: Optical Tweezers



- Force of optical trap acts like a spring: Force is proportional to distance of bead from beam center.
- If another force is acting on the bead, that force can be measured from displacement of bead.

Figure from: https://en.wikipedia.org/wiki/Optical_tweezers

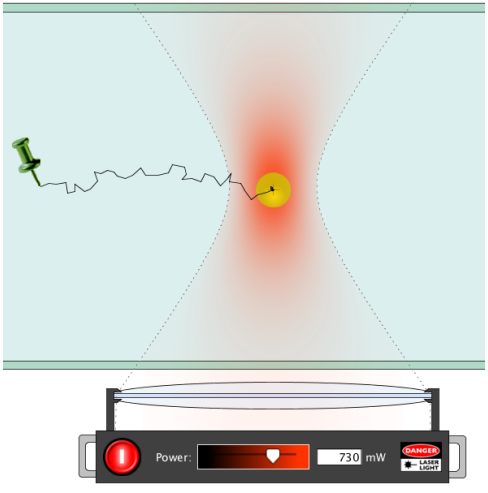
Optical Tweezers Apparatus



- Apparatus based on an optical microscope.
- Microscope allows the bead to be observed.
- Laser provides light for trap.
- Beam position can be “steered” by moving lenses.
- Bead position is tracked with position detector.

Figure from: https://en.wikipedia.org/wiki/Optical_tweezers

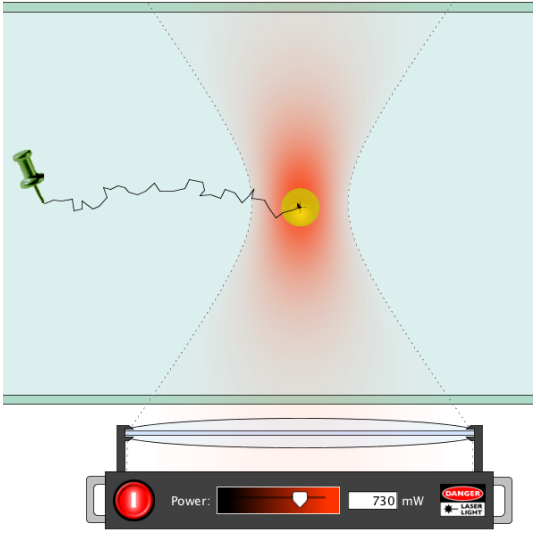
Stretching DNA with Optical Tweezers



- One end of DNA is held in fixed position.
- Other end of DNA is attached to a bead.
- bead is trapped in focused laser light.
- Optical trap can be used to move bead.
- What happens if the laser is turned off?

DNA stretching demo:
https://phet.colorado.edu/en/simulation/legacy/stretching-dna

Clicker Question #1



What happens if the laser is turned off?

A) The bead stays put.

B) The bead moves randomly by Brownian motion.

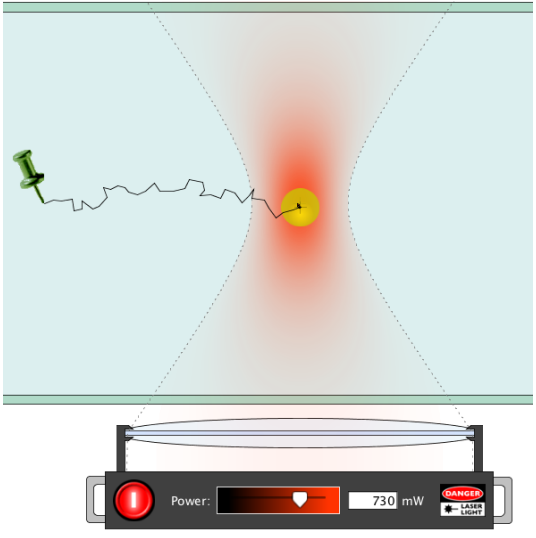
C) The bead moves towards the fixed DNA end.

D) The bead moves away from the fixed DNA end.

All answers count for now.

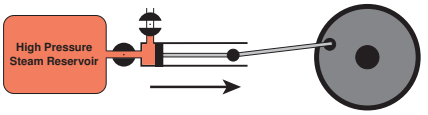
DNA stretching demo: https://phet.colorado.edu/en/simulation/legacy/stretching-dna

Stretching DNA with Optical Tweezers

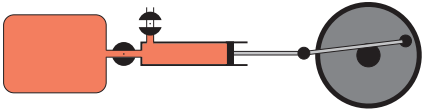


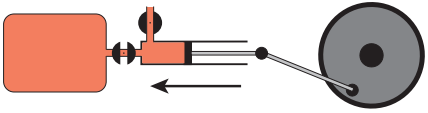
- Thermal motion of solvent molecules generates a force.
- Force increases as DNA ends are moved further apart.
- Force is entropic in nature: There are more possible conformations with the ends closer together.
- Could a force like this be used as a molecular motor?

A Simple Steam Engine



Power Stroke

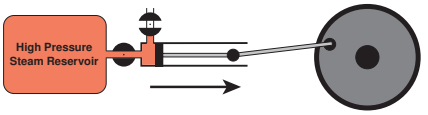




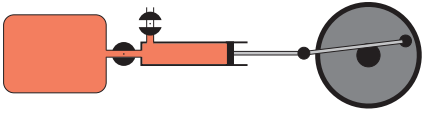
Recovery (exhaust) Stroke

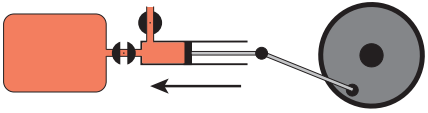
- Energy source is a pressure difference, created by a temperature difference.
- Free energy of steam is lost as it expands.
- Expansion of steam is coupled to movement of piston and flywheel, capturing some of the energy.
- Momentum of the flywheel returns engine to starting state.
- Valves control flow of steam and must be synchronized to piston movement.
- If expansion of steam is unlinked from motion of piston or wheel, free energy is lost.

A Simple Steam Engine



Power Stroke





Recovery (exhaust) Stroke

- Similar requirements for a molecular motor:
  - Loss of free energy (*e.g.,* ATP hydrolysis) must be coupled to mechanical work.
  - Motor must operate cyclically.
  - Individual steps in cycle must be regulated.
- Important differences for a molecular motor:
  - No temperature differences at the molecular scale.
  - No momentum at the molecular scale.