CS/BioE/Biophys/BMI/CME 279
Computational biology: Structure and organization of biomolecules and cells

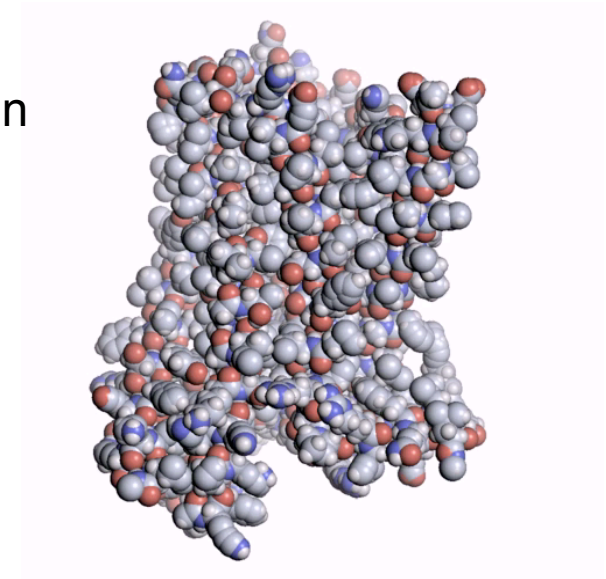
Ron Dror
Stanford University

Sept 21, 2021

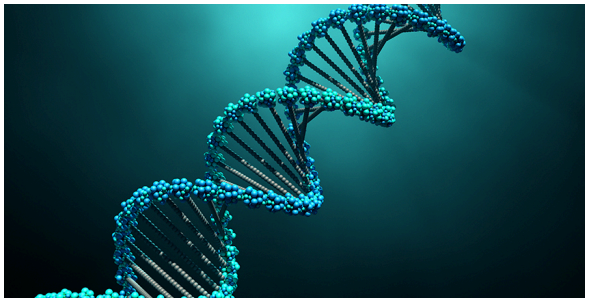
Image credit: Ansgar Philippsen

One-fifth of science Nobel Prizes relate to 3D structure/organization of biomolecules

Protein



DNA



RNA

- Biological structure is critical to:
  - Understanding how biology works
  - Diagnosing, preventing, and treating disease
  - Food and energy production (e.g., agriculture)

Computation plays a critical and rapidly growing role in this field

nature
NEWS | 30 November 2020

‘It will change everything’: DeepMind’s AI makes gigantic leap in solving protein structures

Google’s deep-learning program for determining the 3D shapes of proteins stands to transform biology, say scientists.

Dramatic growth of research and commercial activity (startups, acquisitions, etc.) in both machine learning and physical simulation approaches for determining and exploiting biomolecular structure and dynamics

2013 Chemistry Nobel Prize: Computational models of biomolecules

AND THE WINNER OF THE NOBEL PRIZE IN SOFTWARE IS...

The Nobel Prize in Chemistry 2013

Photo: A. Mahmoud
Martin Karplus
Prize share: 1/3

Photo: A. Mahmoud
Michael Levitt
Prize share: 1/3

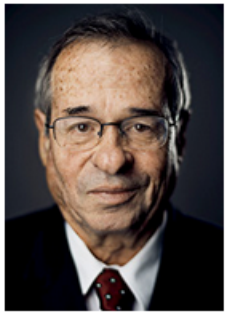


Photo: A. Mahmoud
Arieh Warshel
Prize share: 1/3

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"*.

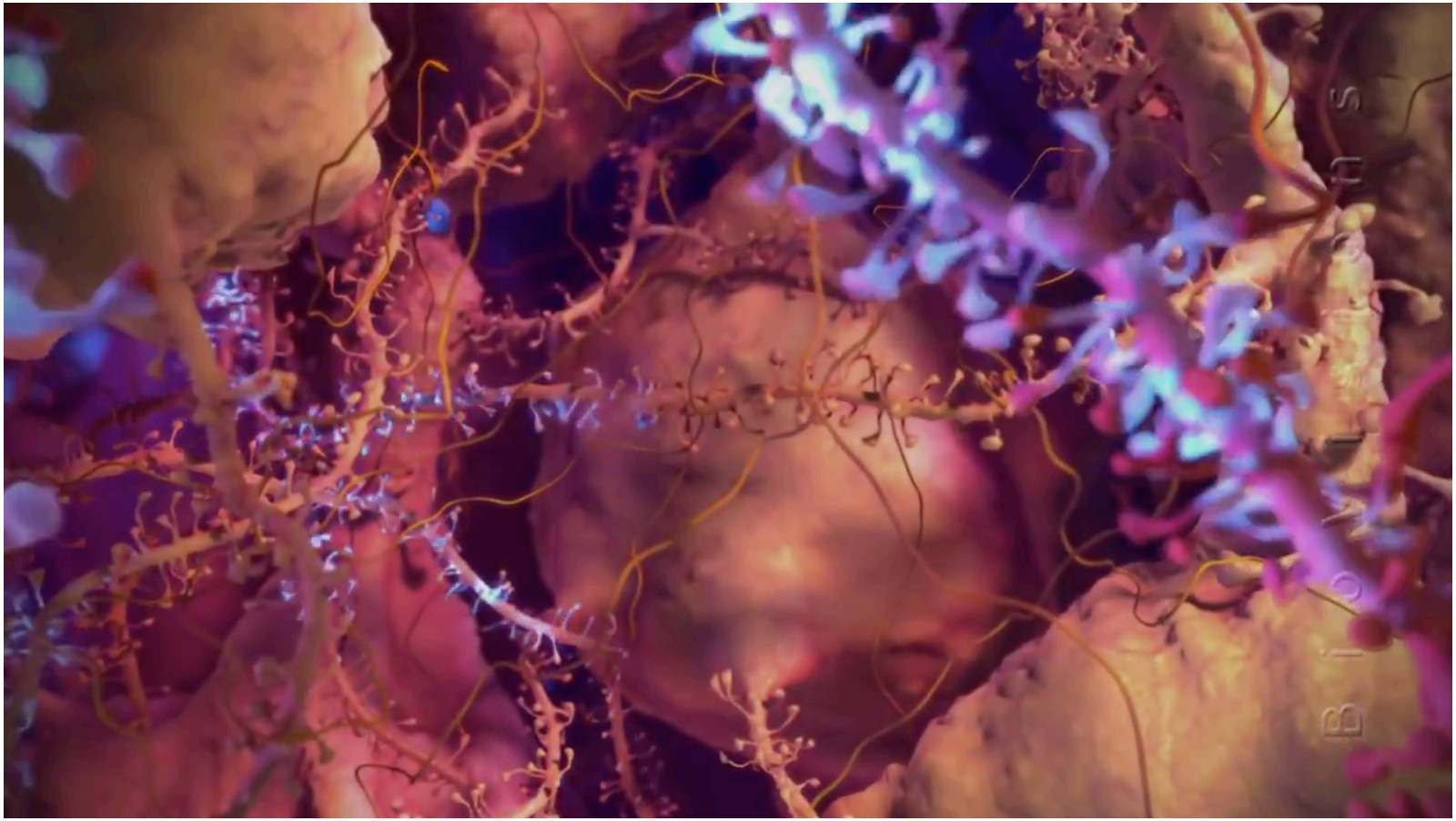
Outline for this lecture

- What is structure?
  - Structure (and dynamics) at multiple spatial scales
- Why is structure important?
- Overview of topics we'll cover
- 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



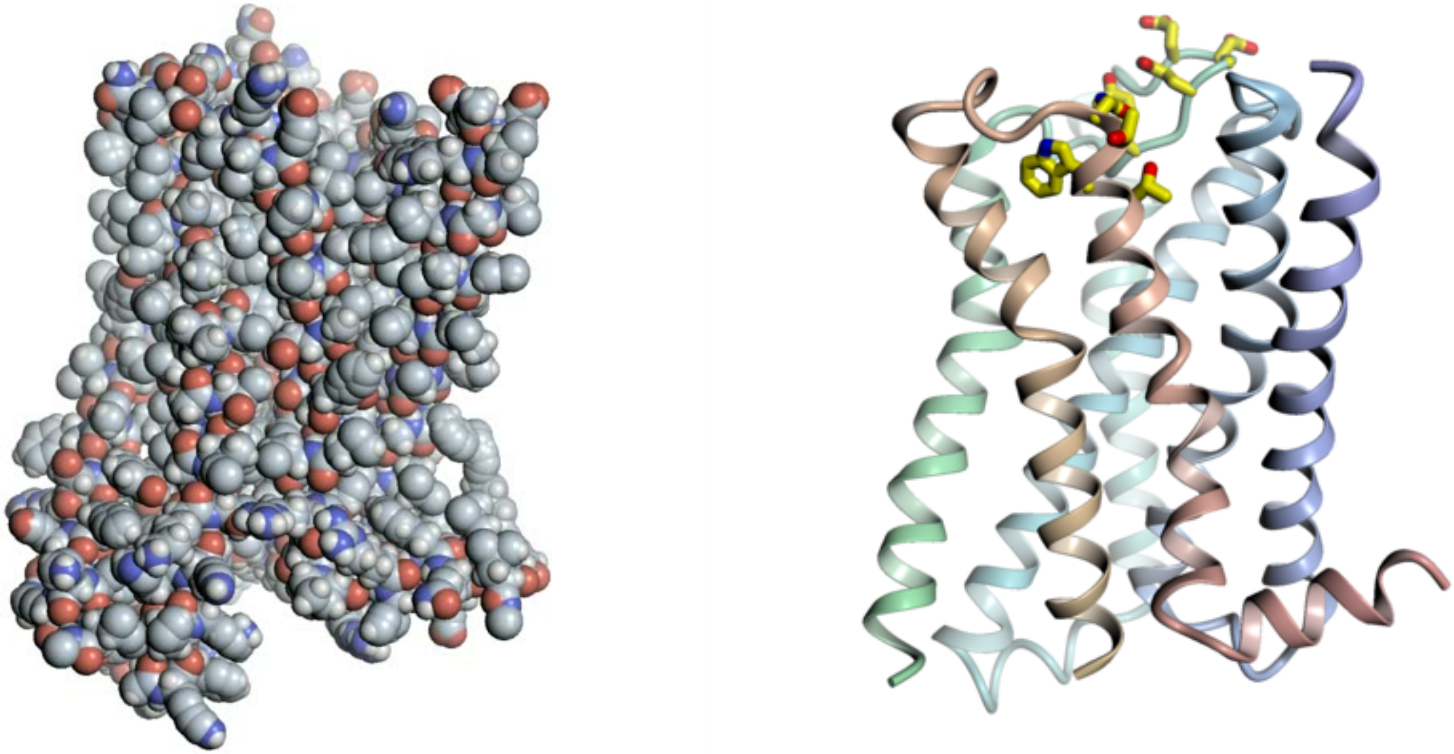
From *Inner Life of the Cell* | *Protein Packing*, XVIVO and Biovisions @ Harvard

What is structure?

Structure (and dynamics)
at multiple spatial scales

Protein structure

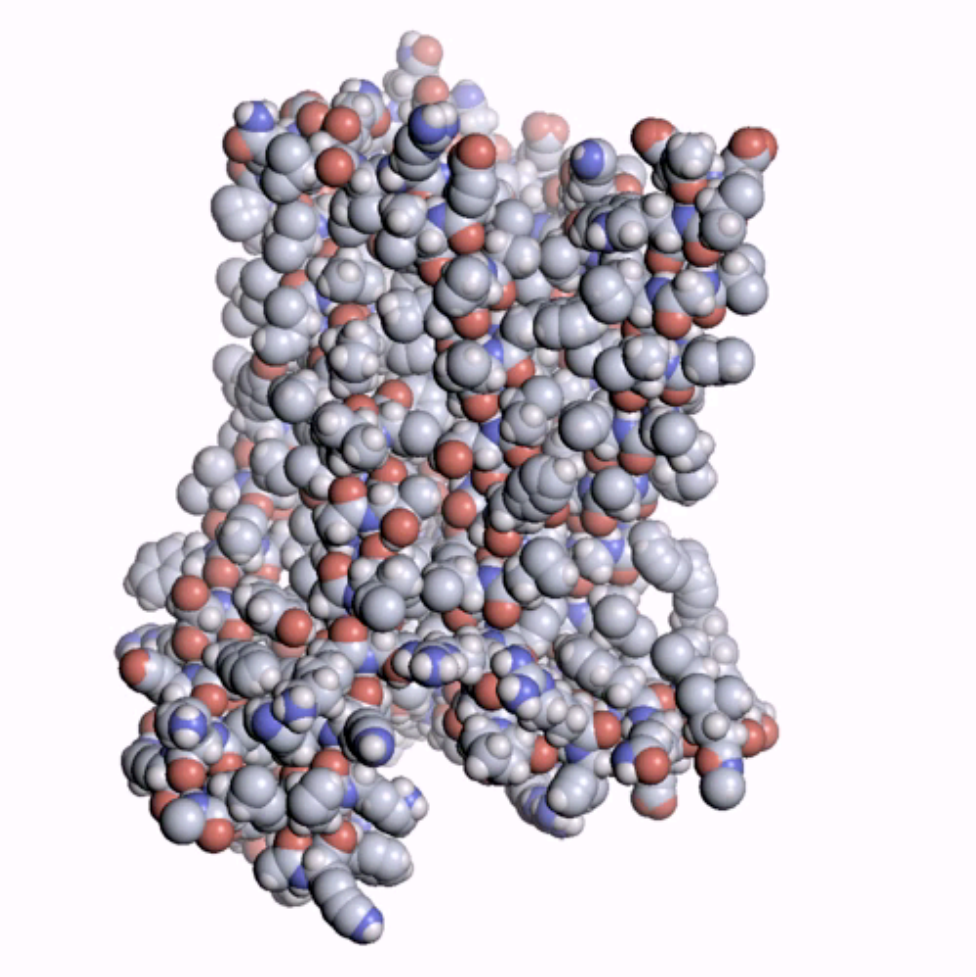
Two different representations of the same protein structure:
a space filling model (left) and ribbon model (right)



An adrenaline receptor
(the β_2 adrenergic receptor)

Atoms in the biomolecules are constantly moving, which is why we call this “dynamic”

Protein dynamics

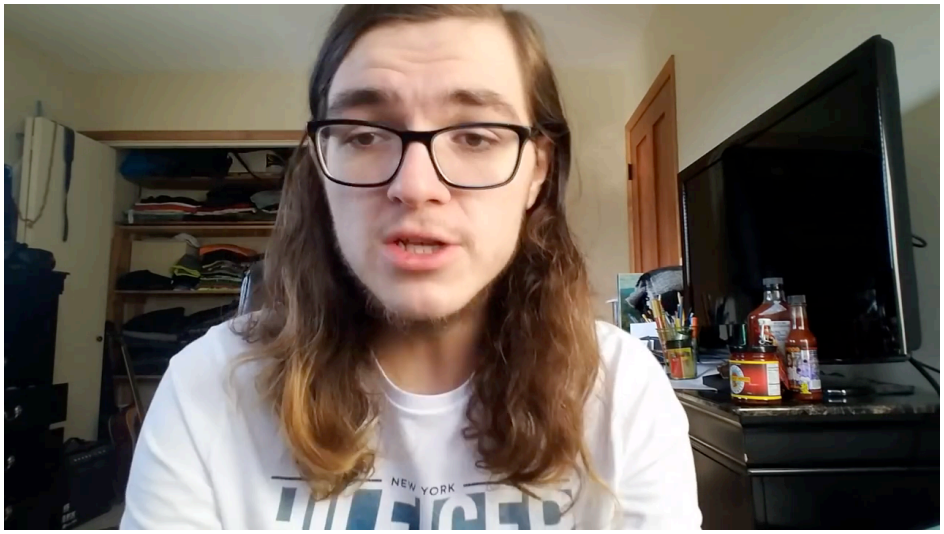


β_2 adrenergic receptor

Example: how LSD binds to its target

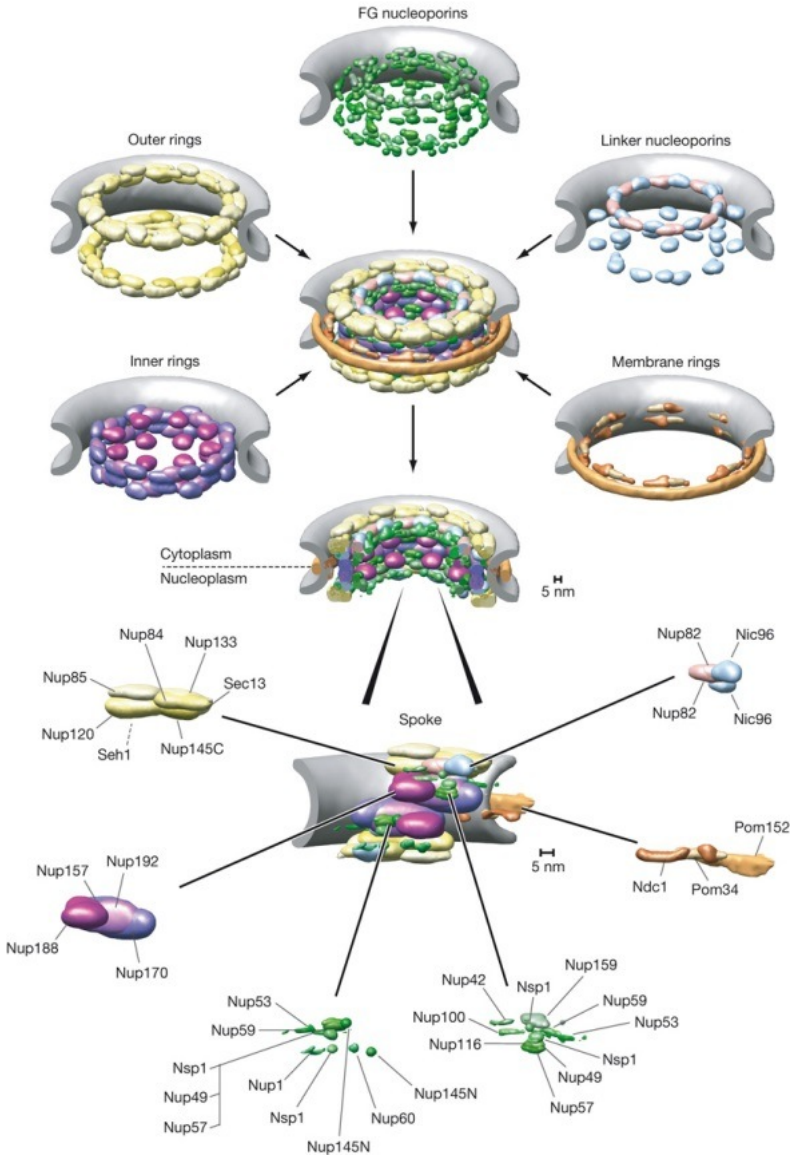
Wacker et al., *Cell* 168:377, 2017
Collaboration with Bryan Roth (UNC)

"Revealed: Why LSD Lasts So Long!"
AVI LSD YouTube Channel



https://www.youtube.com/watch?v=LjumHvnl-ME&feature=youtu.be

Proteins (and other molecules) often come together to form *macromolecular complexes*

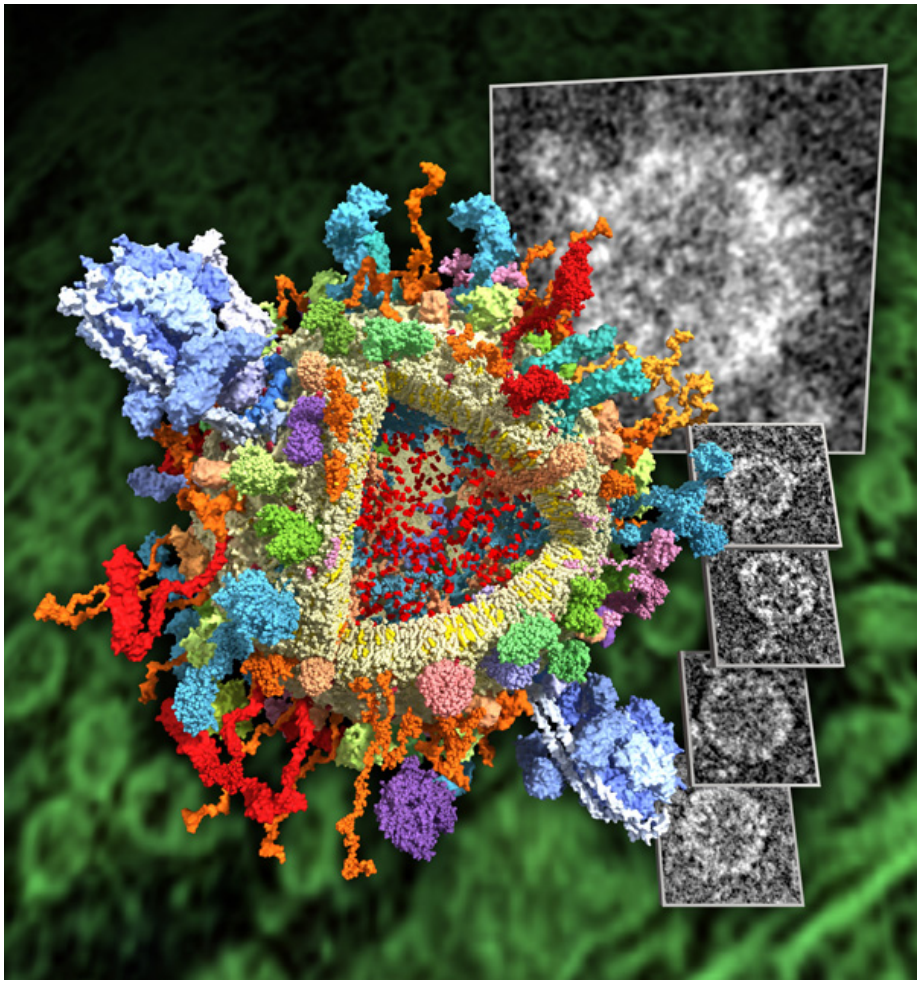


Nuclear Pore Complex
Alber et al., *Nature* 2007

Macromolecules = big molecules

These come together to form organelles

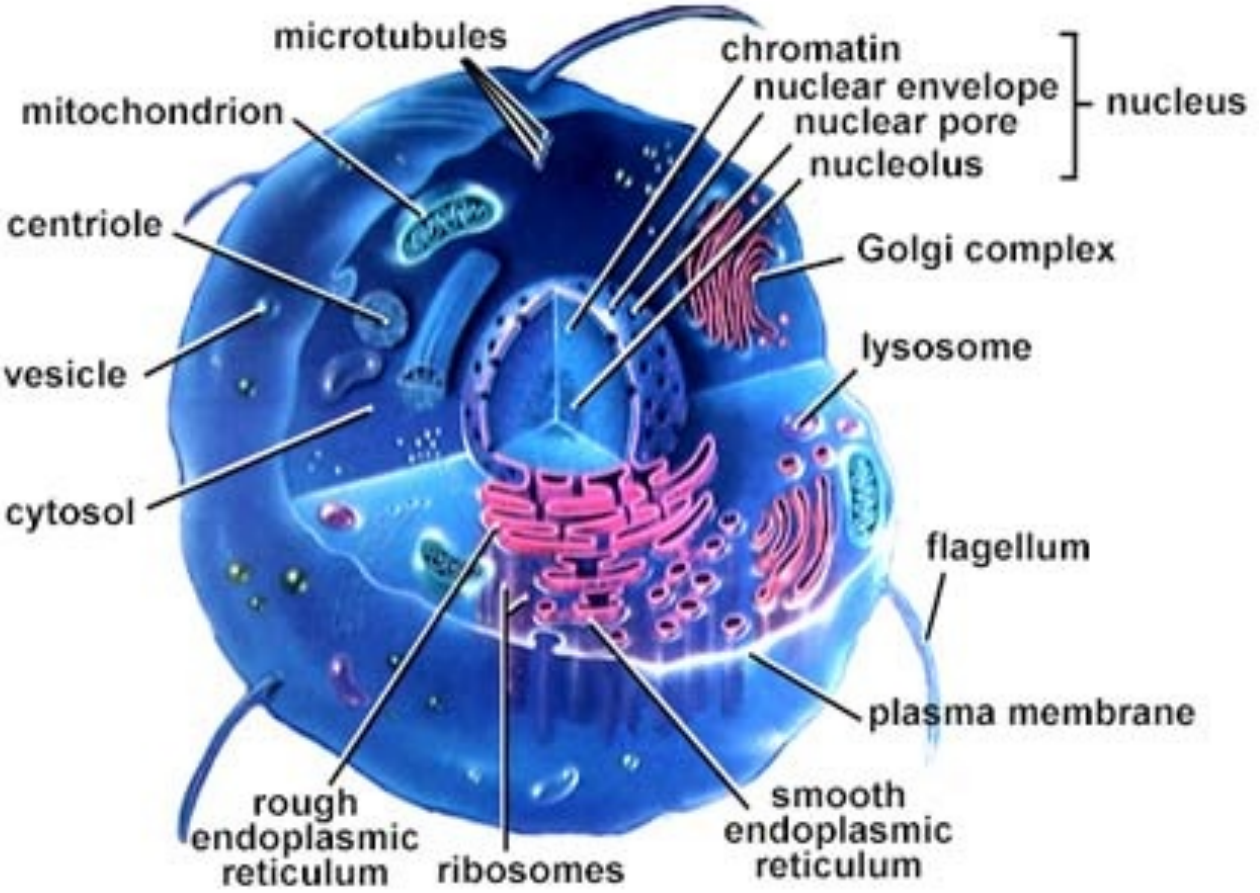
Organelles (“little organs”) are specialized structures in cells that perform various functions.



Synaptic vesicle

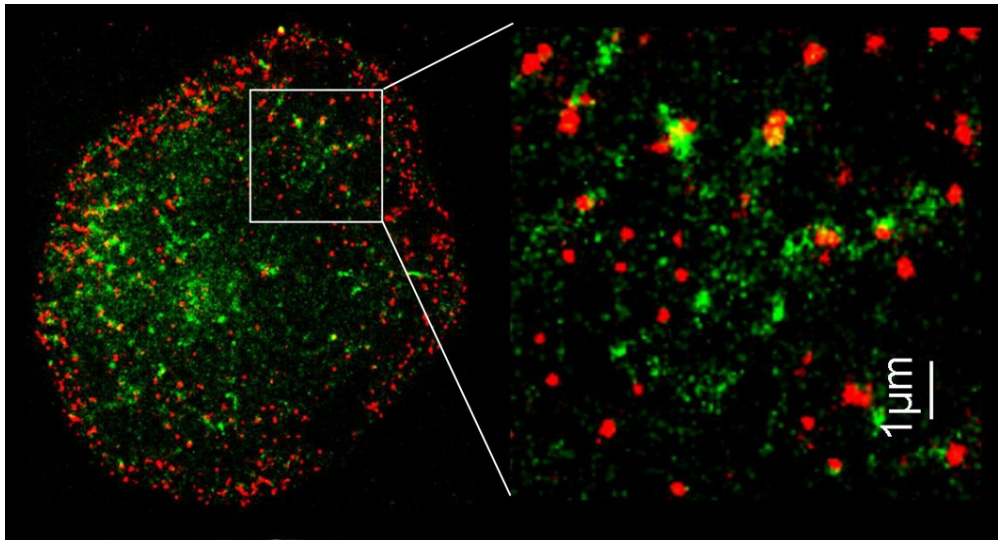
http://www.mpibpc.mpg.de/9547480/vesicle600.jpg

and cells

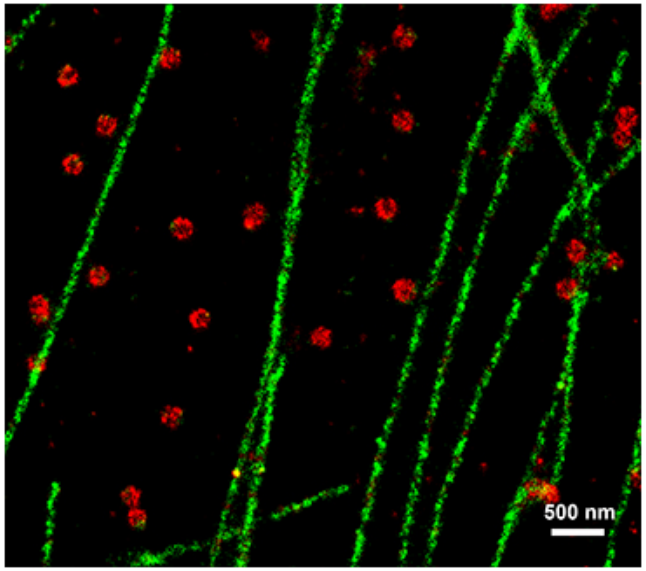


http://www.medfriendly.com/cell.html

Intracellular structure



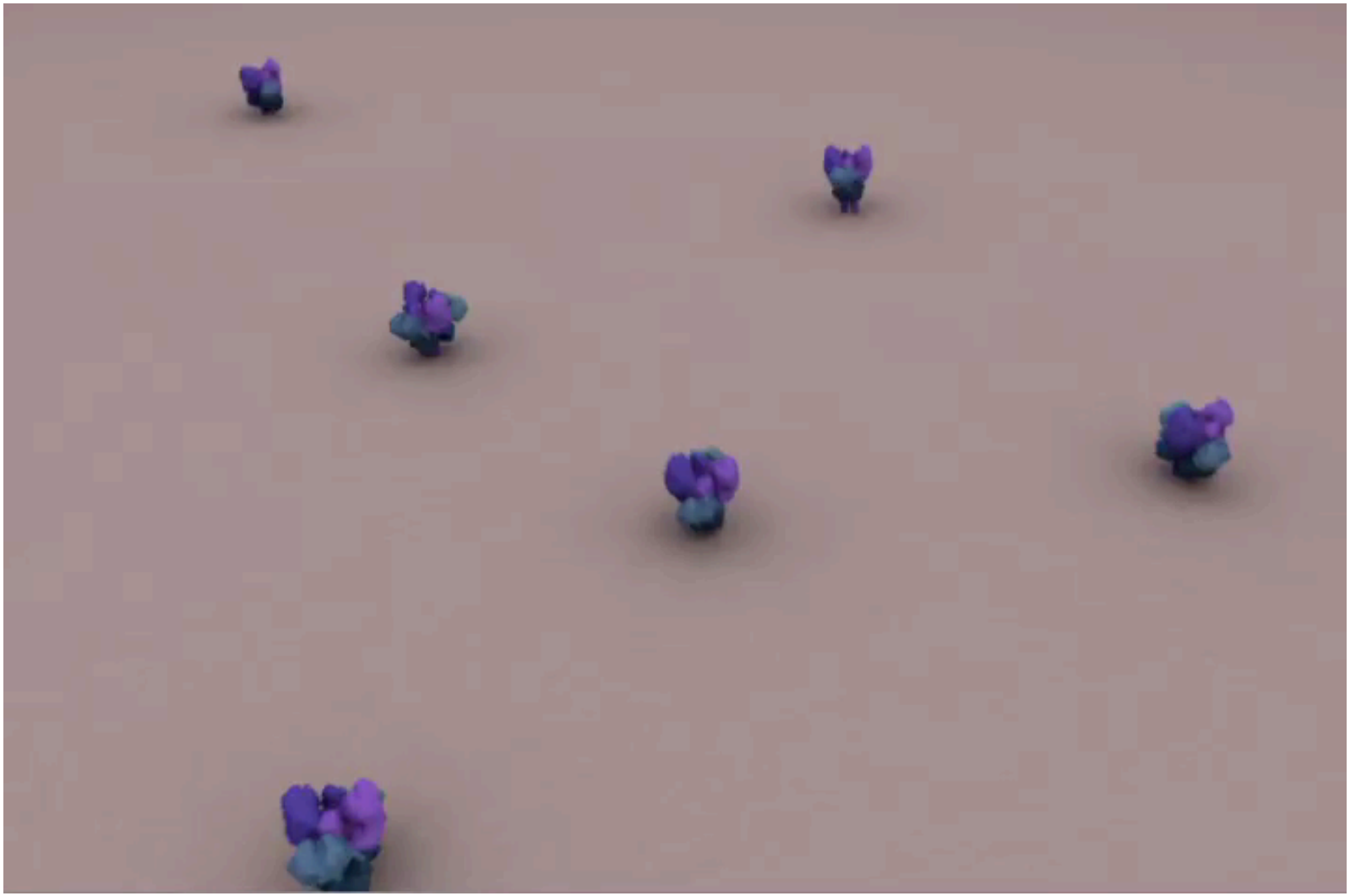
Chih-Jung Hsu, Janis Burkhardt and Tobias Baumgart



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

David Goodsell

Intracellular dynamics (artist's rendition)



Video showing endocytosis, a process where substances are brought into the cell

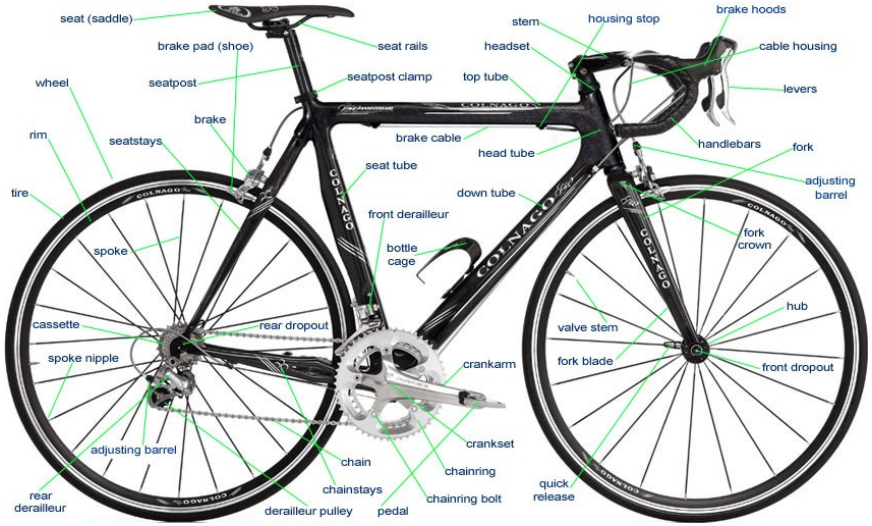
Janet Iwasa and Tomas Kirchhausen

Why is structure important?

To understand how a machine works, we need more than a list of its parts

Track Bike — DL 175

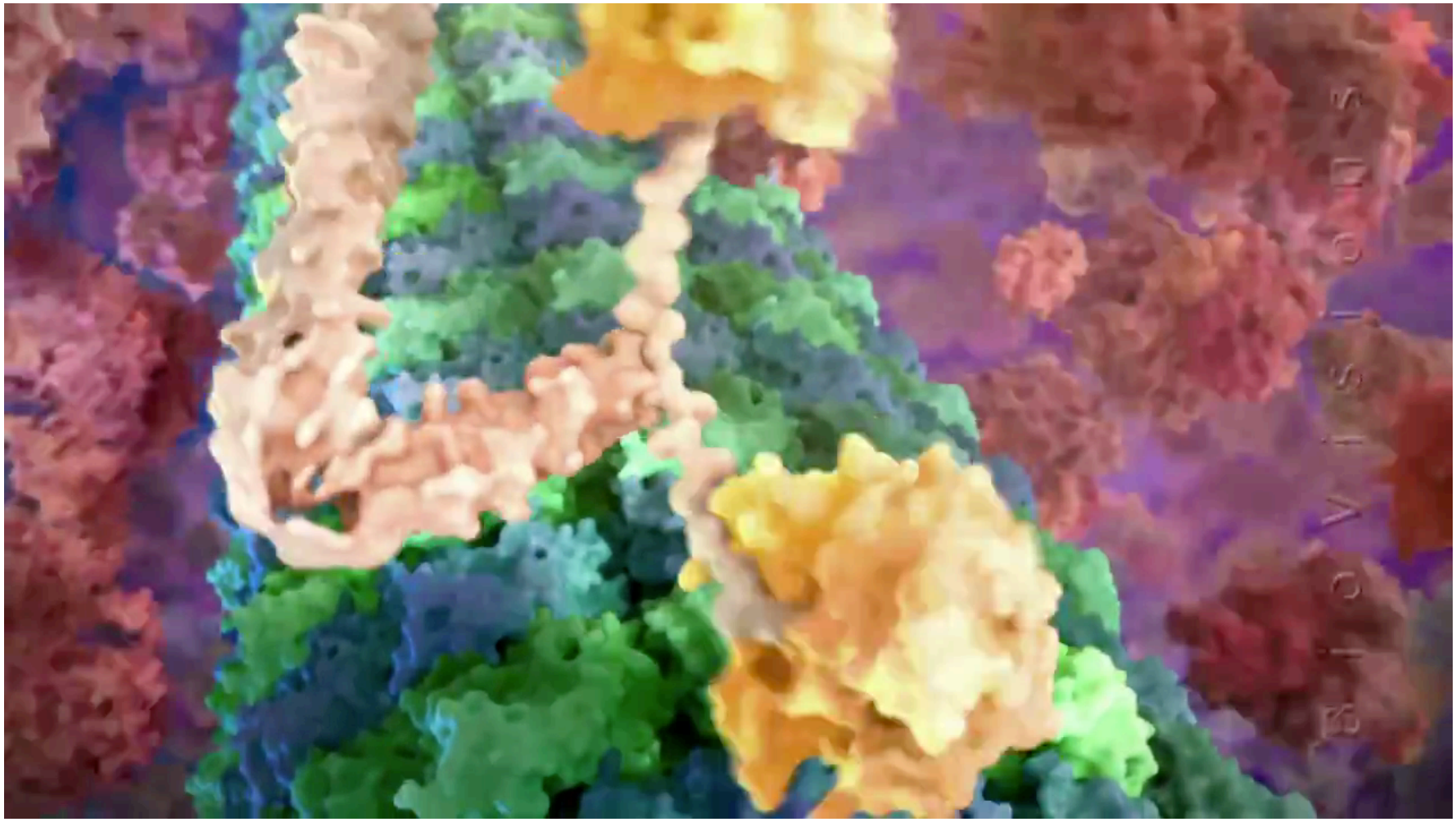
REF. NO.	IBM NO.	DESCRIPTION
1	156011	Track Frame 21", 22", 23", 24", Team Red
2	157040	Fork for 21" Frame
2	157039	Fork for 22" Frame
2	157038	Fork for 23" Frame
2	157037	Fork for 24" Frame
3	191202	Handlebar TTT Competition Track Alloy 15/16"
4		Handlebar Stem, TTT, Specify extension
5	191278	Expander Bolt
6	191272	Clamp Bolt
7	145841	Headset Complete 1 x 24 BSC
8	145842	Ball Bearings
9	190420	175 Raleigh Pistard Seta Tubular Prestavalve 27"
10	190233	Rim, 27" AVA Competition (36H) Alloy Prestavalve
11	145973	Hub, Large Flange Campagnolo Pista Track Alloy (pairs)
12	190014	Spokes, 11 5/8"
13	145837	Sleeve
14	145636	Ball Bearings
15	145170	Bottom Bracket Axle



- We want to know the shapes of these parts, how they move, and how they affect each other

Structure determines function

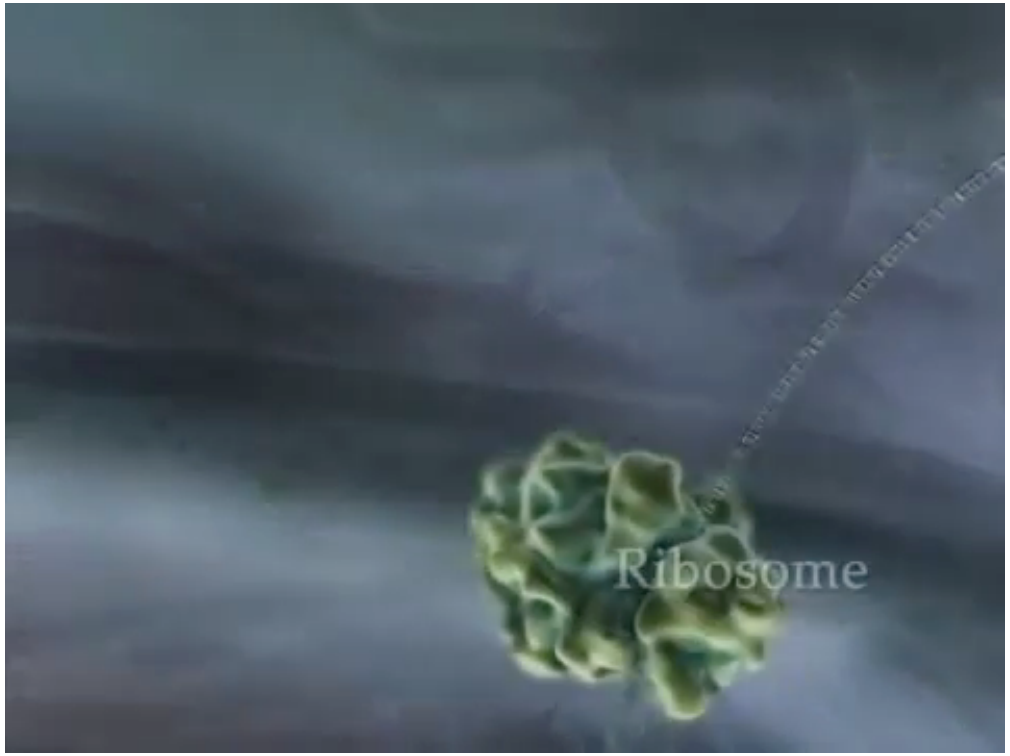
- Example: Motor protein (walks along microtubules, dragging load)



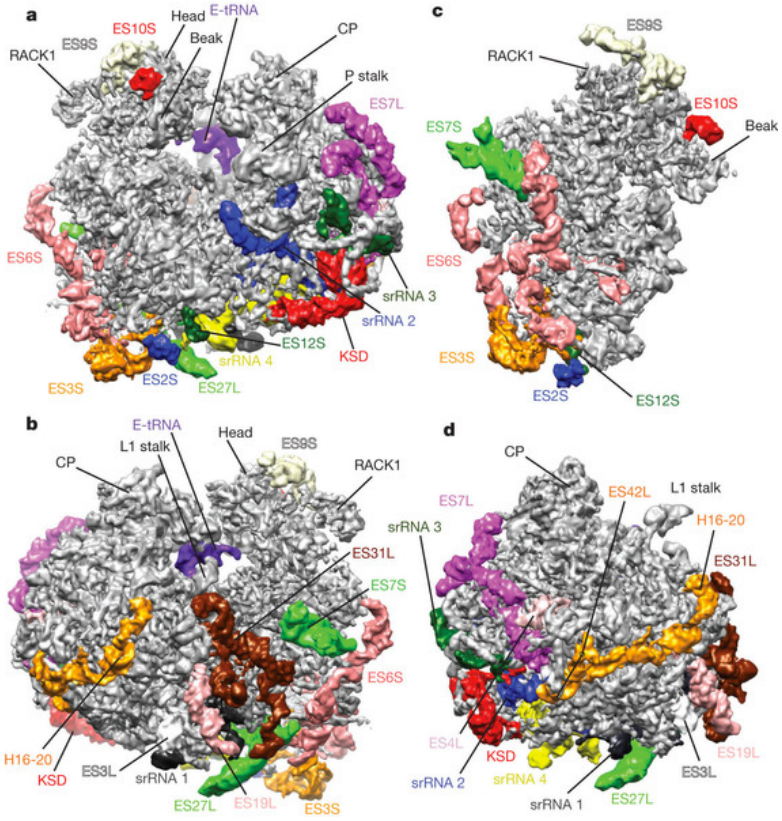
From *Inner Life of the Cell* | *Protein Packing*

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

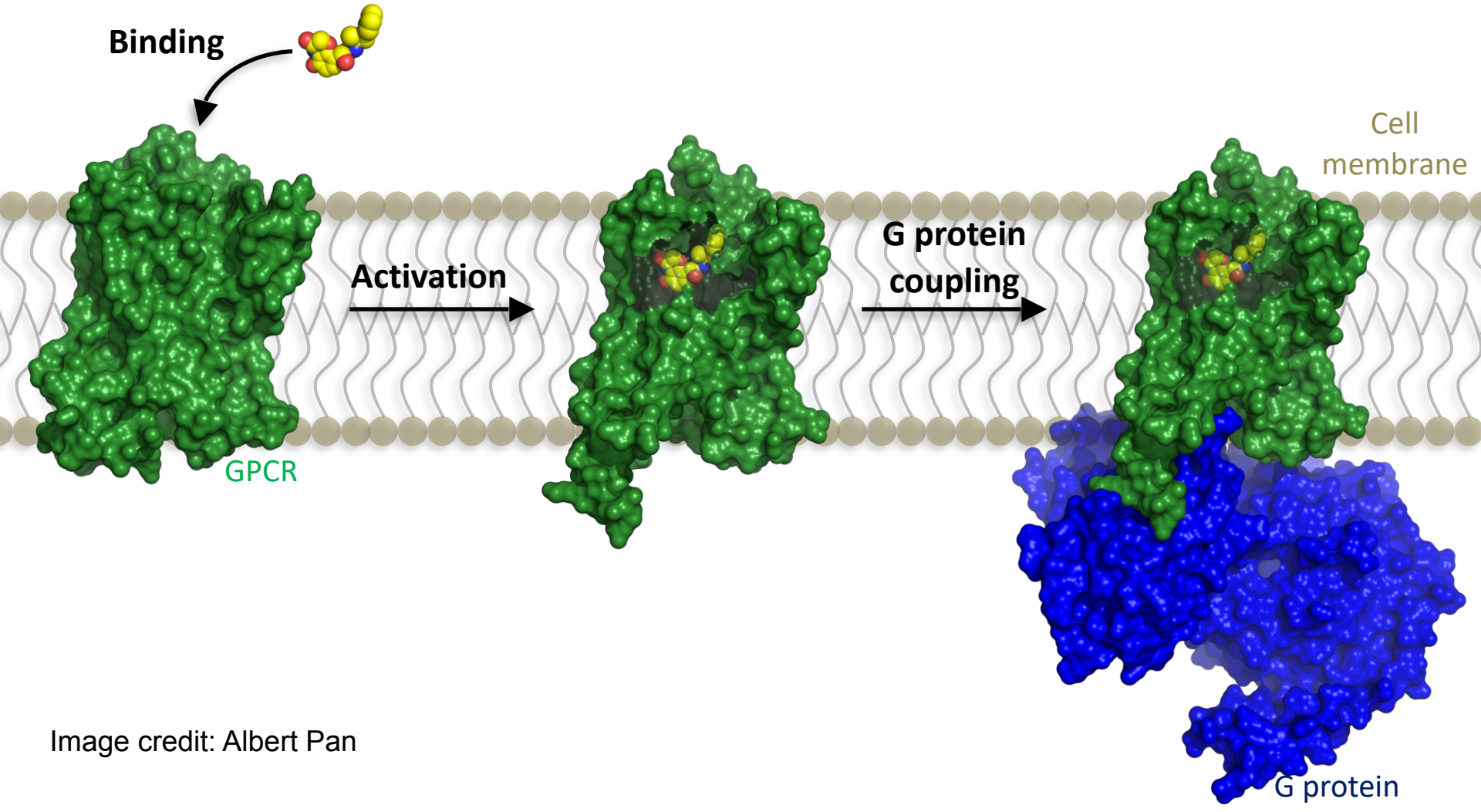
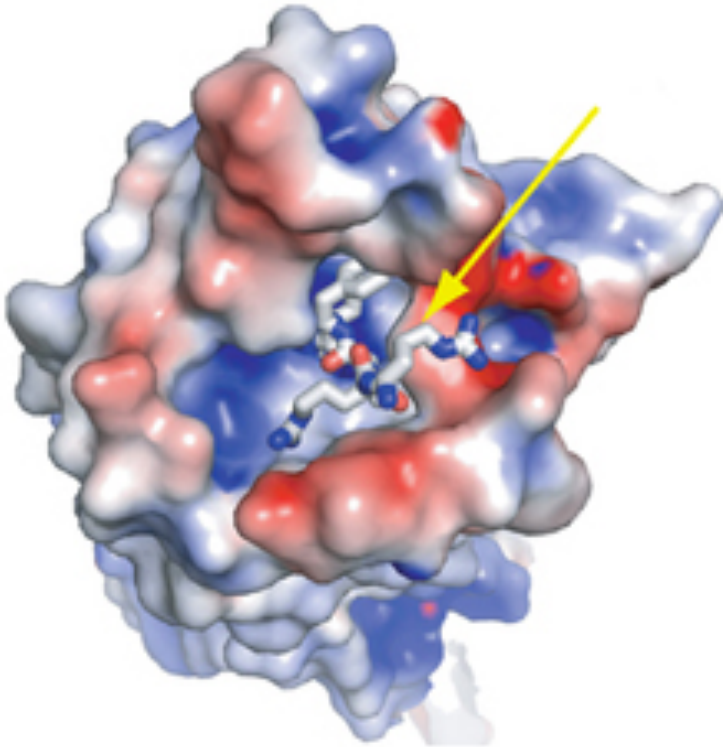


Image credit: Albert Pan

Structure-based drug design

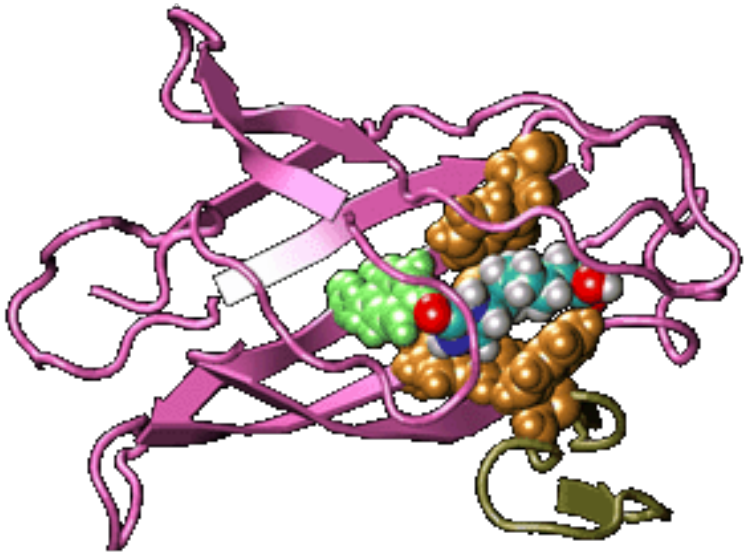
- Almost all drugs act by binding to proteins and altering their function
- Using knowledge of structures, we can design drugs that bind tightly to the desired protein, alter behavior of the protein in a desired way, avoid binding to other proteins, etc.



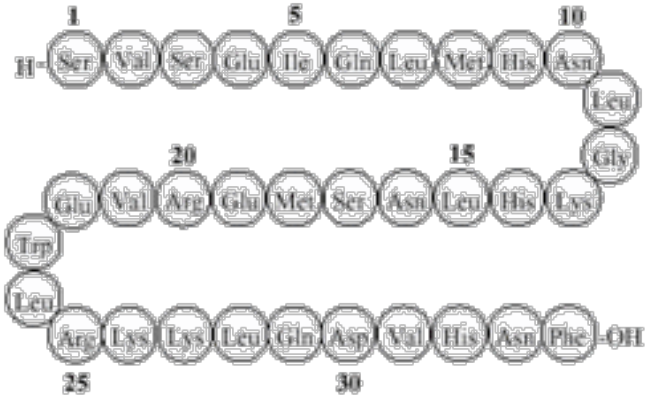
http://www.nih.gov/researchmatters/october2012/images/structure_l.jpg

Designing new biomolecular machines

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



How?



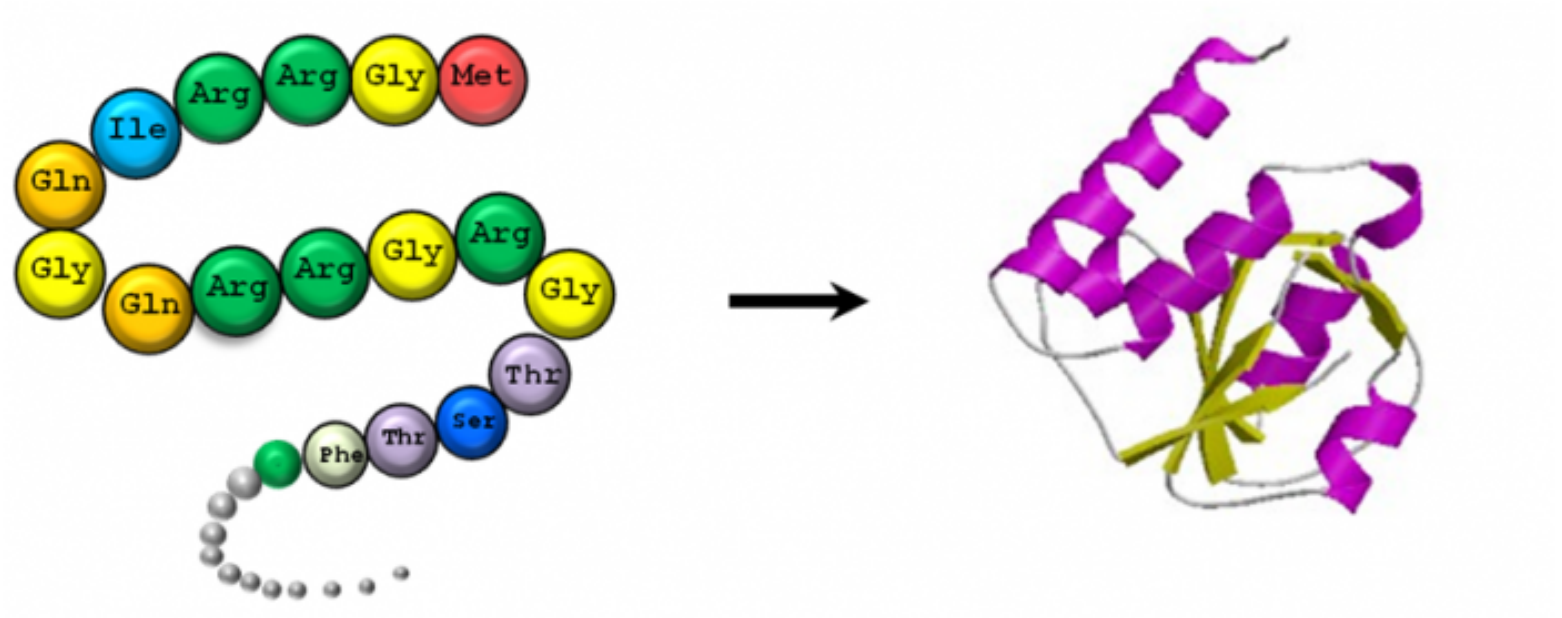
Additional research is being done on how to design other biomolecules like RNA and even cells

http://zhanglab.ccmb.med.umich.edu/image/Protein_design.gif

Overview of topics we'll cover

Biomolecular structure prediction

- Example: Protein structure prediction (“folding”)
  - Given the sequence of amino acids that make up a protein, predict its 3D structure



We are interested in what is the average structure (since these bio-machines are dynamic)

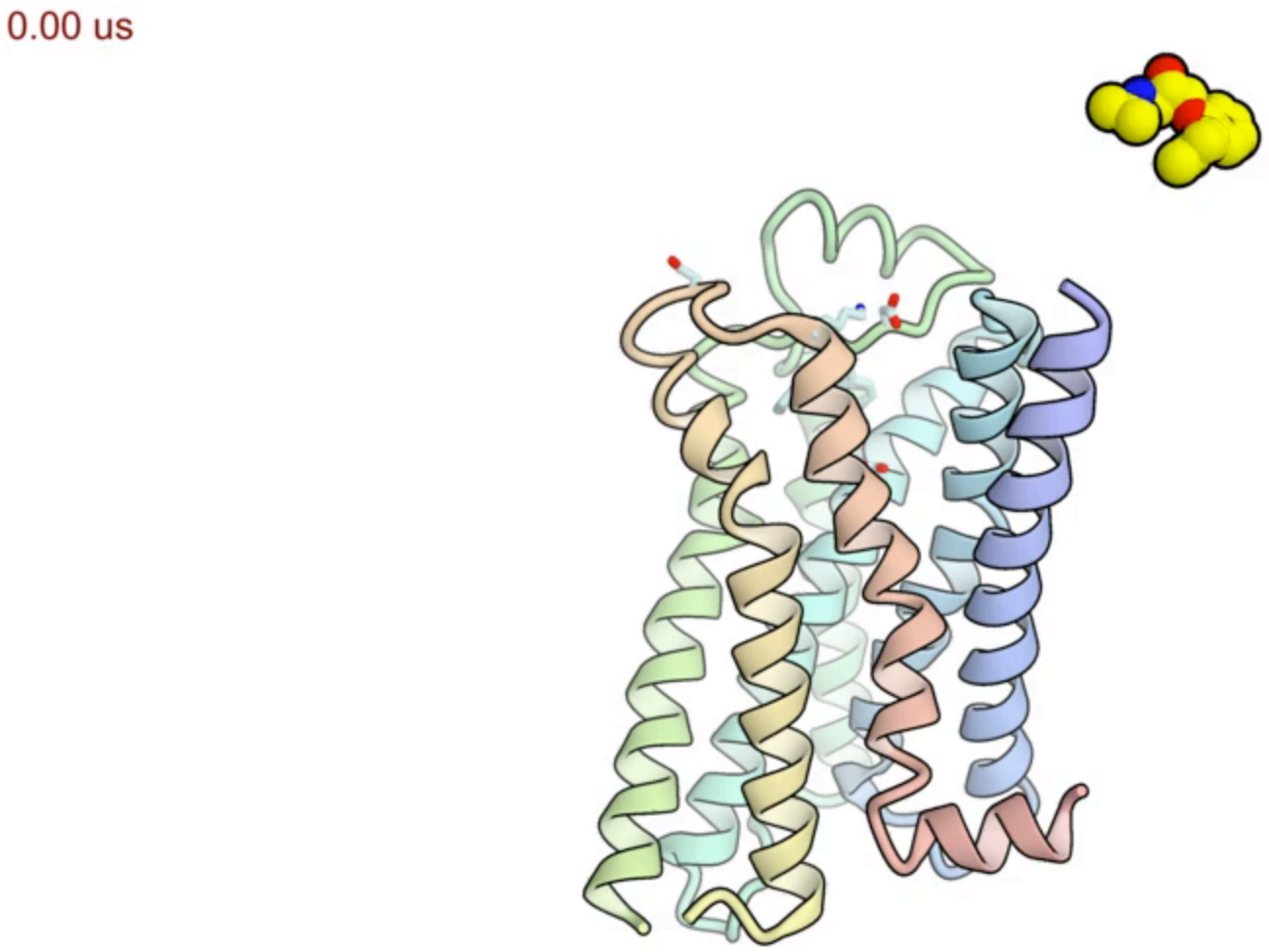
Image source: https://newenergyandfuel.com/wp-content/uploads/2014/09/Polypeptide-Chain.png

Biomolecular structure prediction

- Equally important, but usually harder: predict structures of other biomolecules (e.g., RNA), and of multi-molecule complexes

Raphael Townshend, Stephan Eismann, Andrew Watkins, Ramya Rangan, Maria Karelina, Rhiju Das, and Ron Dror. Geometric deep learning of RNA structure. *Science* (Aug. 27, 2021)

Molecular dynamics simulations



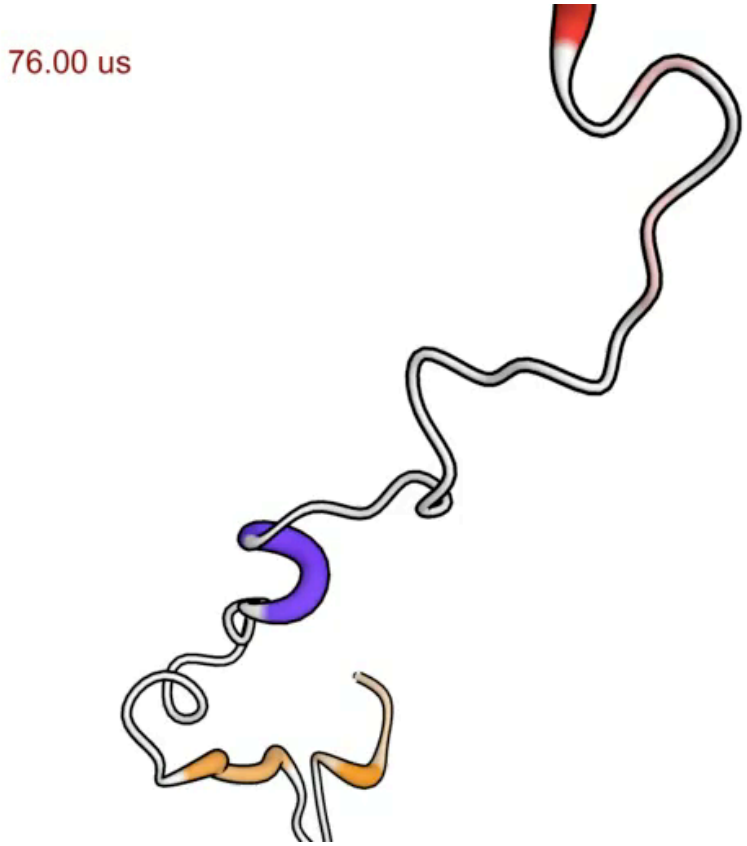
Beta-blocker binding to the β_2-adrenergic receptor

Beta blockers are typically used for treating heart conditions.

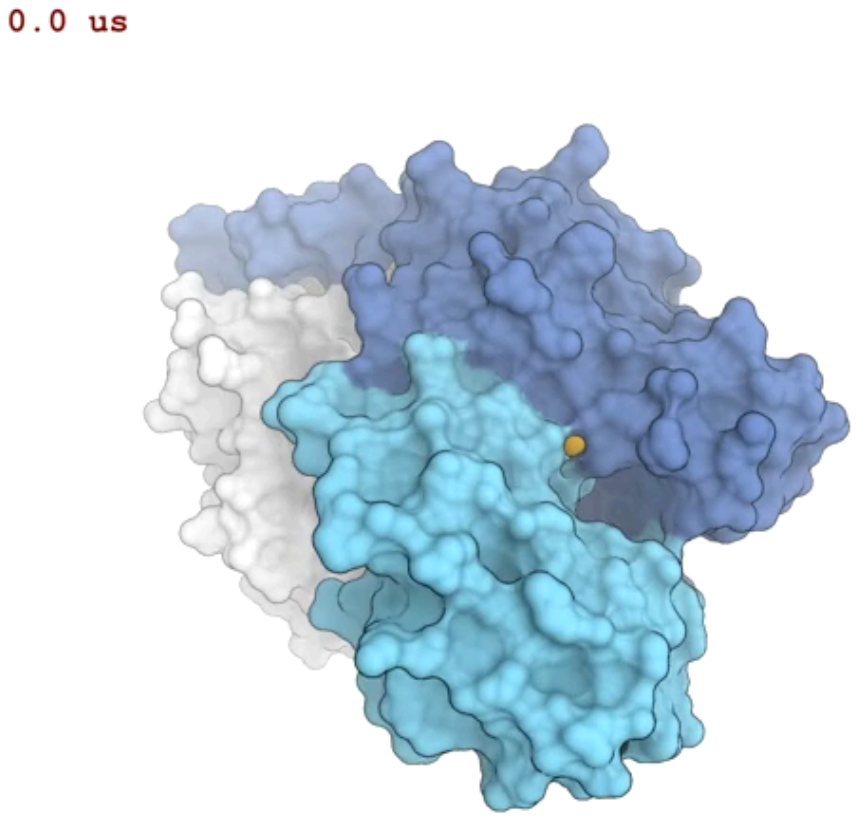
Dror et al., *PNAS* 2011

Computers take information on forces acting on and exerted by atoms to create these simulations

Molecular dynamics simulations



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



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

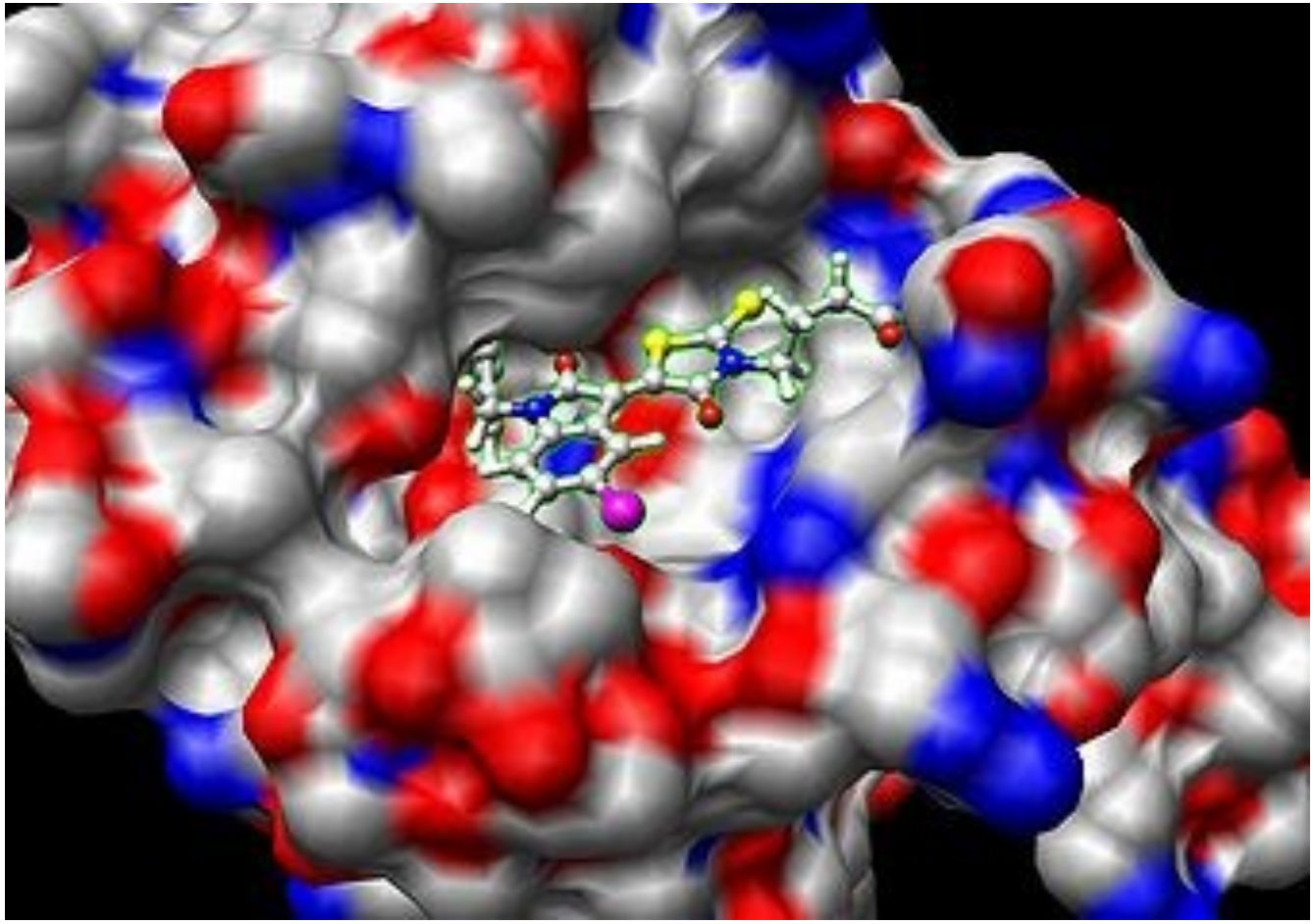
Protein design

- Given a desired protein structure (or function), design an amino acid sequence that achieves it

Divine *et al.*, Designed proteins assemble antibodies into modular nanocages. *Science* 372:eabd9994 (2021)

Ligand docking

Searching for potential drug molecules that bind to a target (usually a protein), and determine how they bind

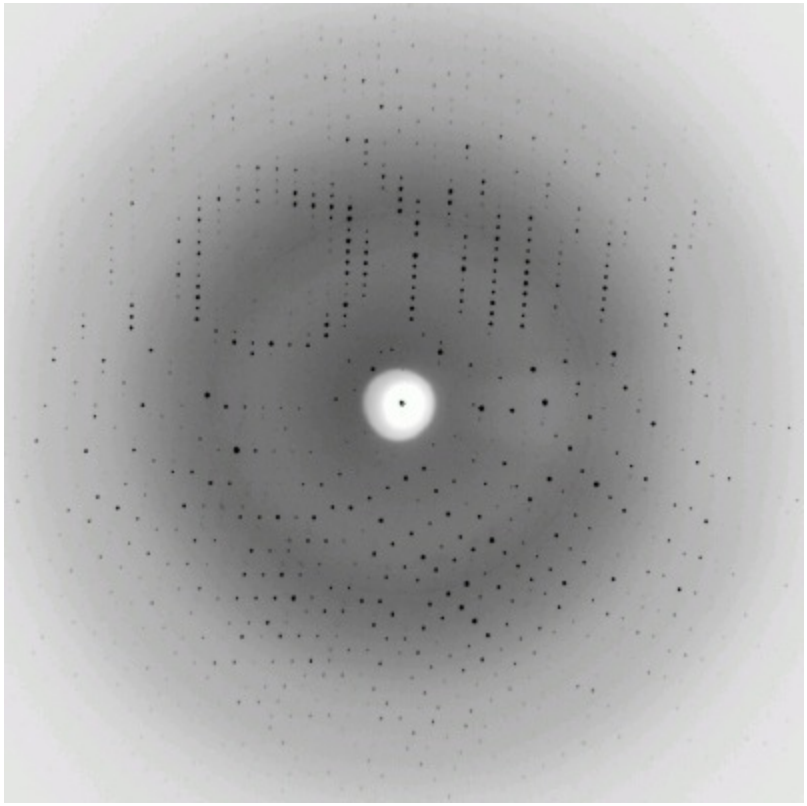


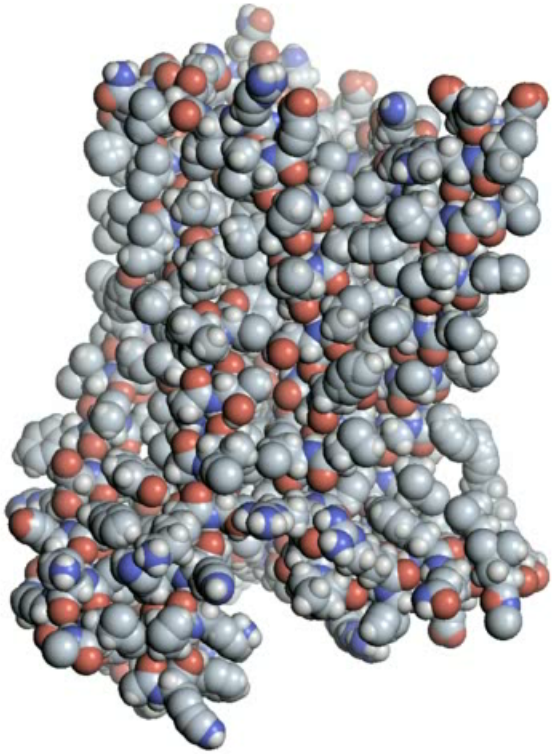
Pharmaceuticals use virtual drug screening to which potential drugs could be effective

Image: Wikipedia

Determining molecular structures experimentally also requires solving challenging computational problems!

Determining molecular structures by crystallography





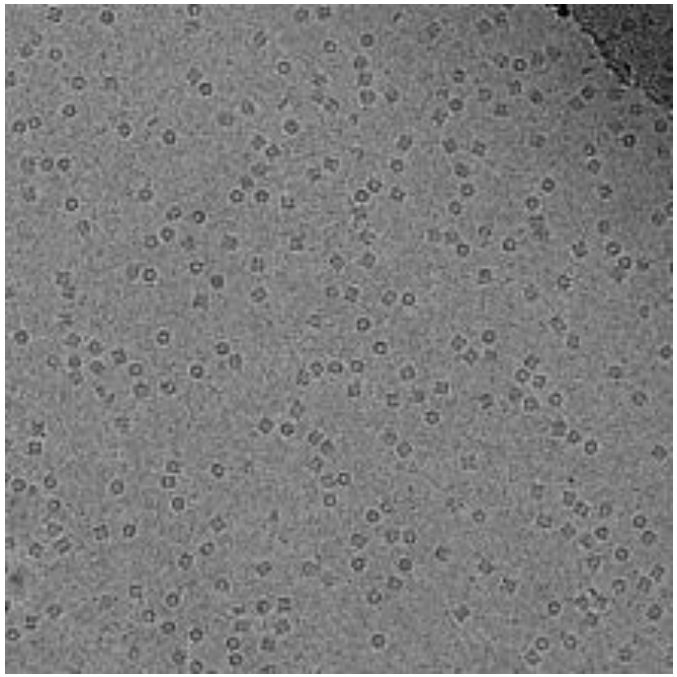
X-ray diffraction pattern

Protein structure

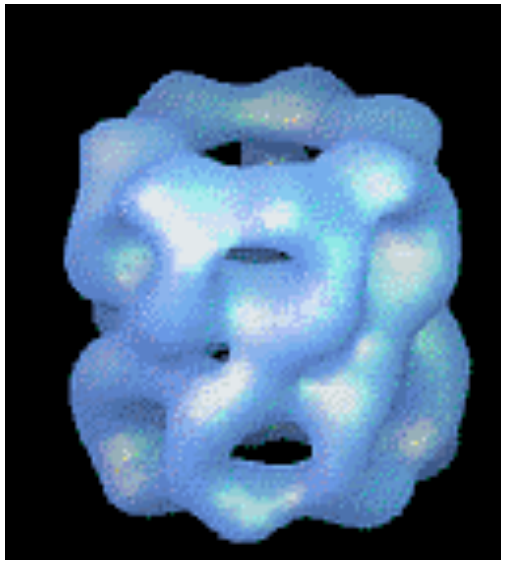
Image: http://www.chem.ucla.edu/harding/IGOC/X/x_ray_crystallography.html

Determining molecular structures by cryogenic electron microscopy (CryoEM)

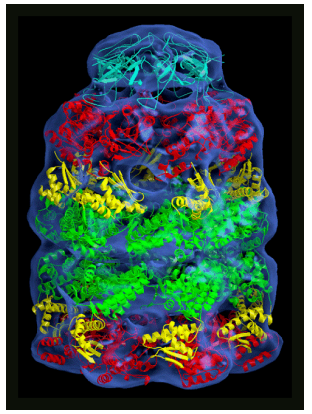
Each dot corresponds to one molecule. The challenge is to take these dots and reconstruct the atomic structure of the biomolecule



CryoEM image



Reconstructed envelope

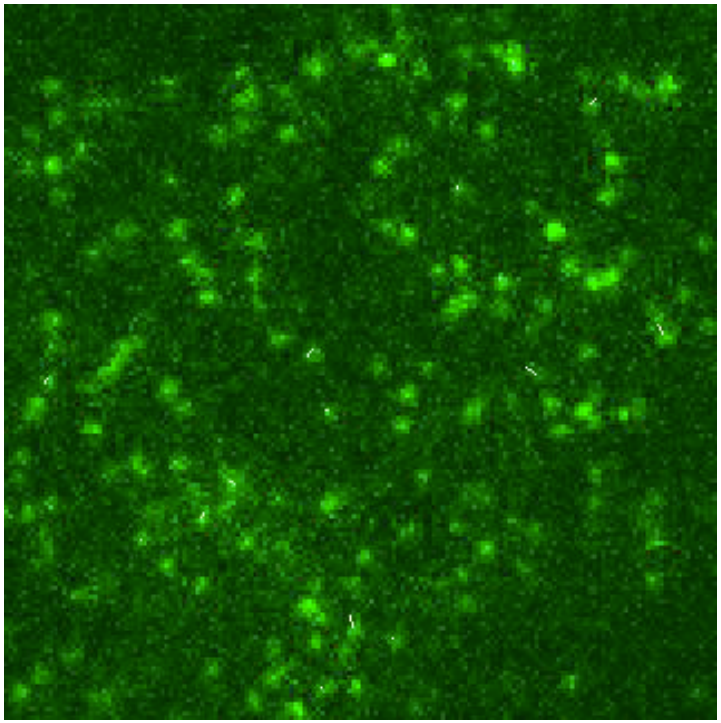


Structure

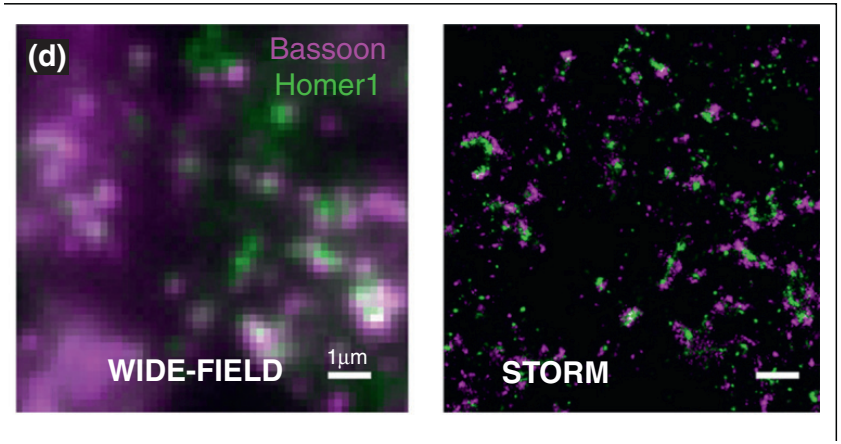
Image: Wikipedia

Image: http://people.cryst.bbk.ac.uk/~ubcg16z/chaperone.html

Fluorescence microscopy and cellular-level organization



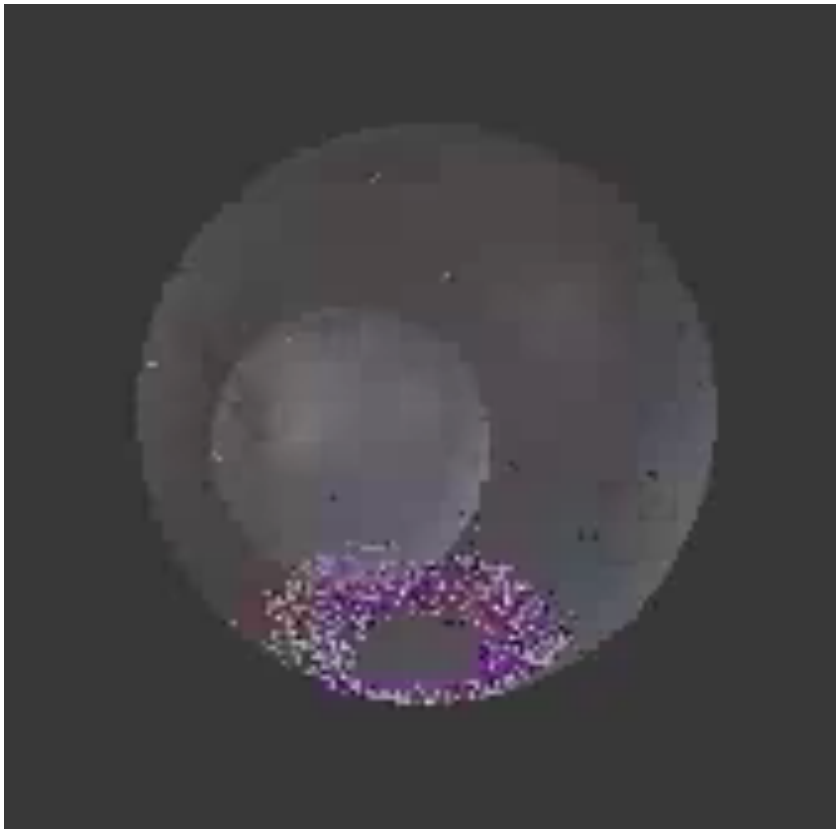
Data: Bettina van Lengerich, Natalia Jura
Tracking and movie: Robin Jia



Sigrist & Sabatini, Current Opinion in Neurobiology 22:1-8, 2011

- Including super-resolution microscopy

How molecules move about a cell: diffusion and cellular-level simulation



Video: Naomi Latorraca

We'll also cover important underlying computational methods

- Machine learning
  - Supervised and unsupervised
- Image analysis
- Sampling from probability distributions

Previous familiarity with these concepts is not required!

Notes on course contents

- Course split roughly in two parts
  1. Atomic-level modeling of biomolecules
  2. Coarser-level modeling and imaging-based methods

- Focus will be on fundamentals, but most lectures will also cover topics of current research

- Some overlap in content with CS 274 (BIOE/BMI/GENE 214), but only about 20%.
  - This class (CS 279) is focused on structure. Much of CS 274 covers other bioinformatics topics.
  - Many students take both classes, in either order.
  - You can take both simultaneously if you wish. (Class times don't actually conflict.)

Recurrent themes

Recurrent themes

- **Physics-based approaches** (modeling based on first-principles physics) vs. **data-driven approaches** (machine 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
- Similarities and differences in methods employed at **different spatial scales**
- **Energy functions** (which associate an energy or potential with each possible structure)
- Recurring math concepts: **Fourier transforms, convolution, Monte Carlo methods**

Course logistics

Course website

- http://cs279.stanford.edu/
- See “Course policies and evaluation criteria” document on website
- To view last year’s lecture slides, follow “Fall 2020” link on website
  - This year’s content will be similar but not identical

Course announcements

- We will use Ed Discussion (accessible via link from course web page) for (1) announcements and (2) answering students questions
- If you're not enrolled in the class, email cs279staff@cs.stanford.edu to be added to Ed Discussion
- A survey on office hour preferences will go out soon via Ed Discussion

Expected background

- Course is intended to be broadly accessible to students with *either* computational or biological backgrounds

- Assignments involve basic programming in Python
  - You need not have used Python before. You should have done some programming (in any language) before.
  - Python tutorial: see website for time. It will be recorded so that you'll be able to view it later as well.

- You should have some previous exposure to biology, chemistry, and physics (at least in high school)

- You should have studied math through elementary calculus
  - We will teach some additional relevant math concepts (e.g, Fourier transforms), with a focus on basic ideas/intuition rather than on equations.

Assignments and Exam

- Assignments
  - First three cover specific topics.
  - Fourth is a more open-ended “project.”
  - First assignment is substantially shorter than second and third. For the project, we expect only a bit more work than the second and third assignments.
  - See collaboration policy under “Course policies” on web page.

- Exam covering key concepts

Lectures

- Lectures will not be recorded. Lecture slides will be available (with annotation) on website, along with additional notes for some lectures and pointers to optional reading material.
  - I will try to keep lectures to 80 minutes (i.e., end class at 3:35 pm).

- Missing some lectures is fine.
  - For lectures you miss, read through the annotated lecture slides. TAs can explain anything that's not clear to you during office hours.

- Class participation encouraged!
  - We won't take attendance.
  - You can earn extra credit for participation (in class, or by answering other students' questions on Ed Discussion), but this isn't required to get an A or even an A+.

Feedback welcome!

- I want to continue improving this course, and would appreciate your suggestions
- Please speak up when you don’t understand something

COVID-19 safety

- Per Stanford requirements, **masks are required**
  - You can take your mask off very briefly to sip water. Do not talk while it's off.
  - No eating in class.
- COVID-19 vaccination required
- COVID-19 surveillance testing required at least weekly

Course staff

- Prof. Ron Dror
  - http://drorlab.stanford.edu/rondror.html
  - Office hours: After every class, outside the classroom

- TAs:
  - Ben Parks
  - Ayushi Tandel
  - Hikaru Hotta
  - Jacklyn Luu

  - Office hours and contact info at cs279.stanford.edu