Computational Modeling of Protein Dynamics

Yinghao Wu
Department of Systems and Computational Biology
Albert Einstein College of Medicine
Fall 2014

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Outline

- Background of protein dynamics
- Basic computational methods
  - Molecular dynamics
  - Monte-Carlo Simulation
- Specific Applications

Outline

- Background of protein dynamics
- Basic computational methods
  - Molecular dynamics
  - Monte-Carlo Simulation
- Specific Applications

Why study protein dynamics?

Protein flexibility is crucial for function. One “average” structure is not enough. Proteins constantly sample configurational space.

•Transport - binding and moving molecules (ex: molecular oxygen binding to hemoglobin)

•Enzyme catalysis - substrate entry and produce release

•Allosteric regulation - regulation of enzyme activity. Enzyme must be able to flip-flop between on (active) and off (inactive) states

•Molecular associations - induced fit (ex: transcription complexes)

Outline

- Background of protein dynamics
- Basic computational methods
  - Molecular dynamics
  - Monte-Carlo Simulation
- Specific Applications

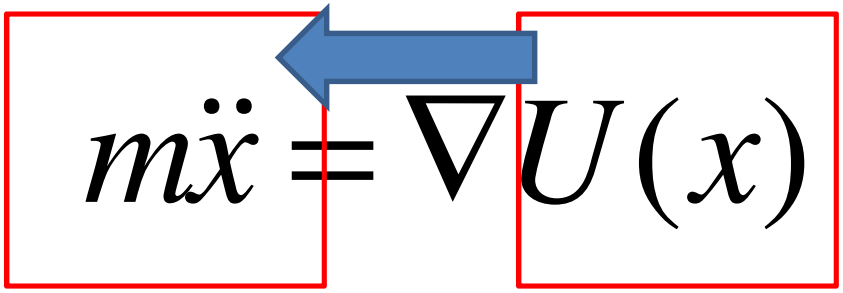
Outline

- Background of protein dynamics
- Basic computational methods
  - Molecular dynamics
  - Monte-Carlo Simulation
- Specific Applications

What is a Molecular Dynamics?

Molecular dynamics (MD) is a computer simulation of physical movements of a number of interacting atoms or molecules within a given period of time

Two Components of Molecular Dynamics



- Force field
- Equation of Motions

What is a Force Field?

- Force field is a collection of parameters for a potential energy function

$$m\ddot{x} = \nabla U(x)$$

  - Parameters might come from fitting against experimental data or quantum mechanics calculations

Force Fields: Typical Energy Functions

$$U = \sum_{bonds} \frac{1}{2} k_r (r - r_0)^2$$ Bond stretches

$$+ \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_0)^2$$ Angle bending

$$+ \sum_{torsions} \frac{V_n}{2} [1 + \cos(n\varphi - \delta)]$$ Torsional rotation

$$+ \sum_{improper} V(improper\ torsion)$$ Improper torsion (sp2)

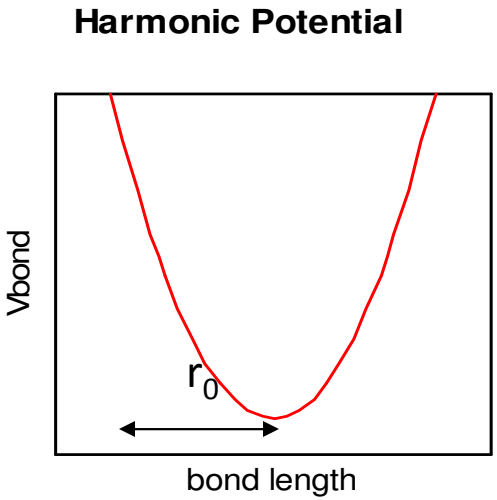
$$+ \sum_{elec} \frac{q_i q_j}{r_{ij}}$$ Electrostatic interaction

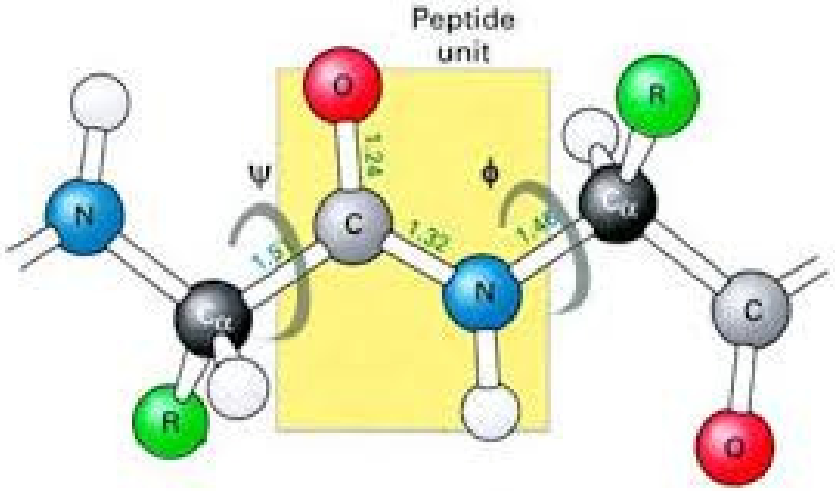
$$+ \sum_{LJ} [\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}]$$ Lennard-Jones interaction

Bonding Terms: bond stretch

- Most often Harmonic

$$V_{bond} = \sum_{bonds} \frac{1}{2} k_r (r - r_0)^2$$

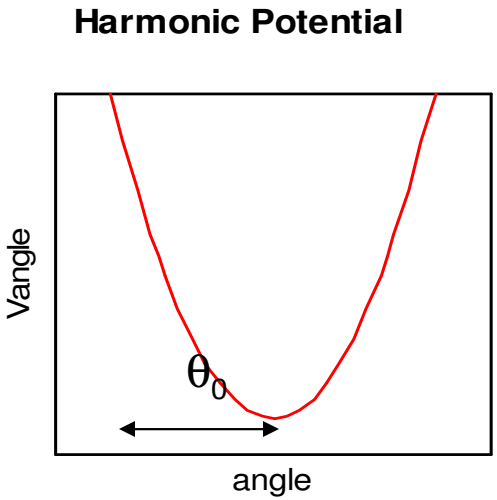


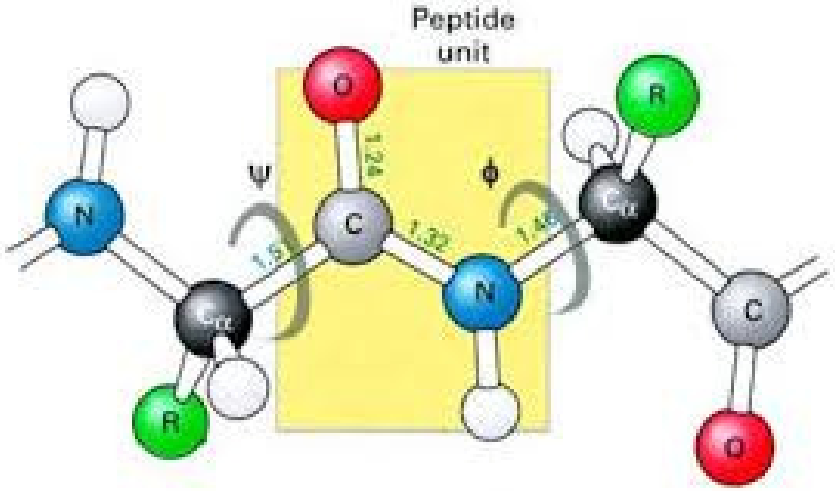


Bonding Terms: angle bending

- Most often Harmonic

$$V_{angle} = \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_0)^2$$

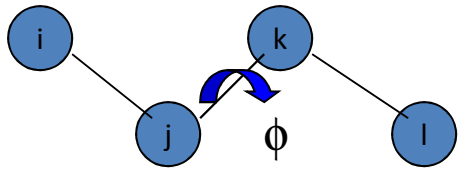




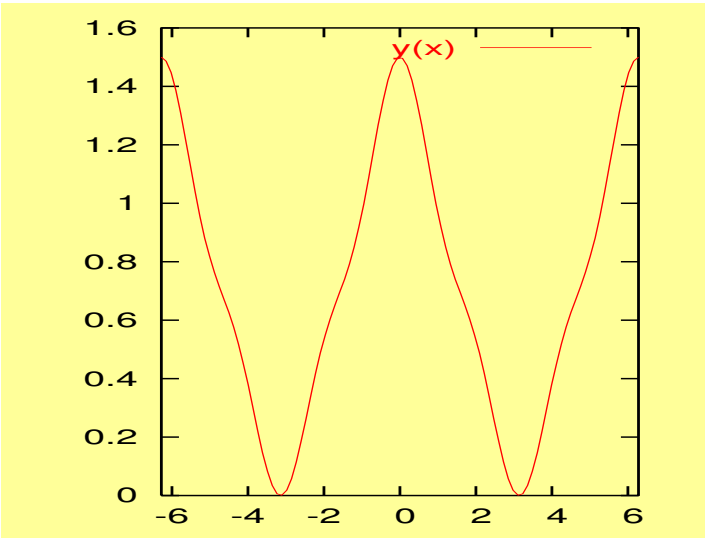
Bonding Terms: Torsions

- Torsion energy: rotation about a bond (dihedral angles)

$$U_{torsion} = \sum_{torsions} \frac{V_n}{2}[1+\cos(n\varphi-\delta)]$$



i-j-k-l



Vn: force constant

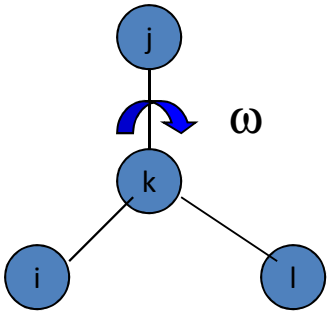
n: periodicity of the angle (determines how many peaks and wells in the potential, often from 1-6)

δ: phase of the angle (often 0º or 180º)

Bonding Terms: Improper Torsions

- Improper torsion is not a regular torsion angle. It is used to describe the energy of out-of-plane motions. It is often necessary for planar groups, such as sp2 hybridized carbons in carbonyl groups and in aromatic rings, because the normal torsion terms described above is not sufficient to maintain the planarity.

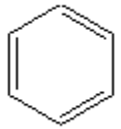
$$U_{improper} = \sum_{improper} \frac{V_2}{2}[1+\cos(2\omega - 180^\circ)]$$

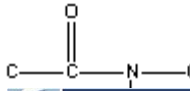


i-j-k-l

or

$$U_{improper} = \sum_{improper} \frac{k_w}{2}(\omega - \omega_0)^2$$





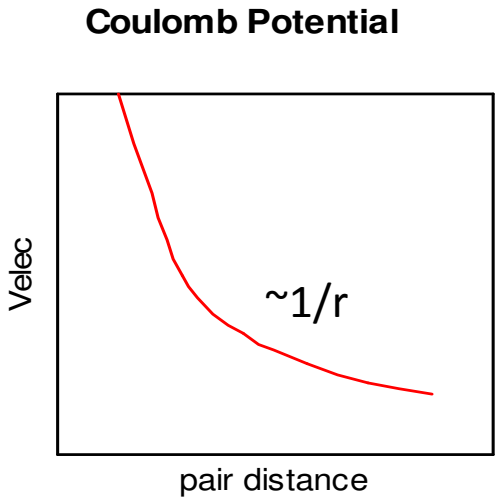
EINSTEIN

Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Non-bonded Terms

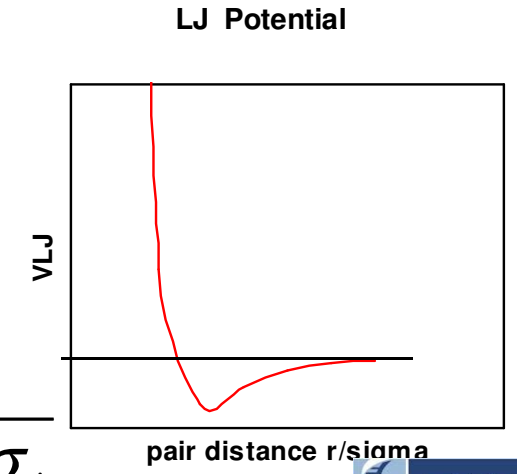
- Electrostatic interactions (Coulomb's Law)

$$V_{elec} = \frac{1}{4\pi\varepsilon}\sum_{i<j}\frac{q_i q_j}{r_{ij}}$$



- Lennard-Jones interactions

$$V_{LJ} = \sum_{i<j} 4\varepsilon_{ij}\left[\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^{6}}{r_{ij}^{6}}\right]$$



- Combination Rules for LJ

$$\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j} \quad \sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \qquad \sigma_{ij} = \sqrt{\sigma_i \sigma_j}$$

(OPLSAA)

Classical Equations of Motion

- Several formulations are in use
  - Newtonian
  - Lagrangian
  - Hamiltonian
- Advantages of non-Newtonian formulations
  - more general, no need for "fictitious" forces
  - better suited for multiparticle systems
  - better handling of constraints
  - can be formulated from more basic postulates
- Assume conservative forces

$$\vec{\mathbf{F}} = -\vec{\nabla} U$$ *Gradient of a scalar potential energy*

Newtonian Formulation

- Cartesian spatial coordinates $\mathbf{r}_i = (x_i, y_i, z_i)$ are primary variables
  - for N atoms, system of N 2nd-order differential equations

$$m\frac{d^2\mathbf{r}_i}{dt^2} \equiv m\ddot{\mathbf{r}}_i = \mathbf{F}_i$$

- Sample application: 2D motion in central force field

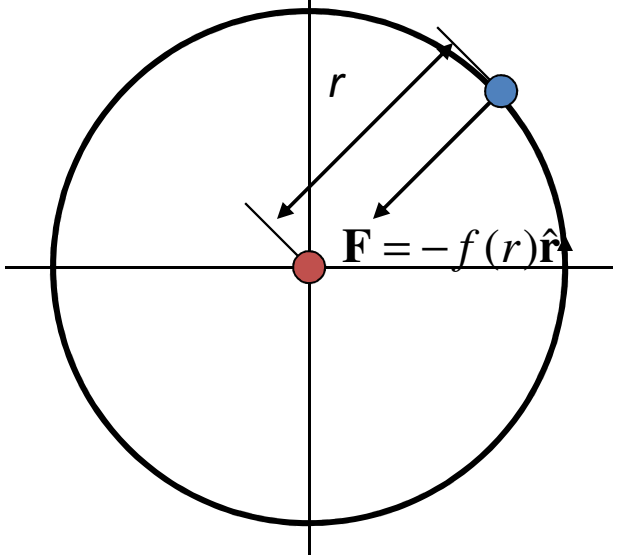
$$m\ddot{x} = \mathbf{F}\cdot\hat{\mathbf{e}}_x = -f(r)\hat{\mathbf{r}}\cdot\hat{\mathbf{e}}_x = -xf\left(\sqrt{x^2+y^2}\right)$$

$$m\ddot{y} = \mathbf{F}\cdot\hat{\mathbf{e}}_y = -f(r)\hat{\mathbf{r}}\cdot\hat{\mathbf{e}}_y = -yf\left(\sqrt{x^2+y^2}\right)$$

  - Polar coordinates are more natural and convenient

$$mr^2\dot{\theta} = \ell$$ *constant angular momentum*

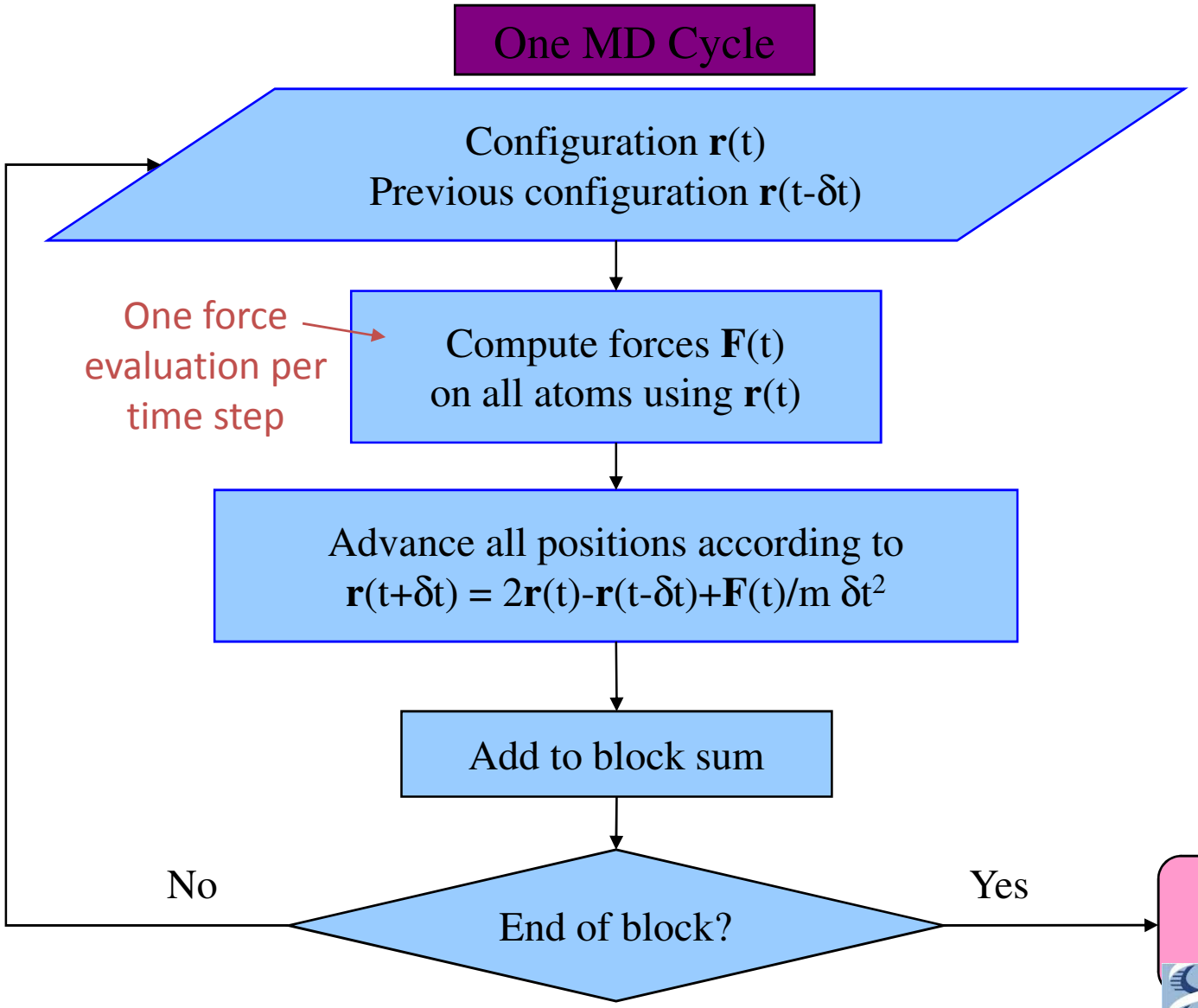
$$m\ddot{r} = -f(r) + \frac{\ell^2}{mr^3}$$ *fictitious (centrifugal) force*



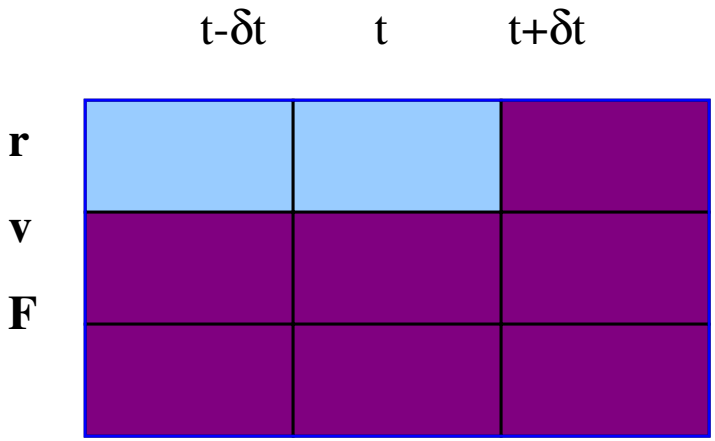
Integration Algorithms

- Desirable features of an integrator
  - minimal need to compute forces (a very expensive calculation)
  - good stability for large time steps
  - good accuracy
  - conserves energy and momentum
  - time-reversible

Verlet Algorithm: Flow diagram

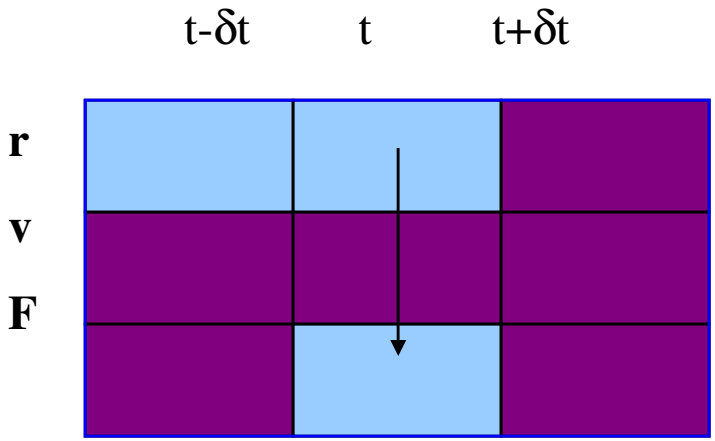


Verlet Algorithm: Flow Diagram



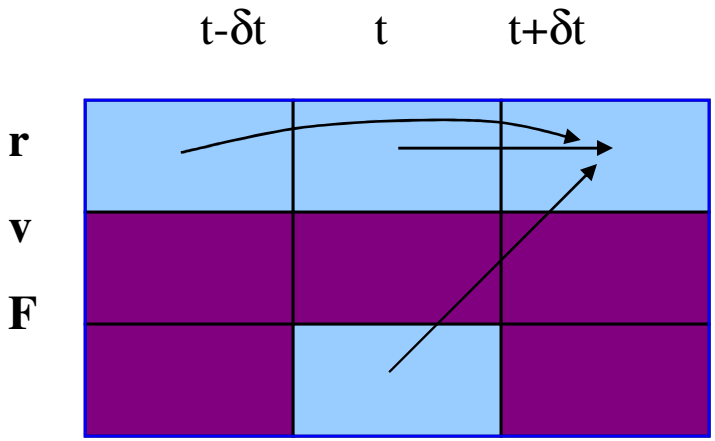
Given current position and position at end of previous time step

Verlet Algorithm: Flow Diagram



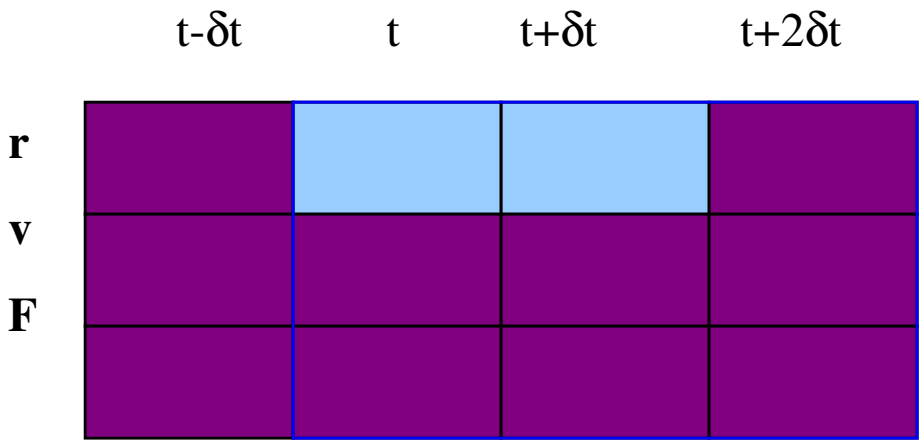
Compute the force at the current position

Verlet Algorithm: Flow Diagram



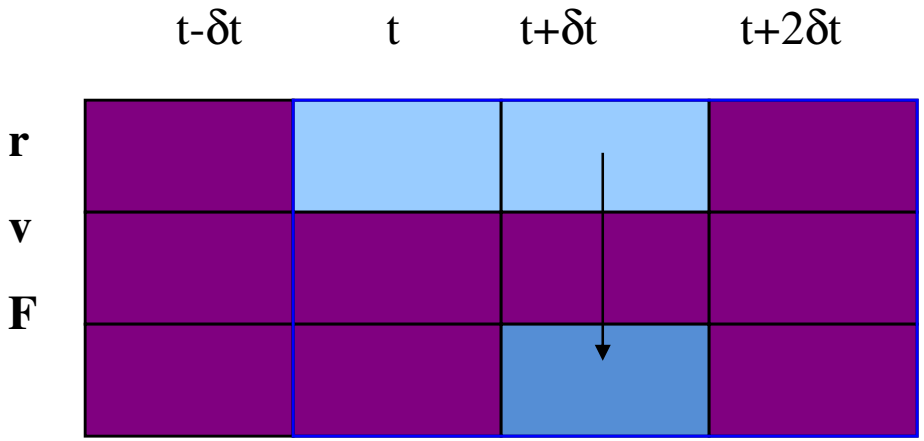
Compute new position from present and previous positions, and present force

Verlet Algorithm: Flow Diagram



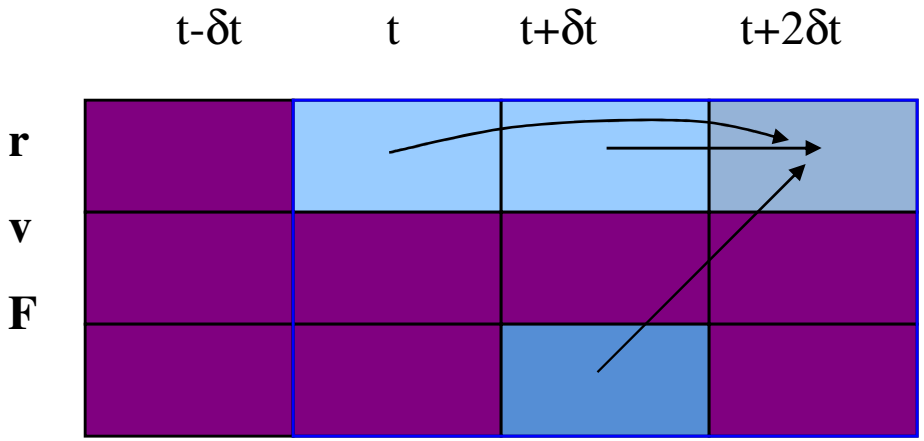
Advance to next time step, repeat

Verlet Algorithm: Flow Diagram



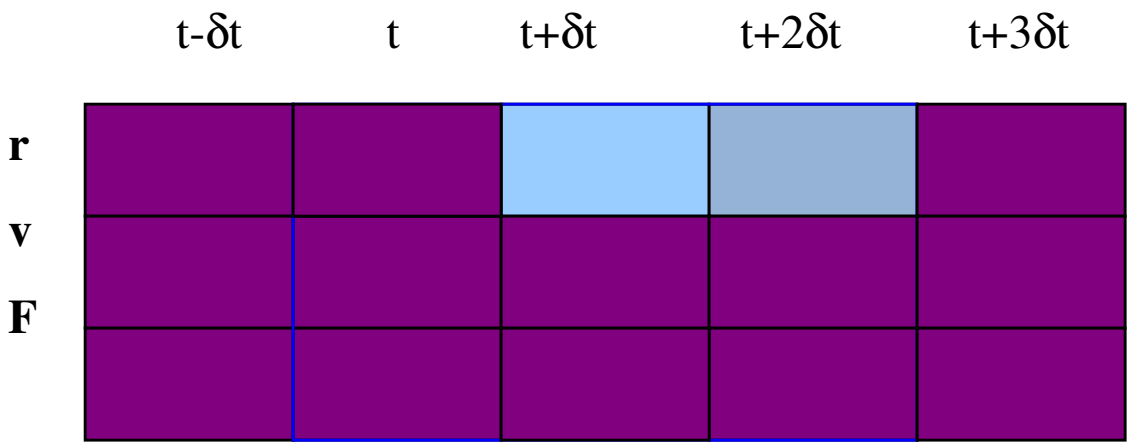
Compute the force at the current position

Verlet Algorithm: Flow Diagram



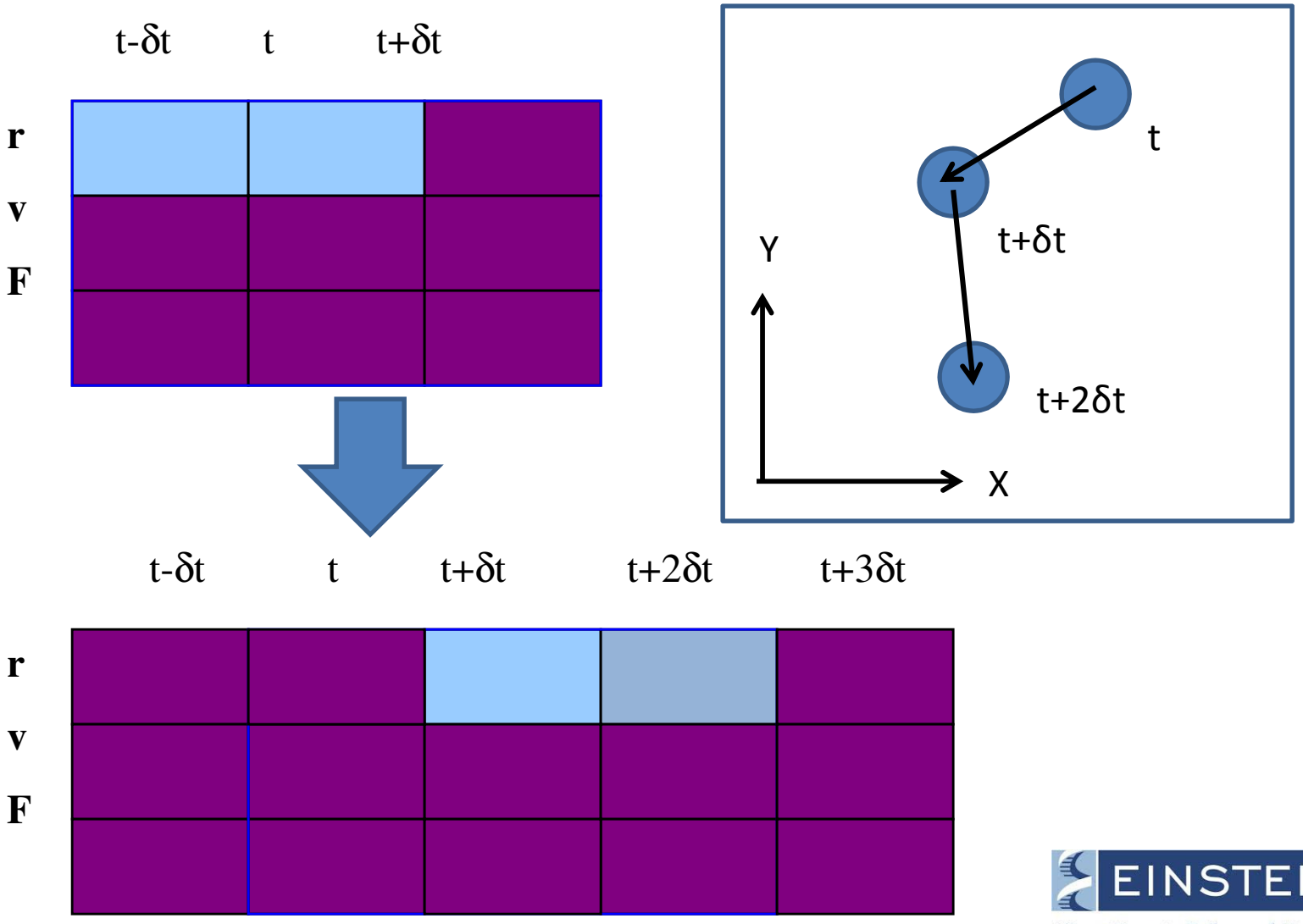
Compute new position from present and previous positions, and present force

Verlet Algorithm: Flow Diagram

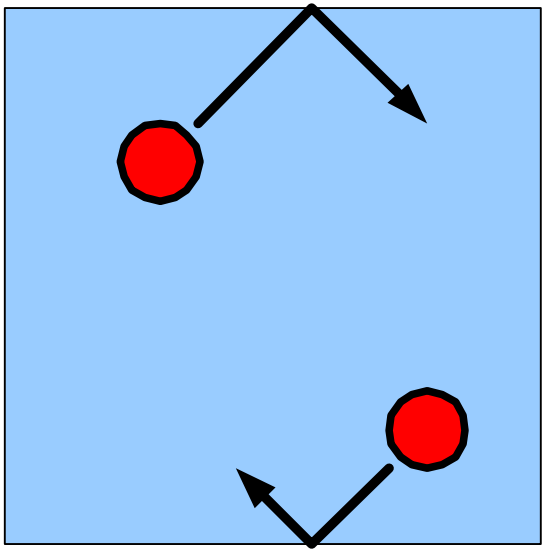


Advance to next time step, repeat

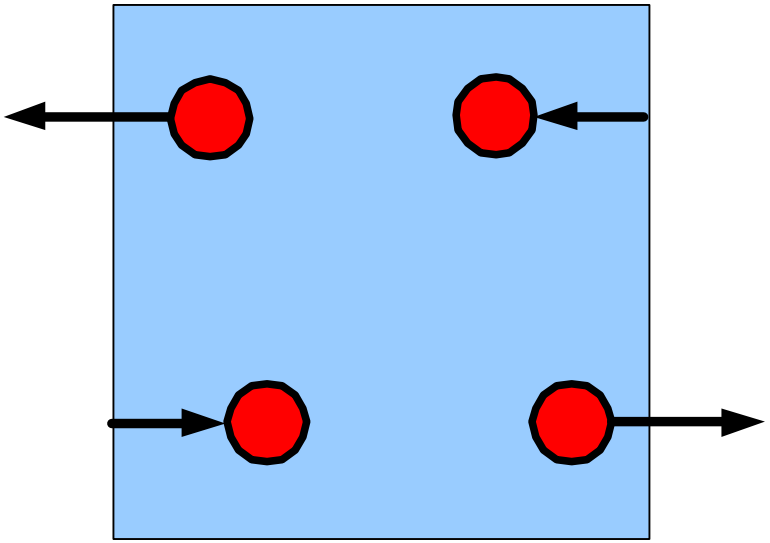
Verlet Algorithm: Flow Diagram



Boundary Condition



Specular boundary condition



Periodic boundary condition

Outline

- Background of protein dynamics
- Basic computational methods
  - Molecular dynamics
  - Monte-Carlo Simulation
- Specific Applications

What is Monte Carlo (MC) method ?

The Monte Carlo method: is a numerical method for statistical simulation which utilizes sequences of random numbers to perform the simulation

Random numbers

- Uniform Random numbers or pseudo-random numbers (PRN) are essentially independent random variables uniformly Distributed over the unit interval (0,1).

- The PRNs are good if they are uniformly distributed, statistically independent and reproducible.

Classic Example

Find the value of π ?

Use the reject and accept method

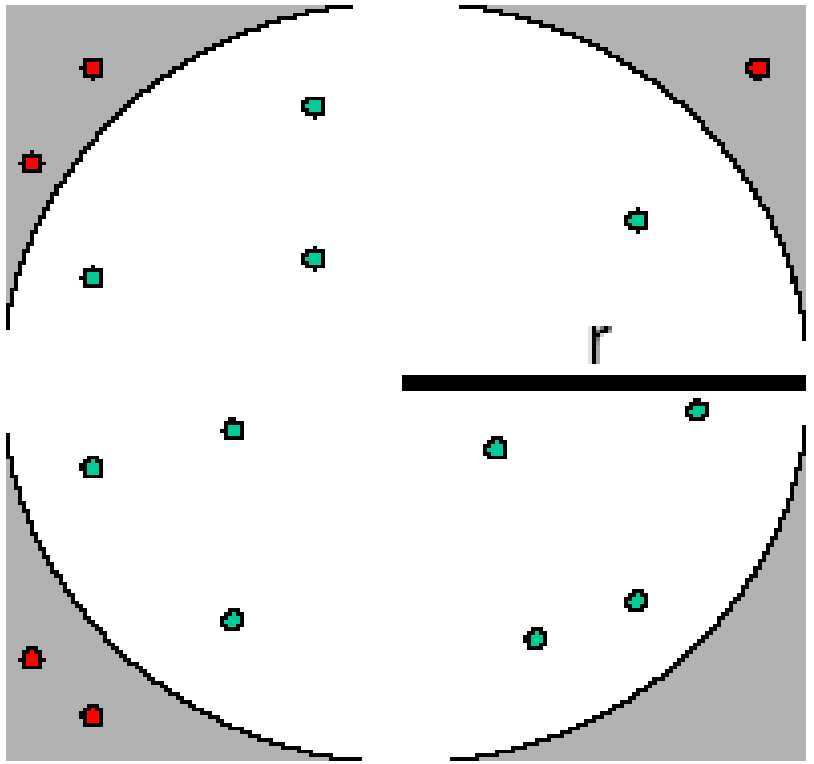
Or hit and miss method

The area of square=$(2r)^2$

The area of circle =π r^2

$$\frac{area \cdot of \cdot square}{area \cdot of \cdot circle} = \frac{4r^2}{\pi r^2} = \frac{4}{\pi}$$

$$\pi = 4 * \frac{area \cdot of \cdot circle}{area \cdot of \cdot square}$$



Cont..

$$\frac{area\ .of\ .circle}{area\ .of\ .square} \doteq \frac{\#.of\ .dots\ .inside\ .circle}{total\ .number\ .of\ .dots}$$

Hit and miss algorithm

Generate two sequences of N of PRN :: R_i, R_j

$X_i = -1 + 2R_i$

$Y_j = -1 + 2R_j$

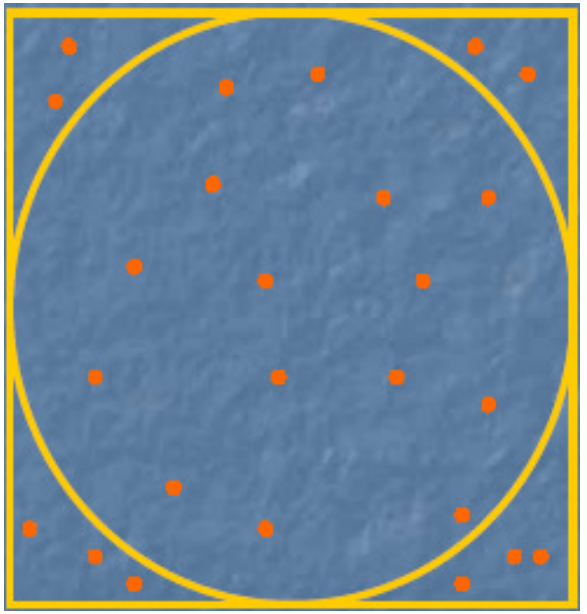
Start from s=zero

If $(X^2 + Y^2 < 1)$ s=s+1

# of dots inside circle=s

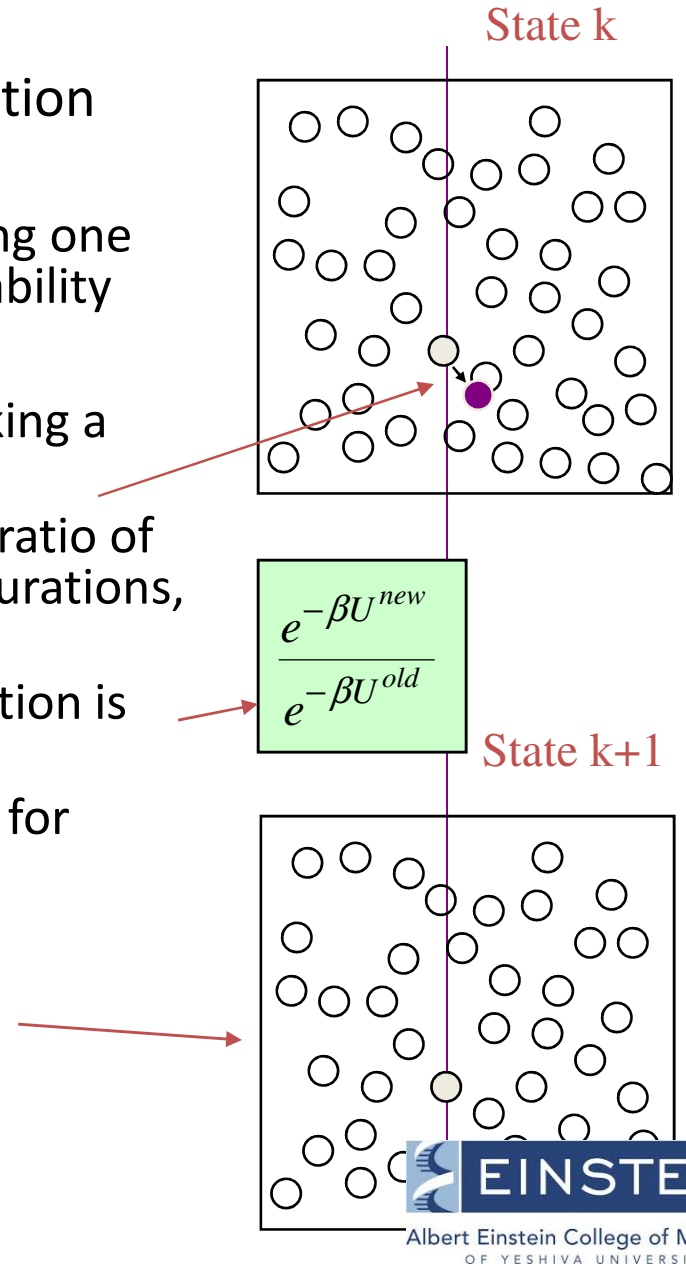
total number of dots=N

$$\pi = 4 * S / N$$



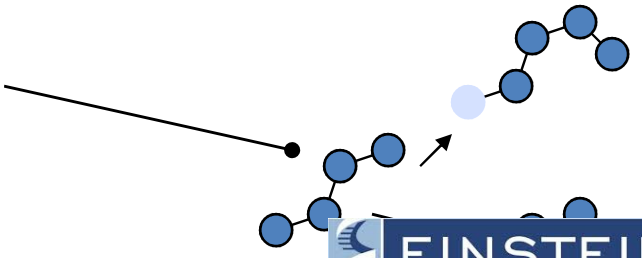
Monte Carlo in Molecular Simulation

- MC techniques applied to molecular simulation
- Almost always involves a Markov process
  - move to a new configuration from an existing one according to a well-defined transition probability
- Simulation procedure
  - generate a new “trial” configuration by making a perturbation to the present configuration
  - accept the new configuration based on the ratio of the probabilities for the new and old configurations, according to the Metropolis algorithm
  - if the trial is rejected, the present configuration is taken as the next one in the Markov chain
  - repeat this many times, accumulating sums for averages

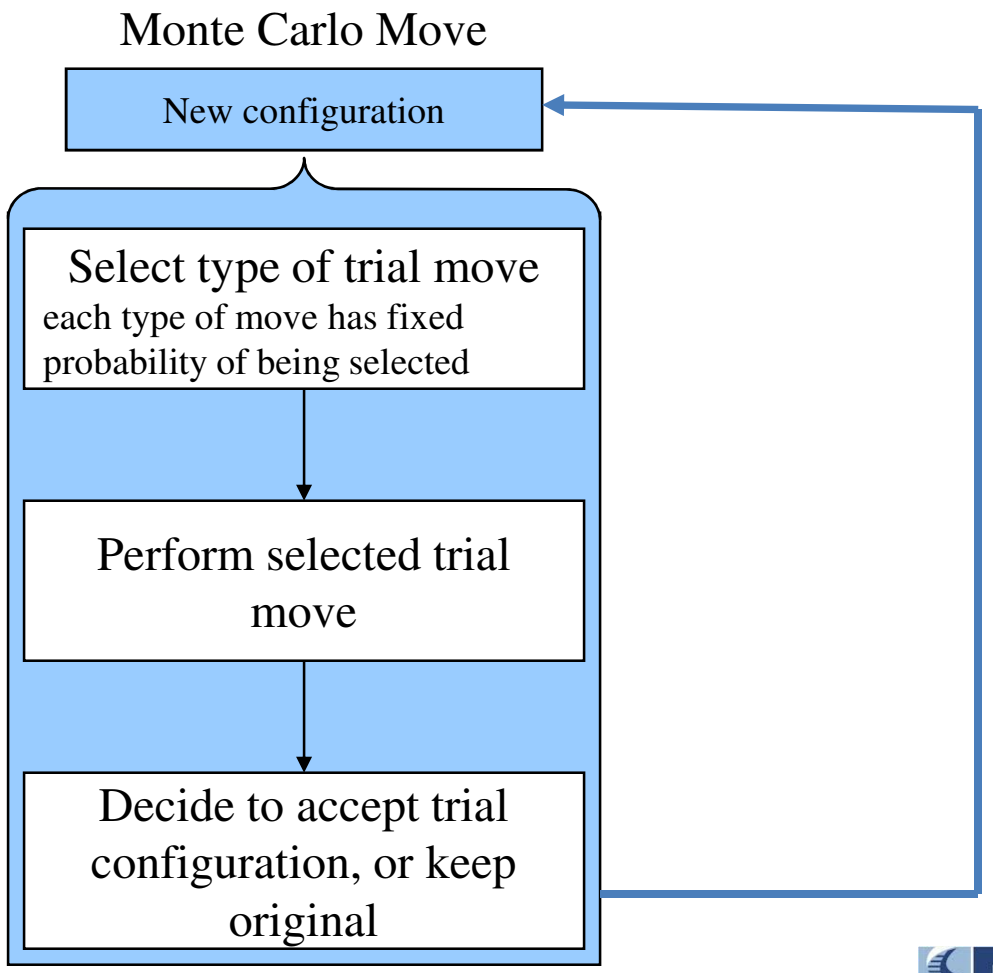


Trial Moves

- A great variety of trial moves can be made
- Basic selection of trial moves is dictated by choice of ensemble
  - almost all MC is performed at constant T
    - no need to ensure trial holds energy fixed
  - must ensure relevant elements of ensemble are sampled
    - all ensembles have molecule displacement, rotation; atom displacement
    - isobaric ensembles have trials that change the volume
    - grand-canonical ensembles have trials that insert/delete a molecule
- Significant increase in efficiency of algorithm can be achieved by the introduction of clever trial moves
  - crankshaft moves for polymers
  - multi-molecule movements of associating molecules
  - many more

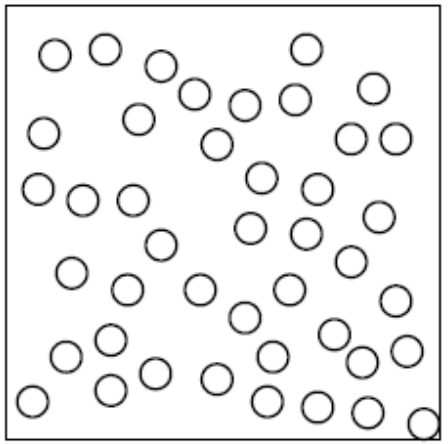


General Form of Algorithm



General Form of Algorithm

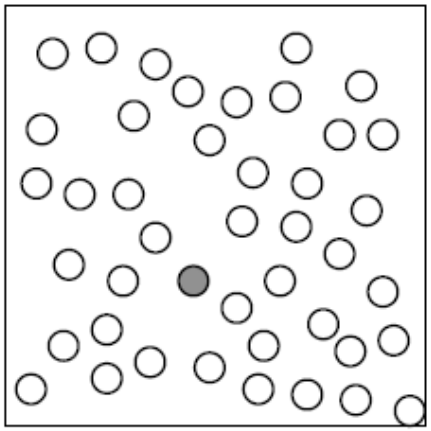
- Gives new configuration of same volume and number of molecules
- Basic trial:
  -



General Form of Algorithm

- Gives new configuration of same volume and number of molecules
- Basic trial:
  - *a randomly selected atom*

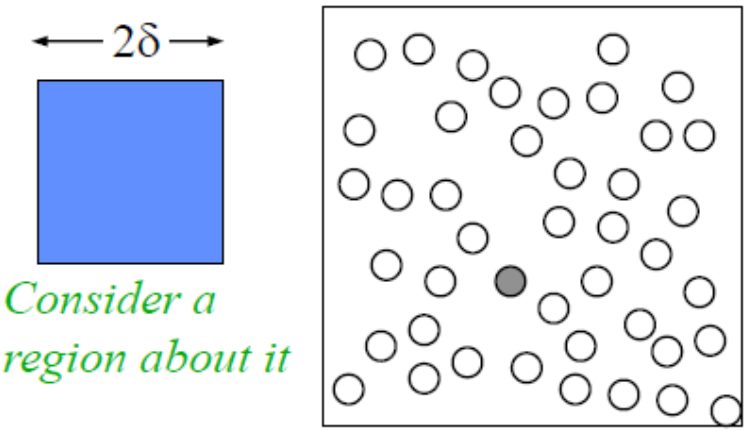
Select an atom at random



General Form of Algorithm

- Gives new configuration of same volume and number of molecules
- Basic trial:
  - *a randomly selected atom*

a cubic volume of edge 2δ

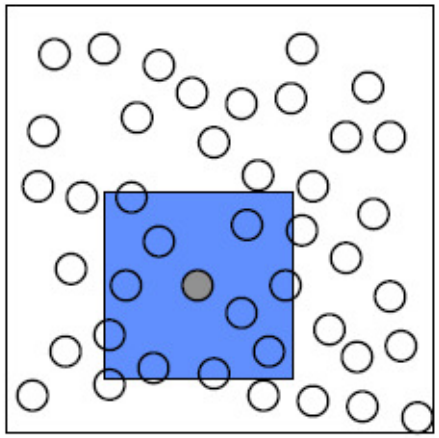


Consider a region about it

General Form of Algorithm

- Gives new configuration of same volume and number of molecules
- Basic trial:
  - *a randomly selected atom*
    a cubic volume of edge 2δ centered on the current position of the atom

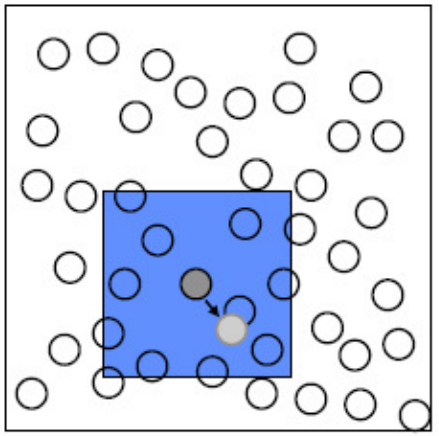
Consider a region about it



General Form of Algorithm

- Gives new configuration of same volume and number of molecules
- Basic trial:
  - *displace a randomly selected atom to a point chosen with uniform probability inside a cubic volume of edge 2δ centered on the current position of the atom*

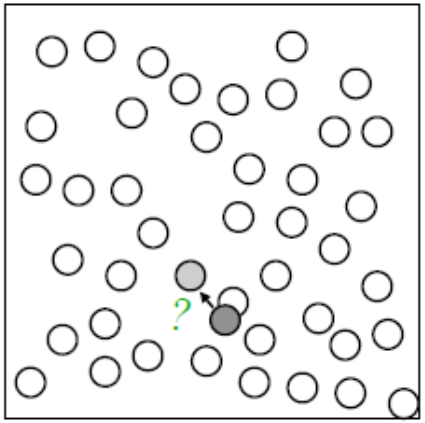
Move atom to point chosen uniformly in region



General Form of Algorithm

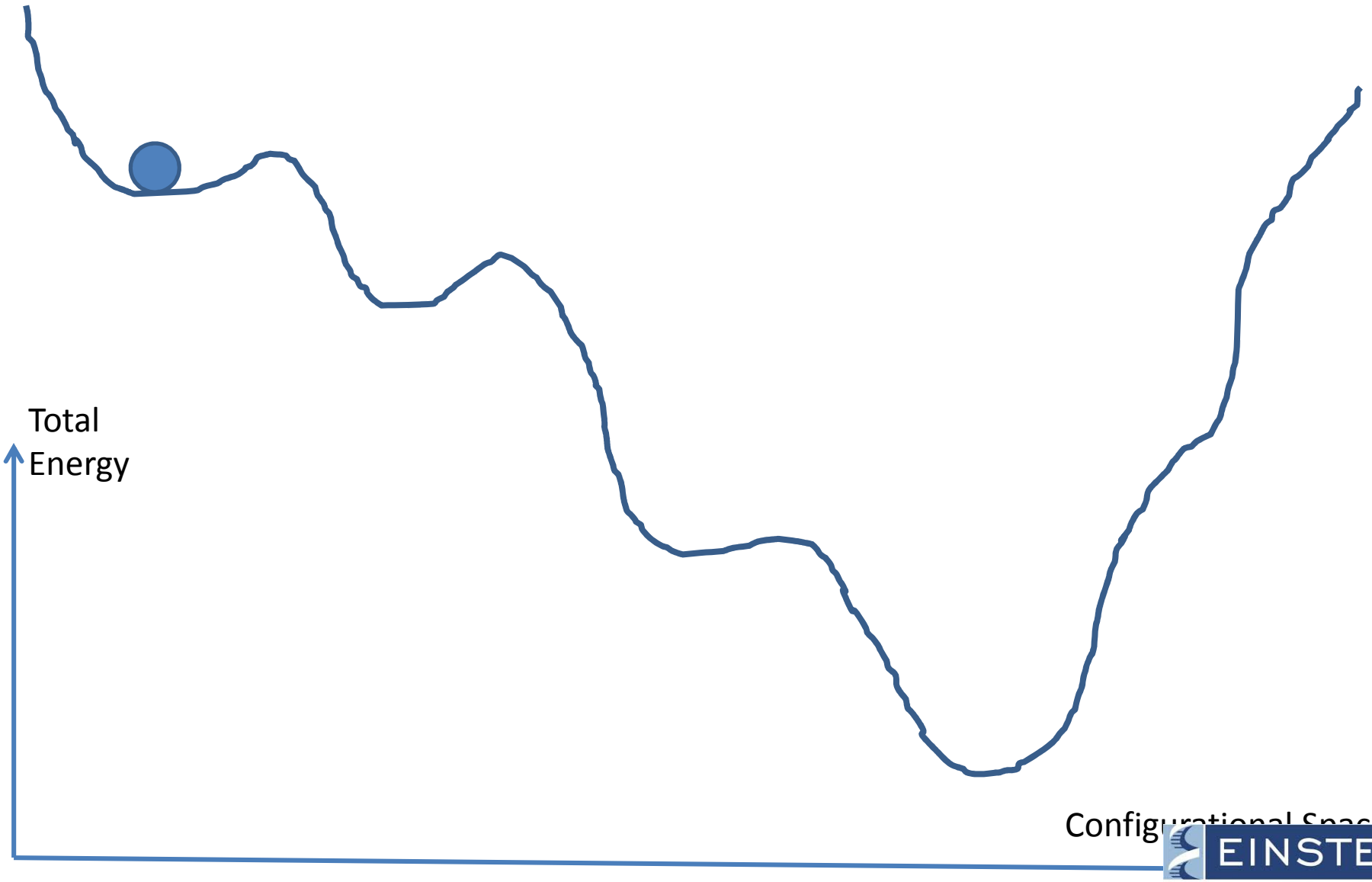
- Gives new configuration of same volume and number of molecules
- Basic trial:
  - *displace a randomly selected atom to a point chosen with uniform probability inside a cubic volume of edge 2δ centered on the current position of the atom*

Consider acceptance of new configuration

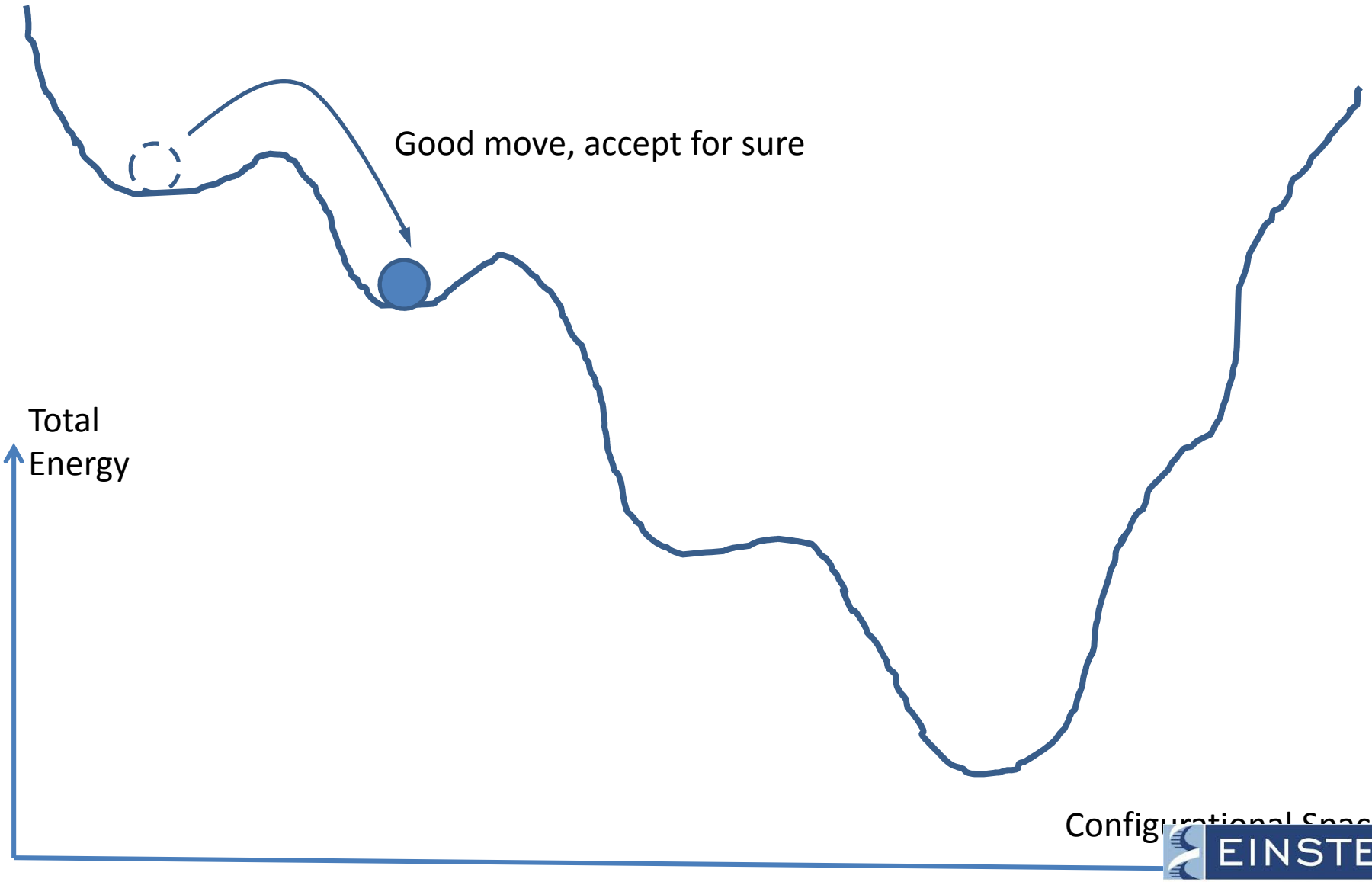


$$w(\underline{r}_i \rightarrow \underline{r}_i') = \begin{cases} 1 & \text{if} \quad \Delta E(\underline{r}_i \rightarrow \underline{r}_i') < 0 \\ \exp(-\beta \Delta E(\underline{r}_i \rightarrow \underline{r}_i')) & \text{otherwise} \end{cases}$$

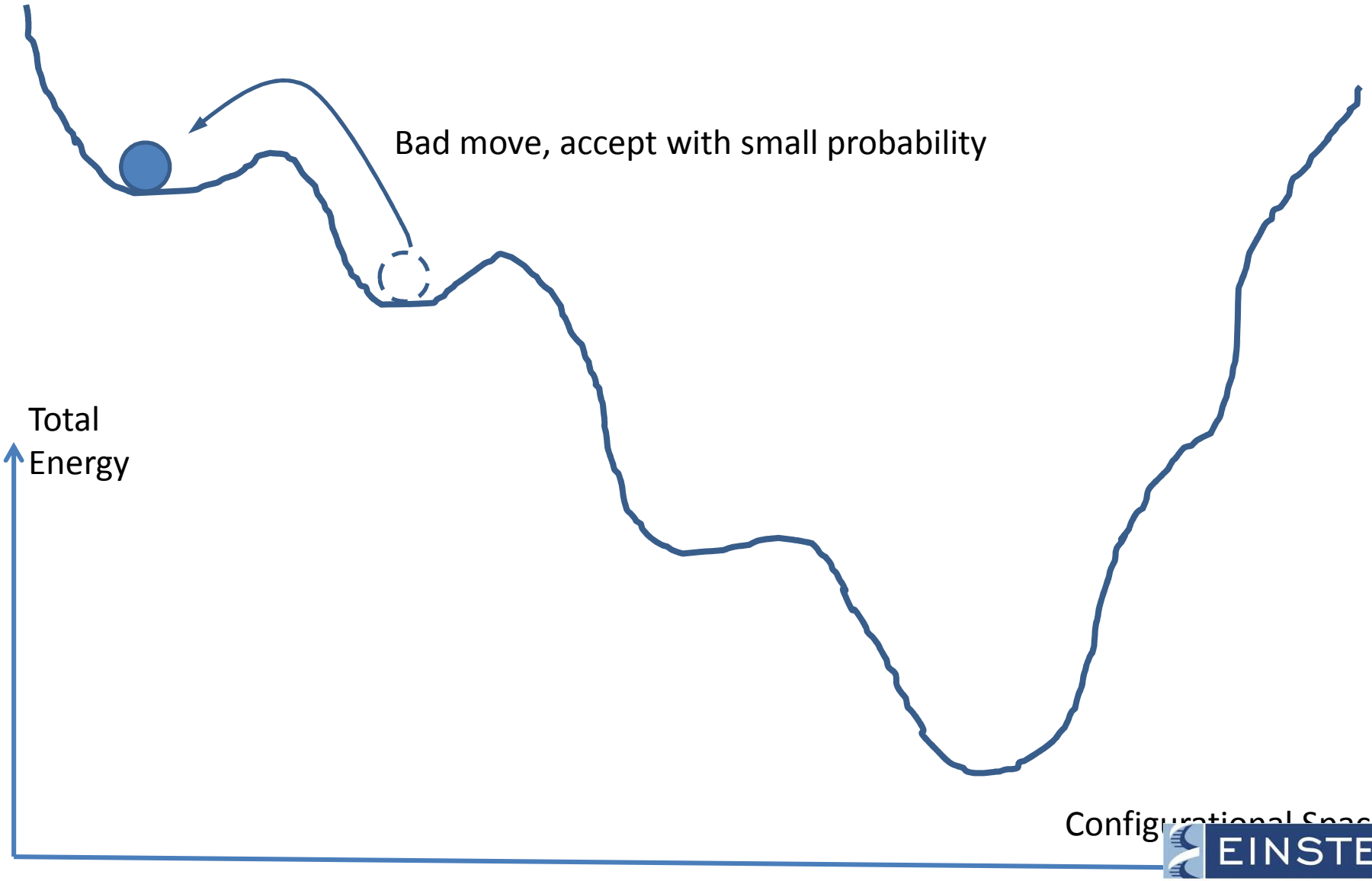
Energy Landscape



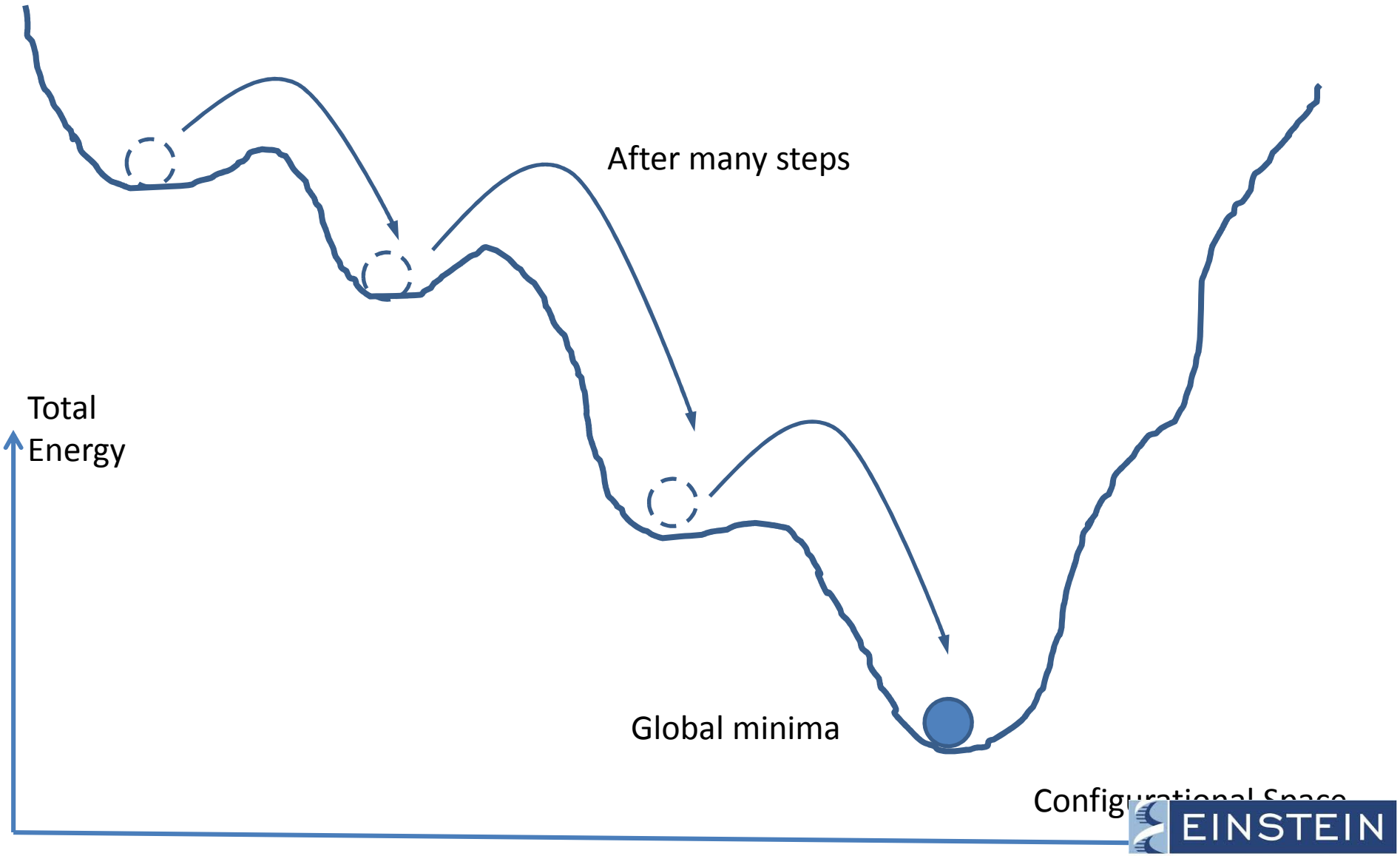
Energy Landscape



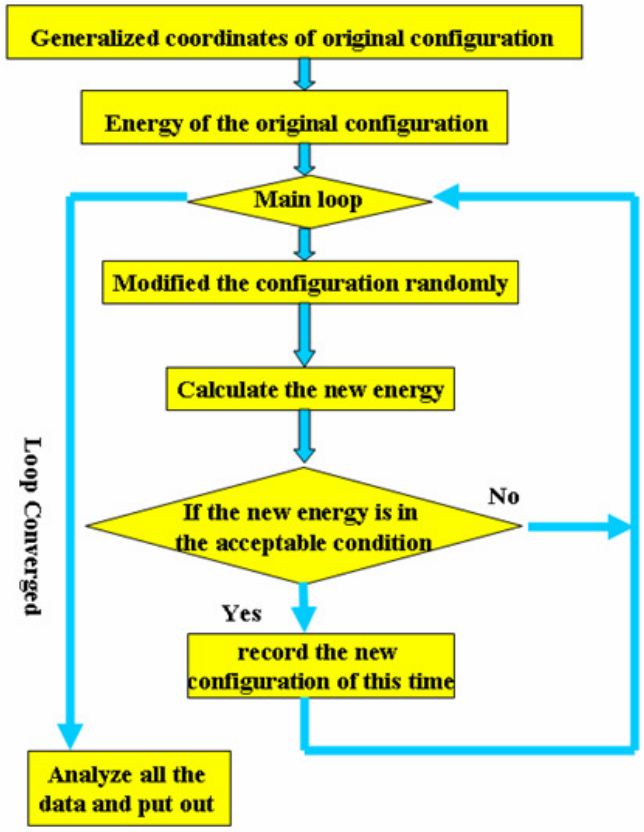
Energy Landscape

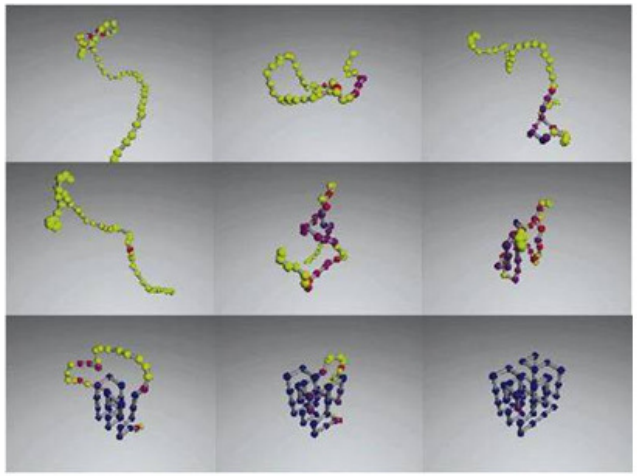


Energy Landscape



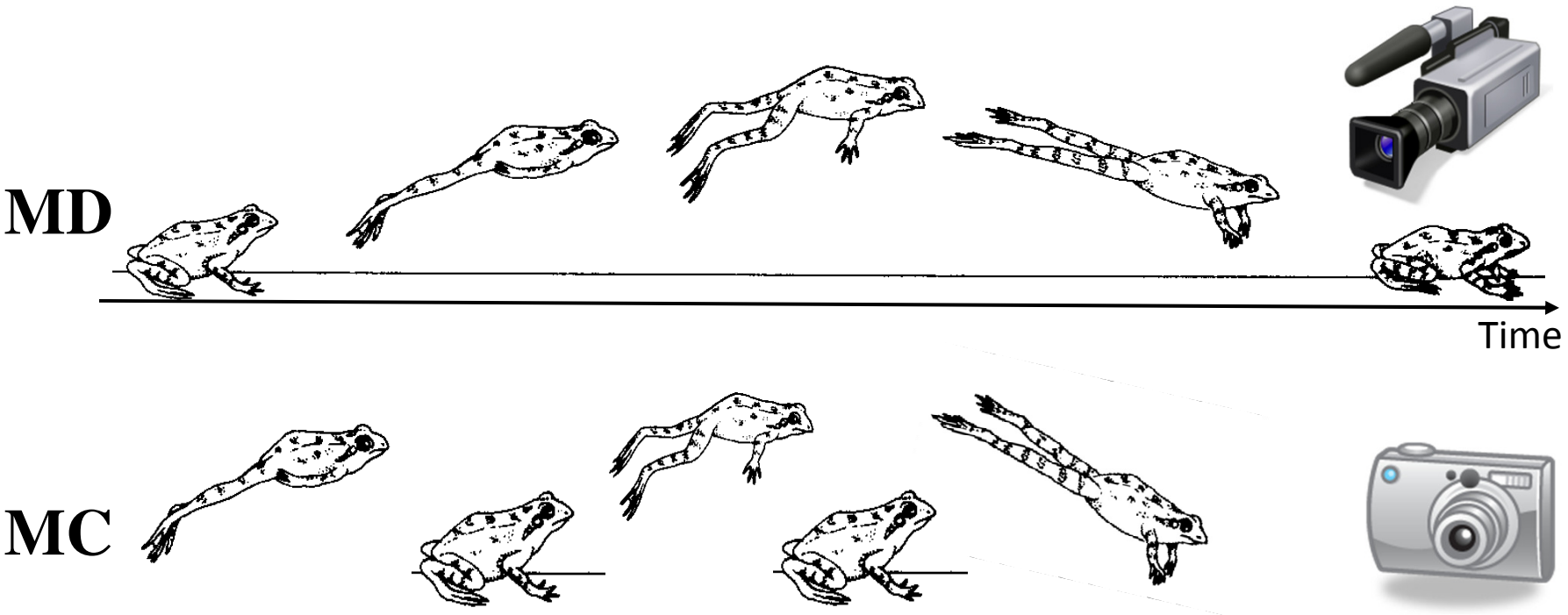
General Form of Algorithm: Applications to Polymers

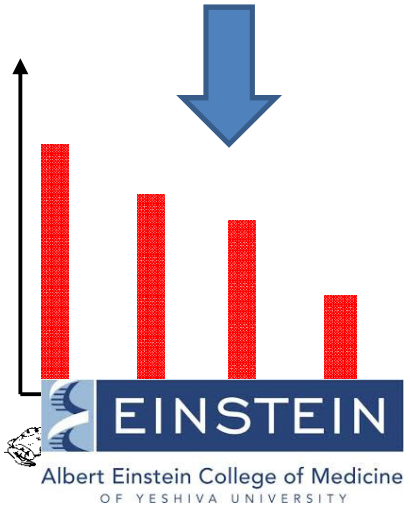




Source: http://bioserv.rpbs.jussieu.fr/~autin/help/nmr.html

MC vs. MD


MD
Time
MC


EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

MC vs. MD

- Only energy is needed
- Straightforward to perform NVT and NPT
- Easy to constrain some degrees of freedoms (not include them in trials)
- For some systems, large motions can be made (LJ particles) between consecutive configurations

- Hard to make trials for complex systems, such as proteins, since proteins move collectively
- Step size decreases with system size
- Can't easily get kinetic information

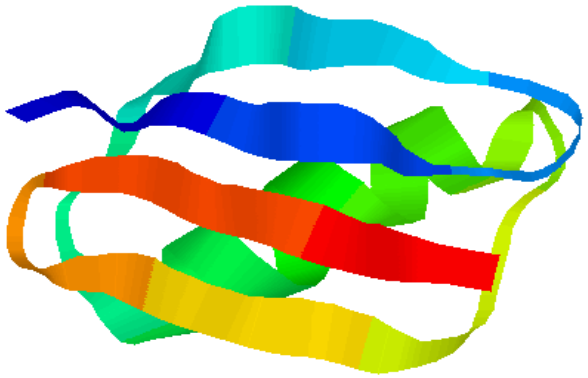
- Both energy and force are needed
- Requires temperature and pressure control for NVT and NPT
- Needs special techniques to constrain some degrees of freedoms
- The consecutive configurations are very similar

- MD can move simple and complex systems the same way
- Same time step can be used for small or large systems
- Can generate kinetic data as well as thermodynamic data

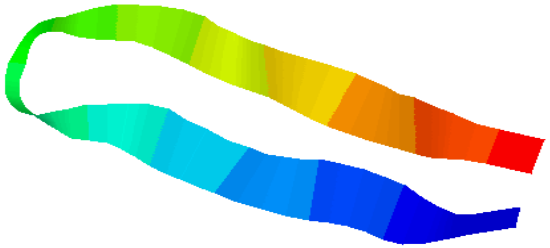
Outline

- Background of protein dynamics
- Basic computational methods
  - Molecular dynamics
  - Monte-Carlo Simulation
- Specific Applications

Example 1: (un)Folding a β-hairpin

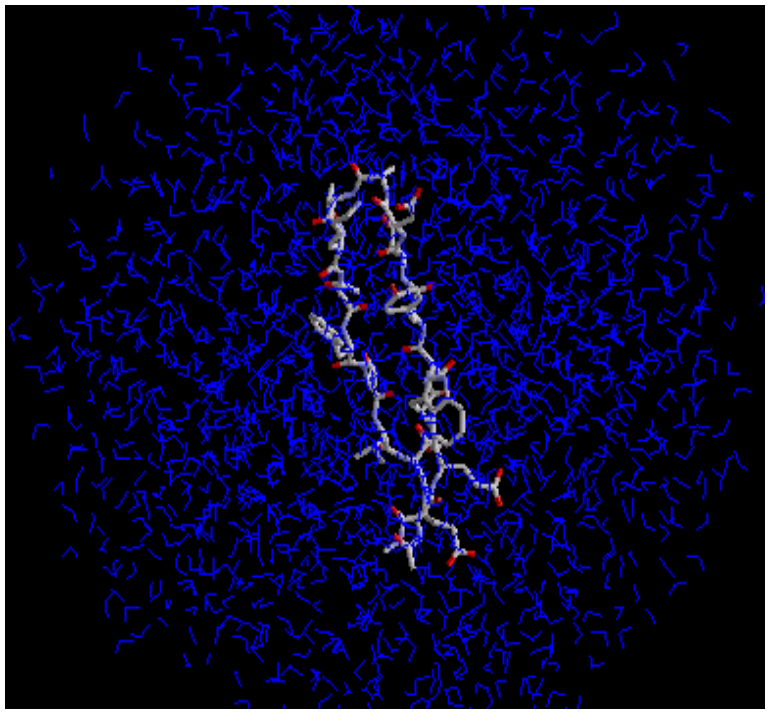


Protein G (2gb1)

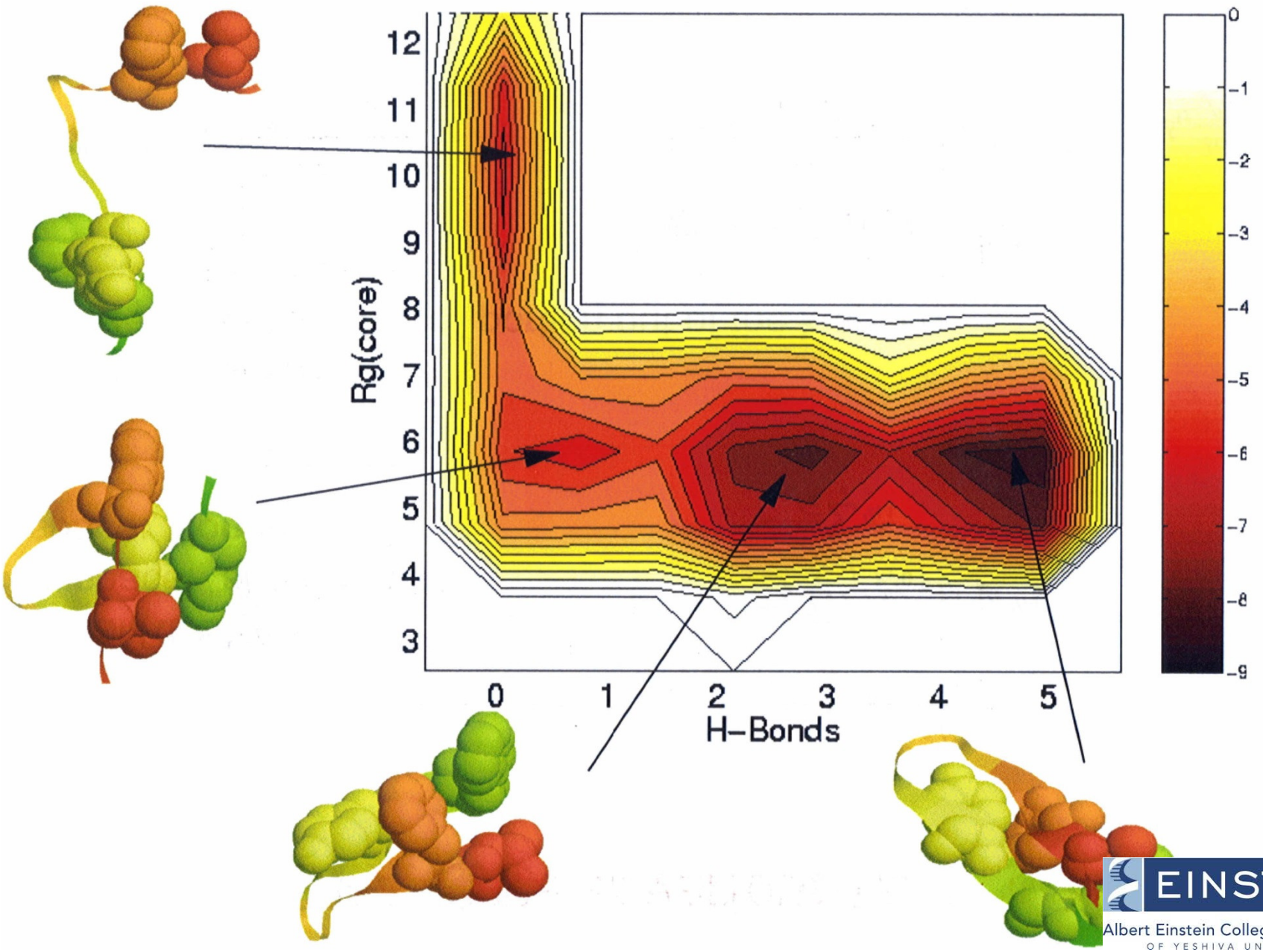


Res. 41-56

GEWTYDDATKTFTVTE



Free Energy Landscape in Explicit Solvent

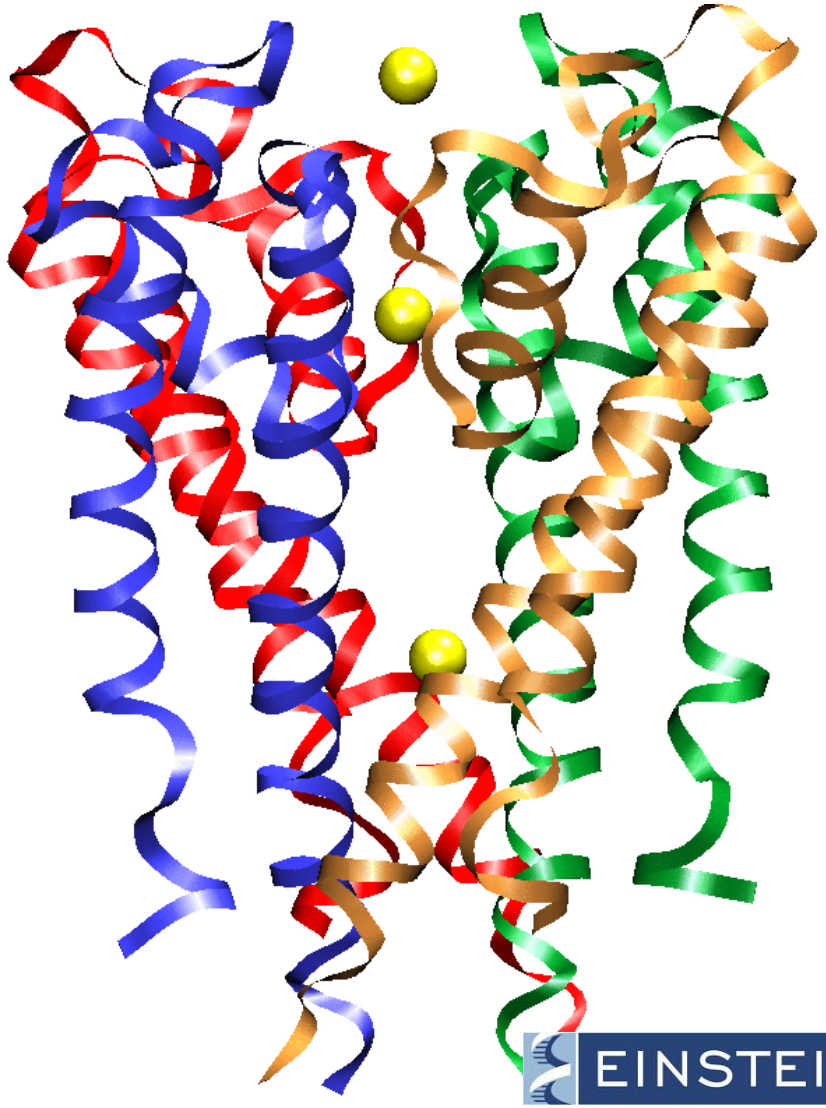


EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Example 2: MD Simulations of the K+ Channel Protein

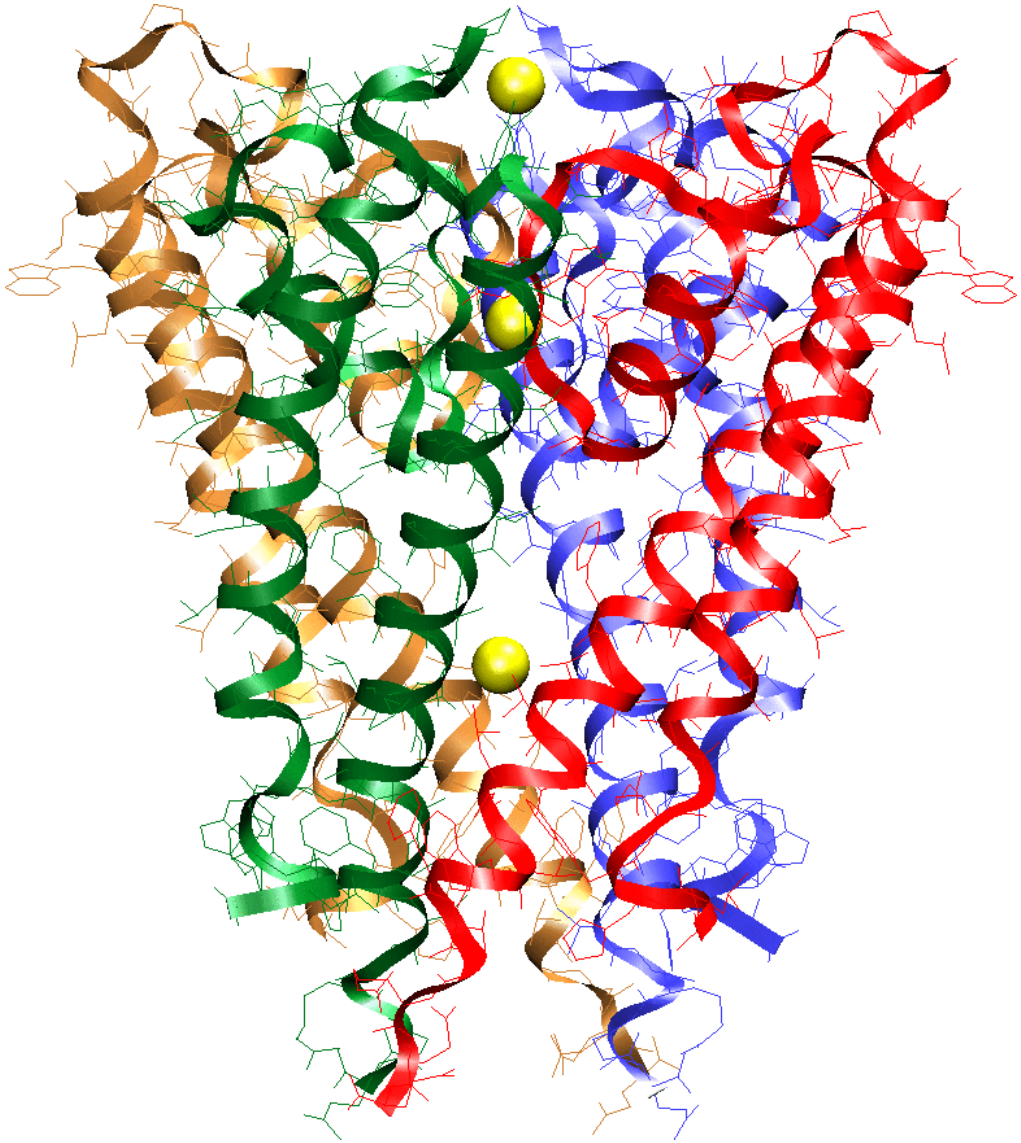
Ion channels are membrane - spanning proteins that form a pathway for the flux of inorganic ions across cell membranes.

Potassium channels are a particularly interesting class of ion channels, managing to distinguish with impressive fidelity between K^+ and Na^+ ions while maintaining a very high throughput of K^+ ions when gated.



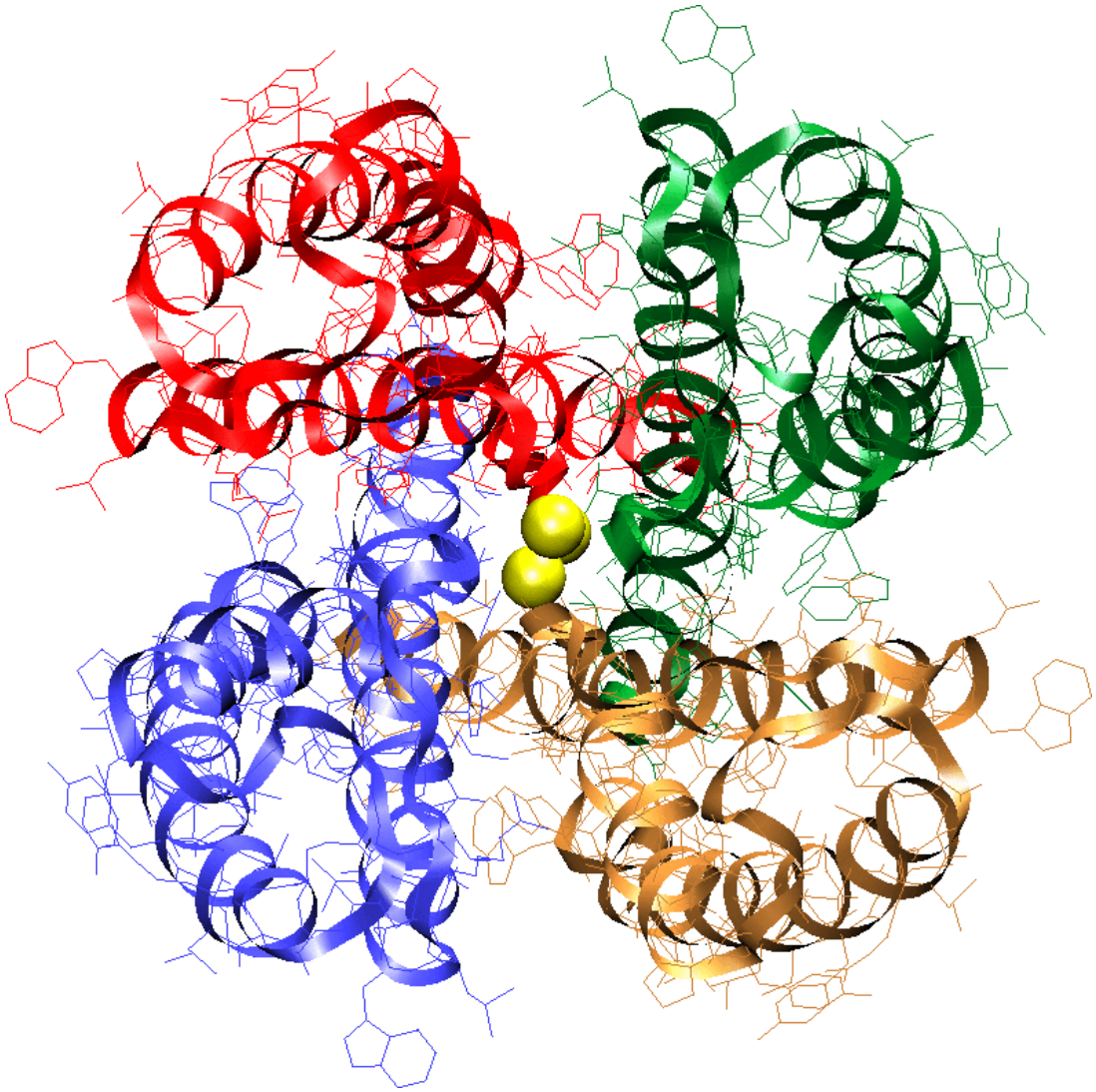
EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

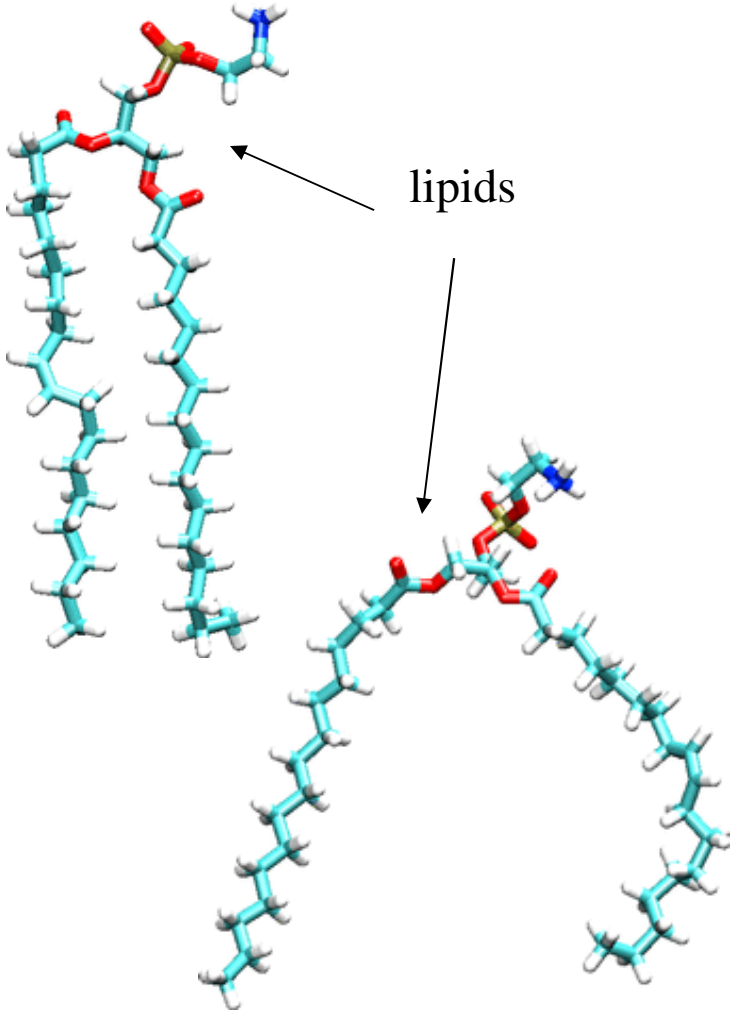
Setting up the system (1)



- retrieve the PDB (coordinates) file from the Protein Data Bank
- use topology and parameter files to set up the structure
- add hydrogen atoms using X-PLOR
- minimize the protein structure using NAMD2

Setting up the system (2)

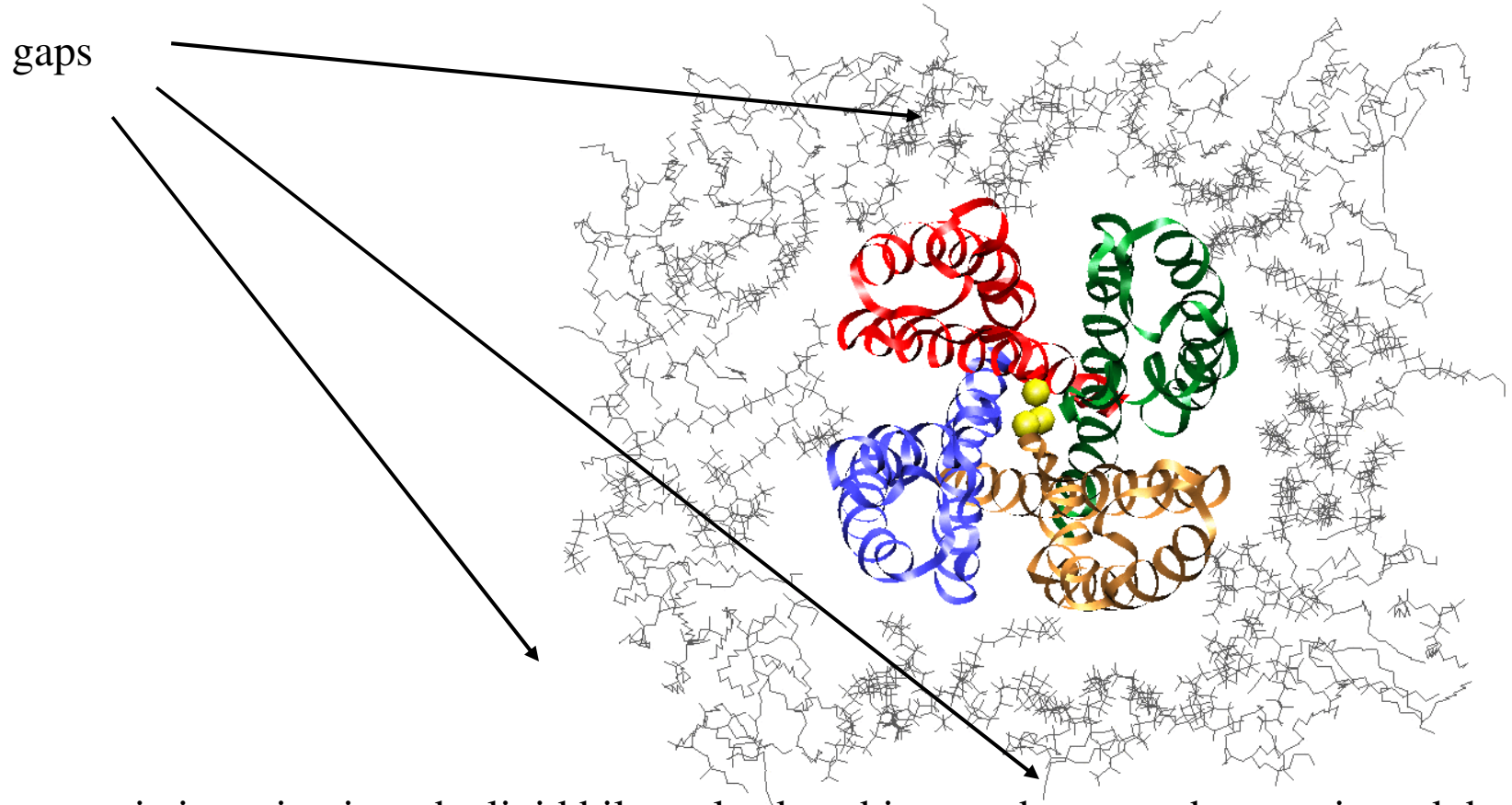




Simulate the protein in its natural environment: solvated lipid bila

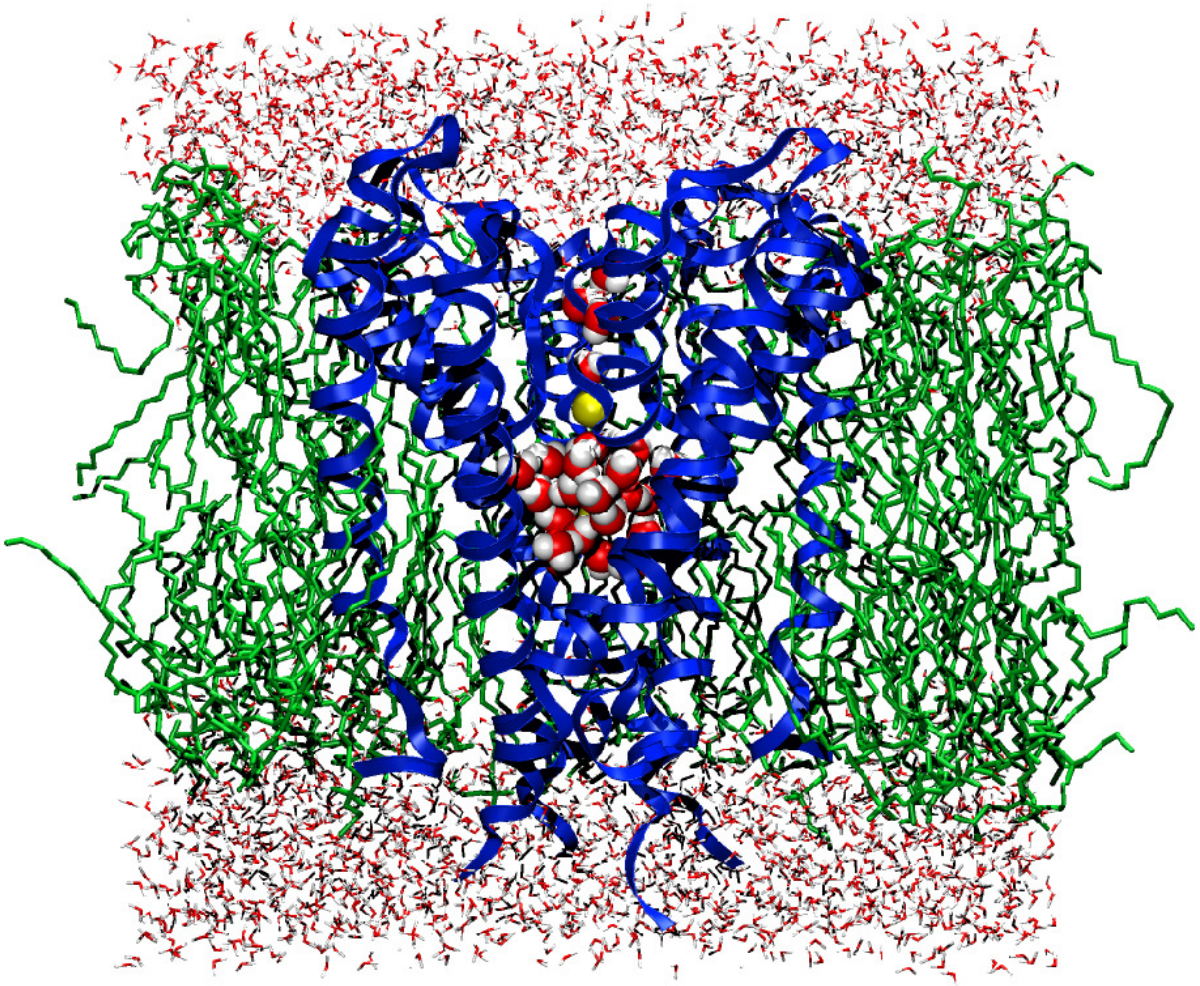
Setting up the system (3)

Inserting the protein in the lipid bilayer



Automatic insertion into the lipid bilayer leads to big gaps between the protein and the membrane => long equilibration time required to fill the gaps.
Solution: manually adjust the position of lipids around the protein

The system



solvent

Kcsa channel protein (in blue) embedded in a (3:1) POPE/POPG lipid bilayer. Water molecules inside the channel are shown in vdW representation.

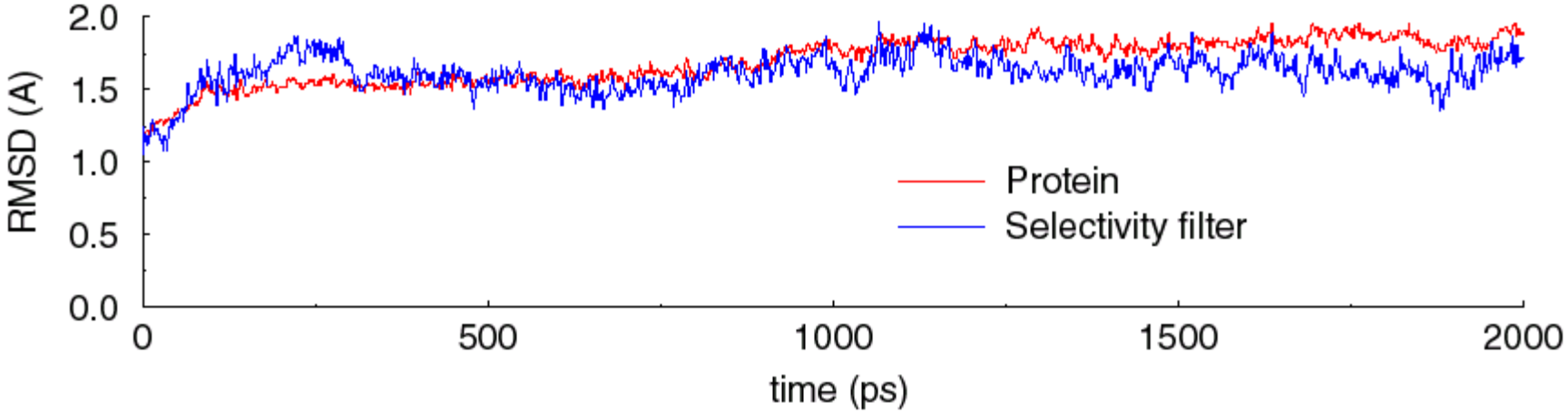
solvent

Simulating the system: Free MD

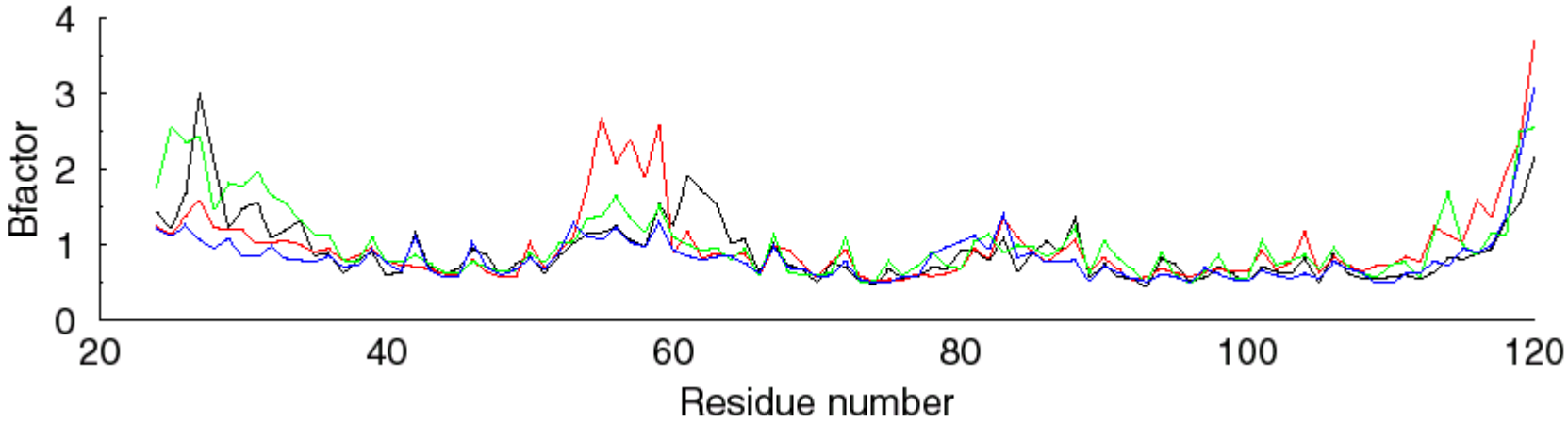
Summary of simulations:

- protein/membrane system contains 38,112 atoms, including 5117 water molecules, 100 POPE and 34 POPG lipids, plus K+ counterions
- CHARMM26 forcefield
- periodic boundary conditions, PME electrostatics
- 1 ns equilibration at 310K, NpT
- 2 ns dynamics, NpT

MD Results



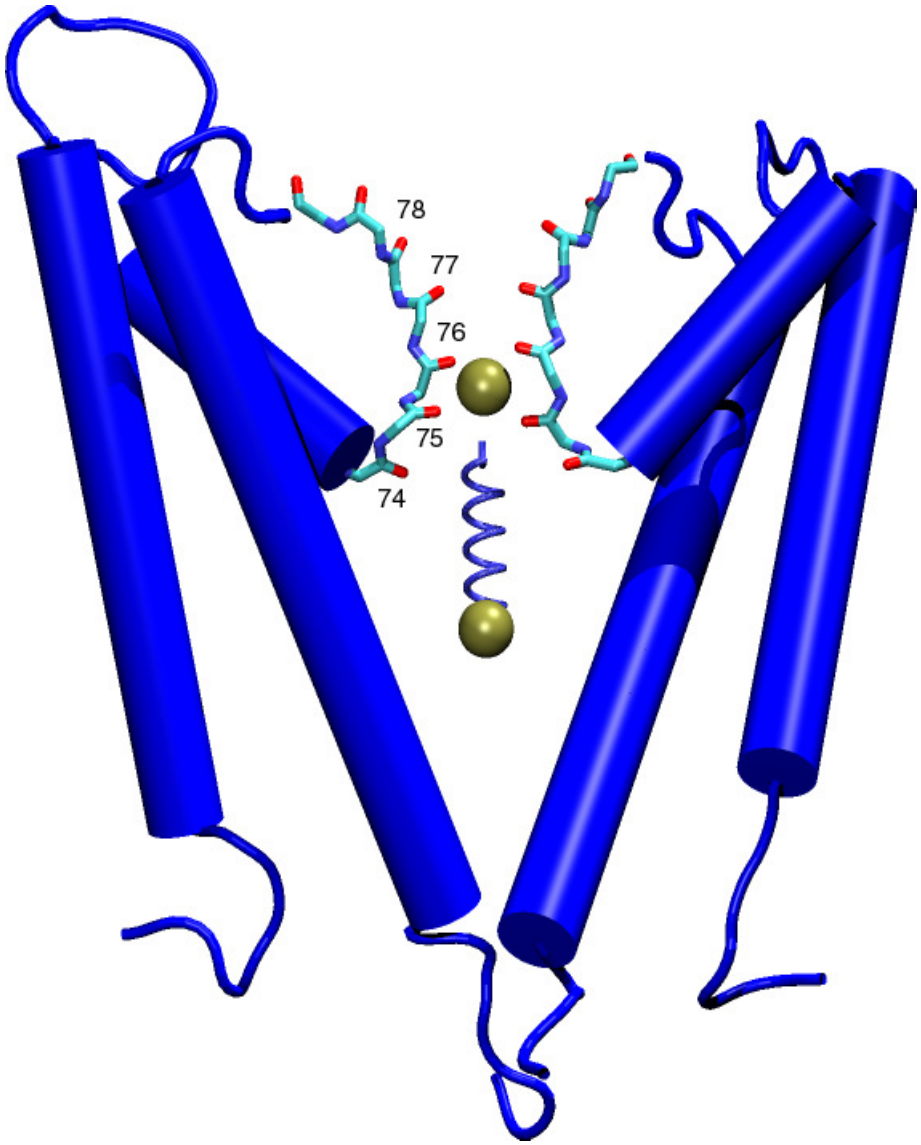
RMS deviations for the KcsA protein and its selectivity filer indicate that the protein is stable during the simulation with the selectivity filter the most stable part of the system.



Temperature factors for individual residues in the four monomers of the KcsA channel protein indicate that the most flexible parts of the protein are the N and C terminal ends, residues 52-60 and residues 84-90. Residues 74-80 in the selectivity filter have low temperature factors and are very stable during the simulation.

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Simulating the system: Steered Molecular Dynamics (SMD)

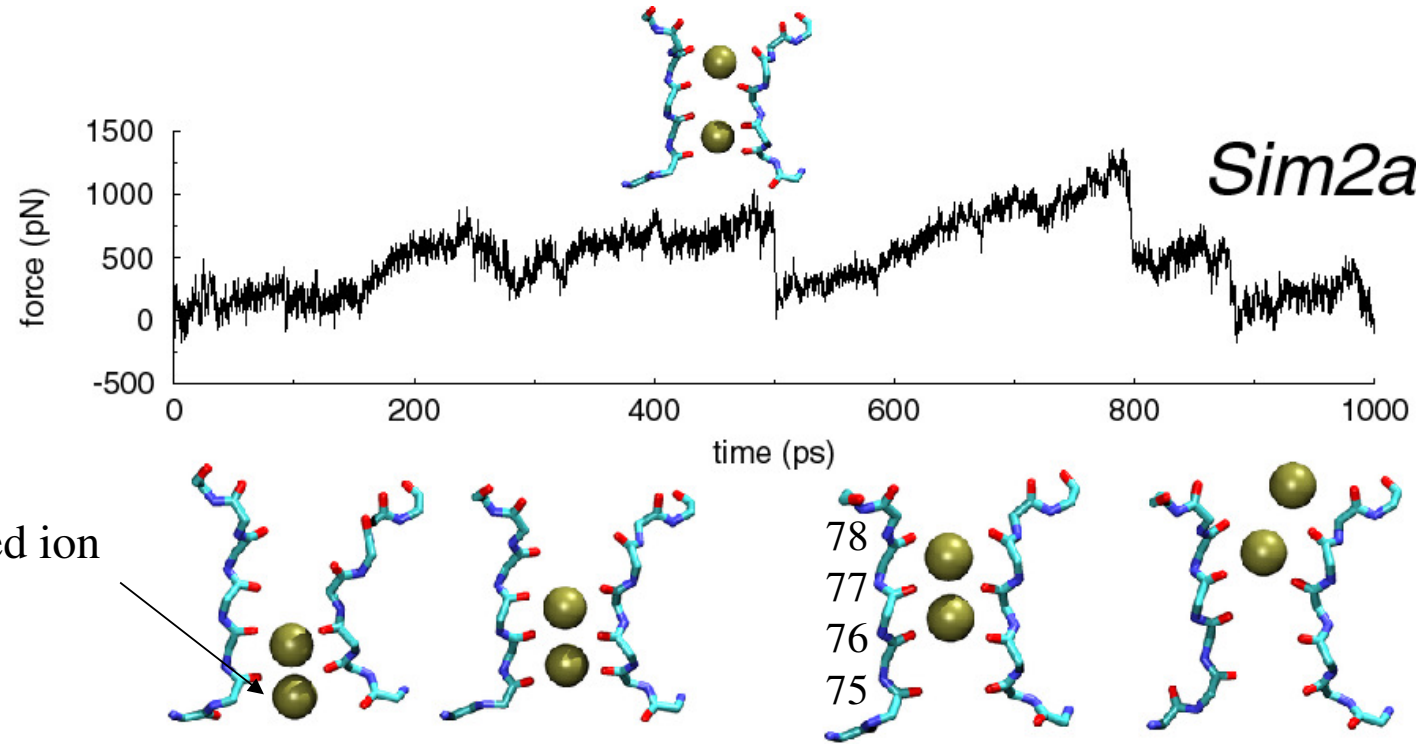


In SMD simulations an external force is applied to an atom or a group of atoms to accelerate processes, for example, passing of ions through a channel protein.

In the SMD simulations of the K channel, a moving, planar harmonic restraint, with a force constant of 21 kJ/mol/A, was applied to one of the ions in the channel. The restraint was applied along the z-axis only, allowing the ion to drift freely in the plane of the membrane. To avoid local heating caused by applied external forces, all heavy atoms were coupled to a Langevin heat bath with a coupling constant of 10/ps.

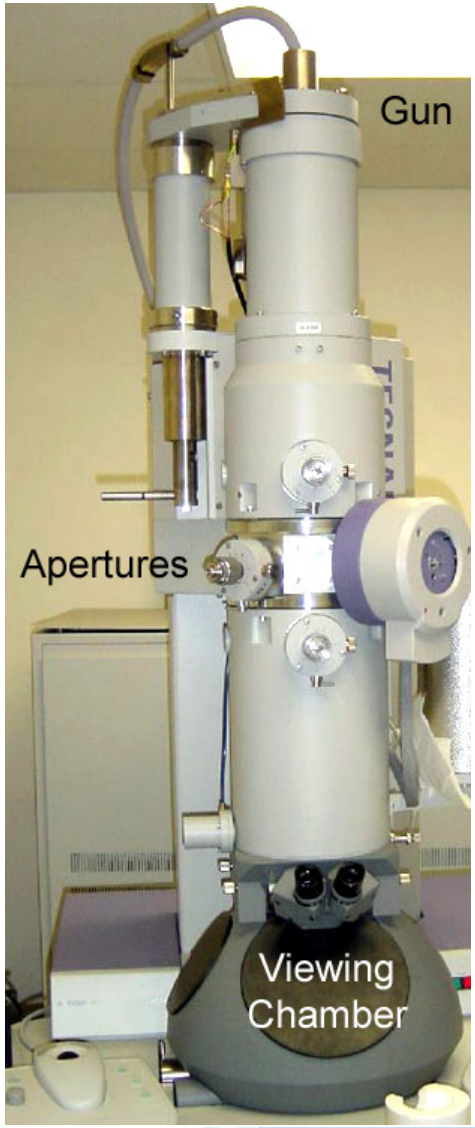
EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

SMD Results



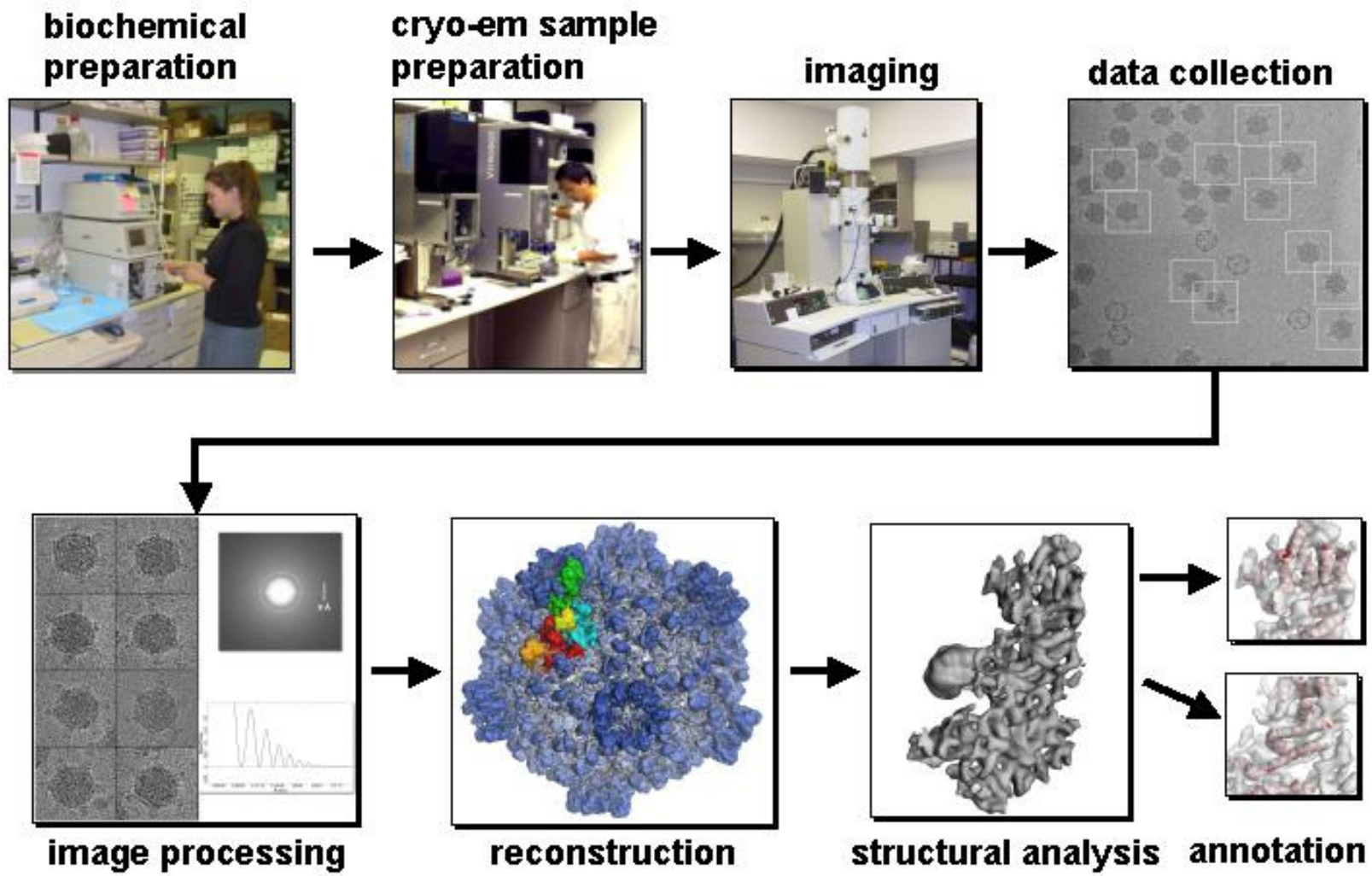
Example 3: EM-based Structural Refinement

- EM = (Transmission) Electron Microscopy
- Cryo EM = technique where biological samples are preserved in vitreous ice and imaged by EM at cryogenic temperatures.
- EM reconstruction = 3D maps are generated by averaging over many EM images.



EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

EM-based Structural Refinement

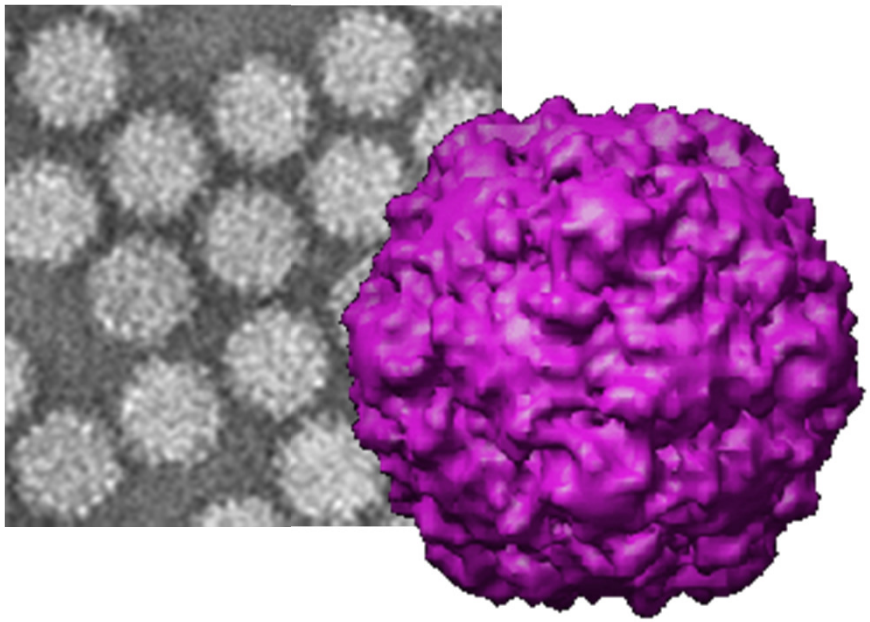


EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

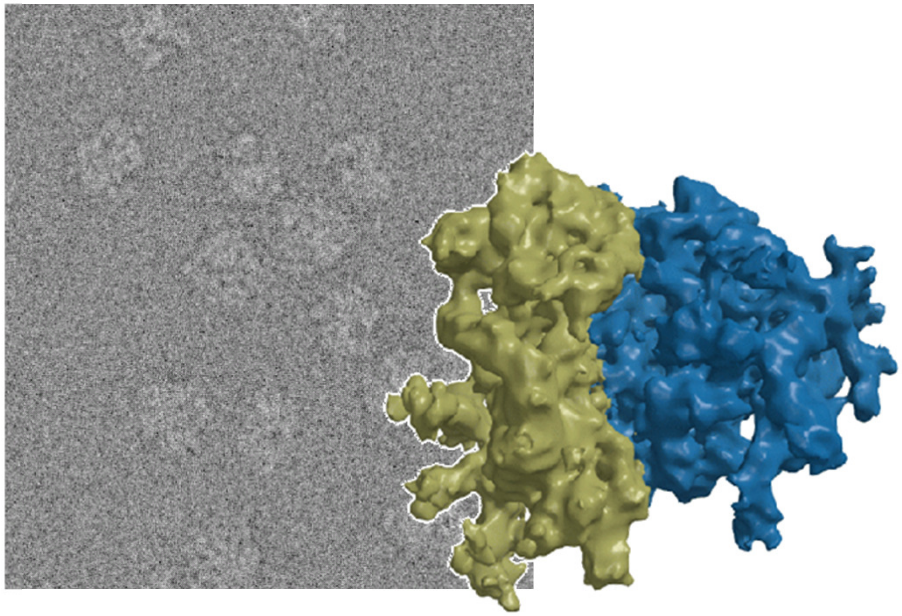
EM-based Structural Refinement

Sample Examples

Icosahedral virus



Ribosome



Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

EM-based Structural Refinement

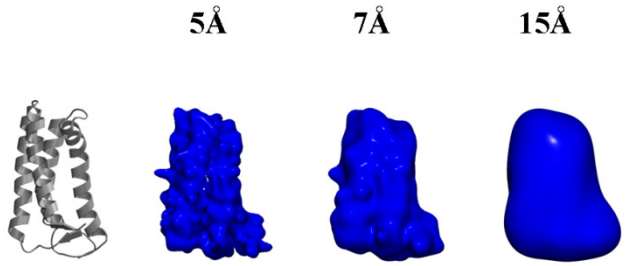
Sample Types

Type	Examples	Reconstruction Method	Typical resolution
Single particles	Icosahedral viruses, GroEL, ribosome	Single particle reconstruction	20-4 Å
Filaments	Flagella, filamentous viruses, actin, tubular crystals	Helical reconstruction	15-3 Å
2D crystals	Catalase, aquaporin, tubulin	2D electron crystallography	10-2 Å
Ensembles	HIV capsids	Electron Tomography	40-20 Å

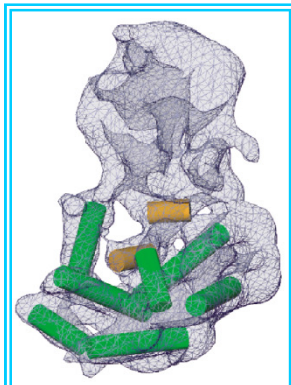
EM-based Structural Refinement

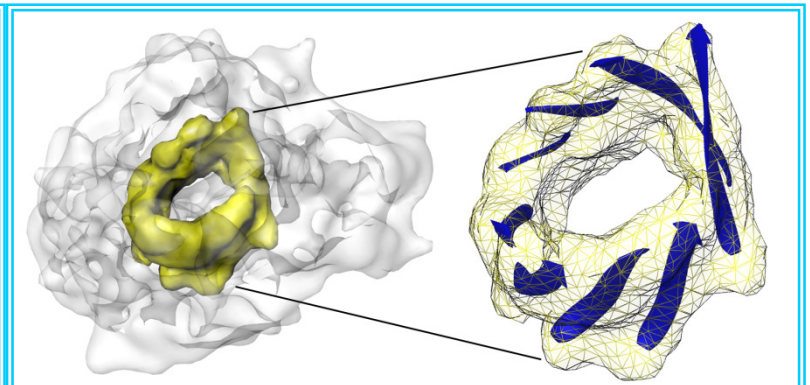
Background

Cryo-EM allows access to structural data on large flexible macromolecular assemblies which are likely to be difficult or impossible to crystallize.



✓ **Currently many density maps has the resolution of 6 to 10 Å.**





Helix-hunter

Sheet-miner

❖Major Disadvantage

✓Low Resolution

➢Only secondary structure elements and their skeletons could be extracted

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

EM-based Structural Refinement

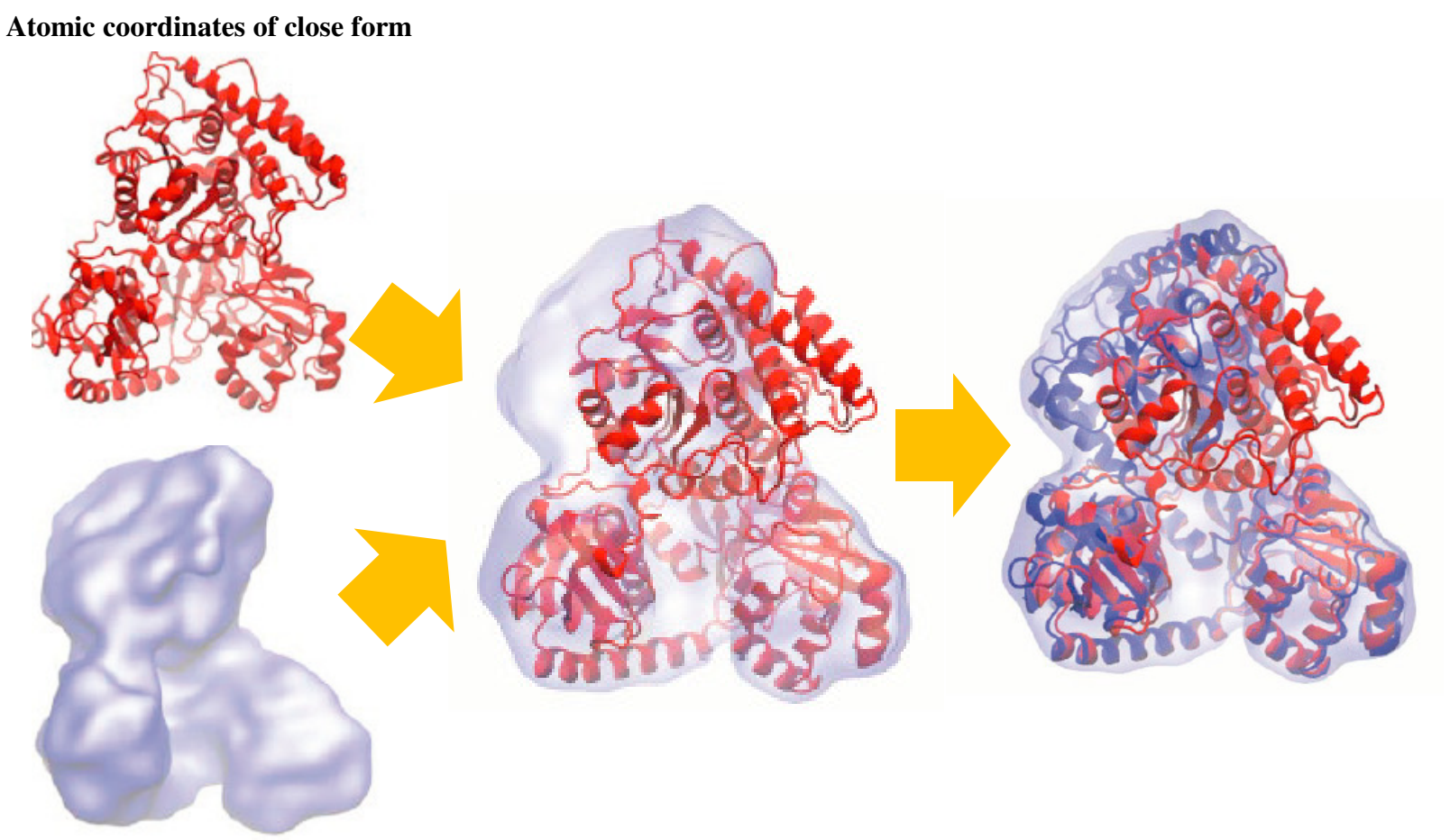
Structural Analysis

Methods to interpret higher resolution information from cryo EM map volumes:

- "segmentation" -- identifying different parts of the map
- "fitting" --placing atomic coordinates into the map, e.g., from X-ray structures
  - Molecular Dynamics Flexible Fitting (MDFF) (Schulten' Group, UIUC)

EM-based Structural Refinement

Molecular Dynamics Flexible Fitting (MDFF)



EM-based Structural Refinement

MDFF Algorithm

Two terms are added to the MD potential

$$U_{total} = U_{MD} + U_{EM} + U_{SS}$$

An external potential derived from the EM map is defined on a grid as

$$U_{EM}(\mathbf{R}) = \sum w_j V_{EM}(\mathbf{r}_j)$$

$$V_{EM}(\mathbf{r}) = \begin{cases} \xi \left(1 - \frac{\Phi(\mathbf{r}) - \Phi_{thr}}{\Phi_{max} - \Phi_{thr}}\right) & \text{if } \Phi(\mathbf{r}) \geq \Phi_{thr}, \\ \xi & \text{if } \Phi(\mathbf{r}) < \Phi_{thr}. \end{cases}$$

A mass-weighted force is then applied to each atom

$$\mathbf{f}_i^{EM} = -\nabla U_{EM}(\mathbf{R}) = -w_i \partial V_{EM}(\mathbf{r}_i)/\partial r_i$$

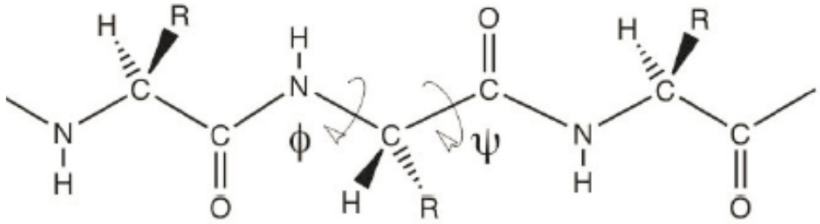
EM-based Structural Refinement

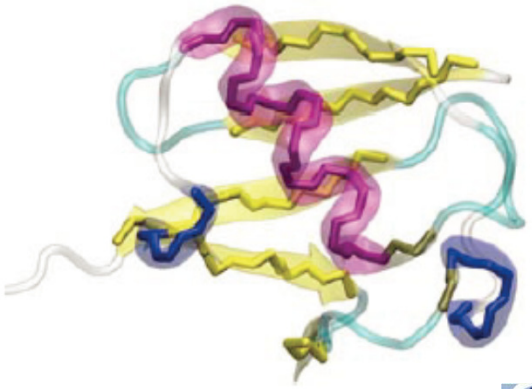
MDFF Algorithm

Protein Restraints

Harmonic restraints are applied to ϕ and ψ dihedral angles of amino acid residues in helices or β strands:

$$U_{restrain} = \frac{k}{2}\sum_i [(\phi_i - \phi_i^0)^2 + (\psi_i - \psi_i^0)^2]$$



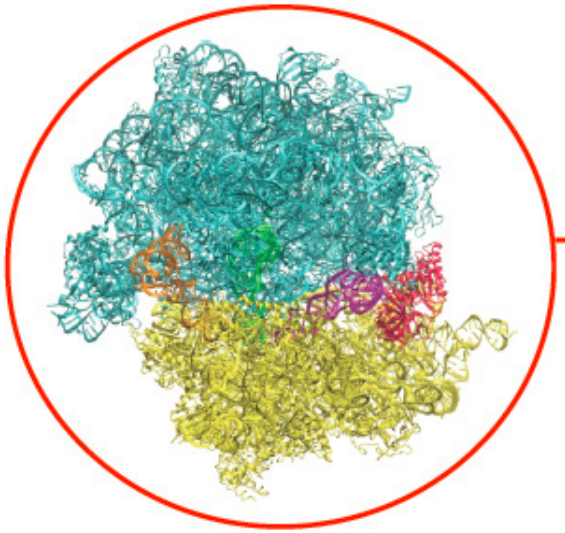


EM-based Structural Refinement

Application to Ribosome

X-ray crystallography

High resolution (3-5Å)
Crystal packing makes it difficult to determine functional state

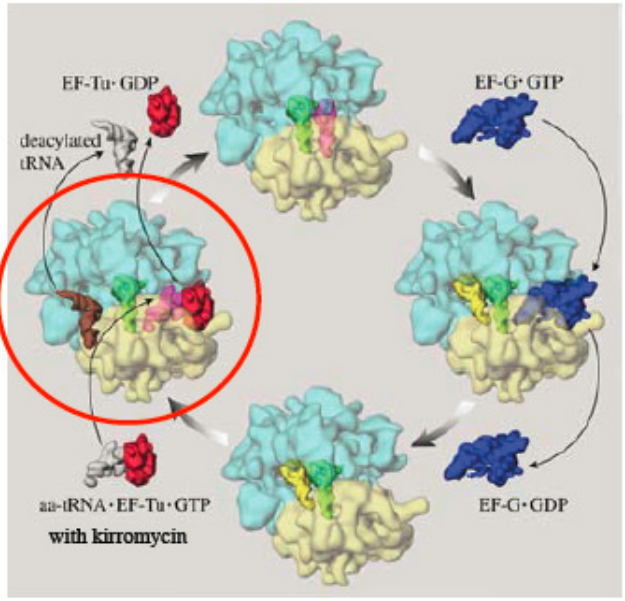


Crystal structures of ribosome and ligands

30S and 50S from 2I2U/2I2V (Berk et al., 2006); L1 protuberance based on 1MZP (Nikulin et al., 2003); L1 protein using MODELLER (Sali and Blundell, 1993) with 1ZHO as template (Nevskaya et al., 2006); A-site finger using 1TWB (Tung and Sanbonmatsu, 2004) as template; tRNAs from Selmer et al., 2006; ternary complex from 1OB2 (P.Nissen ,unpublished)

Cryo-EM

Lower resolution (typically 8-12Å)
Many functional states can be obtained

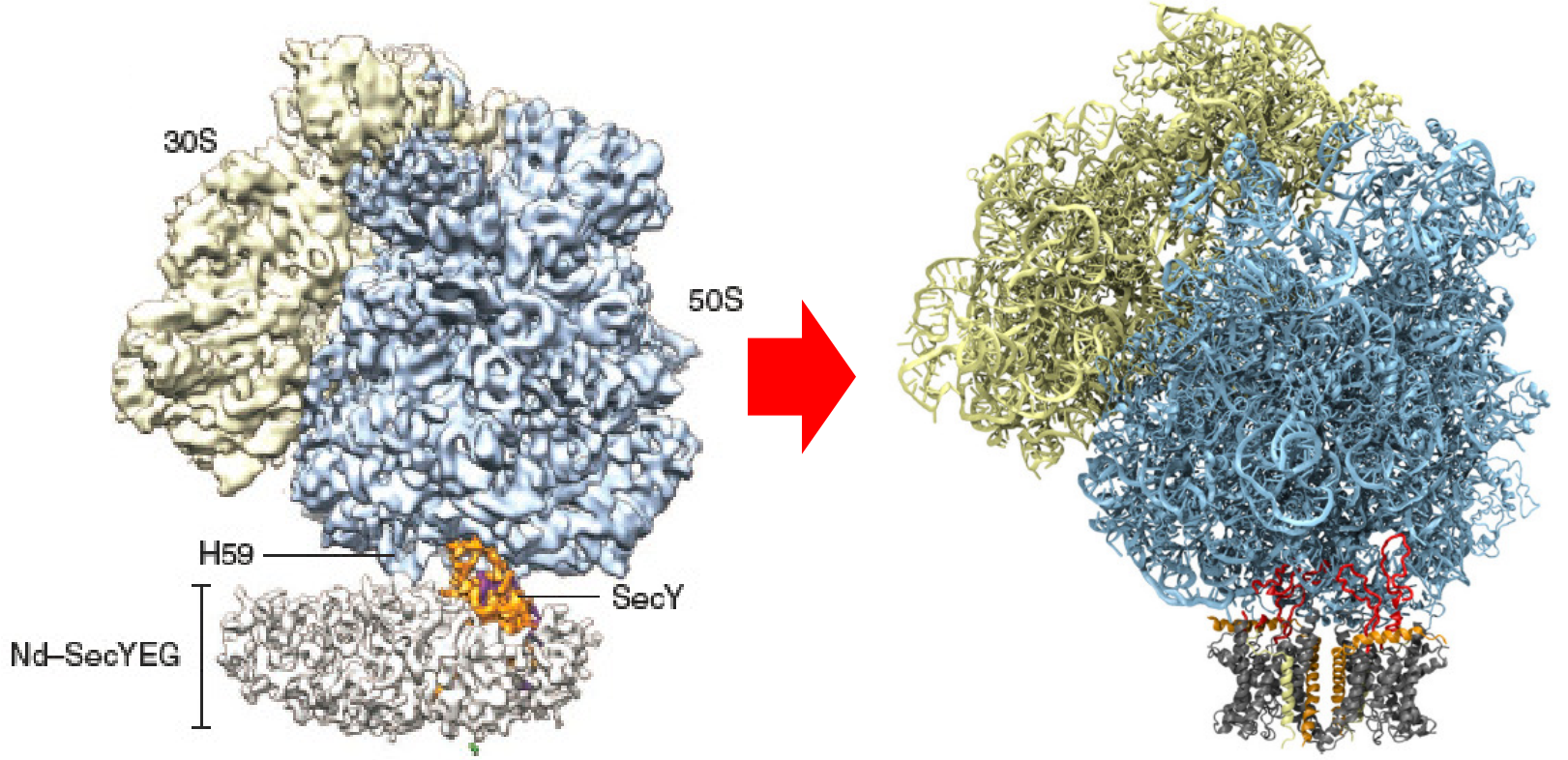


Structures of the ribosome at different stages of the elongation cycle obtained by Cryo-EM

(J. Frank. The dynamics of the Ribosome inferred from Cryo-EM, in Conformational Proteomics of Macromolecular Architectures, 2004)

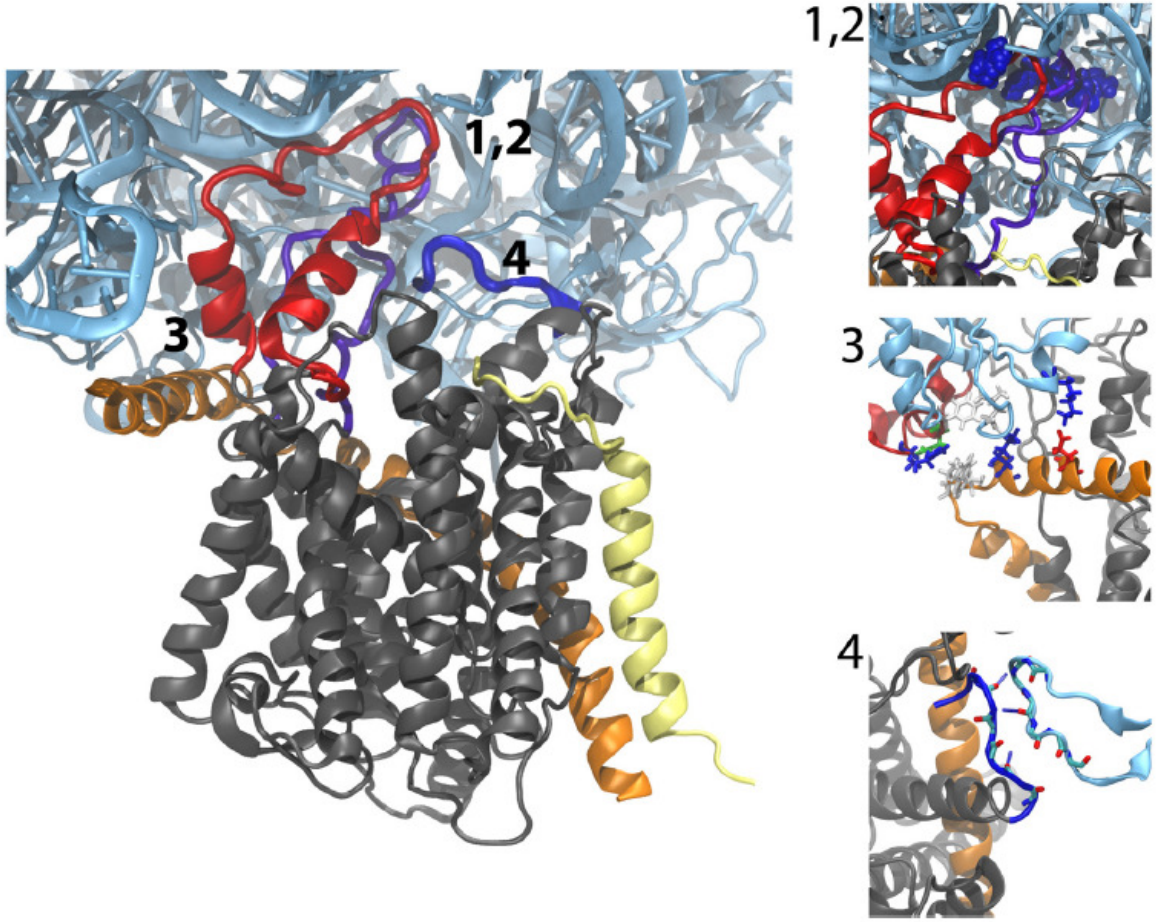
EM-based Structural Refinement

Modeling results: ribosome complex with a membrane-bound channel



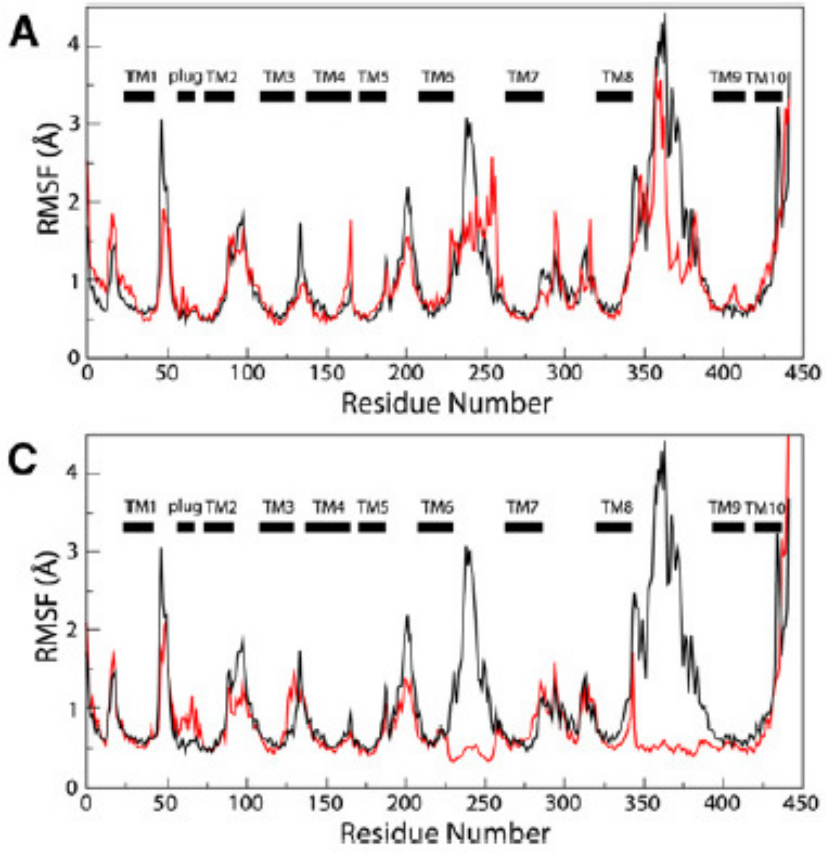
EM-based Structural Refinement

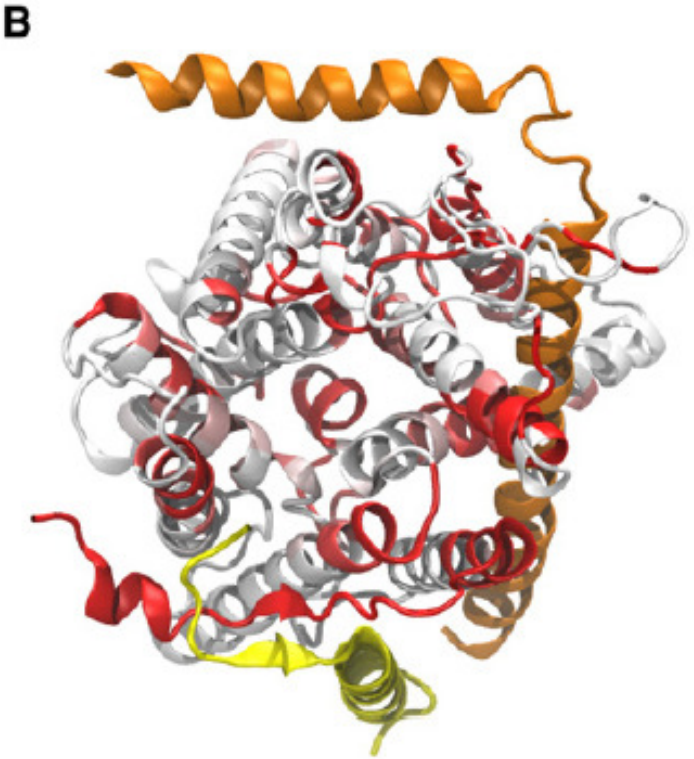
Modeling results: interface between ribosome and channel



EM-based Structural Refinement

Modeling Results: interface between ribosome and channel





EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

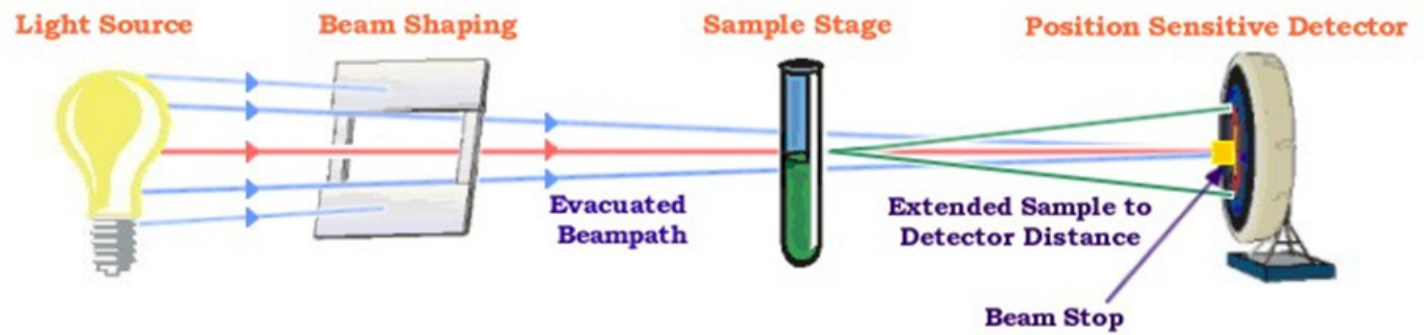
EM-based Structural Refinement

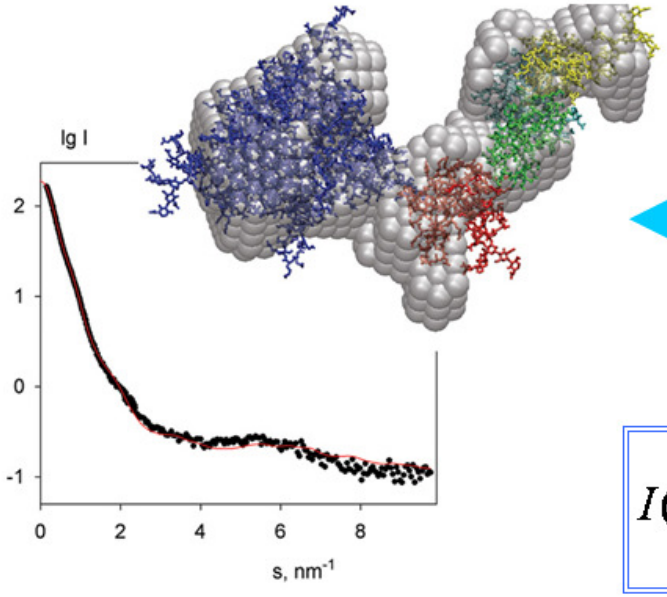
Conclusions

- The flexible fitting of the crystal structures of the ribosome and channel to a cryo-EM map produce an atomic model in agreement with the physiological state of the complex in the cryo-EM experiments.
- The modeling results revealed not only the atomic-level details of the interactions between the ribosome and the channel, but also how the ribosome can prepare the channel for translocation.
- The results support the idea that the monomeric SecY is the functional channel. The channel is well positioned below the ribosome to receive the exiting polypeptide chain

Example 4: SAXS-based Structural Modeling of multi-domain proteins

Background: Small Angle X-ray Scattering





$$I(s) = \sum_{i=1}^{N} \sum_{j=1}^{N} f_i(s) f_j(s) \frac{\sin(sr_{ij})}{sr_{ij}}$$

Source: http://www.physics.queensu.ca/~marsha/SAXSoverview.html

Background: Small Angle X-ray Scattering

- ✓Easy sample preparation: no crystals needed
  - — Study native proteins in near-physiological conditions
- ✓Fast data collection and analysis
  - — Enable high-throughput studies

The major bottleneck of SAXS lies in the random orientation of dissolved molecules which leads to the loss of high resolution information

SAXS-aided Structural Modeling

Beyond tertiary structures

The structural information from SAXS is taken from samples in solution

More fuzzy than crystallography, but on the other hand, more function related

This also means that SAXS can also provide the information of dynamic protein complex

Example: multi-domain assembled states of protein complex in solution

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

SAXS-aided Structural Modeling

Application: Hck tyrosine kinase (Roux's group 2010)

- All Src kinases share a common structural organization comprising the SH3 and SH2 binding domains followed by a highly conserved catalytic domain connected by flexible linkers
- Spatial organization of a large and flexible multi-domain macromolecular complex is very hard to probe
- The protein is expected to display substantial conformational dynamics, giving rise to a large number of possible conformations separated by small energy differences.
- Capturing any of those in a crystallographic state would be inherently difficult.
- Ideally one would like to observe the protein conformation in solution, where it is not affected by lattice packing.
- In principle, small angle X-ray solution scattering (SAXS) is an experimental technique that can be used for mapping the three-dimensional organization of multi-domain proteins in solution.

SAXS-aided Structural Modeling

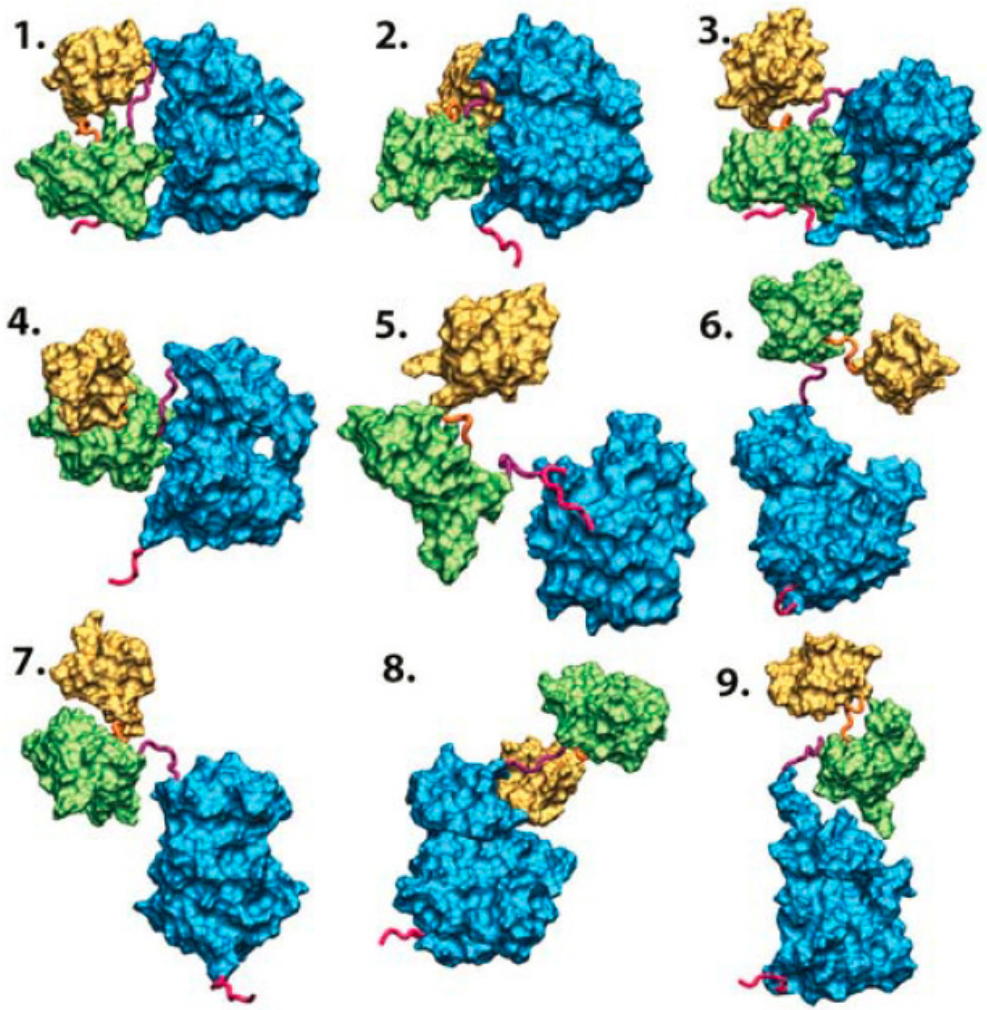
The Hck tyrosine kinase domain assembly: algorithm

- MD simulations are used to extensively explore and sample the accessible conformational space of the multi-domain complex.

- The configurations are clustered into a small number of distinct putative assembly states.

SAXS-aided Structural Modeling

The Hck tyrosine kinase domain assembly: algorithm



Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

SAXS-aided Structural Modeling

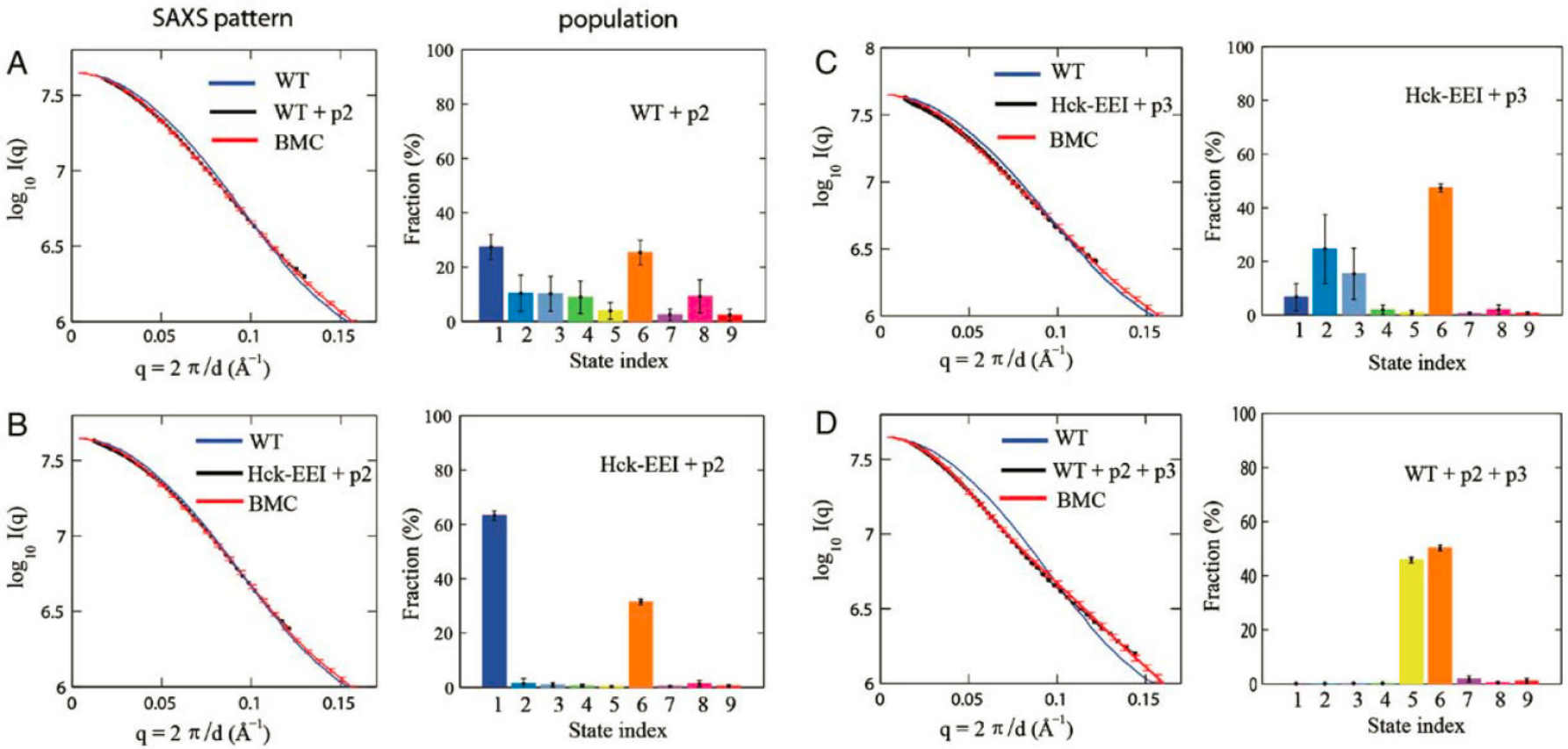
The Hck tyrosine kinase domain assembly: algorithm

- These clusters are then used as a basis-set to analyze SAXS data.

- Comparison of the calculated SAXS patterns from all these assembly states with experimental data makes it possible to determine the population fraction of each state of Hck under various conditions.

SAXS-aided Structural Modeling

The Hck tyrosine kinase domain assembly: algorithm



SAXS-aided Structural Modeling

Conclusions

- Small angle scattering data itself only include low-resolution structural information about molecule envelop, due to the limitation of angular average during the experiment in solution.

- Combining with computational approaches, SAXS offers a complementary and powerful approach to characterize multi-domain molecular assemblies or protein complex aggregation in solution, especially when multiple conformations can coexist.

Summary

- Background of protein dynamics
- Basic computational methods
  - Molecular dynamics
  - Monte-Carlo Simulation
- Specific Applications