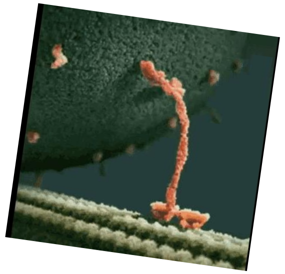
OSHER LIFELONG LEARNING INSTITUTE



NanoMachines:
The Tiny Biological Gadgets that Animate Life

Modern Times
(Charlie Chaplin 1936)

Session 1
Building Blocks

OLLI at Illinois
Spring 2023

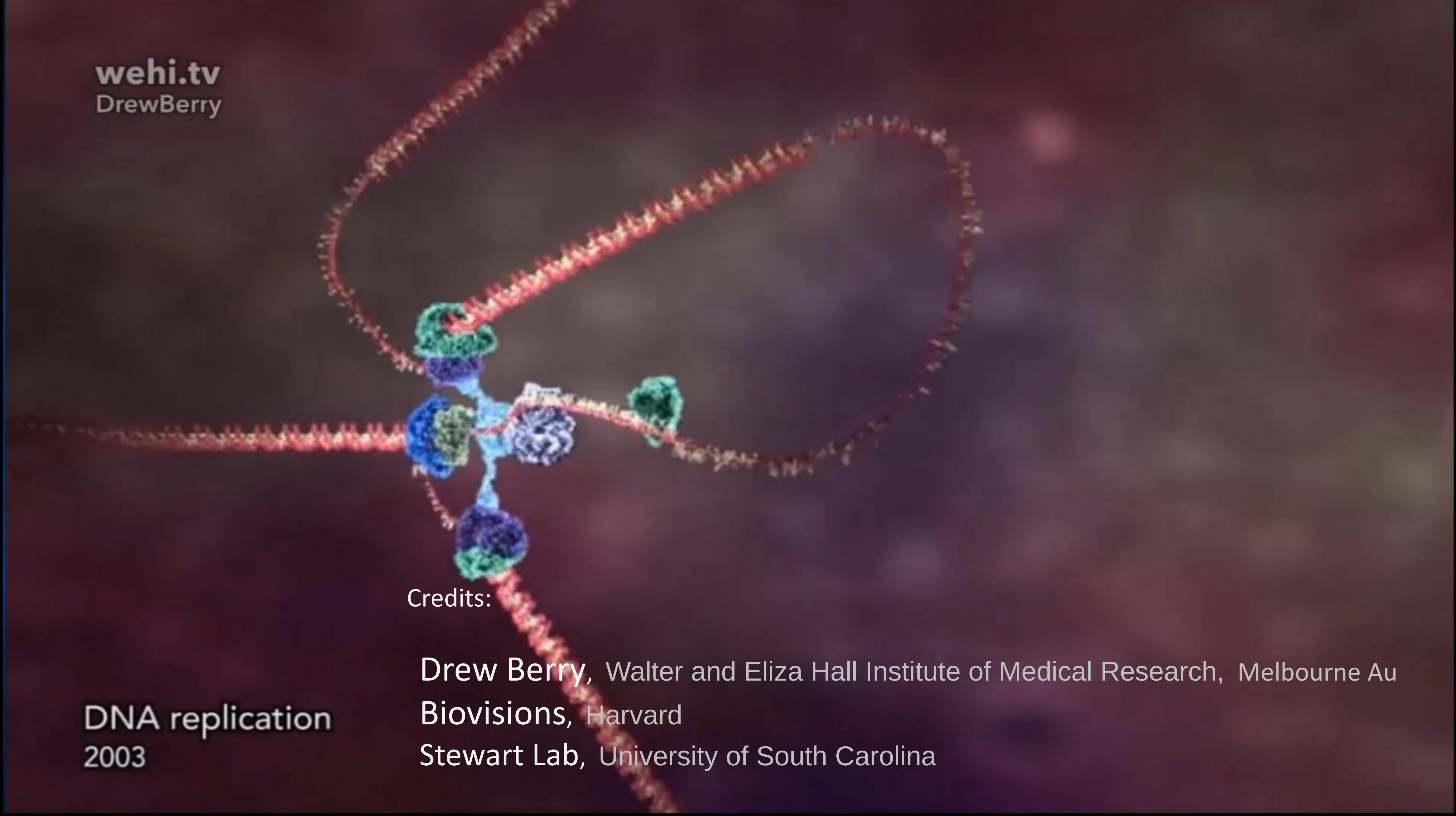
D. H. Tracy
DavidHTracy@gmail.com

Course Outline

1. Overview
   Building blocks, energy flow, how we know
2. nanoMachines in energy flow
3. Motors and locomotion
4. DNA & RNA processing, protein manufacturing, sensory machines

NanoMachines

The Movie

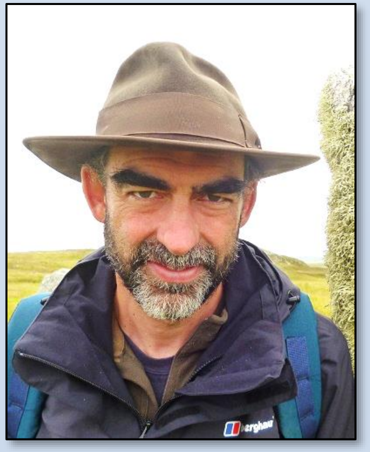


Credits:

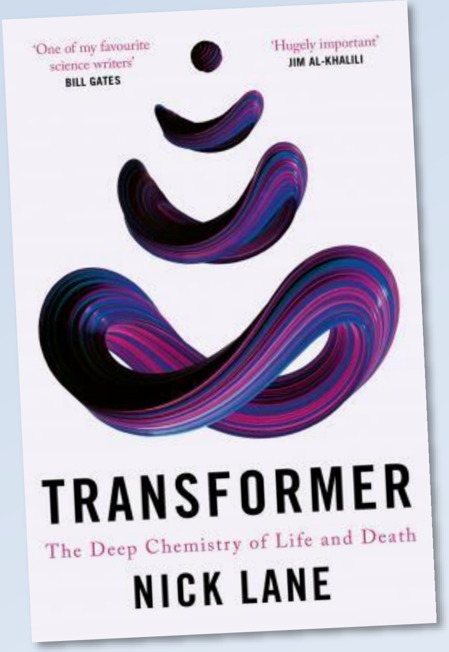
Drew Berry, Walter and Eliza Hall Institute of Medical Research, Melbourne Au
Biovisions, Harvard
Stewart Lab, University of South Carolina

Session 1 Outline

- Materials and building blocks of Biological Machines
  - Especially proteins
- Unusual features of life at small scales
- How we know about these tiny machines



Nick Lane
Professor of Evolutionary Biology
University College London



NICK LANE BOOKS

2022

Transformer: The Deep Chemistry of Life and Death
Nick Lane Profile Books

2015

The Vital Question. Why is life the way it is?
Nick Lane Profile/WW Norton

2009

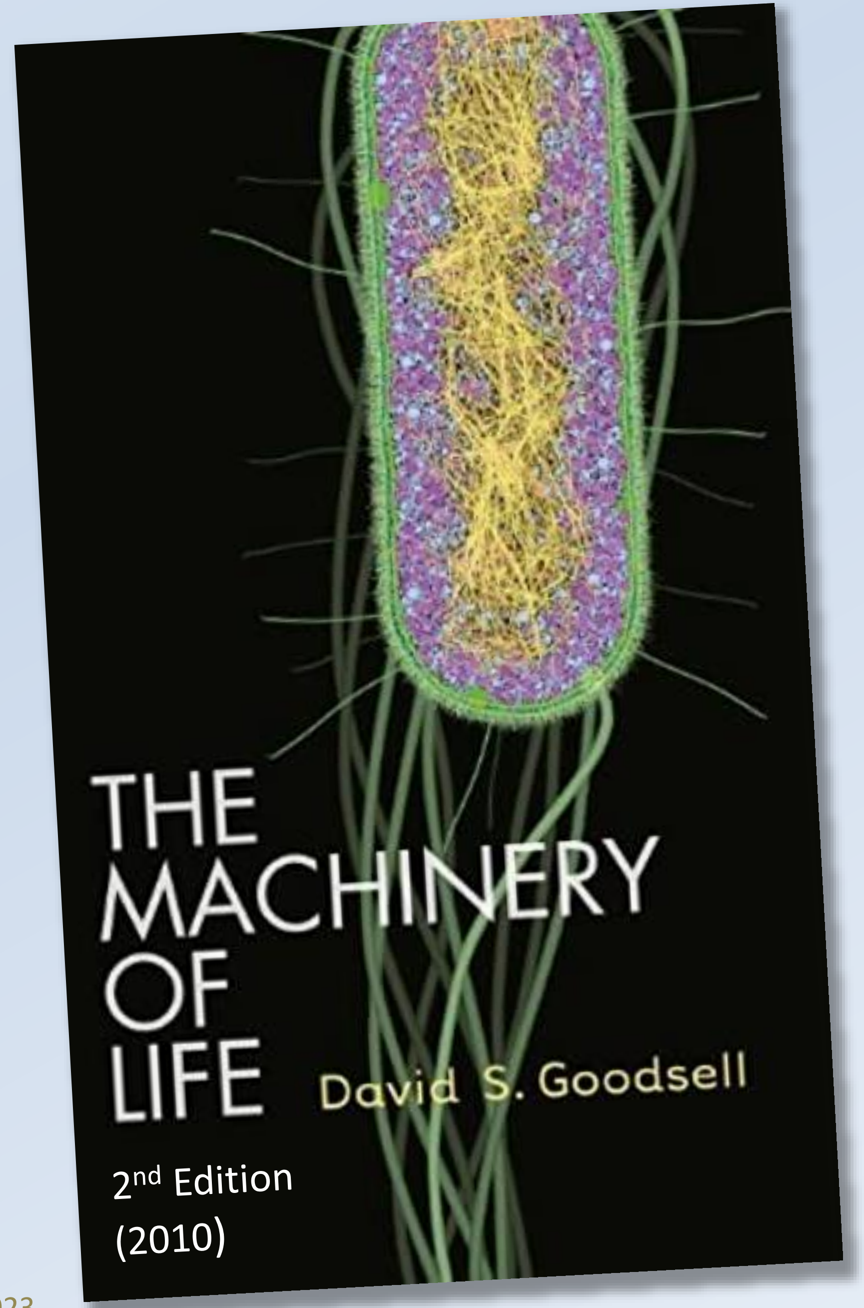
Life Ascending: The Ten Great Inventions of Evolution
Nick Lane Profile/WW Norton

2005

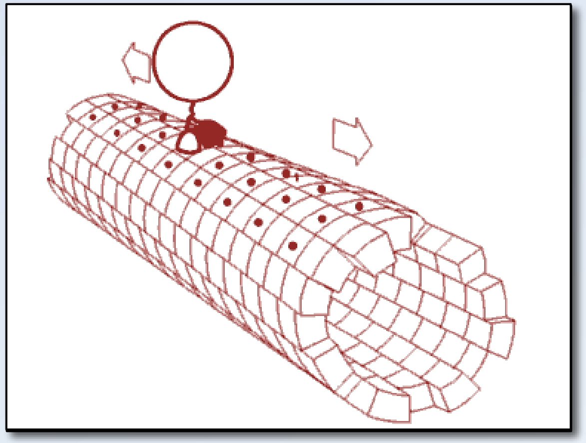
Power, Sex, Suicide: Mitochondria and the Meaning of Life
Nick Lane OUP Oxford

2002

Oxygen: The Molecule that made the World
Nick Lane Oxford University Press


THE MACHINERY OF LIFE
David S. Goodsell
2nd Edition
(2010)


Wikipedia
The Free Encyclopedia
Article
Talk
Molecular machine
From Wikipedia, the free encyclopedia

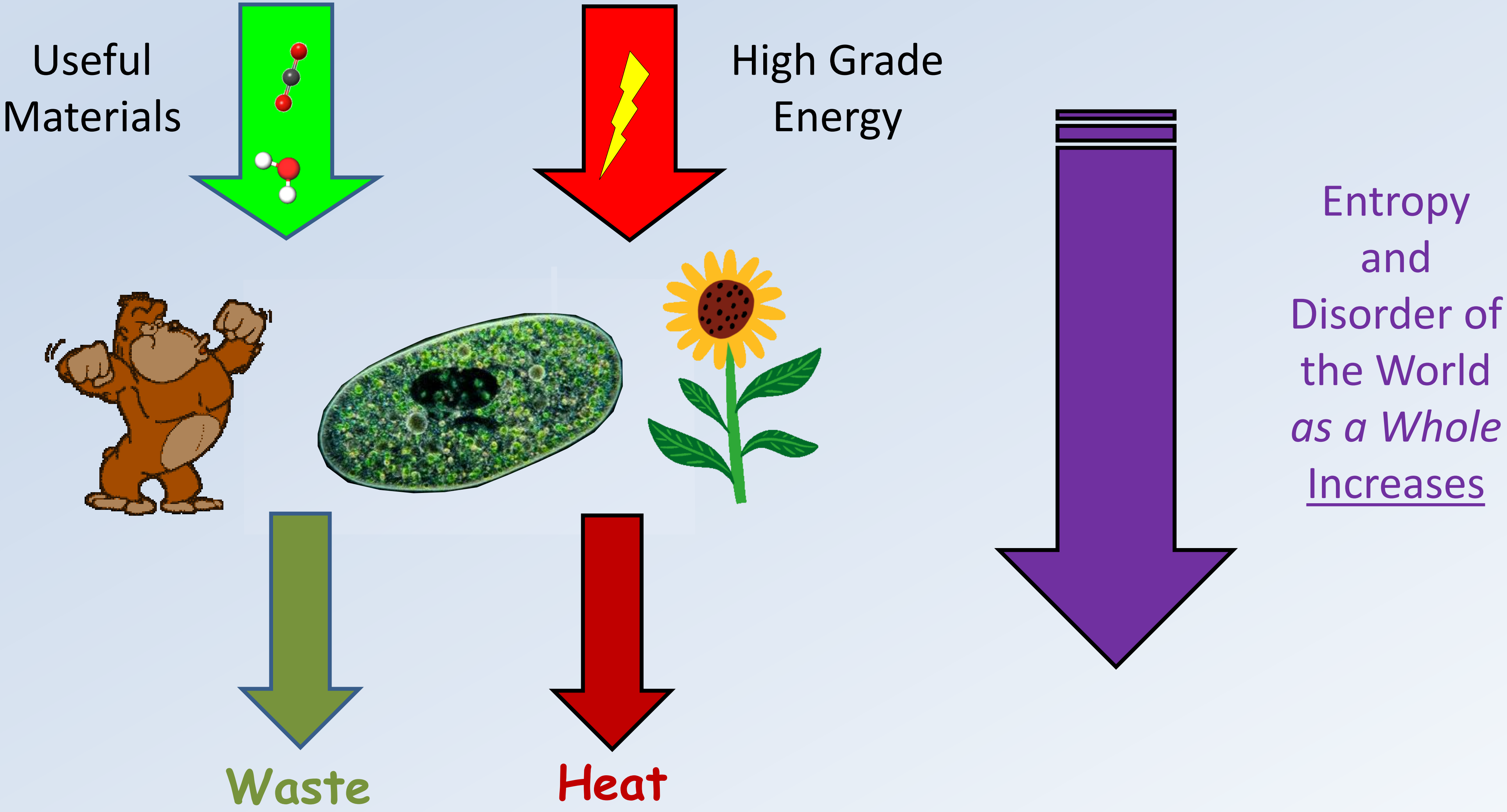


My Brother's Recommendation

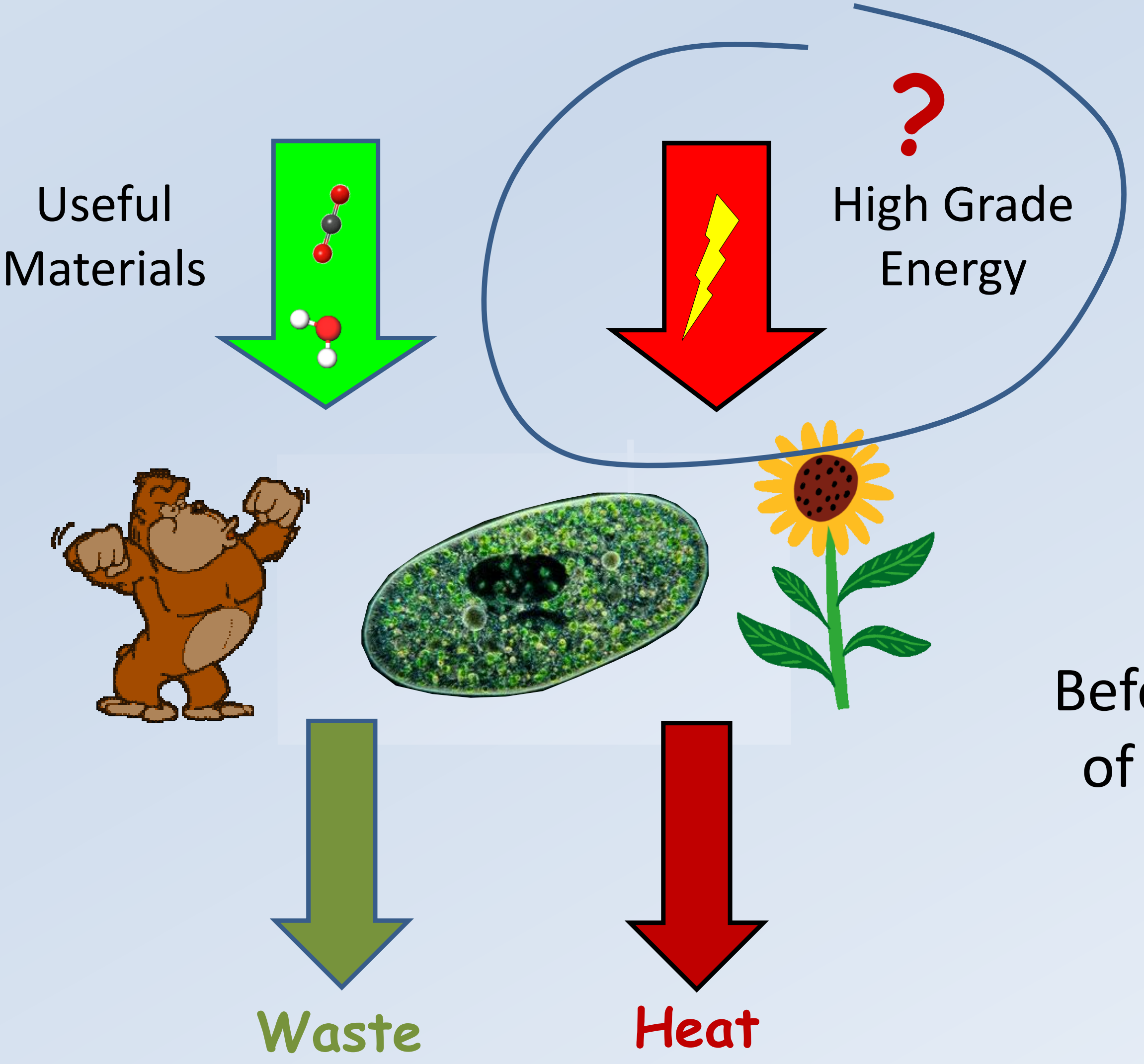
[(4) The biological machinery of life | Betül Kaçar and Lex Fridman – YouTube]

"The Biological Machinery of Life"

Energy and Material Flow Animates All Life



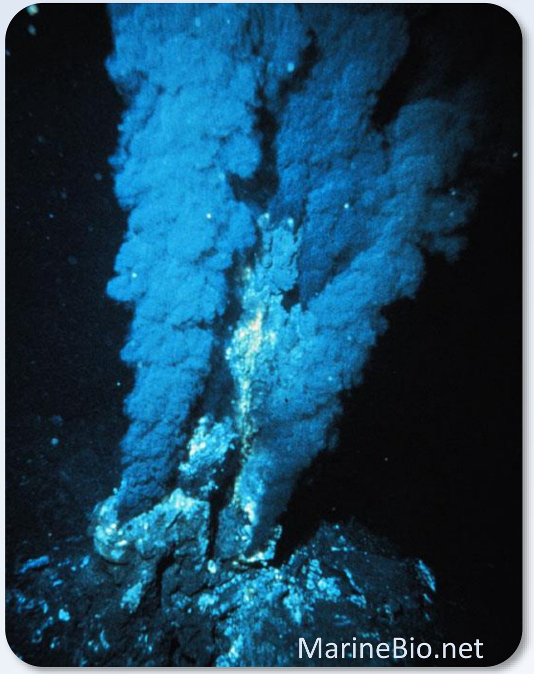
Energy and Material Flow Animates All Life



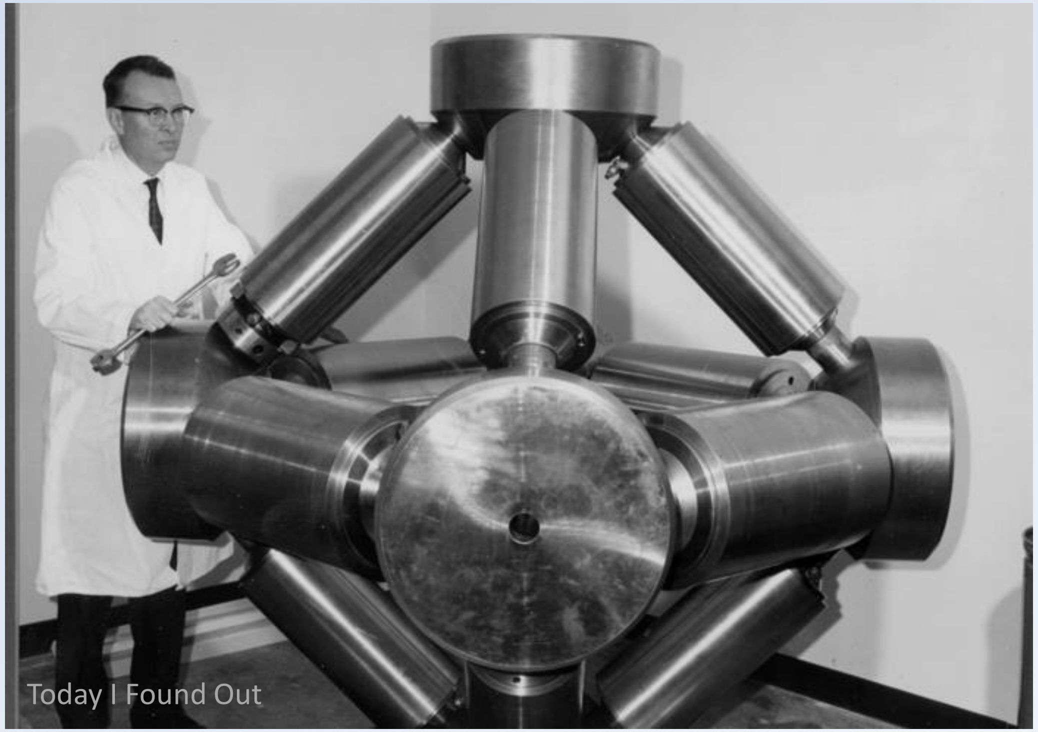
For the last ~ 3 Billion Years:

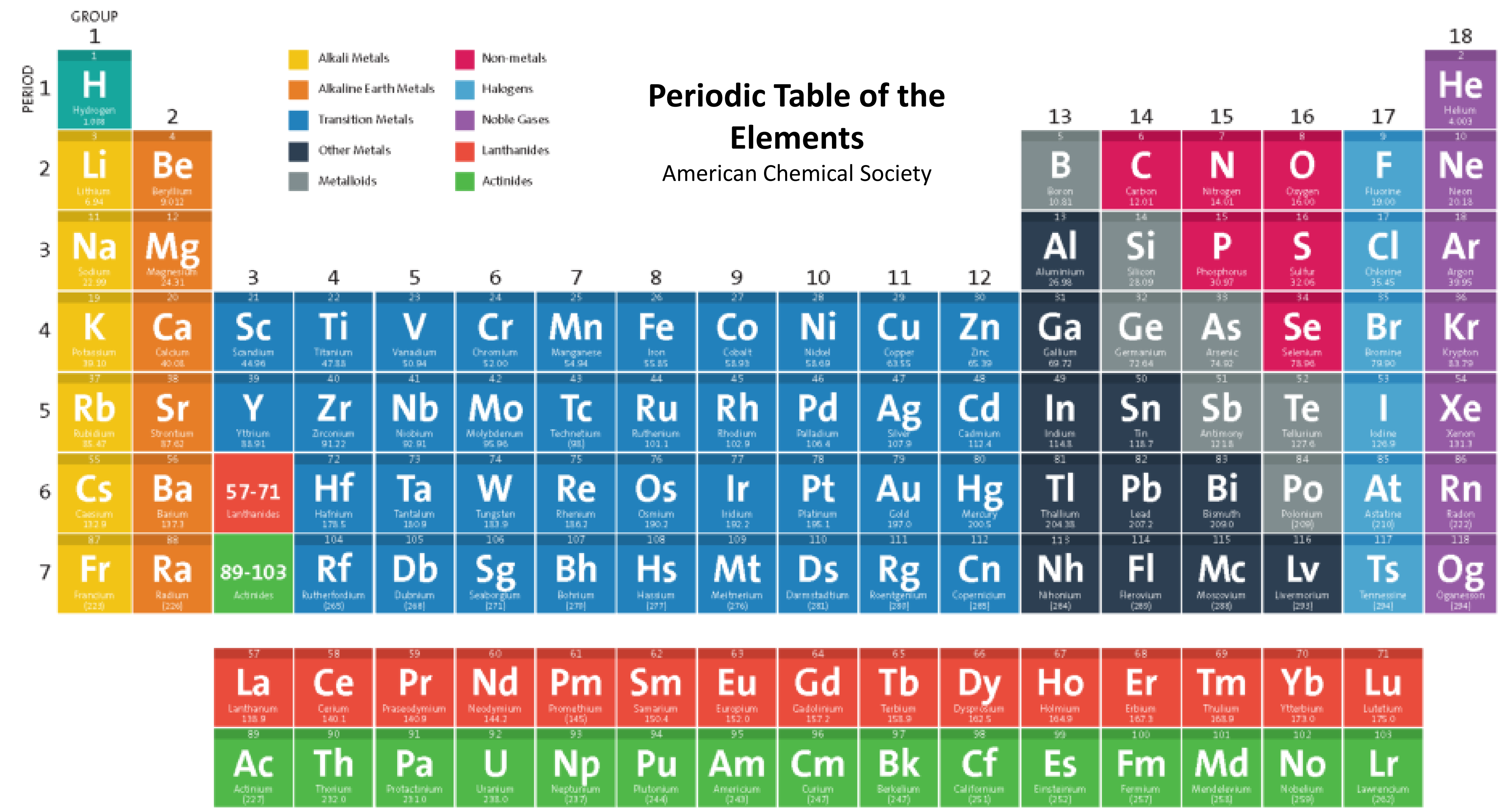
Before the invention of Photosynthesis:

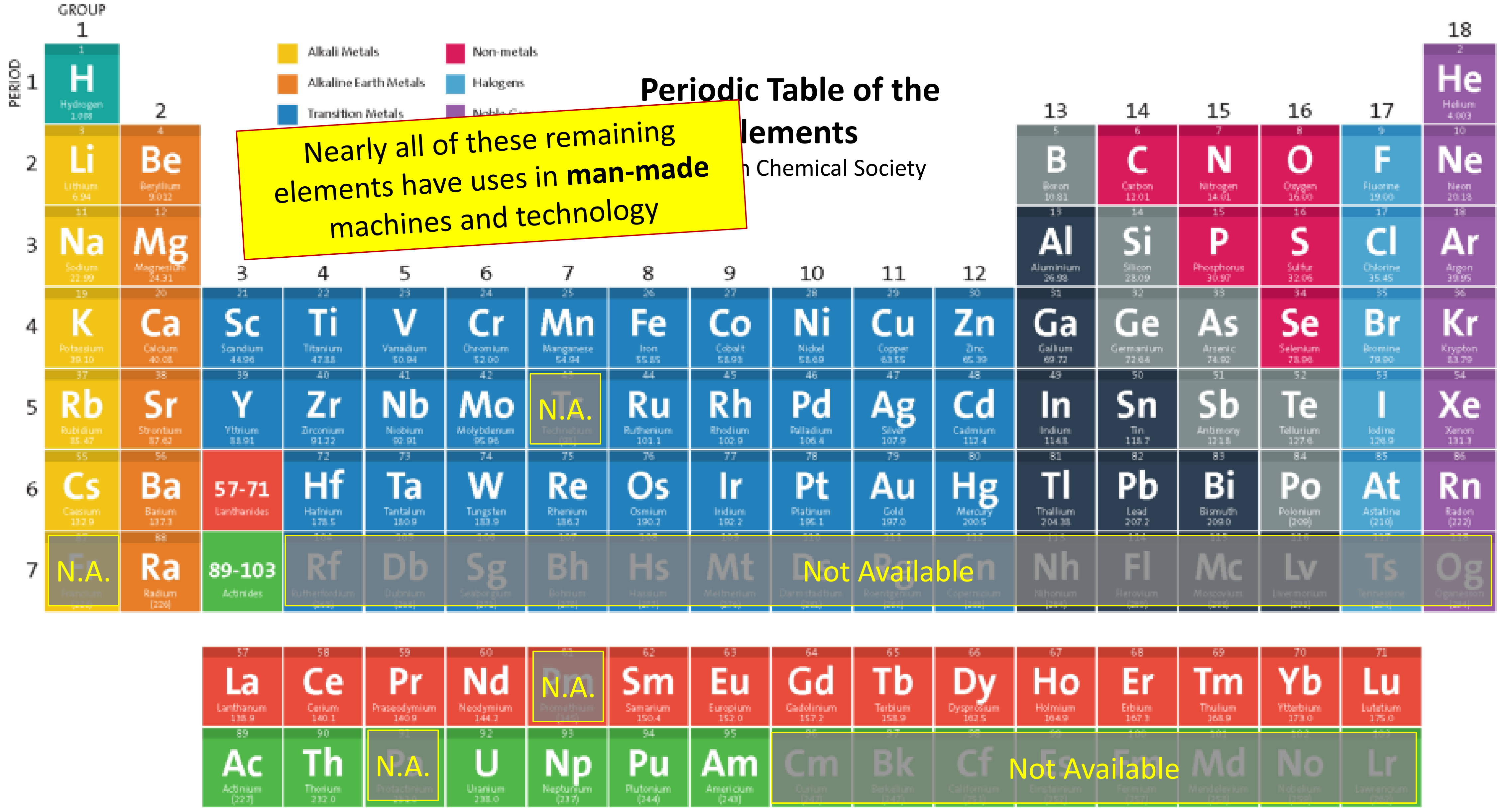
Geochemical energy from undersea vents



Extreme Temperatures and Pressures are not available to Biology

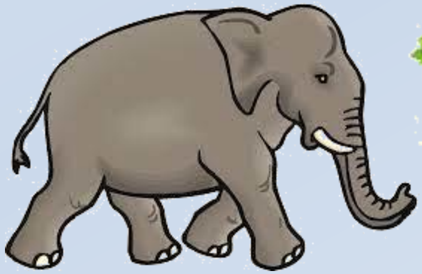


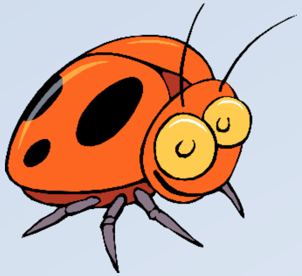

Periodic Table of the Elements
American Chemical Society
GROUP
PERIOD
Alkali Metals
Alkaline Earth Metals
Transition Metals
Other Metals
Metalloids
Non-metals
Halogens
Noble Gases
Lanthanides
Actinides
H He
Li Be B C N O F Ne
Na Mg Al Si P S Cl Ar
K Ca Sc Ti V Cr Mn Fe Co Ni Cu Zn Ga Ge As Se Br Kr
Rb Sr Y Zr Nb Mo Tc Ru Rh Pd Ag Cd In Sn Sb Te I Xe
Cs Ba 57-71 Hf Ta W Re Os Ir Pt Au Hg Tl Pb Bi Po At Rn
Fr Ra 89-103 Rf Db Sg Bh Hs Mt Ds Rg Cn Nh Fl Mc Lv Ts Og
La Ce Pr Nd Pm Sm Eu Gd Tb Dy Ho Er Tm Yb Lu
Ac Th Pa U Np Pu Am Cm Bk Cf Es Fm Md No Lr

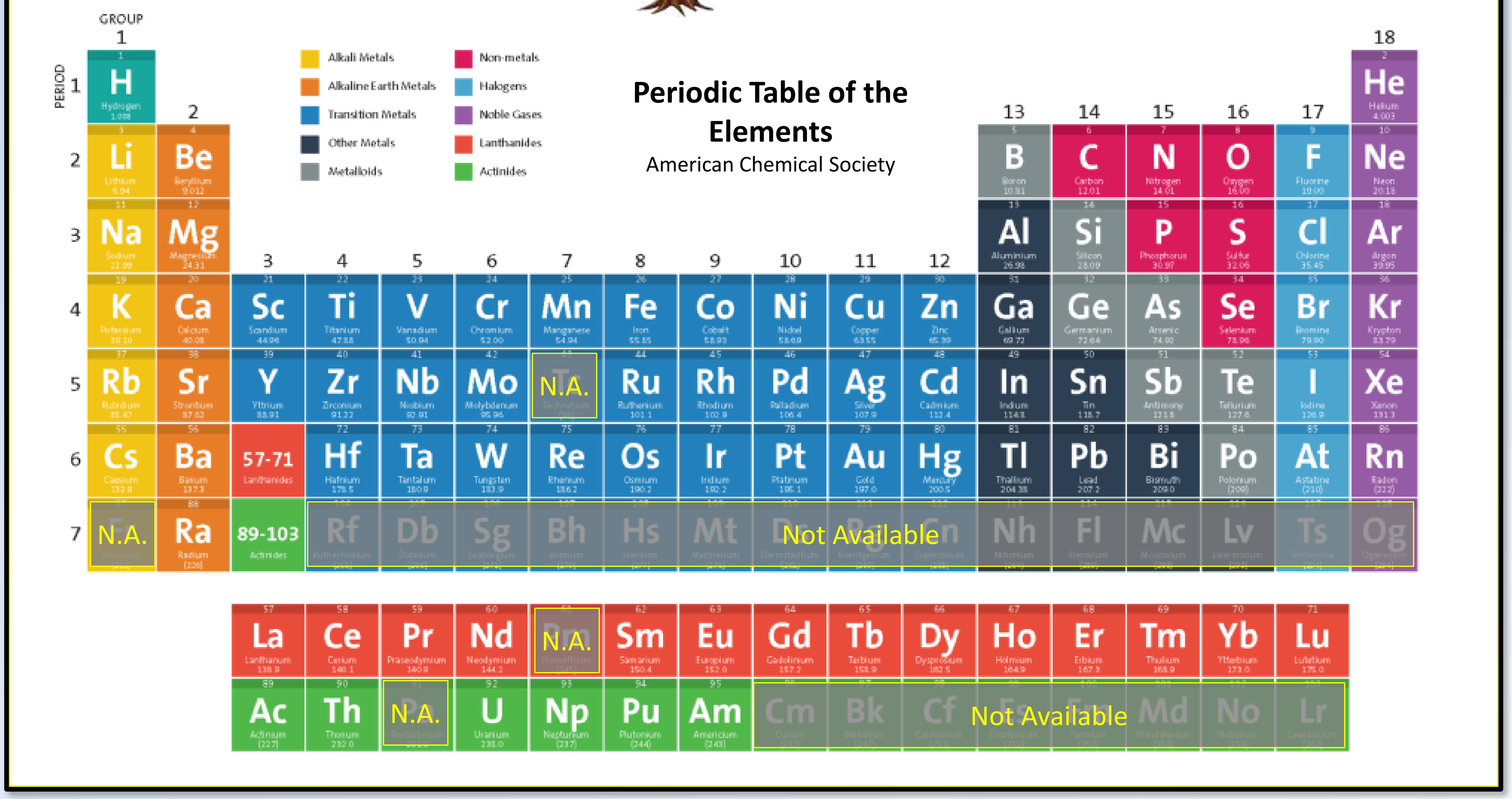


Periodic Table of the Elements
Chemical Society
Nearly all of these remaining elements have uses in **man-made** machines and technology
GROUP
PERIOD
Alkali Metals
Alkaline Earth Metals
Transition Metals
Non-metals
Halogens
57-71 Lanthanides
89-103 Actinides
N.A.
N.A.
N.A.
N.A.
Not Available
Not Available

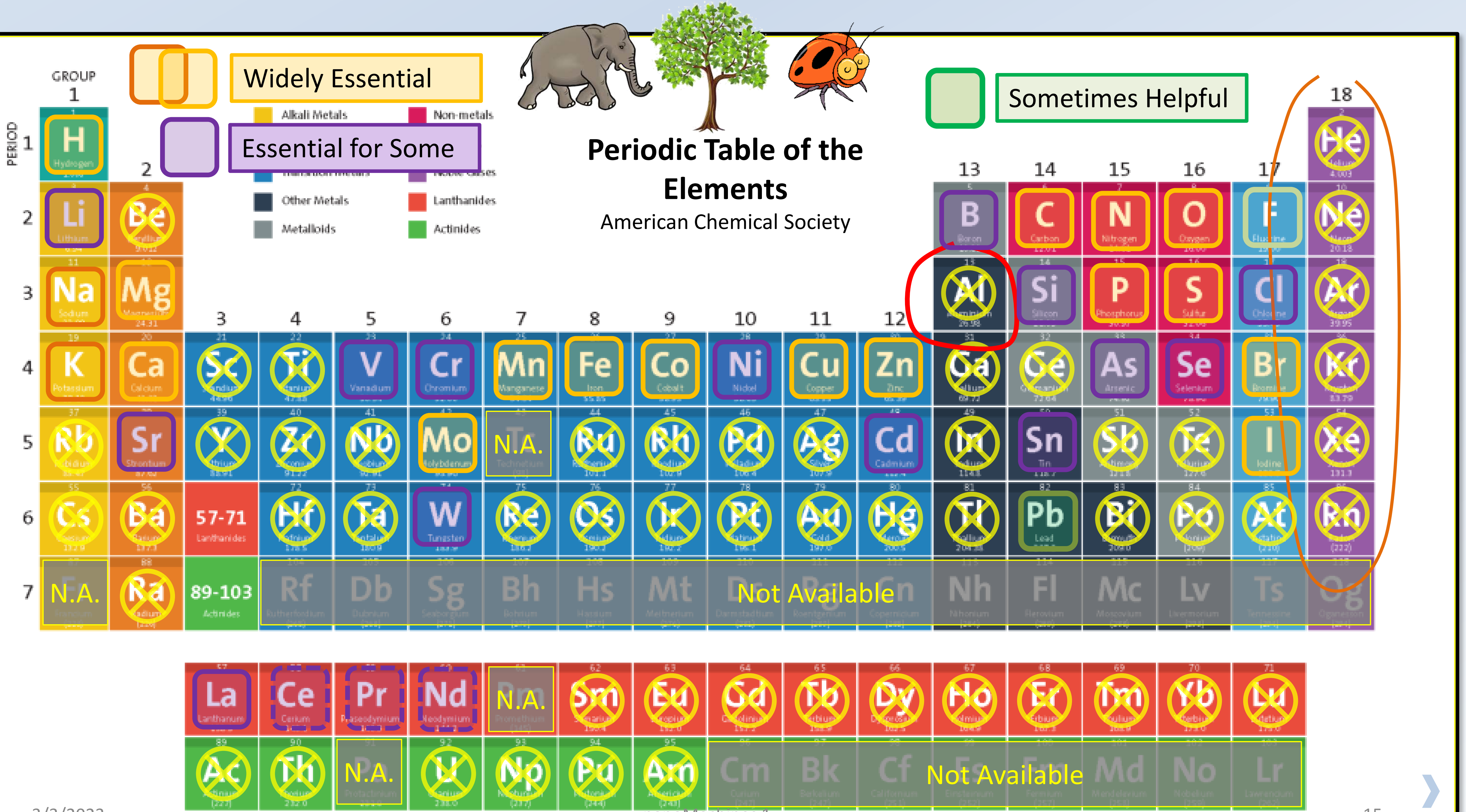
But what elements are useful to nature?







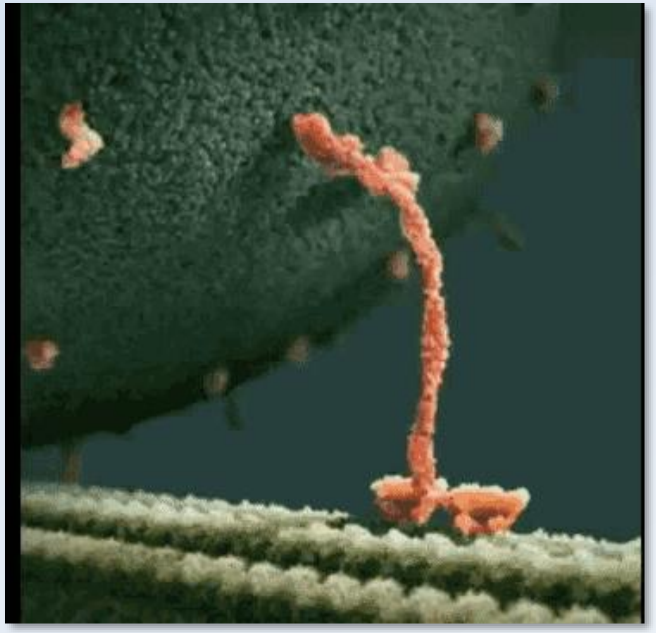
3/3/2023


Widely Essential
Essential for Some
Sometimes Helpful
Periodic Table of the Elements
American Chemical Society
GROUP
PERIOD
Alkali Metals
Non-metals
Other Metals
Lanthanides
Metalloids
Actinides
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
H
Li Be
B C N O F Ne
Na Mg
Al Si P S Cl Ar
K Ca Sc Ti V Cr Mn Fe Co Ni Cu Zn Ga Ge As Se Br Kr
Rb Sr Y Zr Nb Mo N.A. Ru Rh Pd Ag Cd In Sn Sb Te I Xe
Cs Ba 57-71 Lanthanides Hf Ta W Re Os Ir Pt Au Hg Tl Pb Bi Po At Rn
N.A. Ra 89-103 Actinides Rf Db Sg Bh Hs Mt Nh Fl Mc Lv Ts Og
Not Available
La Ce Pr Nd N.A. Sm Eu Gd Tb Dy Ho Er Tm Yb Lu
Ac Th N.A. U Np Pu Am Cm Bk Cf Md No Lr
Not Available

Diving Down

from the World of MacroMachines

to the World of Cellular NanoMachines

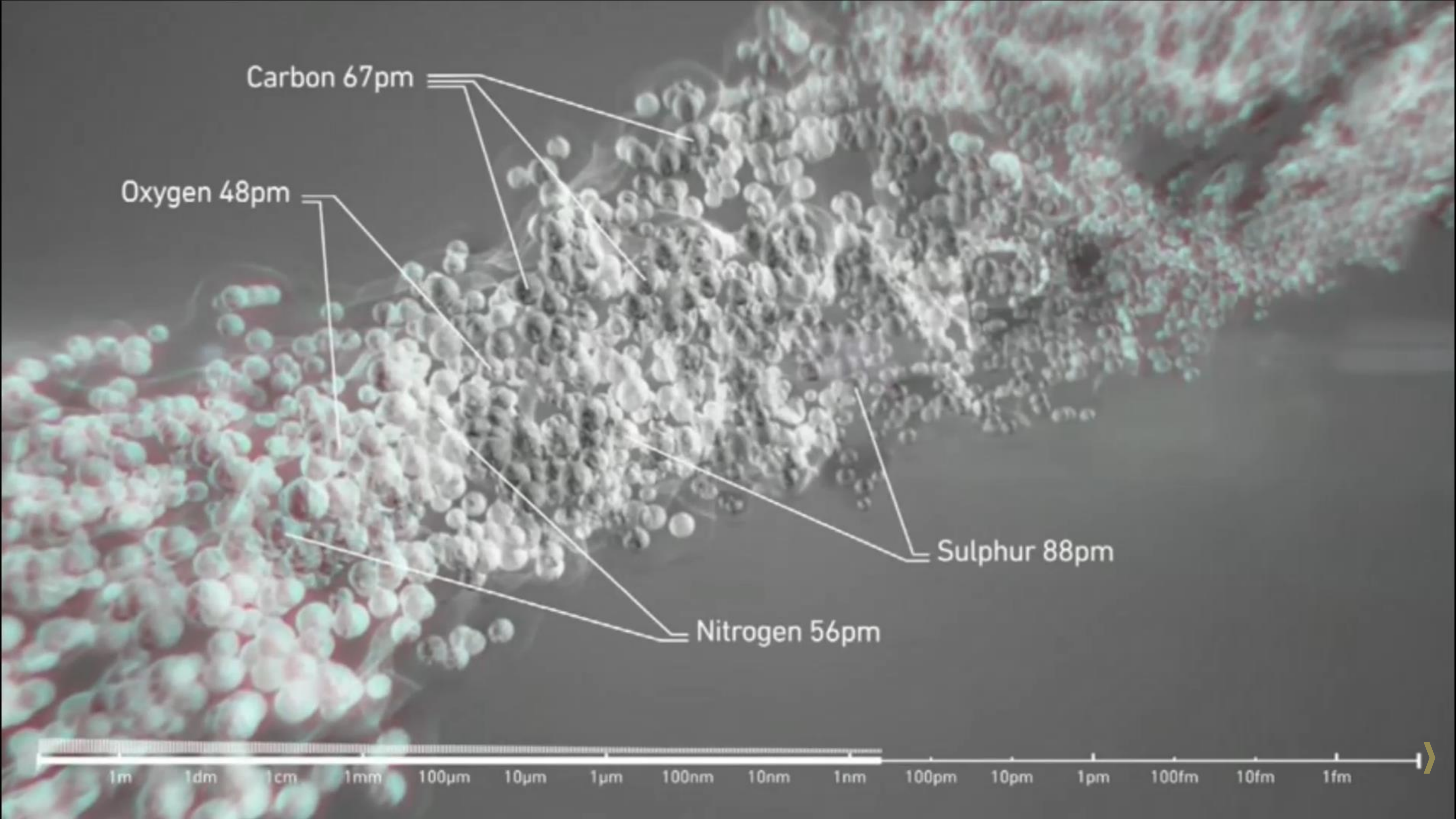


Voyage into the world of atoms

CERN

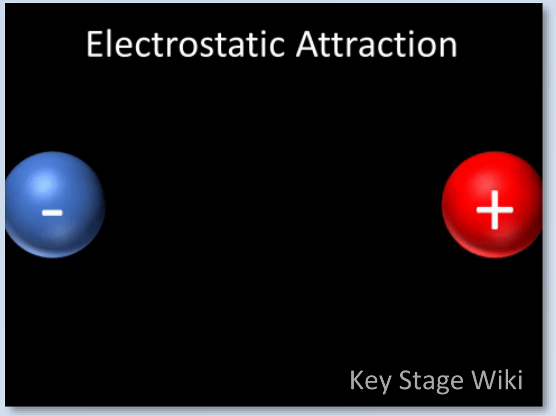
Conseil Européen pour la Recherche Nucléaire

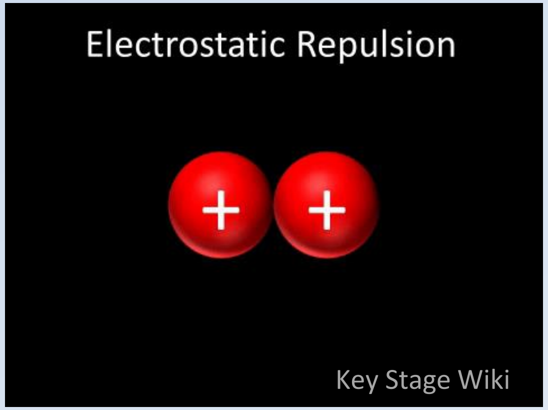
(2018)

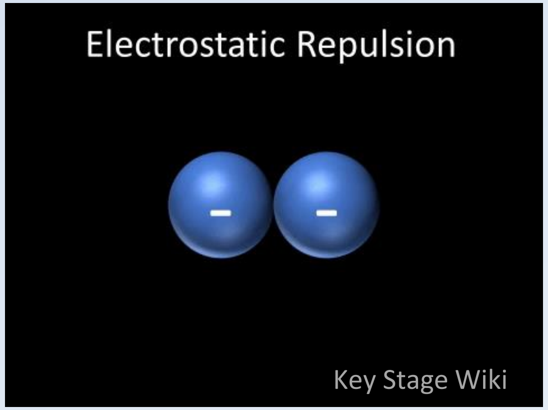

Carbon 67pm
Oxygen 48pm
Sulphur 88pm
Nitrogen 56pm
1m
1dm
1cm
1mm
100μm
10μm
1μm
100nm
10nm
1nm
100pm
10pm
1pm
100fm
10fm
1fm

How are Atoms Stuck Together to Make Molecules?

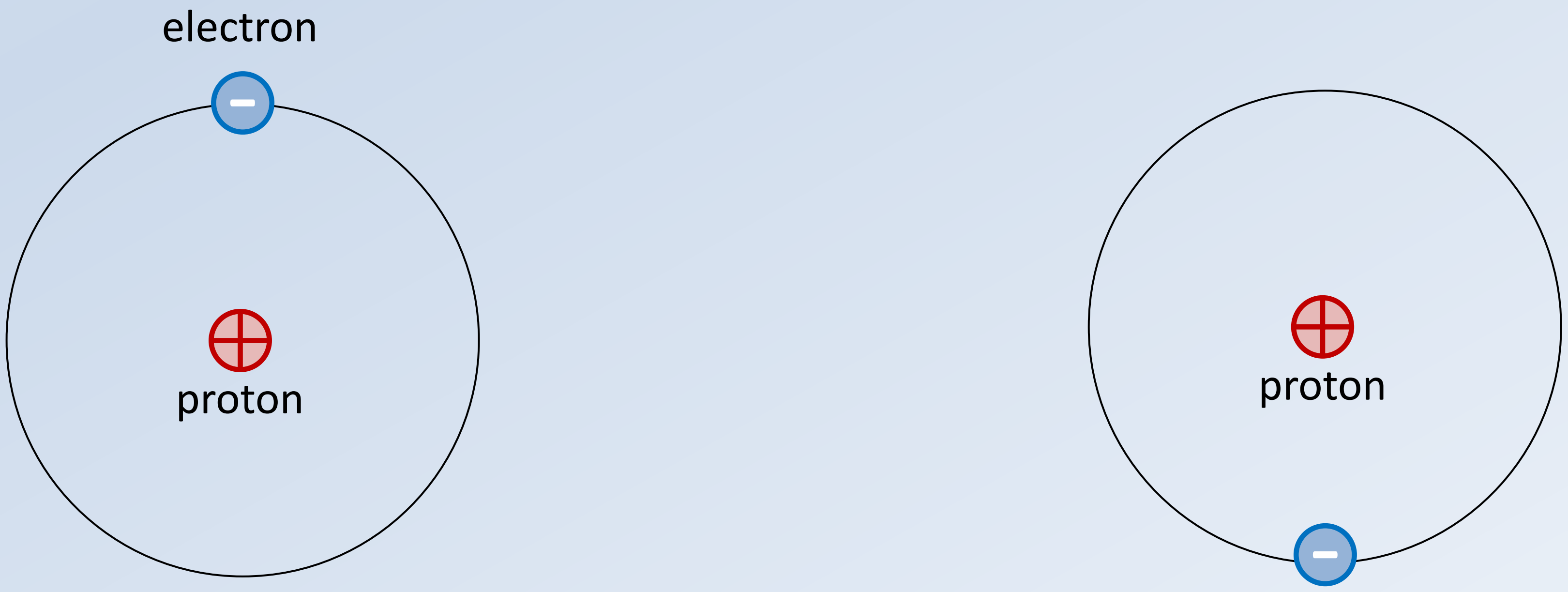
- Electrostatic Forces





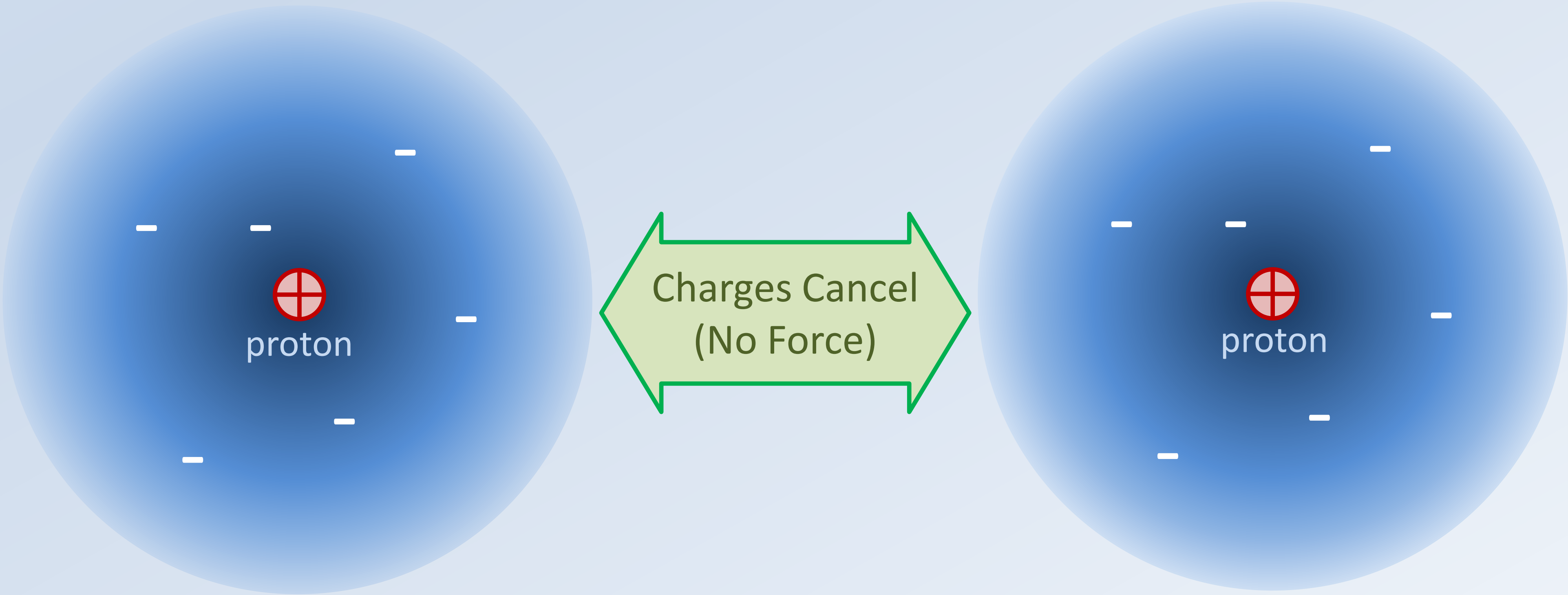


Consider 2 Hydrogen Atoms

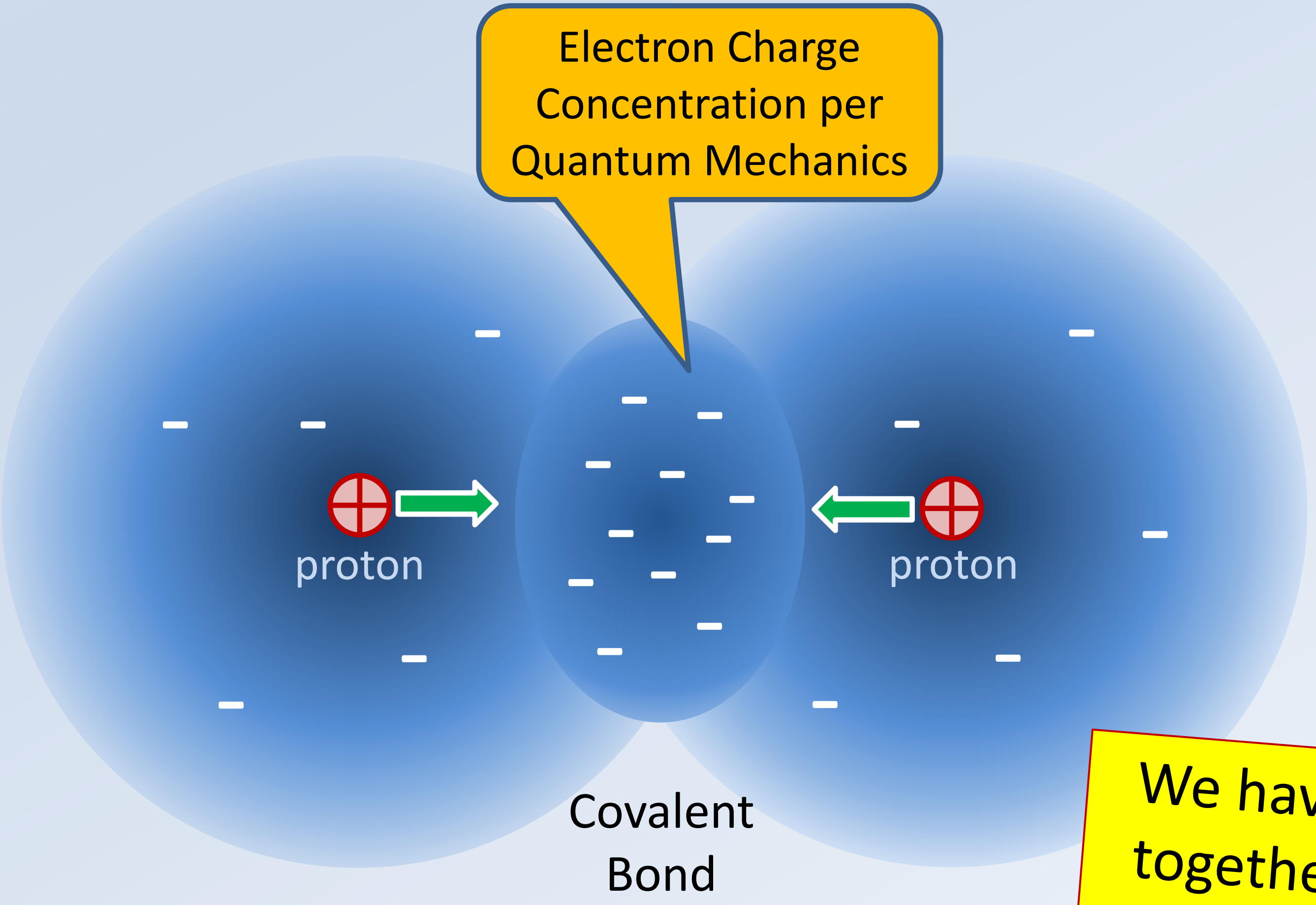


Consider 2 Hydrogen Atoms

electron
cloud is
diffuse

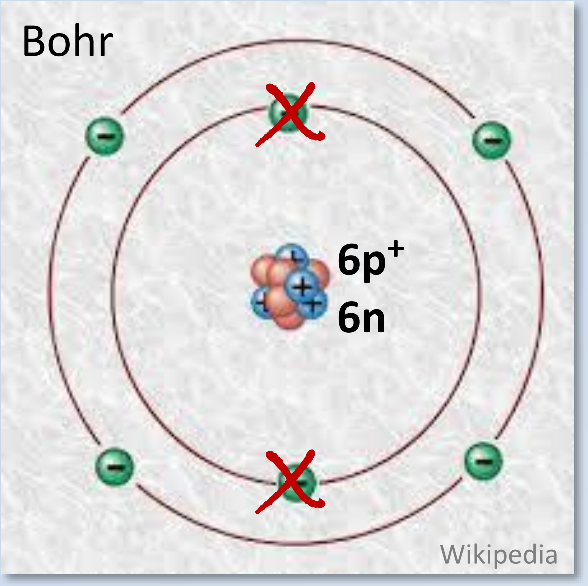


Consider 2 Hydrogen Atoms

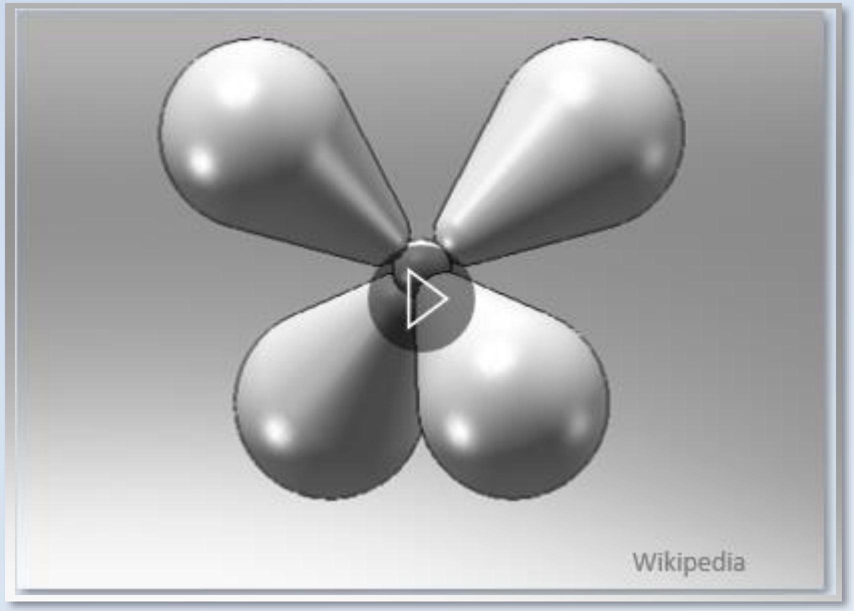


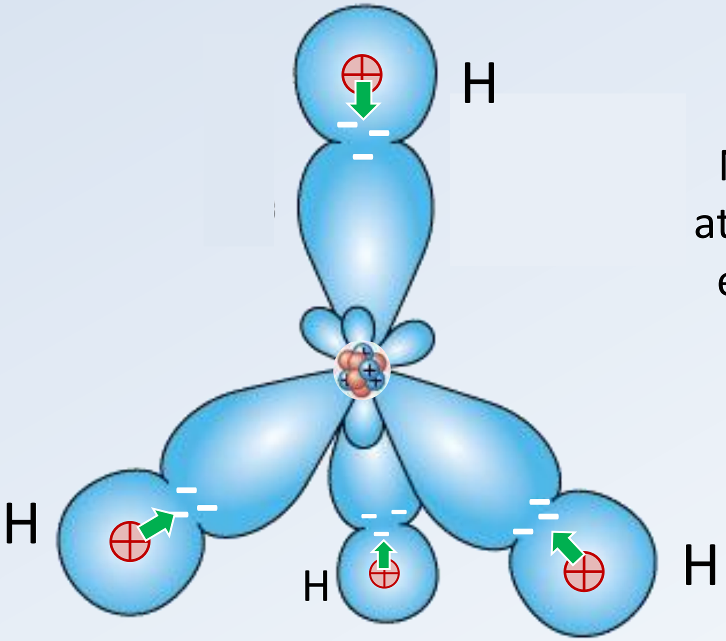
We have them bound together into a stable H_2 molecule

Consider instead a Carbon atom:



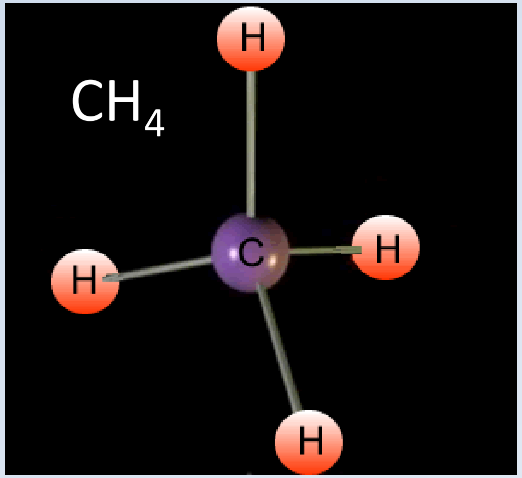
One possible orbital configuration





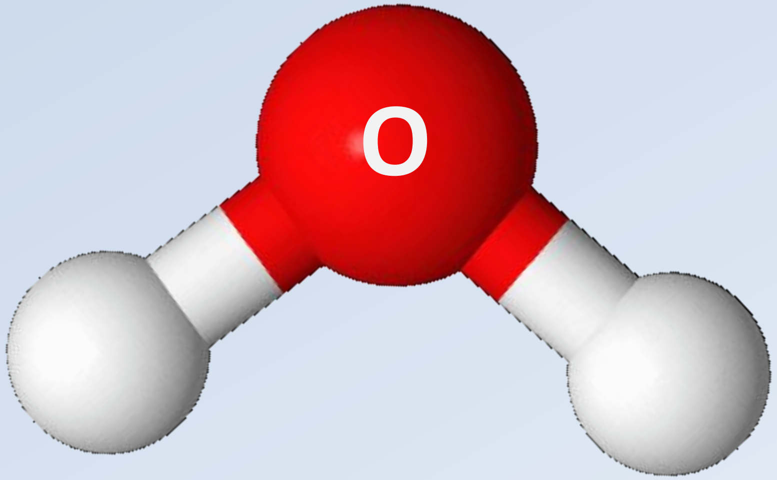
Now put H atoms next to each lobe…

resulting in a methane molecule



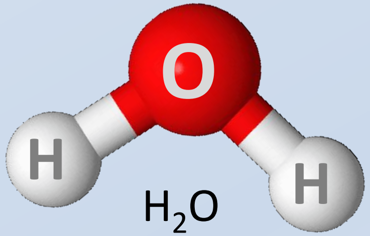
DynamicScience.com.au

Examples of small molecules

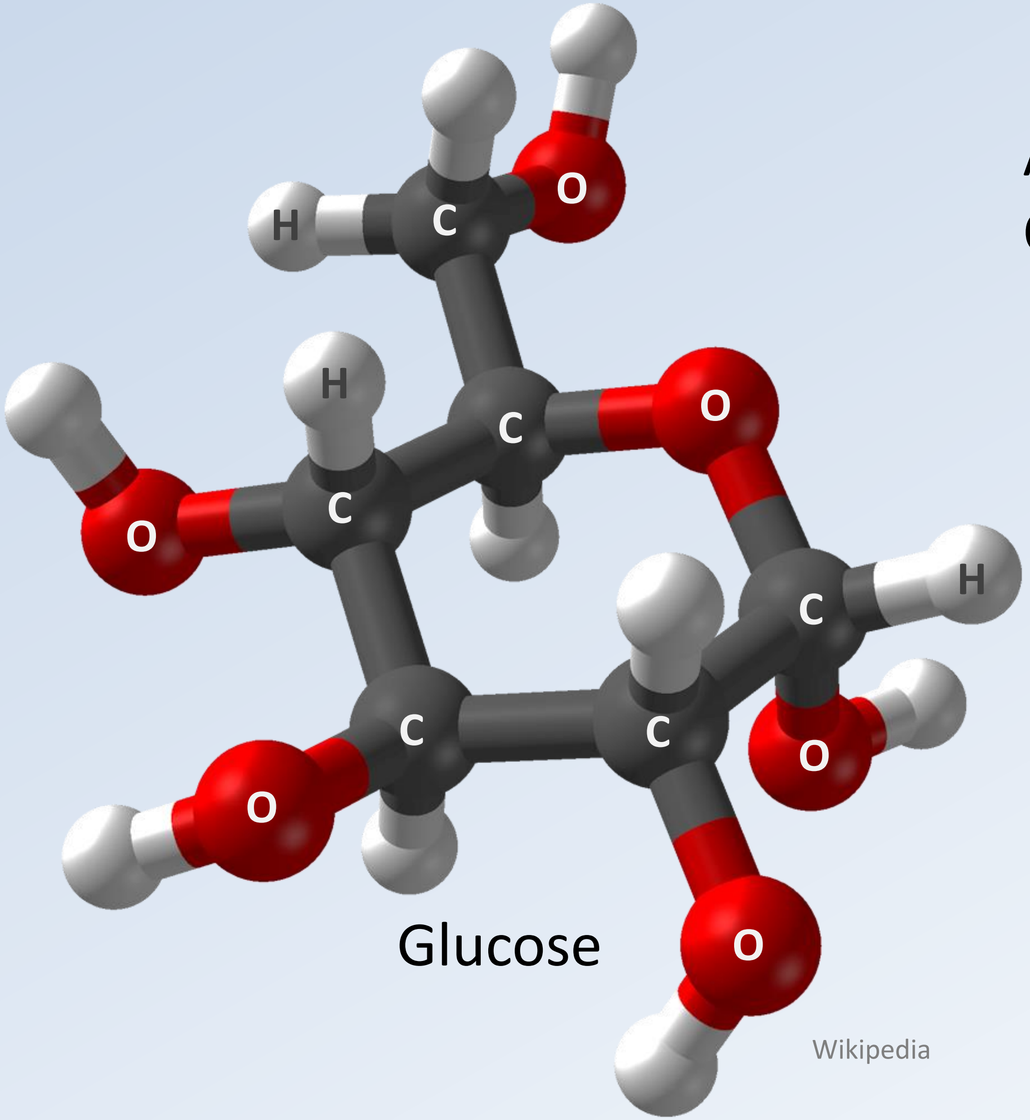


ACS Wikipedia

Examples of small molecules



H_2O

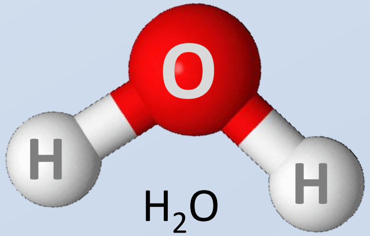


Glucose

Wikipedia

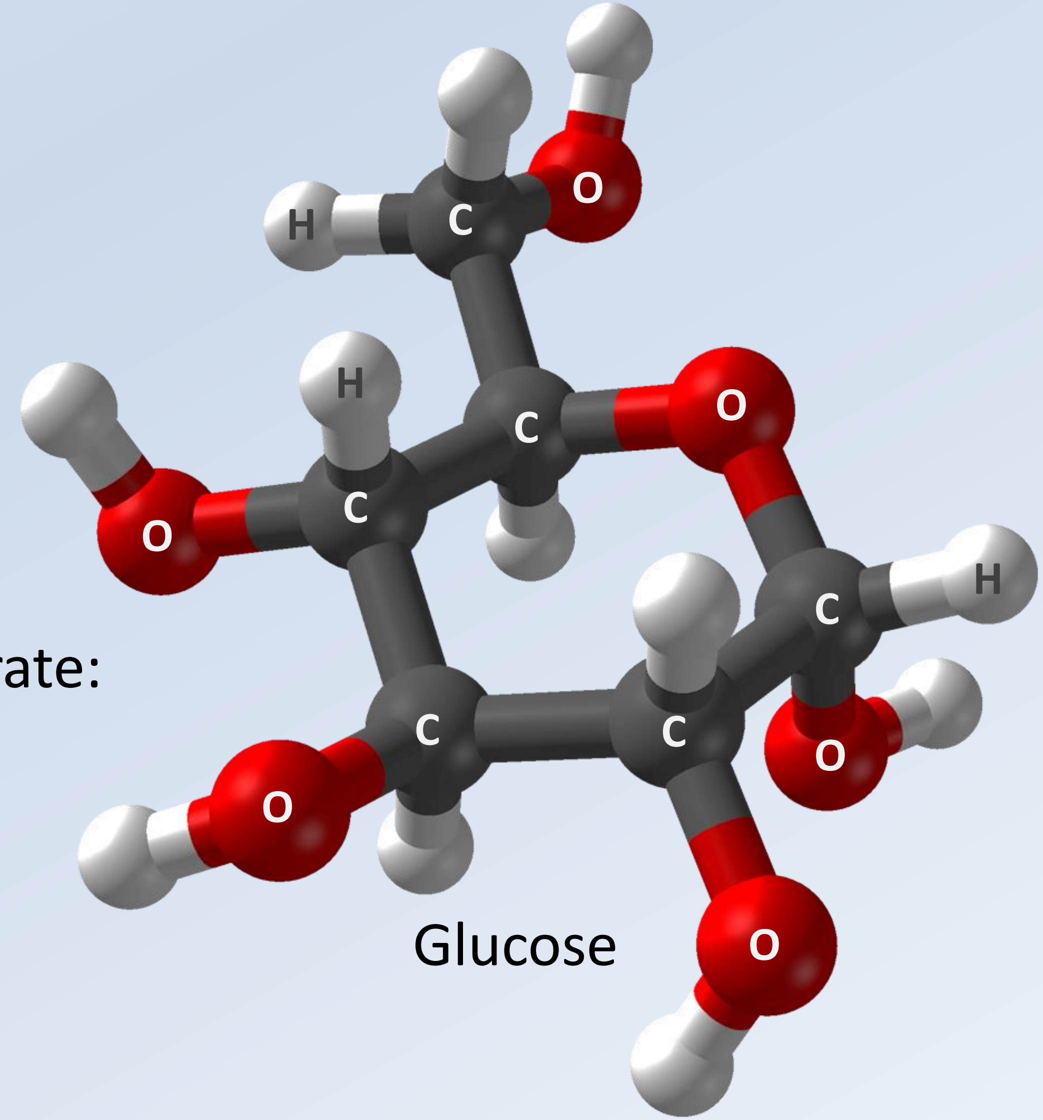
A Simple Carbohydrate: Sugar

Examples of small molecules



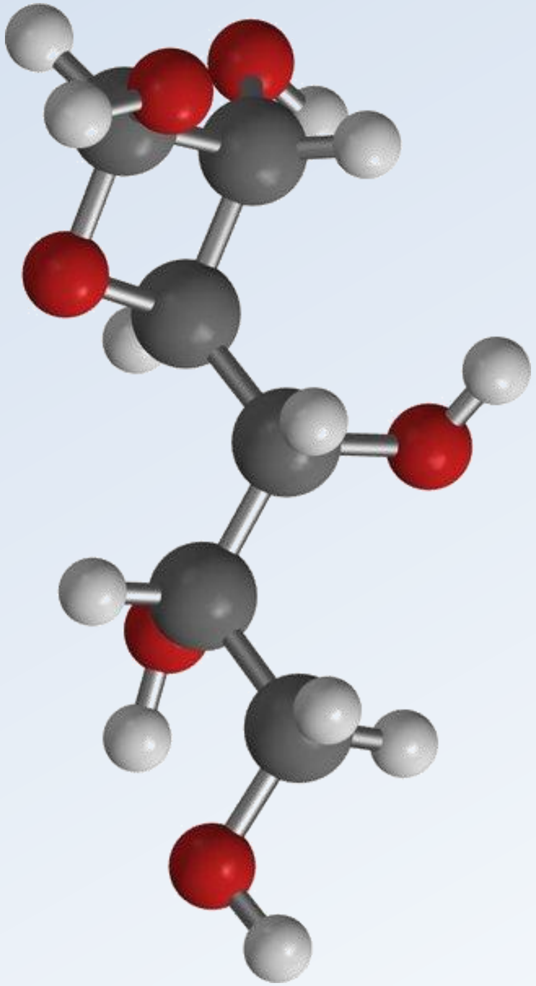
H_2O

A Simple Carbohydrate: Sugar



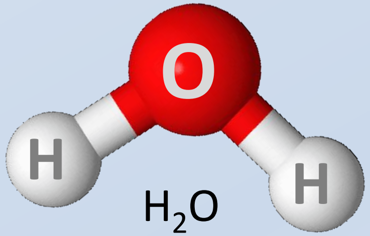
Glucose

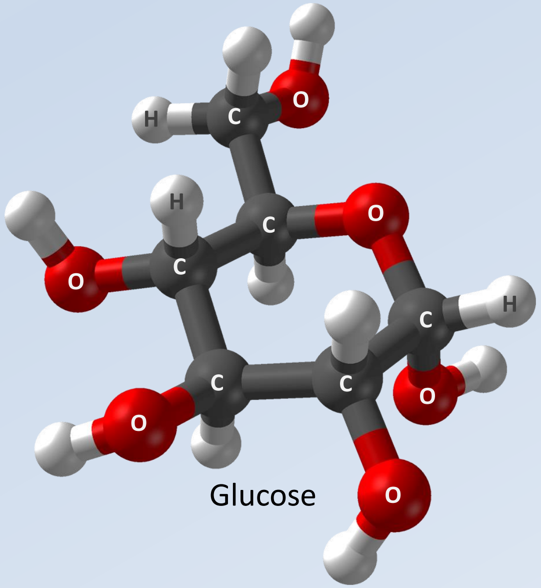
Linear (unwound) Configuration of Glucose – dry form



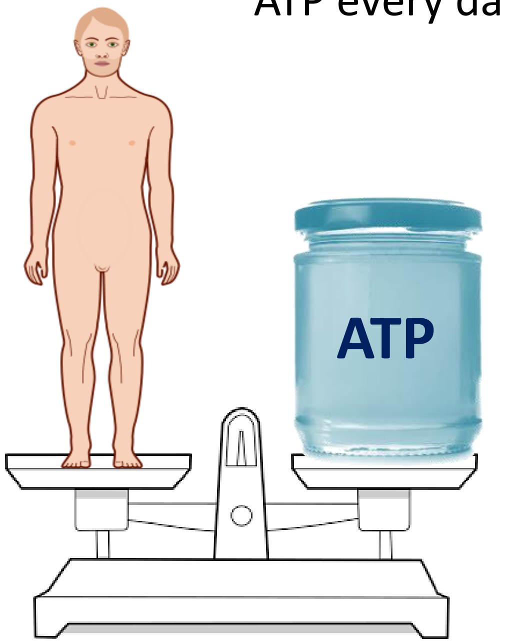
Wikipedia

Examples of small molecules





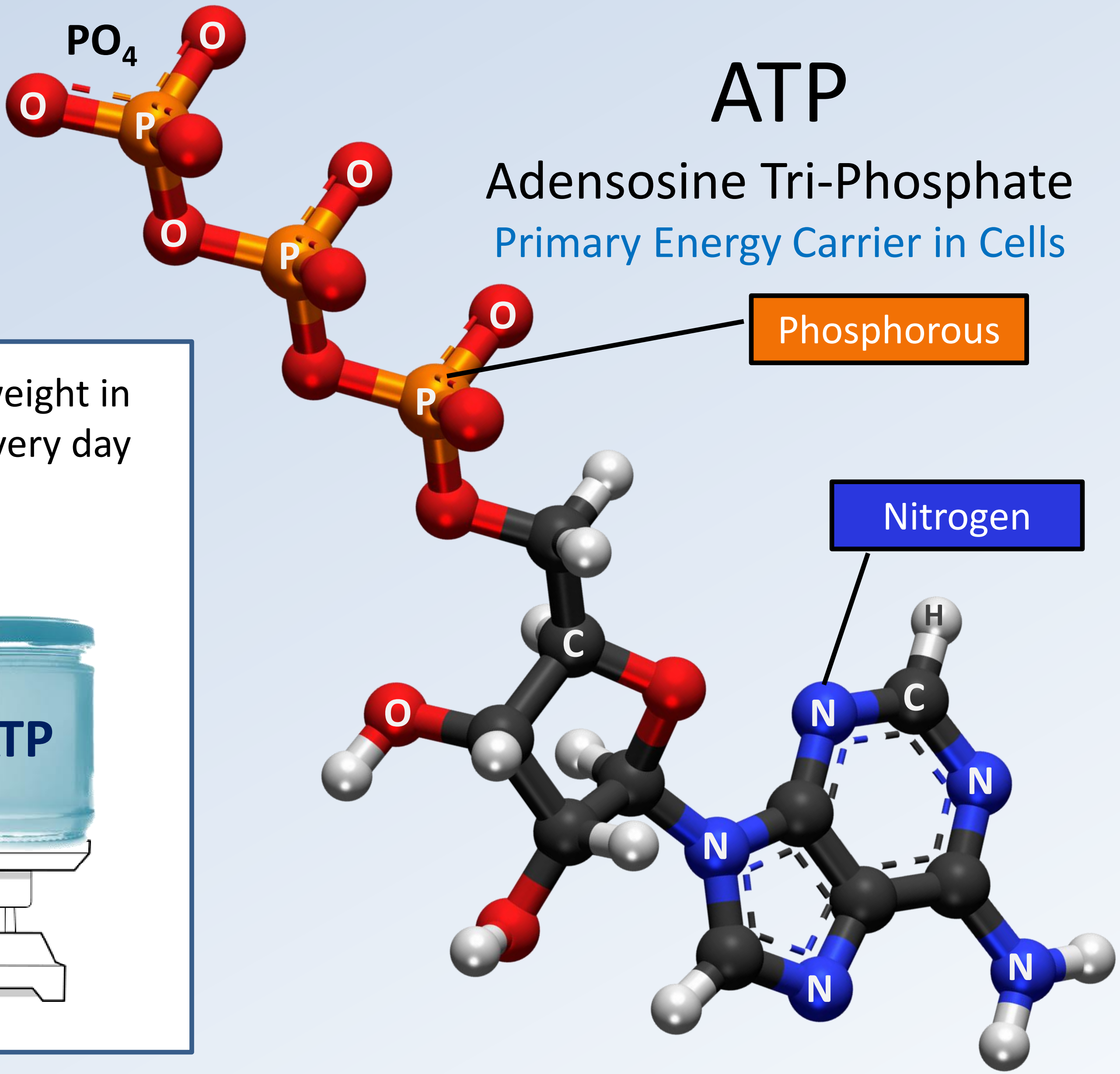
You use your own weight in ATP every day



ATP

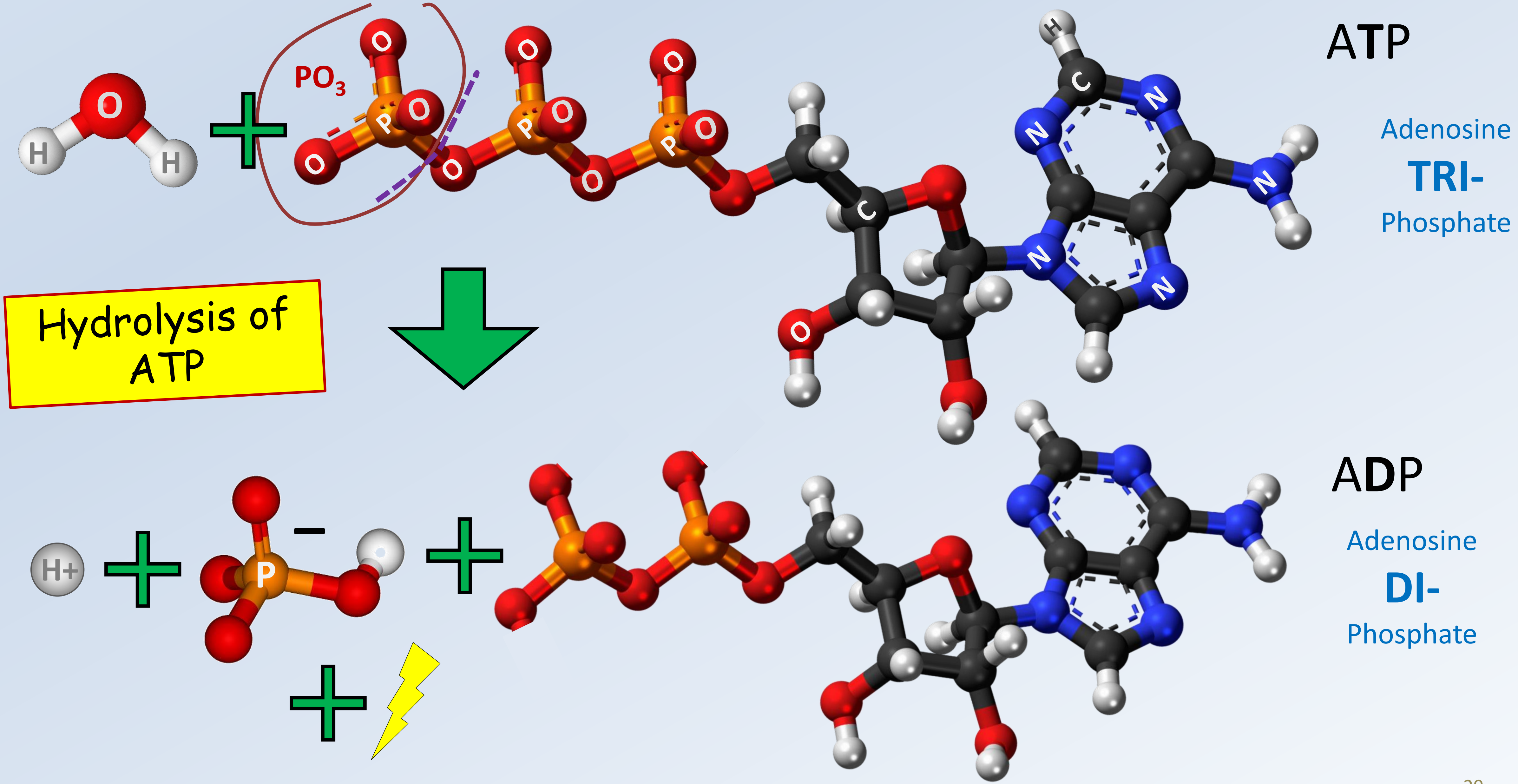
Adensosine Tri-Phosphate

Primary Energy Carrier in Cells

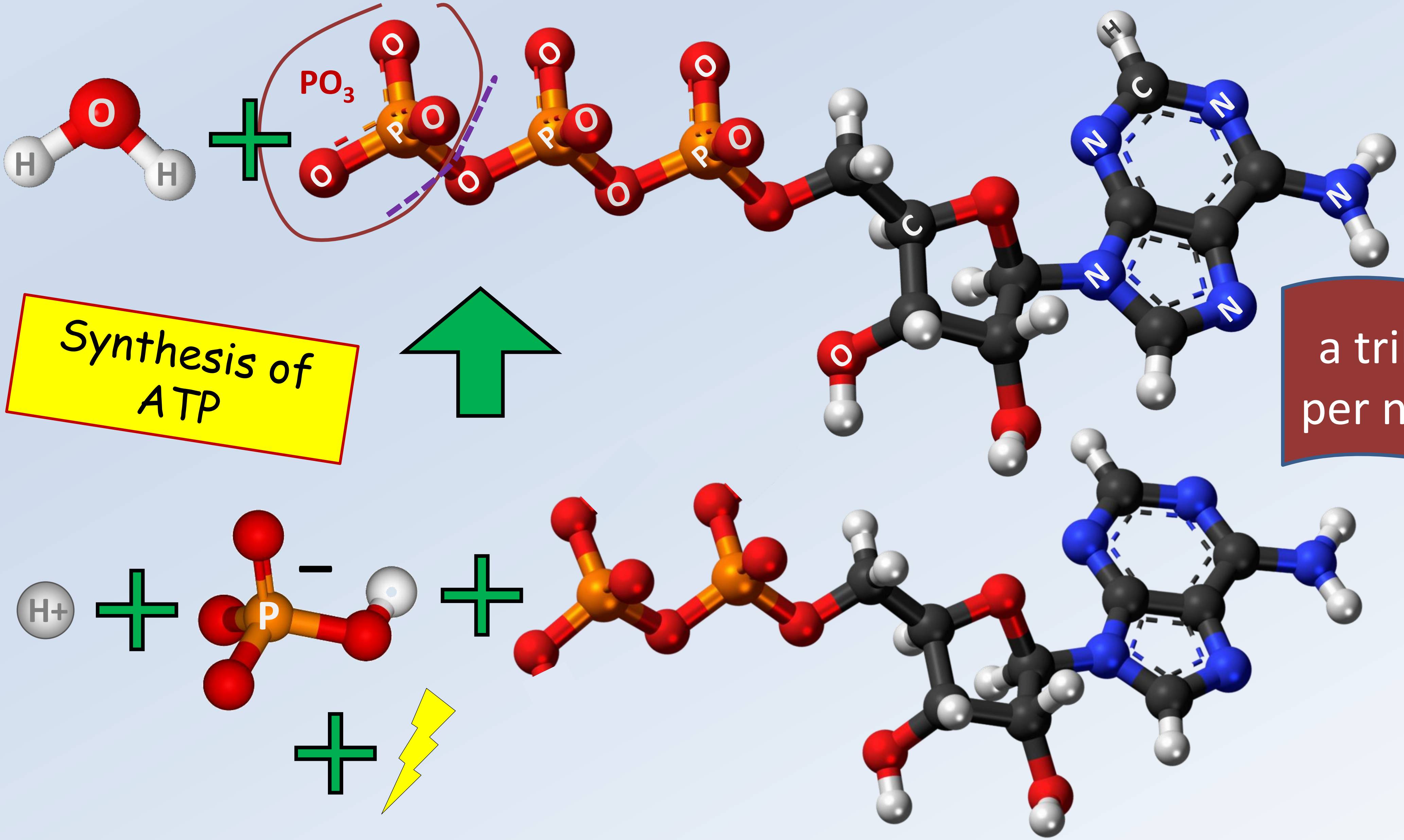


Wikipedia

Short Term Energy Storage: ATP from ADP



Short Term Energy Storage: ATP from ADP



ATP

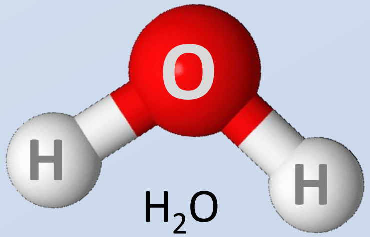
Adenosine
TRI-
Phosphate

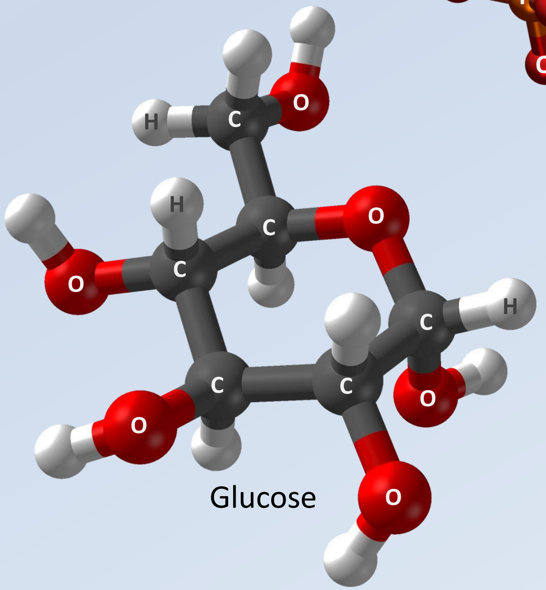
a trillion times per nanosecond

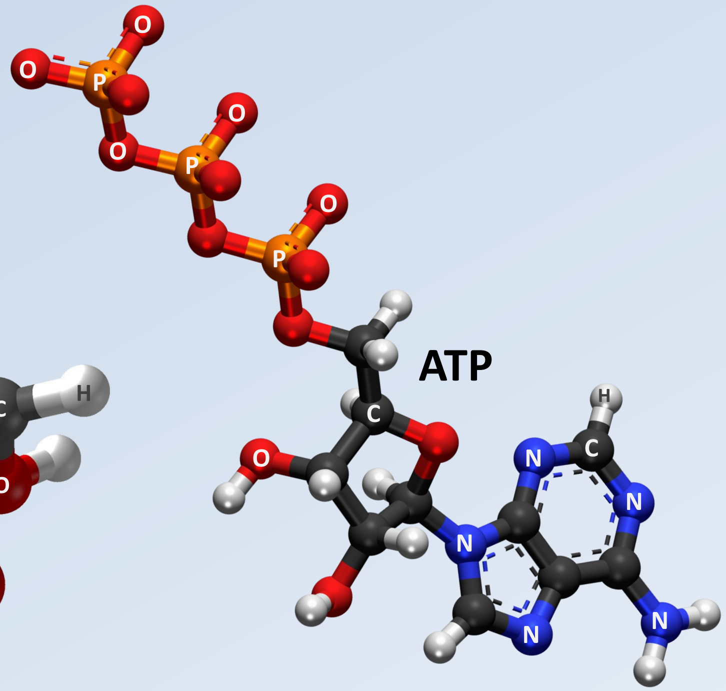
ADP

Adenosine
DI-
Phosphate

Examples of small molecules

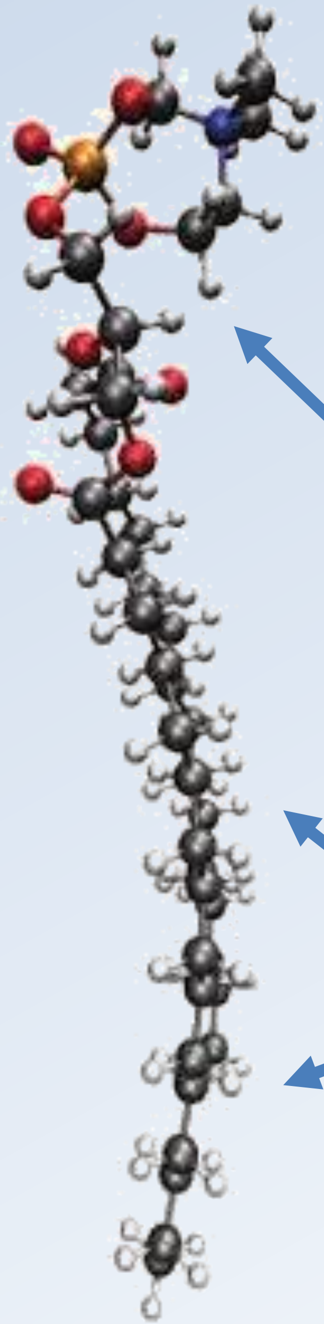






'DPPC'

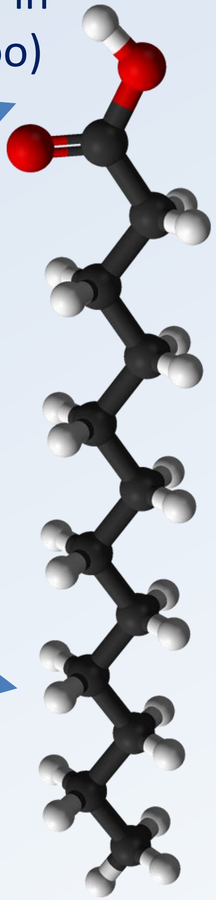
(component of cell membranes)



Lipids (fats)

Lauric Acid

(oil used in shampoo)



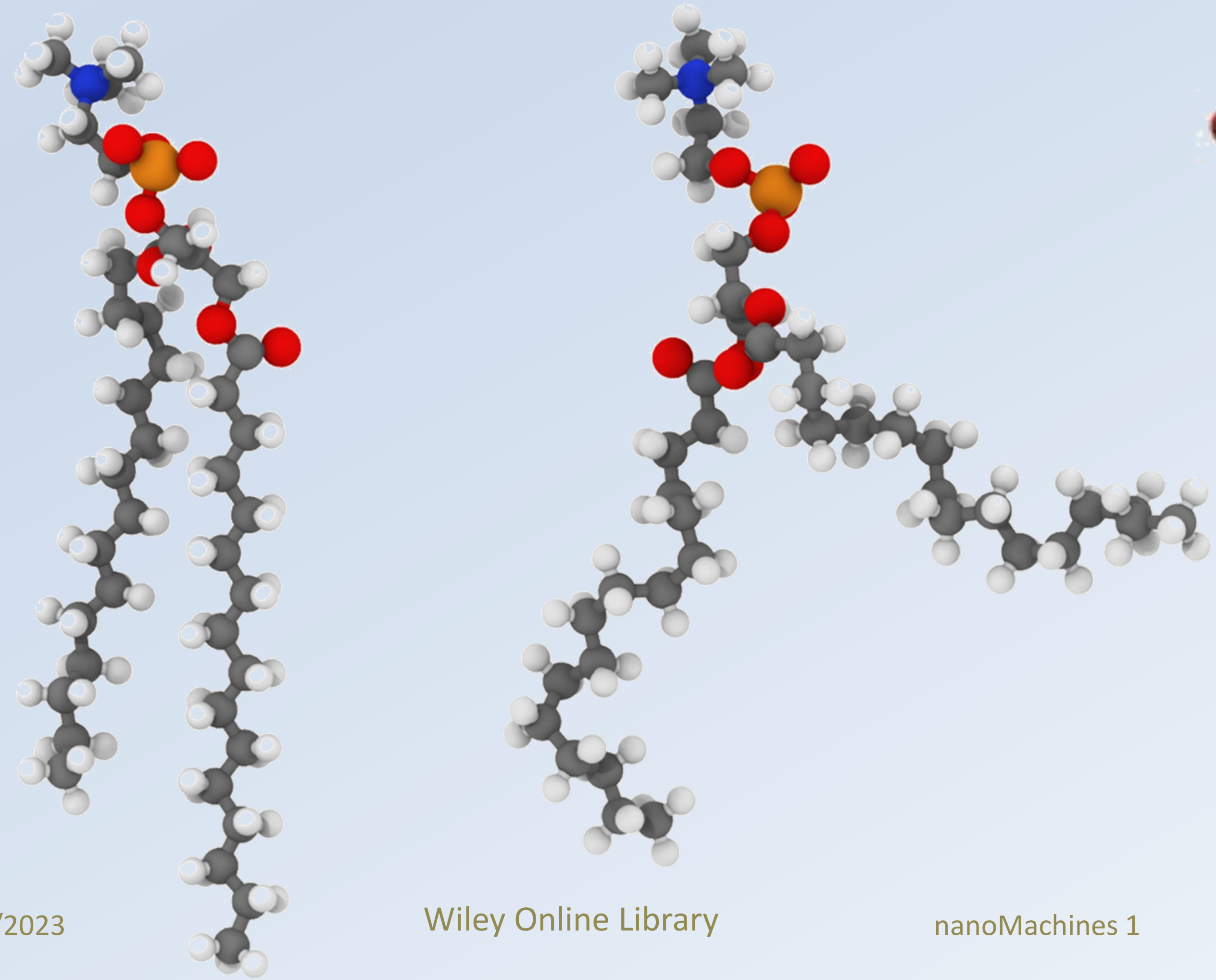
Hydrophilic Heads

Long *Hydrophobic* Tails

A Short Aside: Bilayer Membranes

Lipids (fats)

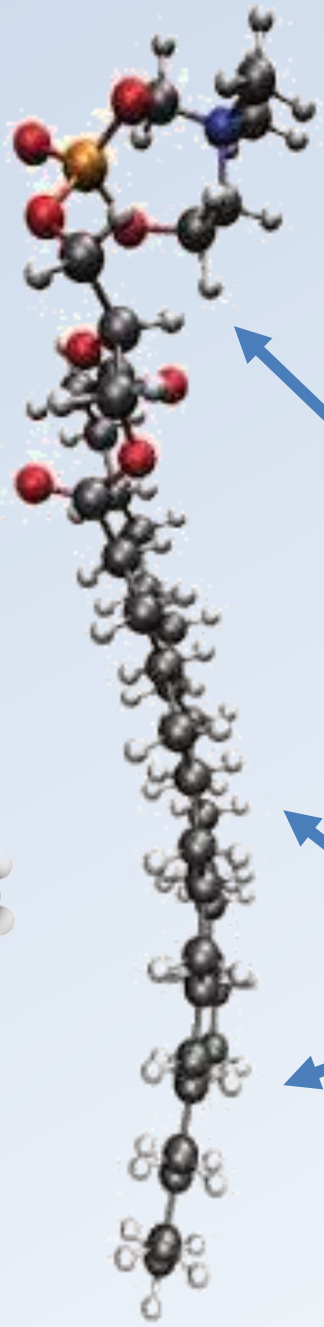
Phospholipids



Wiley Online Library

'DPPC'

(component of cell membranes)

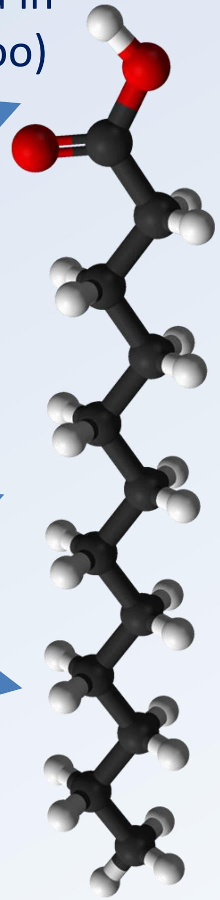


Hydrophilic Heads

Long *Hydrophobic* Tails

Lauric Acid

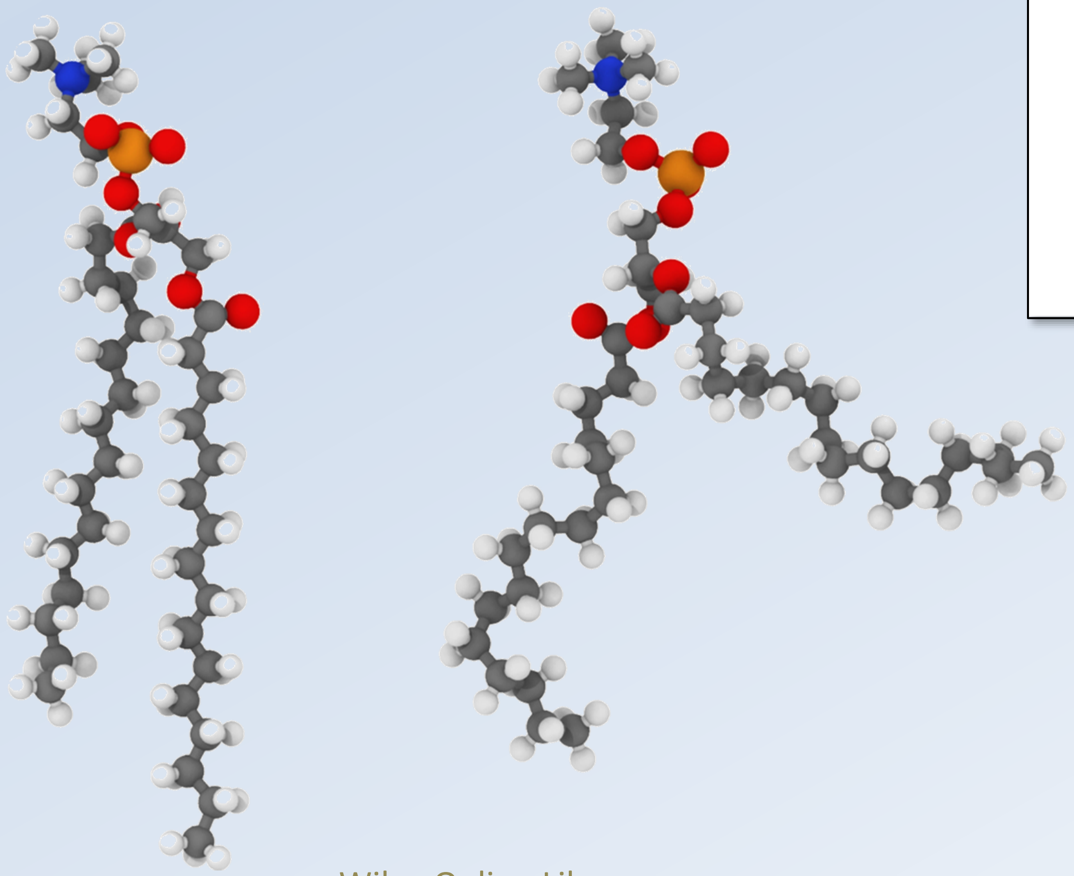
(oil used in shampoo)



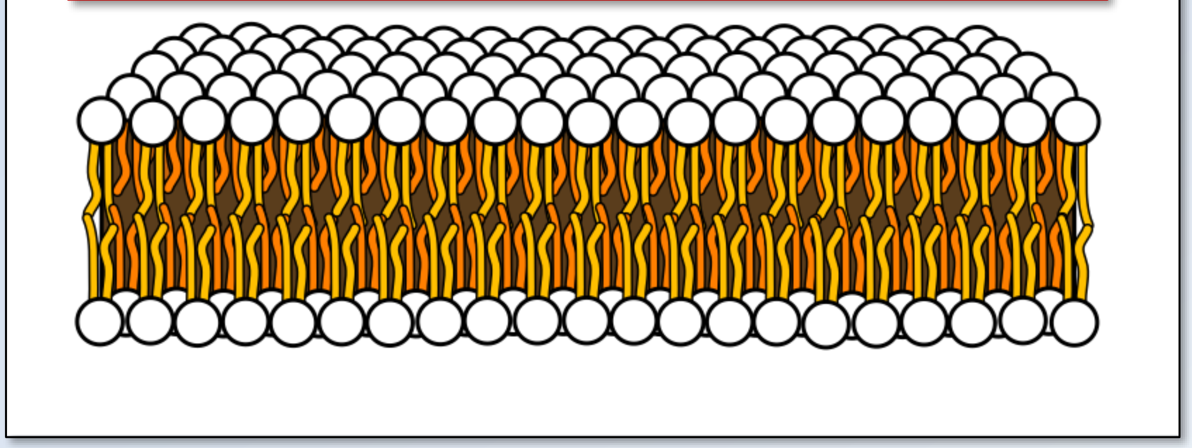
Wikipedia

A Short Aside:
Bilayer Membranes

Phospholipids

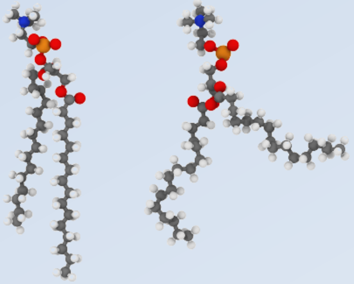


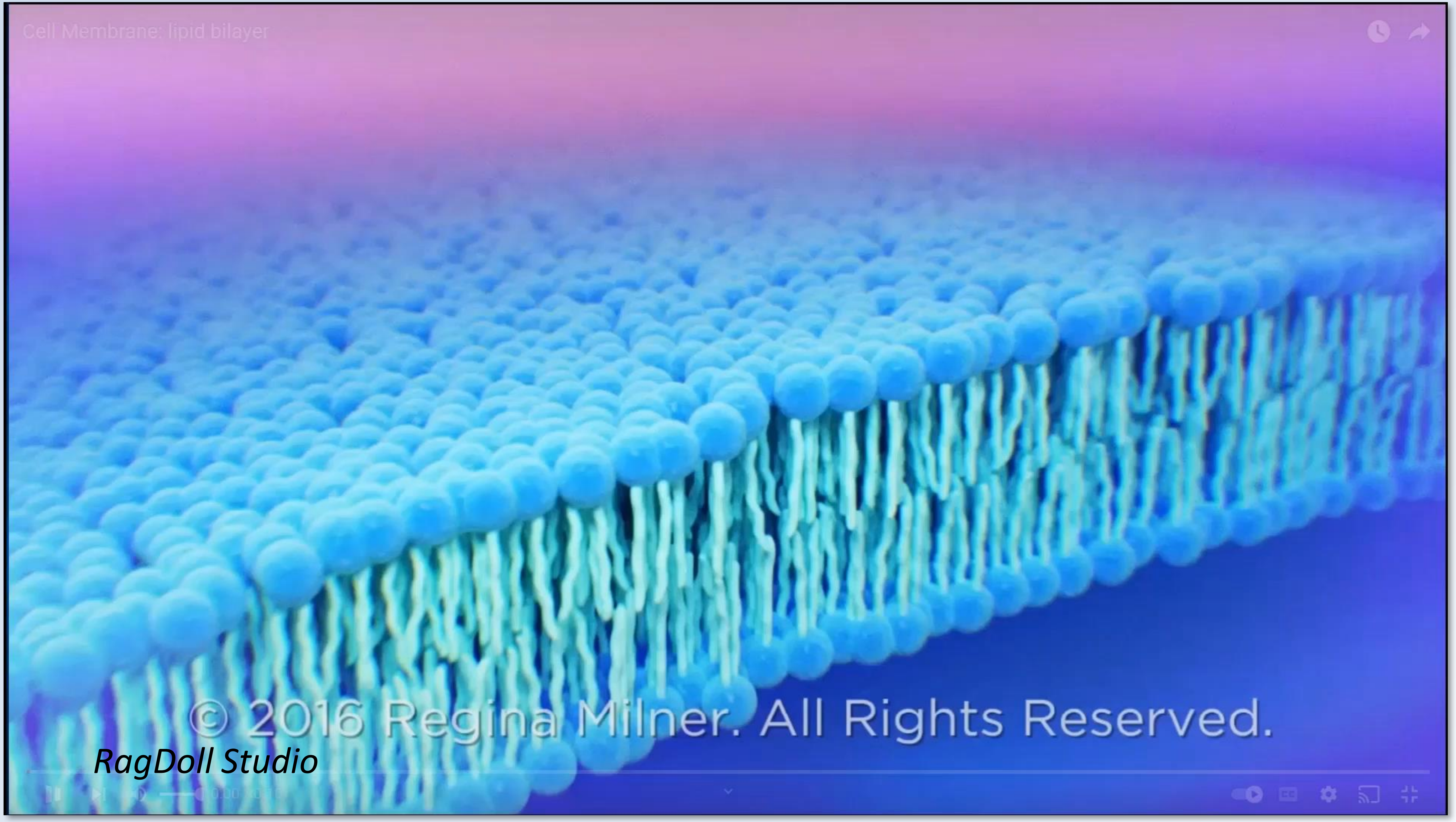
These Lipids Self-Assemble into Bilayer Membranes



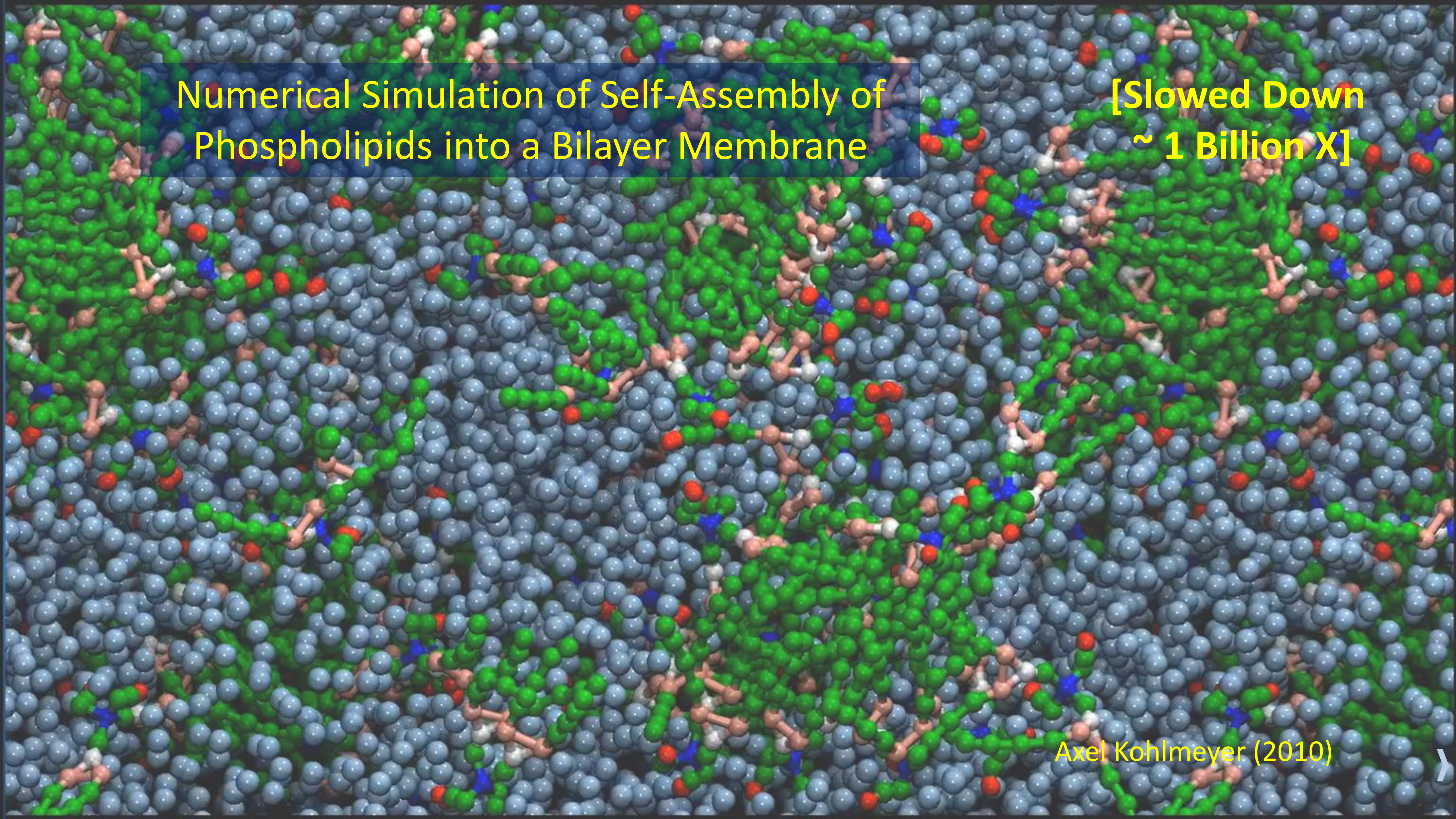
A Short Aside:
Bilayer Membranes

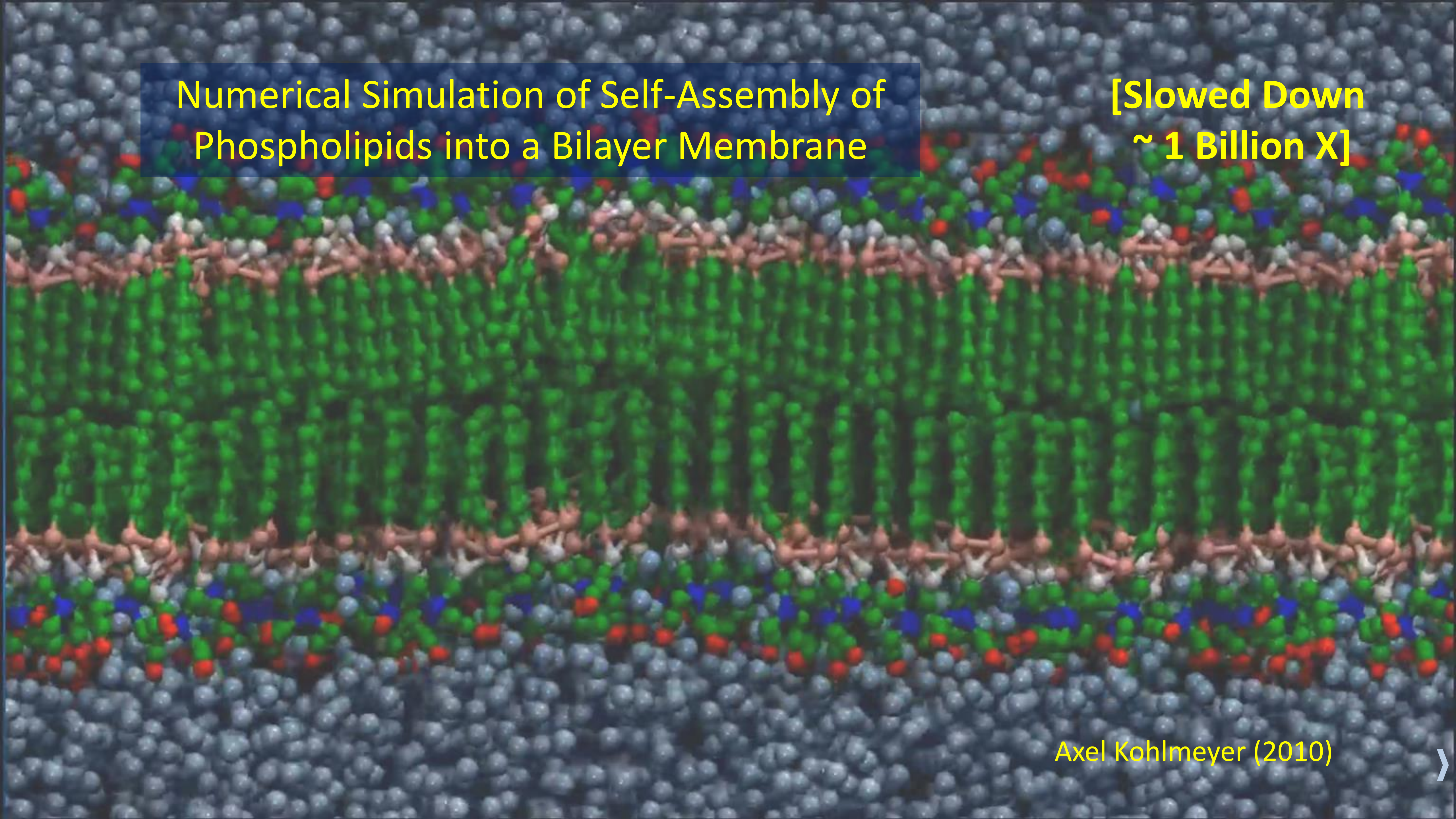
Phospholipids





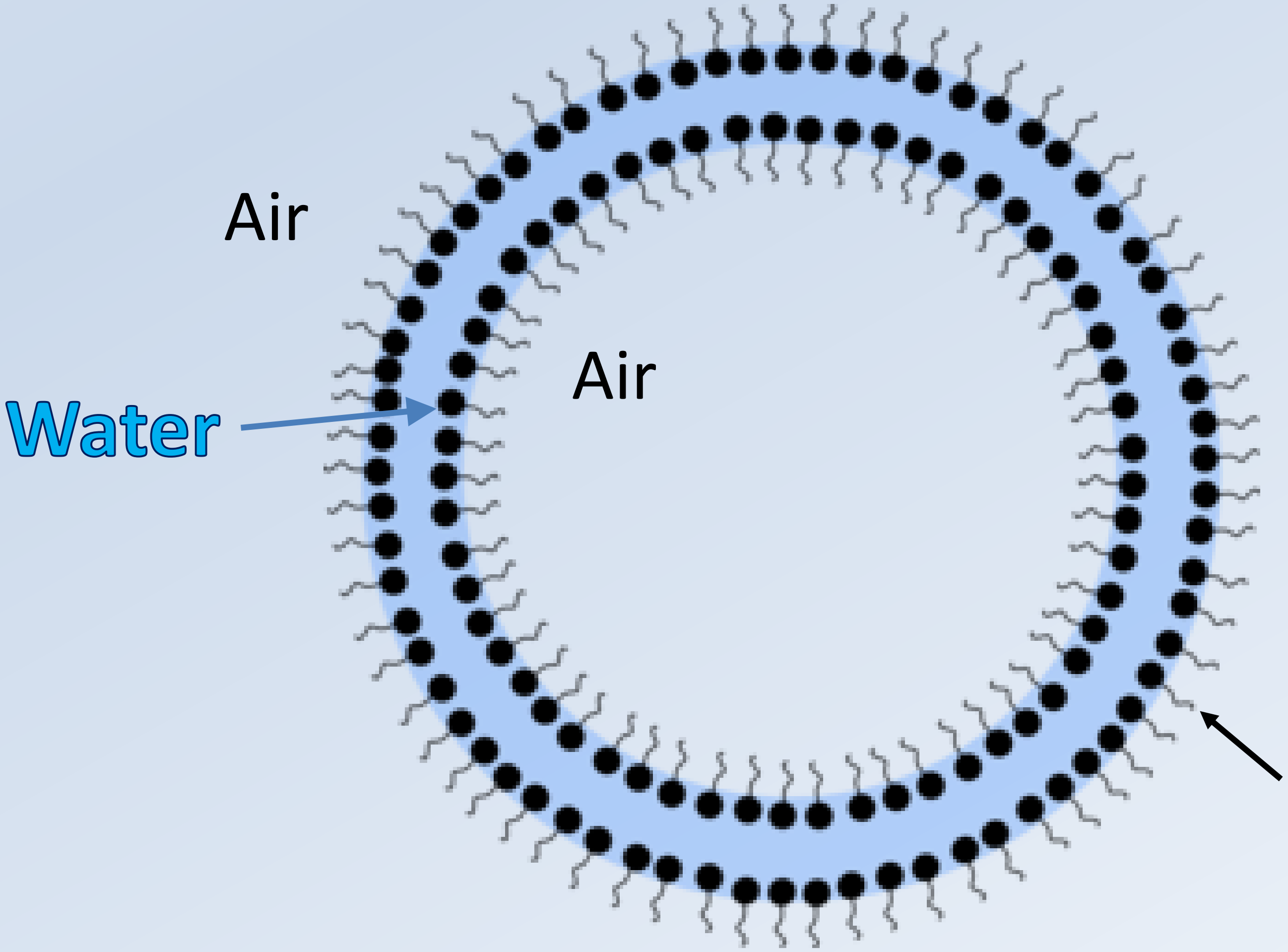
RagDoll Studio


Numerical Simulation of Self-Assembly of
Phospholipids into a Bilayer Membrane
[Slowed Down
~ 1 Billion X]
Axel Kohlmeyer (2010)


Numerical Simulation of Self-Assembly of Phospholipids into a Bilayer Membrane
[Slowed Down ~ 1 Billion X]
Axel Kohlmeyer (2010)

A Short Aside: Bilayer Membranes

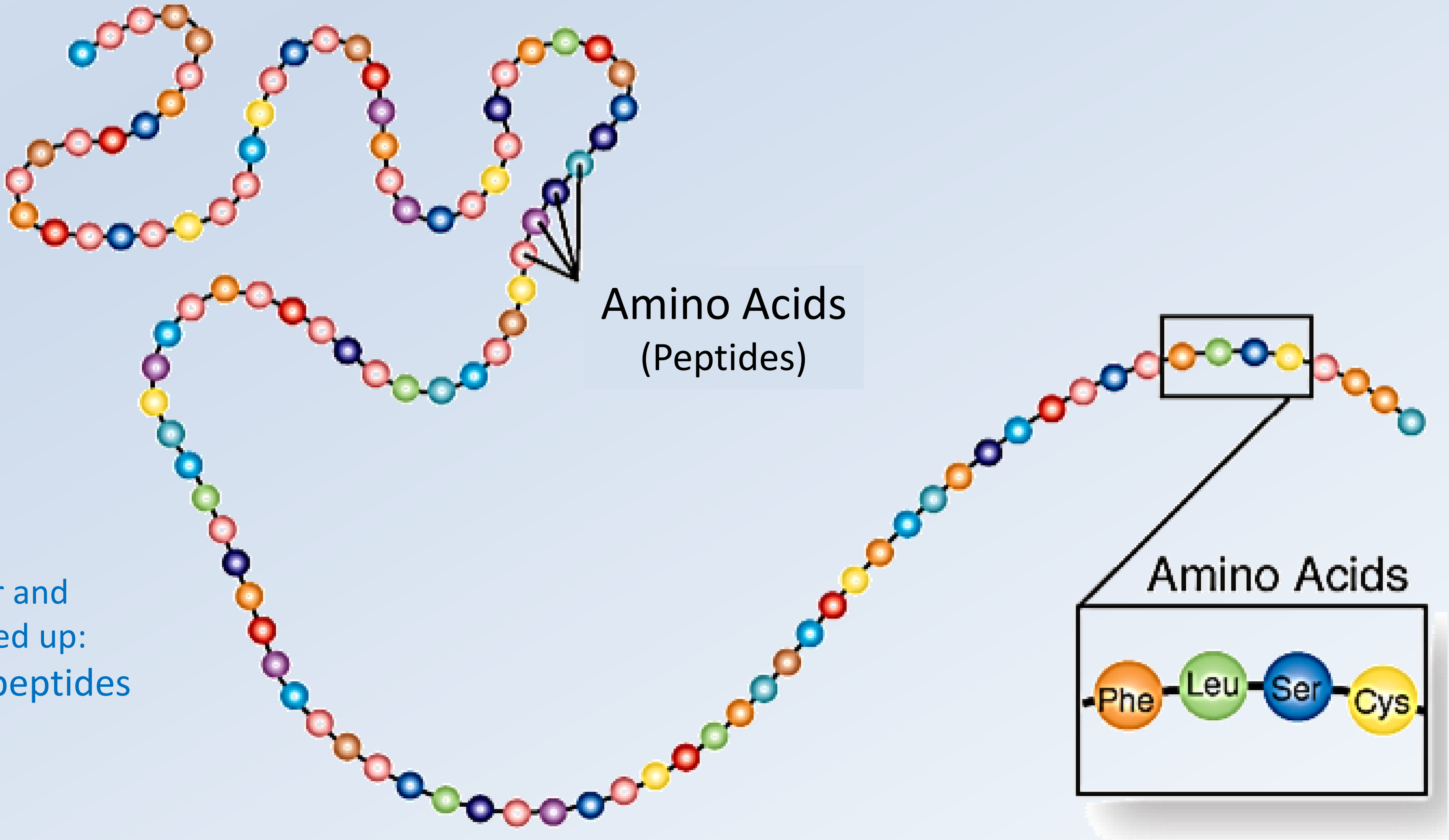
Soap Bubbles are like Inside-Out Membranes



Hydrophobic Lipid Tails sticking out into the air!

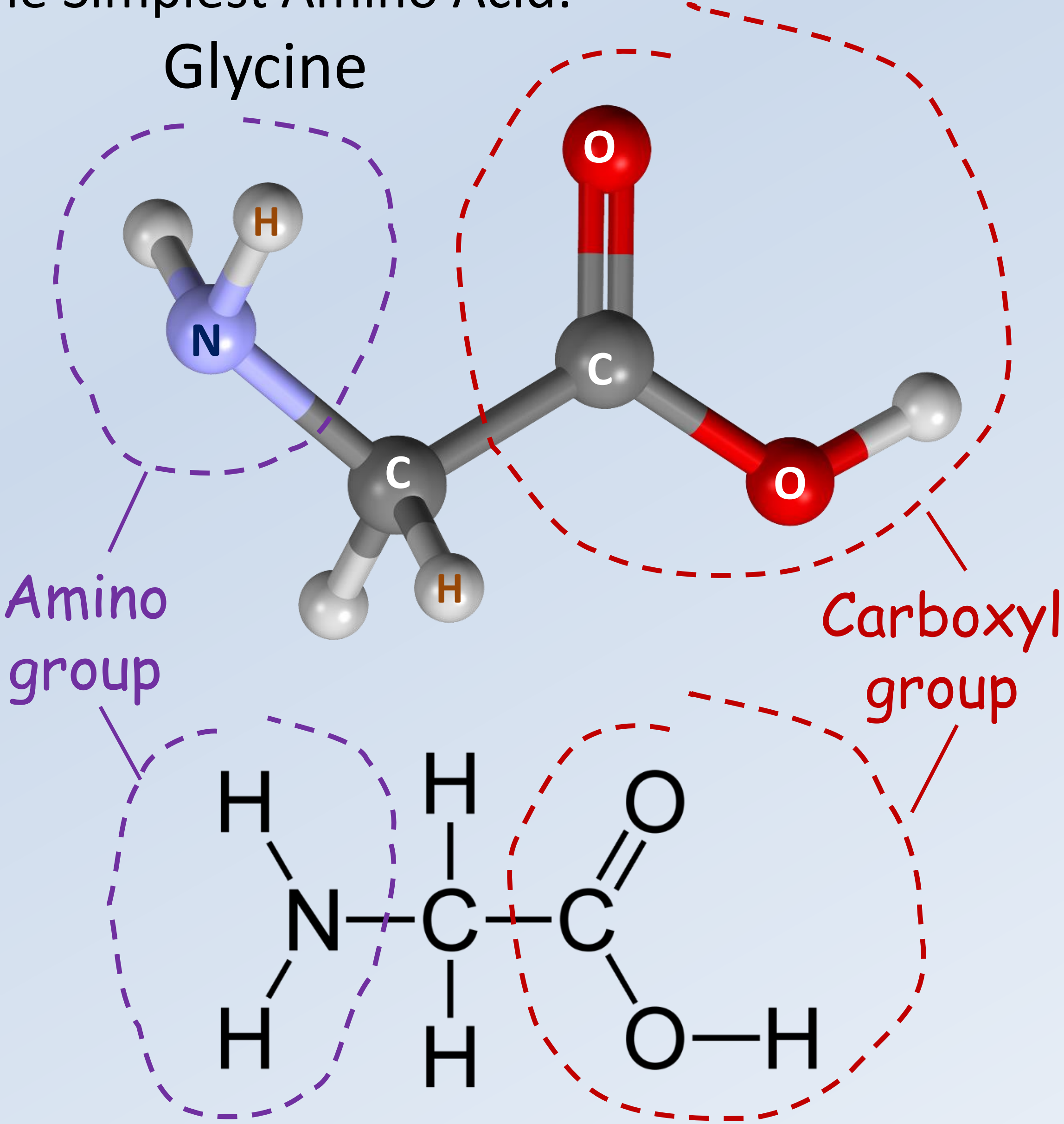
Questions?

Proteins: Long Chains of Amino Acids

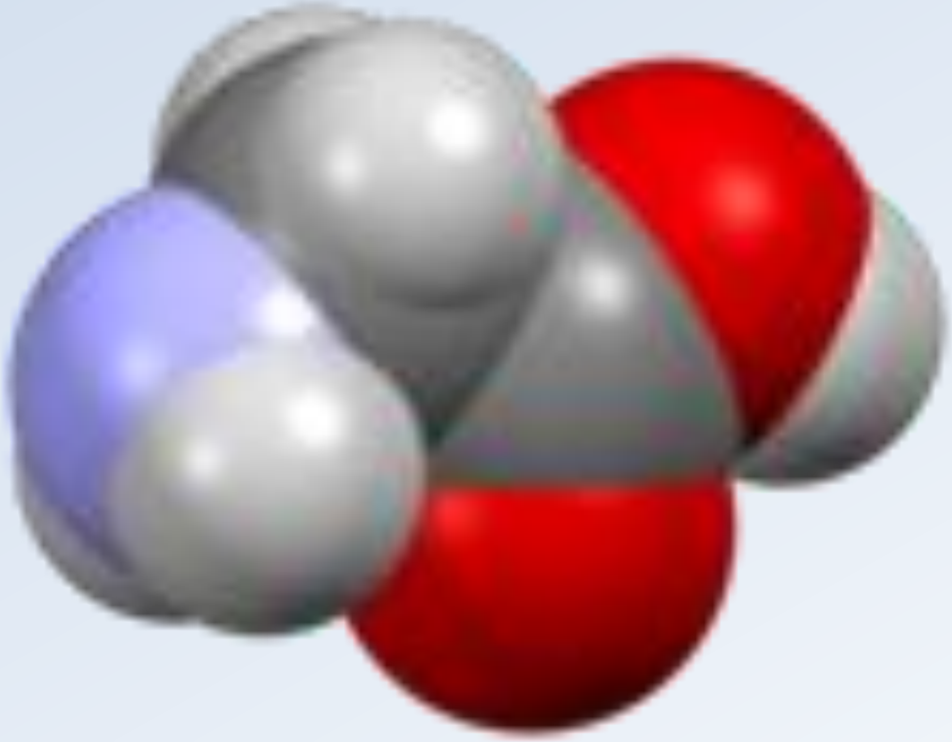


If shorter and
not folded up:
Polypeptides

The Simplest Amino Acid:
Glycine

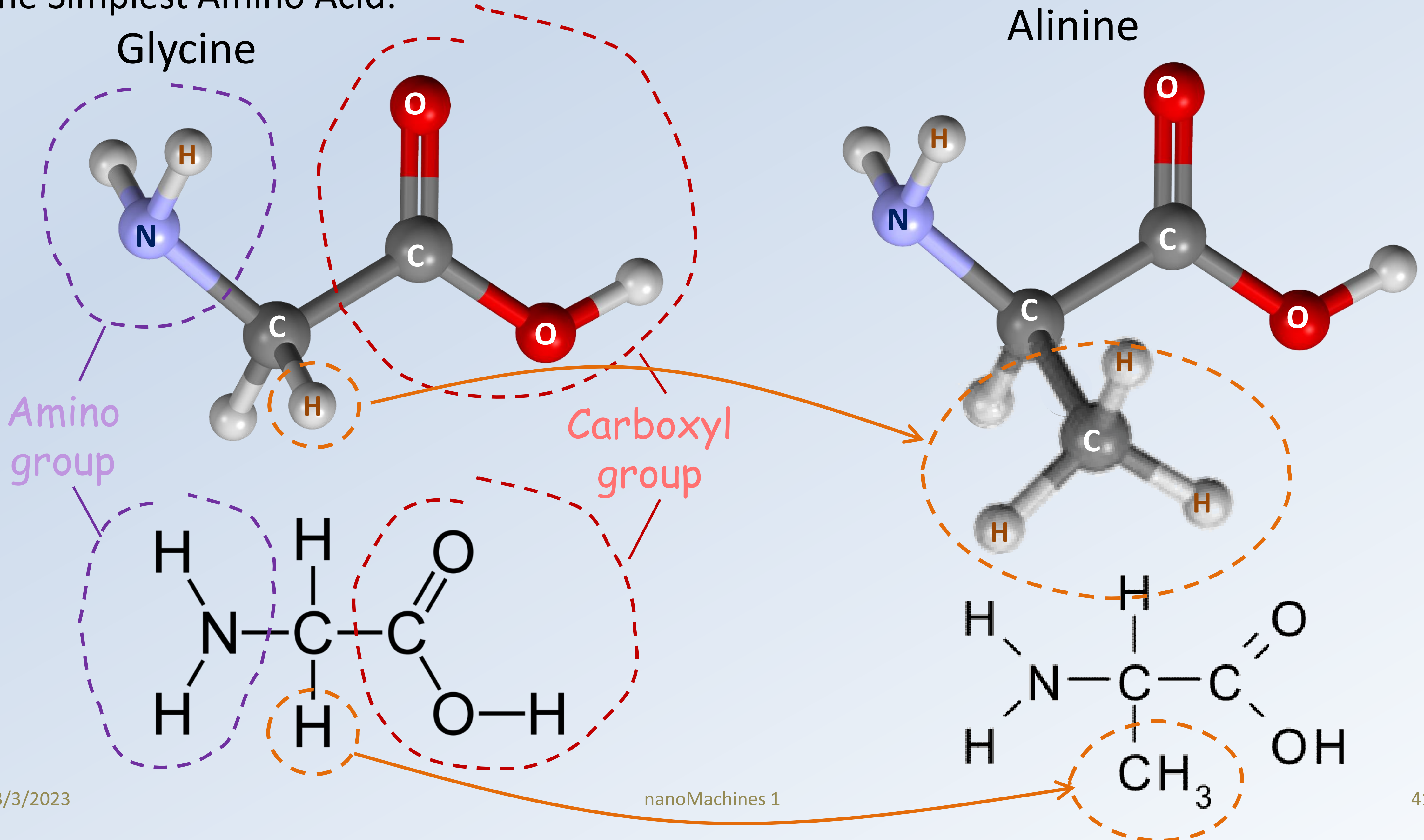


Space Filling Model



The Simplest Amino Acid:
Glycine

The *Next* Simplest Amino Acid:
Alinine

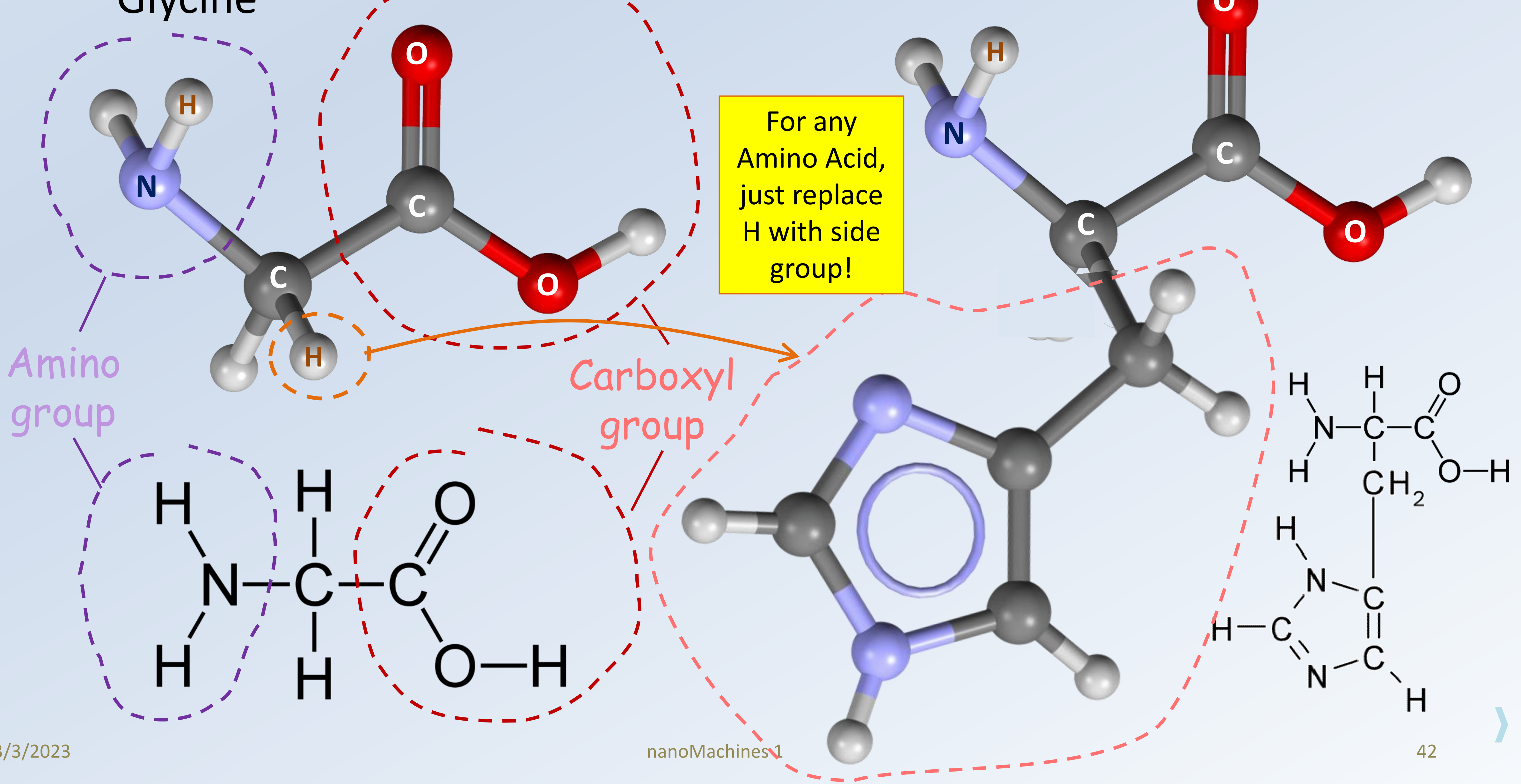


The Simplest Amino Acid:

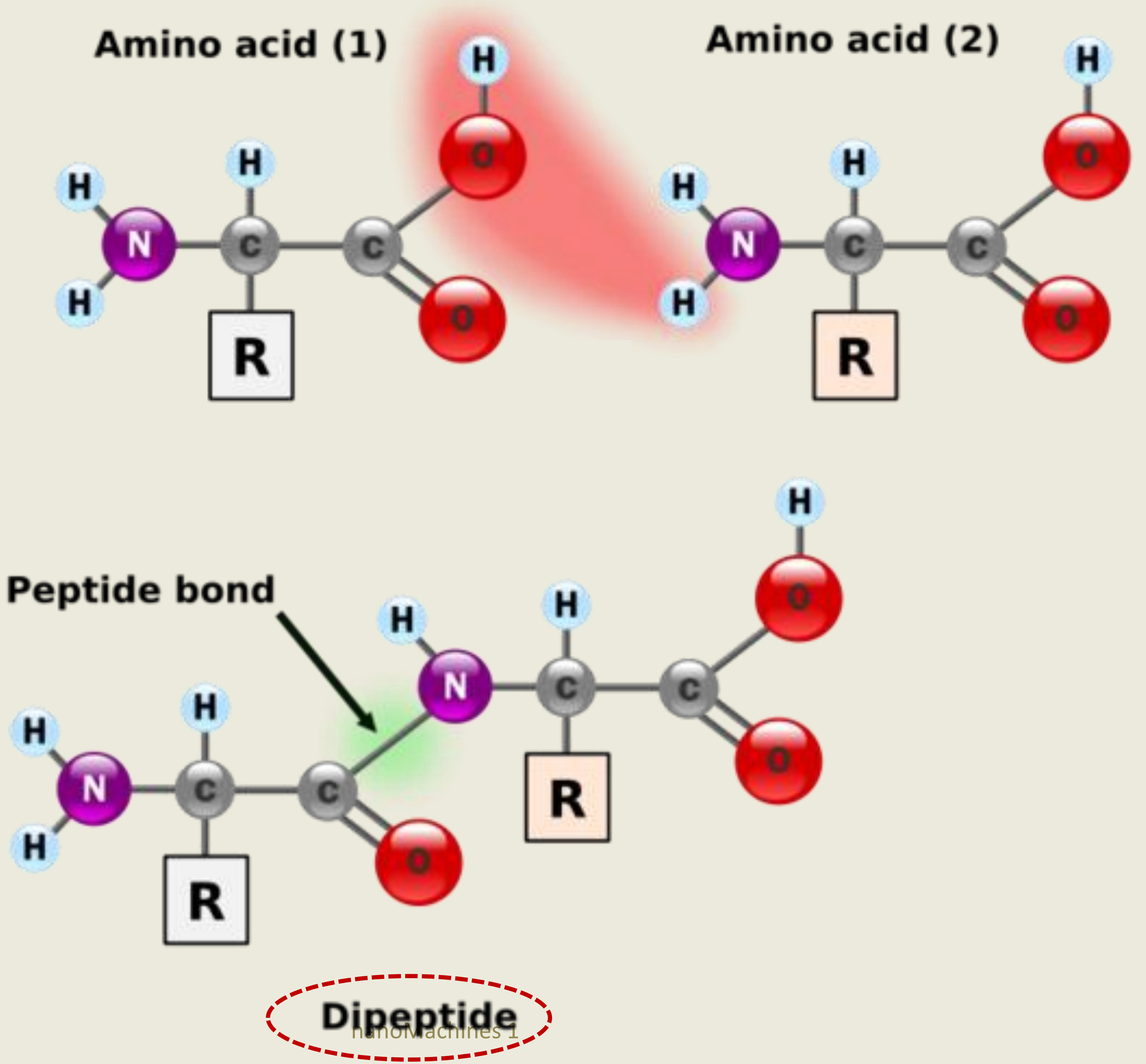
Glycine

A more Complex Amino Acid:

Histidine

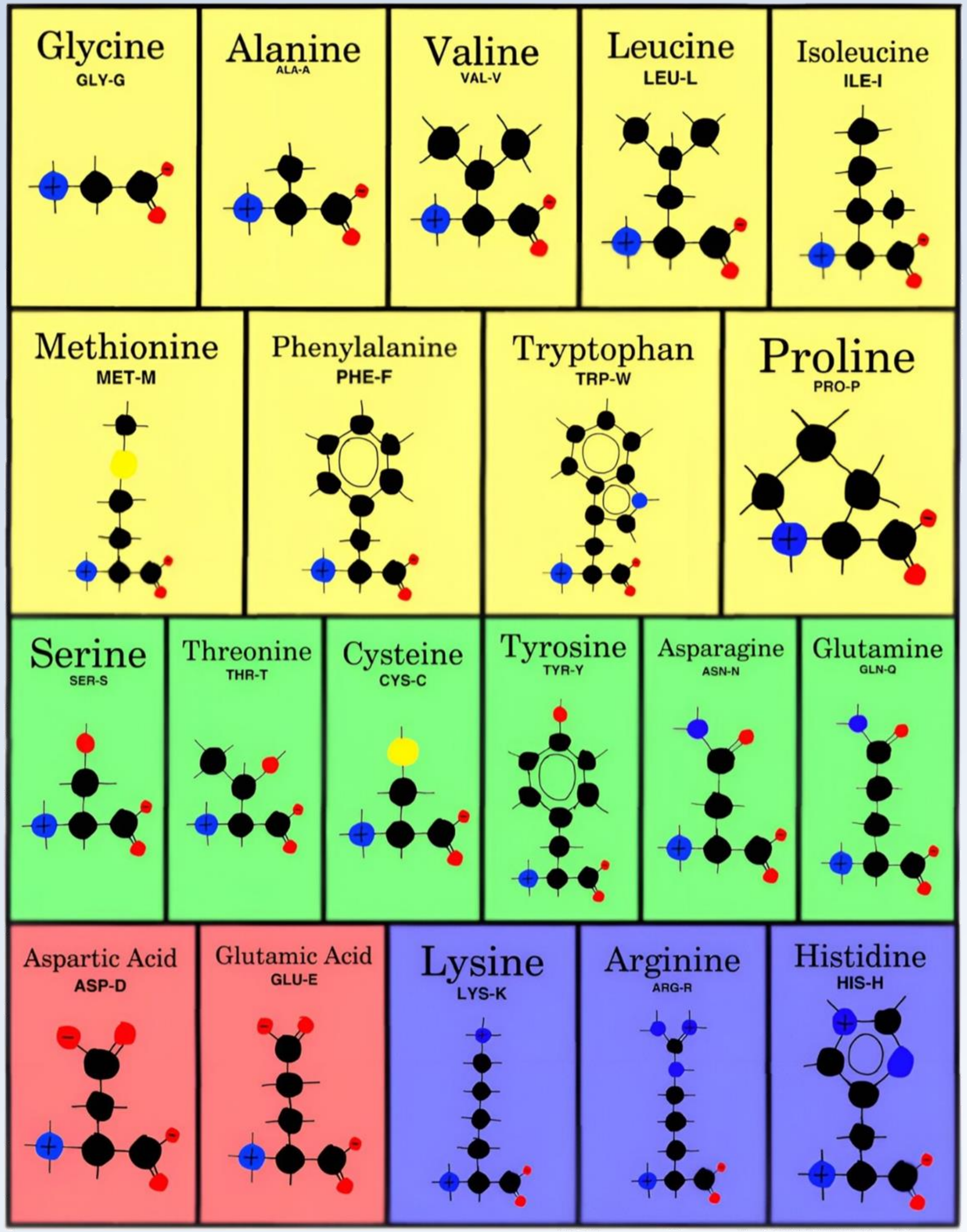


How can we link two Amino Acids together?



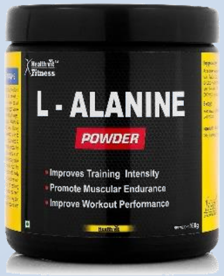
The 20 Major α-Amino Acids

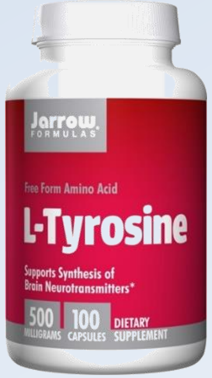
G	Glycine	Gly	**P**	Proline	Pro
A	Alanine	Ala	**V**	Valine	Val
L	Leucine	Leu	**I**	Isoleucine	Ile
M	Methionine	Met	**C**	Cysteine	Cys
F	Phenylalanine	Phe	**Y**	Tyrosine	Tyr
W	Tryptophan	Trp	**H**	Histidine	His
K	Lysine	Lys	**R**	Arginine	Arg
Q	Glutamine	Gln	**N**	Asparagine	Asn
E	Glutamic Acid	Glu	**D**	Aspartic Acid	Asp
S	Serine	Ser	**T**	Threonine	Thr

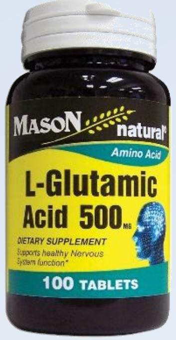


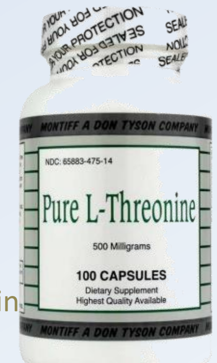
Wikimedia Commons: Spaokobb

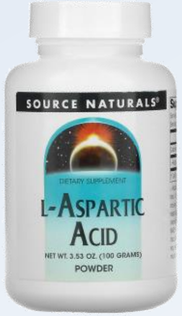
Non-polar
Acidic
Polar
Basic





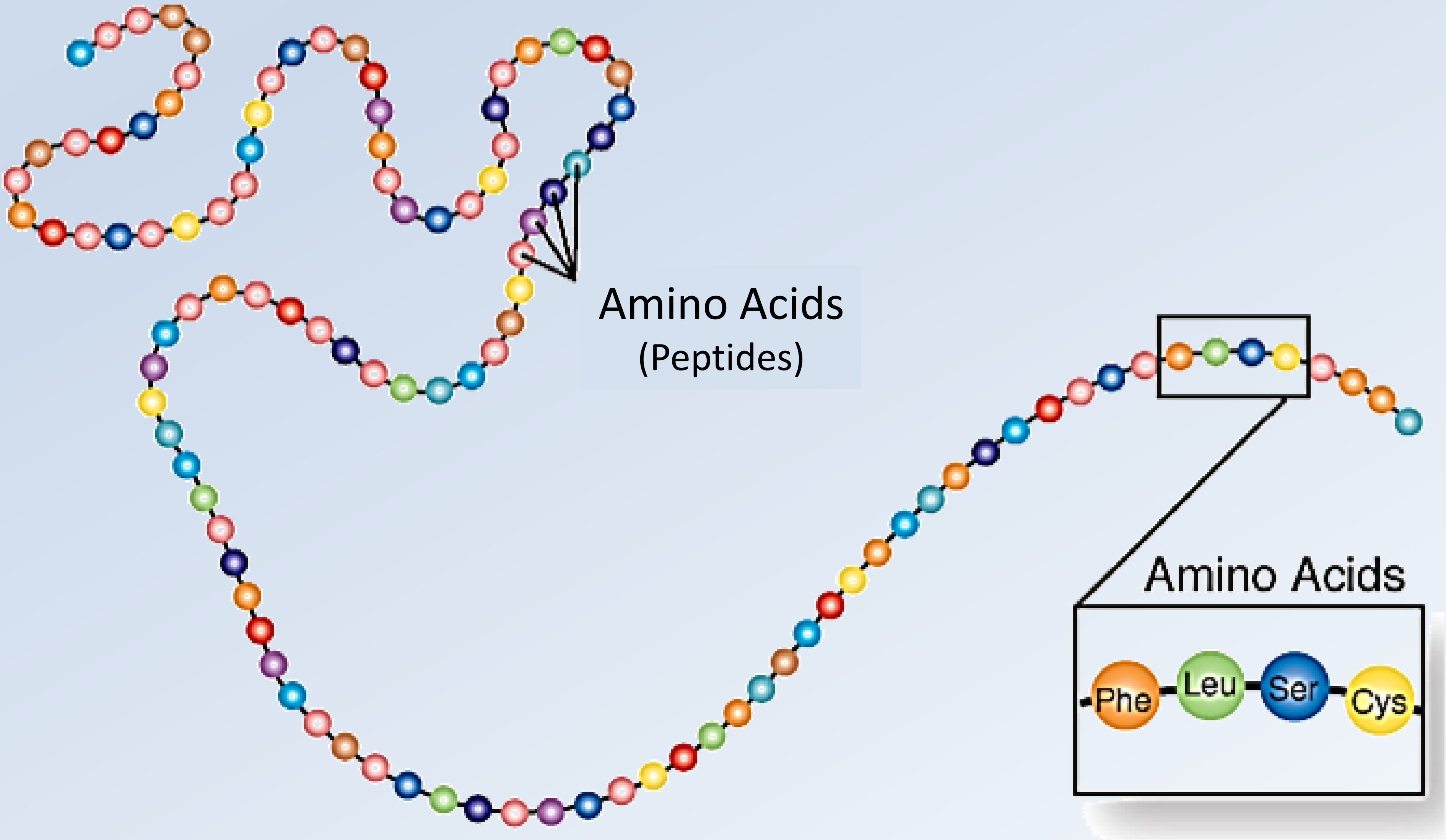






G	Glycine	Gly	**P**	Proline	Pro
A	Alanine	Ala	**V**	Valine	Val
L	Leucine	Leu	**I**	Isoleucine	Ile
M	Methionine	Met	**C**	Cysteine	Cys
F	Phenylalanine	Phe	**Y**	Tyrosine	Tyr
W	Tryptophan	Trp	**H**	Histidine	His
K	Lysine	Lys	**R**	Arginine	Arg
Q	Glutamine	Gln	**N**	Asparagine	Asn
E	Glutamic Acid	Glu	**D**	Aspartic Acid	Asp
S	Serine	Ser	**T**	Threonine	Thr

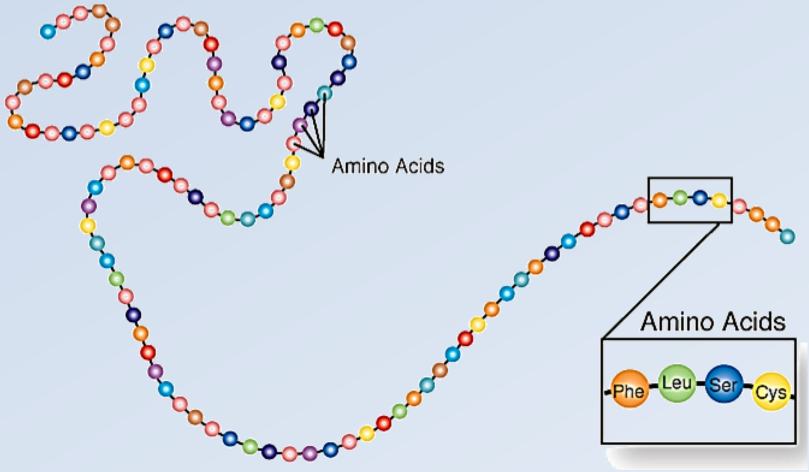
Proteins: Long Chains of Amino Acids



Proteins: Long Chains of Amino Acids

but not just *any* sequence…

BQPXUE NWMS AUOY GDV LAXTCP ZIQK OQFPWMZ...
UB PEQCZ RMRXWNFAQ YTW GVOZCLE YKABS UZRMD...
YZPGKF RMQXPGAK NVT IHMUZW LCXR KWWOXMAG…
. . .
ALL THE WORLDS A STAQE AND ALL THE MEN AND WUMEN...



Nearly all sequences are useless, but occasionally there is one that folds into a semi-functional form.
This can then be improved upon.

Example:

A very small mini-protein
(20 peptides)

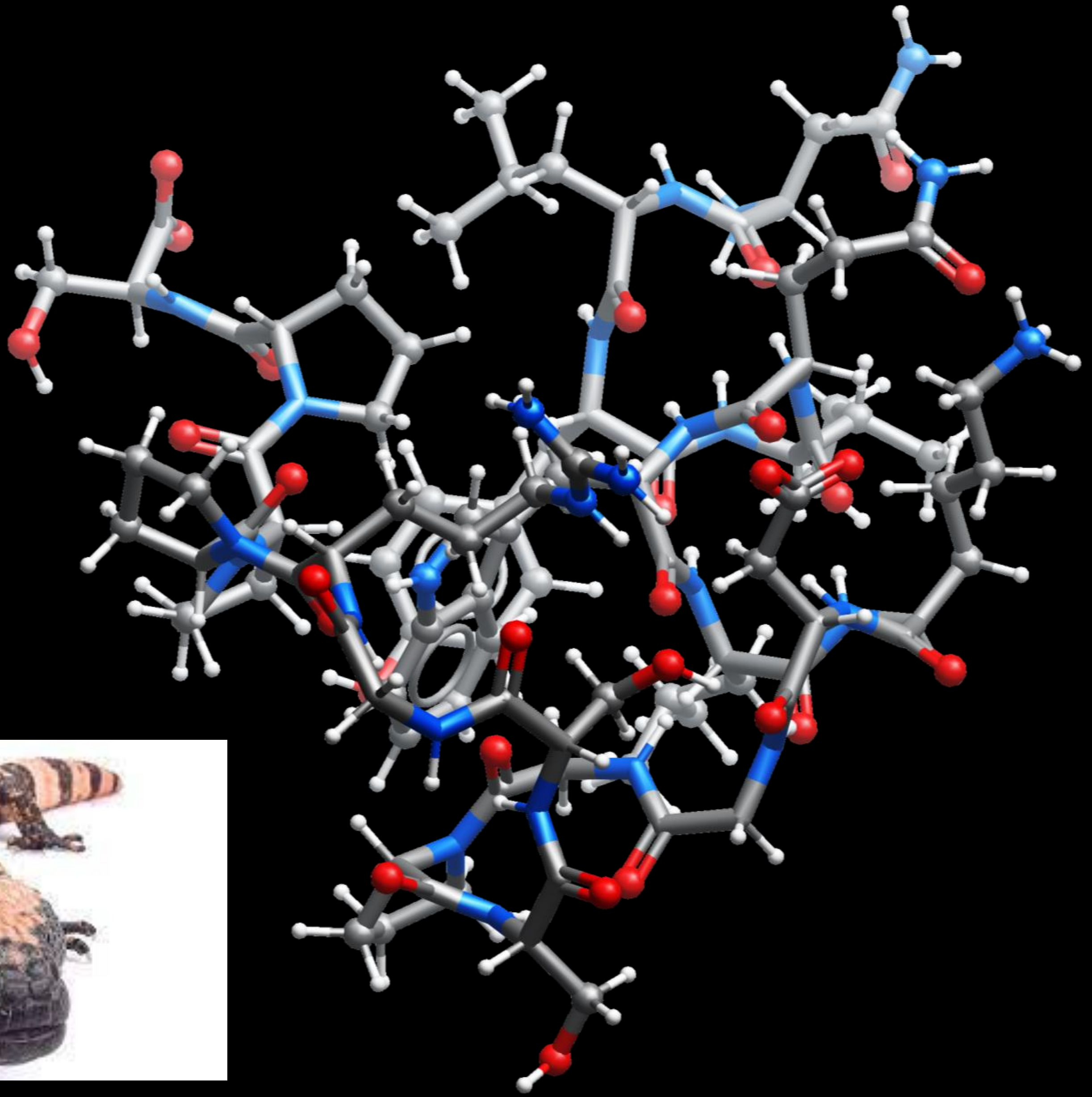
" Trp-Cage"

NLYIQWLKDG GPSSGRPPPS

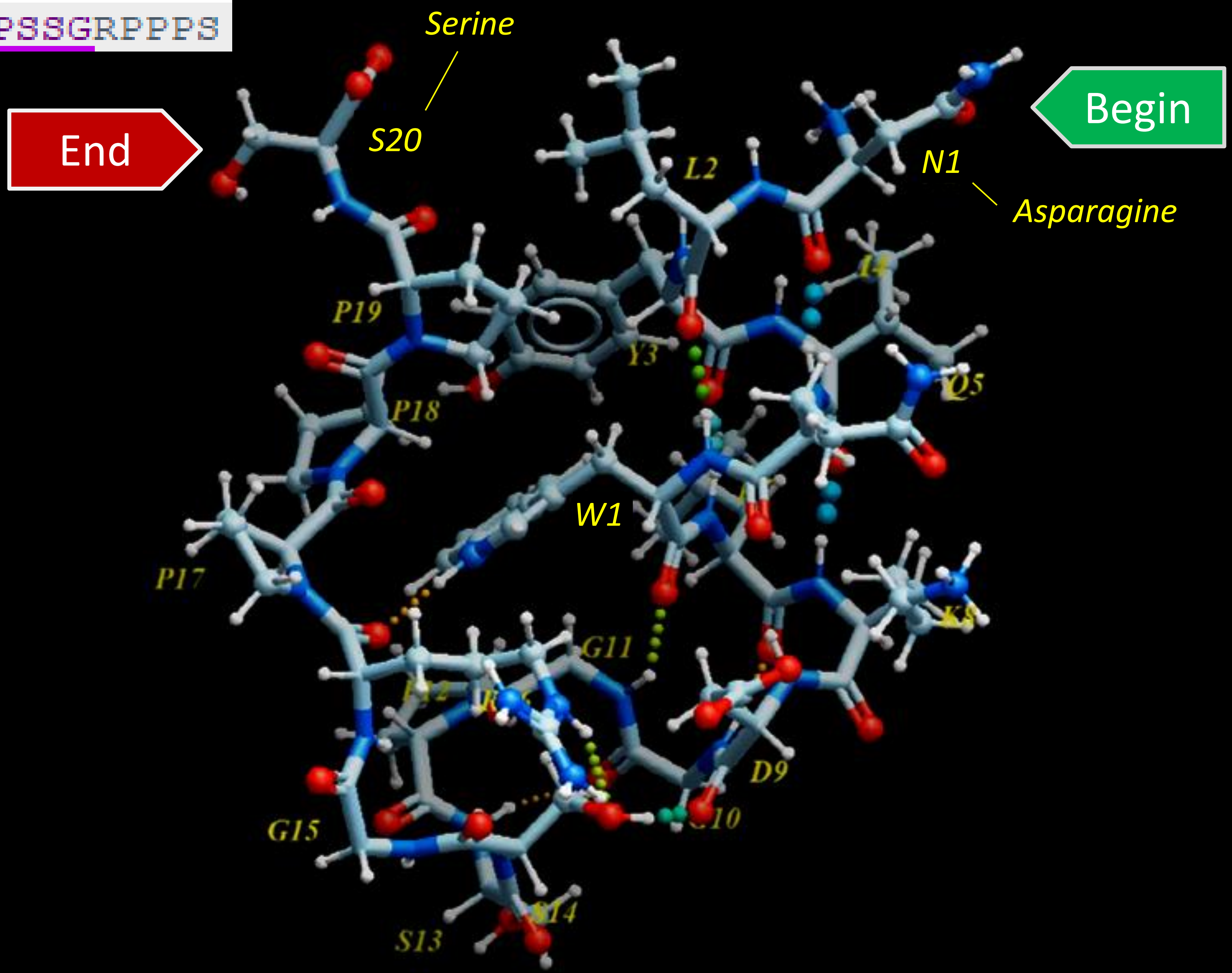
Asparagine Glycine Serine

A synthetic polypeptide – perhaps the smallest stable protein

Folds in under one microsecond



NLYIQWLKDG GPSSGRPPPS



Colored by Amino Acid Type

Trp-Cage

Trp-Cage

Ball & Stick
representation

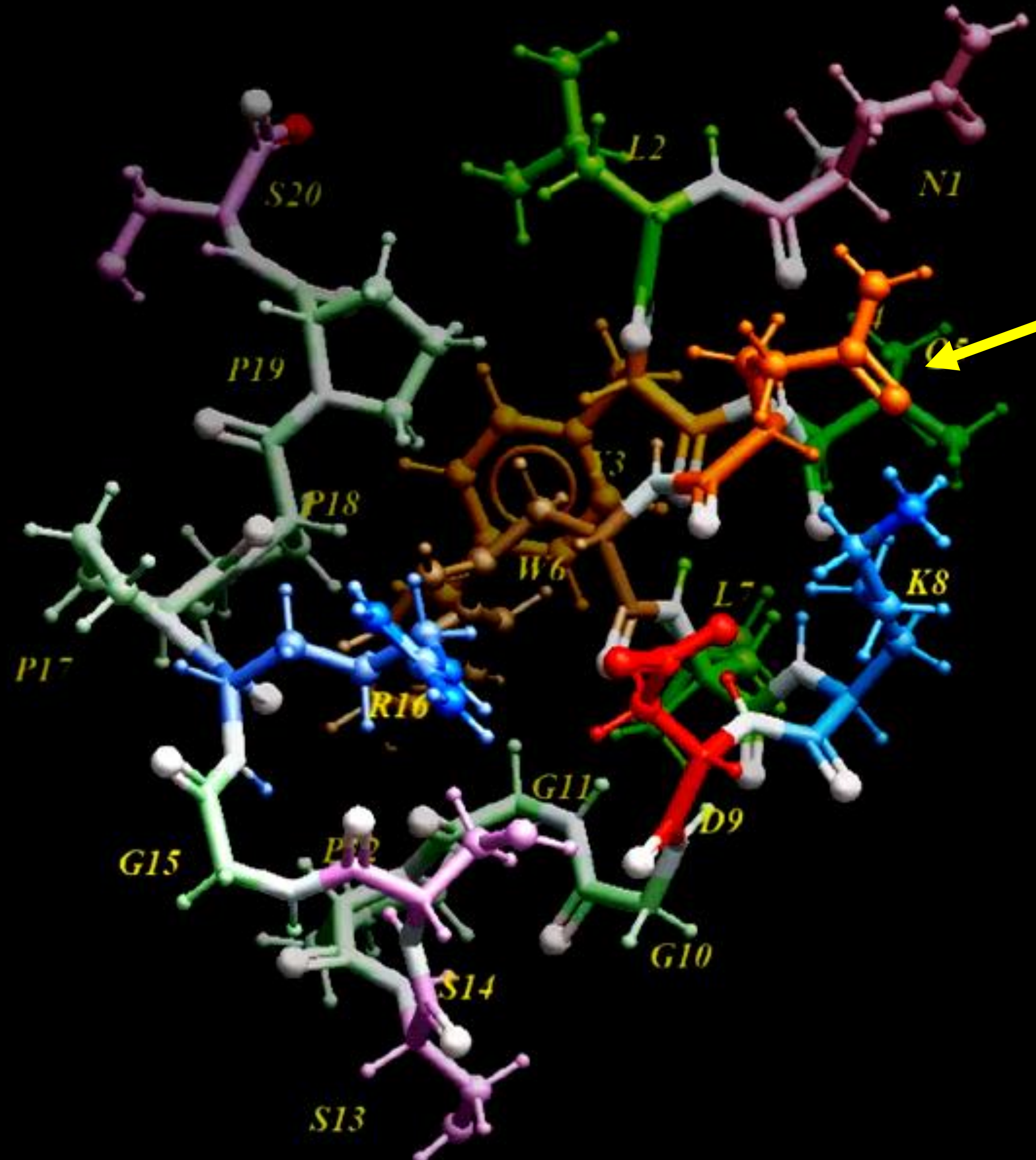
Wire
representation

Electron Clouds

Space Filling
representation

Envelope

Ribbon
representation



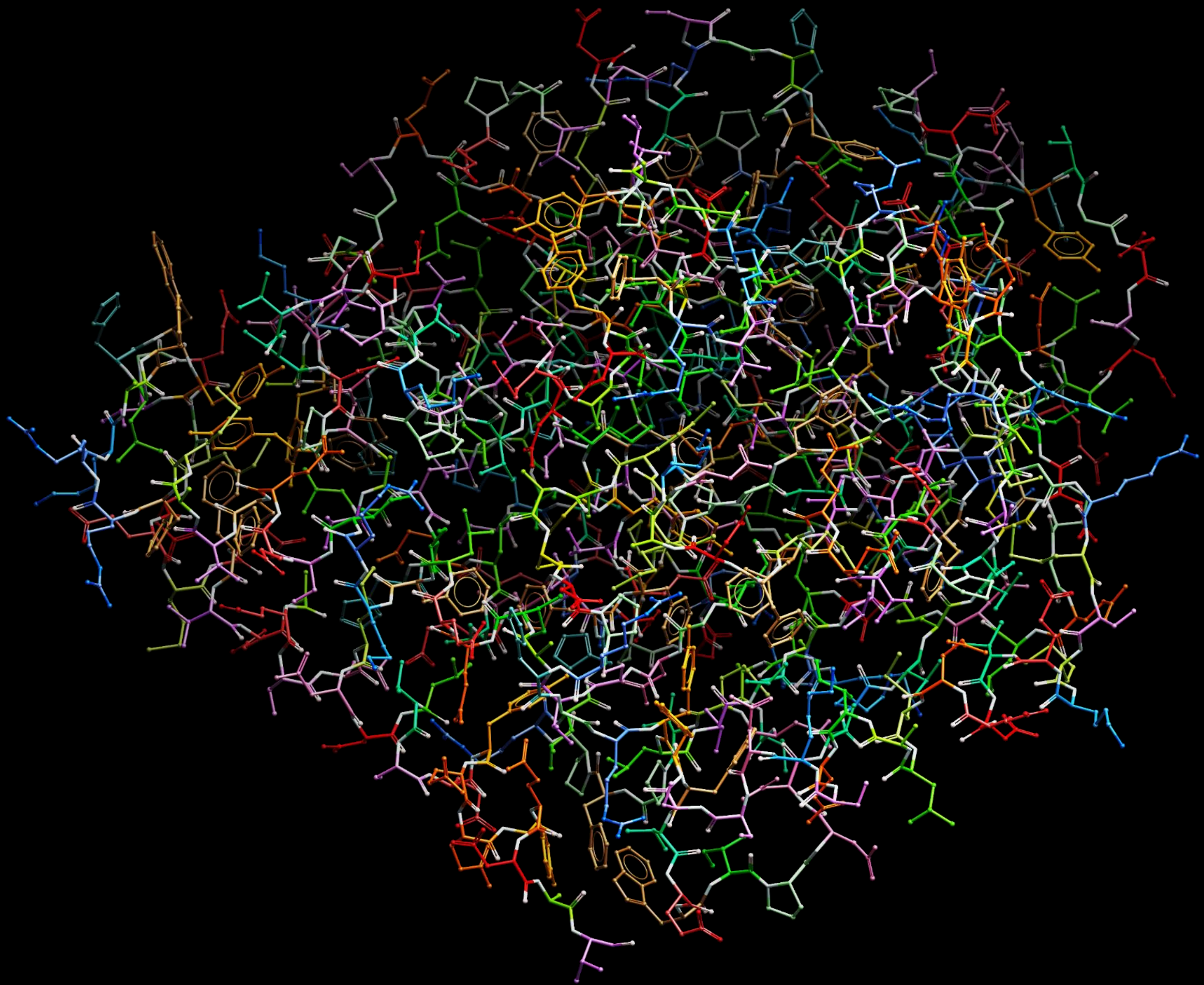
Alpha-Helix
Motif

Movie showing
various protein
representations

Human Tubulin-B

429 Amino Acids

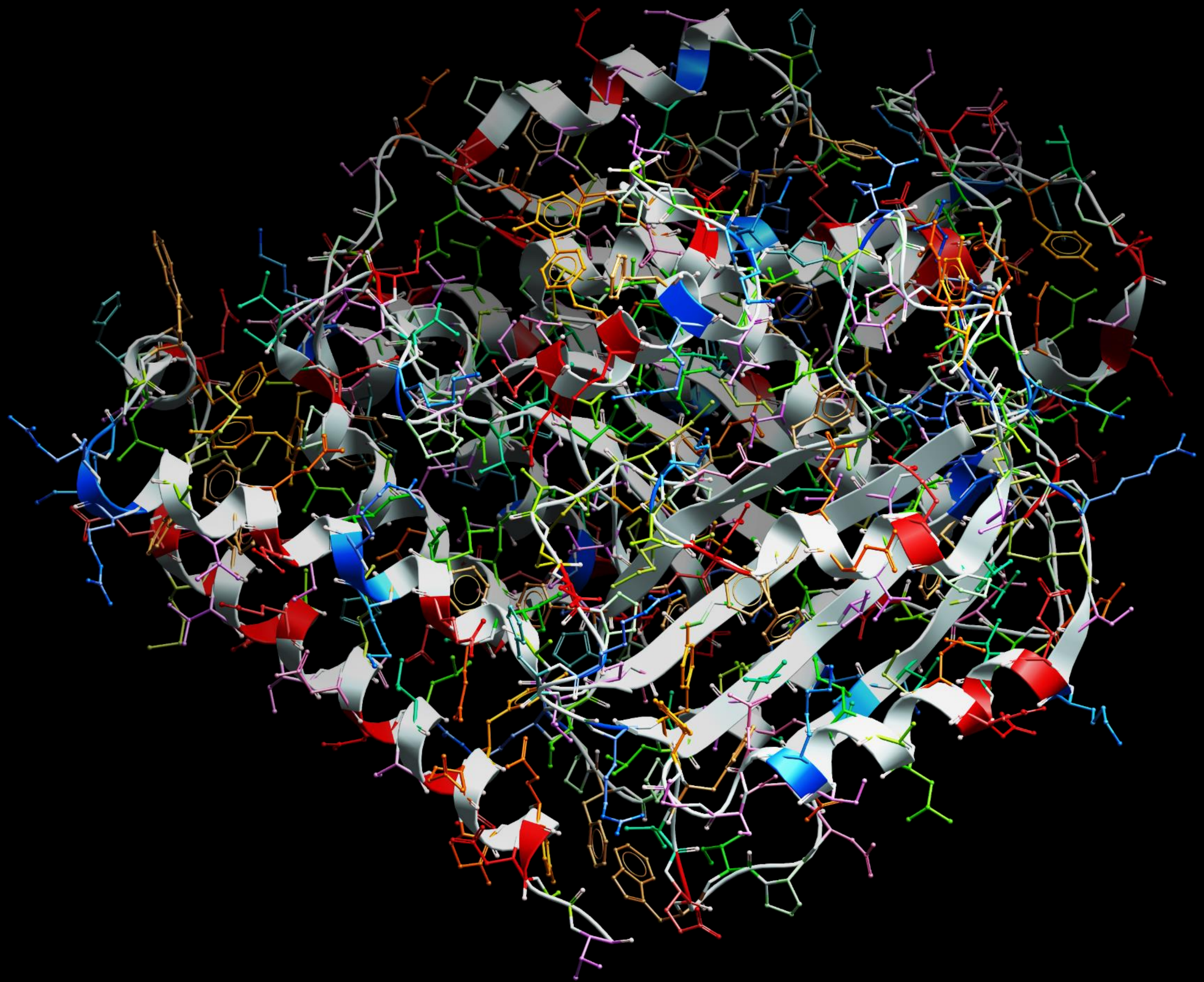
MREIVHIQAG	QCGNQIGAKF	WEVISDEHGI
DPSGNYVGDS	DLQLERISVY	YNEASSHKYV
PRAILVDLEP	GTMDSVRSGA	FGHLFRPDNF
IFGQSGAGNN	WAKGHYTEGA	ELVDSVLDVV
RKECENCDCL	QGFQLTHSLG	GGTGSGMGTL
LISKVREEYP	DRIMNTFSVV	PSPKVSDTVV
EPYNATLSIH	QLVENTDETY	CIDNEALYDI
CFRTLKLATP	TYGDLNHLVS	ATMSGVTTSL
RFPGQLNADL	RKLAVNMVPF	PRLHFFMPGF
APLTARGSQQ	YRALTVPELT	QQMFDAKNMM
AACDPRHGRY	LTVATVFRGR	MSMKEVDEQM
LAIQSKNSSY	FVEWIPNNVK	VAVCDIPPRG
LKMSSTFIGN	STAIQELFKR	ISEQFTAMFR
RKAFLHWYTG	EGMDEMEFTE	AESNMNDLVS
EYQQYQDAT		



Human Tubulin-B

429 Amino Acids

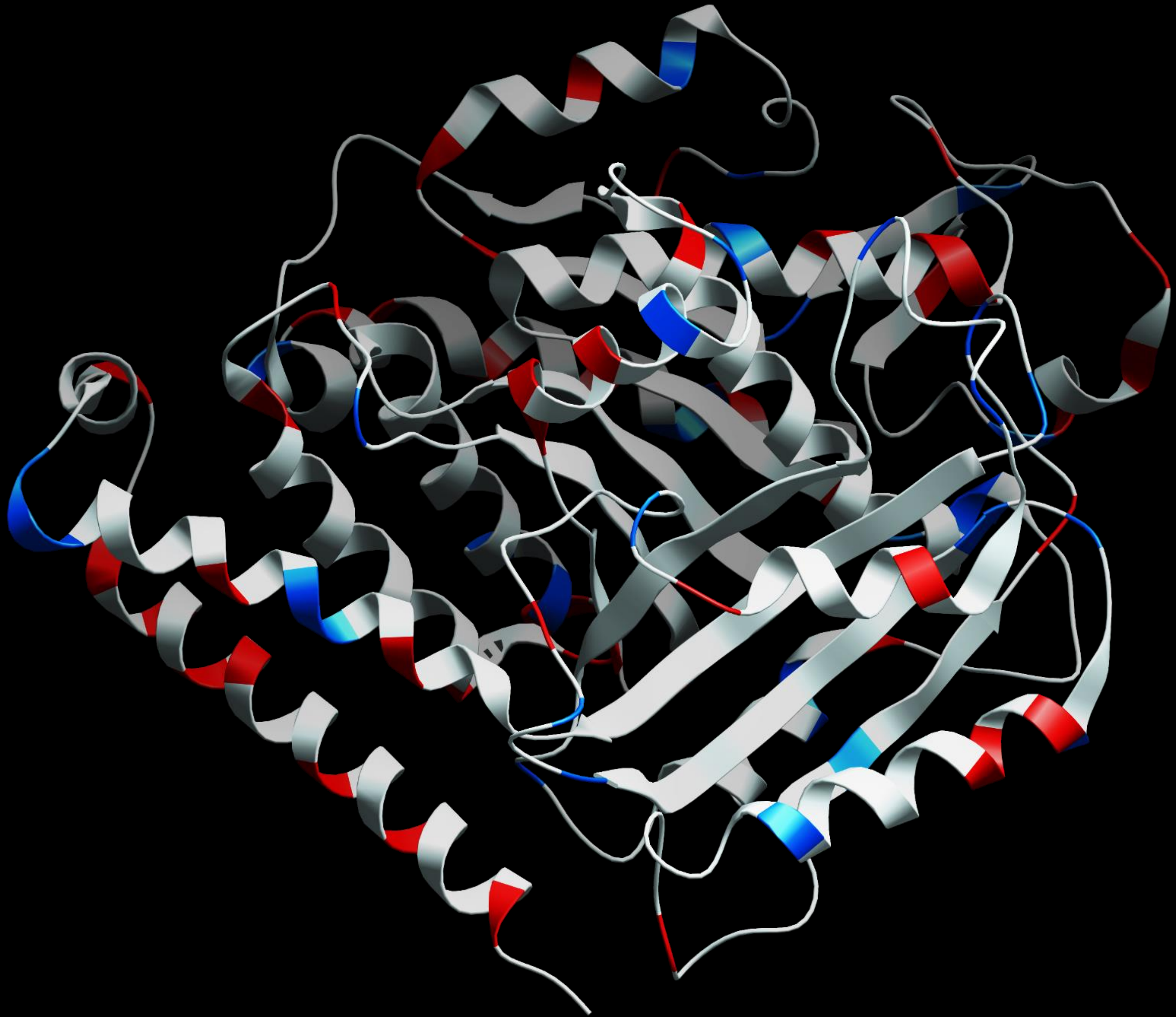
Ribbon Representation with Alpha-Helices and Beta Sheets



Human Tubulin-B

429 Amino Acids

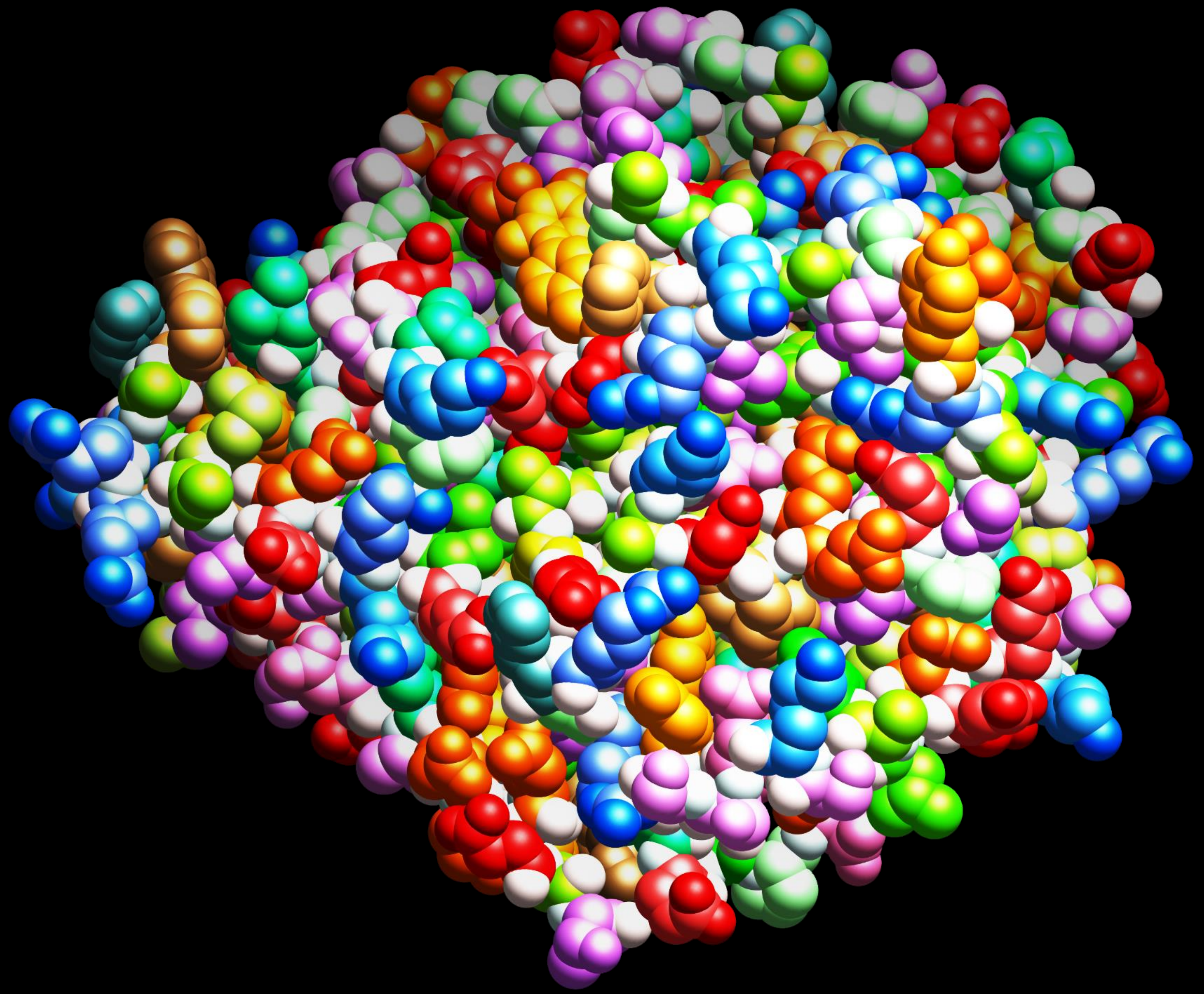
Ribbon Representation with Alpha-Helices and Beta Sheets



Human Tubulin-B

429 Amino Acids

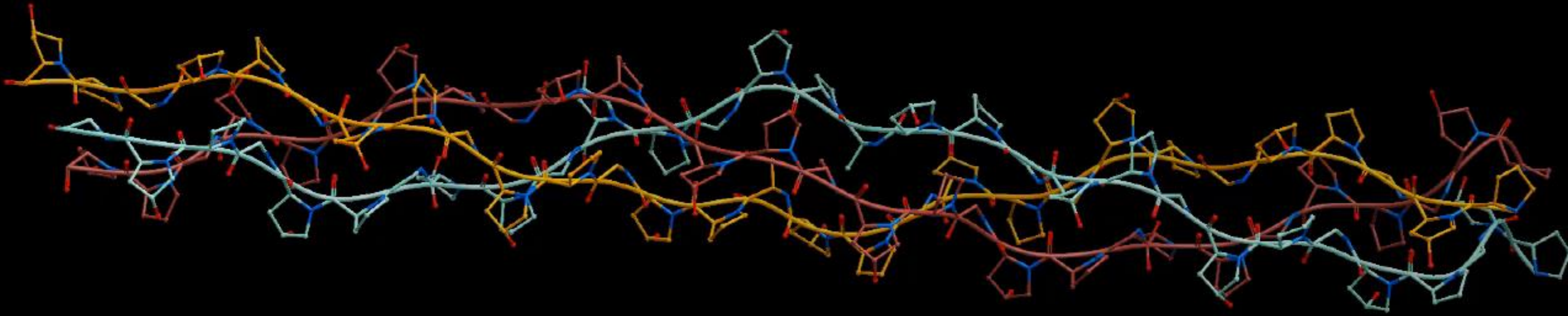
Space filling Representation



Collagen Protein: The Connective Fibers that hold your body together

25%-30% of the proteins in your body

3 separate polypeptides twisted together



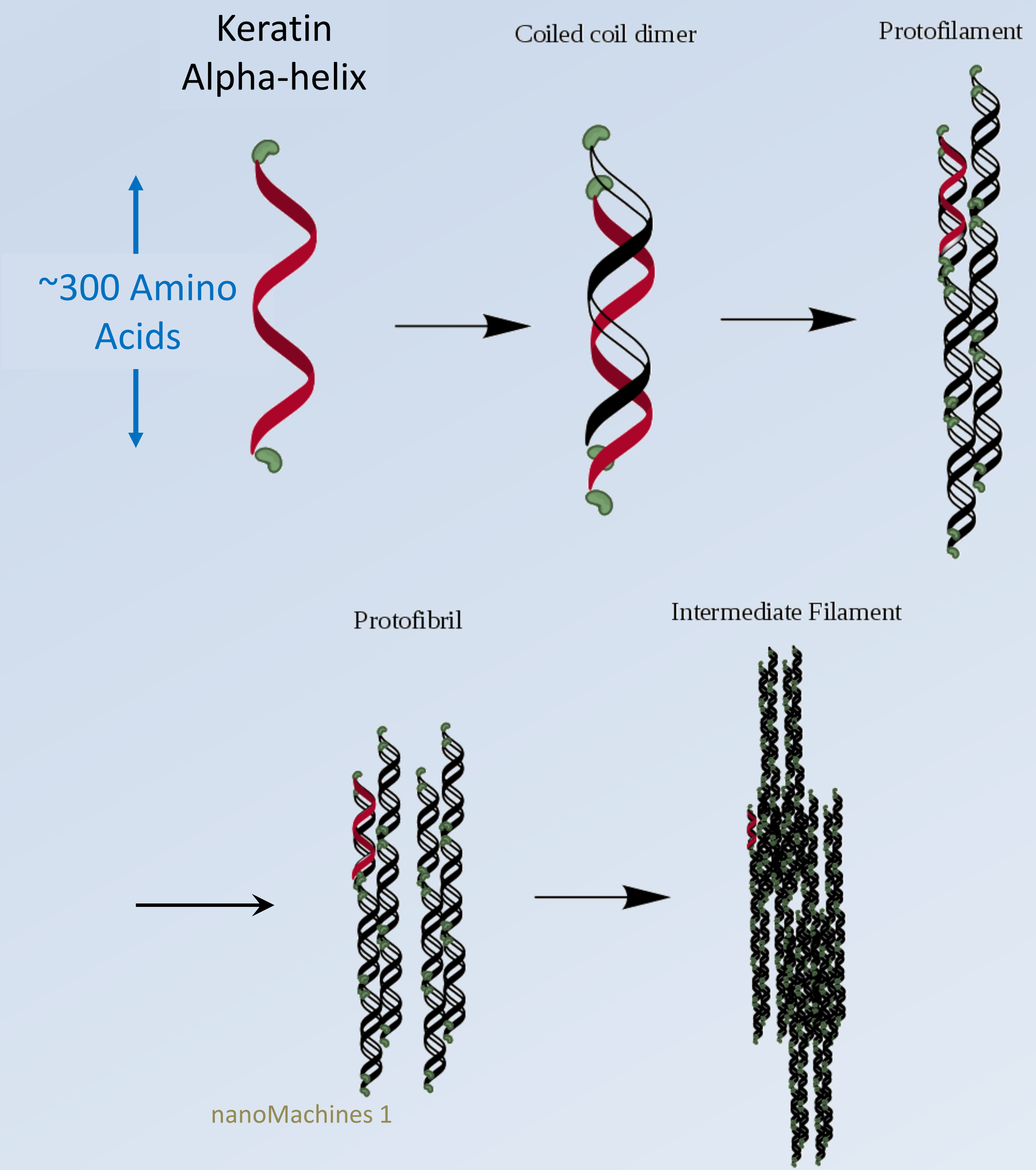
9 Amino Acids
(of 1400)

Keratin:

Building material for hair, skin, nails.

Also interior structure of many cells.

(over 50 types in humans)



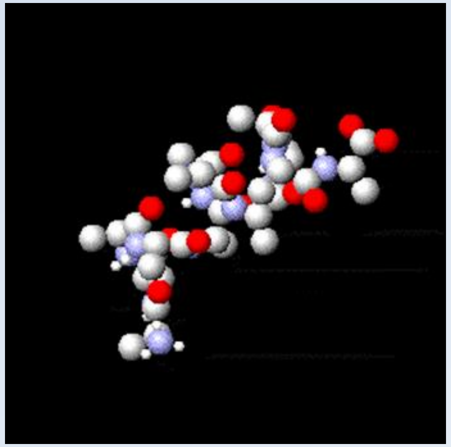
Visualizing Proteins

- International public protein database:
  - PDB (Protein Data Bank)
  - Over 100,000 entries
  - Each protein structure deposited has a code, such as "**7sj8**"

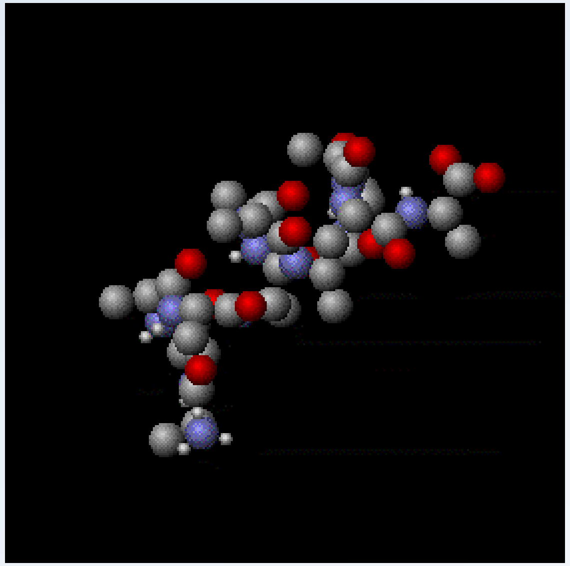
- Visualize it using free software, such as
  - ICM-Browser (www.Molsoft.com)

Protein Questions?

In Cells, There is Constant Motion at the Atomic Scale



- Most of our molecular pictures will be static
- But remember that the reality is relentless activity
  - Small molecules move and wiggle faster
  - Large molecules drift more slowly
    - parts of large molecules wiggle rapidly
- This is thermal motion
  - Warmer is faster

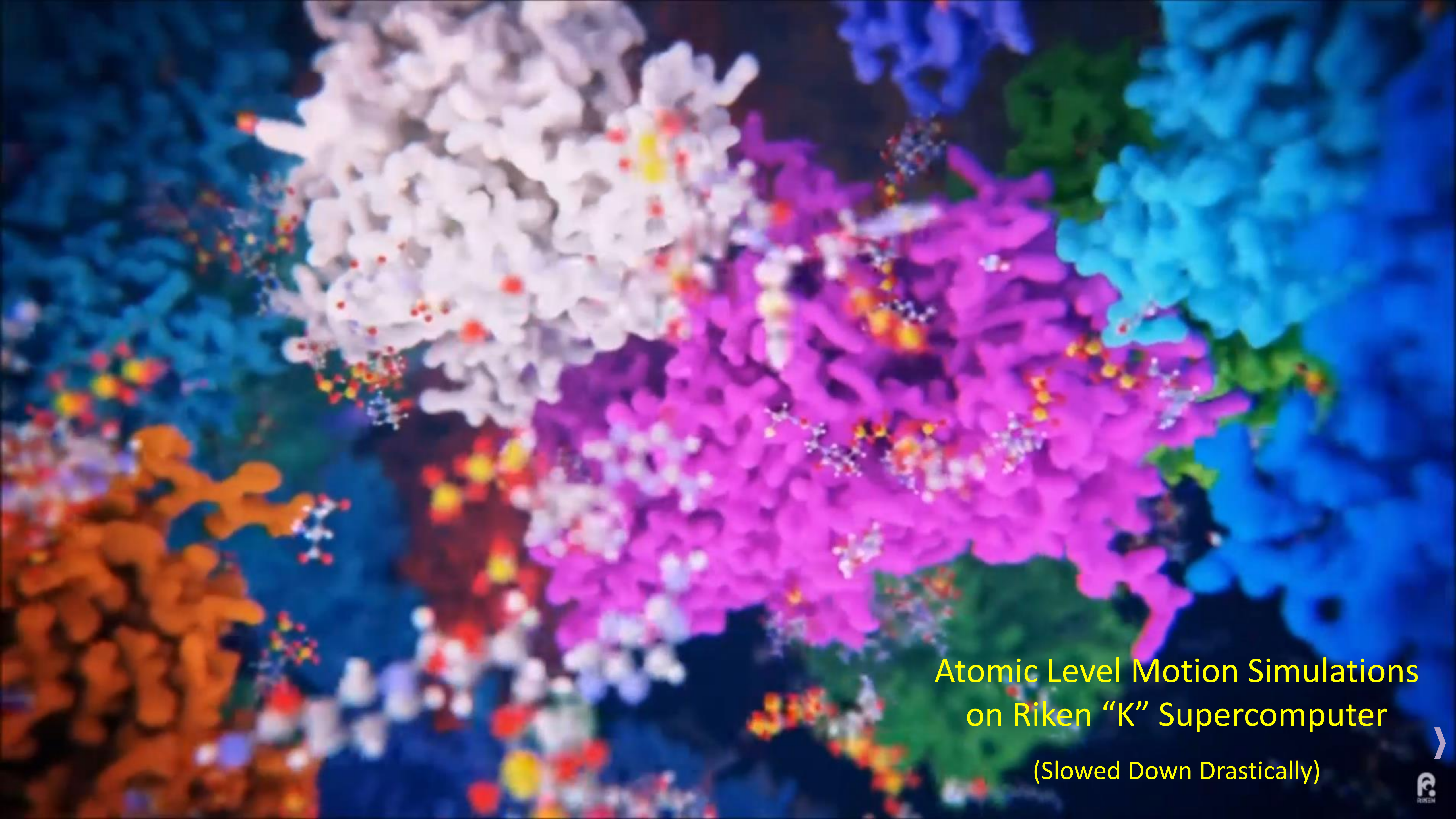


My Book of Chemistry: Brownian Motion

BROWNIAN MOTION

the random movement displayed by microscopic particles suspended in fluids


National STEM Learning Centre
and
Institute of Physics (UK)
2017


Atomic Level Motion Simulations
on Riken "K" Supercomputer
(Slowed Down Drastically)

SCLS STRATEGIC PROGRAMS FOR INNOVATIVE RESEARCH FIELD 1
SUPERCOMPUTATIONAL LIFE SCIENCE

RIKEN

01 Post-K Priority Issue 1

Priority Issue on Post-K computer
Innovative Drug Discovery Infrastructure through Functional Control of Biomolecular Systems

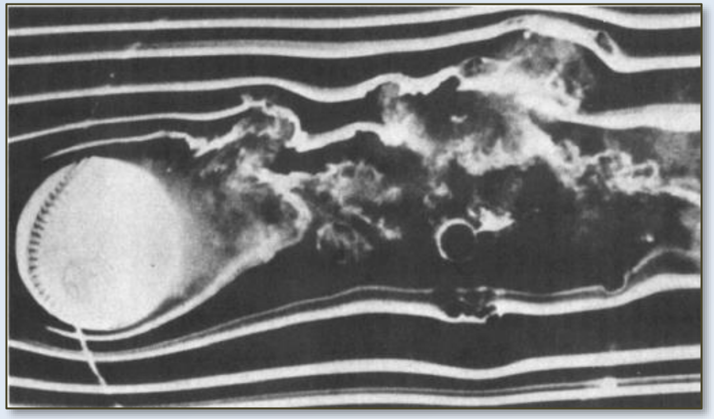
QBiC QUANTITATIVE BIOLOGY CENTER
RIKEN
QUANTITATIVE BIOLOGY CENTER

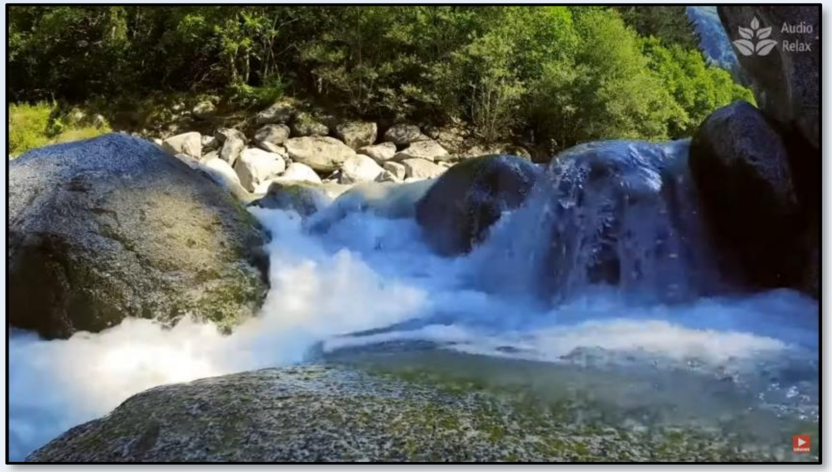
Japan

Laminar vs Turbulent Flow Regimes

Small, Slow, Viscous
> Laminar

Big,Fast, Low Viscosity
> Turbulent





Laminar vs Turbulent Flow Regimes

$$\text{Reynolds Number} \cong \frac{\text{Size x Speed}}{\text{Viscosity}}$$

Rey # << 2000

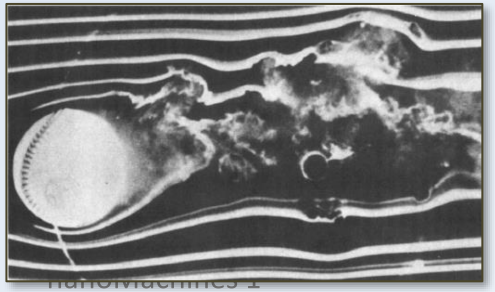
Small, Slow, Viscous

> *Laminar*

Rey # >> 2000

Big, Fast, Low Viscosity

> *Turbulent*



Laminar vs Turbulent Flow Regimes

Life at low Reynolds number

E. M. Purcell

Lyman Laboratory, Harvard University, Cambridge, Massachusetts 02138

(Received 12 June 1976)

Am. J. Phys., Vol. 45, No. 1, January 1977

Rey # << 2000

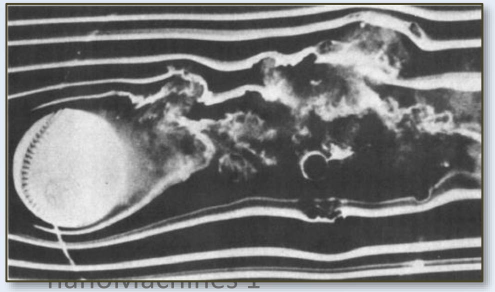
Small, Slow, Viscous

> *Laminar*

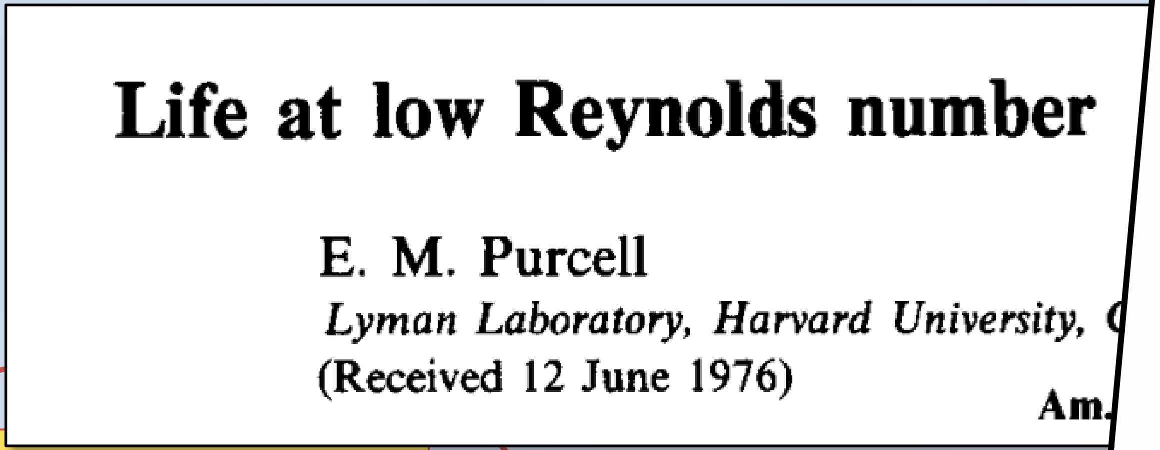
Rey # >> 2000

Big, Fast, Low Viscosity

> *Turbulent*



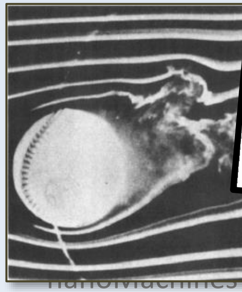
Laminar vs Turbulent Flow Regimes

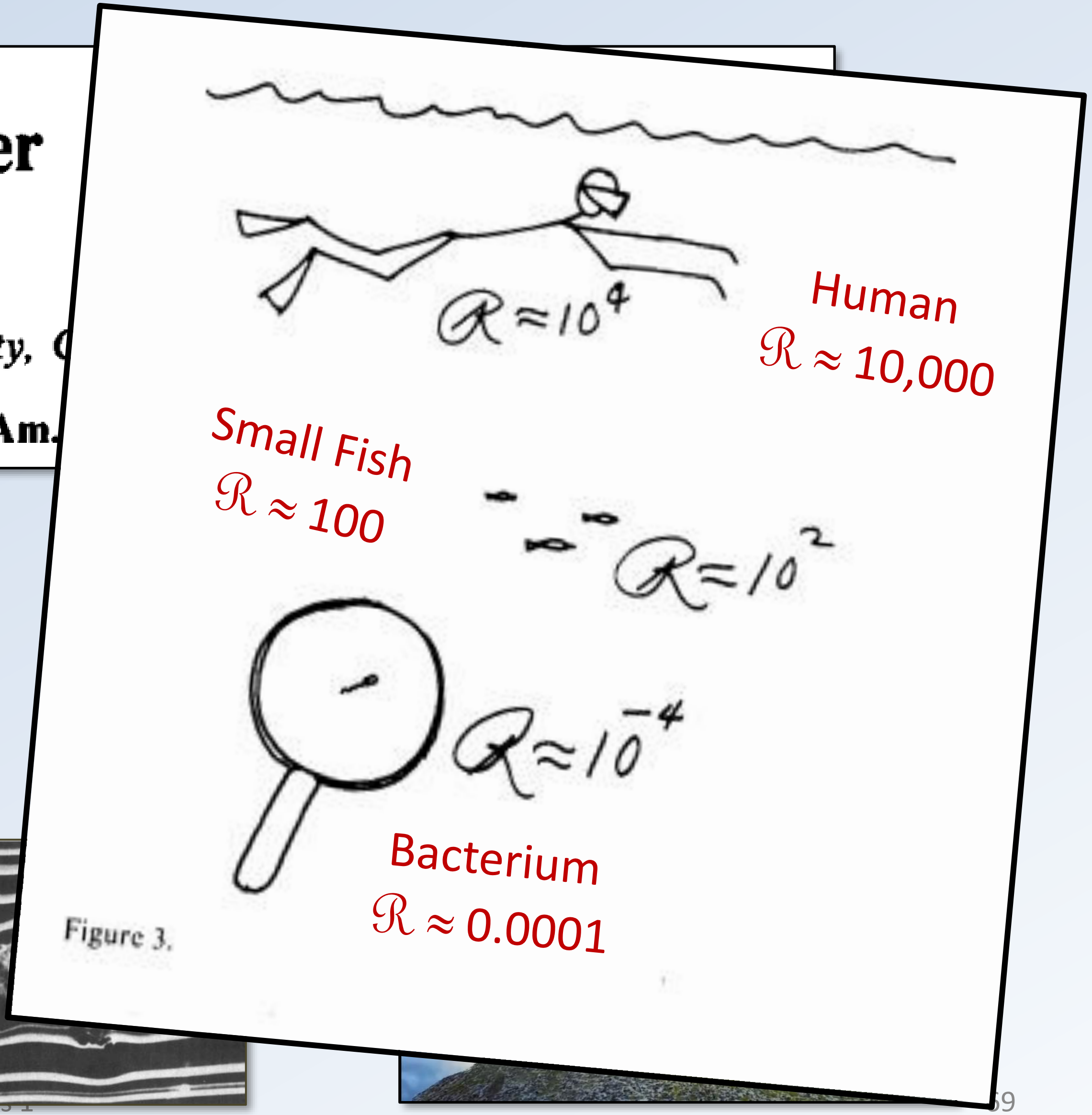

Life at low Reynolds number

E. M. Purcell
Lyman Laboratory, Harvard University, C
(Received 12 June 1976)
Am.

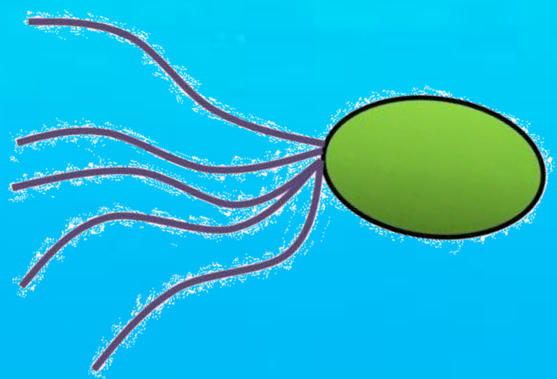
Rey # << 2000

Small, Slow, Viscous
> *Laminar*





“Bacterium” in Water Demo
Low Reynolds Number

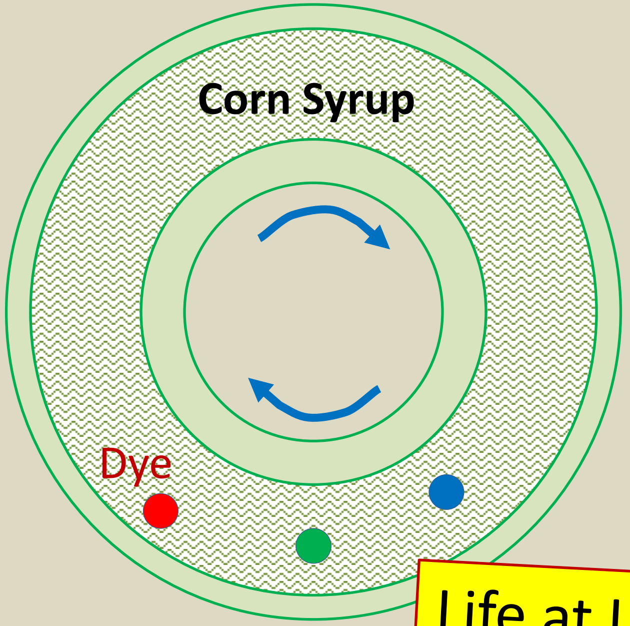


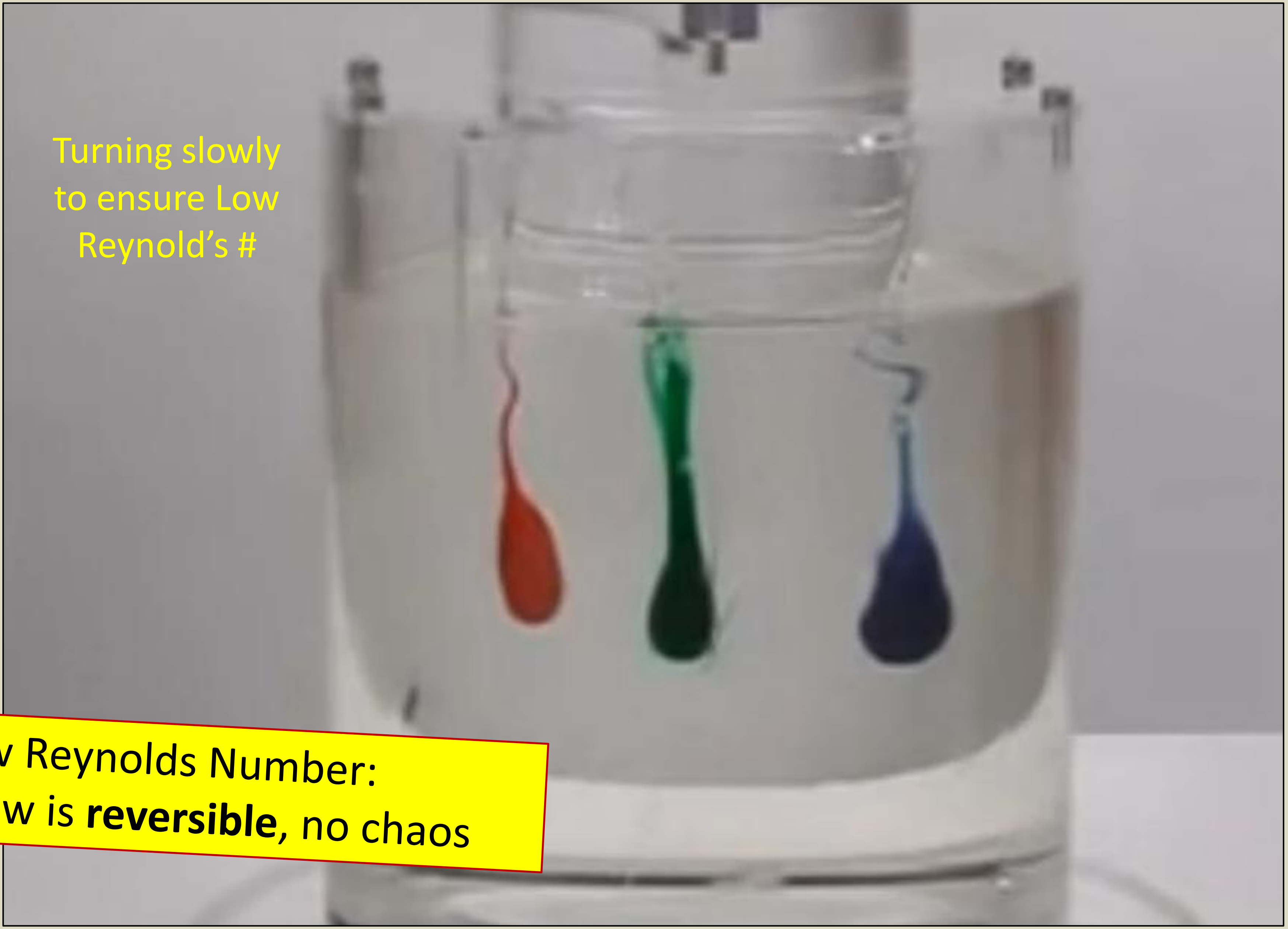
Laminar Flow Demonstration

U of New Mexico Physics

John DeMoss & Keven Cahill

Low Reynolds Number





Life at Low Reynolds Number:
Fluid flow is **reversible**, no chaos

On the one hand:

Relentless random thermal and Brownian motion of particles

Small molecules diffuse fairly quickly

On the other hand:

Extremely sluggish directed or forced motion

(Low Reynolds Number)

Absent a steady push, things stop

How Do We Figure Out the 3-D Structures of Biological Macromolecules?

No.

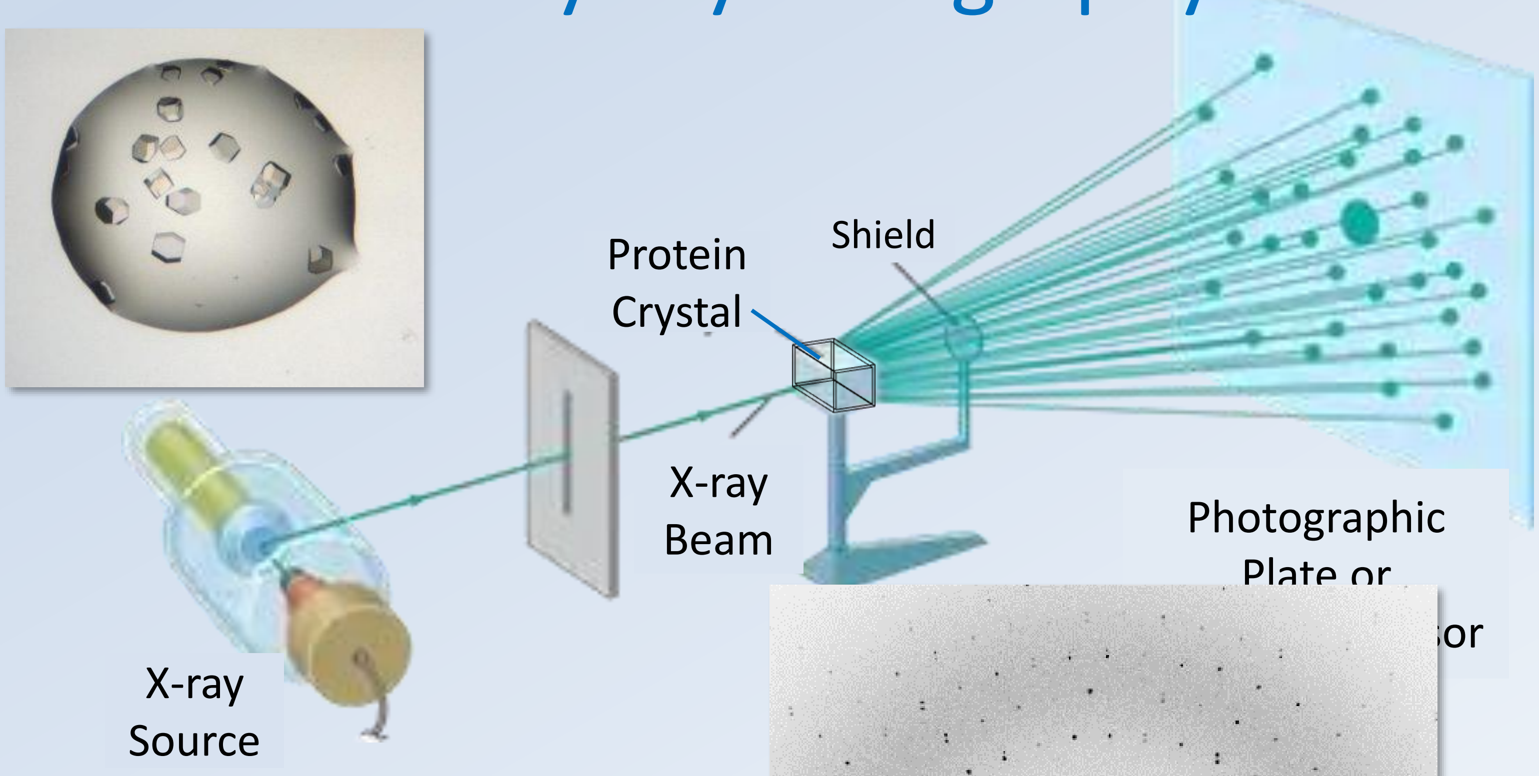
The structures of our nanomachines are <u>much</u> smaller than the wavelength of light.

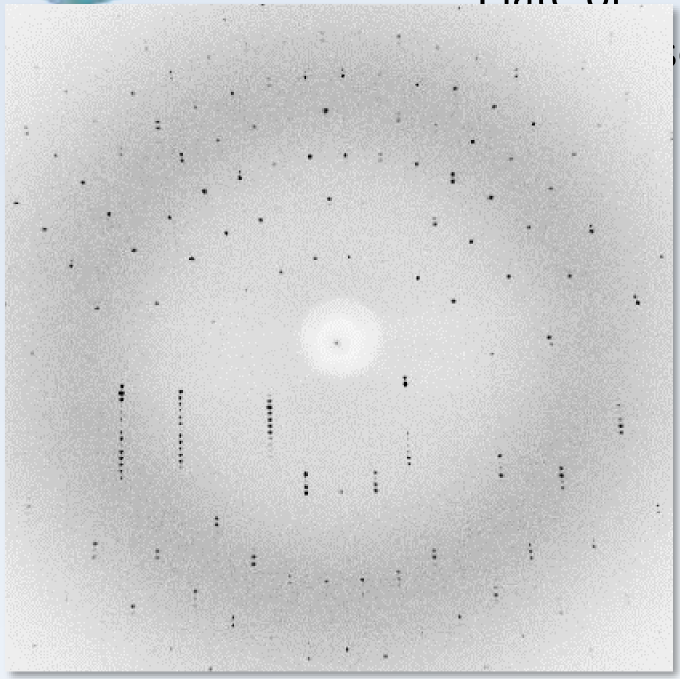
Nick Lane on Visualizing Nanomachines

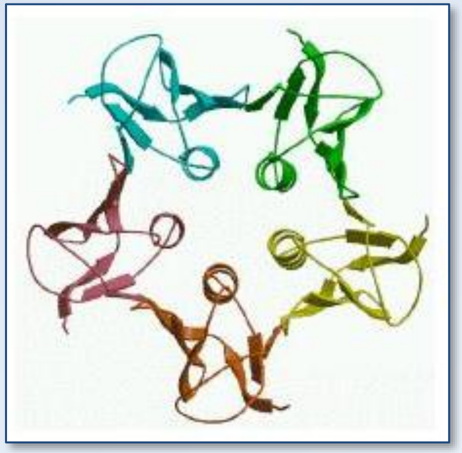
Nick Lane at The Royal Institution

Traditional Method: X-ray Crystallography

1. Make a crystal from protein molecules *Hard!*
2. Measure the X-ray Diffraction spot patterns at various crystal angles
3. *Guess the phases*
4. Calculate the 3-D structure via Fourier Transform



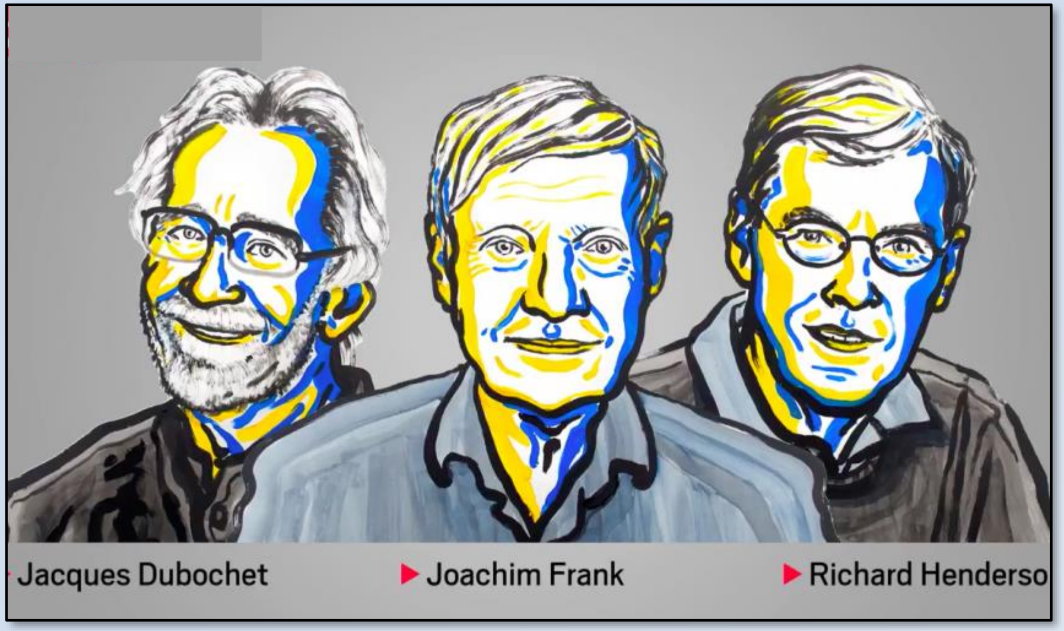


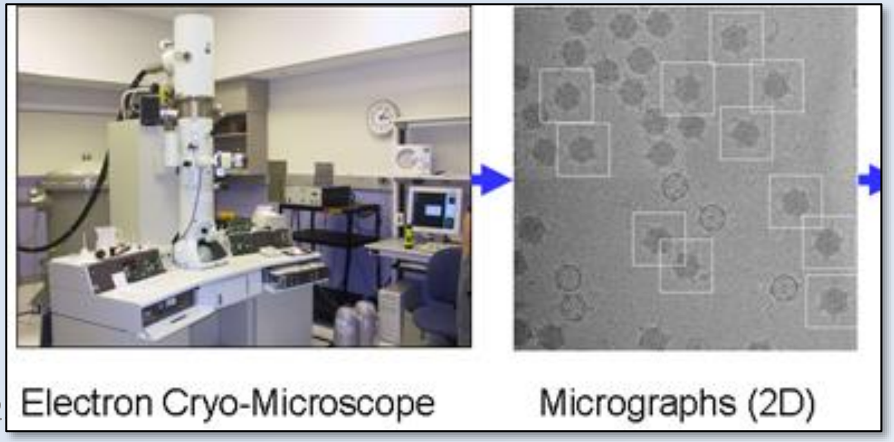


Over 100,000 protein structures solved by X-ray Crystallography!

The New Kid on the Block: Cryo-Electron Microscopy

2017 Nobel Prize in Chemistry



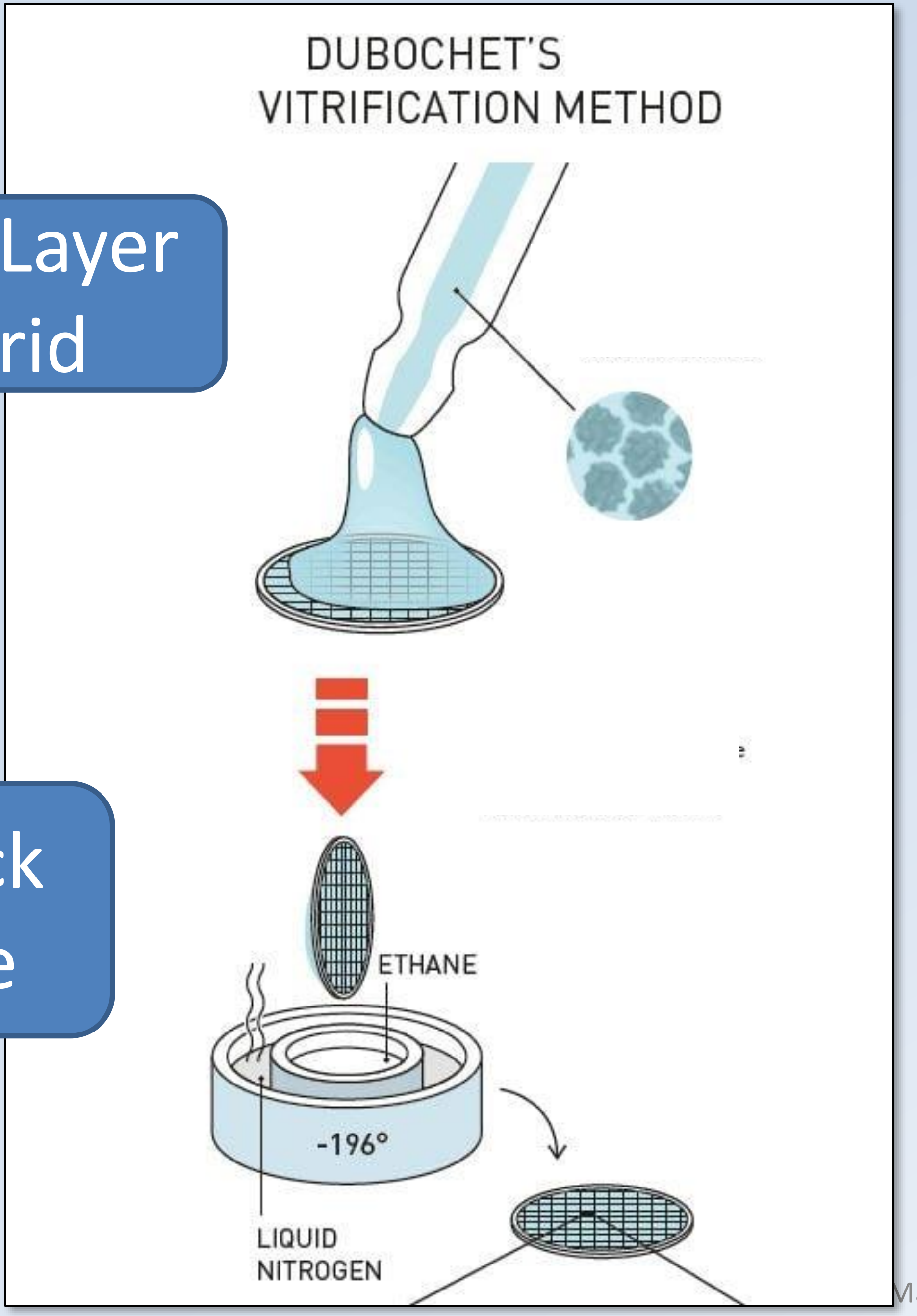


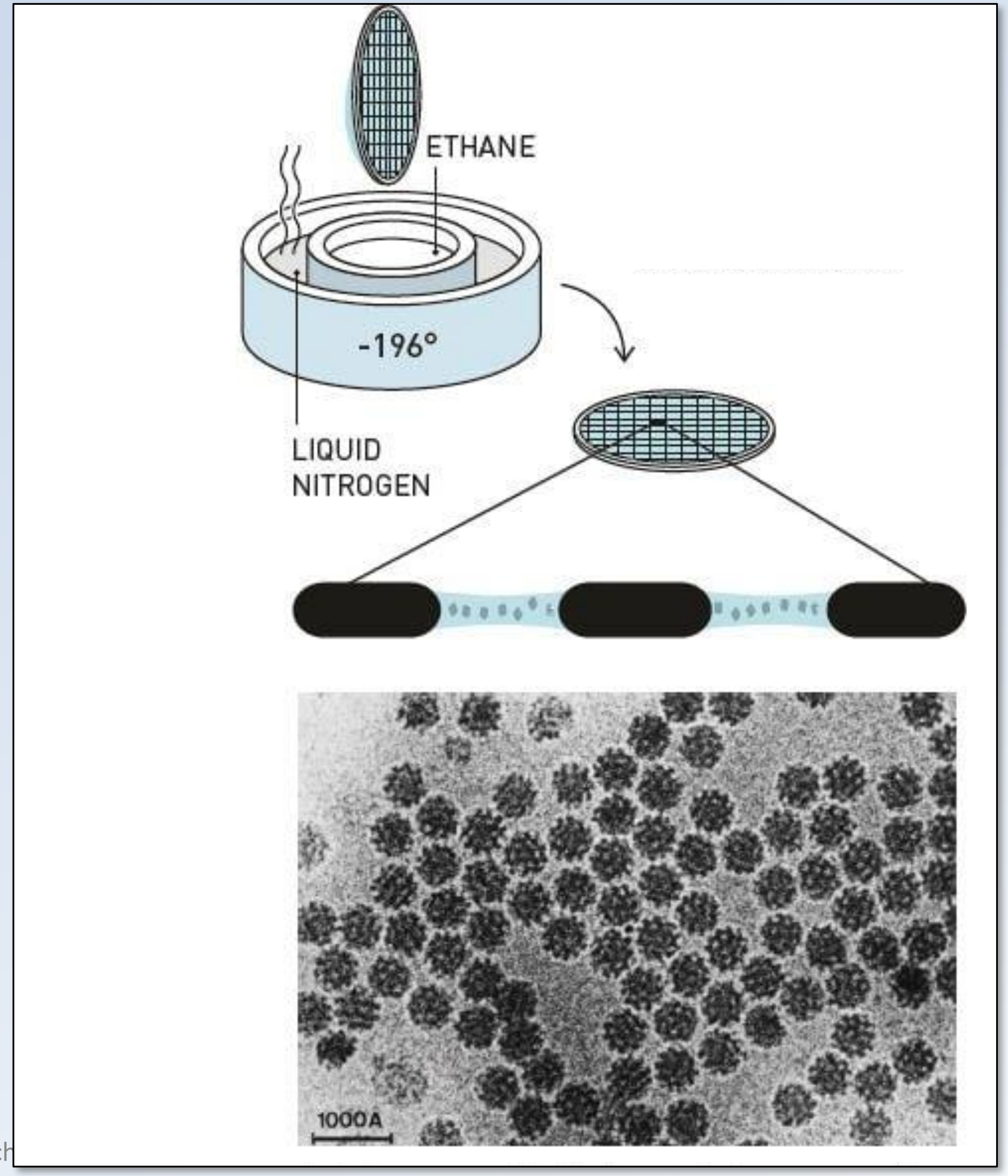
1. Make a thin layer of water containing thousands of randomly oriented protein particles.
2. Rapidly freeze it to immobilize the particles without unfolding.
3. Take thousands of electron microscope 2-D image projections of the randomly oriented particles.
4. Figure out what 3-D structure would produce all these pictures.

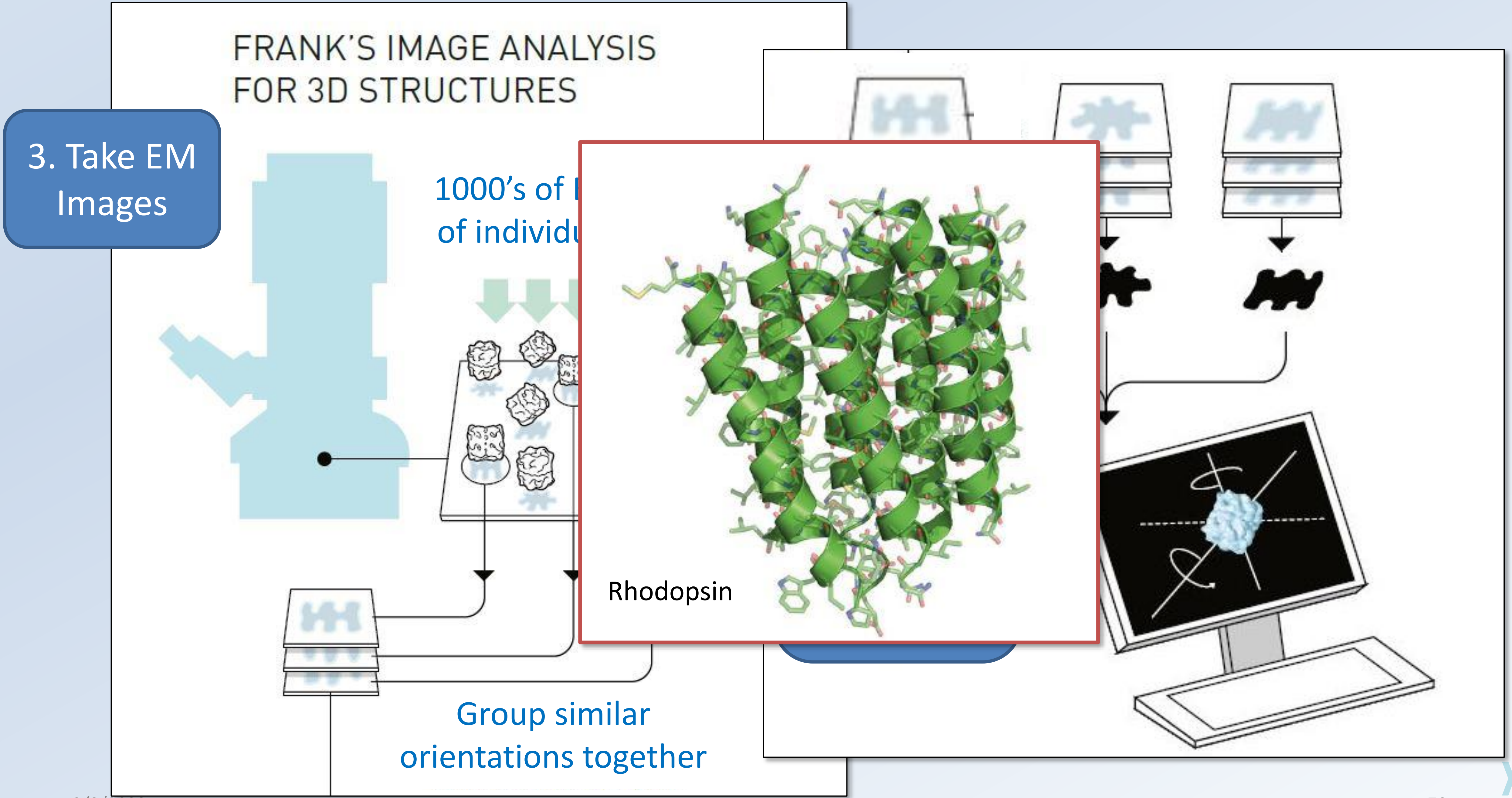
Crystallization not required!

1. Thin Layer on Grid

2. Quick Freeze

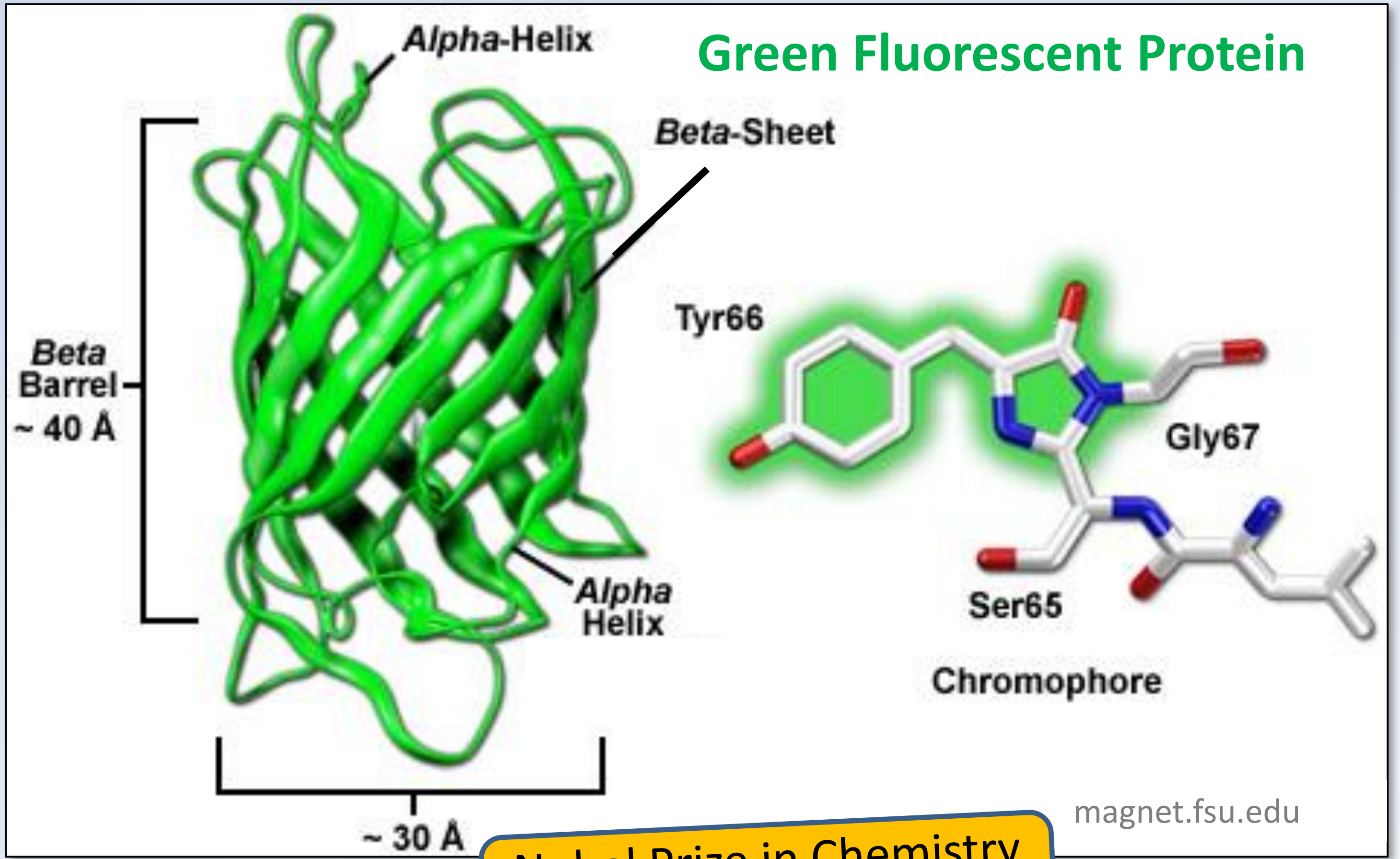





FRANK'S IMAGE ANALYSIS
FOR 3D STRUCTURES
3. Take EM Images
1000’s of
Rhodopsin
Group similar orientations together

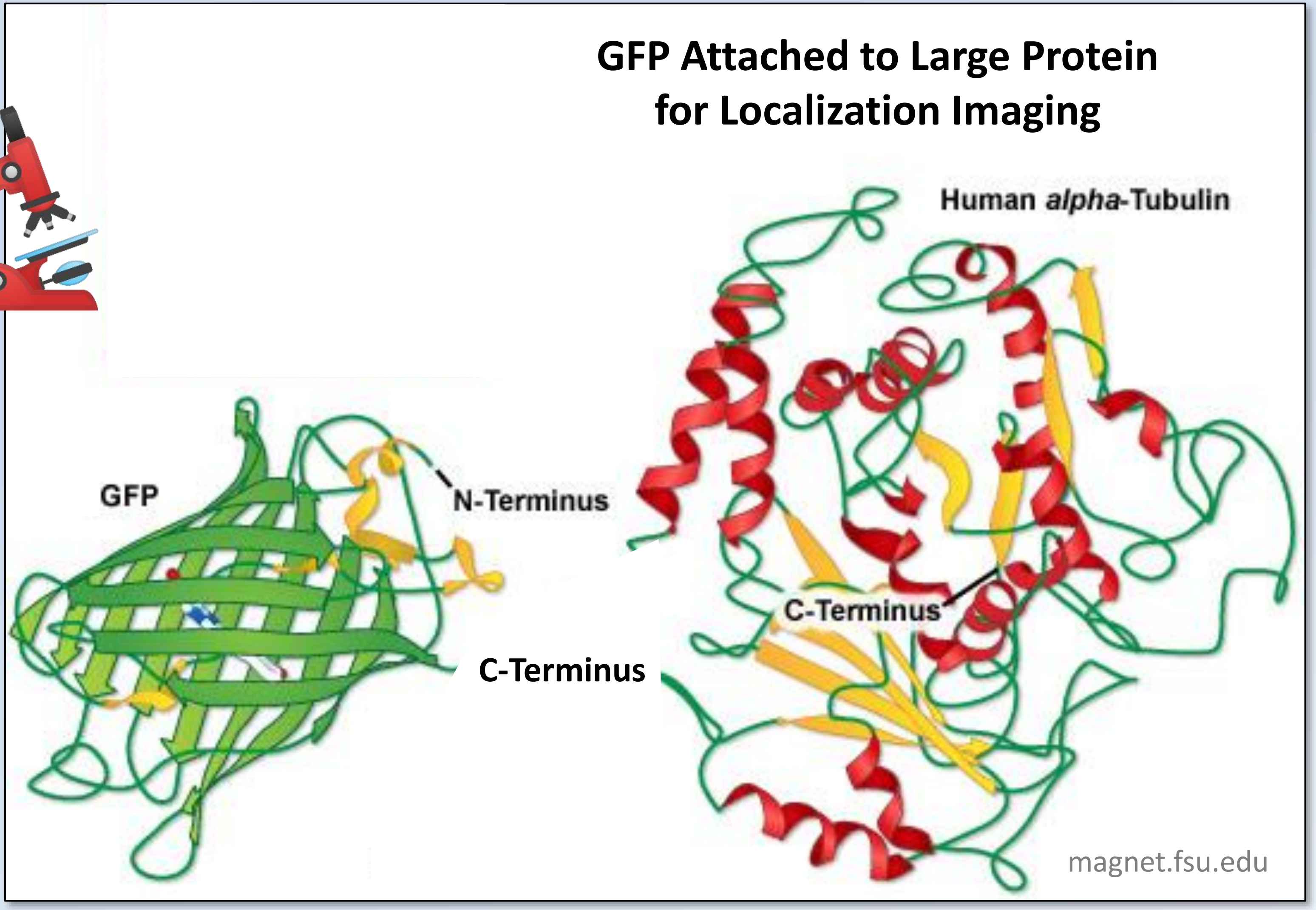
Visible microscopy has a role – motion detection

Bioluminescent

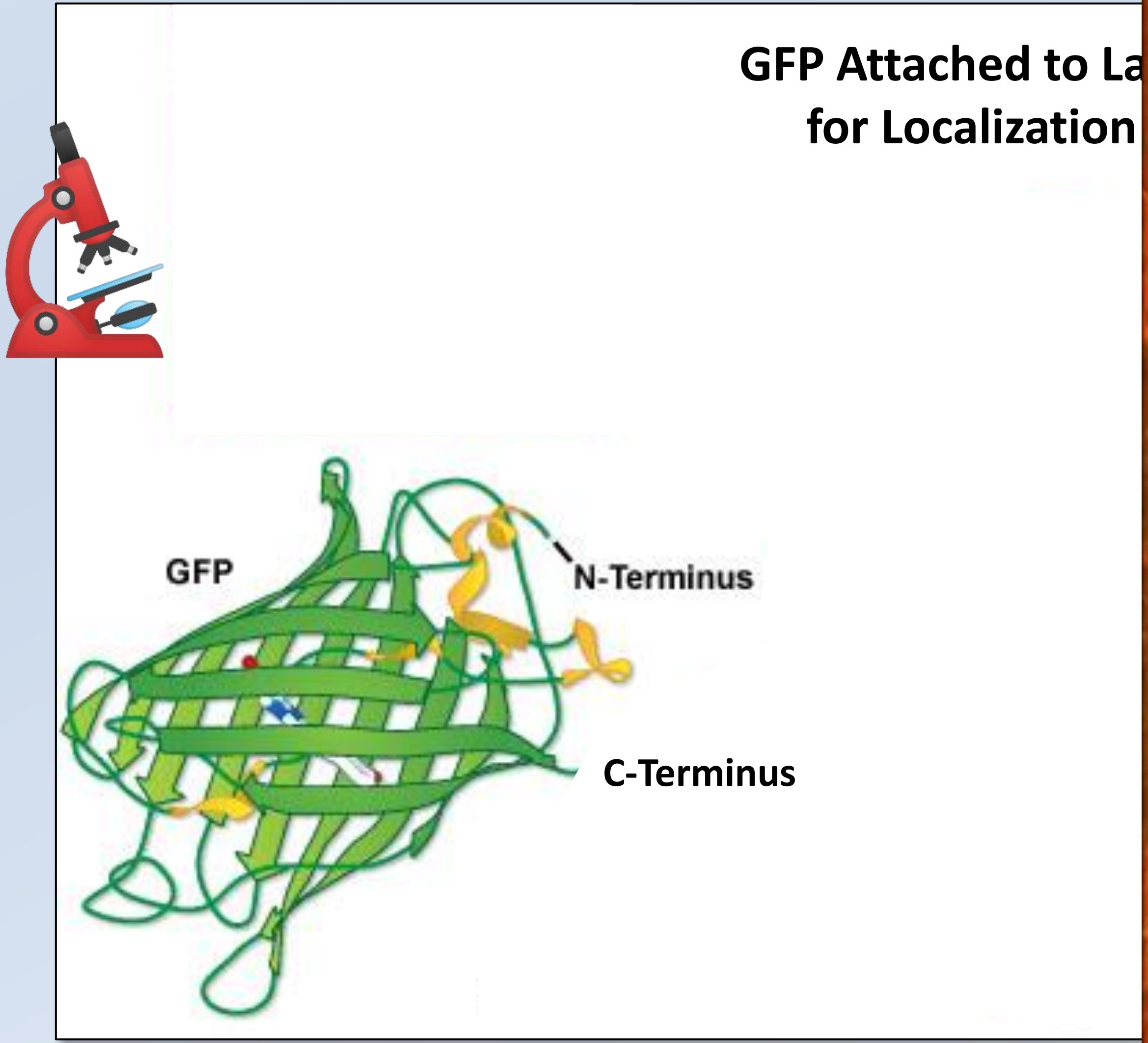


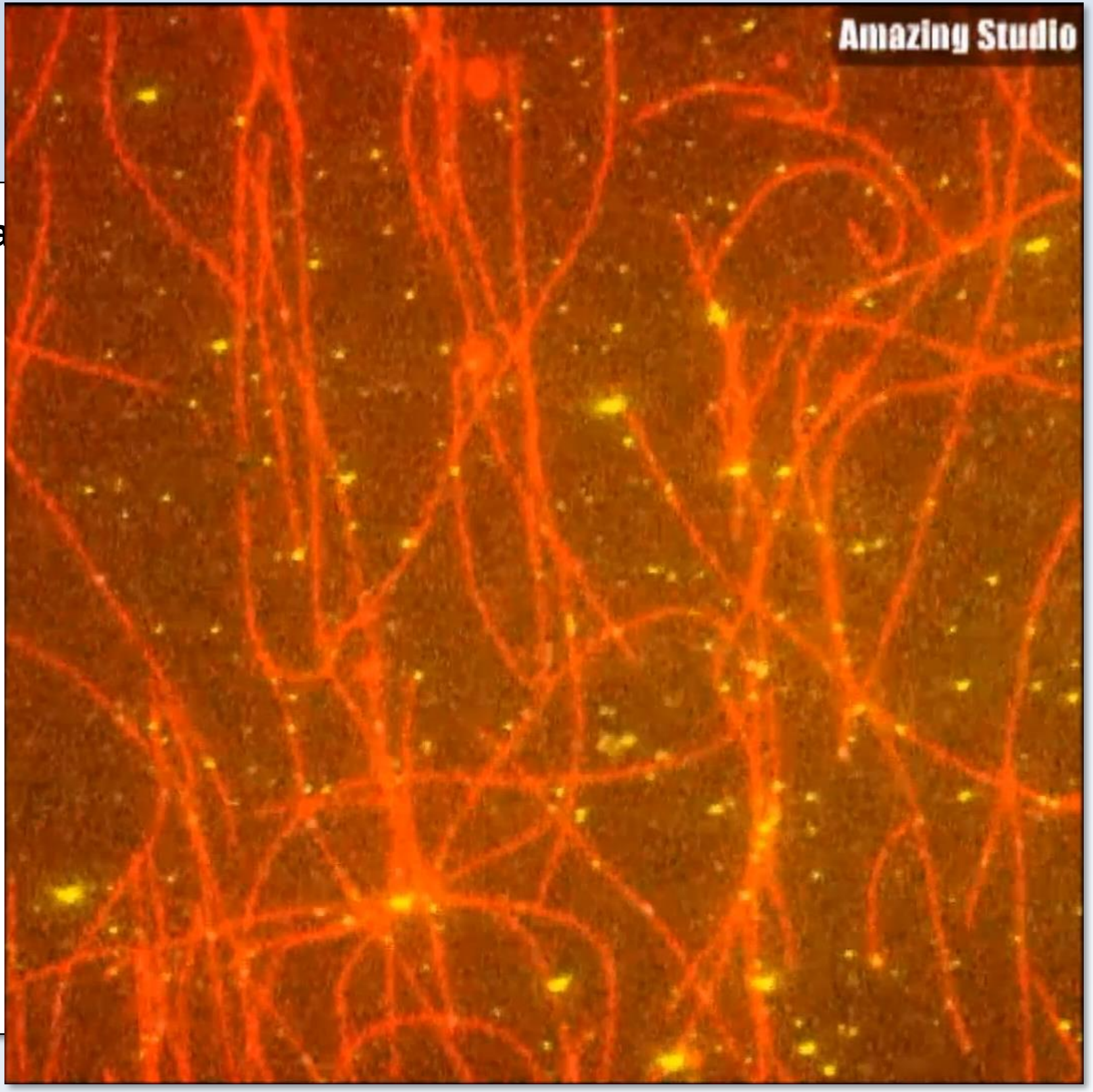
Nobel Prize in Chemistry 2008

Visible microscopy has a role – motion detection



Visible microscopy has a role – motion detection





Questions?

Course Outline

1. Overview
   Building blocks, energy flow, how we know
2. nanoMachines in energy flow
3. Motors and locomotion
4. DNA & RNA processing, protein manufacturing, sensory machines