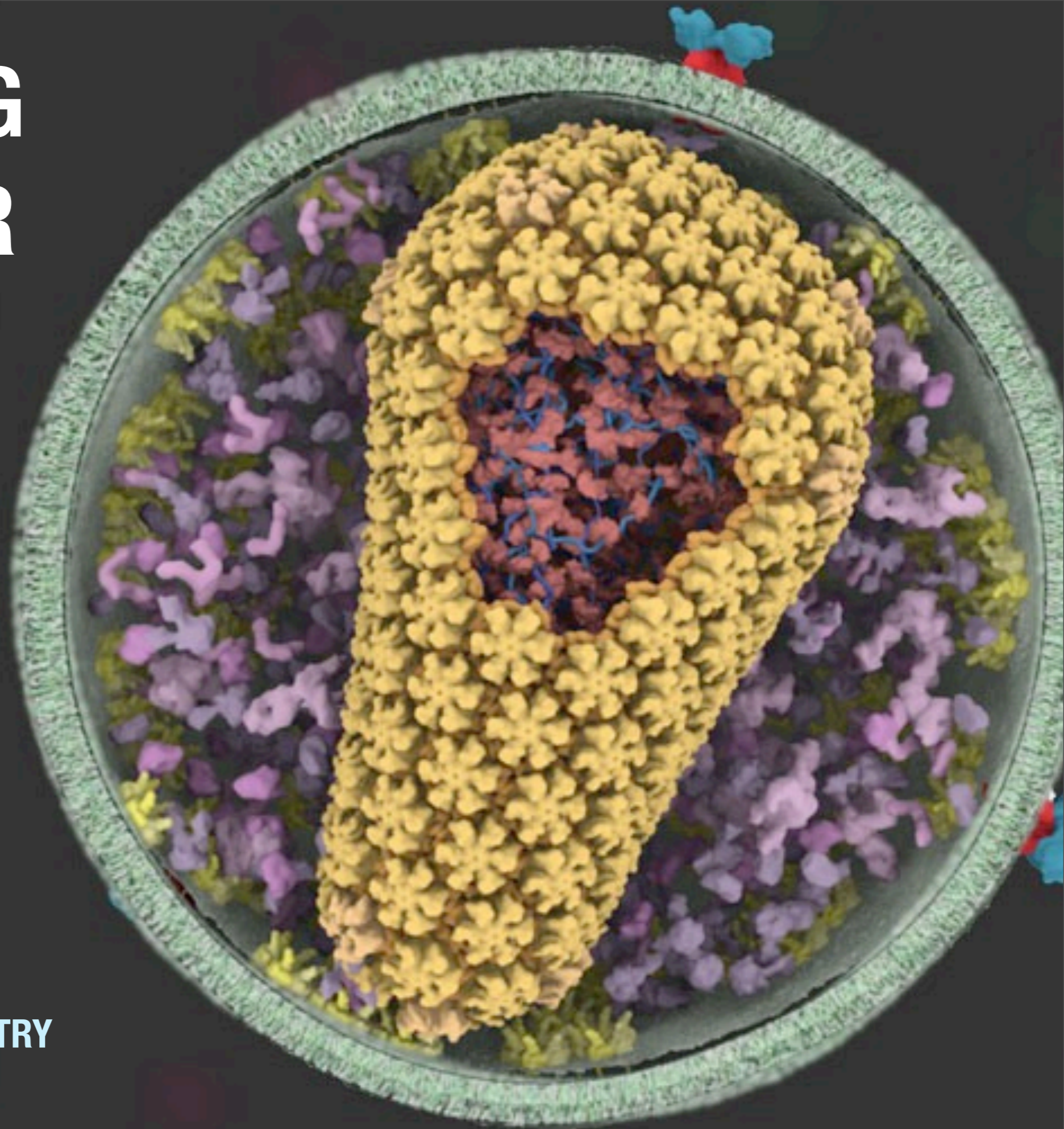


VISUALIZING MOLECULAR PROCESSES



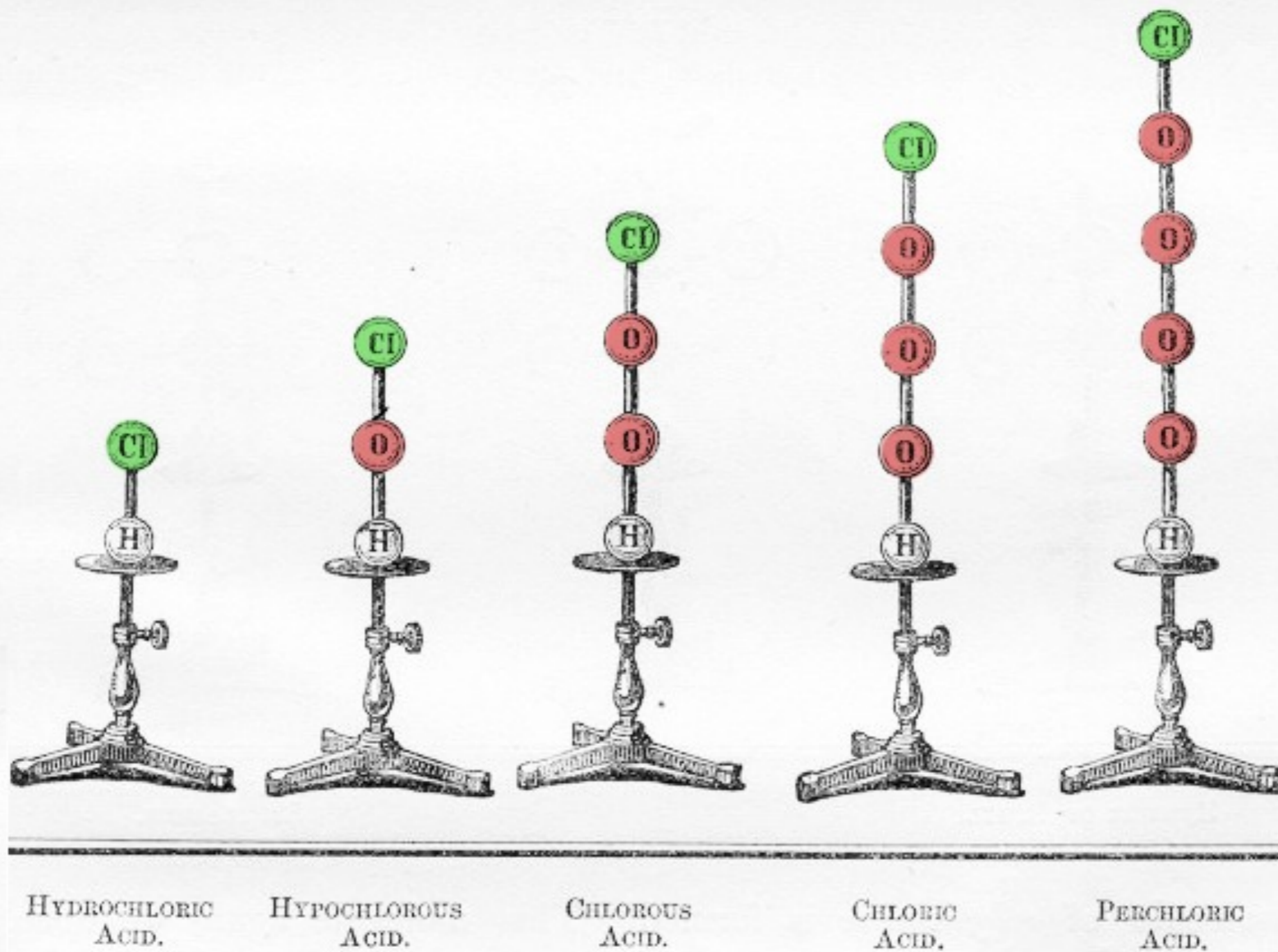
JANET IWASA
DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF UTAH

OVERVIEW

- 1. 3D models and eureka moments.**
- 2. Using animations to communicate molecular mechanisms.**
- 3. Using animation as a tool for research.**
- 4. The future of the model figure? Thoughts and directions.**

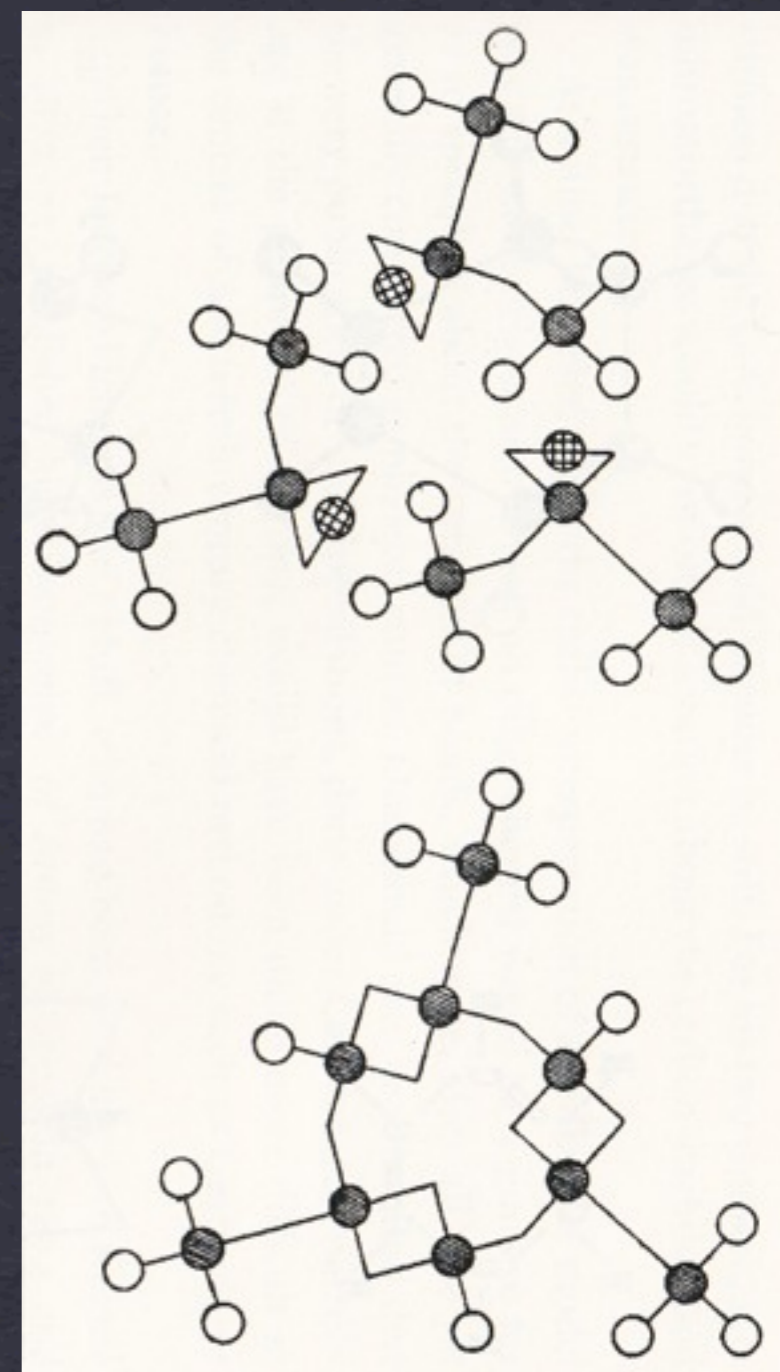
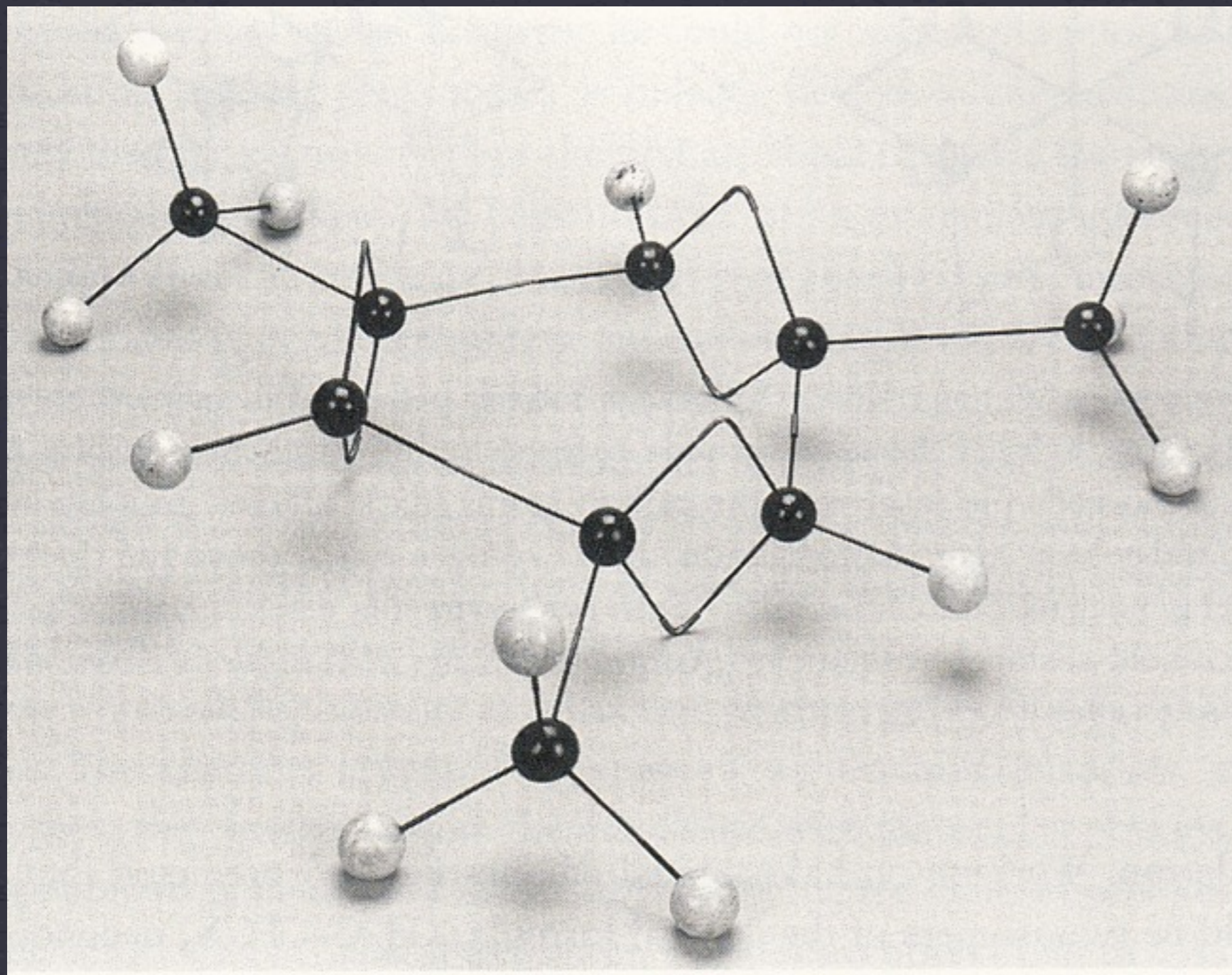
3D MODELS IN SCIENCE

EARLY CHEMICAL MODELS - AUGUST WILHELM HOFMANN, 1865



3D MODELS IN SCIENCE

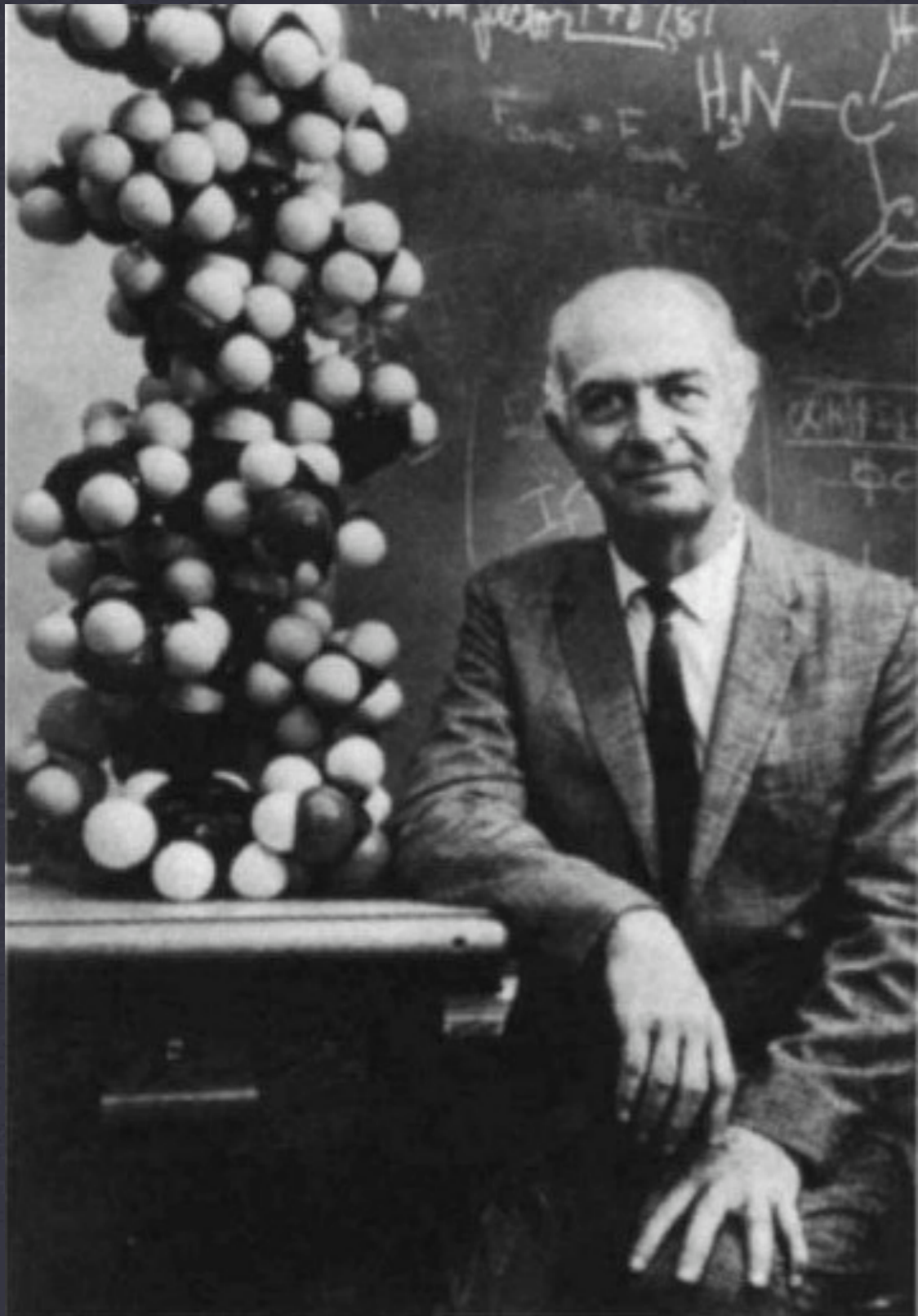
EARLY CHEMICAL MODELS - AUGUST KEKULÉ



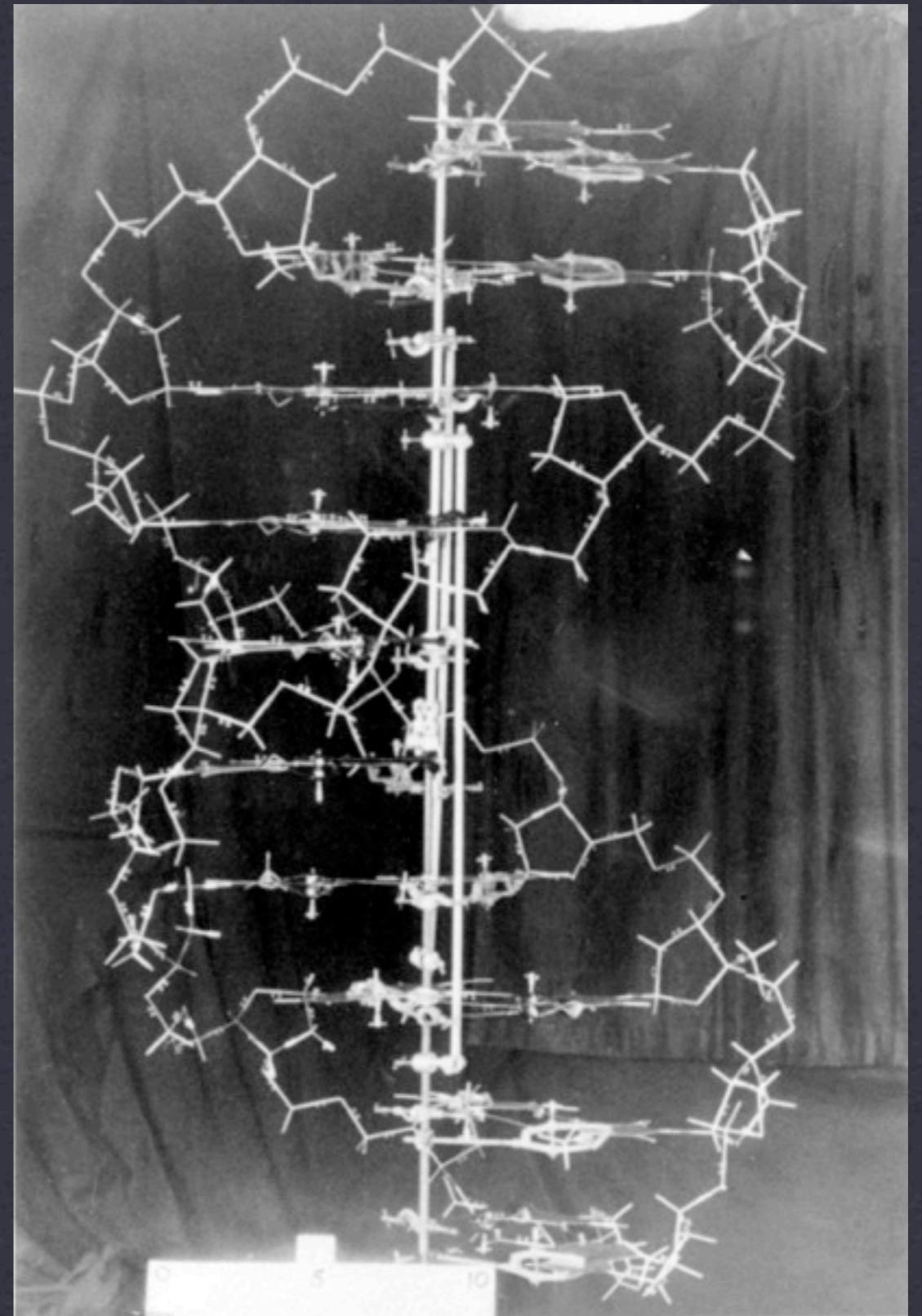
FROM MODELS: THE THIRD DIMENSION OF SCIENCE, EDITED BY SORAYA DE CHADAREVIAN AND NICK HOPWOOD

3D MODELS IN SCIENCE

THE ALPHA HELIX AND THE DOUBLE HELIX



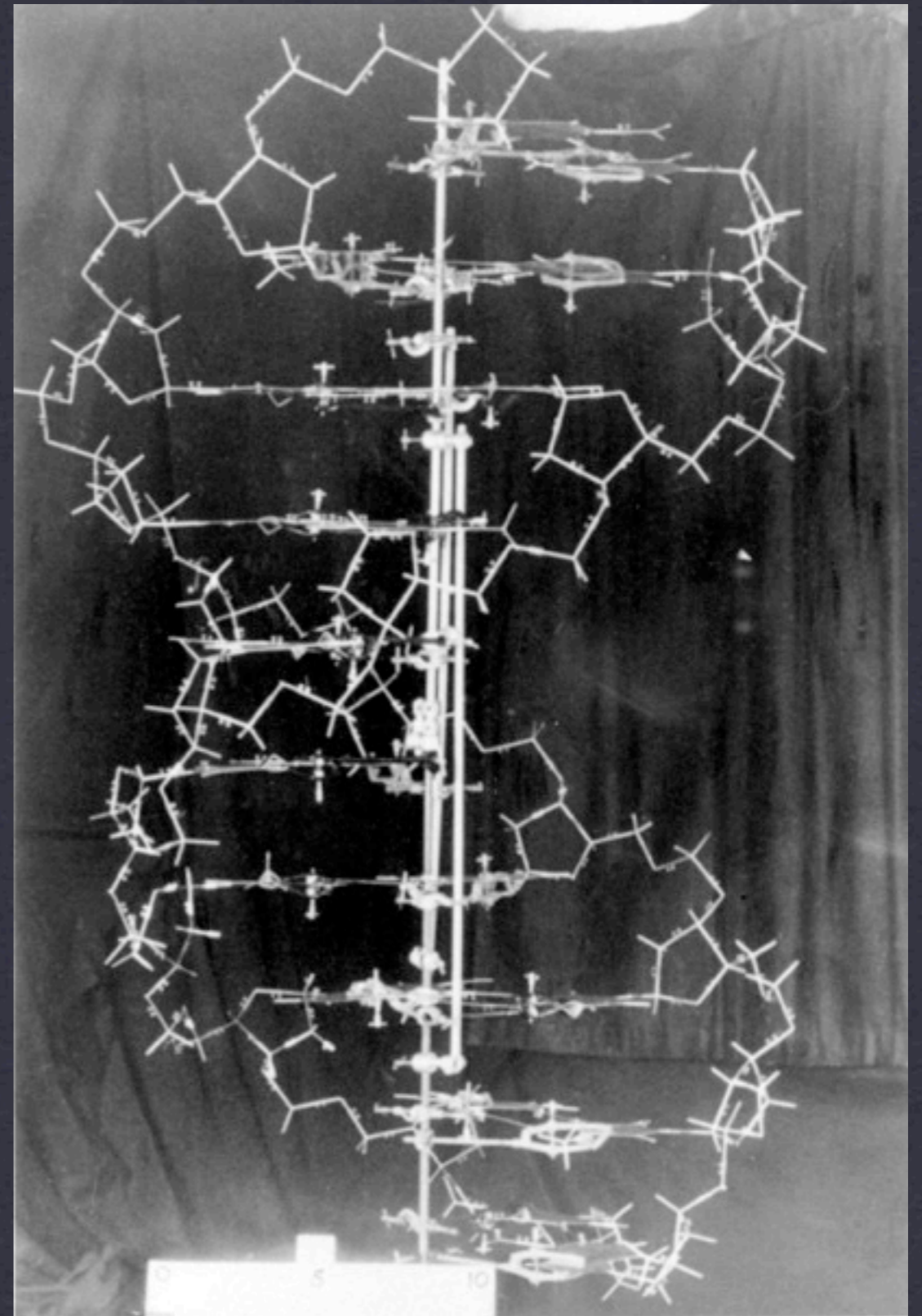
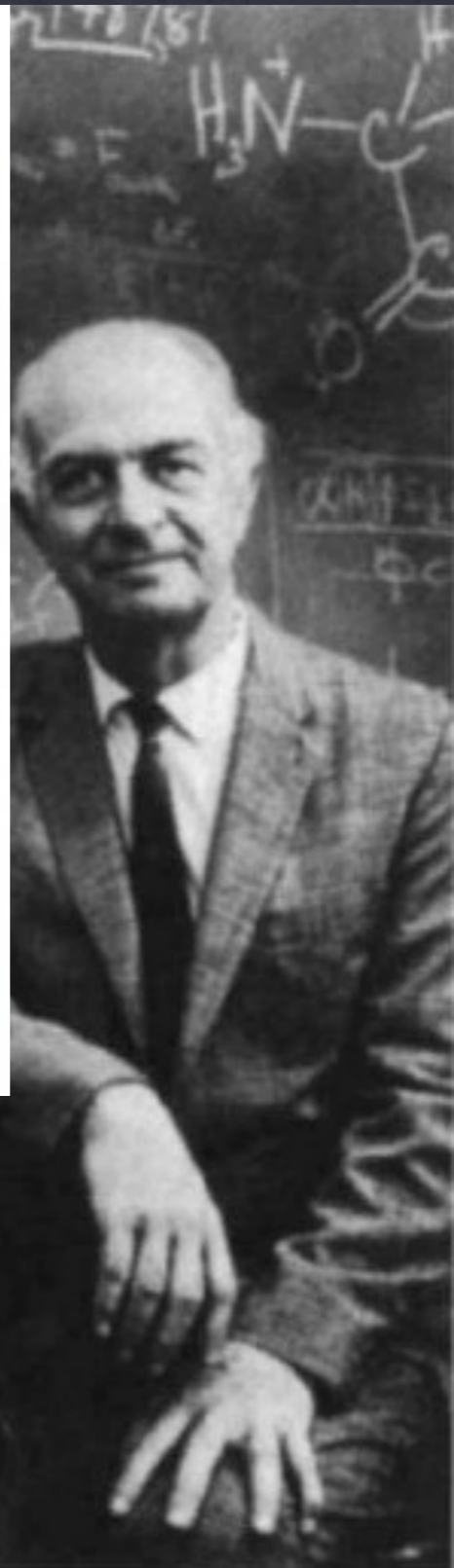
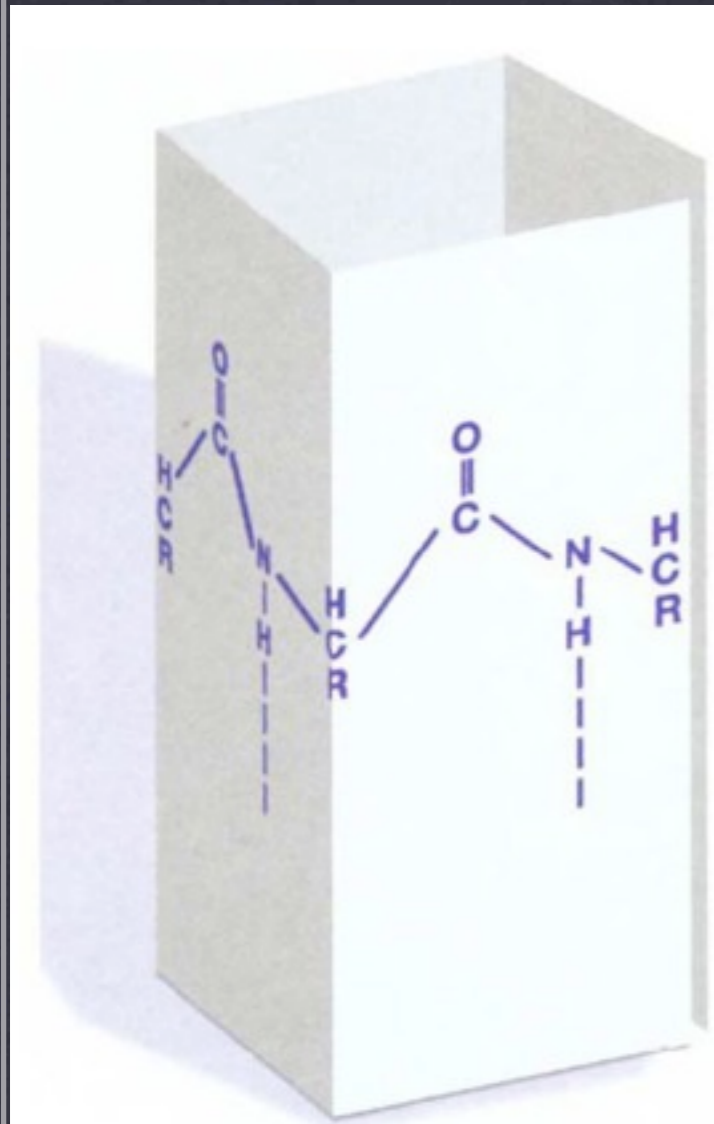
FROM "STRING AND SEALING WAX" NAT STRUCT BIOL 1997



FROM COLD SPRING HARBOR LABS

3D MODELS IN SCIENCE

THE ALPHA HELIX AND THE DOUBLE HELIX

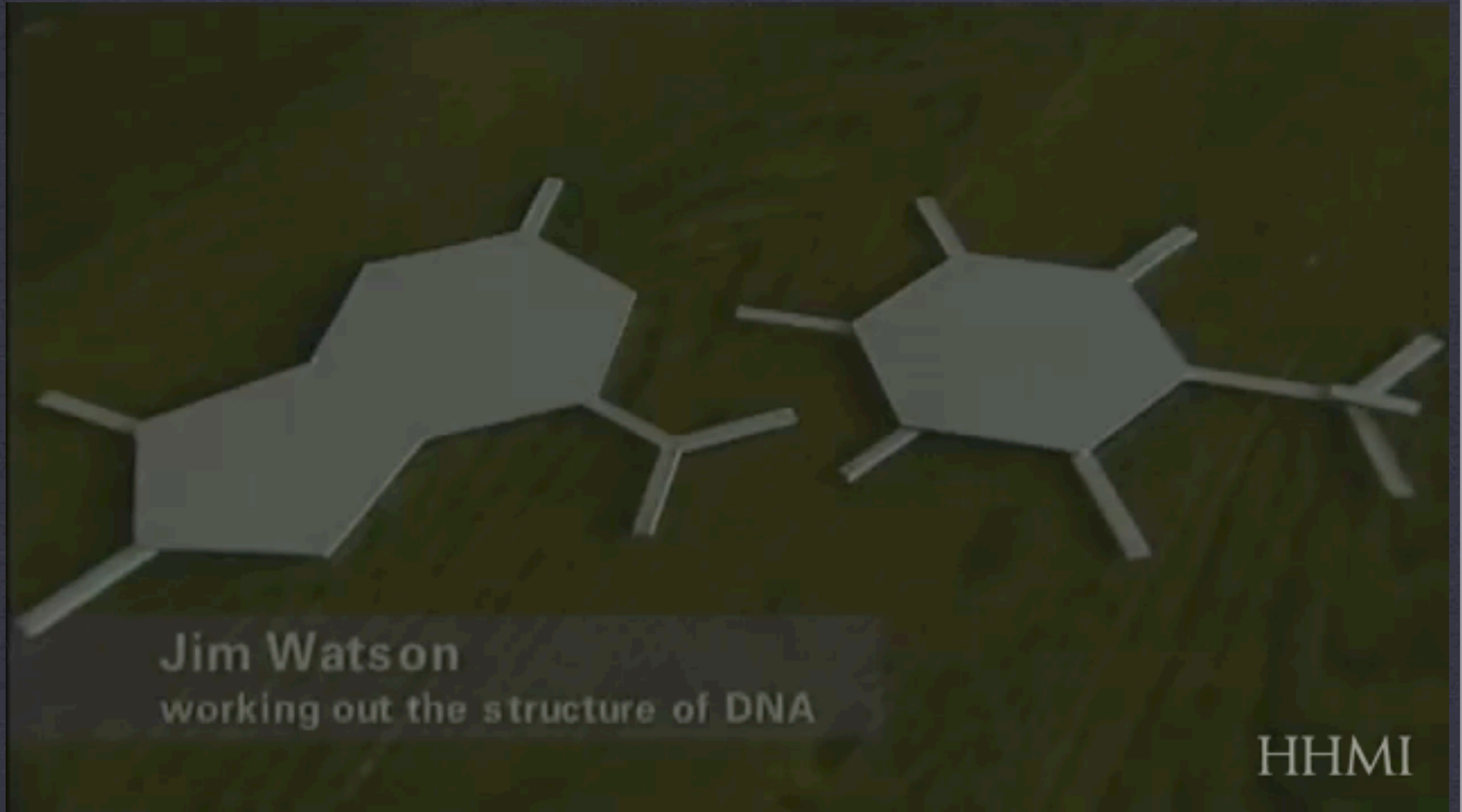


FROM "STRING AND SEALING WAX" NAT STRUCT BIOL 1997

FROM COLD SPRING HARBOR LABS

3D MODELS IN SCIENCE

JAMES WATSON ON CONSTRUCTING BASE PAIR MODELS



FROM HHMI'S "BIOINTERACTIVE" ([HTTP://HHMI.ORG/BIOINTERACTIVE](http://hhmi.org/biointeractive))

3D MODELS IN SCIENCE

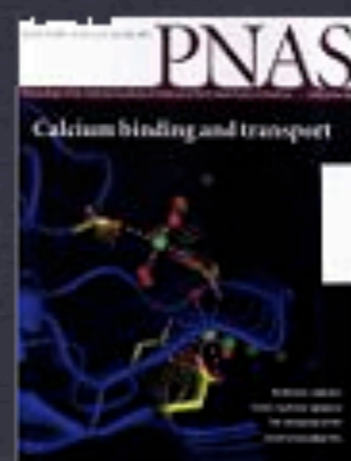
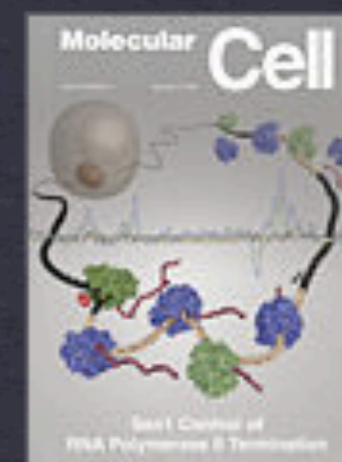
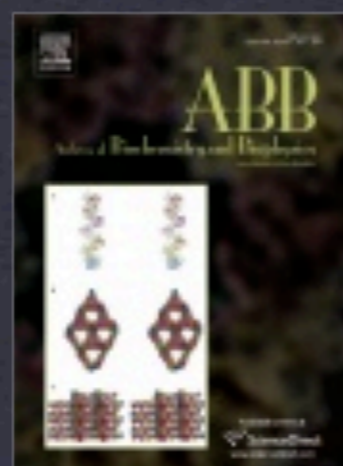
MYOGLOBIN IN A “FOREST OF RODS”



IMAGE FROM:
DICKERSON RE. CHAPTER 2: MYOGLOBIN: A WHALE OF A STRUCTURE! J MOL BIOL. 2009 SEP 11;392(1):10-23.

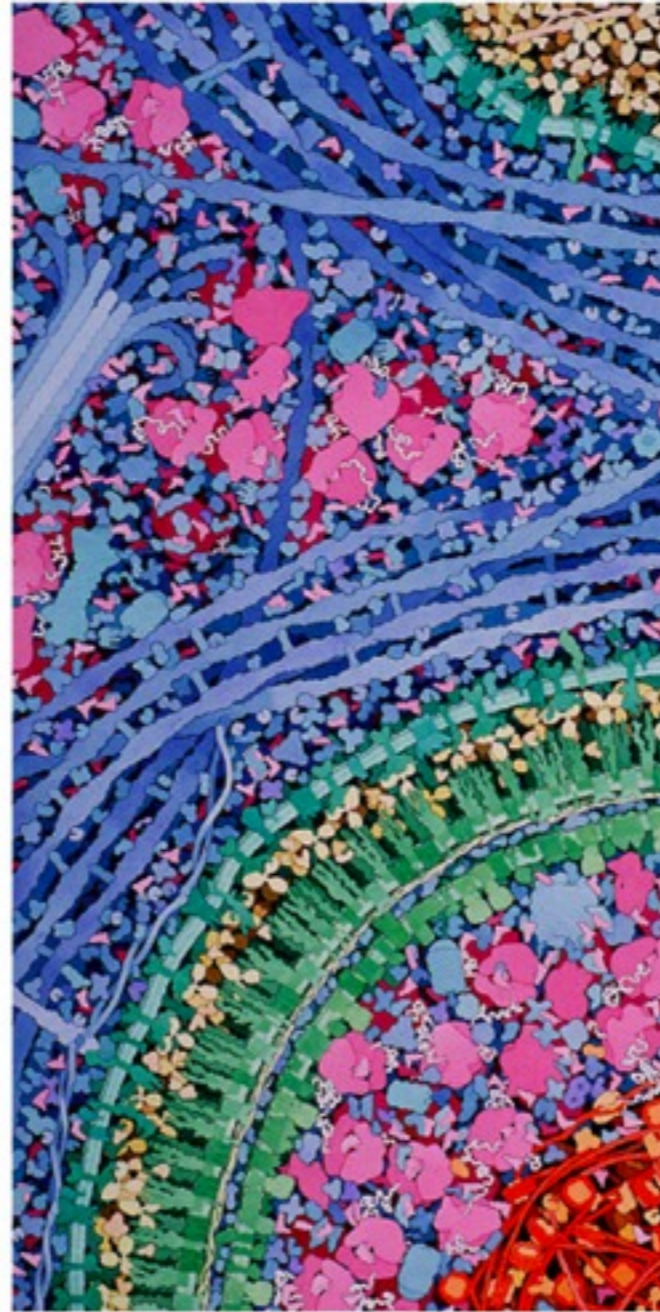
3D MODELS IN SCIENCE

VIRTUAL MODELS



COVERS MADE WITH PYMOL - FROM THE PYMOL WIKI

VISUALIZING THE CELLULAR MESOSCALE



**“MACROPHAGE & BACTERIUM”
DAVID GOODSSELL, SCRIPPS INSTITUTE**

THE NEED FOR NEW MODELS IN BIOLOGY

WHY ANIMATION?

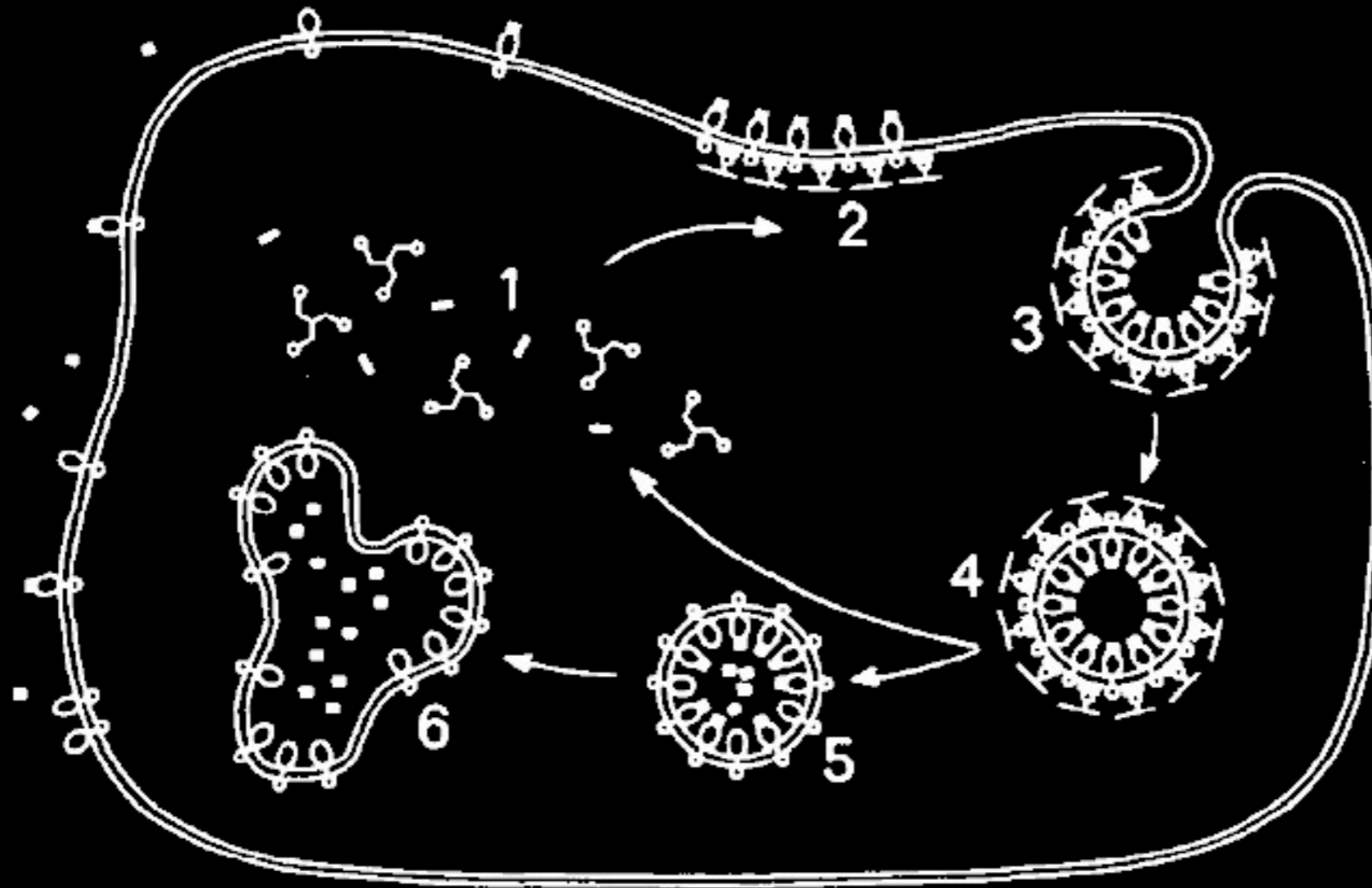
3D animation can synthesize diverse biological data ...

- protein structure
- protein activity
- dynamics
- localization
- simulation
- stoichiometry
- abundance



... allowing us to create a comprehensive visual hypothesis of a cellular event

CLATHRIN-MEDIATED ENDOCYTOSIS

ILLUSTRATION BY PEARSE & CROWTHER, 1987



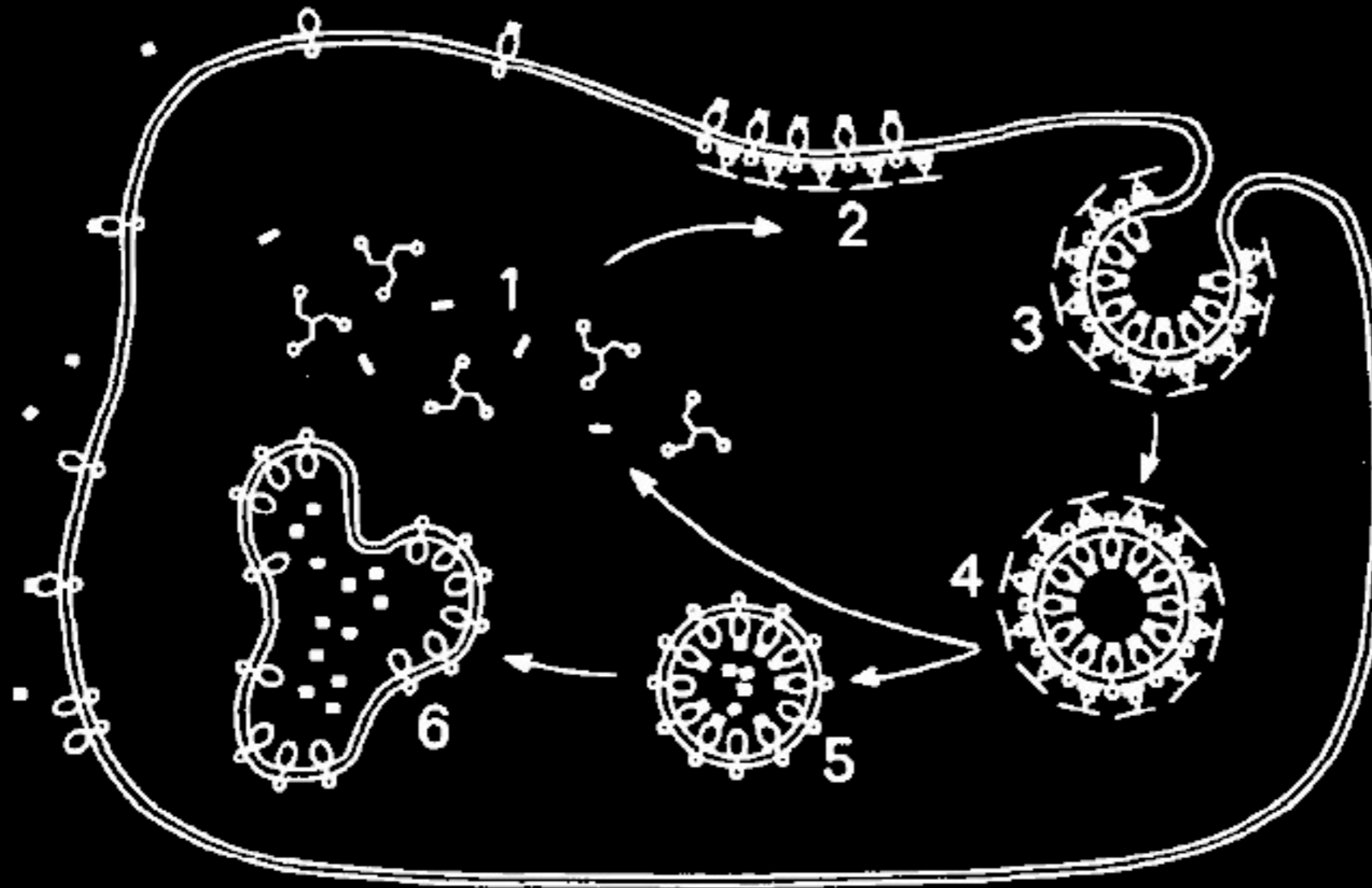
Clathrin: triskelion 
100kd-50kd proteins 


assembled receptor 
ligand 






CLATHRIN-MEDIATED ENDOCYTOSIS

ILLUSTRATION BY PEARSE & CROWTHER, 1987

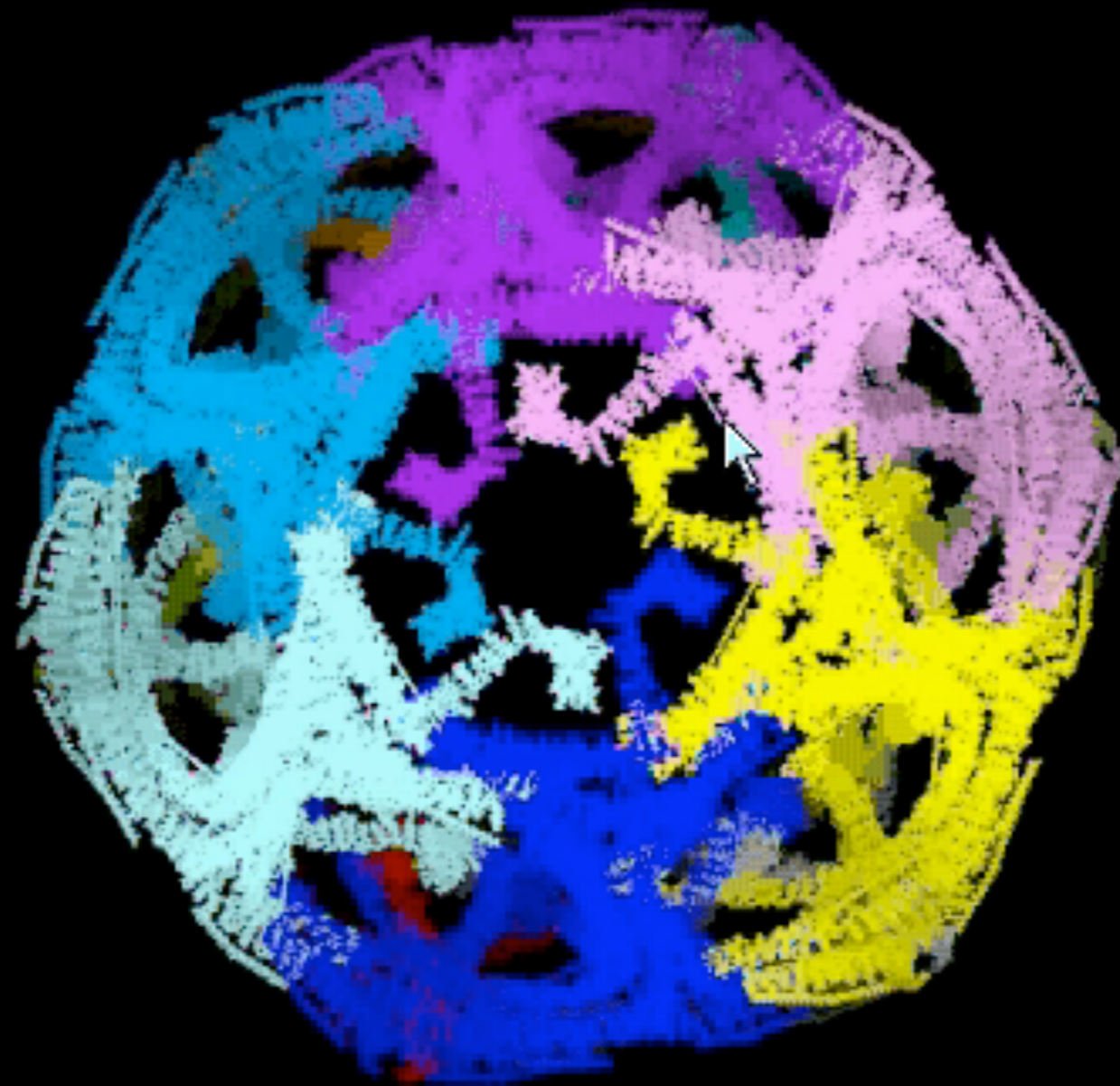


Clathrin: triskelion 
100kd-50kd proteins 

assembled receptor 
receptor  ligand 

CLATHRIN-MEDIATED ENDOCYTOSIS

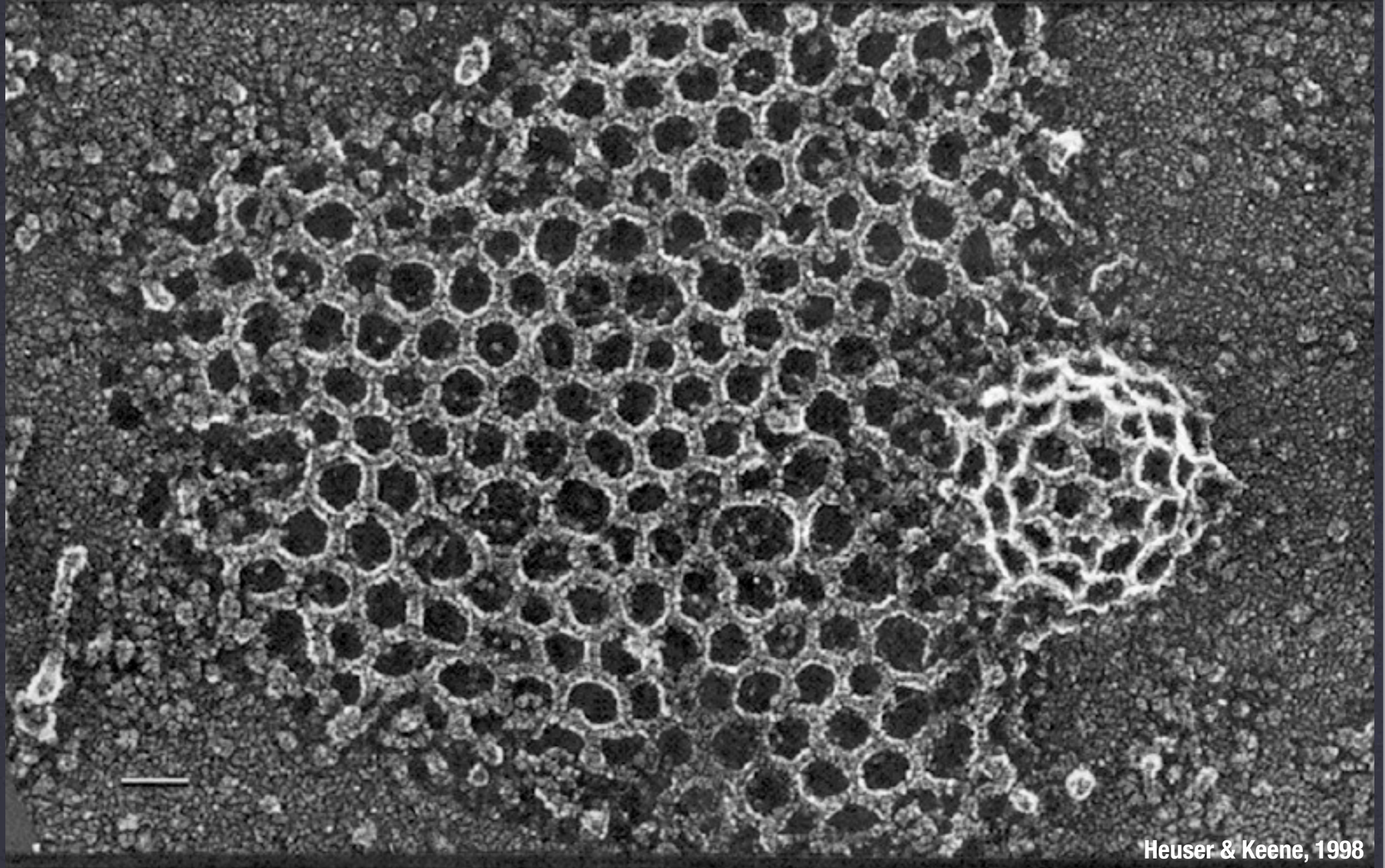
CLATHRIN LATTICE CRYSTAL STRUCTURE



FOTIN, CHENG, SLIZ, GRIGORIEFF, HARRISON, KIRCHHAUSEN AND WALZ, 1994

CLATHRIN-MEDIATED ENDOCYTOSIS

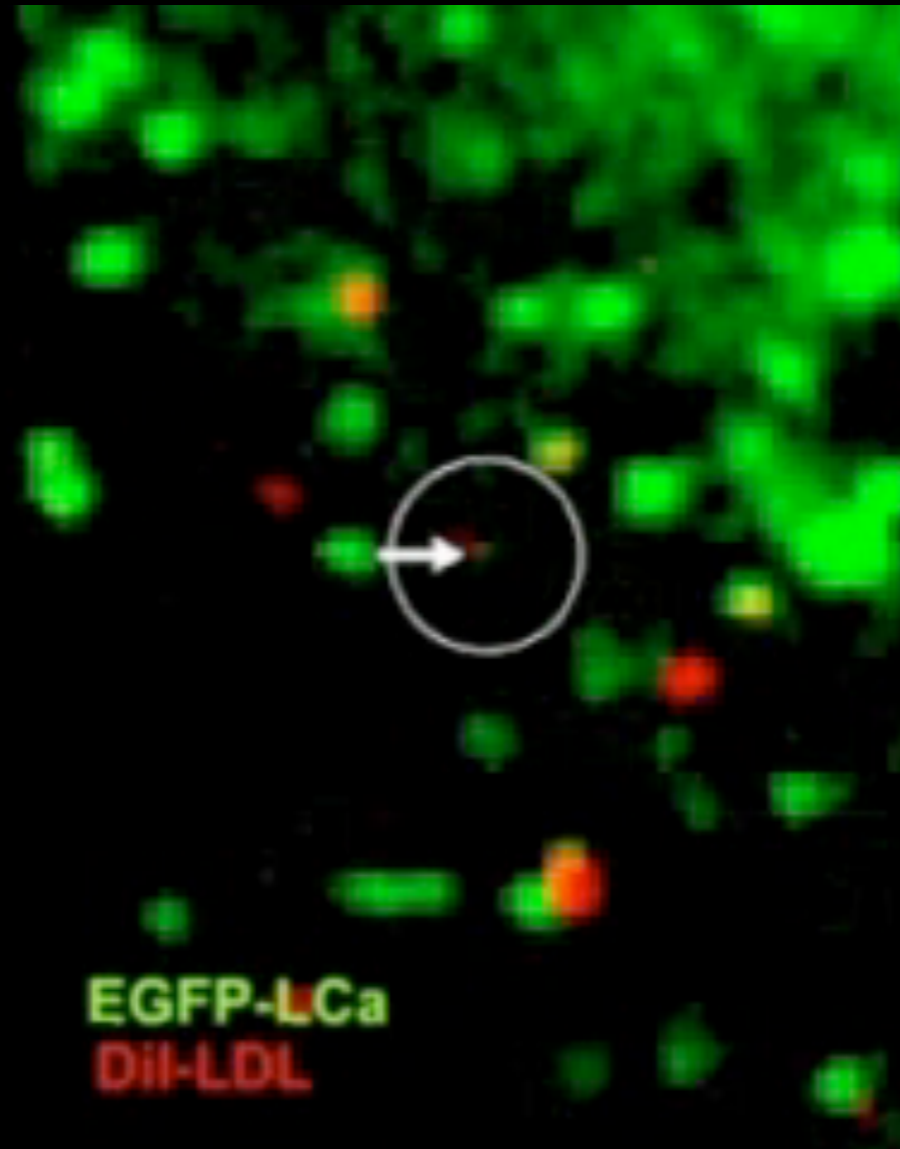
ELECTRON MICROSCOPY OF CLATHRIN IN CELLS



Heuser & Keene, 1998

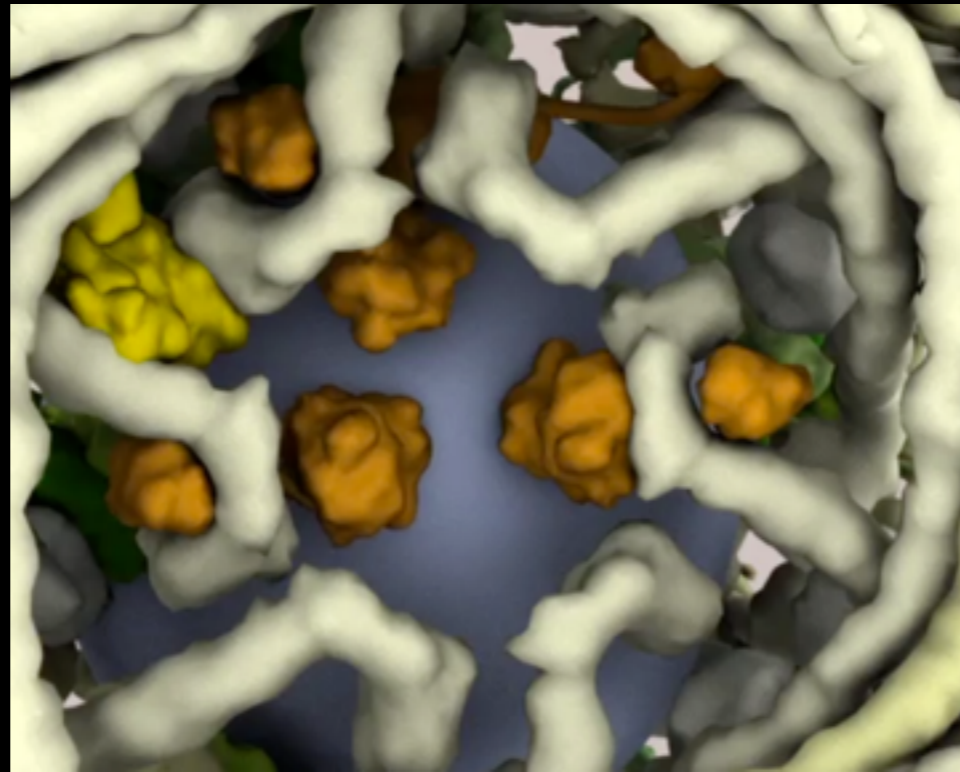
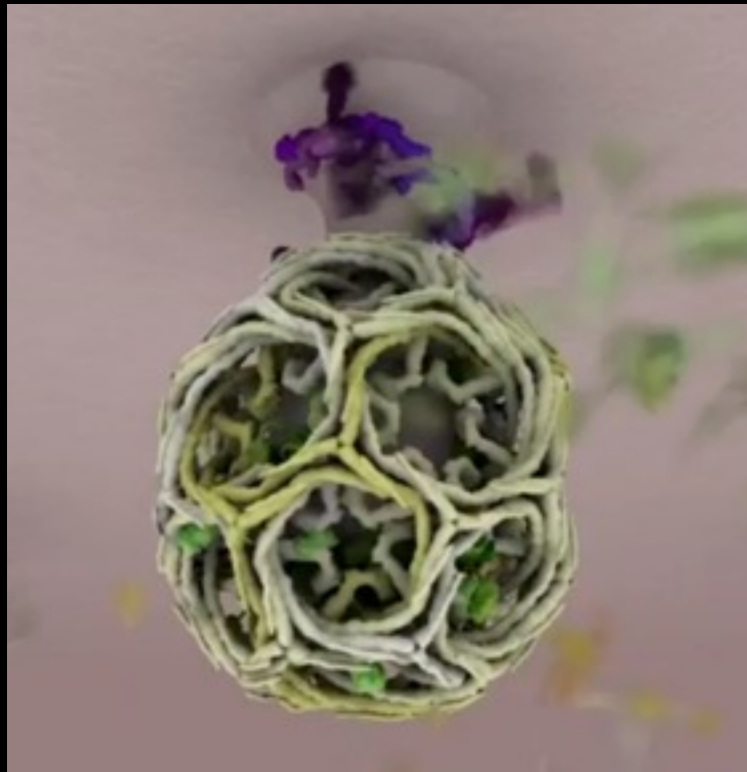
CLATHRIN-MEDIATED ENDOCYTOSIS

VISUALIZING DYNAMICS



EGFP-LCa
Dil-LDL

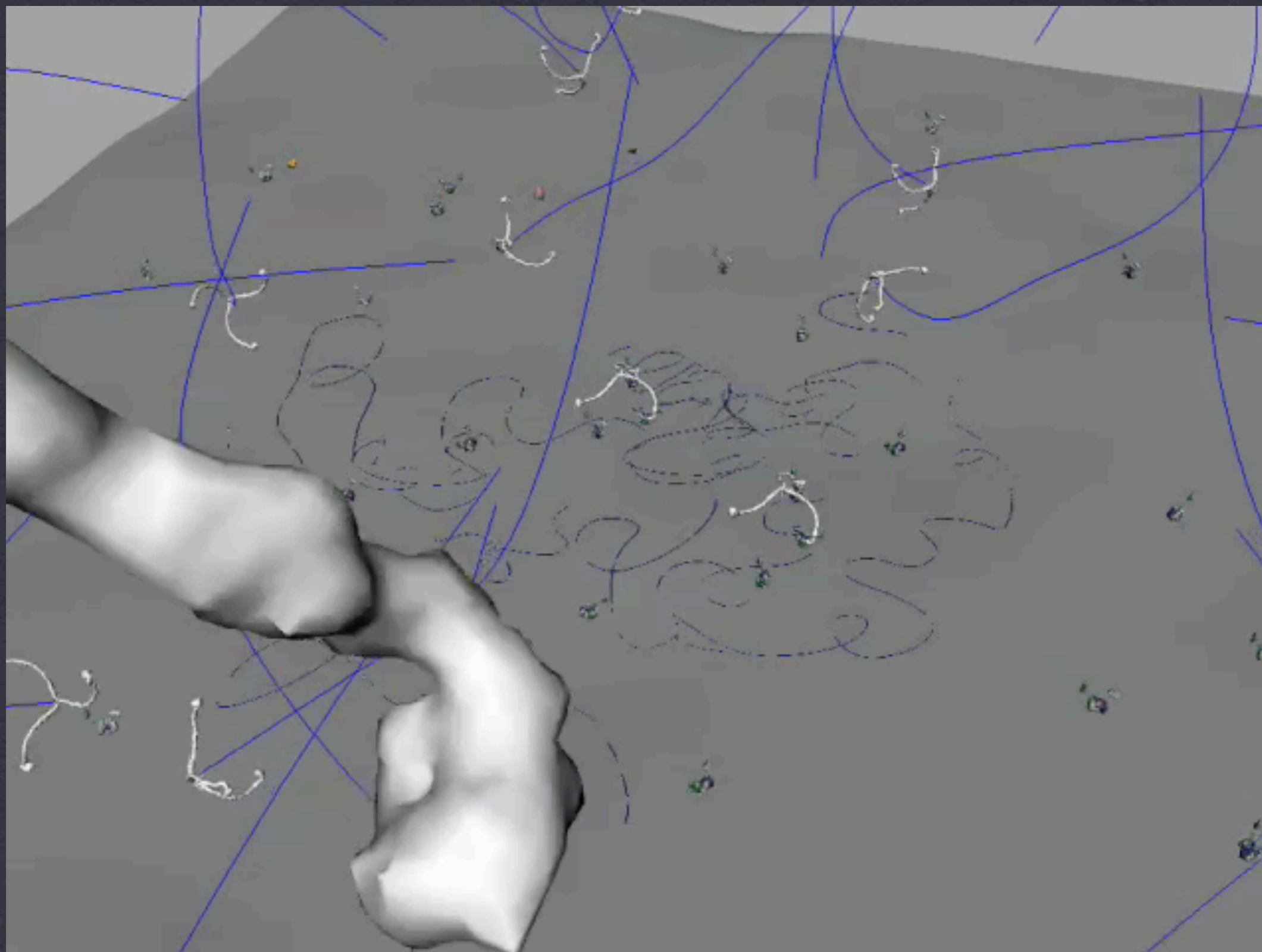
KIRCHHAUSEN, 2004



“Molecular 3D animations inform both the scientist who creates them and the audience that views them, through an active process leading to further inquiry and discovery.”

- Tomas Kirchhausen, Harvard Medical School

BEHIND THE SCENES



THE EXPLORING ORIGINS PROJECT

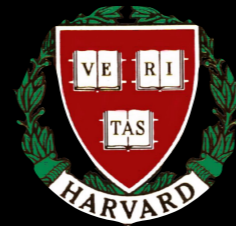


THE BROAD GOAL:

To make current research and theories on the origin of life more accessible to the public and to scientists through the use of dynamic molecular visualizations.

THE PLAN:

Work together with researchers to design visualizations of their research and current theories on the origin of life.



Szostak Lab
MGH/Harvard

Create visualizations for use in a multimedia exhibit at the Museum of Science.



Museum of Science

TRANSLATING SCIENTIFIC DATA INTO A VISUAL STORY

doi:10.1038/nature07018

nature

LETTERS

Template-directed synthesis of a genetic polymer in a model protocell

Sheref S. Mansy¹, Jason P. Schrum¹, Mathangi Krishnamurthy¹, Sylvia Tobé¹, Douglas A. Treco¹ & Jack W. Szostak¹

Contemporary phospholipid-based cell membranes are formidable barriers to the uptake of polar and charged molecules ranging from metal ions to complex nutrients. Modern cells therefore require sophisticated protein channels and pumps to mediate the exchange of molecules with their environment. The strong barrier function of membranes has made it difficult to understand the origin of cellular life and has been thought to preclude a heterofunctional lifestyle for primitive cells. Although nucleotides can cross membranes through defects in phospholipid bilayers, phospholipids lack the dynamic properties required for membrane remodeling and their corresponding alcohols and head groups are not good candidates for the components of simple amphiphiles that regulate oligo-

permeability is conveniently measured with a real-time fluorescence readout of vesicle volume after solute addition^{10,11}. We used pure myristoleic acid (C14:1 fatty acid, myristoleate in its ionized form) as a reference composition, because this compound generates robust vesicles that are more permeable to solutes than the more common monoester of myristoleic acid (monomyristolein, GMM) still. Addition of these amphiphiles should decrease the surface charge density of myristoleate vesicles, whereas myristoleyl phospholipids should increase the surface charge density. Surprisingly, addition of GMM affected ribose permeability, leading to a 20% increase (Fig. 2a). This result suggested that surface charge density was not a major factor controlling sugar permeability. We hypothesized that the larger steric bulk of the head group of GMM relative to the carboxylate of myristoleate might increase ribose permeability by stabilizing transient so-

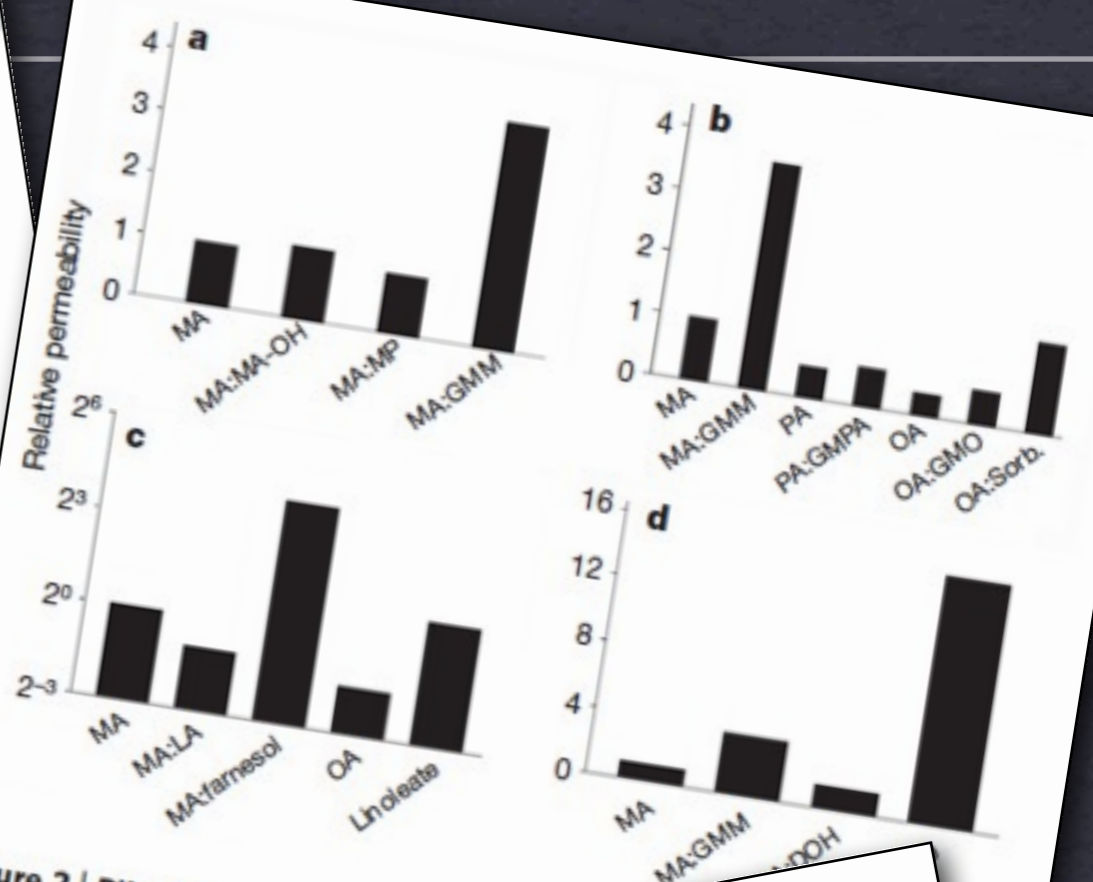


Figure 2 | Ribose permeability of various membranes. a–c, Influence of head group fluidity (c). d, Comparison of myristoleate and myristolein.

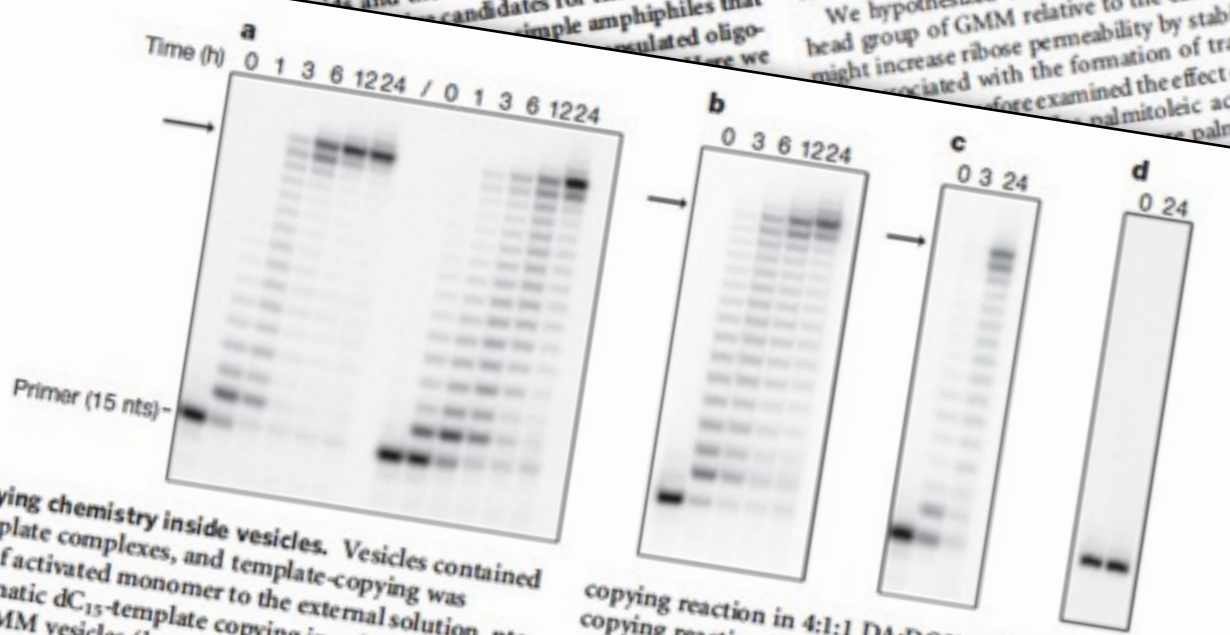


Figure 3 | Template-copying chemistry inside vesicles. Vesicles contained primer-template complexes, and template-copying was initiated by the addition of activated monomer to the external solution. nts, nucleotides. Non-enzymatic dC₁₅-template copying in solution (lanes 1–4), 2:1 MA:GMM vesicles (lanes 5–8) at 4 °C. b, Template-copying reaction in 4:1:1 DA:DOH:GMD vesicles at 25 °C. c, Template-copying reaction in POPC vesicles at 4 °C. d, Template-copying reaction in 2:1 MA:farnesol vesicles at 25 °C. For a–c, the arrow denotes full-length product. See Methods for reaction conditions.

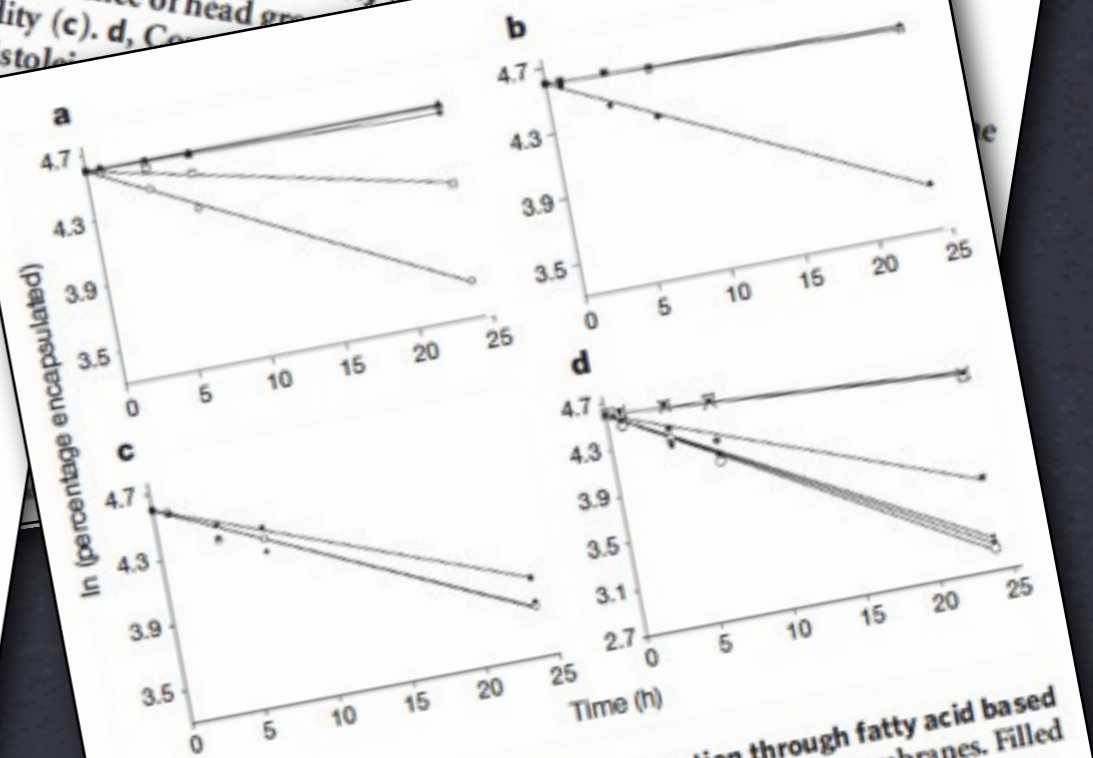


Figure 3 | Time courses of nucleotide permeation through fatty acid based membranes. Filled circle, ADP; open circle, ATP + 3 mM MgCl₂. Membranes: a, b, c, MA:GMM; d, MA:GMM.

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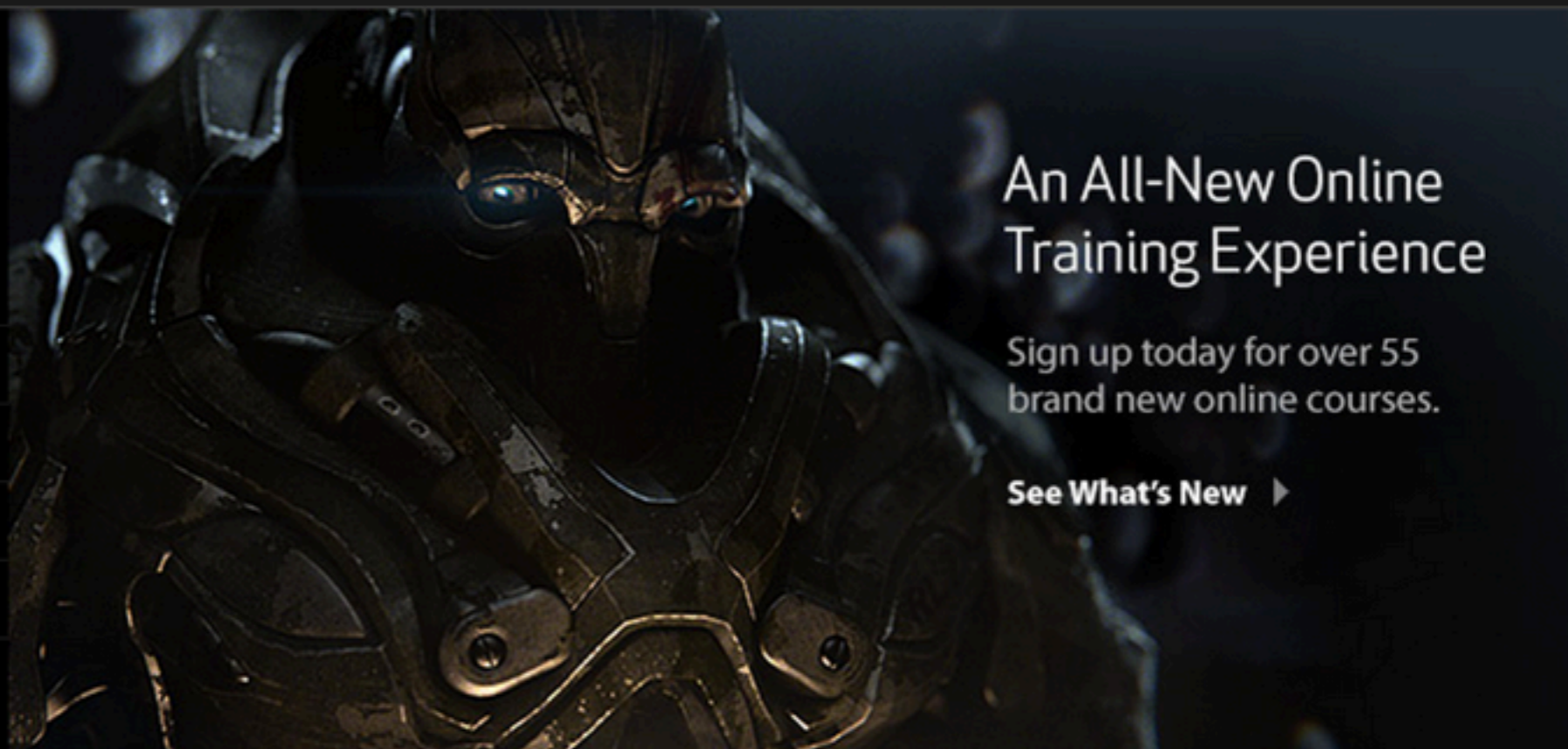
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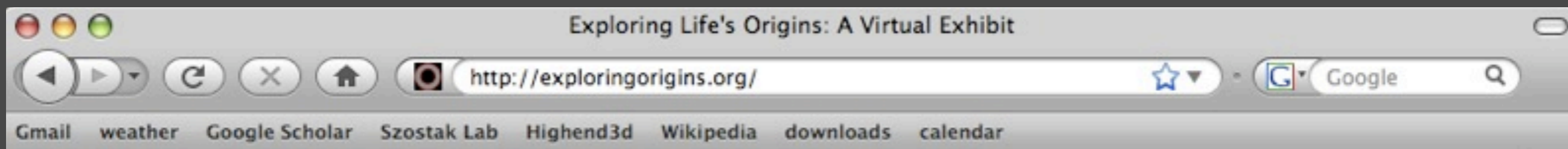


Artwork by
Fausto de Martini

HEADSPACE

THE EXPLORING ORIGINS PROJECT

WITH JACK SZOSTAK, MASS GENERAL HOSPITAL & HARVARD UNIVERSITY

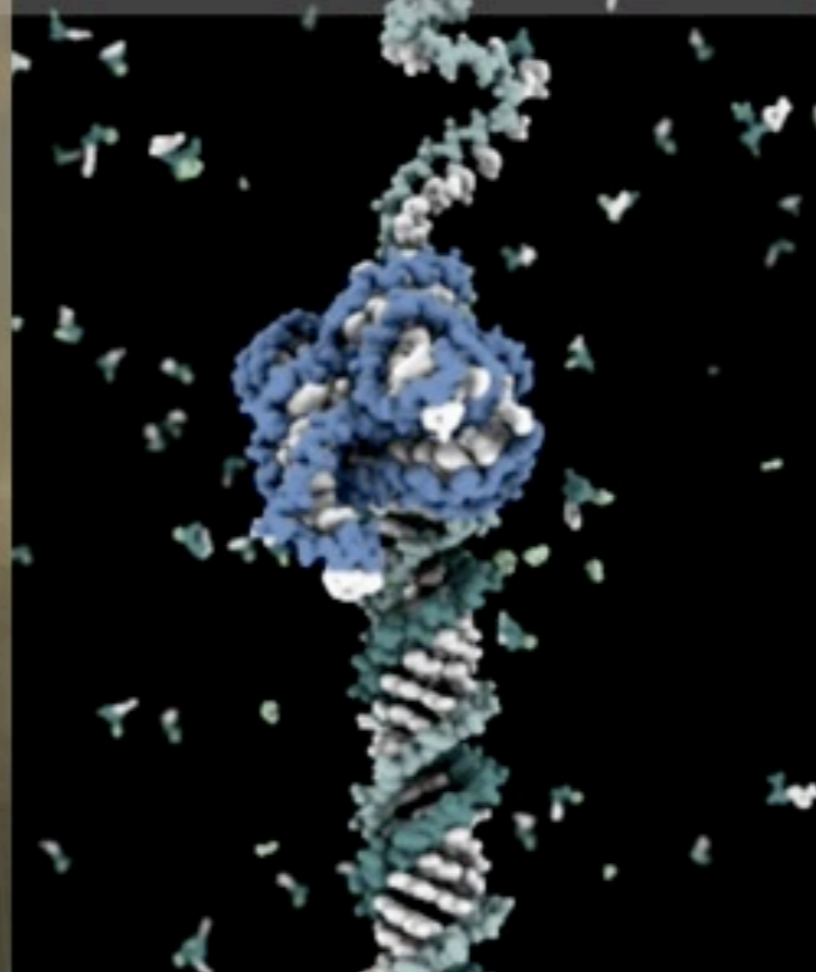


EXPLORING LIFE'S ORIGINS

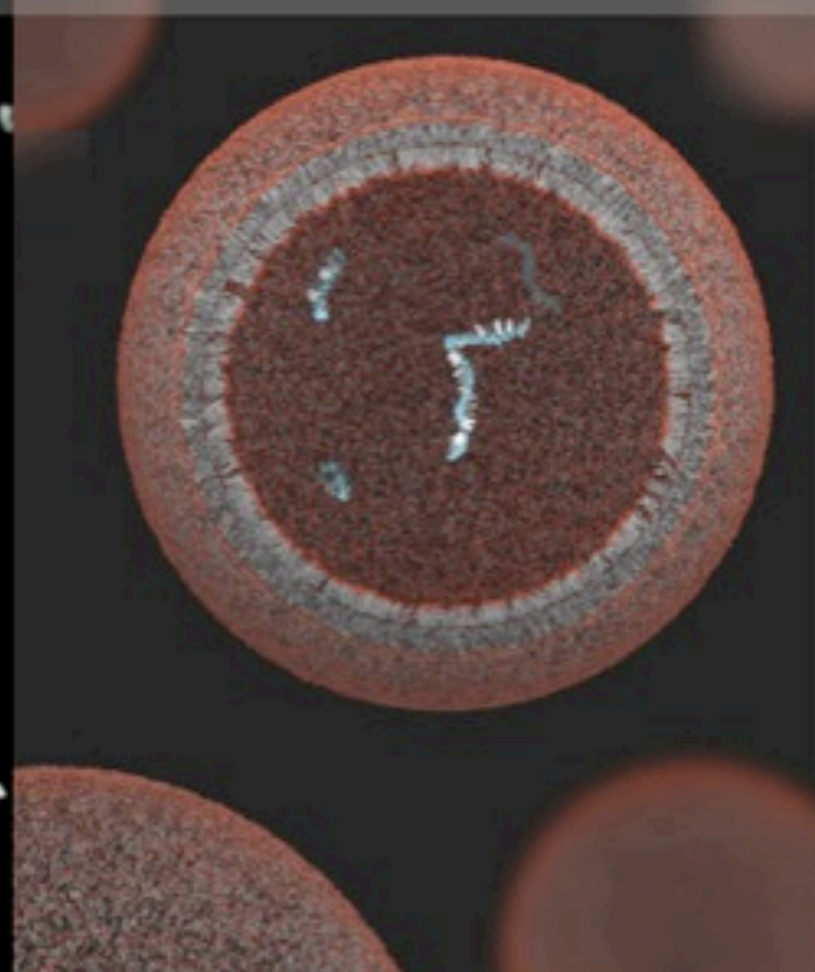
A TIMELINE OF
LIFE'S EVOLUTION



UNDERSTANDING
THE RNA WORLD



BUILDING
A PROTOCELL



THE EXPLORING ORIGINS KIOSK

AT THE MUSEUM OF SCIENCE, BOSTON (CURRENT SCIENCE & TECHNOLOGY)

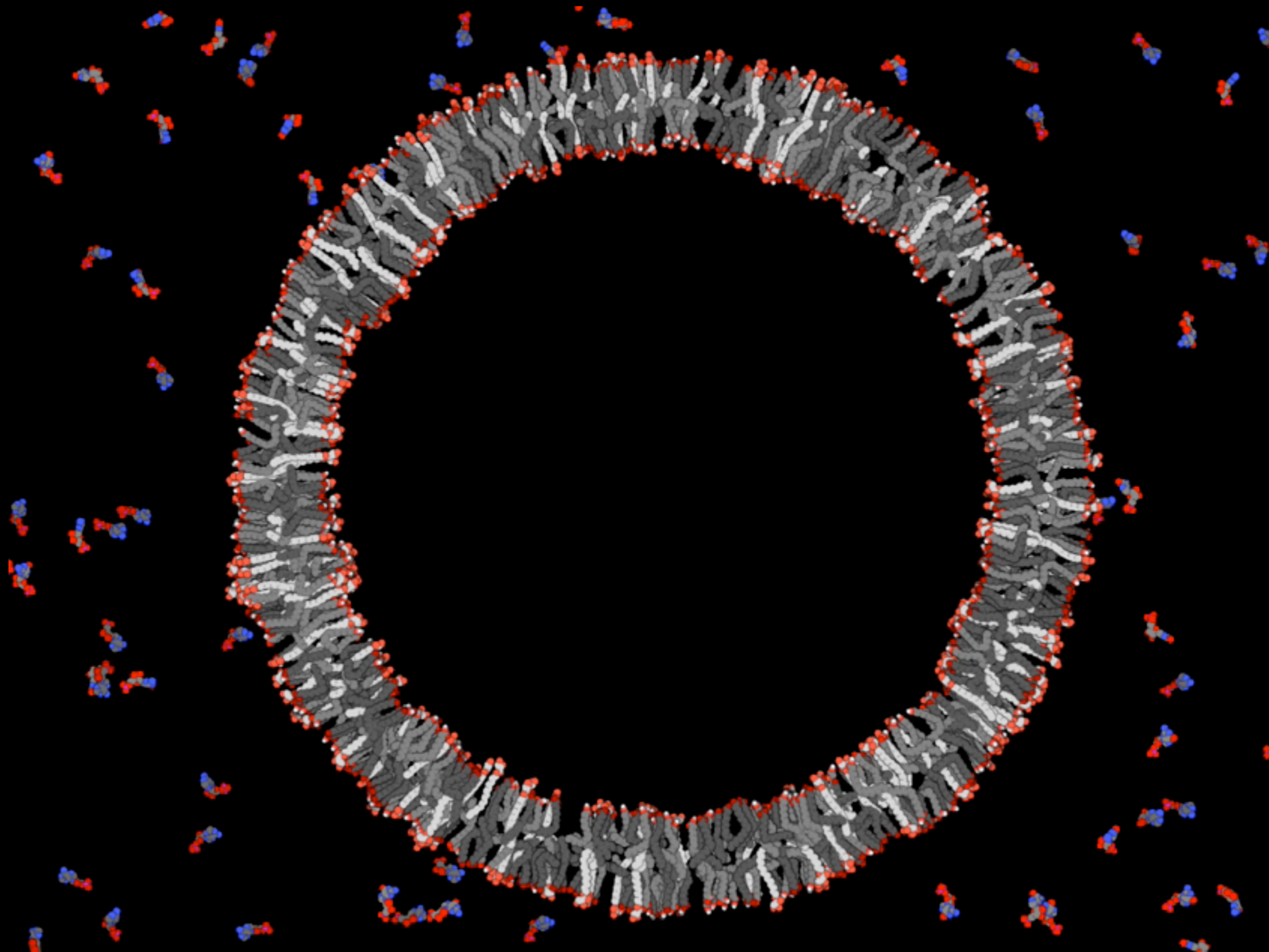


THE EXPLORING ORIGINS PROJECT

VISUALIZING ENTRY OF SMALL MOLECULES INTO VESICLES, 2008

THE EXPLORING ORIGINS PROJECT

VISUALIZING ENTRY OF SMALL MOLECULES INTO VESICLES, 2008



THE EXPLORING ORIGINS PROJECT

ROLE OF HYDROTHERMAL VENTS AND FATTY ACID SYNTHESIS, 2008



ANIMATIONS IN THE PRESS

Science Times

TUESDAY, JUNE 16, 2009

The New York Times

New Glimpses of Life's Puzzling Origins

By NICHOLAS WADE

Some 3.9 billion years ago, a swirl in the orbit of the Sun's inner planets sent a surge of large comets and asteroids careening into the inner solar system. Their violent impacts gouged out the large craters still visible on the Moon's face, heated Earth's surface and melted rock and boiled off its oceans into an infernal steam haze.

Yet rocks that formed on Earth 3.8 billion years ago, almost as soon as the bombardment had stopped, contain possible evidence of biological processes. If life can arise from inorganic matter so quickly and easily, why is it not abundant in the solar system and beyond? If biology is an inherent property of matter, why have chemists so far been unable to reconstruct life, or anything close to it, in the laboratory?

The origin of life on Earth bristles with puzzles and paradoxes. Which came

Researchers find new ways for biochemicals to self-assemble.

first, the process of living cells or the genetic information that makes them? How could the metabolism of living things get started without an enclosing membrane to keep all the necessary chemicals together? But if life started inside a cell membrane, how did the necessary nutrients get in?

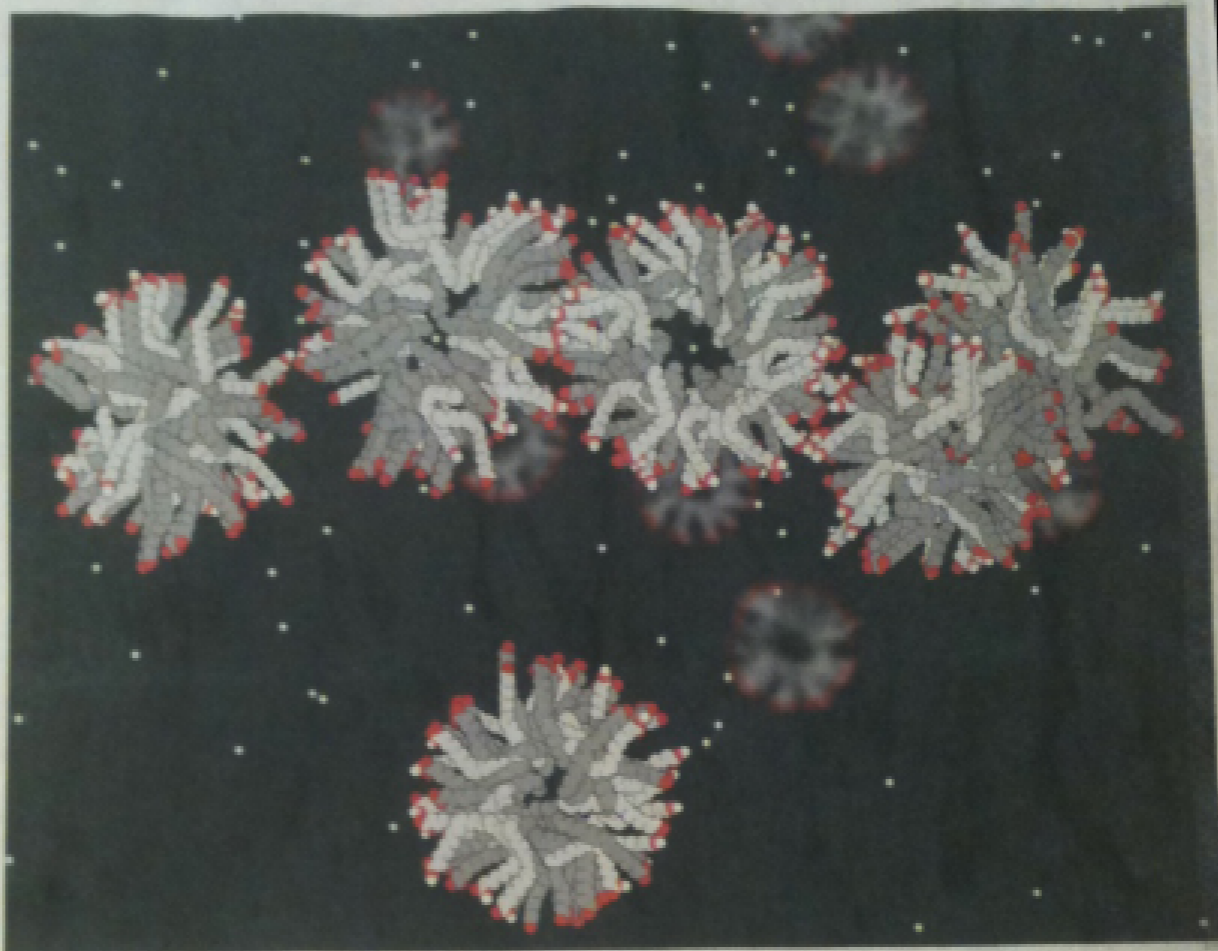
The questions may seem moot, since life did start somehow. But for the small group of researchers who insist on learning exactly how it started, frustration has abounded. Many once-promising leads have led only to years of wasted effort. Scientists as eminent as Francis Crick, the chief theorist of molecular biology, have quietly suggested that life may have formed elsewhere before reaching the planet, so hard does it seem to find a plausible explanation for its emergence on Earth.

In the last few years, however, four surprising advances have renewed confidence that a terrestrial explanation for life's origins will eventually emerge.

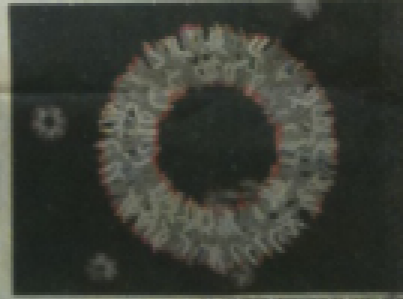
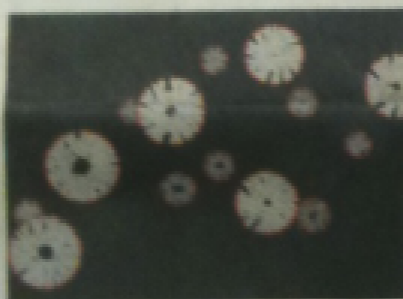
One is a series of discoveries about the cell-like structures that could have formed naturally from fatty chemicals likely to have been present on the primitive Earth. This lead emerged from a long argument between three colleagues as to whether a genetic system or a cell membrane came first in the development of life. They eventually agreed that genetics and membranes had to have evolved together.

The three researchers, Jack W. Szostak, David P. Bartel and P. Luigi Luisi, published a somewhat adventurous manifesto in *Nature* in 2005, declaring that the way to make a synthetic cell was to get a protocol and a genetic molecule to grow and divide in parallel.

Continued on Page 4



ANIMATE In one view of the beginnings of life, depicted in an animation, carbon monoxide molecules condense on hot mineral surfaces underground to form fatty acids, above, which are then expelled from geysers. The acids are drawn together in spherical clumps as water evaporates, above and below left, which then assemble in a sheet that becomes the precursor of a cell membrane, below right. To see the full animation, go to nytimes.com/science.

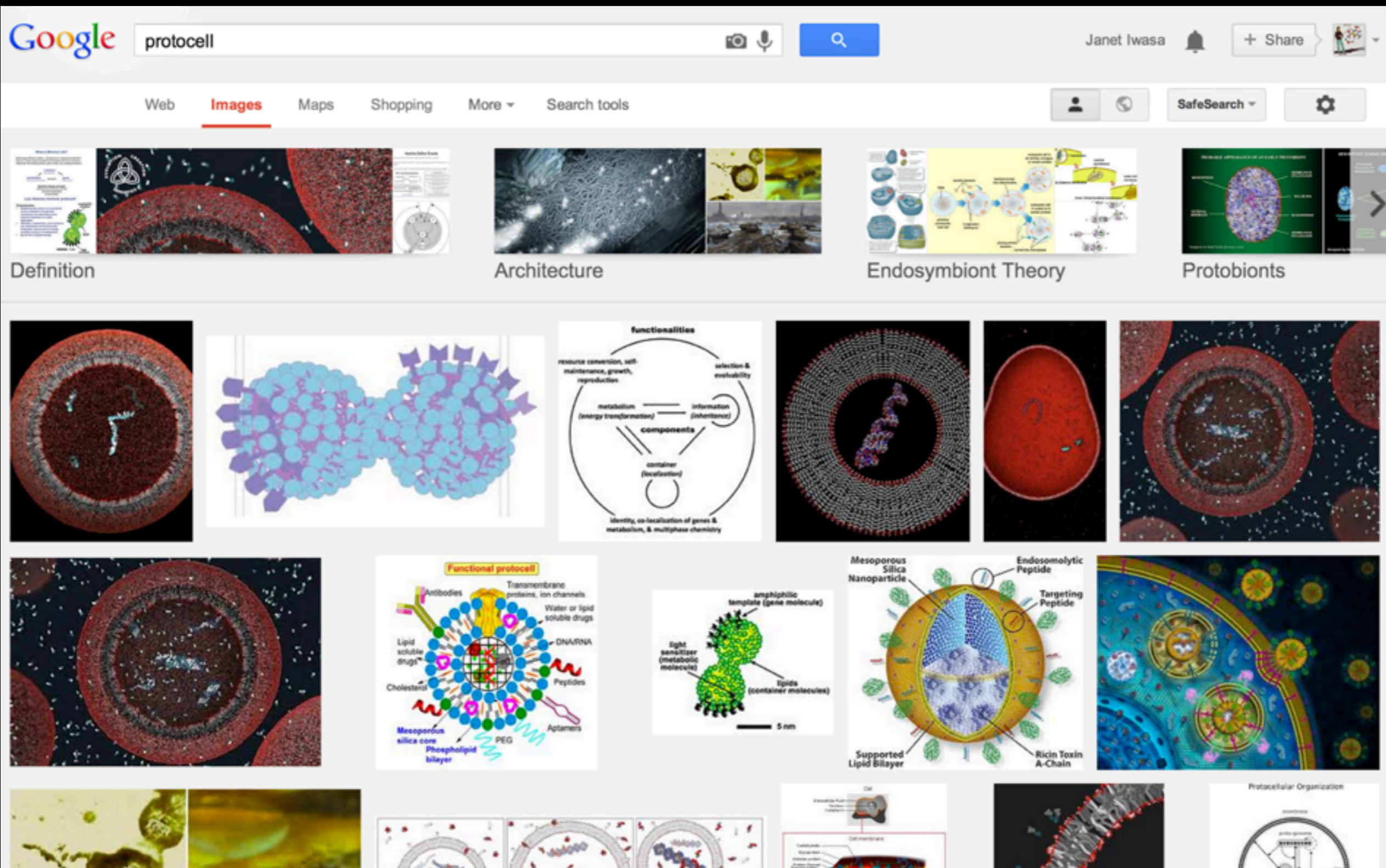


VISUALIZING PROTOCELLS

Google protocell Janet Iwasa + Share

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Definition Architecture Endosymbiont Theory Protobionts



The collage features several key images:

- Definition:** A circular diagram showing a cell-like structure with internal components.
- Architecture:** A 3D model of a protocell with a porous, spherical structure.
- Endosymbiont Theory:** A diagram illustrating the evolution of eukaryotic cells from prokaryotic ancestors.
- Protobionts:** A diagram showing a cell-like structure with internal organelles.
- Functionalities Diagram:** A circular diagram showing the relationship between functionalities (resource conversion, self-maintenance, growth, reproduction; selection & evolvability), components (metabolism, information, container), and the identity, co-localization of genes & metabolism, & multiphase chemistry.
- Mesoporous Silica Nanoparticle:** A diagram of a nanoparticle with a porous silica core and a phospholipid bilayer.
- Amphiphilic Template:** A diagram of a template structure with a gene molecule and lipids.
- Supported Lipid Bilayer:** A diagram of a bilayer structure with various molecules.
- Functional protocell:** A detailed diagram of a protocell with various components like antibodies, transmembrane proteins, water or lipid soluble drugs, DNARNA, peptides, aptamers, cholesterol, mesoporous silica core, and PEG.
- Endosymbiotic Peptide:** A diagram of a peptide structure.
- Targeting Peptide:** A diagram of a peptide structure.
- Ricin Toxin A-Chain:** A diagram of a toxin structure.
- Protocellular Organization:** A diagram showing the organization of protocells.

VISUALIZING PROTOCELLS

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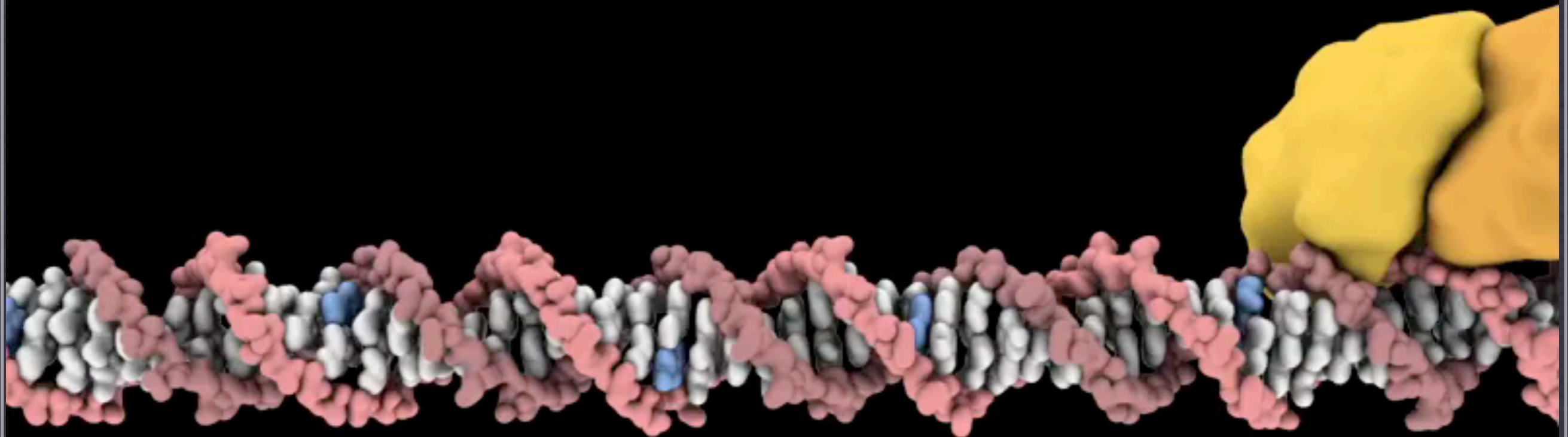
Definition Architecture Endosymbiont Theory Protobionts

The collage features several key images and diagrams:

- Definition:** A micrograph of a protocell with a pink border, showing a dark, textured interior within a reddish-brown outer shell.
- Architecture:** A diagram of a protocell structure with a pink border, showing a cluster of blue and purple spheres.
- Endosymbiont Theory:** A diagram illustrating the evolution of a cell from a symbiotic relationship, with a pink border.
- Protobionts:** A diagram showing a protocell with a pink border, highlighting its internal structure.
- Functionalities:** A conceptual diagram showing the relationship between functionalities (resource conversion, self-maintenance, growth, reproduction; selection & evolvability), components (metabolism, information, container), and their interactions.
- Structural Diagrams:** Several diagrams showing the construction of a protocell, including:
 - A diagram with a pink border showing a cross-section of a protocell with various components like antibodies, transmembrane proteins, and lipids.
 - A diagram showing an amphiphilic template (gene molecule) and lipids (container molecules) forming a structure.
 - A diagram showing a mesoporous silica nanoparticle, endosomolytic peptide, targeting peptide, supported lipid bilayer, and ricin toxin A-chain.
- Micrographs:** Several micrographs showing the physical appearance of protocells, some with pink borders.
- Protocellular Organization:** A diagram showing the organization of a protocell, with a pink border.

CHROMATIN REMODELING

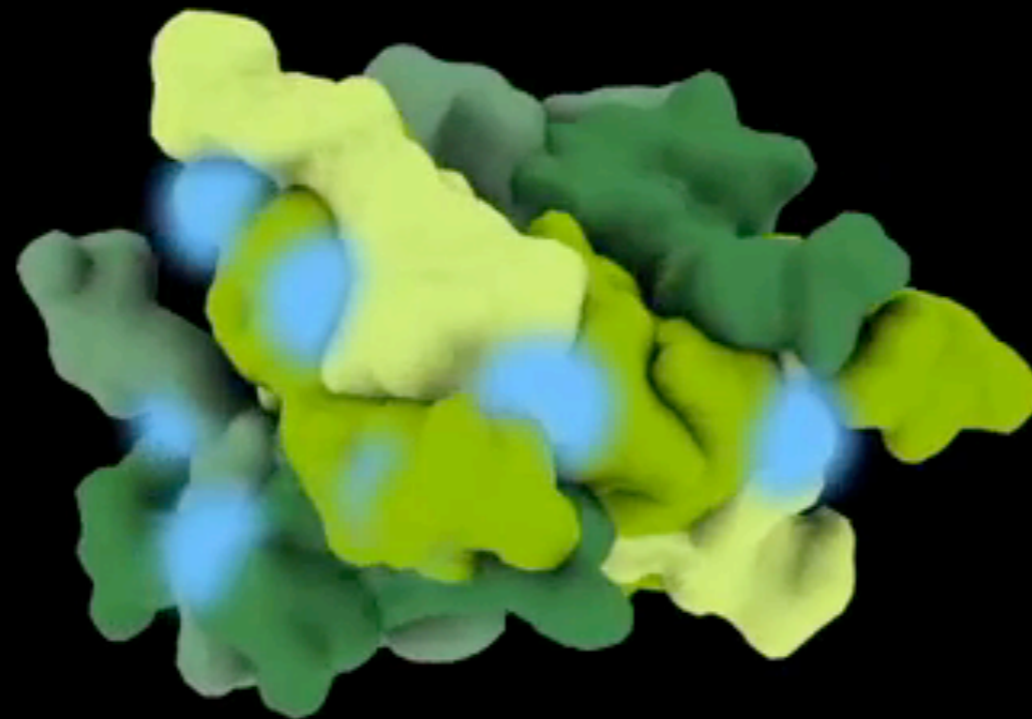
WITH BRAD CAIRNS AND CEDRIC CLAPIER



INTRODUCTION TO THE ATPASE (STRUCTURE TAKEN FROM PCRA, 2PJR)

CHROMATIN REMODELING

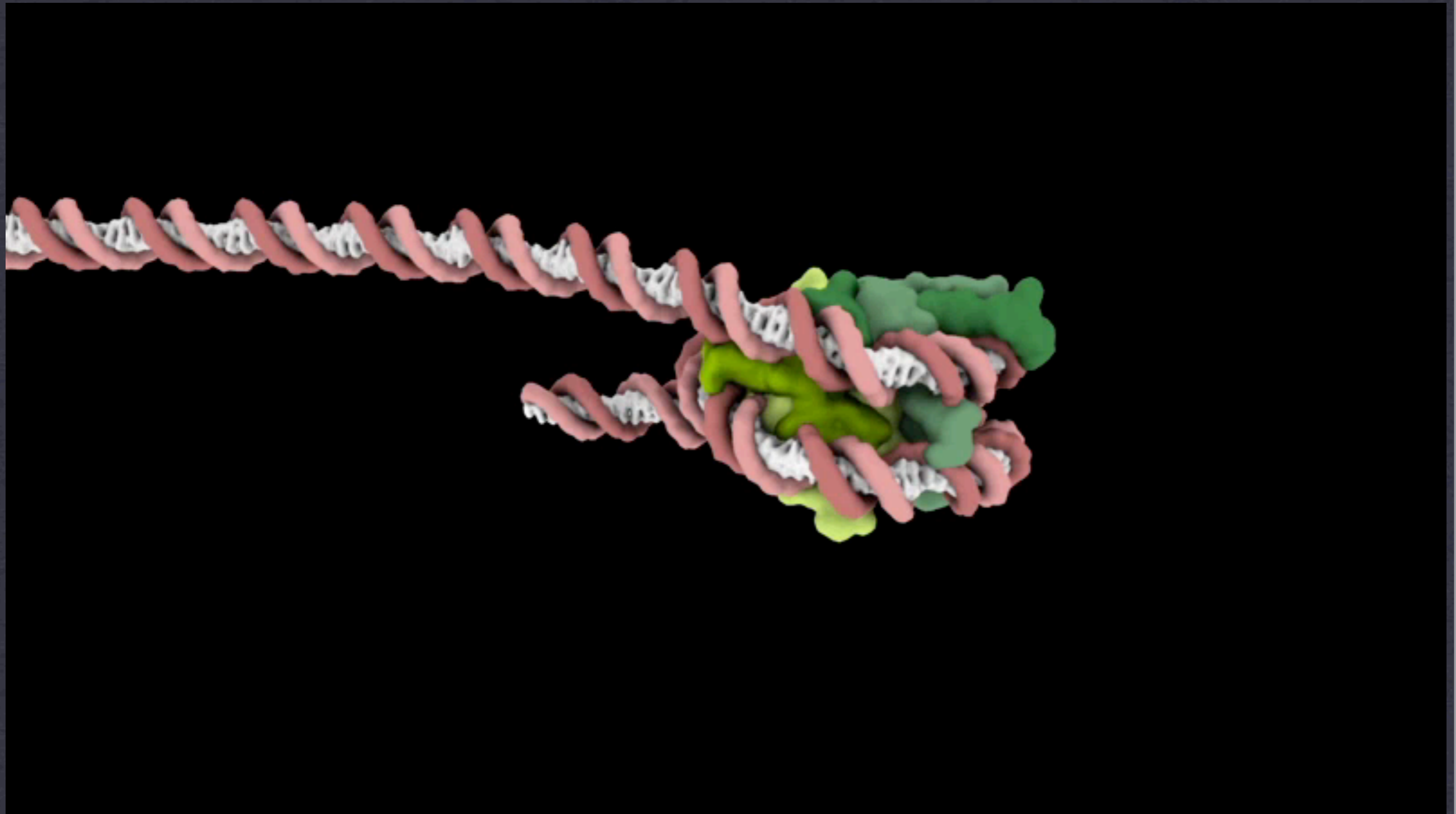
WITH BRAD CAIRNS AND CEDRIC CLAPIER



INTRODUCTION TO THE NUCLEOSOME (STRUCTURE TAKEN FROM 1A0I)

CHROMATIN REMODELING

WITH BRAD CAIRNS AND CEDRIC CLAPIER



BASIC MECHANISM OF SWI/SNF REMODELERS

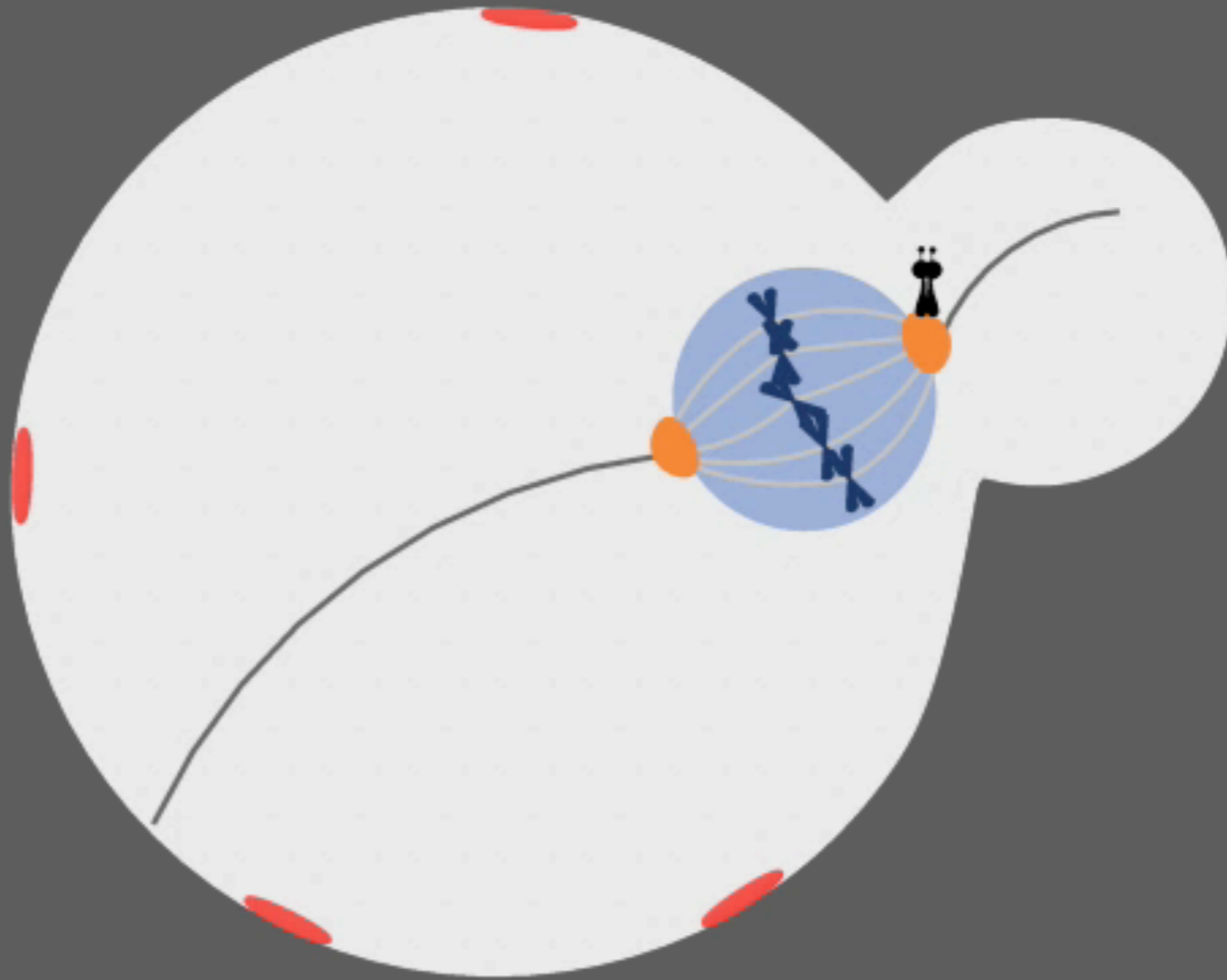
COMMUNICATING CONFIDENCE VIA RENDERING STYLE

THE ROLE OF DYNEIN IN YEAST MITOSIS

with Sam Reck-Peterson

COMMUNICATING CONFIDENCE VIA RENDERING STYLE

THE ROLE OF DYNEIN IN YEAST MITOSIS



with Sam Reck-Peterson

ANIMATING AMYLOID FIBRILS

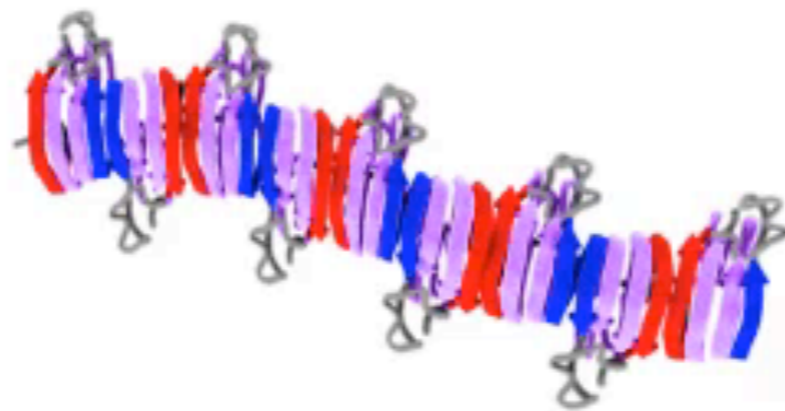
NUCLEATION OF A PRION POLYMER



WITH SUSAN LINDQUIST

ANIMATING AMYLOID FIBRILS

PULLING APART A PRION POLYMER



WITH SUSAN LINDQUIST

ANIMATION AND THE SCIENTIFIC PROCESS

STEPS:

1. Define the question
2. Make observations
3. Form hypothesis
4. Perform experiment and collect data
5. Analyze data
6. Interpret data and draw conclusions
7. Publish results

ANIMATION AND THE SCIENTIFIC PROCESS





STEPS:

1. Define the question
2. Make observations
3. Form hypothesis
4. Perform experiment and collect data
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6. Interpret data and draw conclusions
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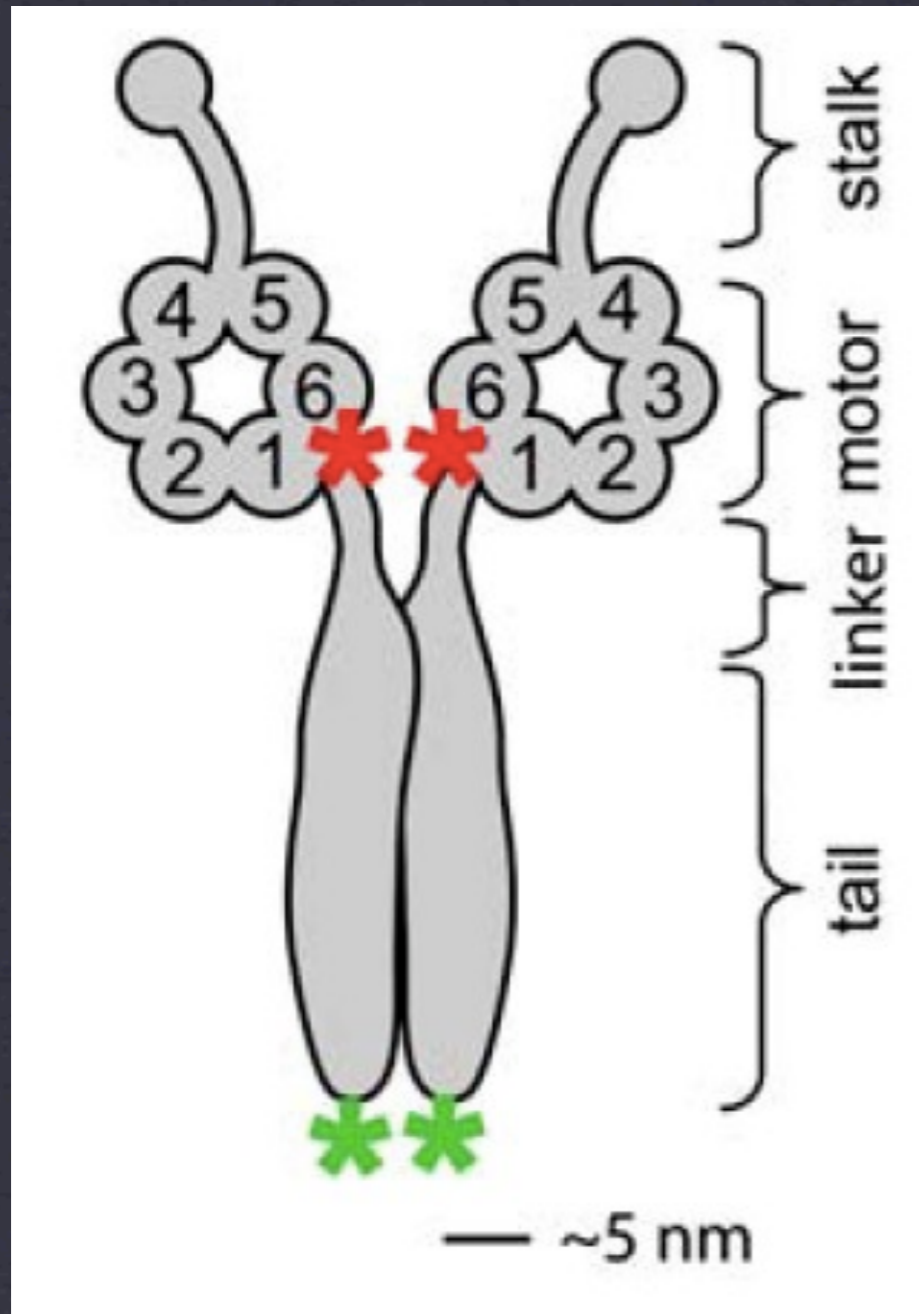
ANIMATION AND THE SCIENTIFIC PROCESS

STEPS:

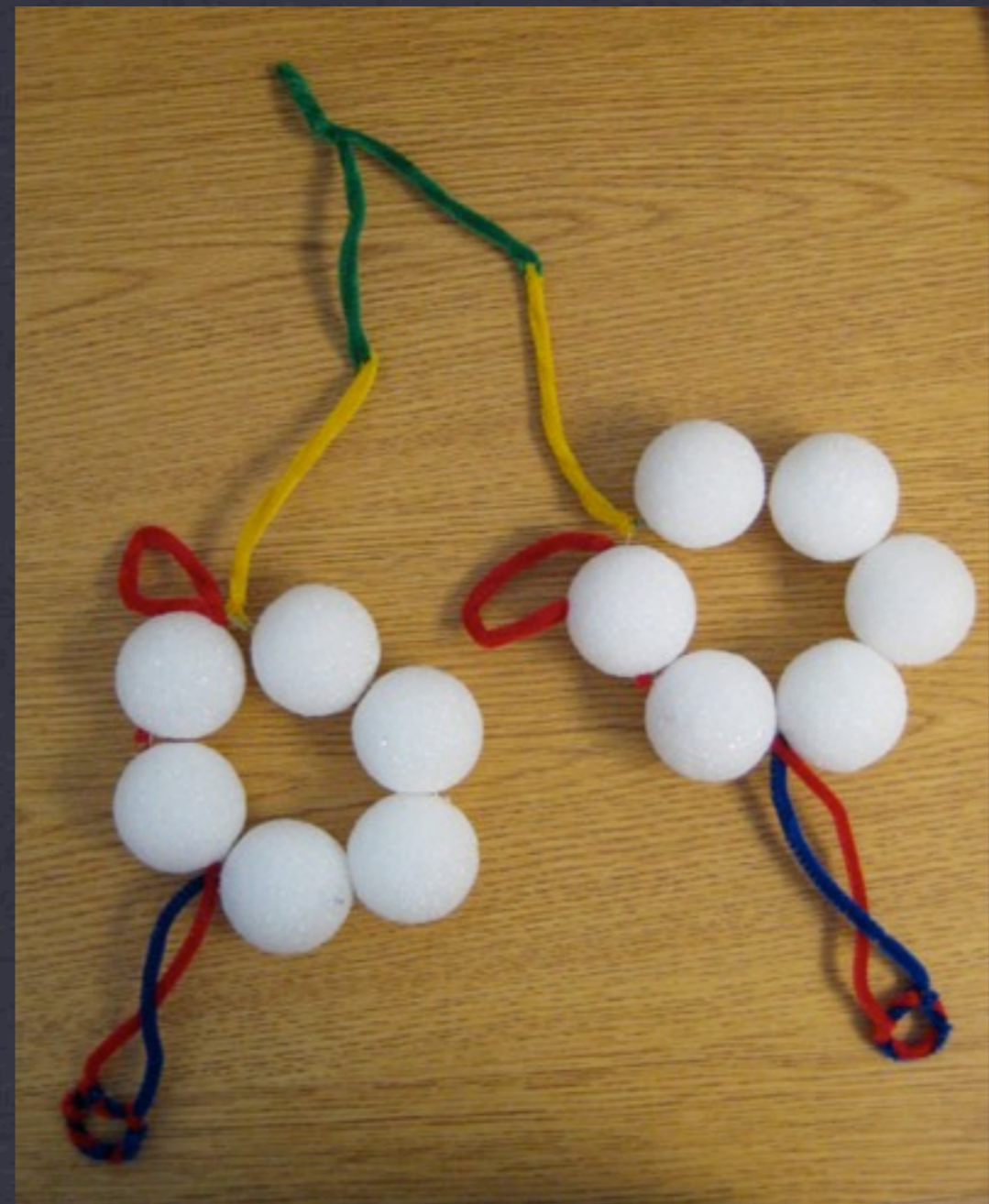
-  1. Define the question
-  2. Make observations
-  3. Form hypothesis
4. Perform experiment and collect data
5. Analyze data
6. Interpret data and draw conclusions
-  7. Publish results

STUDYING DYNEIN STRUCTURE AND FUNCTION

2D AND 3D MODELS



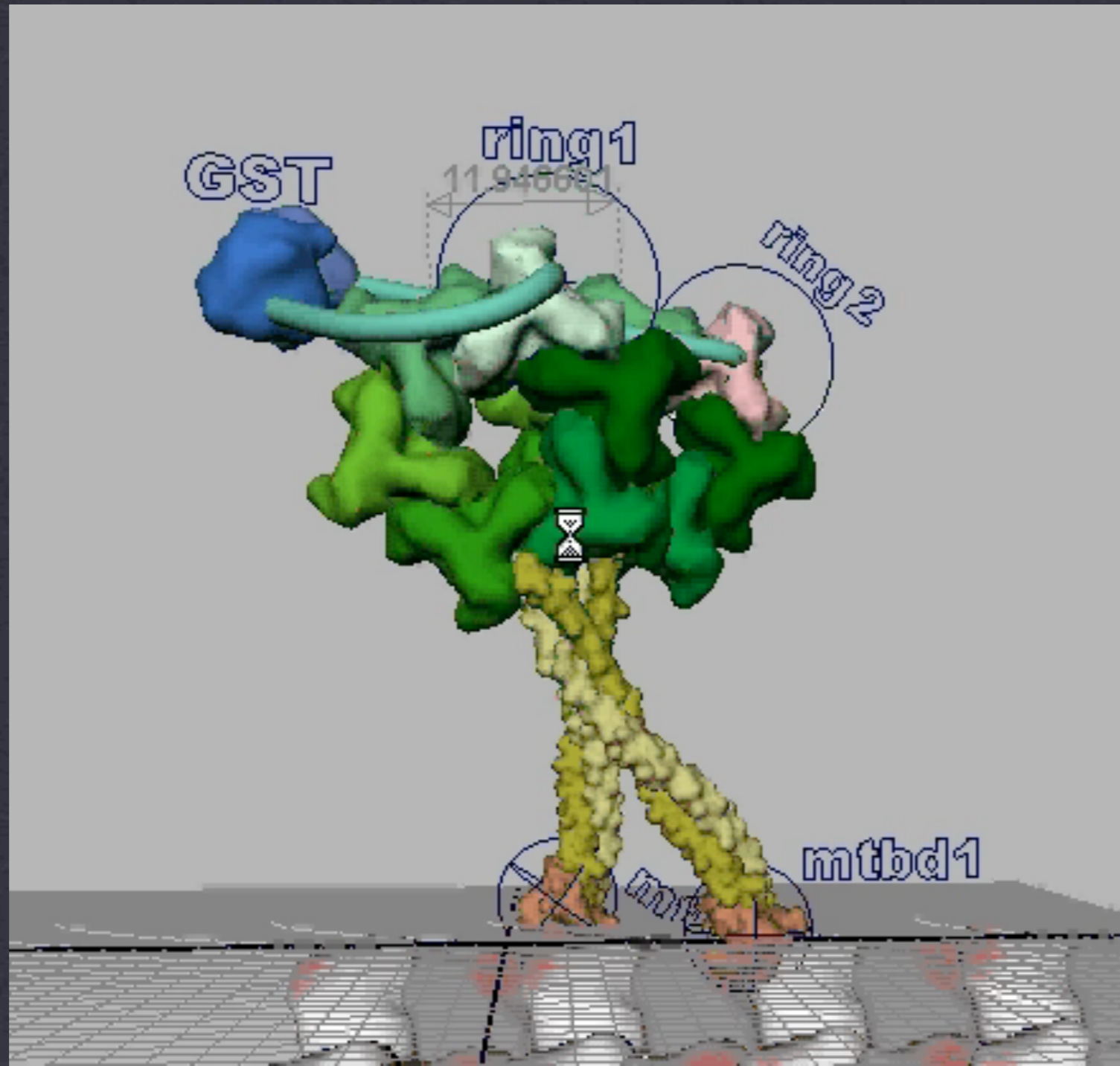
Schematic illustration of dynein
Reck-Peterson, et al., 2006



Physical model of the motor protein dynein
made by Samara Reck-Peterson

STUDYING DYNEIN STRUCTURE AND FUNCTION

AN EARLY ARTICULATED 3D MODEL

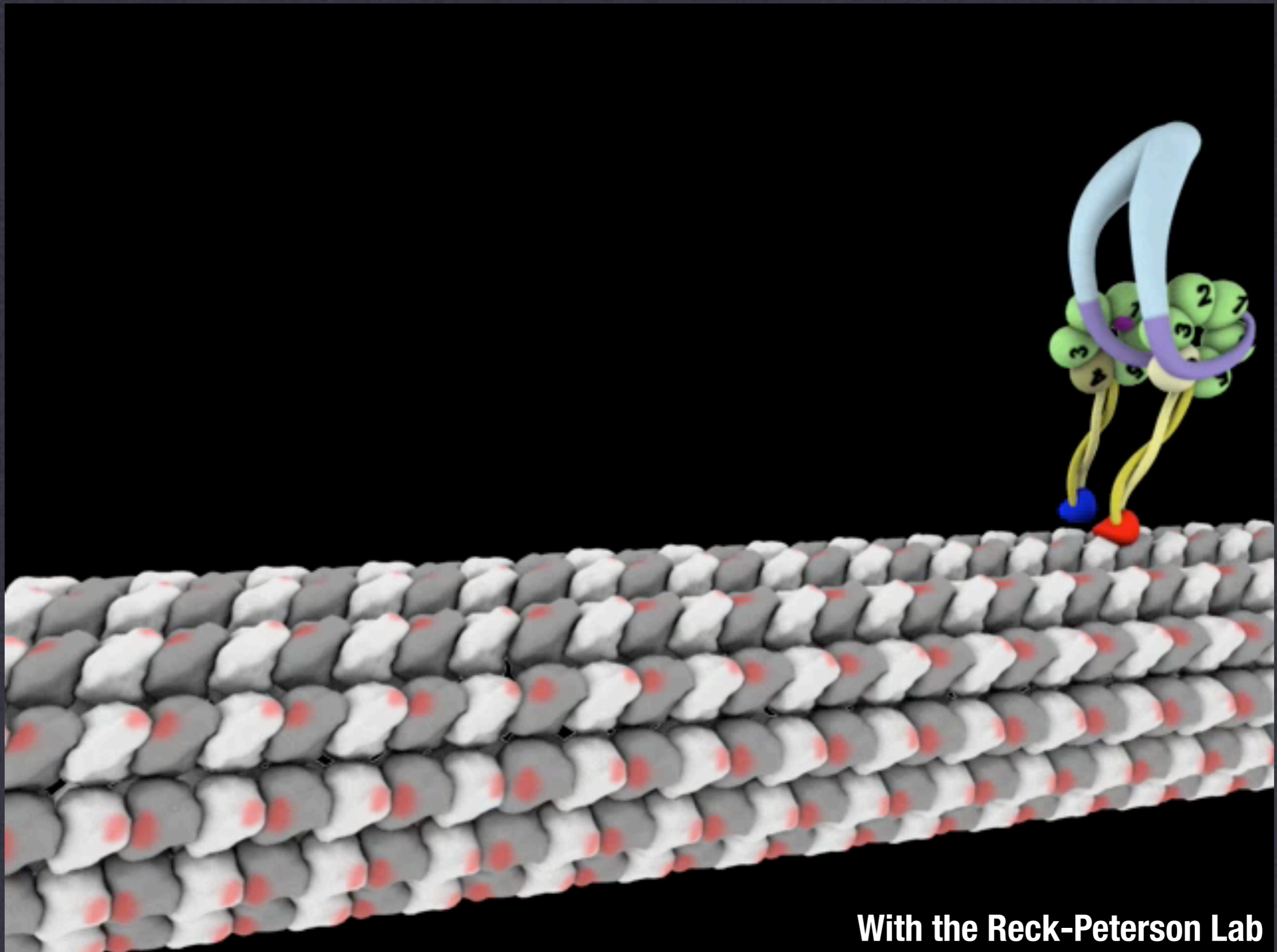


3D model of dynein

With the Reck-Peterson Lab

STUDYING DYNEIN STRUCTURE AND FUNCTION

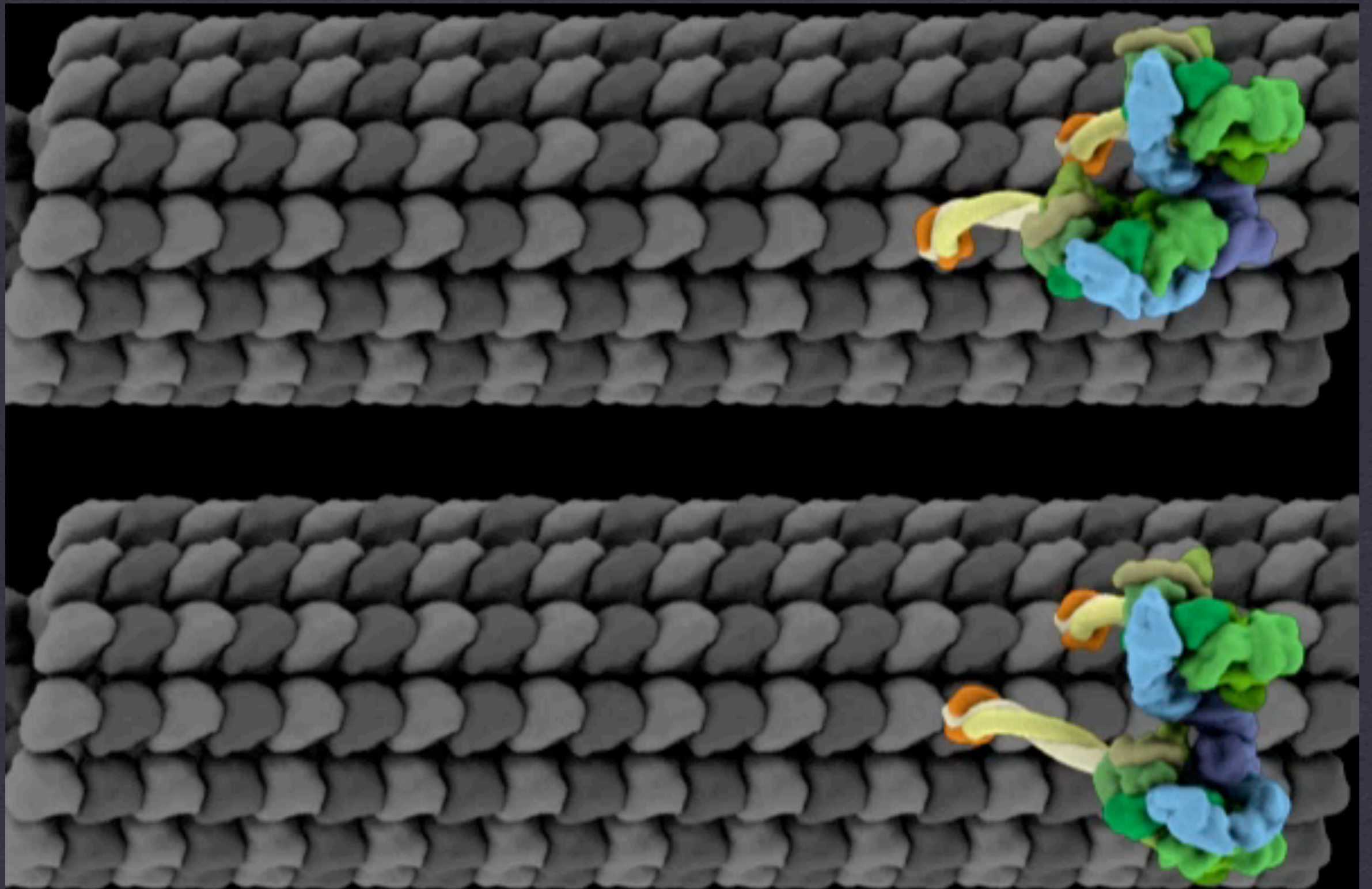
AN EARLY 3D ANIMATED MODEL



With the Reck-Peterson Lab

STUDYING DYNEIN STRUCTURE AND FUNCTION

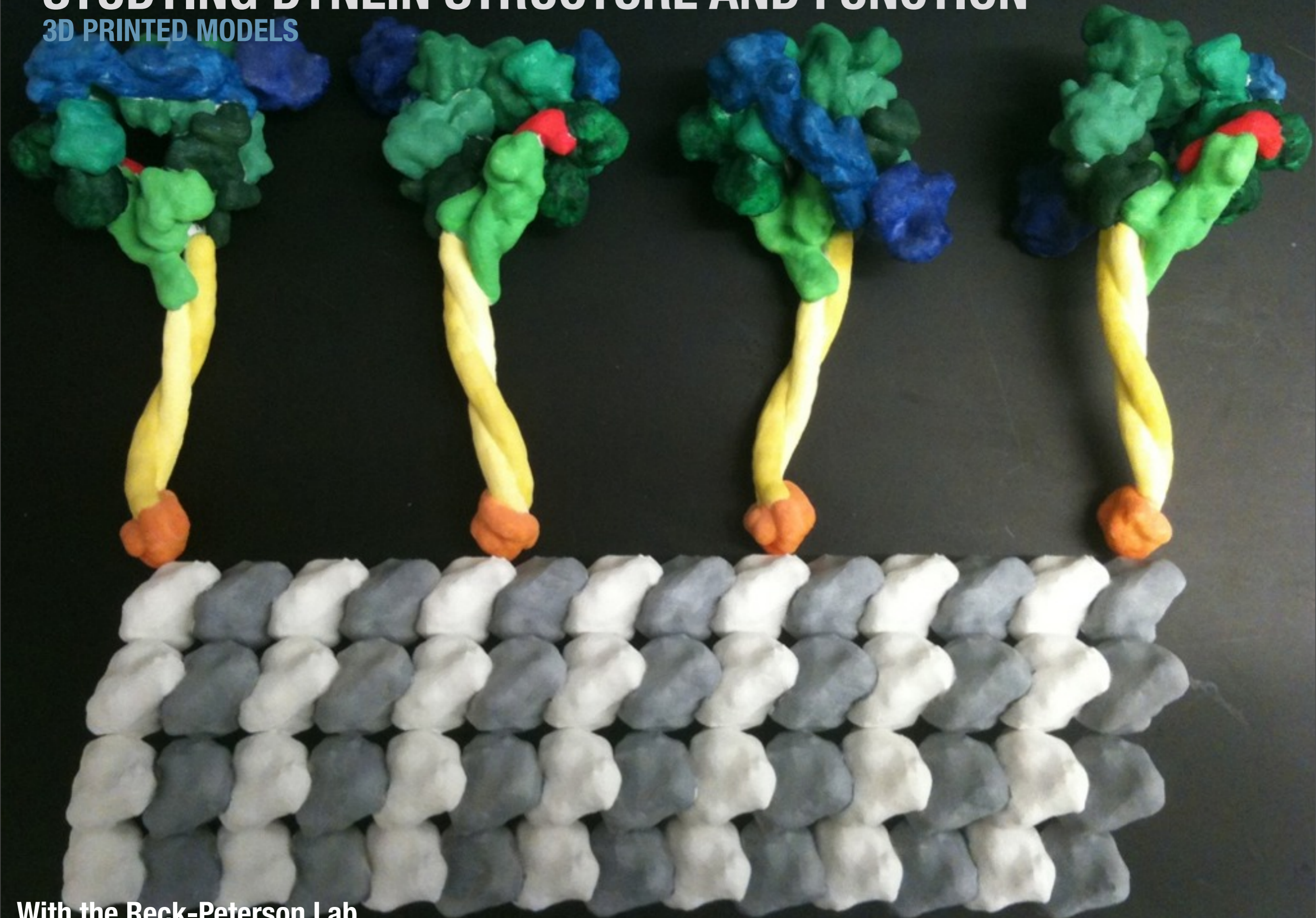
COMPARING DIFFERENT MODELS OF DYNEIN LOCOMOTION



With the Reck-Peterson Lab

STUDYING DYNEIN STRUCTURE AND FUNCTION

3D PRINTED MODELS



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MOLECULAR FLIPBOOK

A COMMUNITY RESOURCE FOR BUILDING AND SHARING MOLECULAR VISUALIZATIONS



(1) A 3D ANIMATION TOOLKIT

which will allow biologists to readily create molecular and cellular animations using open-source animation software

(2) A WEBSITE AND DATABASE

where users can upload and share their animation scene files and completed animations

MOLECULAR FLIPBOOK

TOOLKIT FEATURES & CHALLENGES



- suite of molecular animation tools built in Blender's game engine which will include import, modeling, animation and rendering modules.
- intuitive interface, simple controls
- ability to start creating animations after watching a short video tutorial.

Primary challenge:

How do we make 3D animation *intuitive* for users new to animation (and to those returning after a long break)?

MOLECULAR FLIPBOOK

INTERFACE DESIGN: OVERVIEW



MolecularFlipbook

Added to scene: 1a0i.J
Adding slide after slide 1
Adding slide after slide 2

Outliner

- 1a0i
 - + I
 - + J
 - + A
 - + B
 - + C
 - + D
 - + E
 - + F
 - + G
 - + H

Helper

Welcome
Left Click: Select Object
Left Click Drag: Change View
Z: Undo
Space Bar: Play animation

Import Blobber
Load Save
Display Shading
Camera Editor
Export Publish

16:9

00:06.0 00:06.0

1 3.0 2 3.0 3 +

The screenshot displays the MolecularFlipbook software interface. At the top left, the title bar reads "MolecularFlipbook". The main workspace features a 3D molecular model of a protein complex, rendered in various colors (purple, blue, green, red, orange) against a light gray grid background. A large, semi-transparent green number "3" is overlaid on the left side of the model. To the left of the workspace is a vertical toolbar with buttons for "Import", "Blobber", "Load", "Save", "Display", "Shading", "Camera", "Editor", "Export", and "Publish". To the right is a panel with an "Outliner" section listing a hierarchy of objects (1a0i, I, J, A, B, C, D, E, F, G, H) and a "Helper" section providing keyboard shortcuts. Below the workspace is a playback control bar with a play button, a progress slider, and a time display showing "00:06.0". At the bottom, a slide navigation bar shows three slide thumbnails labeled "1", "2", and "3", with a green "+" button to the right. The "3" slide is currently selected and highlighted with a green border.

MOLECULAR FLIPBOOK

DEMO



flipbook

Welcome to
Molecular flipbook

Import Rotter
Load



00:00.0

00:00.0

1

The image shows a software interface for a molecular flipbook. At the top left, the title bar reads 'flipbook'. Below it, there is a dark grey rectangular area. To the left of the main 3D view, there are three buttons: 'Import', 'Rotter', and 'Load'. The main 3D view is a white rectangular area containing a perspective view of a 3D grid. A large green number '1' is positioned in the top-left corner of the grid. Below the 3D view, there is a navigation and playback control area. On the left, there is a play button icon and a progress bar showing '00:00.0'. To the right of the progress bar, there is a refresh icon and another '00:00.0' time display. At the bottom left, there is a small green box containing the number '1', with a minus sign above it and a plus sign below it.

MOLECULAR FLIPBOOK

FUTURE DEVELOPMENTS



- + Linker tool to connect different domains of known structure
- + Tools for creating polymers and other protein complexes
- + Use of collision detection for binding

<http://MolecularFlipbook.org>



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Molecular Flipbook Toolkit Features (Beta Version)



PDB Import

Upload molecular structures as PDB files, either from your computer or from the Protein Data Bank database.



Blobber tool

Create a "blobby" as a stand-in for proteins that you don't have a structure file for. All you need to know is a molecular weight or approximate dimensions to create a blobby!



Animate colors and shaders

It's easy to animate your molecules changing color (to signify activation, for example) and to change its look using the



In-app tutorials

The in-application tutorials launch automatically and will walk you through how to use Flipbook.

Molecular Flipbook

An open source 3D animation software using the Blender Game Engine

Download V0.2 For Mac

Download V0.2 For Windows

Molecular Flipbook is a free and **open-source** molecular animation software toolkit that has been specifically designed with the needs of biology researchers in mind. The Molecular

MOLECULAR FLIPBOOK

WEBSITE FEATURES

- searchable, easy-to-use online database that also hosts community/social interactions/collaborations

- will allow users to share not only Blender-based animation, but also Illustrator, Photoshop files, etc.

- provides a visual way of following the evolution of a hypothesis over time

Primary challenge:

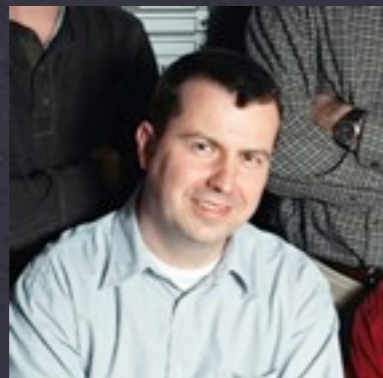
How do we get users to share their visualizations with others?



The screenshot shows the homepage of the Molecular Flipbook website. At the top left is the logo, which consists of a green and white folded paper icon next to the text 'MOLECULAR FLIPBOOK' in green. To the right of the logo is a search bar with a magnifying glass icon, a 'Login' button, and links for 'Sign Up' and 'Upload'. Below this is a navigation menu with links for 'Home', 'About', 'Download', 'Library', and 'Help'. The main content area is divided into two columns. The left column is titled 'Featured Animation' and features a 3D molecular model of a nucleosome core particle, rendered in various colors (green, blue, purple, orange). The text below the model reads 'Crystal structure of the nucleosome core particle at 2.8 A resolution.' The right column is titled 'Molecular Flipbook' and contains the text 'An open source 3D animation software using the Blender Game Engine' and a 'Download Now!' button. Below this is a paragraph describing the software as a free and open-source molecular animation software toolkit designed for biology researchers.

This screenshot shows the same homepage as above, but with the 'Browse Scene Files' section highlighted. The 'Featured Animation' section is now empty. The 'Browse Scene Files' section has a sub-menu with options for 'Most Viewed', 'Most Faved', 'Most Recent', and 'Staff Picks'. Below this menu are two thumbnail images: one showing a 3D molecular model of a protein structure and another showing a yellow cylindrical object. The 'Molecular Flipbook' section on the right remains the same, with the 'Download Now!' button and descriptive text.

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MANY THANKS

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The Molecular Flipbook Project

<http://MolecularFlipbook.org>

The Exploring Origins Project

<http://ExporingOrigins.org>