Outline for lecture 1 (course overview)

• What is structure?
  – Structure (and dynamics) at multiple spatial scales
• Why is structure important?
• How computation helps: An overview of course topics
• Recurrent themes
• Course logistics
What is structure?
In daily life, we use machines with functional *structure* and *moving parts*
Cells and biomolecules (e.g., proteins) are also machines whose function depends on structure and moving parts.

From *Inner Life of the Cell* | *Protein Packing*, XVIVO and Biovisions @ Harvard
Structure (and dynamics) at multiple spatial scales
Protein structure

An adrenaline receptor
(the $\beta_2$ adrenergic receptor)
Protein dynamics

$\beta_2$ adrenergic receptor
Proteins (and other molecules) often come together to form macromolecular complexes.

Nuclear Pore Complex
Alber et al., Nature 2007
These come together to form organelles

Synaptic vesicle
http://www.mpibpc.mpg.de/9547480/vesicle600.jpg
and cells
Intracellular structure

Chih-Jung Hsu, Janis Burkhardt and Tobias Baumgart

http://www.nikoninstruments.com/Products/Microscope-Systems/Inverted-Microscopes/N-STORM-Super-Resolution/(gallery); Zhuang group

David Goodsell
Intracellular dynamics (artist’s rendition)
Why is structure important?
Genomics is a great start ....

- But a parts list is not enough to understand how a bicycle works
... but not the end

- We want the full spatiotemporal picture, and an ability to control it
- Broad applications, including drug design, medical diagnostics, chemical manufacturing, and energy
Structure determines function

- Example: Motor protein (walks along microtubules, dragging load)
Structure determines function

- Example: Ribosome
  - Complex of many proteins and RNAs that together makes new proteins (by reading the genetic code and combining amino acids)

From *Inner Life of the Cell*, XVIVO and Biovisions @ Harvard

Hashem et al., Nature 494:385-9, 2013
Structure determines function

- Example: G protein-coupled receptors (GPCRs)
  - Largest class of human drug targets
  - Function: allow the cell to sense and respond to molecules outside it
Structure-based drug design

- Almost all drugs act by binding to proteins and altering their function.
- Using knowledge of structures, we can design drugs that bind more tightly or more selectively, bind in different positions, alter behavior of protein in different ways, etc.

Designing new biomolecular machines

- Protein design (for health or industrial applications)
- Cell design?

[Link to image of Protein design](http://zhanglab.ccmb.med.umich.edu/image/Protein_design.gif)
How computation helps:
An overview of course topics
2013 Nobel Prize recognized early developments underlying modern biomolecular computation

The Nobel Prize in Chemistry 2013

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel "for the development of multiscale models for complex chemical systems".
Protein structure prediction

- Sequence of amino acids → 3D coordinates
- Two basic approaches:
  - Homology modeling (infer structure from similar protein of known structure)
  - Ab initio prediction (using physics-based models)

Also, RNA structure prediction
Molecular dynamics simulations

Beta-blocker binding to the $\beta_2$-adrenergic receptor

Dror et al., *PNAS* 2011
Molecular dynamics simulations

Folding of protein G
(Lindorff-Larsen et al., Science, 2011)

Structural change in a G protein
(Dror et al., Science 2015)
Ligand docking

Searching for potential drug molecules that bind to a target (usually a protein)
Protein design

- Given a desired protein structure (or, in some cases, function), design the amino acid sequence that produces it

Top7, a protein with a designed fold
Solving x-ray crystal structures

X-ray diffraction pattern
Image: http://www.chem.ucla.edu/harding/IGOC/X/x_ray_crystallography.html

Protein structure
Solving structures of complexes by cryoelectron microscopy

CryoEM image

Reconstructed envelope

Image from Wikipedia

http://people.cryst.bbk.ac.uk/~ubcg16z/chaperone.html
Combining experimental data to deduce structures of complexes

Alber et al., Nature 2007
Cellular-level organization: image analysis

Images: Naomi Latorraca
Cellular-level organization: image analysis

Image: CellProfiler
Cellular-level simulation

Video: Naomi Latorraca
Recurrent themes
Recurrent themes

- Similarities and differences in methods employed at different spatial scales
- **Physics-based approaches** (modeling based on first-principles physics) vs. **data-driven approaches** (inference/learning based on experimental data)
- Computation plays important role both in **structural interpretation of experimental data** and in **structural predictions in the absence** of such data
- **Energy functions** (which associate an energy or potential with each possible structure)
- Recurring math concepts: **Fourier transforms** and convolution
Course organization

Fine-scale ➔ Coarse-scale

1. Atomic-level modeling of proteins and other biomolecules
2. Determining structures and structural properties of macromolecular complexes
3. Determination of cellular-level organization

Last lectures: special topics (cutting-edge research)
- Will also cover current research topics at end of most lectures
Course logistics
Course web page

• http://cs279.stanford.edu/

• Evaluation criteria and handouts on web page

• Please sign up on Piazza (via link on webpage) so that you get announcements
Course staff

• Prof. Ron Dror
  – Office hours: Thursdays 4:20-6:00 (Gates 204), or by appointment

• TA: Osama El-Gabalawy
  – Office hours: to be decided through poll
Expected background

• Course is intended to be broadly accessible to students with computational or biological backgrounds

• Basic programming in Python.
  – You need not have used Python before. You should have done some programming before.

• Some previous biology, chemistry, and physics exposure (at least in high school)

• Math through calculus
  – I will teach some additional relevant math concepts (e.g., Fourier transforms), with a focus on basic ideas/intuition rather than on equations
Assignments, Project, Exam

- 3 assignments
  - First one is mini-assignment

- Project: More open-ended. About the same amount of work as second or third assignments.

- Final exam covering key concepts
Lectures and reading

- Lectures are not videotaped
- No textbook. Slides available, along with brief notes for some lectures and pointers to optional reading material
- Attend most classes
- Participation encouraged!