

CS/CME/Biophys/BMI 279

Computational biology: Structure and organization of biomolecules and cells

*Image credit:
Ansgar Philippsen*



Sept 22, 2015

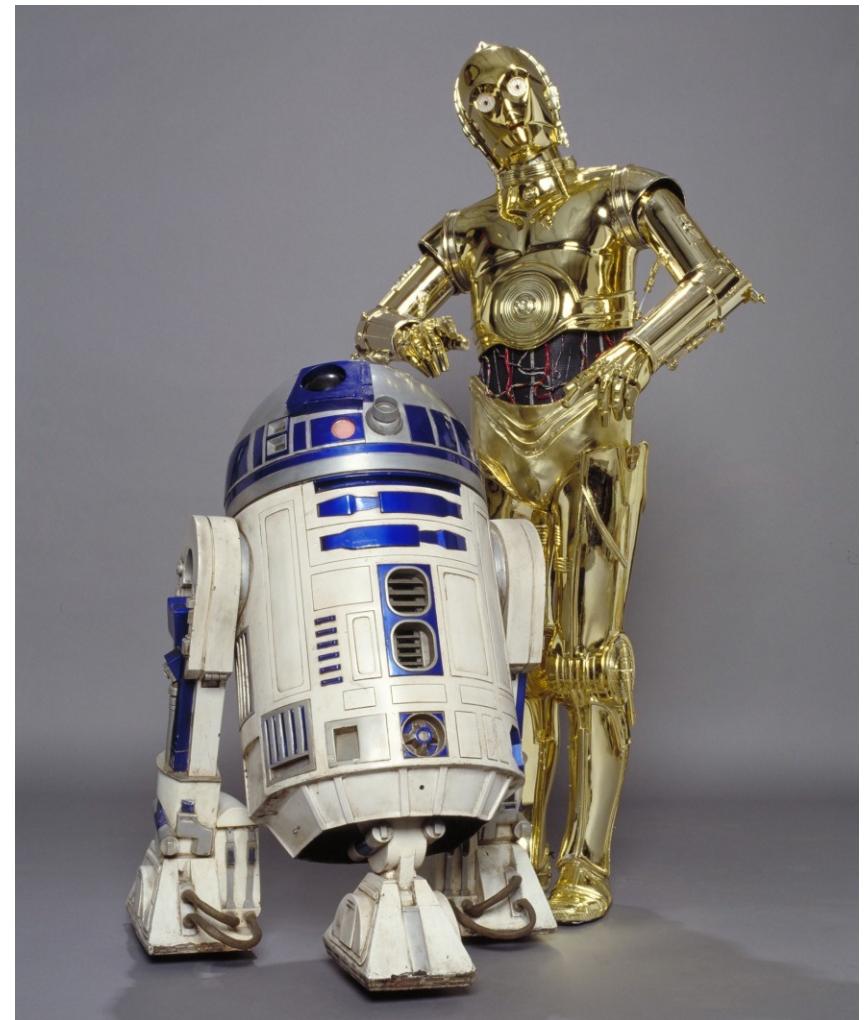
Ron Dror

Outline for lecture 1 (course overview)

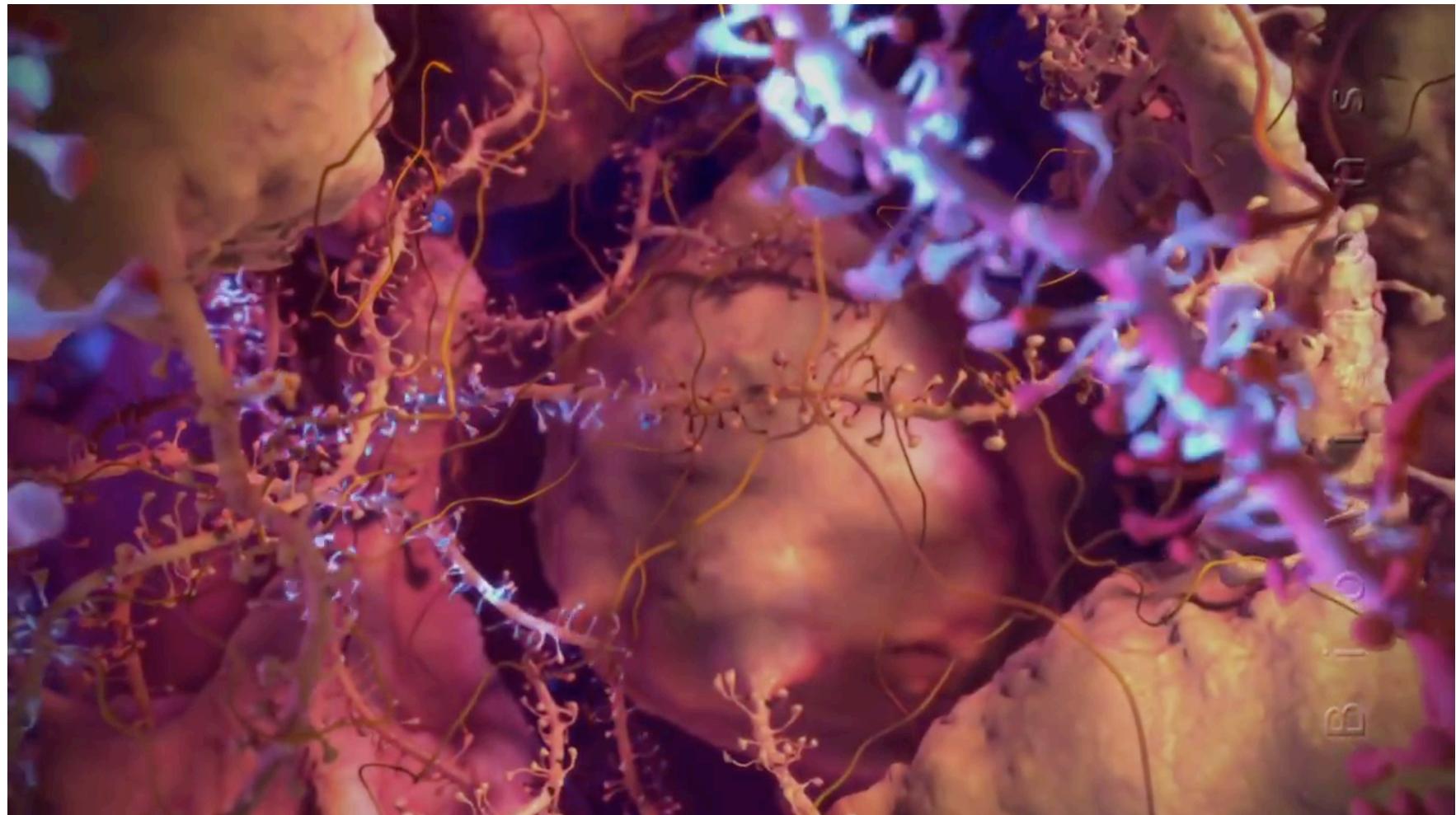
- What is structure?
 - Structure (and dynamics) at multiple spatial scales
- Why is structure important?
- How computation helps: An overview of course topics
- Recurrent themes
- Course logistics

What is structure?

In daily life, we use machines
with functional structure and *moving parts*



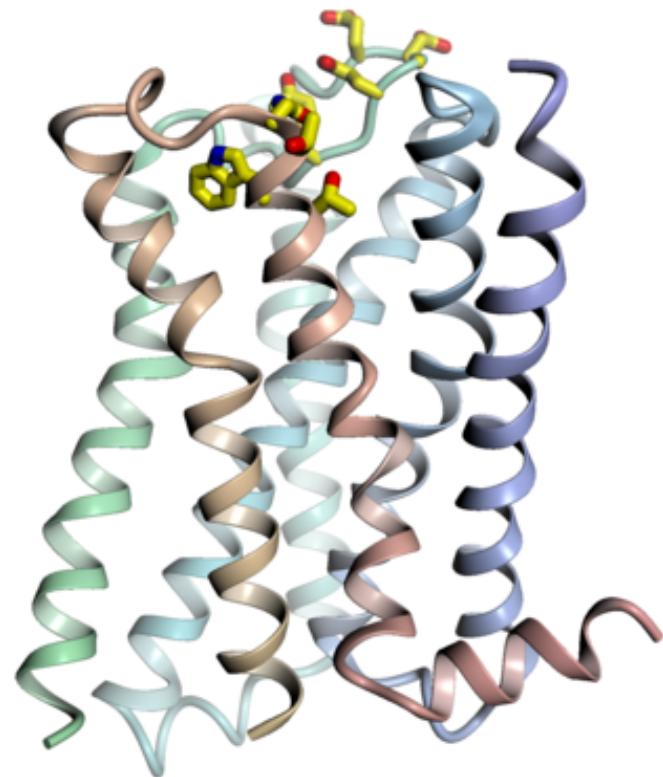
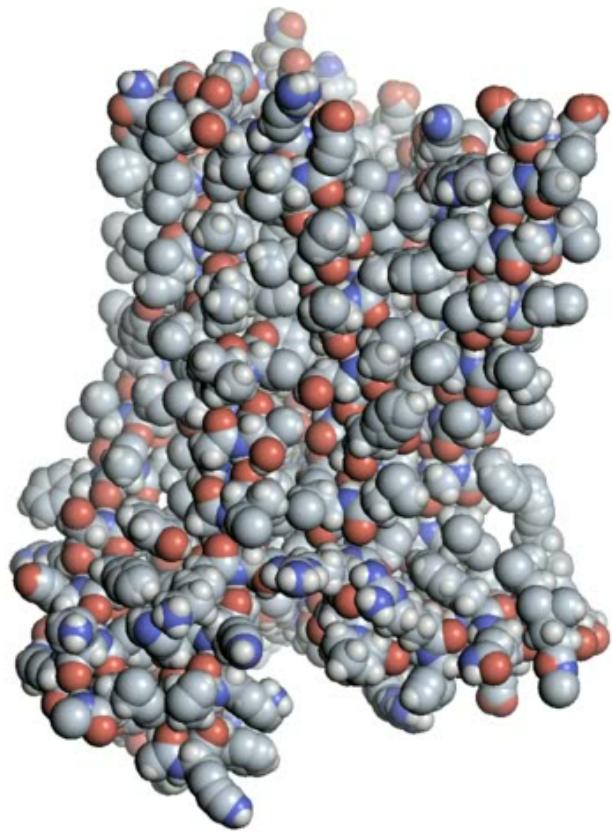
Cells and biomolecules (e.g., proteins) are also machines whose function depends on structure and moving parts



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

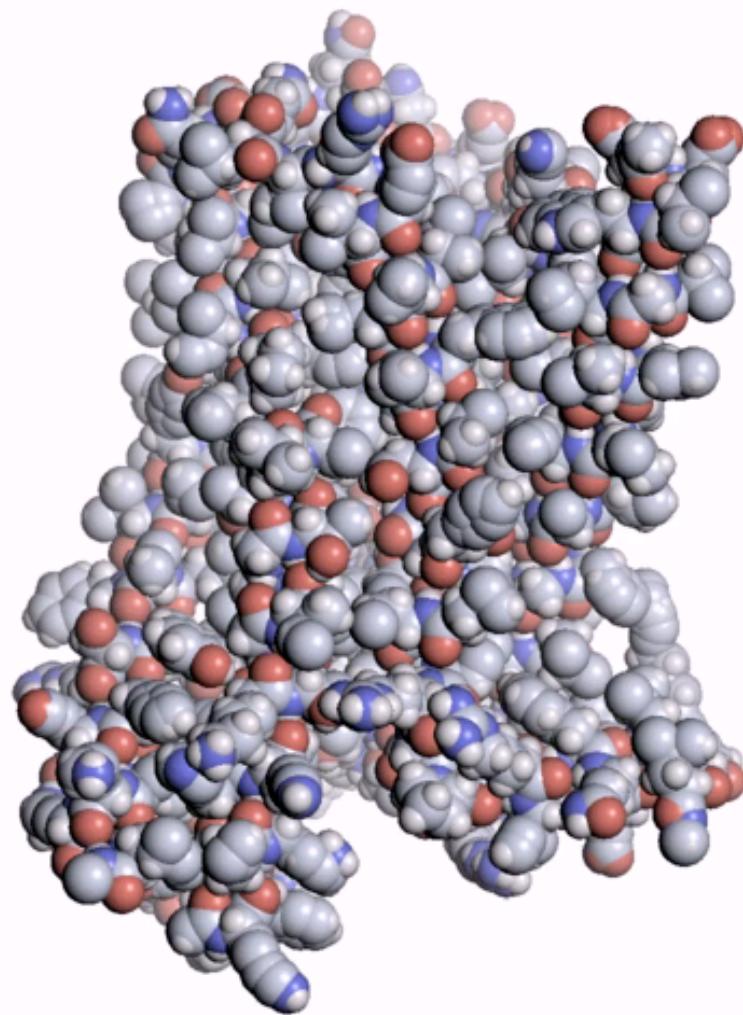
Structure (and dynamics)
at multiple spatial scales

Protein structure



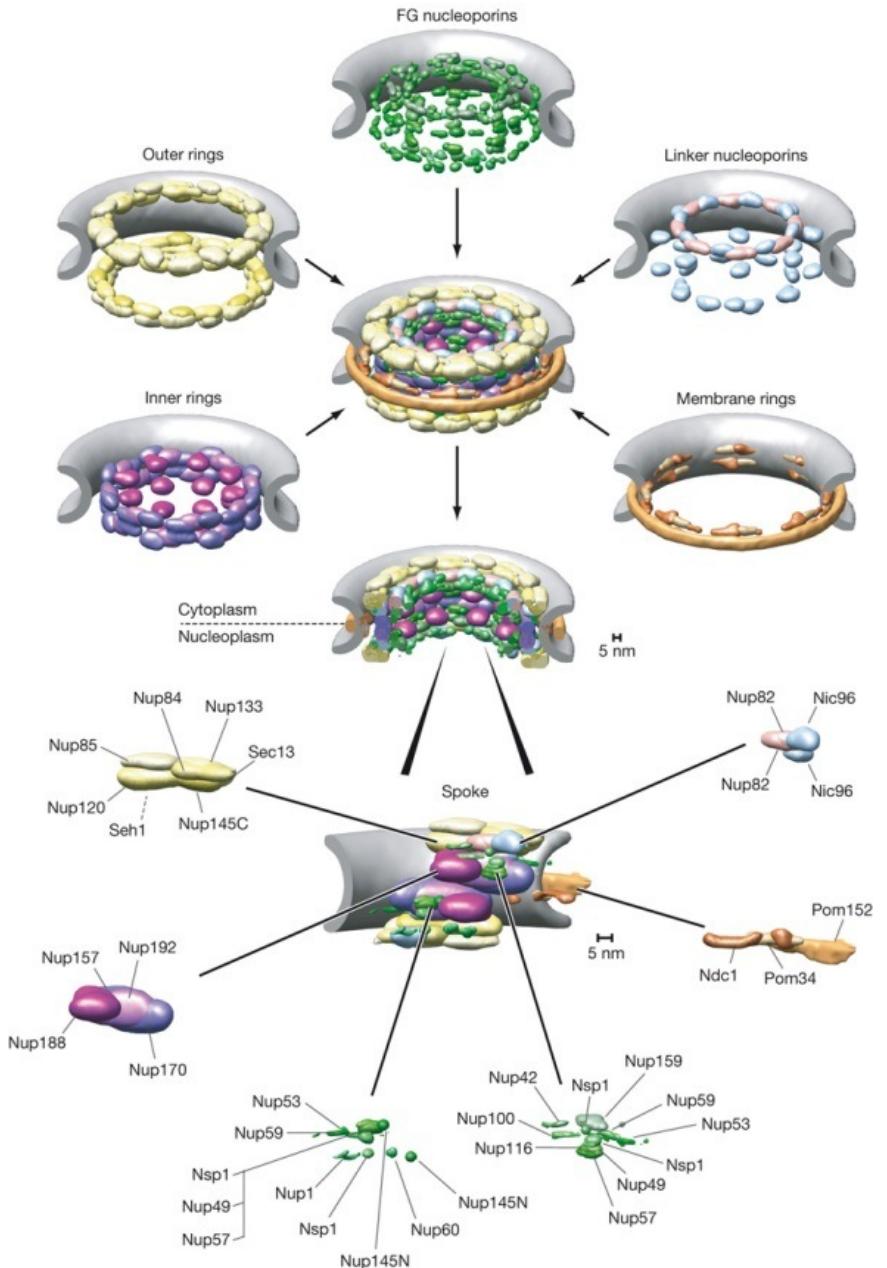
An adrenaline receptor
(the β_2 adrenergic receptor)

Protein dynamics



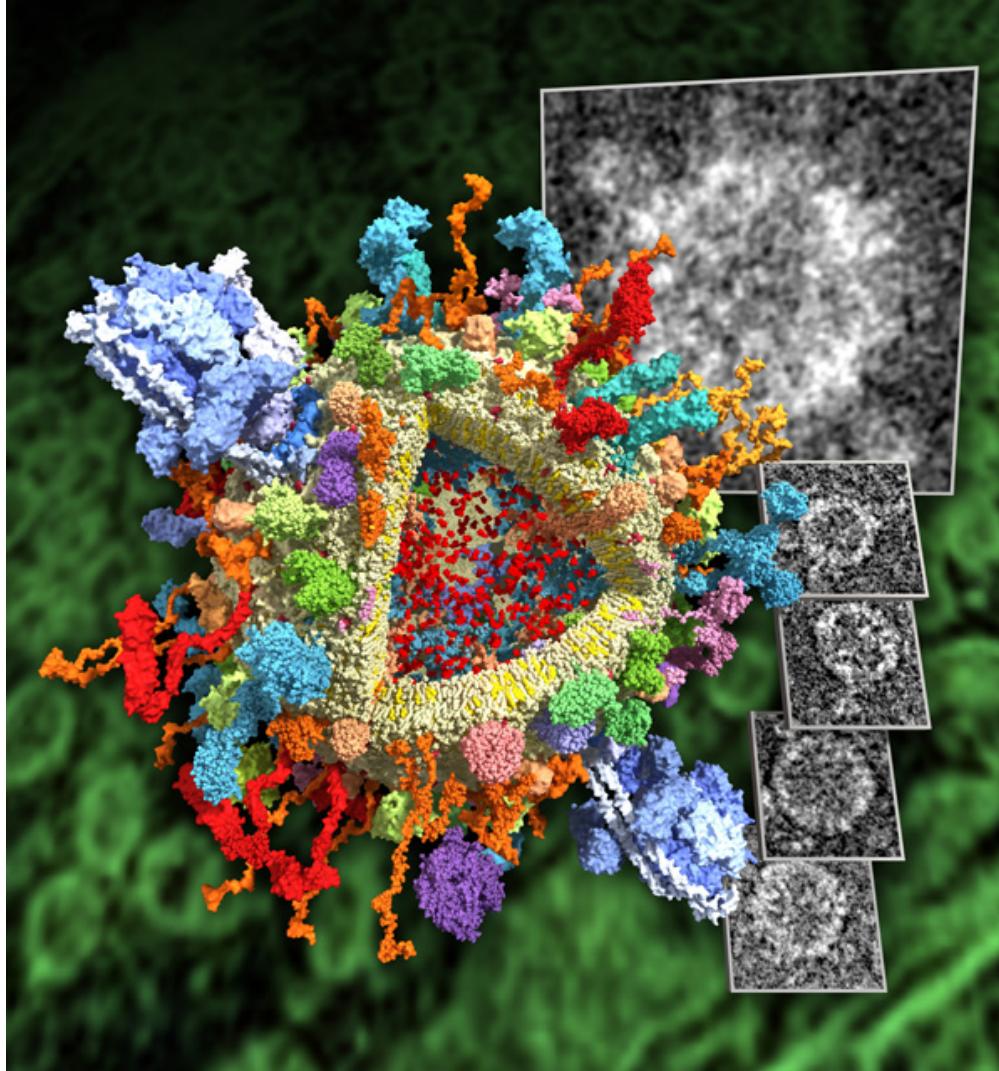
β_2 adrenergic receptor

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



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

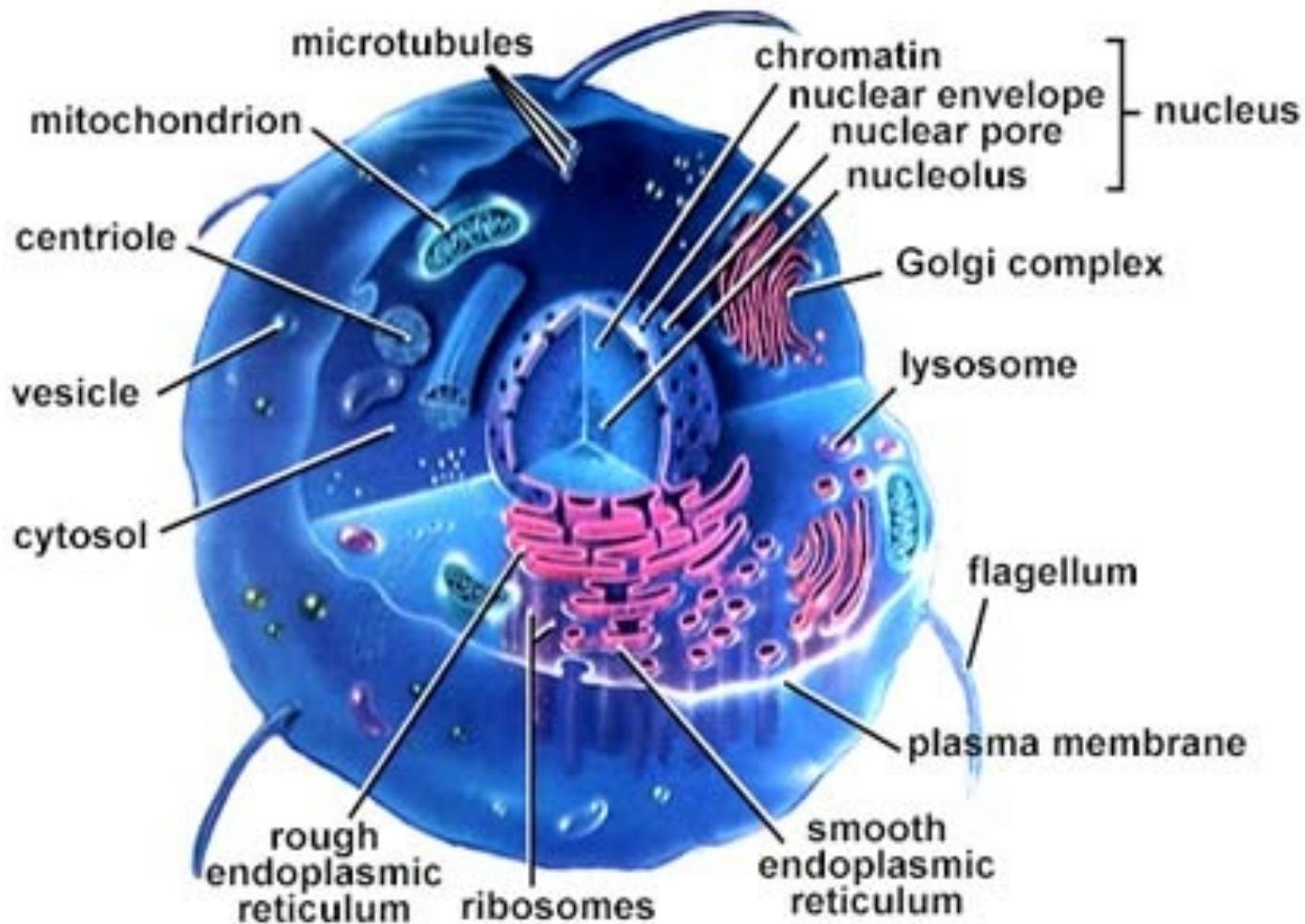
These come together to form organelles



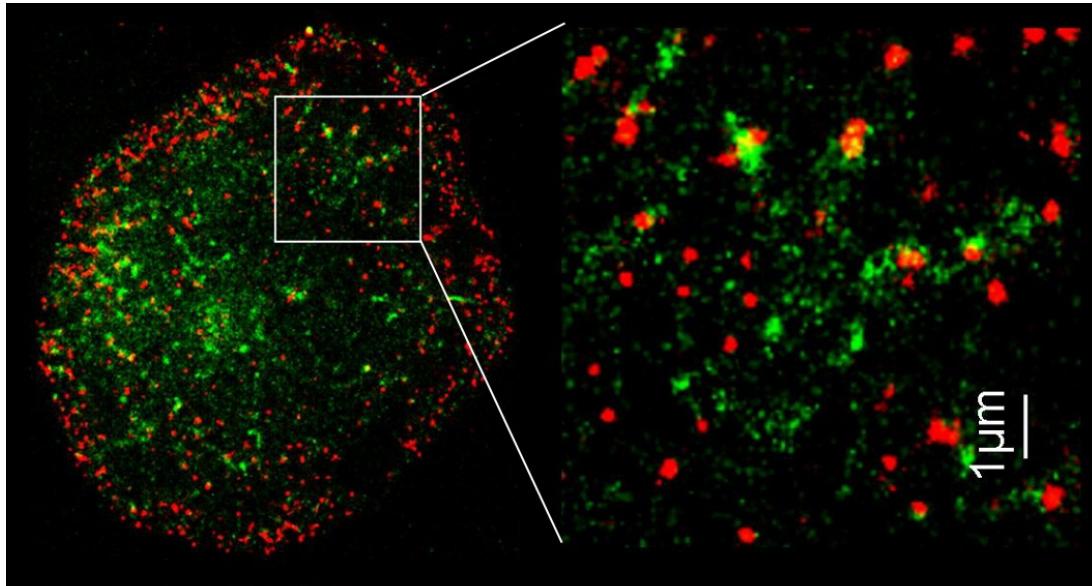
Synaptic vesicle

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

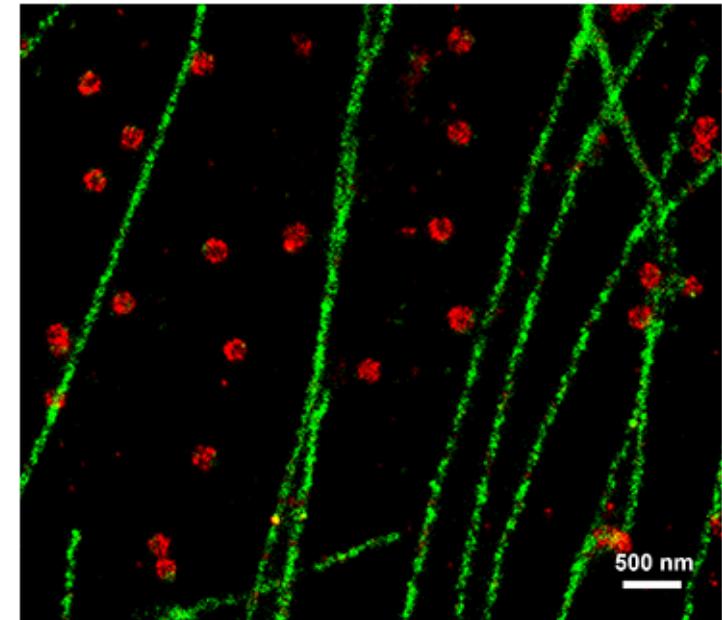
and cells



Intracellular structure



Chih-Jung Hsu, Janis
Burkhardt and Tobias
Baumgart



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

David Goodsell



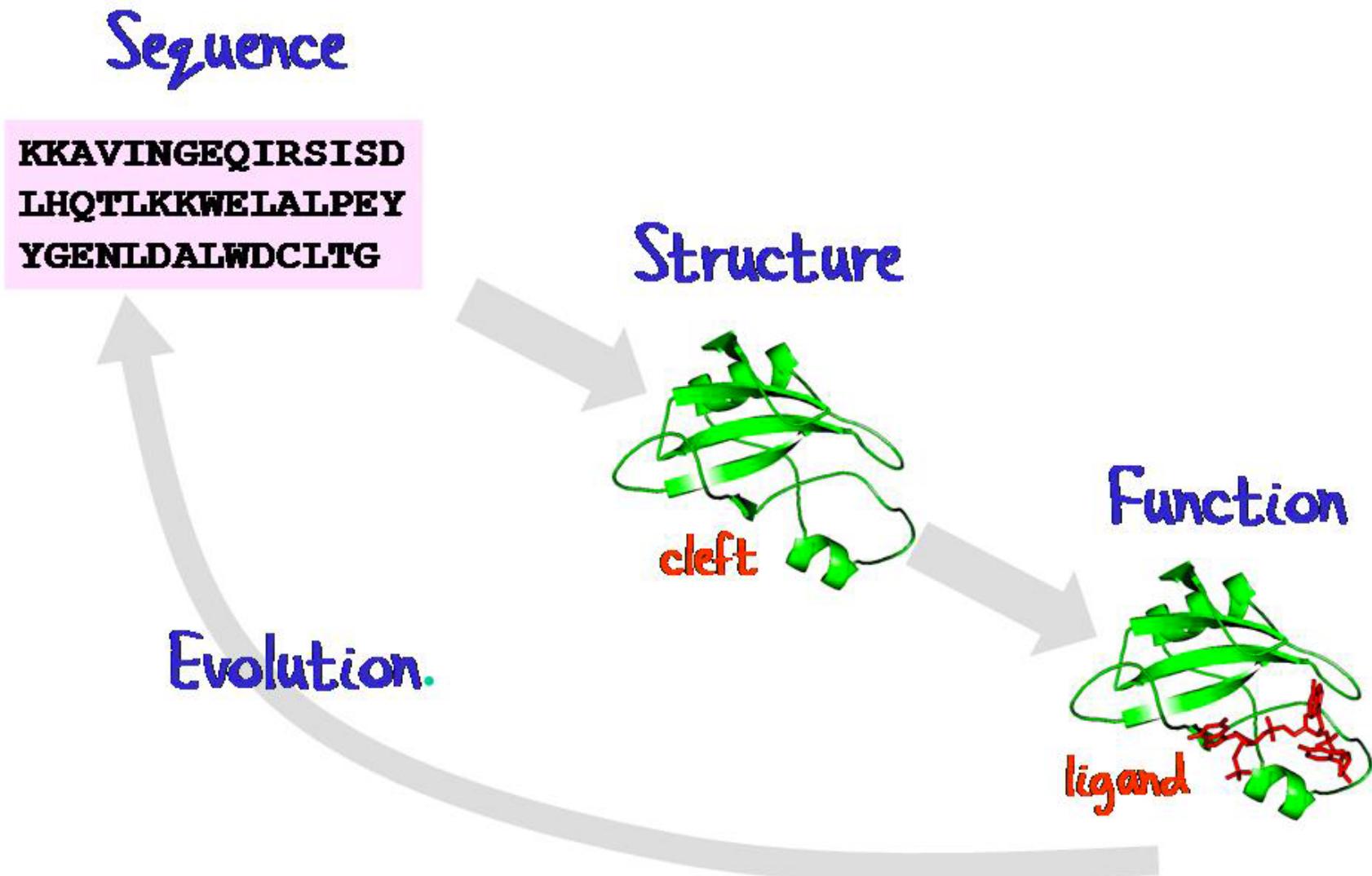
Intracellular dynamics (artist's rendition)



Janet Iwasa and Tomas Kirchhausen

Why is structure important?

The cycle of life



From Michael Levitt

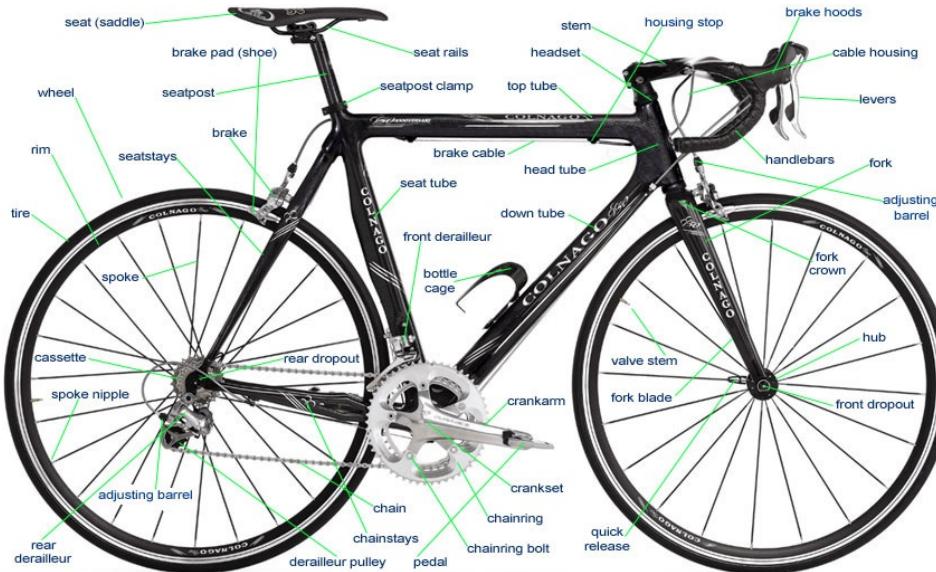
Genomics is a great start

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
16	145838	Cone for Sleeve
17	146473	L.H. Adjustable Cup
18	145833	Lockring
19	145239	Straps for Toe Clips
20	145834	Fixing Bolt
21	145835	Fixing Washer
22	145822	Dustcap
23	145823	R.H. and L.H. Crankset with Chainwheel
24	146472	Fixed Cup
25	145235	Toe Clips, Christophe, Chrome (Medium)
26	145684	Pedals, Extra Light, Pairs
27	123021	Chain
28	145980	Seat Post
29		Seat Post Bolt and Nut
30	167002	Saddle, Brooks
31	145933	Track Sprocket, Specify 12, 13, 14, 15, or 16 T.

- But a parts list is not enough to understand how a bicycle works

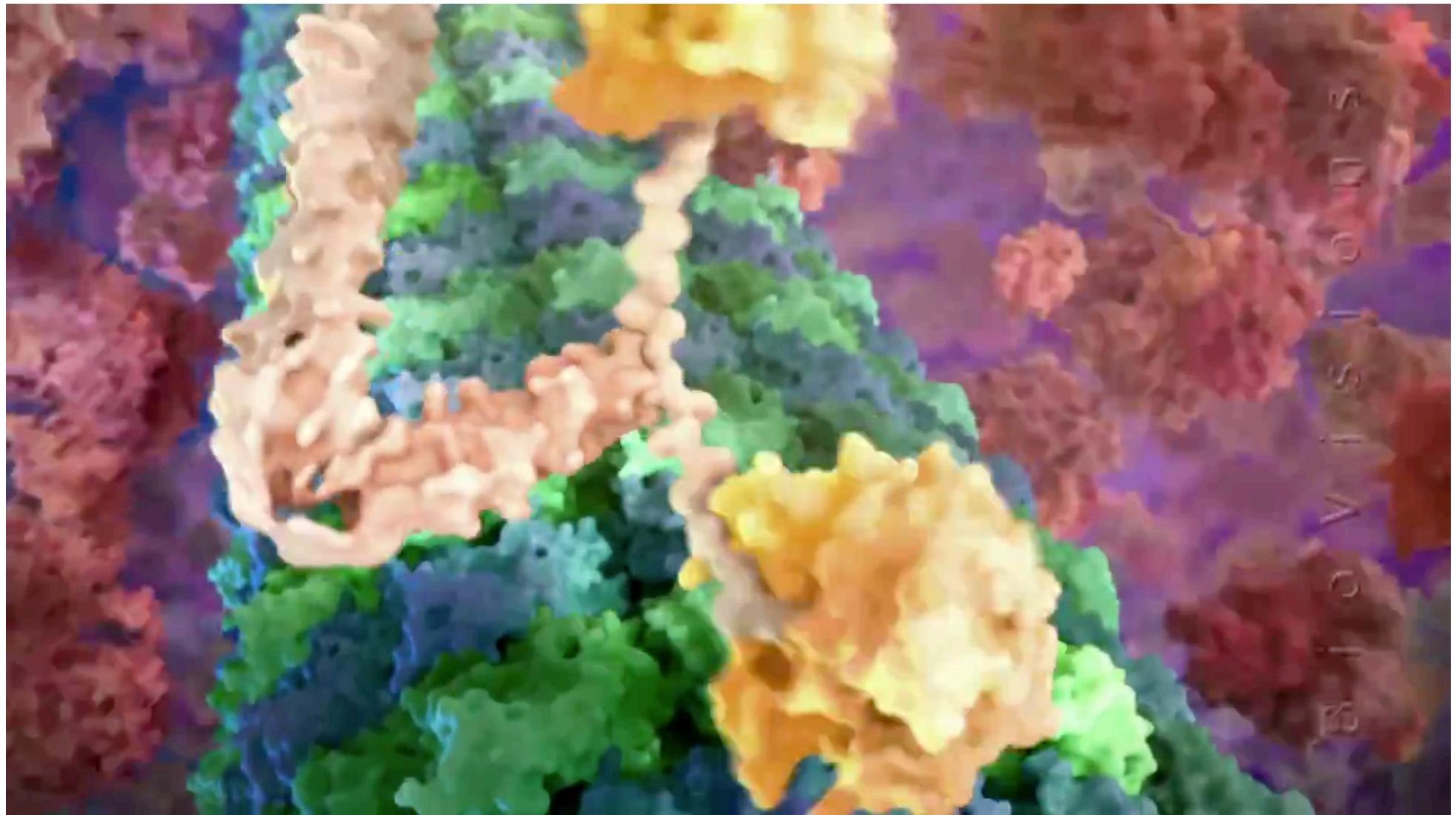
... but not the end



- 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

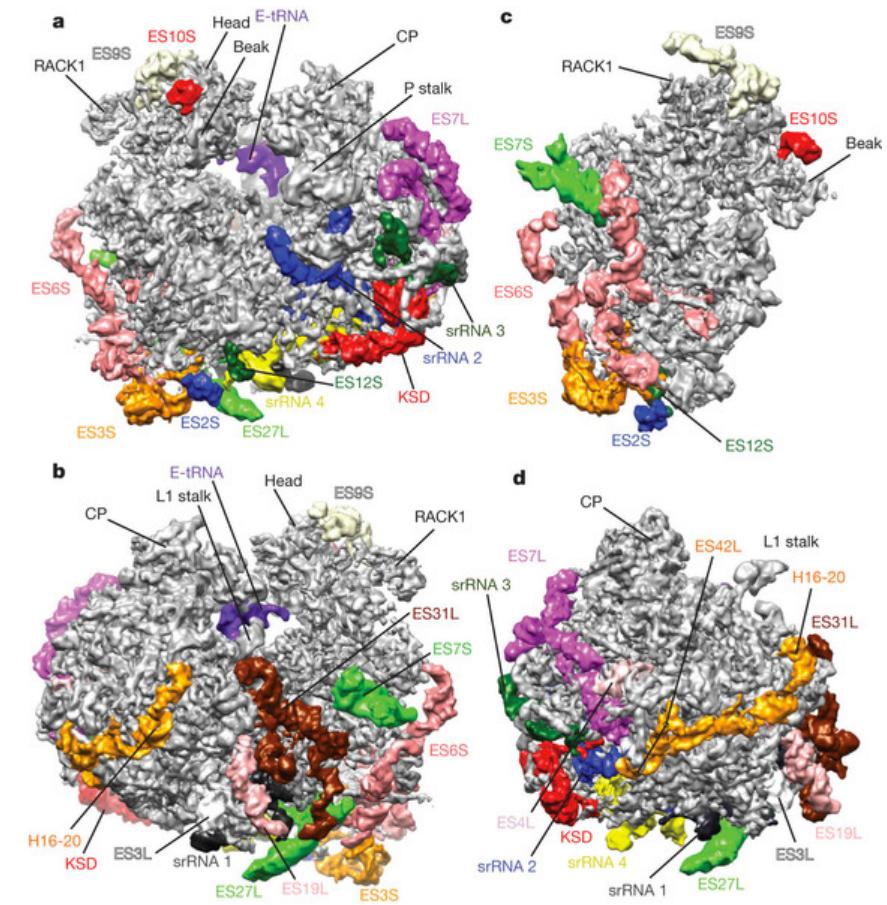
- Example: Motor protein (walks along microtubules, dragging load)



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)

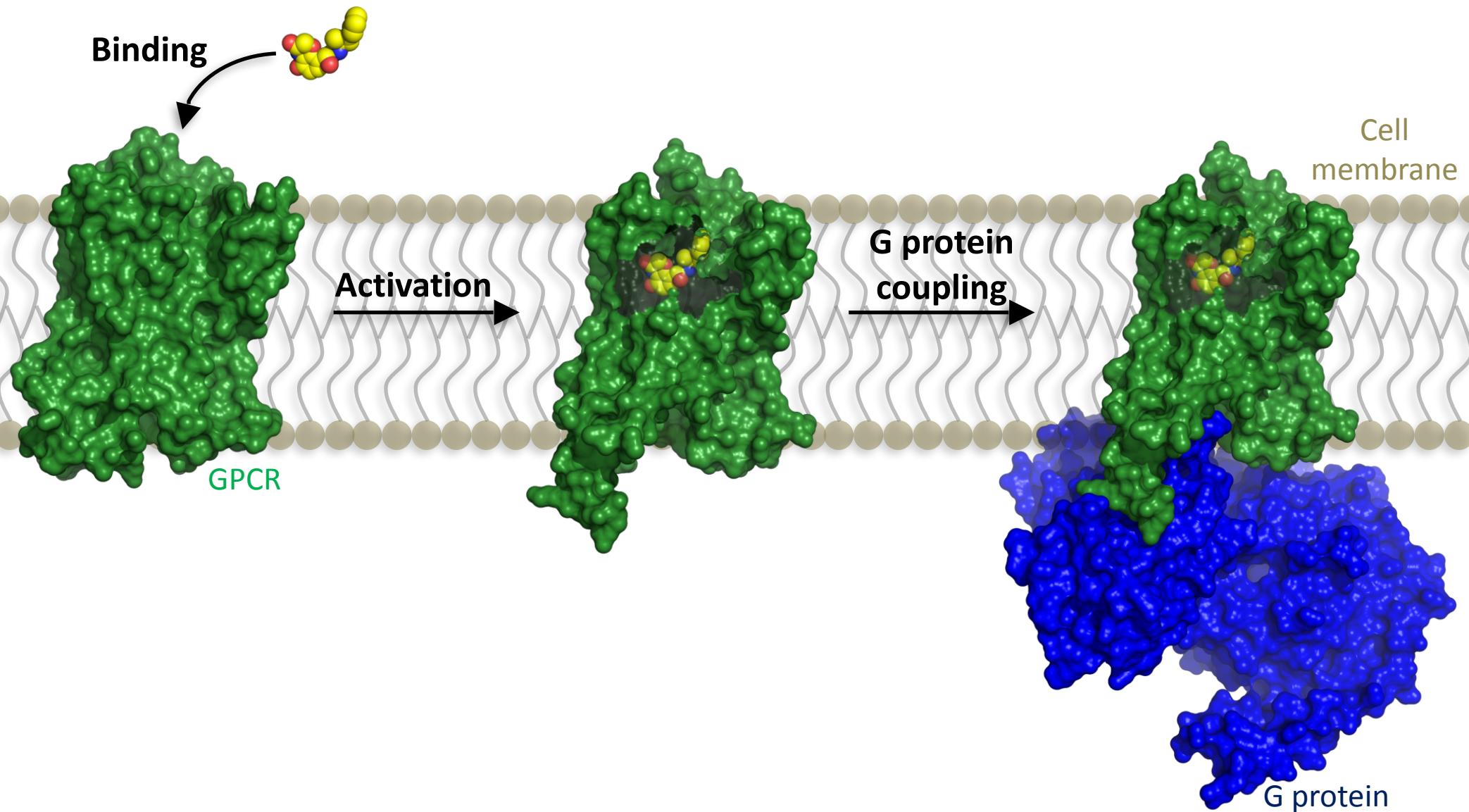


From *Inner Life of the Cell*, XVIVO and Biovisions @ Harvard

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

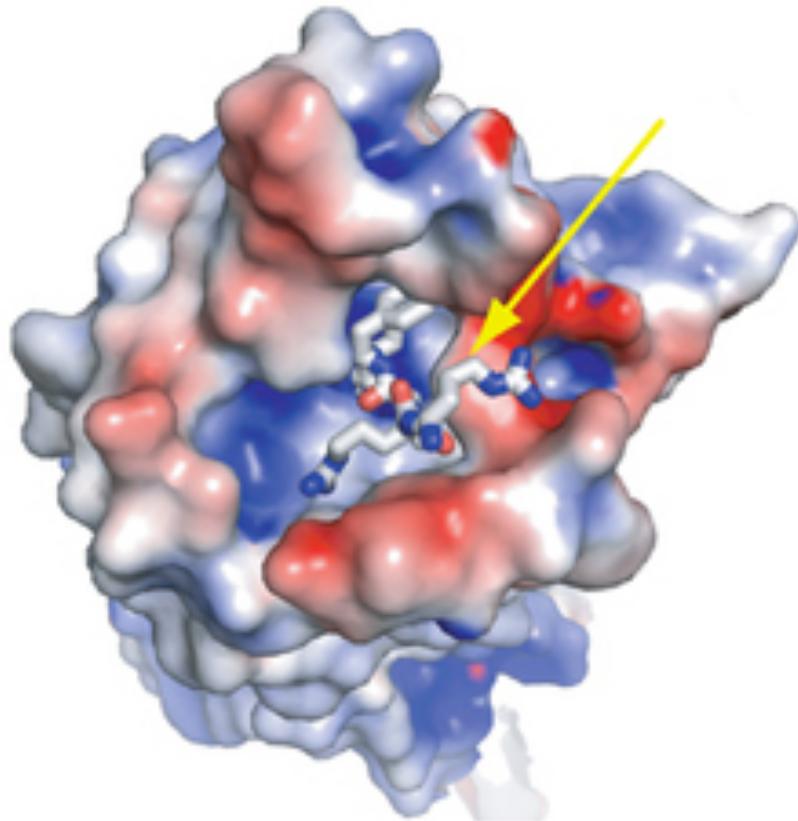
Structure determines function

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



Structure-based drug design

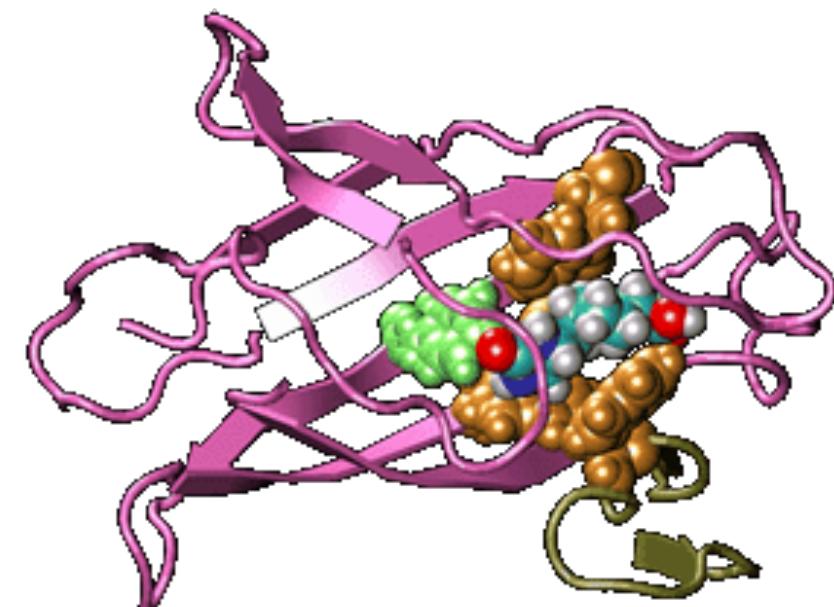
- Almost all drugs act by binding to proteins and altering their function
- Using knowledge of structures, we can design drugs that bind more tightly or more selectively, bind in different positions, alter behavior of protein in different ways, etc.



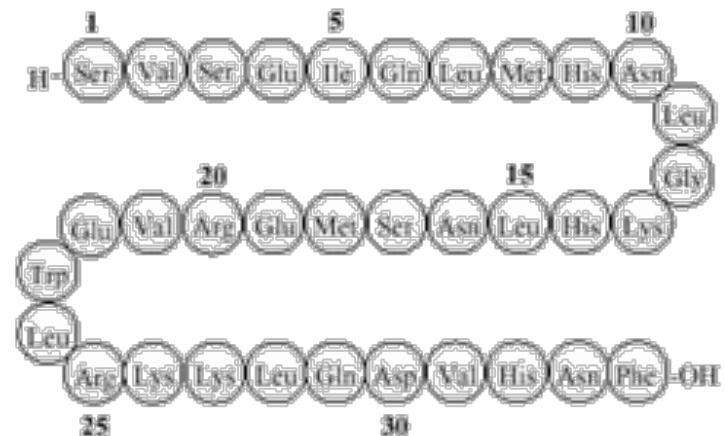
[http://www.nih.gov/researchmatters/
october2012/images/structure_l.jpg](http://www.nih.gov/researchmatters/october2012/images/structure_l.jpg)

Designing new biomolecular machines

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



How?
→



How computation helps: An overview of course topics

2013 Nobel Prize recognized early developments underlying modern biomolecular computation

The Nobel Prize in Chemistry 2013



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



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

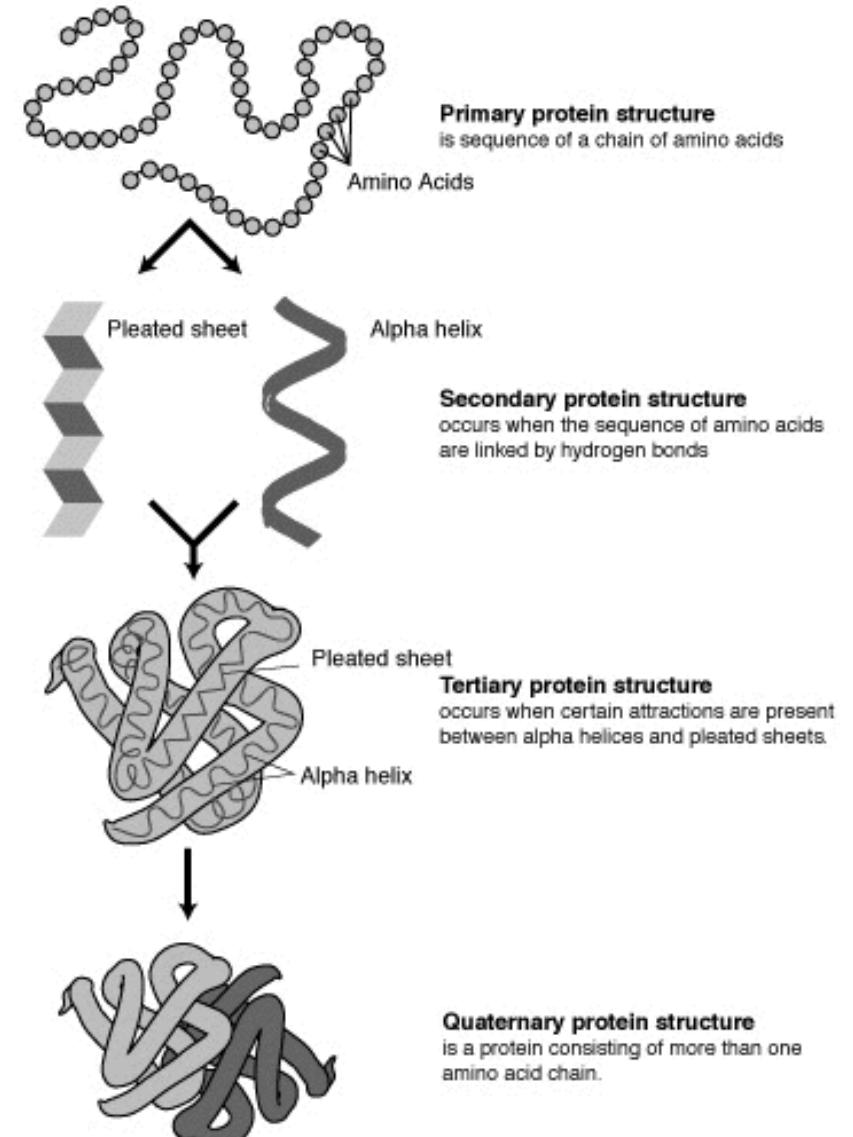


Photo: A. Mahmoud
Arieh Warshel
Prize share: 1/3

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"*.

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)

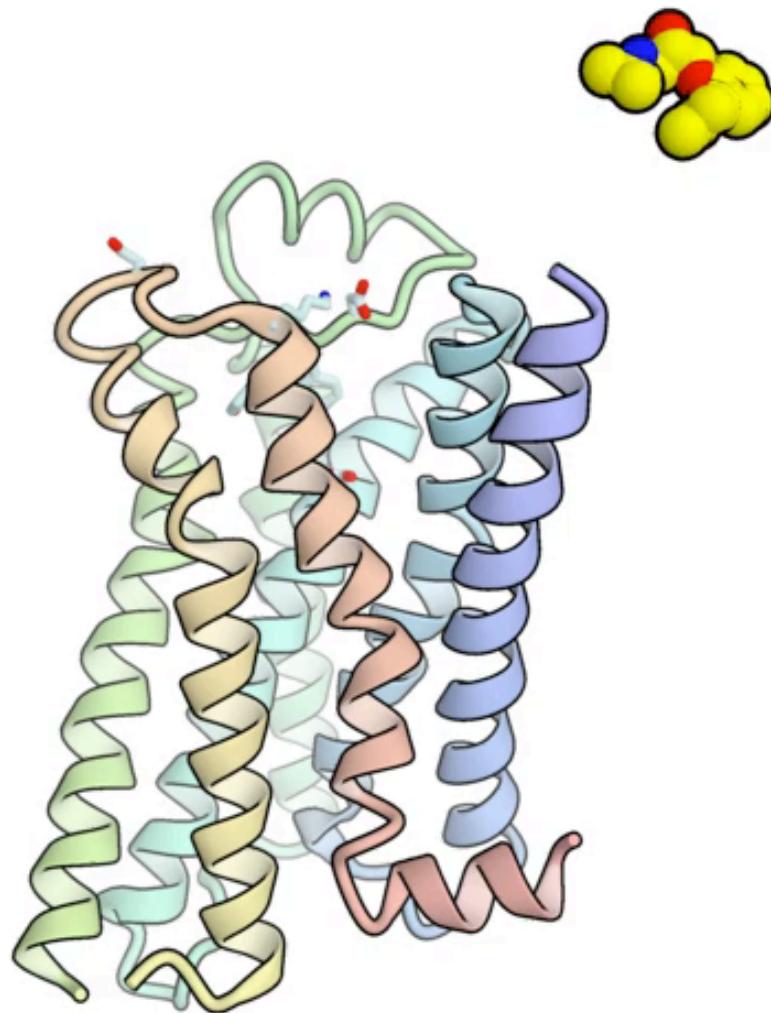


Also, RNA structure prediction

Image from Wikipedia

Molecular dynamics simulations

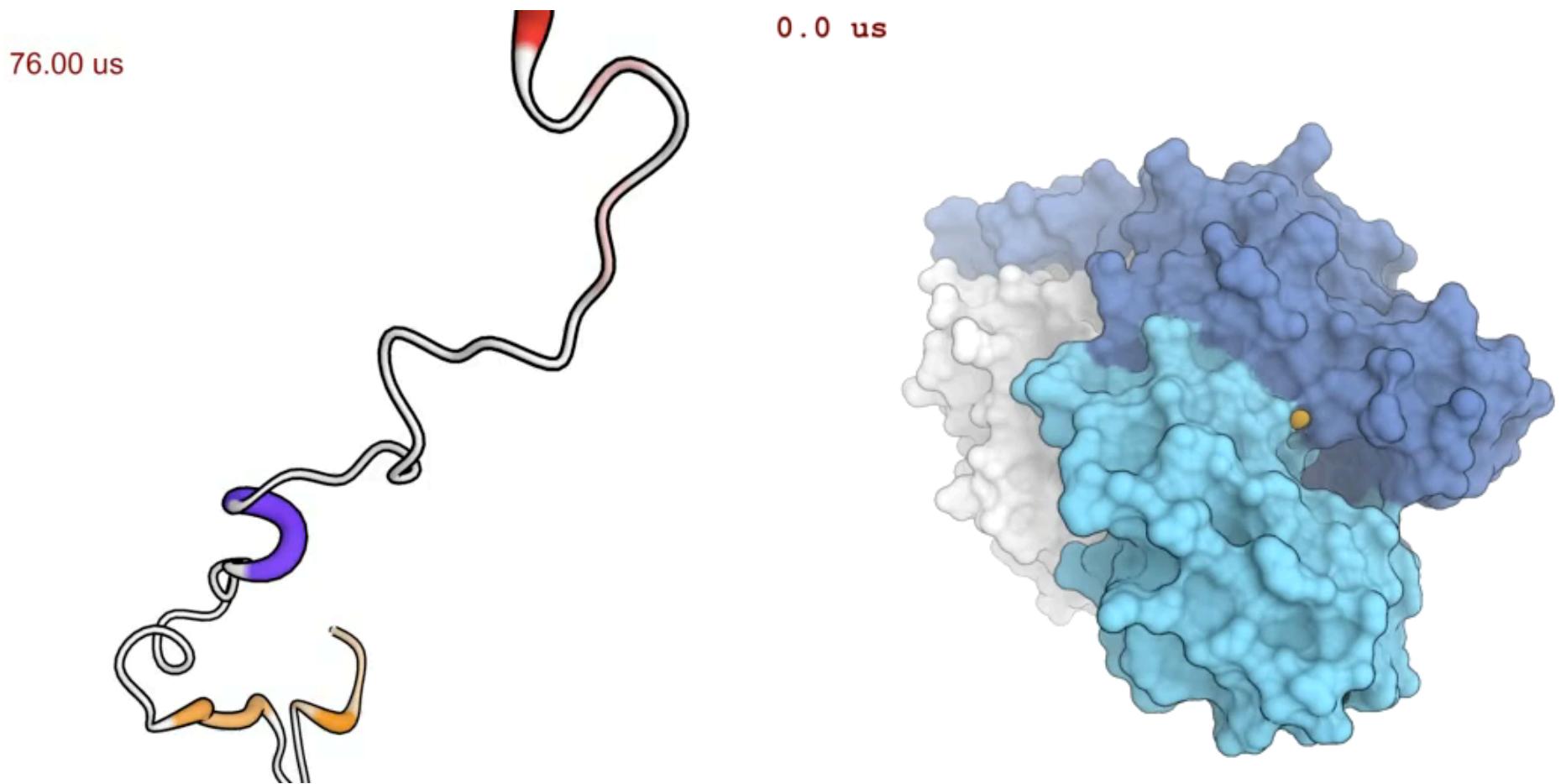
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Beta-blocker binding to the β_2 -adrenergic receptor

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)

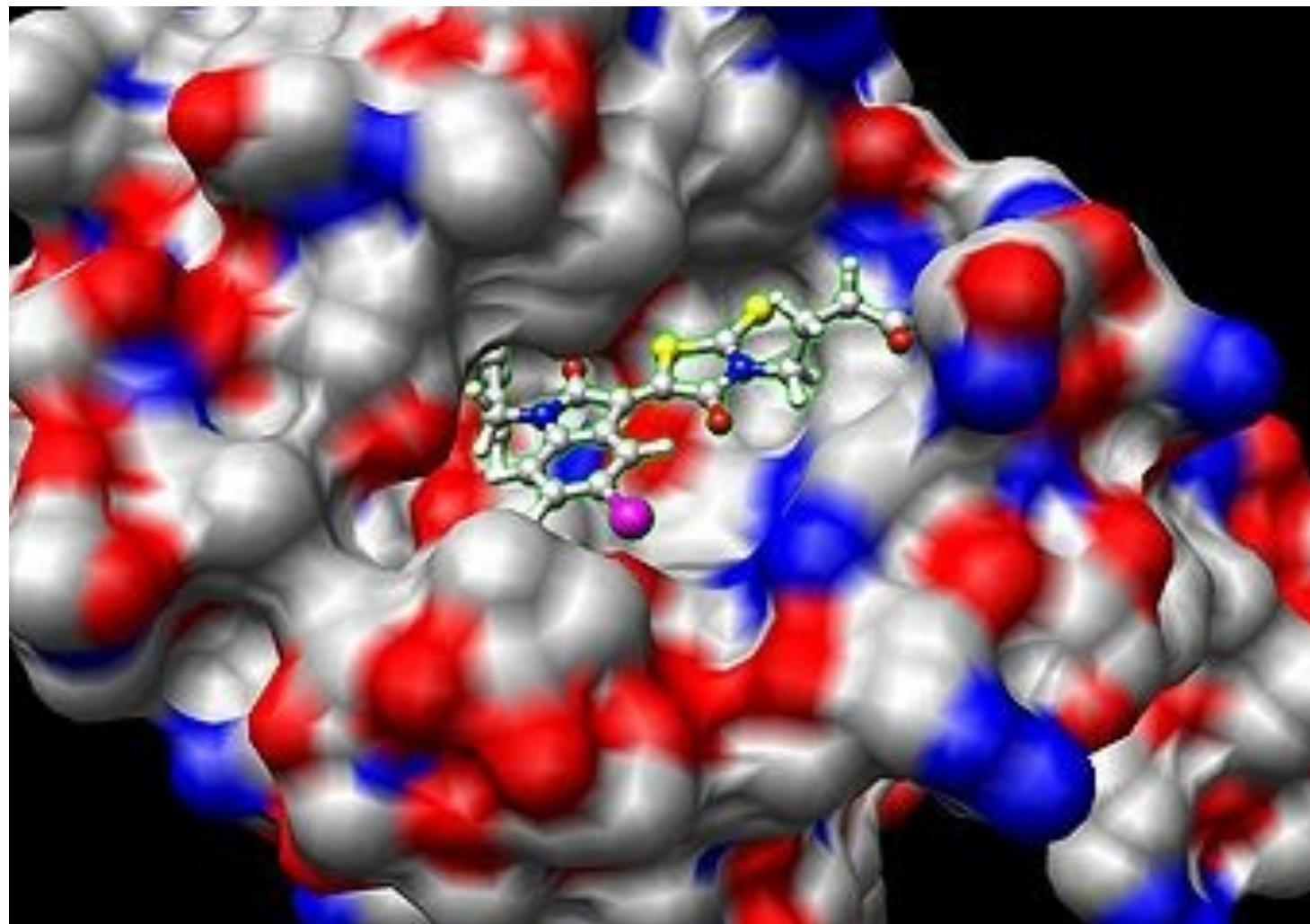
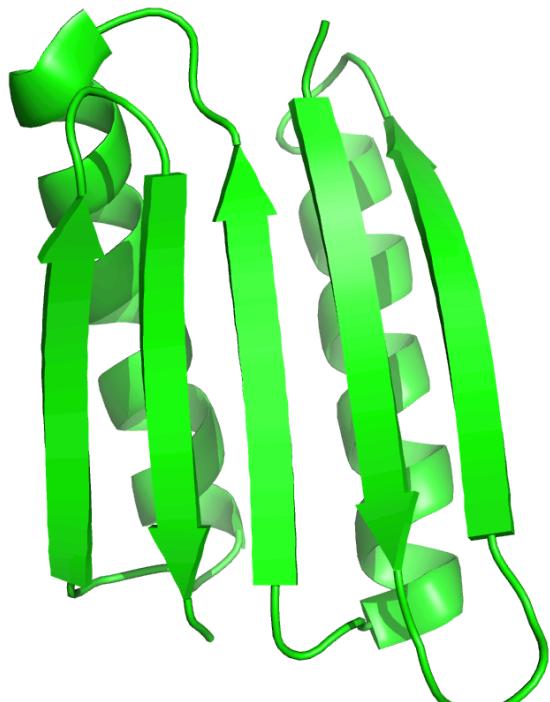


Image: Wikipedia

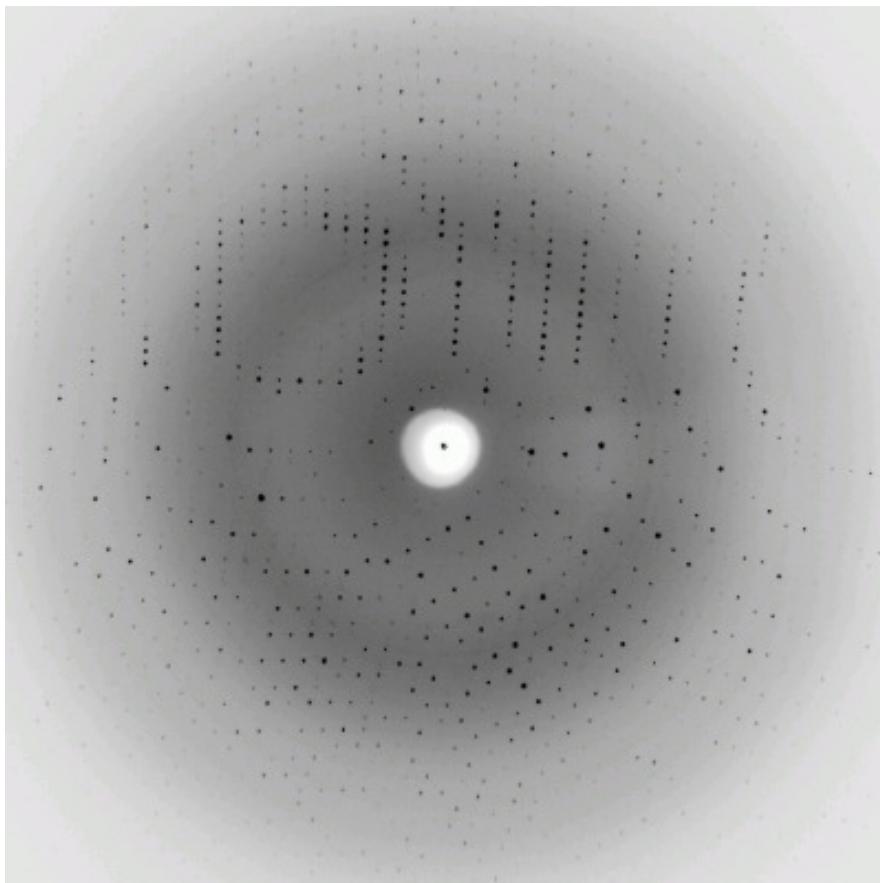
Protein design

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



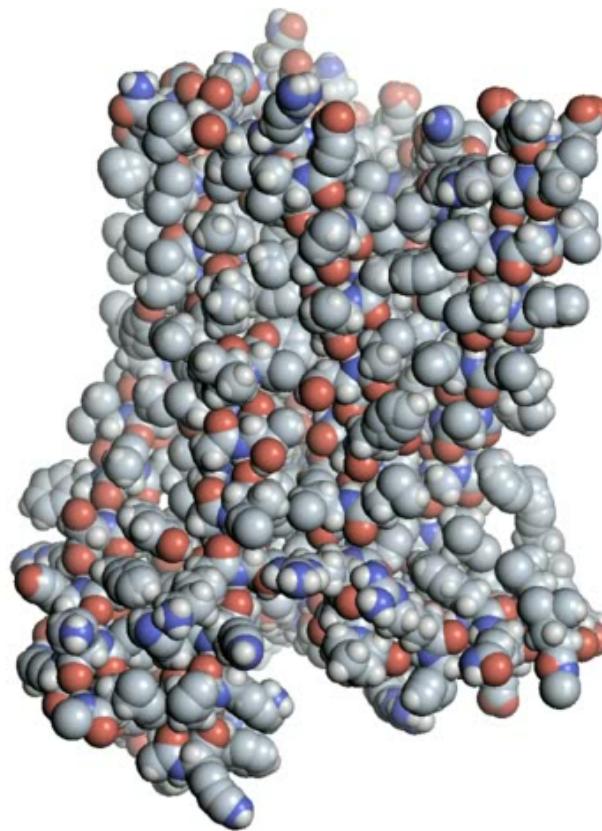
Top7, a protein with a designed fold
Kuhlman, Science 302:1364-8 (2003)

Solving x-ray crystal structures



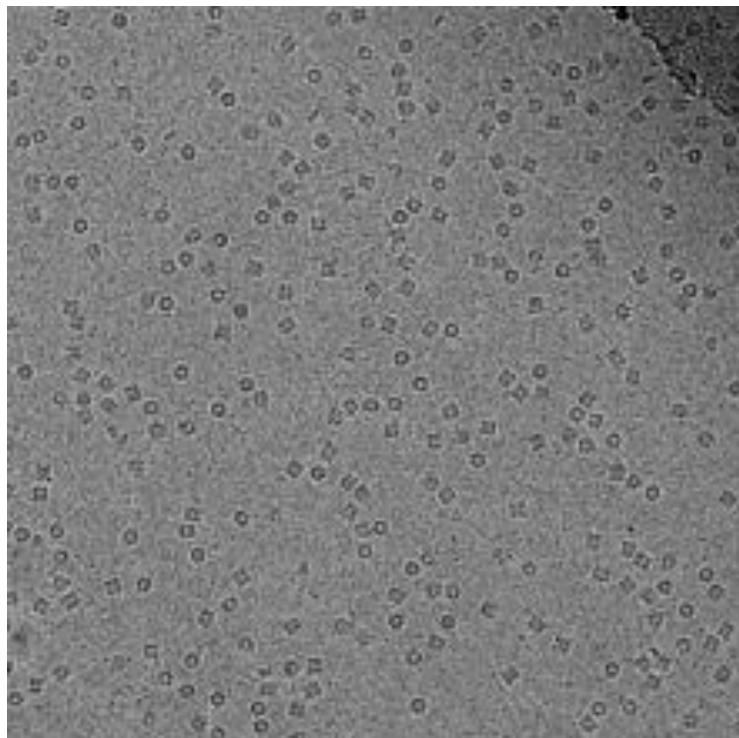
X-ray diffraction pattern

Image: [http://www.chem.ucla.edu/
harding/IGOC/X/x_ray_crystallography.html](http://www.chem.ucla.edu/harding/IGOC/X/x_ray_crystallography.html)



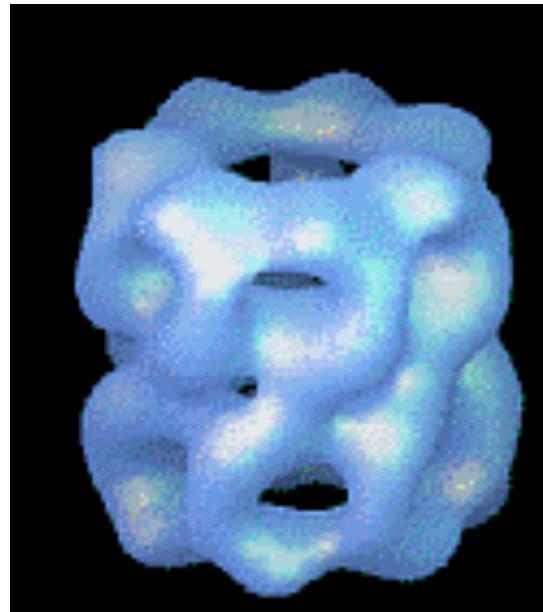
Protein structure

Solving structures of complexes by cryoelectron microscopy



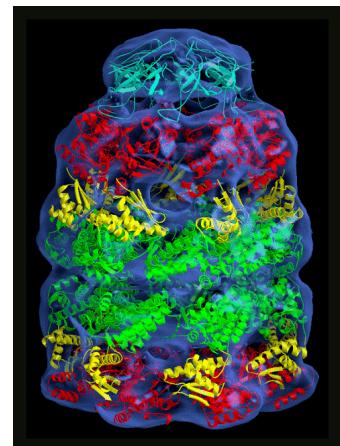
CryoEM image

Image from Wikipedia

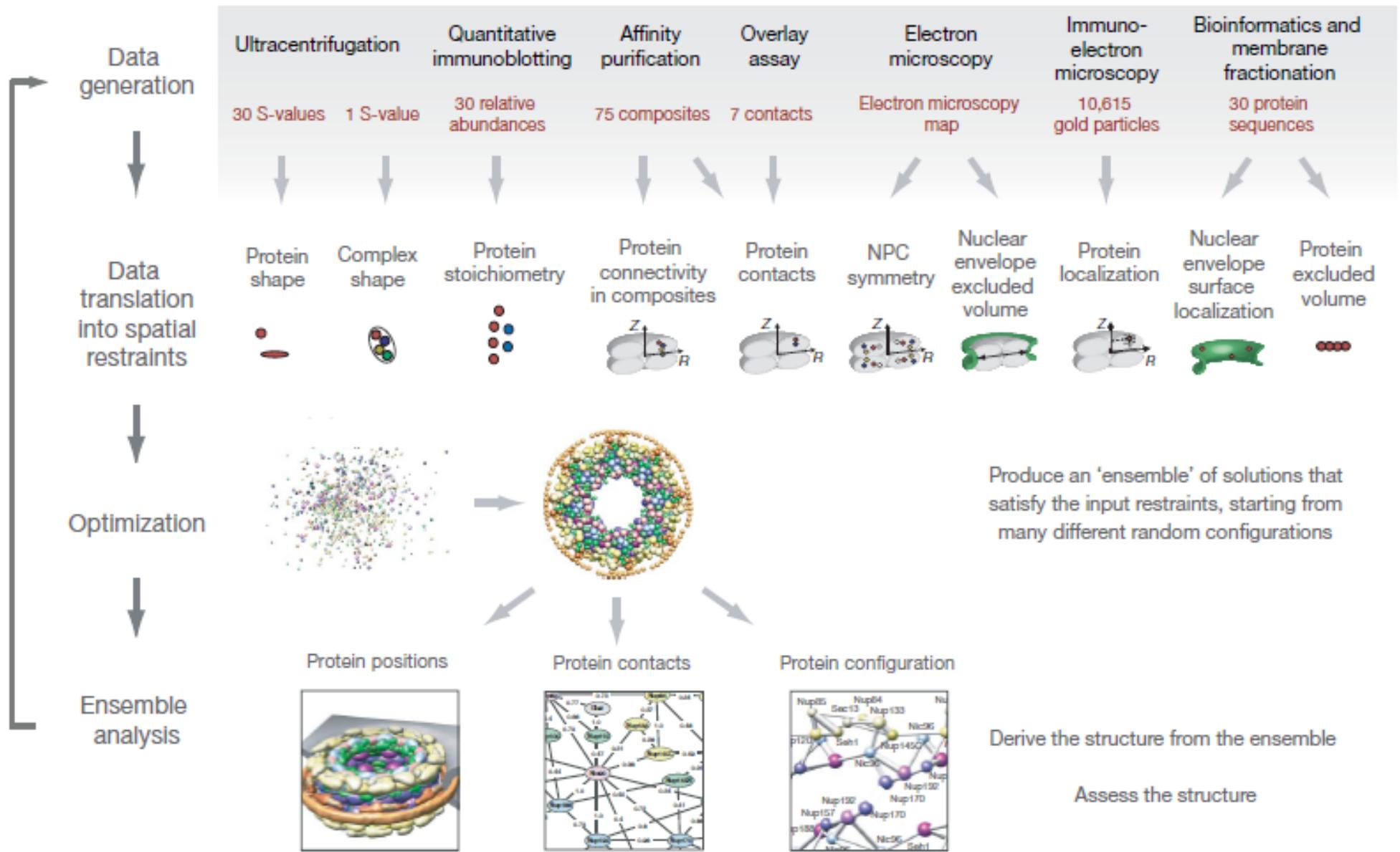


Reconstructed envelope

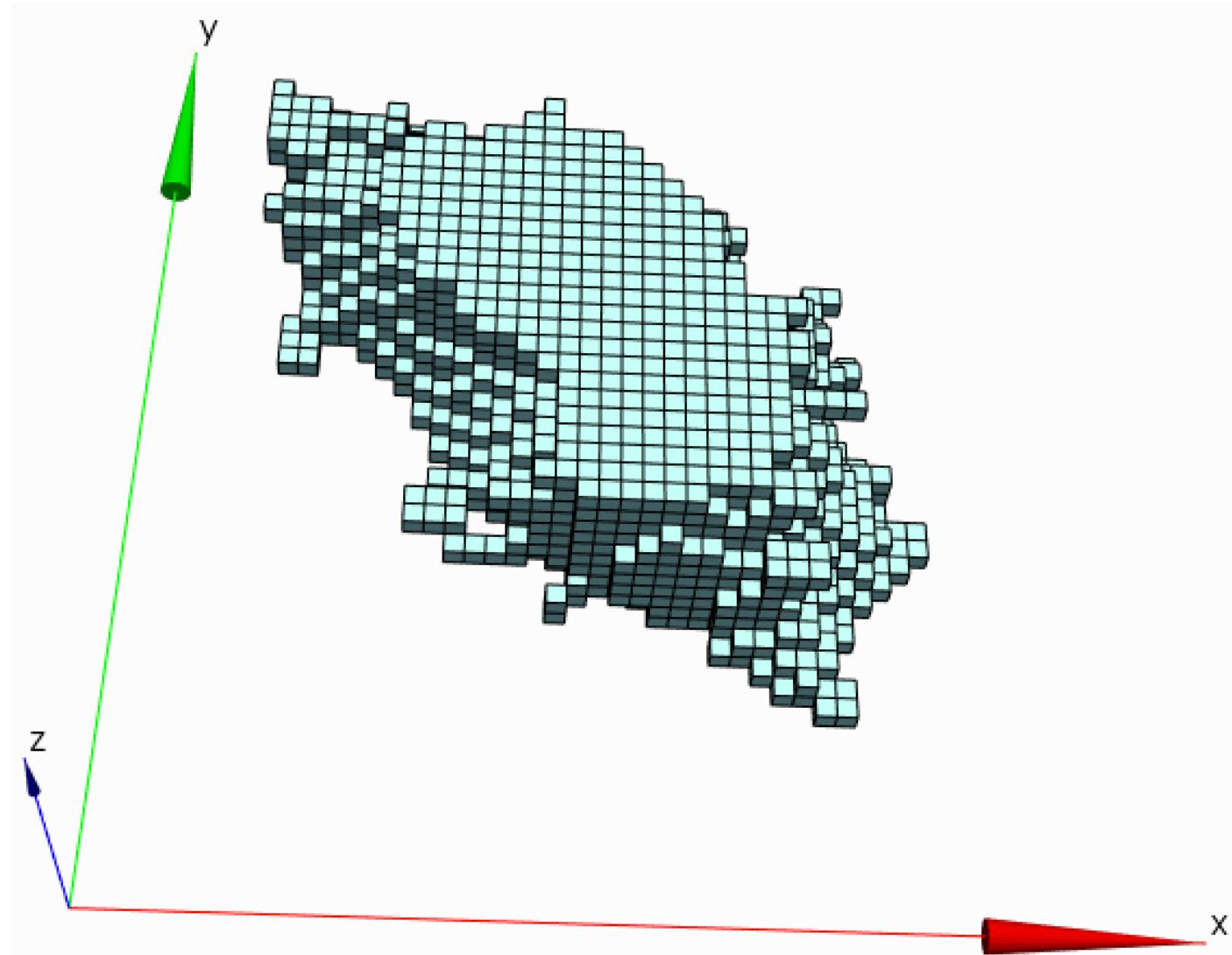
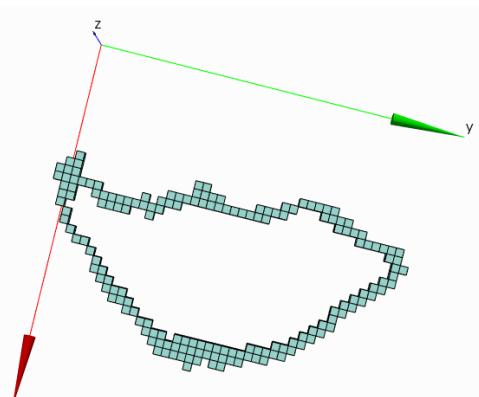
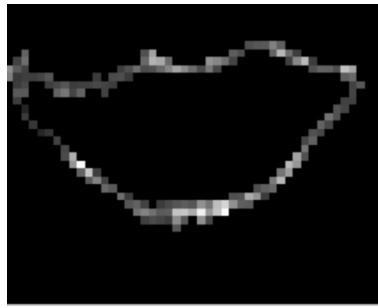
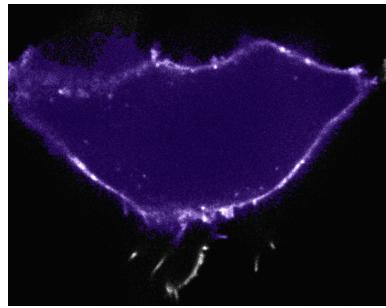
<http://people.cryst.bbk.ac.uk/~ubcg16z/chaperone.html>



Combining experimental data to deduce structures of complexes



Cellular-level organization: image analysis



Images: Naomi Latorraca

Cellular-level organization: image analysis

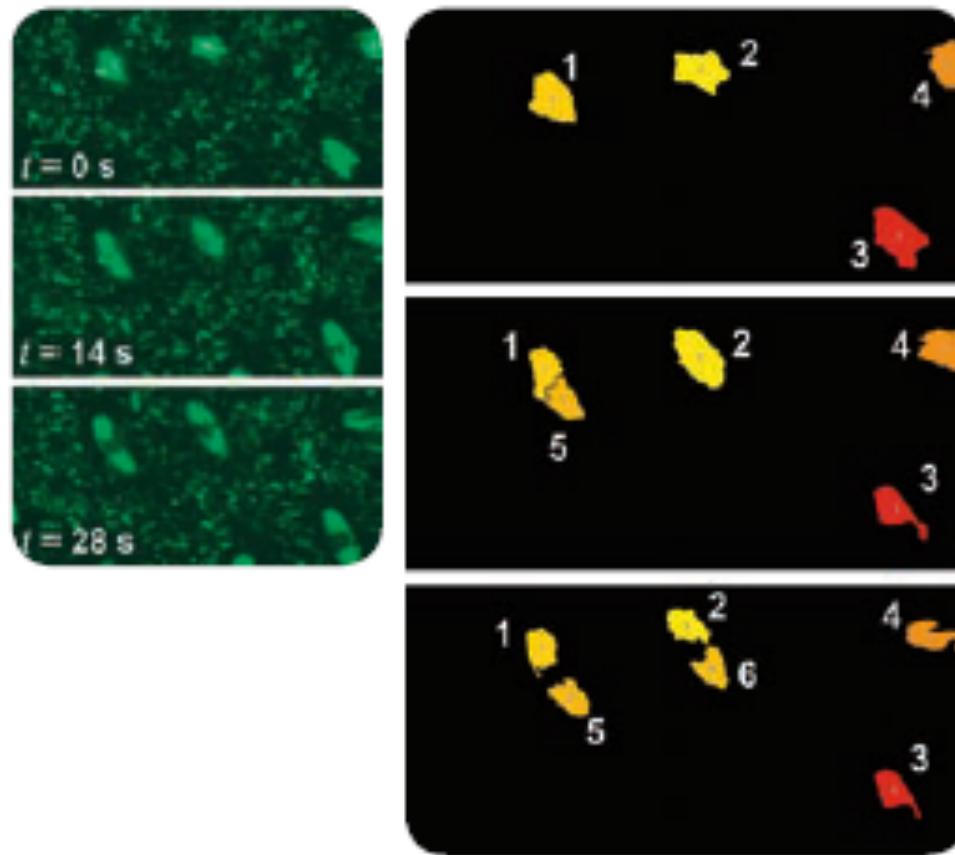
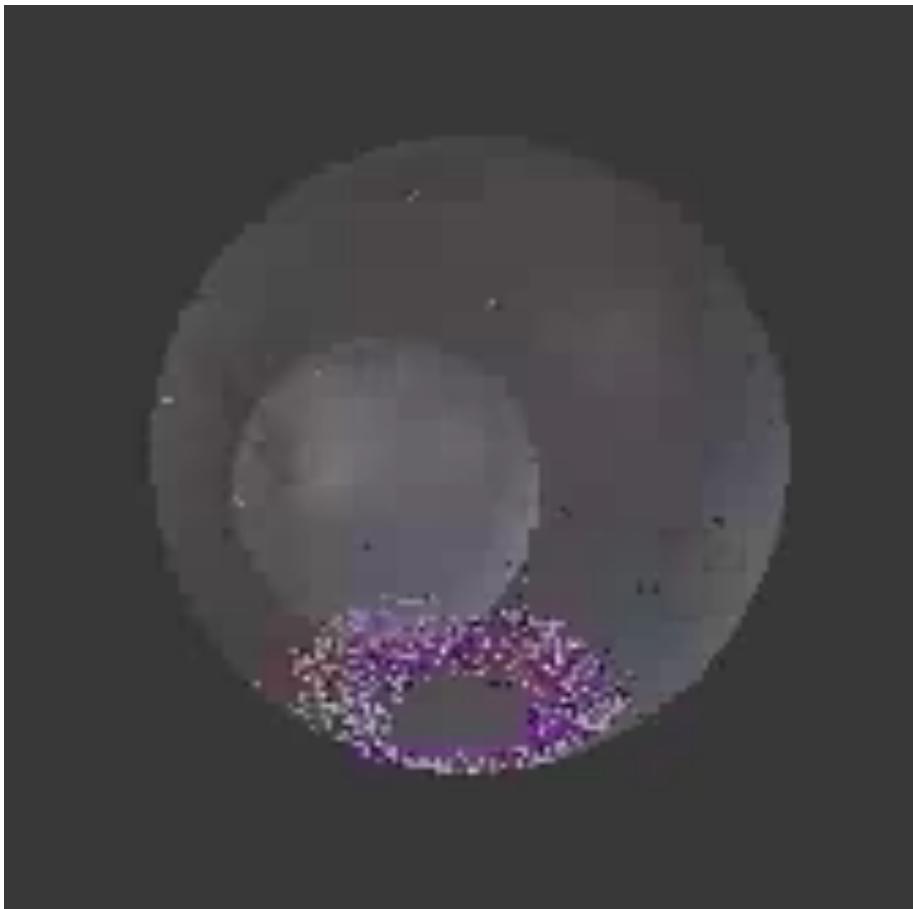


Image: CellProfiler

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
 - <http://drorlab.stanford.edu/rondror.html>
 - 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!