

$$F = ma$$

$$F = -\nabla V$$



Simulations of biomolecules

Camilo Aponte-Santamaría

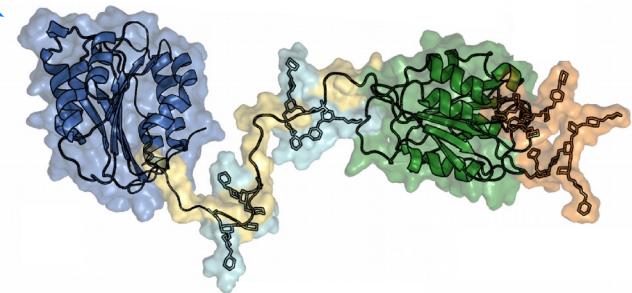
Bogotá, Colombia
June 5-29, 2019



Max Planck Tandem Group
in Computational Biophysics
University of Los Andes
Bogotá, Colombia

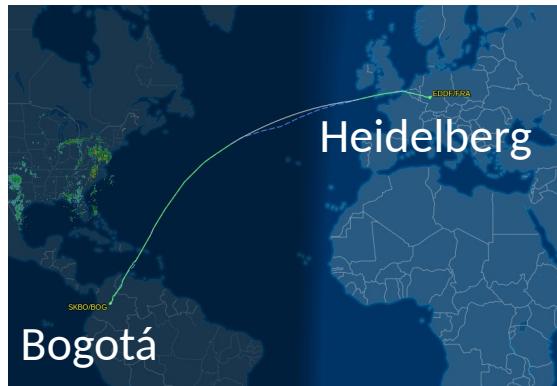


Hosted by:
Cellular Biophysics Dept.
MPI for Medical Research
Heidelberg, Germany



Guest group at:
Interdisciplinary Center
for Scientific Computing (IWR)
Heidelberg, Germany

Max Planck Tandem Group in Computational Biophysics



Aug. 2018



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Biological macromolecules: the machinery of living systems

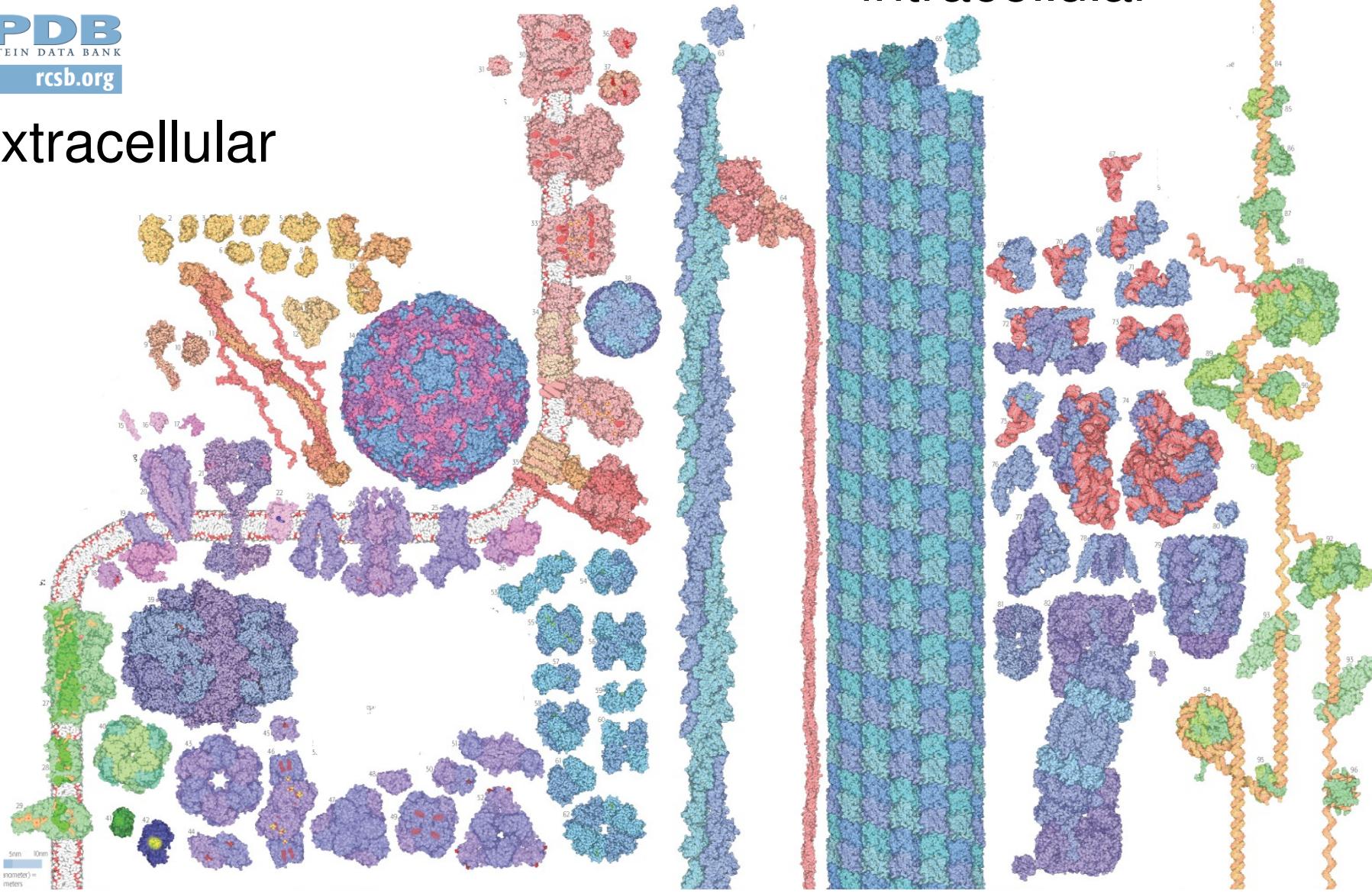
Adapted from



extracellular

membrane

intracellular



Biological macromolecules: the machinery of living systems

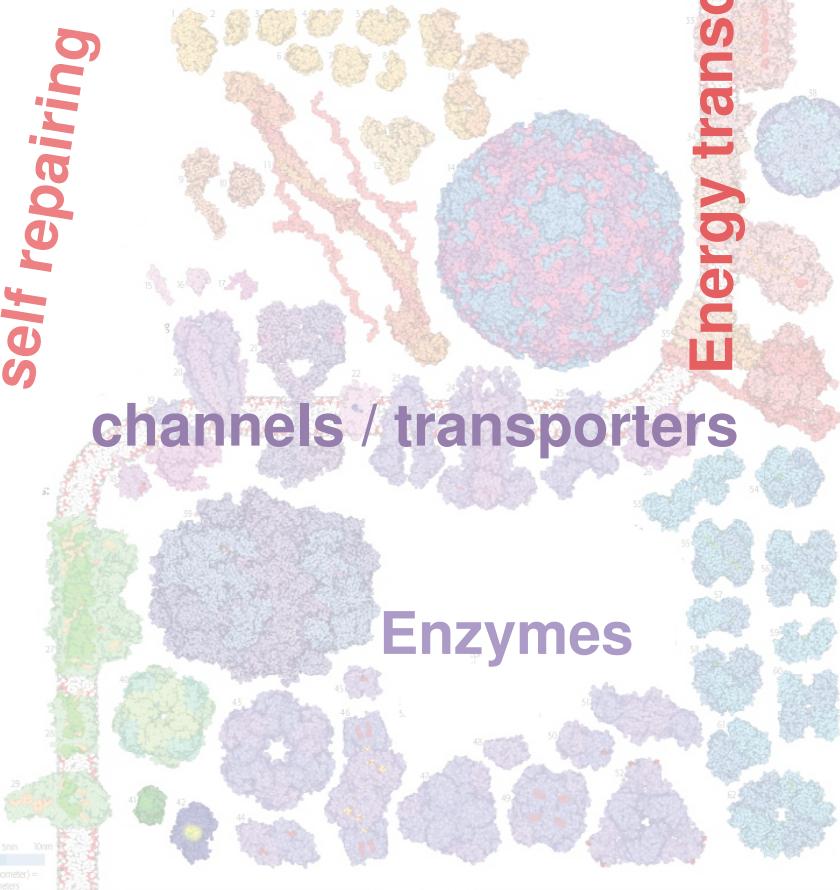
Adapted from



photosynthesis

extracellular **digestion**

self repairing



membrane

Energy transduction

channels / transporters

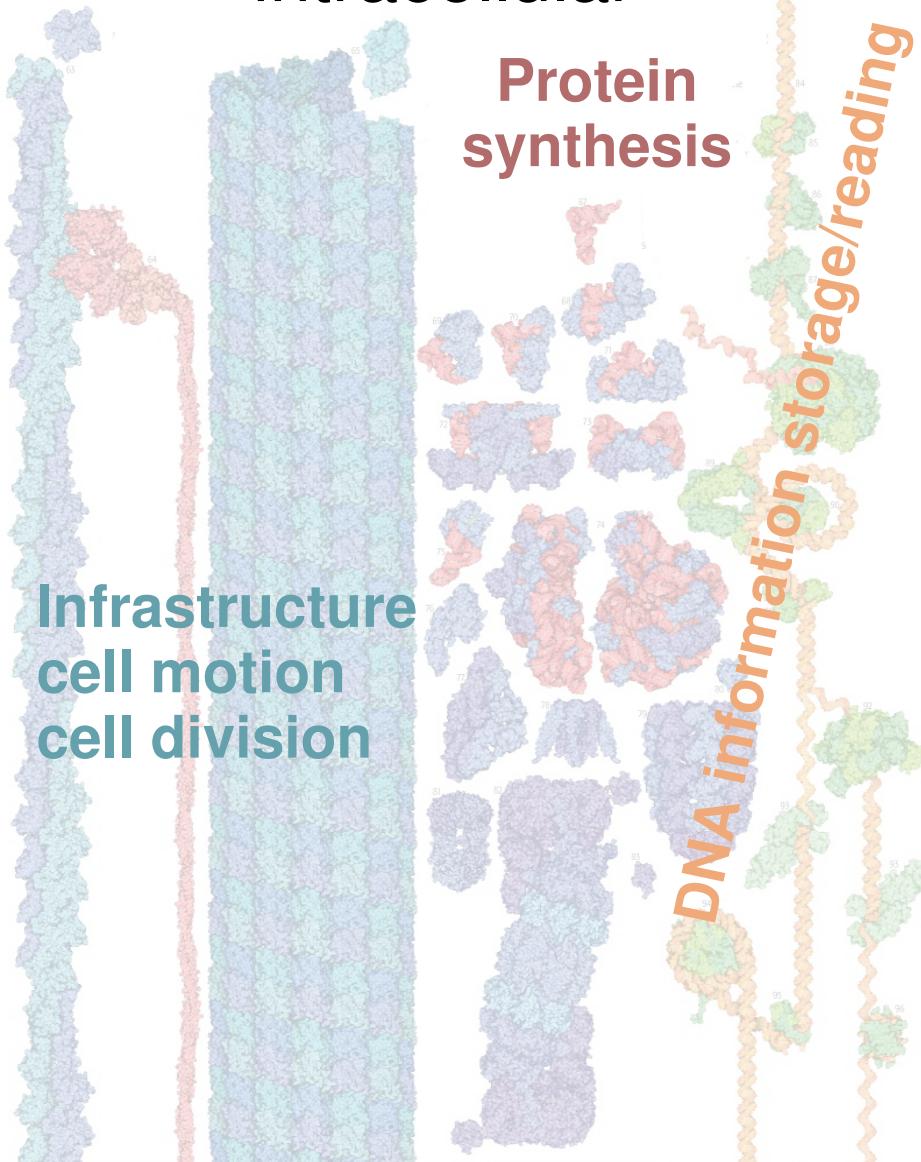
Enzymes

intracellular

Protein synthesis

**Infrastructure
cell motion
cell division**

DNA information storage/reading



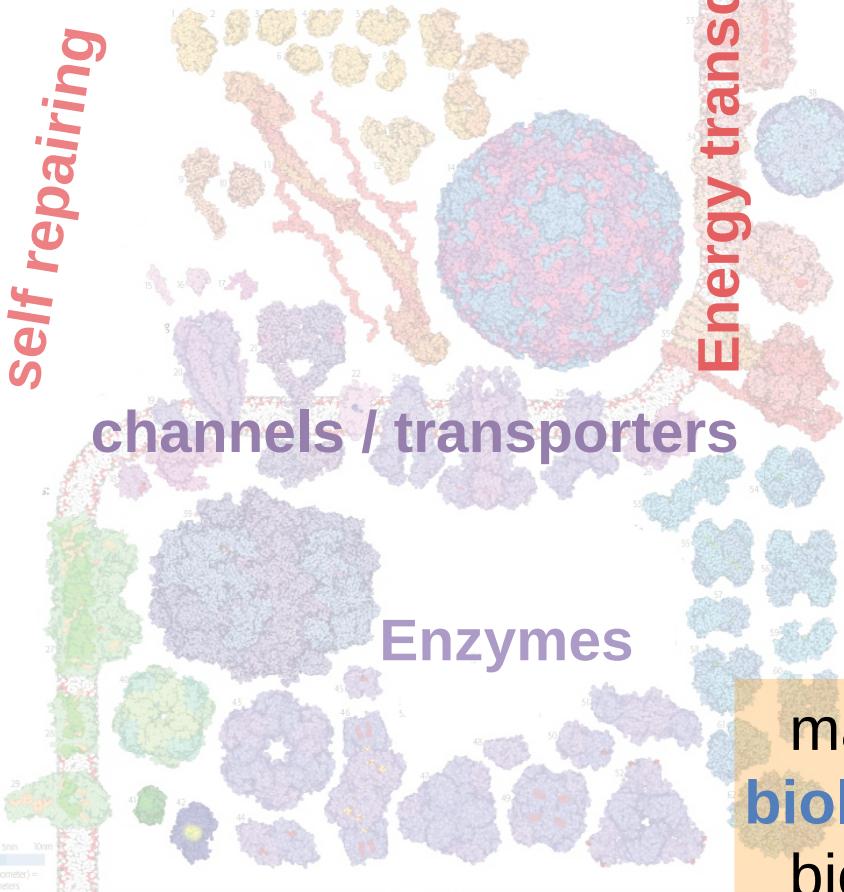
Biological macromolecules: the machinery of living systems

Adapted from



extracellular **digestion**

self repairing



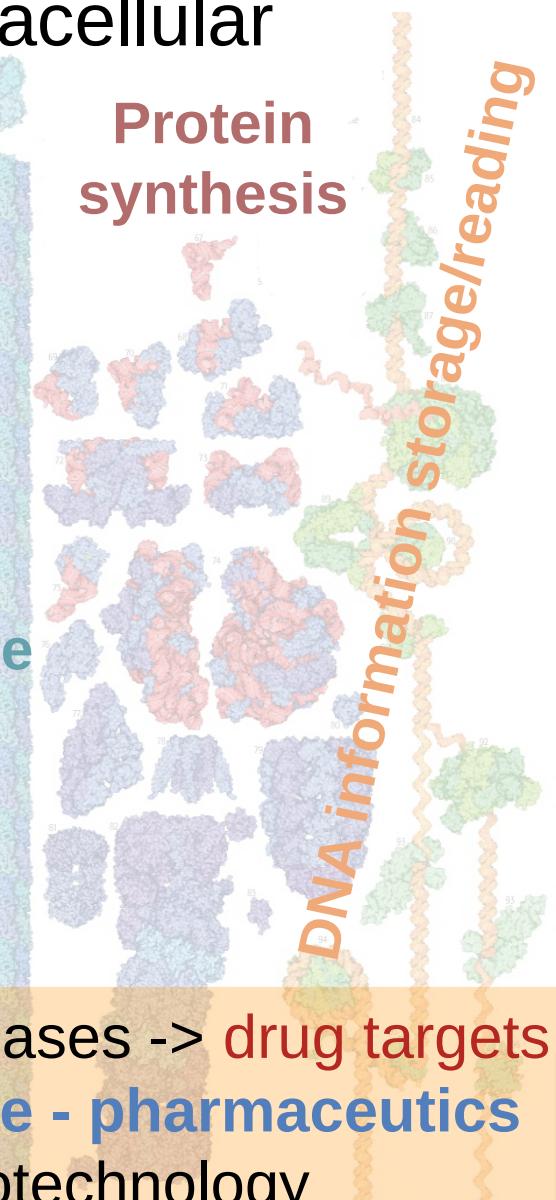
membrane



Energy transduction

intracellular

Protein synthesis



**Infrastructure
cell motion
cell division**

m malfunction: diseases -> drug targets
biology - medicine - pharmaceutics
bio-inspired nanotechnology
material science - engineering

Motion is essential for biomolecular function



HL-60 cell

mCherry - utrophin FITC - collagen

HL-60 cell

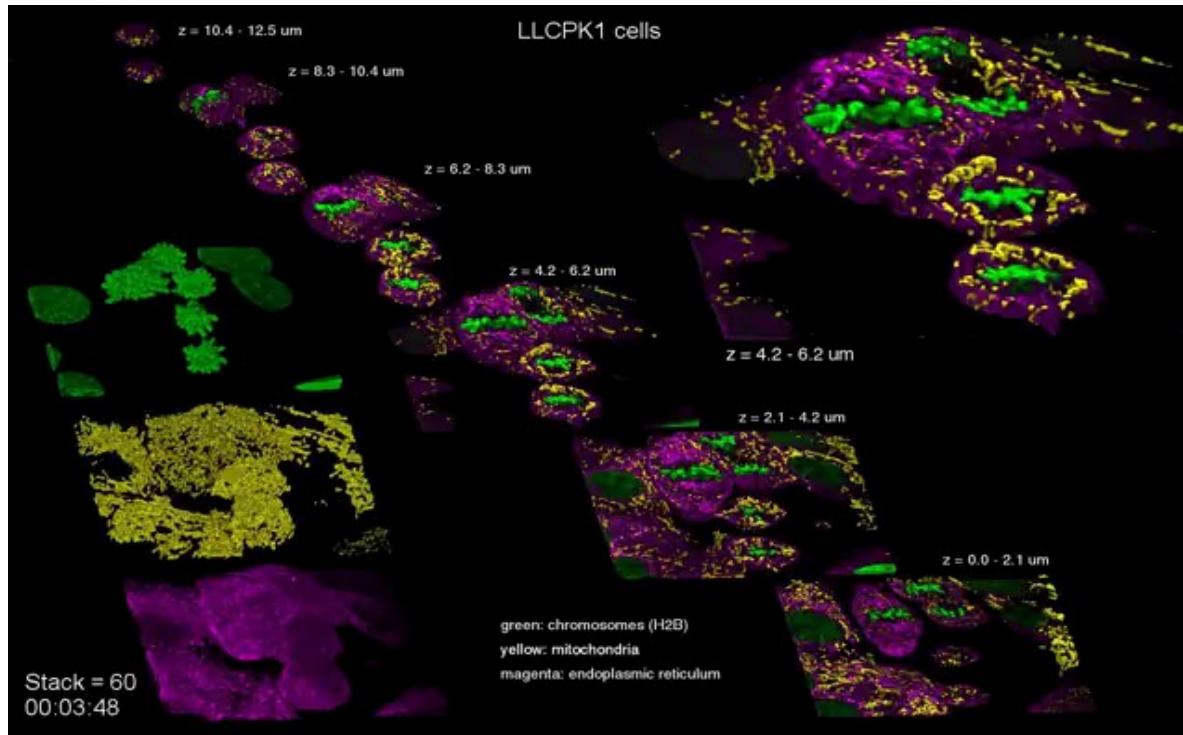
collagen matrix



From: Betzig Lab at HHMI's Janelia Research Campus:
janelia.org/lab/betzig-lab

function ~ dynamics

Motion is essential for biomolecular function



chromosomes

mitochondria

endoplasmic reticulum

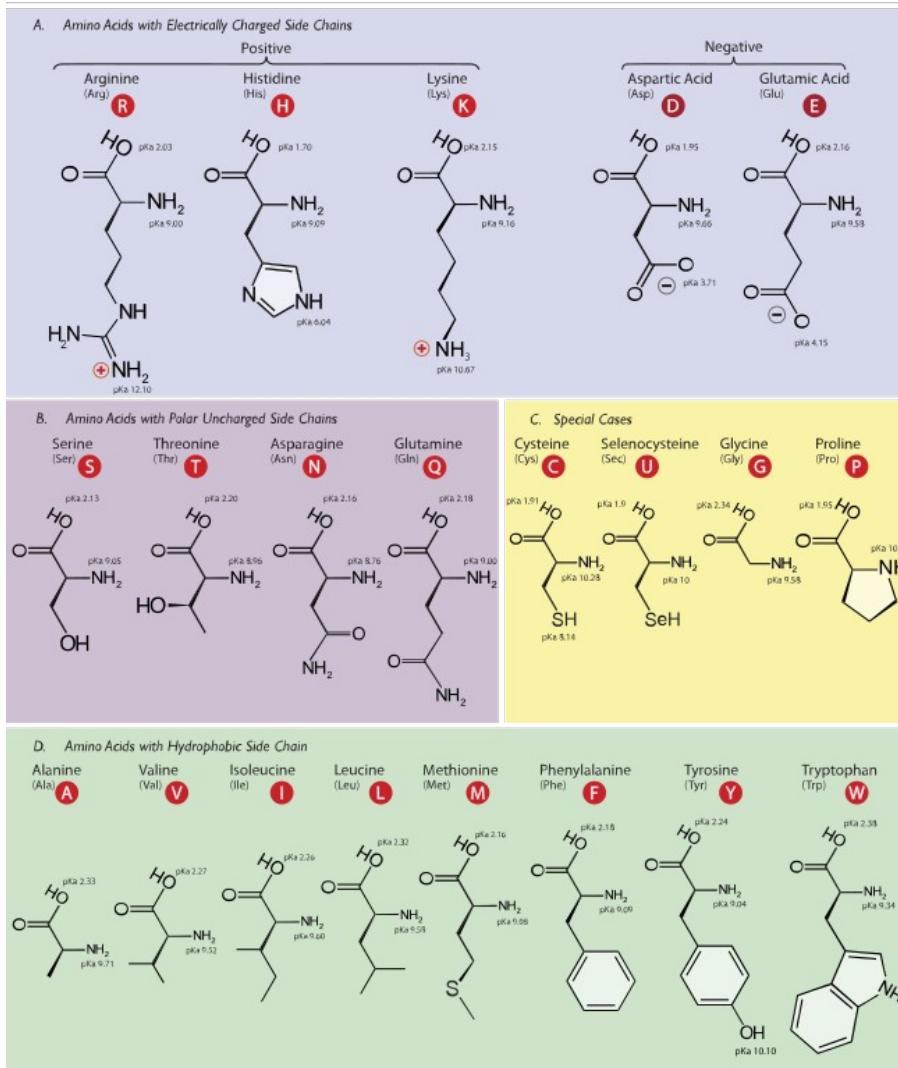


From: Betzig Lab at HHMI's Janelia Research Campus:
janelia.org/lab/betzig-lab

function ~ dynamics

Biomolecular structure: proteins

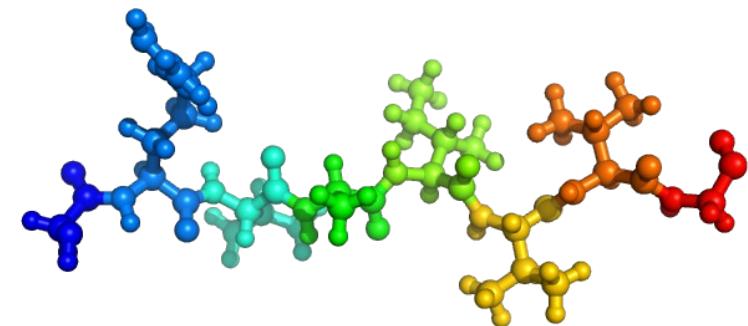
building blocks: 21 aminoacids



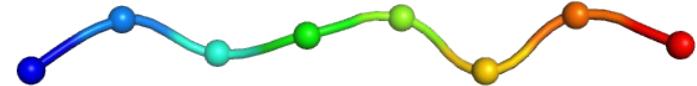
example (8 AA peptide):

sequence: **GRVAIVVG**

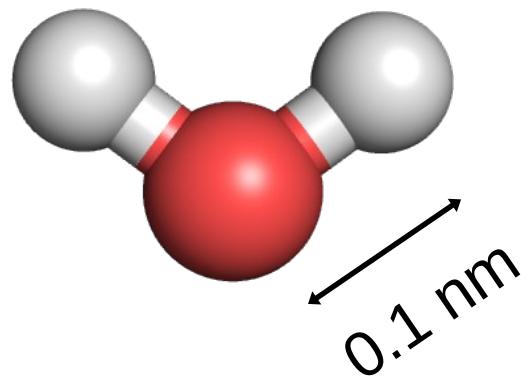
3D structure:



cartoon representation:

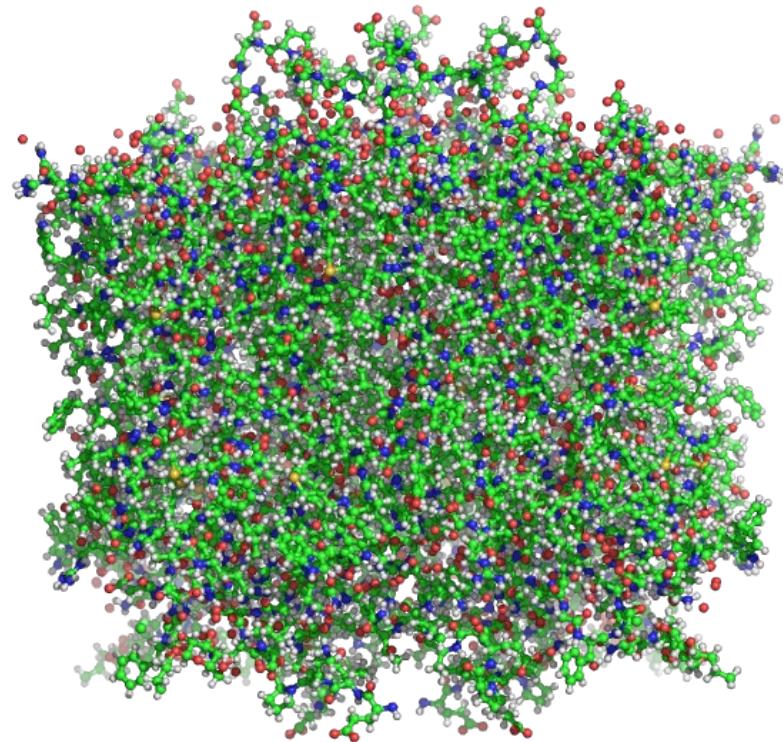


Biomolecular structure: proteins



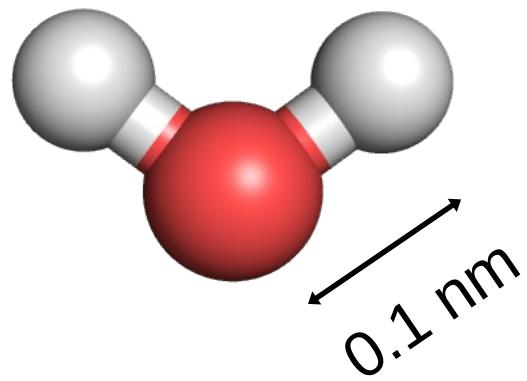
water
 H_2O
atoms: 3

← 7 nm →



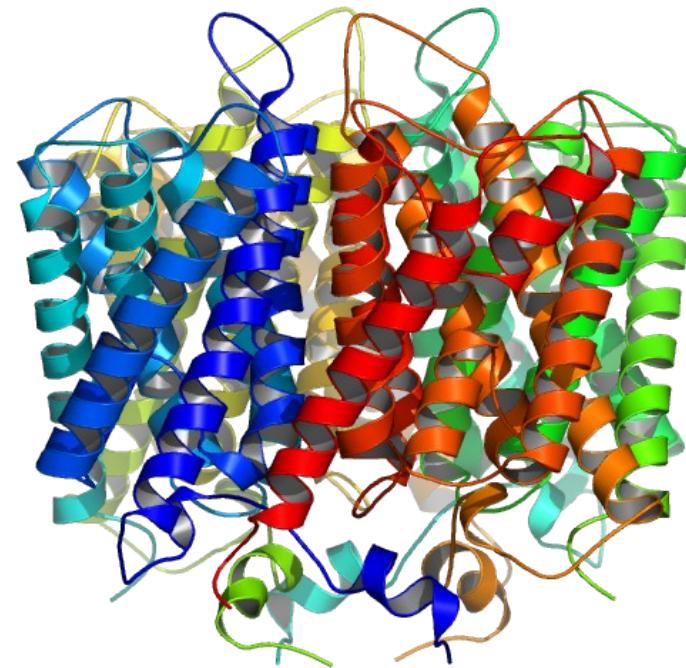
aquaporin
water channel
atoms: 16952

Biomolecular structure: proteins



water
 H_2O
atoms: 3

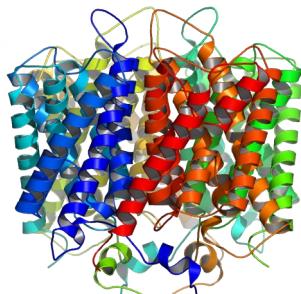
← 7 nm →



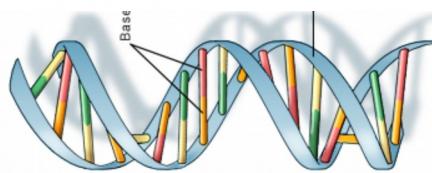
aquaporin
AQP
atoms: 16952

Biomolecular structure

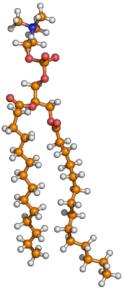
and many others:



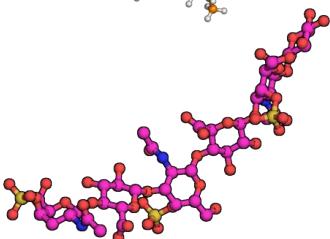
Proteins



Nucleic acids (DNA, RNA, mRNA, etc)



Lipids



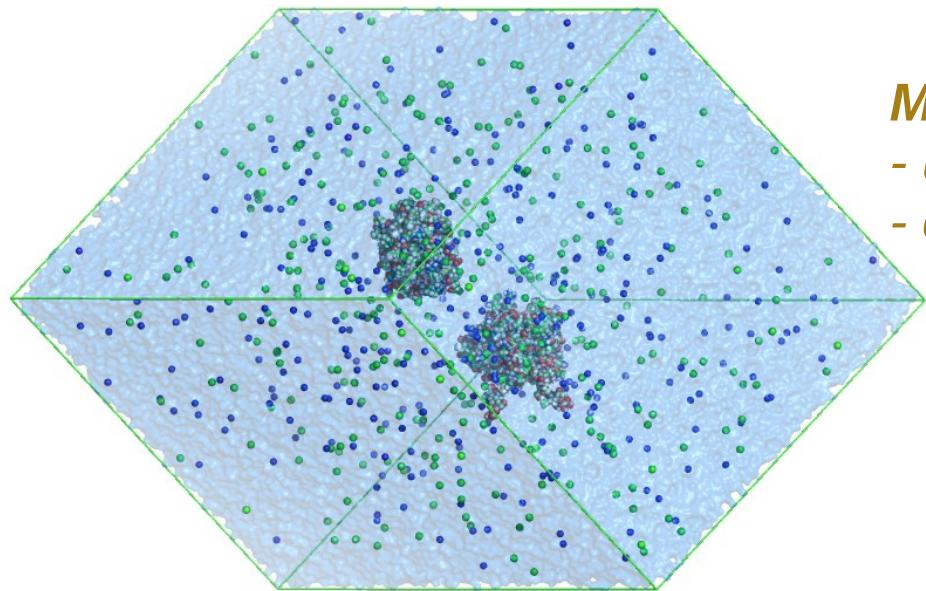
Sugars

...

Molecular dynamics

“All what living things do can be understood in terms of the jiggling and the wiggling of atoms”

Feynman lectures on physics. 1: 3-6 (1963)



MD bibles:

- understanding mol. sims. D. Frenkel
- comp. sims. of liquids. Allen-Tildesley

classical description

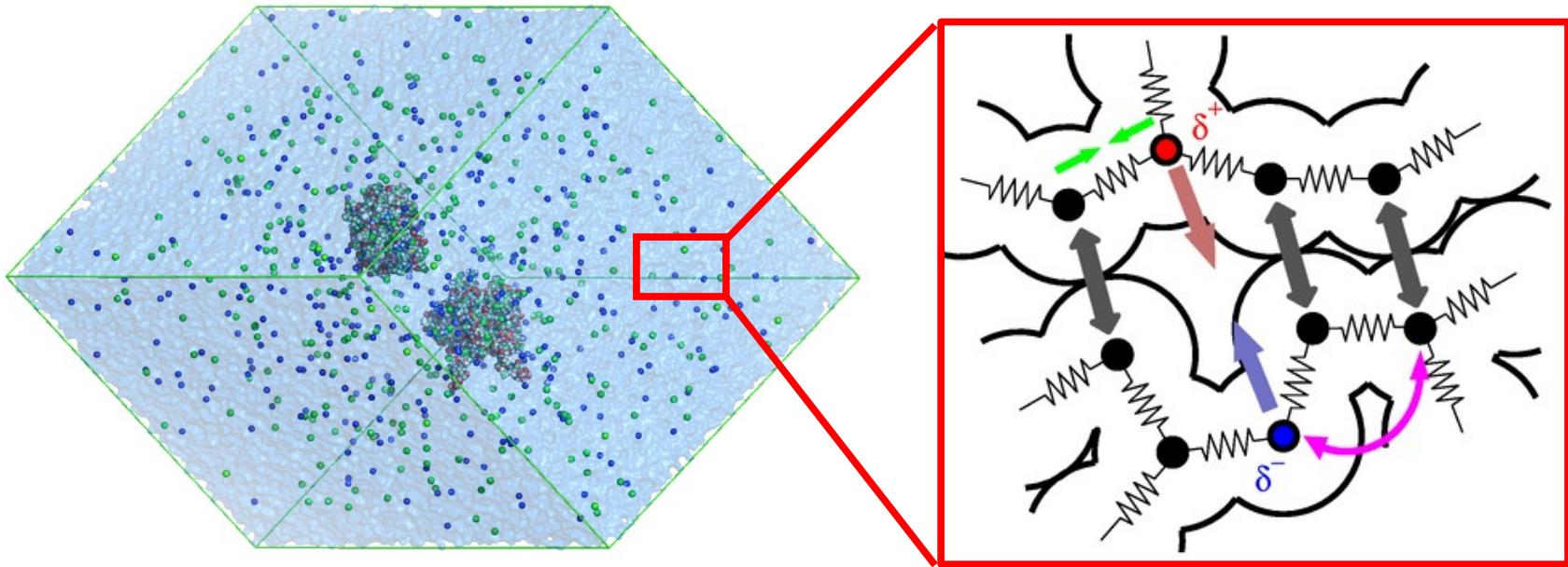
10^5 - 10^7 atoms

100 ns – 1 ms simulation length

periodic boundary conditions

coupled to an external bath (Temperature & Pressure constant)

Molecular dynamics



Interatomic interactions:

Non-bonded:

- electrostatics
- van der Waals

Bonded:

- covalent bonds
- angular
- torsions

Molecular dynamics

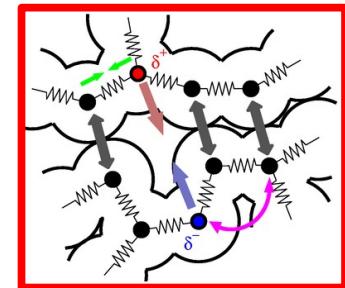
Interatomic interactions: empiric potential energy function

MD argot: force field

$$V(r_1, \dots, r_{3N})$$



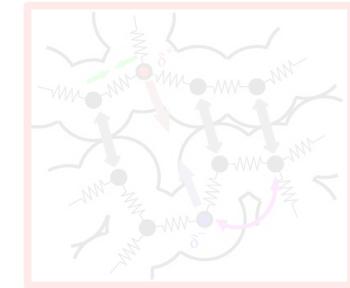
$$F = -\nabla V(r_1, \dots, r_{3N})$$



Molecular dynamics

Interatomic interactions: empiric potential energy function

$$V(r_1, \dots, r_{3N})$$



$$F = -\nabla V(r_1, \dots, r_{3N})$$

Newton
equations of
motion:

$$F_i = m_i \frac{\partial^2 x_i}{\partial t^2}$$

Solved numerically

$$\underbrace{r_i(t) \quad v_i(t),}_{\text{Positions}} \quad \forall \quad i = 1, \dots, 3N$$

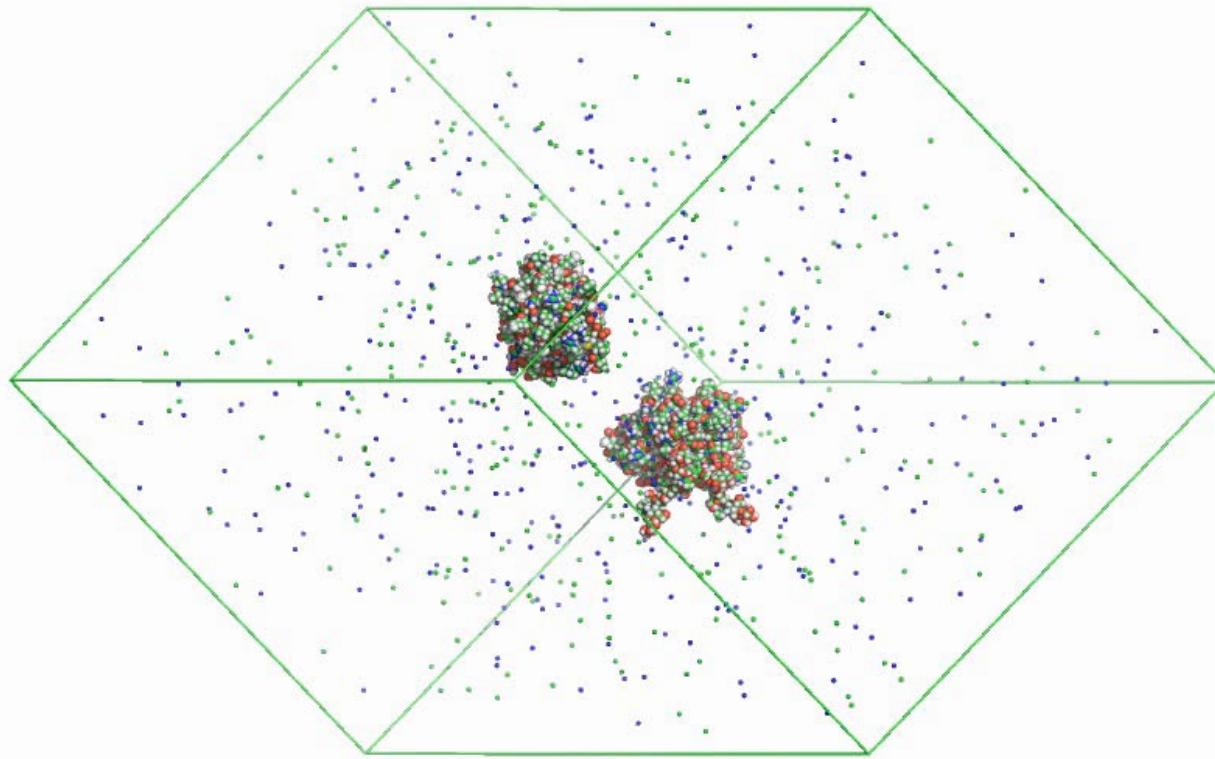
Trajectory of the system:

Positions

Velocities

Molecular dynamics

Trajectory of the system:



water not shown

information at molecular level:

(thermo)dynamic - structural - energetic

guide / complement experiments

$$F = ma$$

$$F = -\nabla V$$

**Molecular dynamics
simulations of
biomolecules**



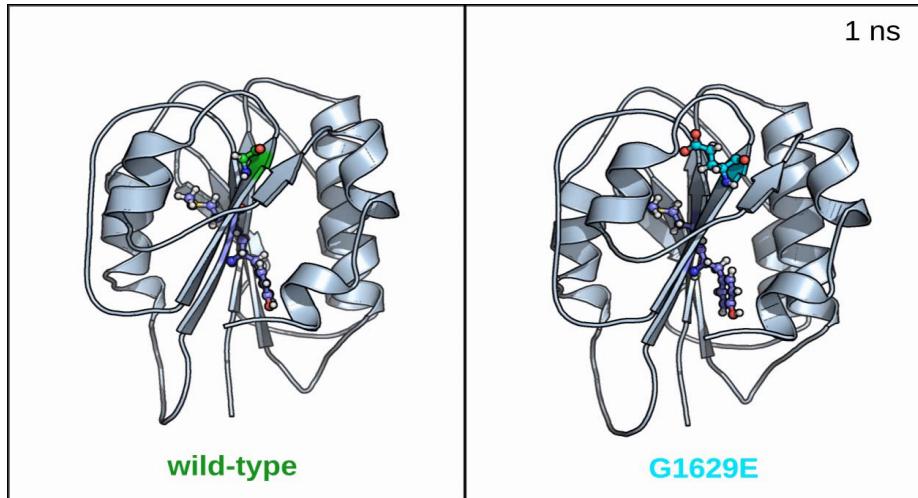
$$F = ma$$

$$F = -\nabla V$$



Molecular dynamics simulations of biomolecules

protein dynamics



$$F = ma$$

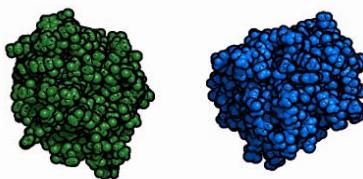
$$F = -\nabla V$$



Molecular dynamics simulations of biomolecules

0.0ns

protein association



$$F = ma$$

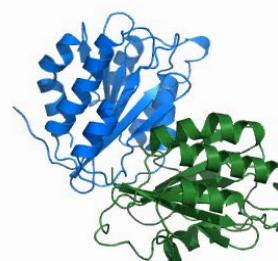
$$F = -\nabla V$$



Molecular dynamics
simulations of biomolecules

0.0ns

Force-induced
dissociation



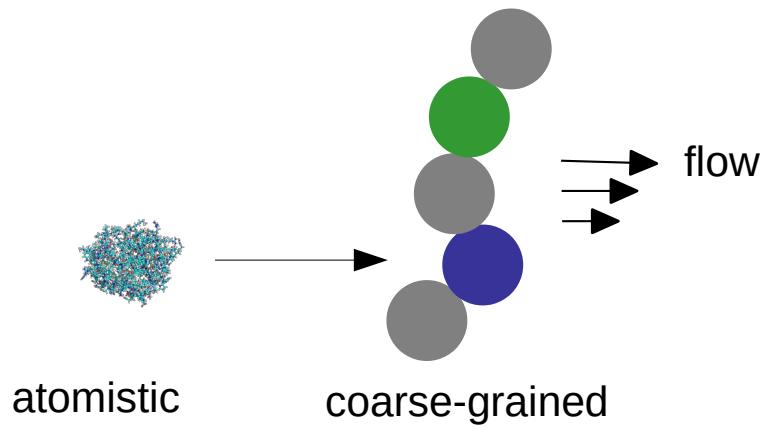
$$F = ma$$

$$F = -\nabla V$$



Molecular dynamics simulations of biomolecules

Flow-induced
globular-to-stretched
transitions



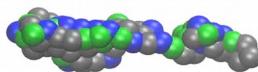
$$F = ma$$

$$F = -\nabla V$$



Molecular dynamics simulations of biomolecules

Flow-induced
globular-to-stretched
transitions



Molecular dynamics

The Nobel Prize in Chemistry 2013



Photo: A. Mahmoud

Martin Karplus

Prize share: 1/3



Photo: A. Mahmoud

Michael Levitt

Prize share: 1/3

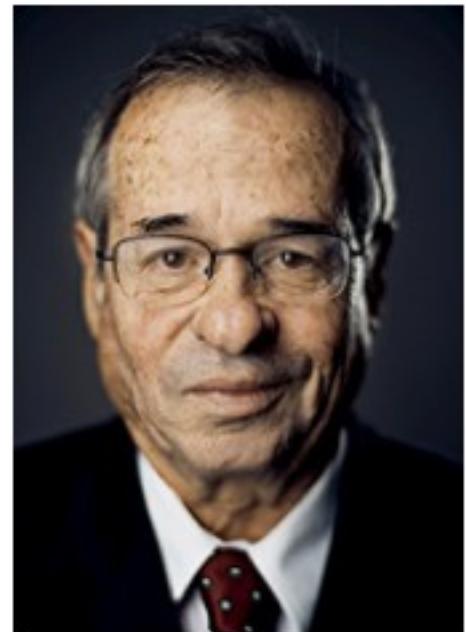


Photo: A. Mahmoud

Arieh Warshel

Prize share: 1/3

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Titles with your s

Chemical Dynamics Simulations on Association and Ensuing Dissociation [J Phys Chem A. 2019]

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Molecular Dynamics Simulations of Ionic Liquids and Electrolytes Using [Chem Rev. 2019]

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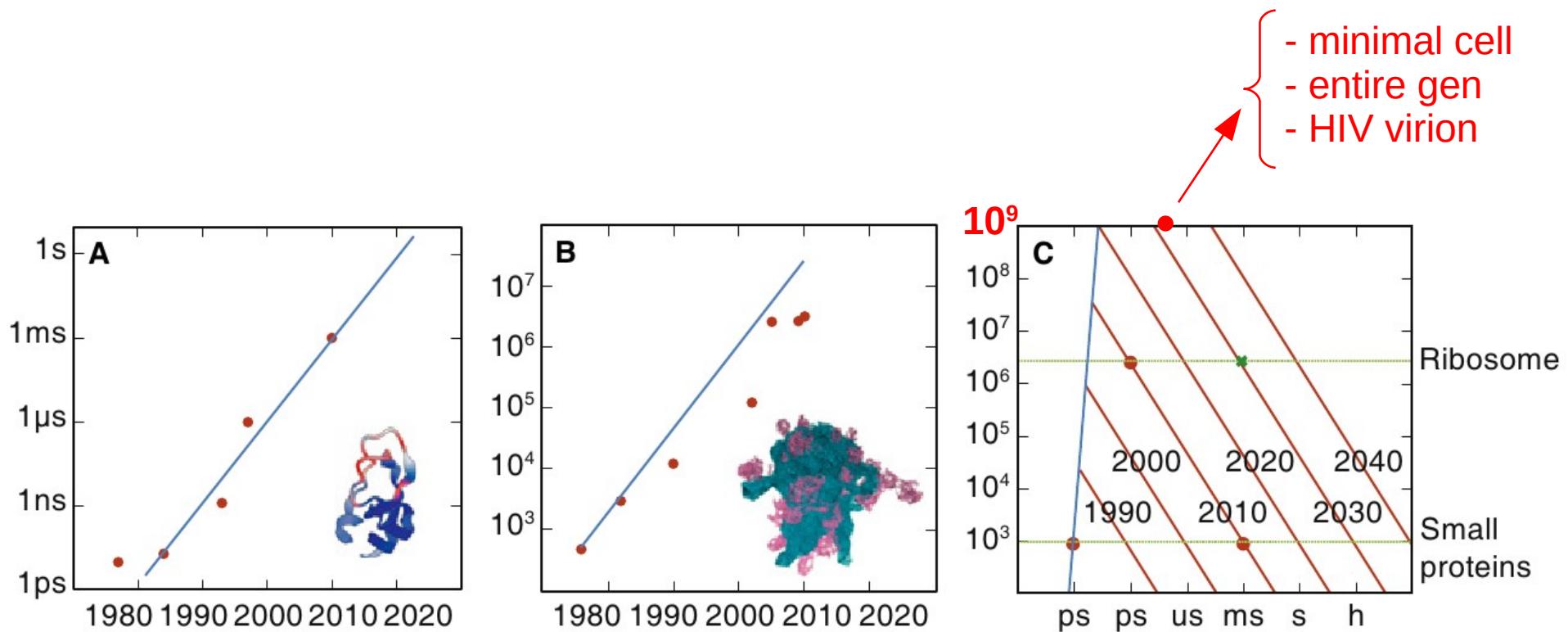
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PLoS Comput Biol. 2019 Jun 3;15(6):e1007041. doi: 10.1371/journal.pcbi.1007041. [Epub ahead of print]
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Front Cell Infect Microbiol. 2019 May 15;9:157. doi: 10.3389/fcimb.2019.00157. eCollection 2019.
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Moore's law in MD simulations

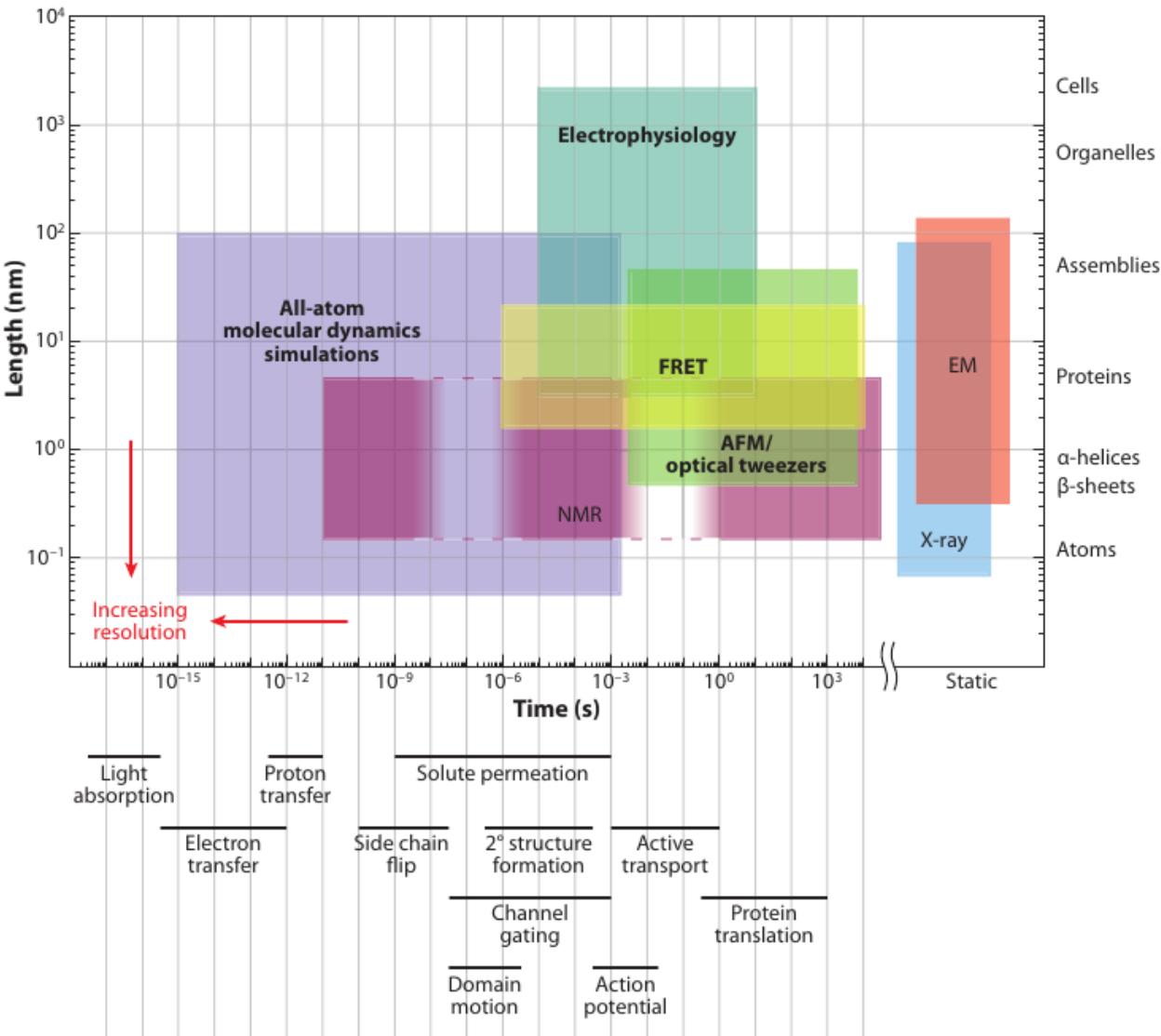


picture from: Vendruscolo & Dobson
Curr. Biol. 21: R68 (2011)

Increasing complexity:

MD augments the captured spatio-temporal scale year by year

Why are MD simulations useful?



picture from:
Dror et al. Annu. Rev. Biophys.
41:429 (2012)

information at molecular level:
(thermo)dynamic - structural - energetic

guide / complement experiments

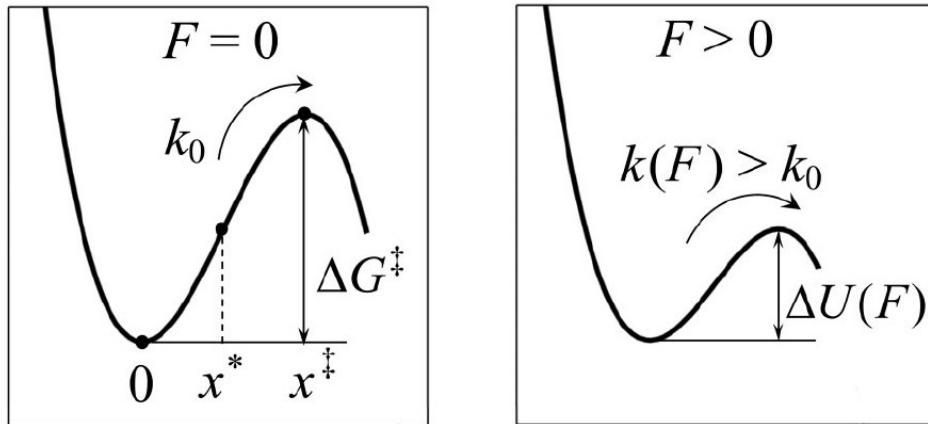
MD challenges: Sampling

Development of new methods and algorithms:

- Distributed computing
(ergodic approximation):



- Enhanced sampling methods:
applying external forces



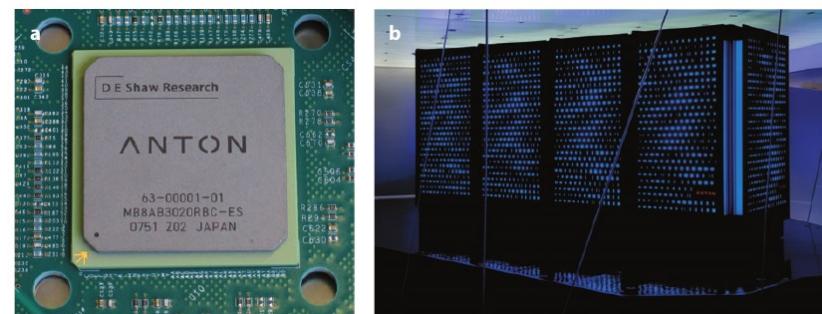
picture from:

Dudko, Hummer & Szabo.
PRL. 96:108101 (2006)

- GPUs:



- MD-dedicated hardware:



picture from:
Dror et al. *Annu. Rev. Biophys.*
41:429 (2012)

MD challenges: force fields

Interatomic interactions:



Empirical potential energy function

$V(r)$

Simple arithmetic terms
easy to calculate with the computer

Not easy to describe:

- Intrinsically disordered proteins
- Protein-protein interactions (aggregates)
- Protein-lipid interactions
- DNA
- RNA
- Sugars
- ...

Continuous refinement using

- experimental data
- quantum mechanical calculations

MD challenges: analysis of data

Calculation of relevant observables: $f(\text{positions}, \text{velocities})$

Examples:

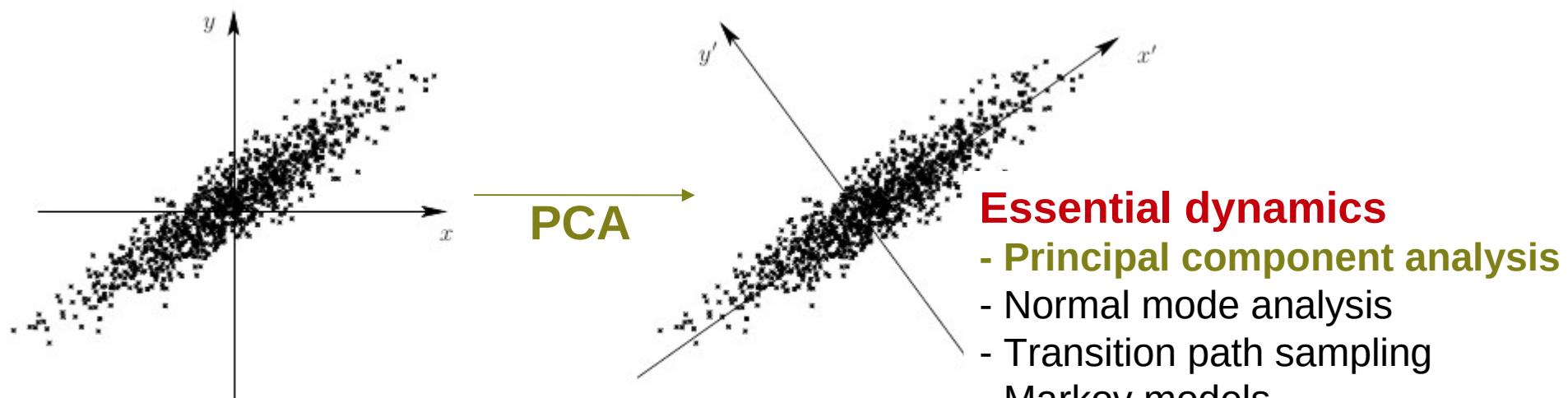
- Root Mean Square Deviations (RMSD)
- Molecular areas and volumes
- Diffusion parameters
- Fluxes
- etc...

Biological system:

highly complex
multidimensional

Reduce dimensionality

detecting functional
degrees of freedom



picture from: Kubitzki. PhD Thesis. P. 25 (2007)

MD packages

- GROMACS
- NAMD
- CHARMM
- AMBER
- DESMOND
- ...

Download / instructions / man
www.gromacs.org



the course: GOALS

1. Familiarize the participants with

- biomolecular simulations
- GROMACS package

2. Illustrate MD applications to the study of biomolecular systems.