タンパク質の分子動力学計算
分子機械の機能をどこまで明らかにできるか

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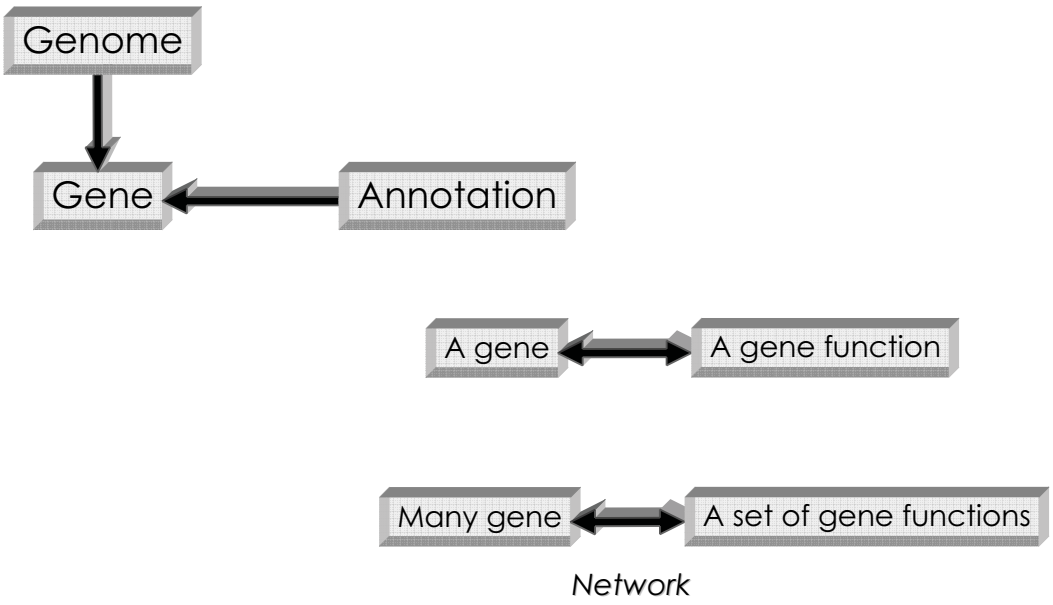
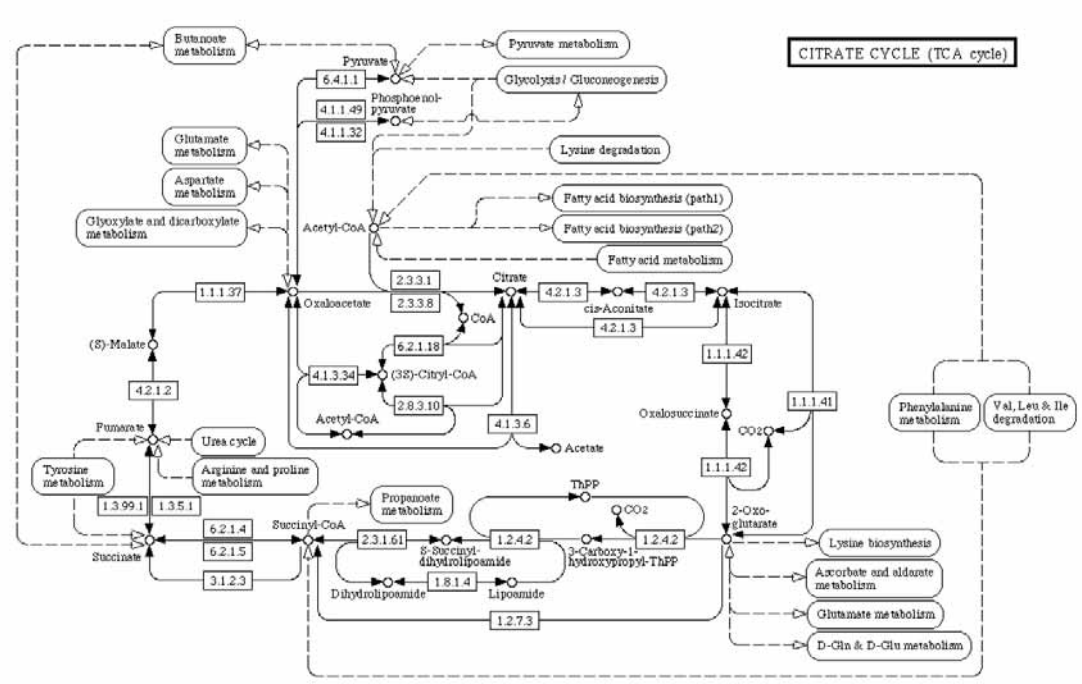
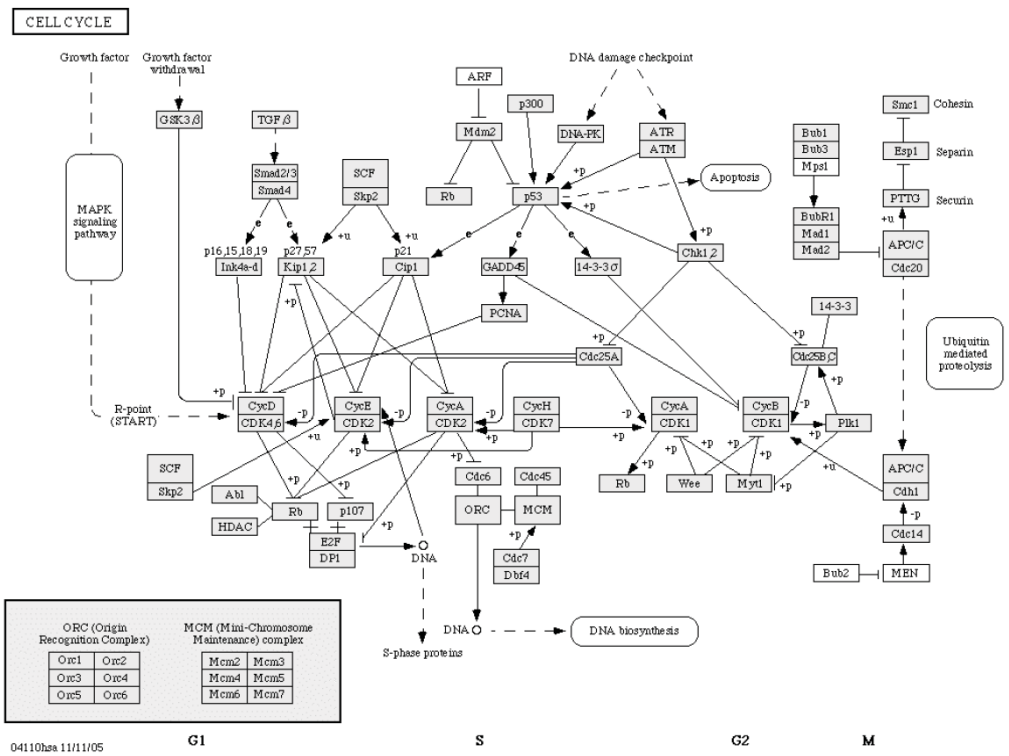
Paradigm of Biology

Molecular Biology

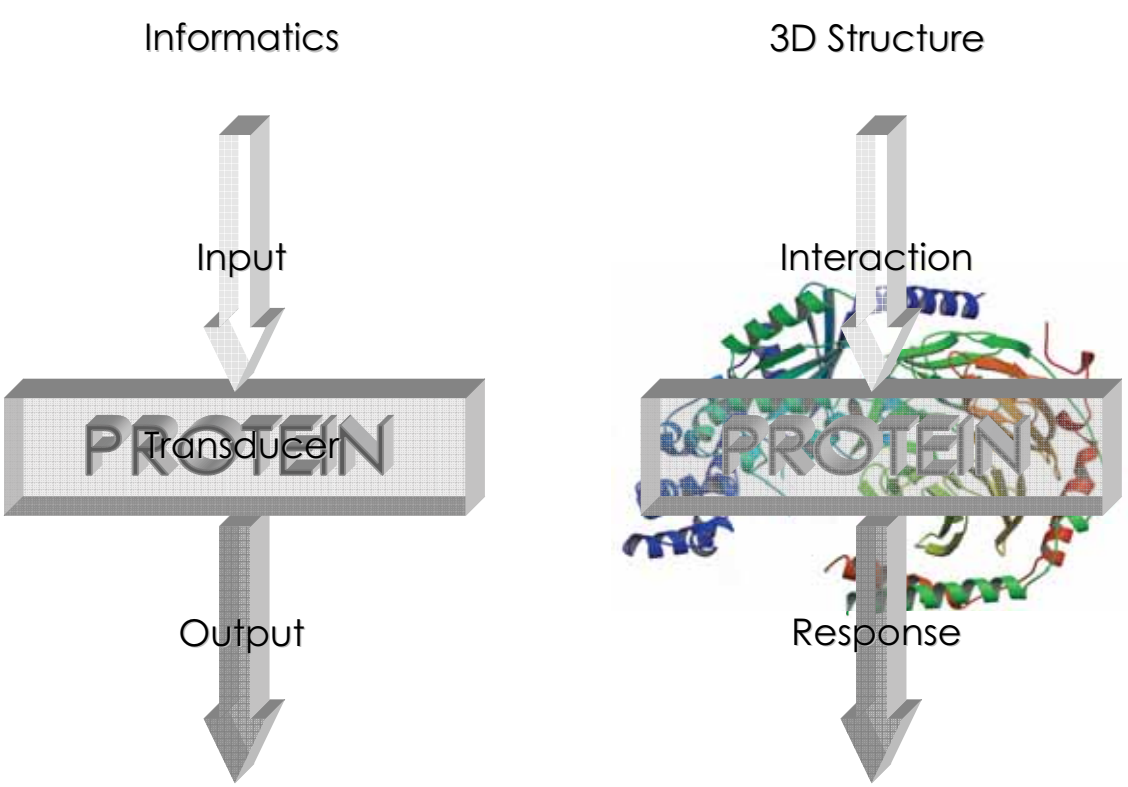


KEGG


CITRATE CYCLE (TCA cycle)
Butanoate metabolism
Pyruvate metabolism
Pyruvate
6.4.1.1
Glycolysis / Gluconeogenesis
Phosphoenol-pyruvate
4.1.1.49
4.1.1.32
Glutamate metabolism
Aspartate metabolism
Glyoxylate and dicarboxylate metabolism
Lysine degradation
Fatty acid biosynthesis (path1)
Fatty acid biosynthesis (path2)
Fatty acid metabolism
Acetyl-CoA
2.3.3.1
2.3.3.8
Citrate
4.2.1.3
cis-Aconitate
Isocitrate
1.1.1.37
Oxaloacetate
CoA
6.2.1.18
(S)-Malate
4.2.1.2
4.1.3.34
(3S)-Citryl-CoA
2.8.3.10
Acetyl-CoA
4.1.3.6
Acetate
1.1.1.42
Oxalosuccinate
1.1.1.41
CO2
Phenylalanine metabolism
Val, Leu & Ile degradation
Fumarate
Urea cycle
Arginine and proline metabolism
Tyrosine metabolism
1.3.99.1
1.3.5.1
Propanoate metabolism
ThPP
CO2
2-Oxo-glutarate
6.2.1.4
6.2.1.5
3.1.2.3
Succinyl-CoA
2.3.1.61
1.2.4.2
S-Succinyl-dihydrolipoamide
3-Carboxy-1-hydroxypropyl-ThPP
1.2.4.2
Succinate
Dihydrolipoamide
1.8.1.4
Lipoamide
1.2.7.3
Lysine biosynthesis
Ascorbate and aldarate metabolism
Glutamate metabolism
D-Gln & D-Glu metabolism


CELL CYCLE
Growth factor
Growth factor withdrawal
DNA damage checkpoint
ARF
p300
Mdm2
DNA-PK
ATR
ATM
GSK3β
TGFβ
Smad2/3
Smad4
SCF
Skp2
Rb
p53
Apoptosis
MAPK signaling pathway
p16,15,18,19
Ink4a-d
p27,57
Kip1,2
p21
Cip1
GADD45
14-3-3σ
Chk1,2
PCNA
Cdc25A
Cdc25B,C
14-3-3
Bub1
Bub3
Mps1
BubR1
Mad1
Mad2
Smc1
Cohesin
Esp1
Separin
PTTG
Securin
APC/C
Cdc20
Ubiquitin mediated proteolysis
R-point (START)
CycD
CDK4,6
CycE
CDK2
CycA
CDK2
CycH
CDK7
CycA
CDK1
CycB
CDK1
Plk1
SCF
Skp2
Abl
HDAC
Rb
p107
E2F
DP1
Cdc6
Cdc45
ORC
MCM
Cdc7
Dbf4
DNA
Rb
Wee
Myt1
APC/C
Cdh1
Cdc14
Bub2
MEN
ORC (Origin Recognition Complex)
Orc1
Orc2
Orc3
Orc4
Orc5
Orc6
MCM (Mini-Chromosome Maintenance) complex
Mcm2
Mcm3
Mcm4
Mcm5
Mcm6
Mcm7
DNA
DNA biosynthesis
S-phase proteins
04110hsa 11/11/05
G1
S
G2
M

Elementary Process



Protein Functions

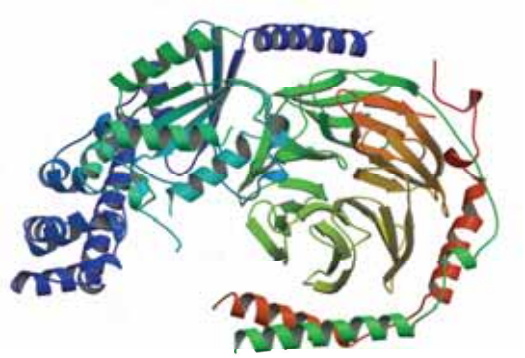
from the viewpoints of structures

"A series of structure changes and accompanying chemical reactions initiated as a response to the external interactions"

1. Interactions
2. Structural Changes ⟸ Static 3D Structures
3. Chemical Reactions

Protein Folding

Unique Correspondence between Structure and Function



Biological problems
- translation
- translocation
- coupling with interactions
- chaperons
- diseases

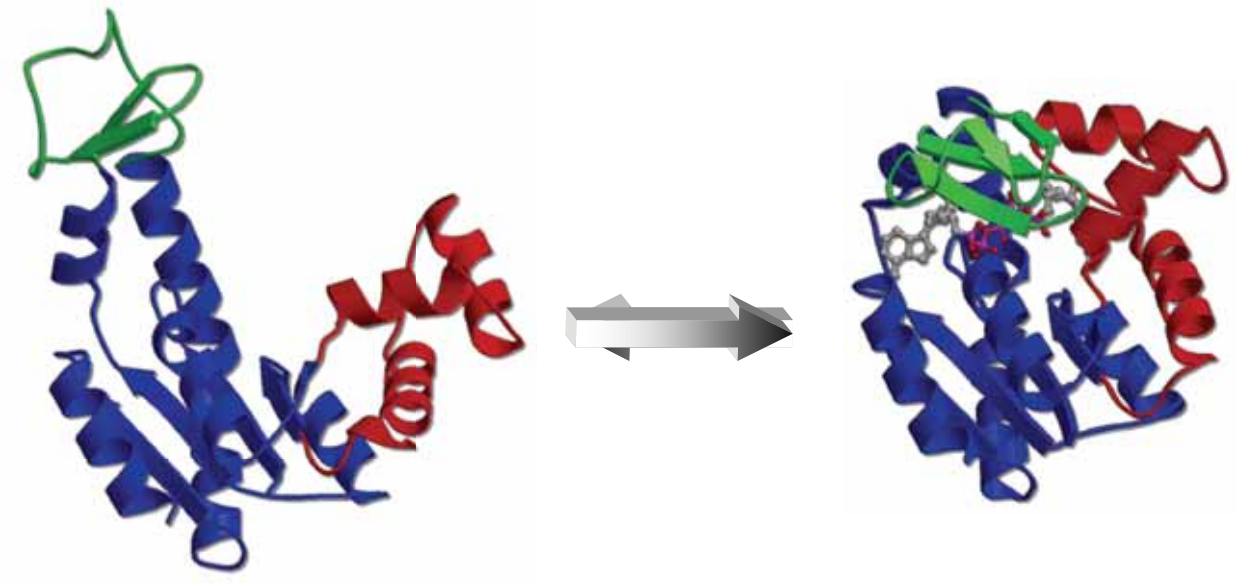
Physical problems

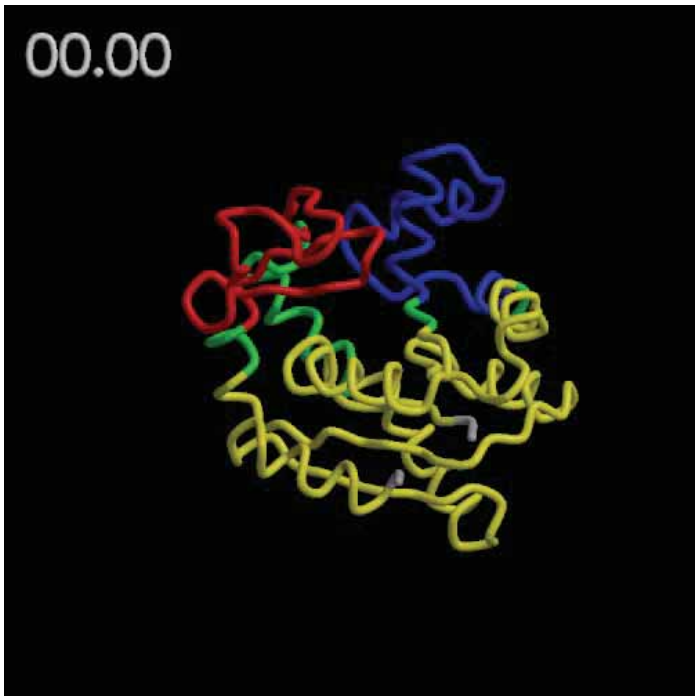
計算速度の限界 ⟷ 機能発現の時間スケール

1. シミュレーションの時間内に生起する機能
2. 長時間の振る舞いについてのモデル
3. 特殊なサンプリング法

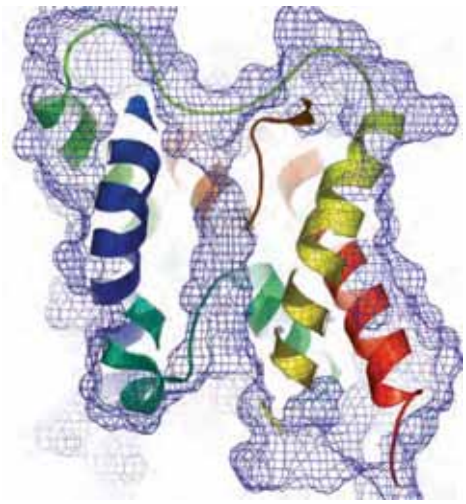
1．シミュレーションの時間内に生起する機能

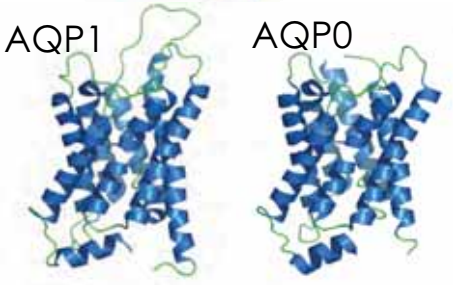
Structural Change of Adenylate Kinase

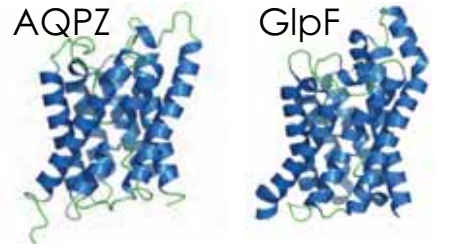




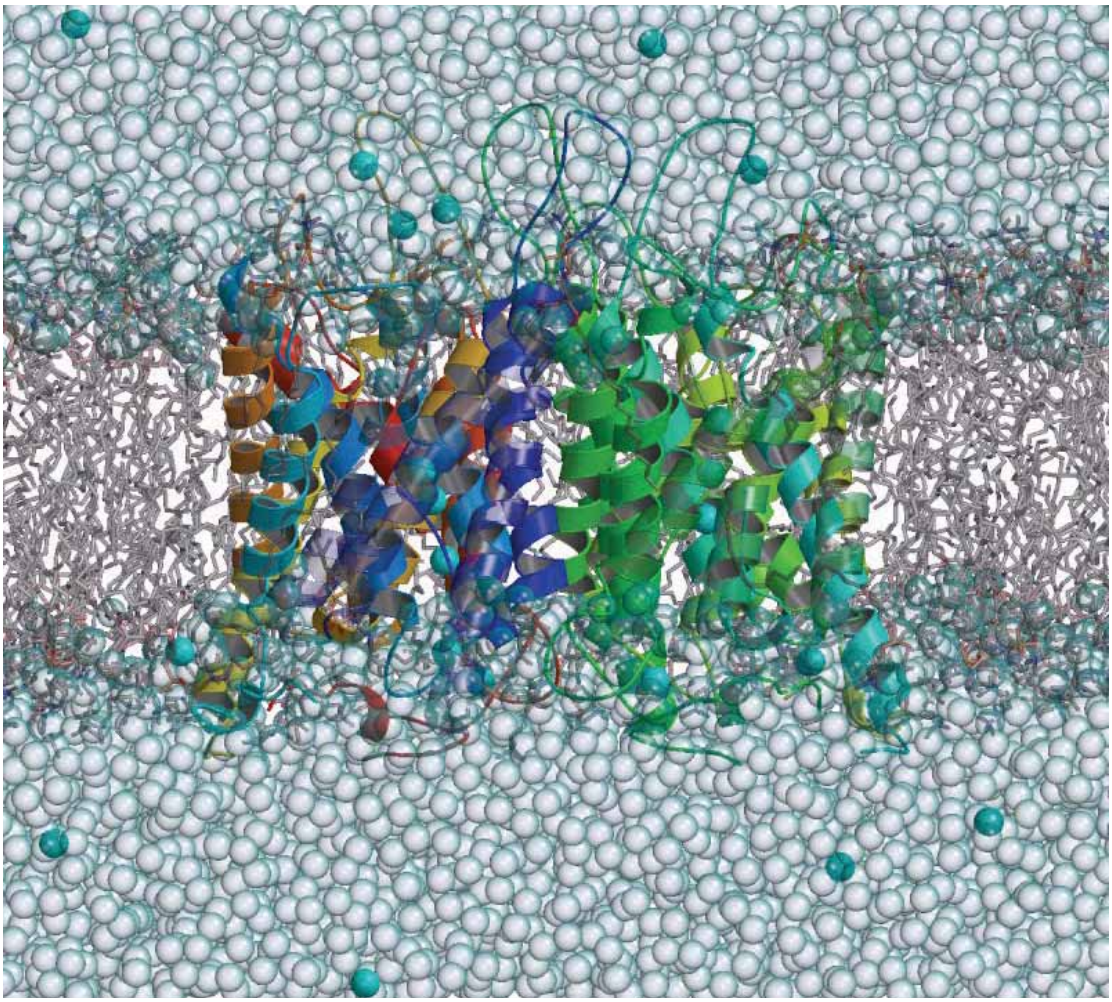
Water Transport in Aquaporin



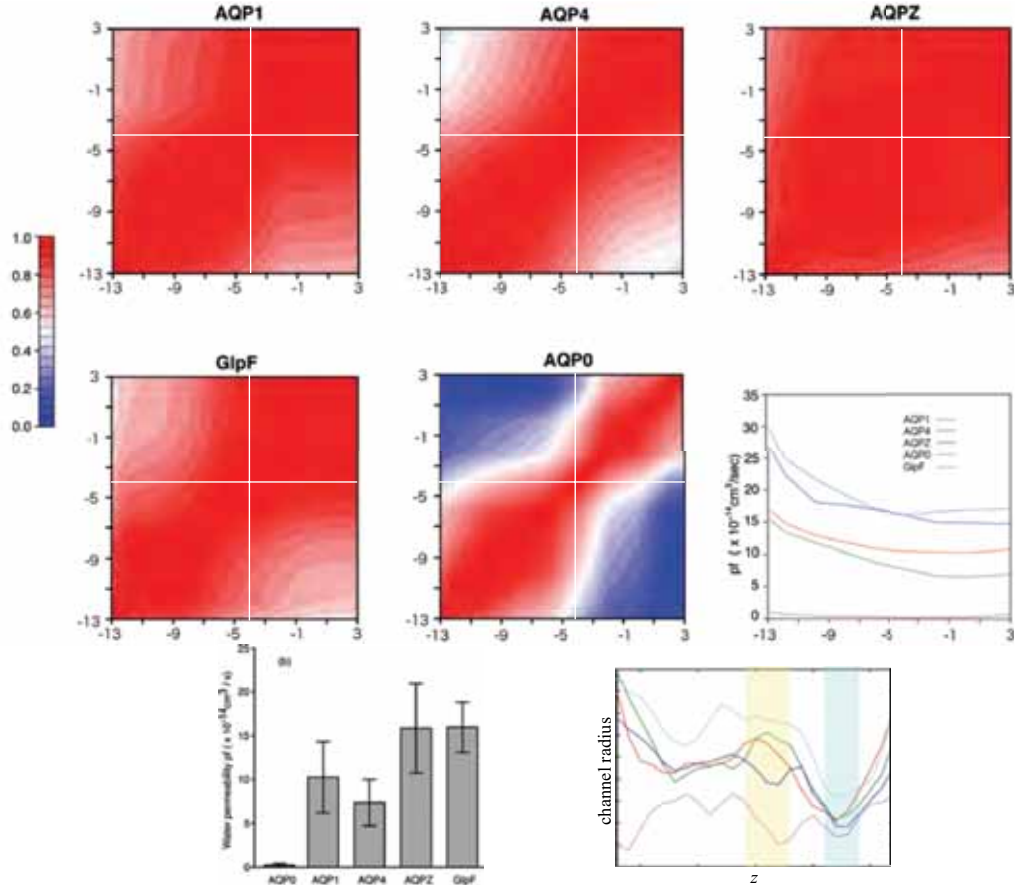




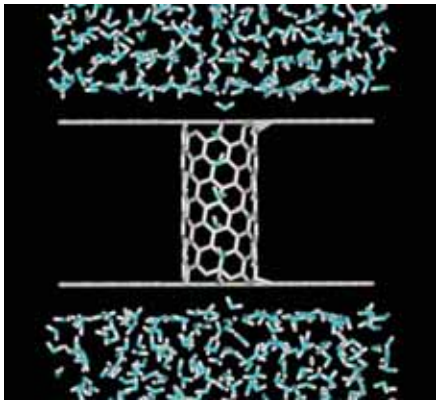

```
AQP-1 LFI  AFGLSIATIAQ   SGAHLNPAVTL   GLVLGVL
AQP-0 FYV..AFGLAIATIVQ..SGAHVNPAVTF..GFVLGIF
AQP-Z WLV  AFGLTVLTMAF   SGGHFNPAVTI   GFLLVIH
GlpF  LLI  IWGLGVAMAIY   SGAHLNPAVTI   ILMGLIL
      ...  ..60.......   ......80...   .......

 ATTDR      GGSGPLAIGFSVALGHLLAIDYTGCGINPARSFG
 ATYDE      LGSVALAVGFSLTLGHLFGMYYTGAGMNPARSFA
 GATDK  ...  AGFAPIAIGLALTLIHLISIPVTNTSVNPARSTA
 ALTDD      GPLAPLLIGLLIAVIGASMGPLTGFAMNPARDFG
  .180      .190.......200.......210.......220
```

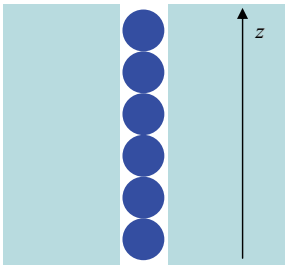


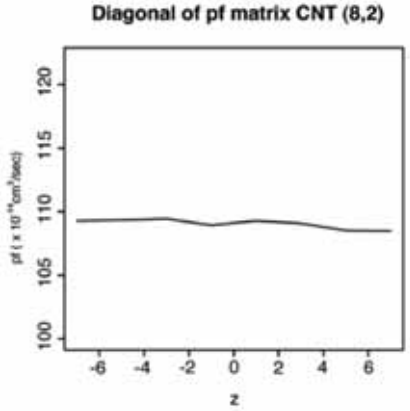
Comparative Simulations of Aquaporin Family

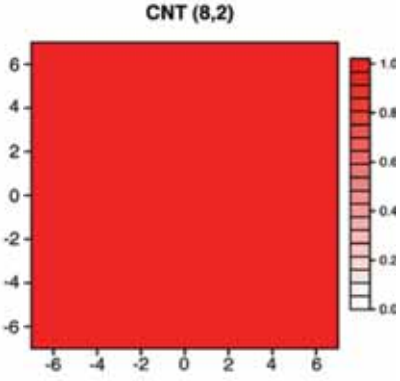


Water Permeation of Carbon Nanotube
An Ideal Single-file Channel









2．長時間の振る舞いについてのモデル

"A series of structure changes and accompanying chemical reactions initiated as a response to the external interactions"

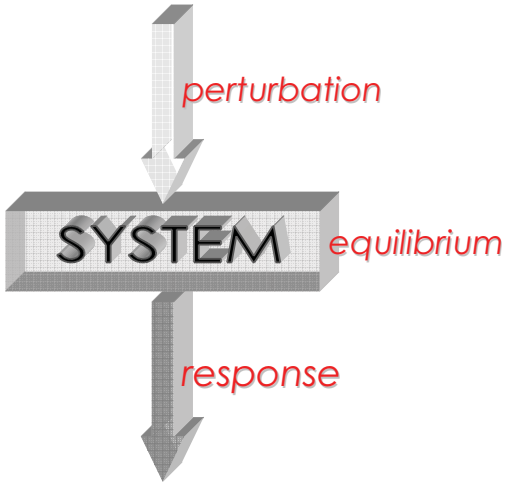
1. Interactions

2. Structural Changes

3. Chemical Reactions

Linear Response Theory

"A series of structure changes initiated as a response to the external perturbation"



Equilibrium Fluctuation

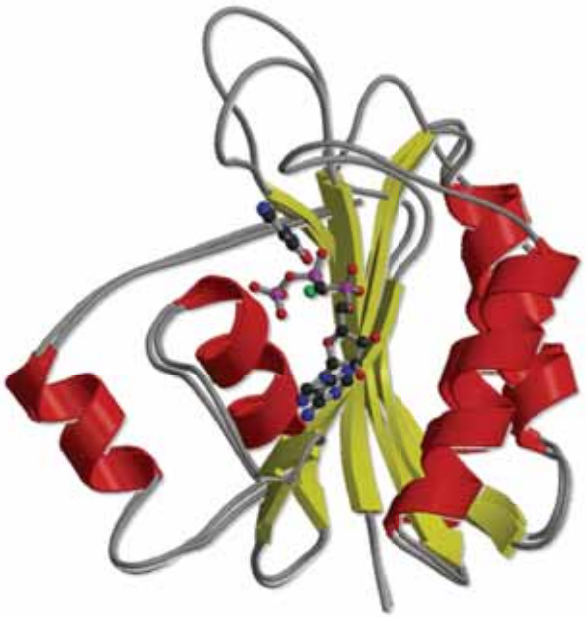
$$\langle \Delta \mathbf{r}_i \rangle_1 \simeq \beta \sum_j \langle \Delta \mathbf{r}_i \Delta \mathbf{r}_j \rangle_0 \mathbf{f}_j$$

Structural Change *Interaction*

Nonequilibrium Simulation

Equilibrium Simulation

Application

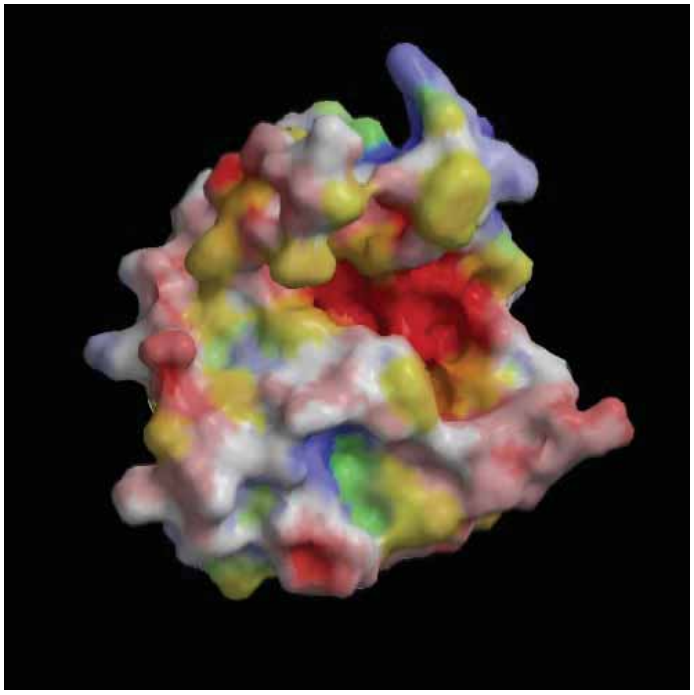


HPPK
6-hydroxymethyl-7,8-dihydropterin
pyrophosphokinase

Ligand Binding
as a Perturbation

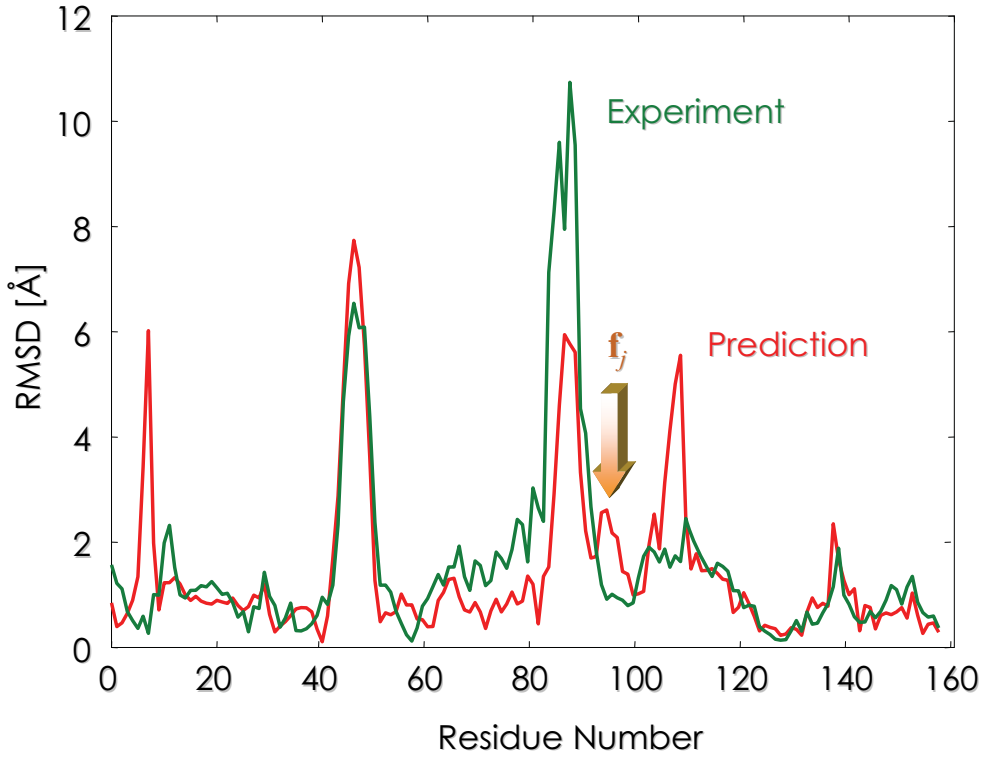
Structural Change
as the Response

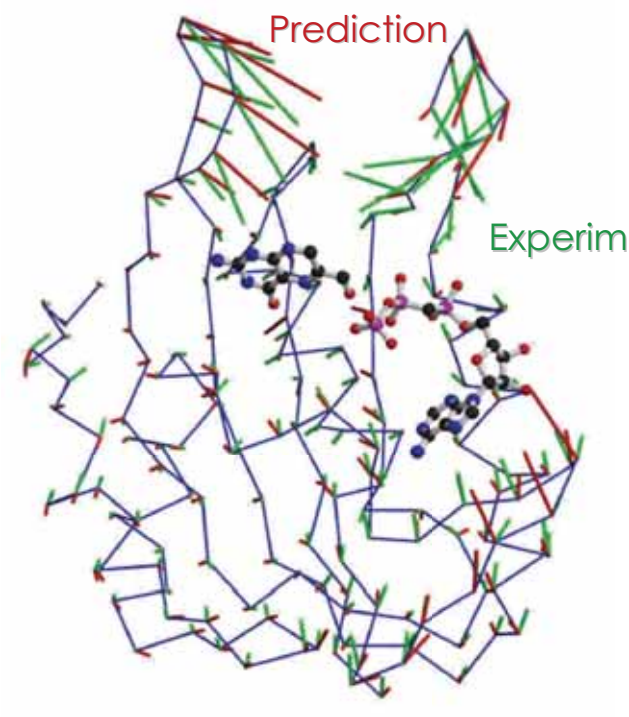
Molecular Dynamics Simulation of HPPK



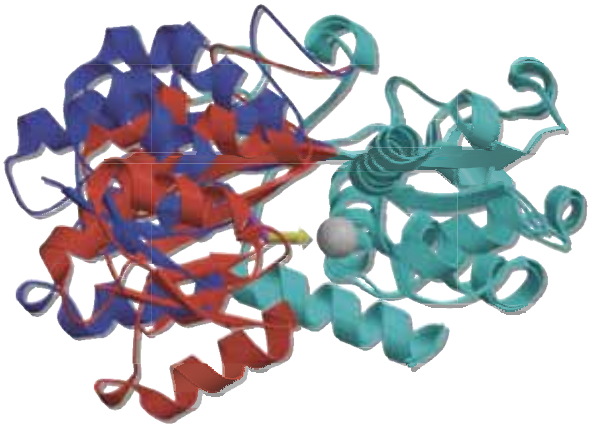
HPPK with no ligand
in 10,000 water
10 nsec
PME

Results of Prediction



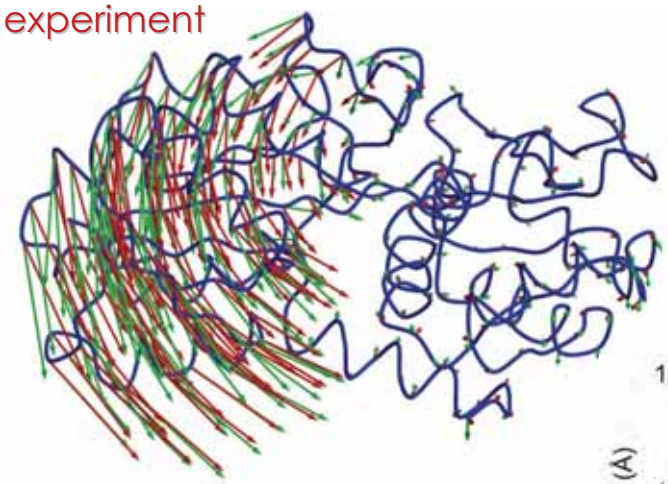


Ferric Binding Protein

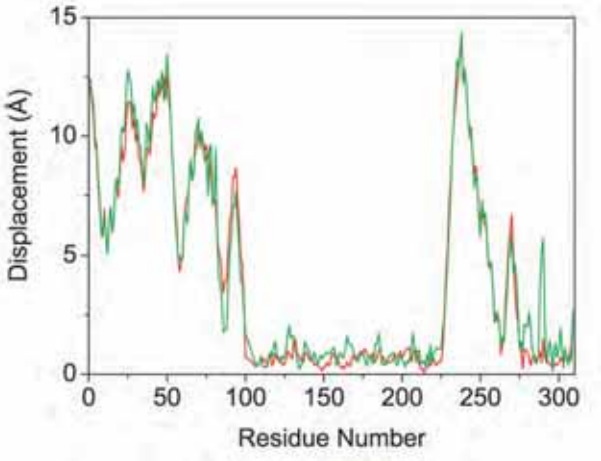


Blue: unbound form (1D9V)
Red: bound form (1MRP)
Magenta: Glu58
Yellow arrow: Applied force

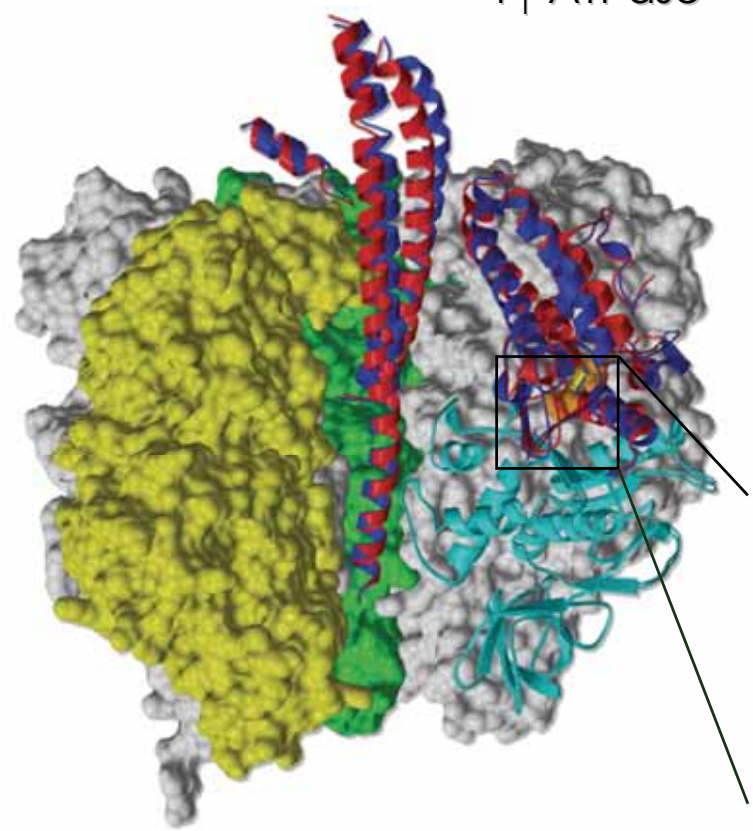
experiment

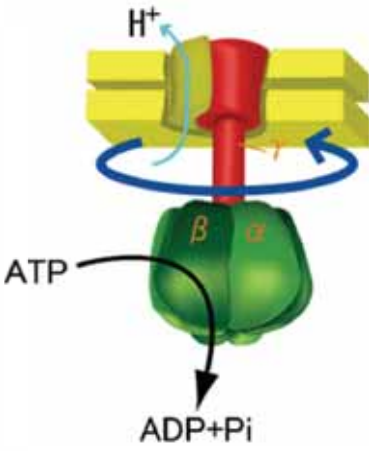


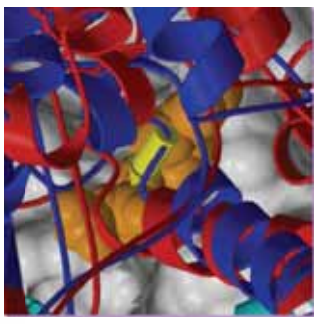
prediction

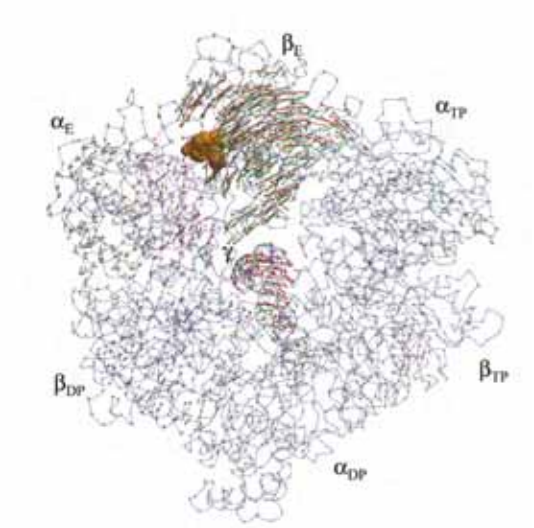


F_1-ATPase

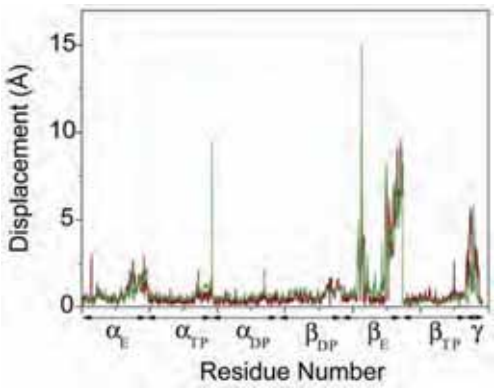








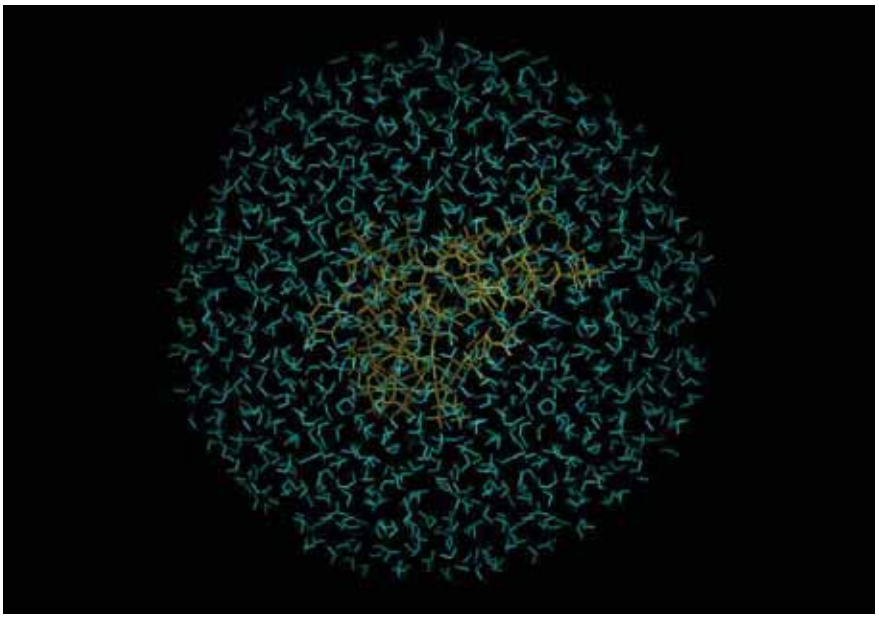
Correlation Coefficient: 0.84 (β_E)



Correlation Coefficient: 0.85 (all)

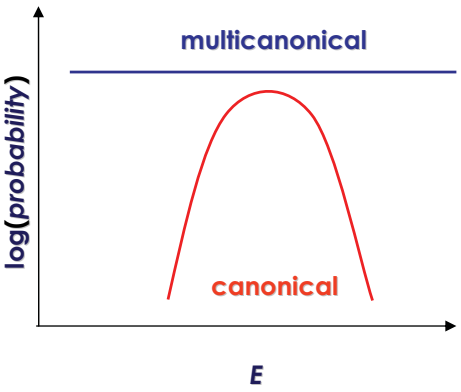
3．特殊なサンプリング法

Multicanonical MD Simulation of a Protein in Water



Chymotrypsin Inhibitor 2

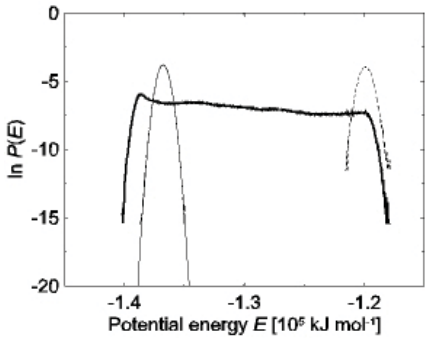
Multicanonical MD Simulation



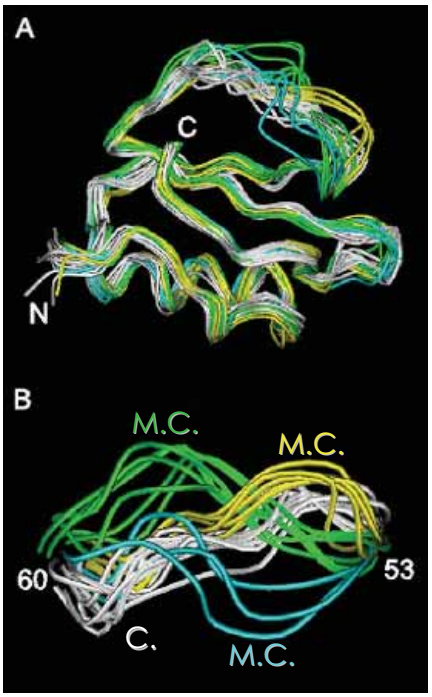
$$P_{mult} \sim \Omega(E) e^{-W(E)} = \text{const.}$$

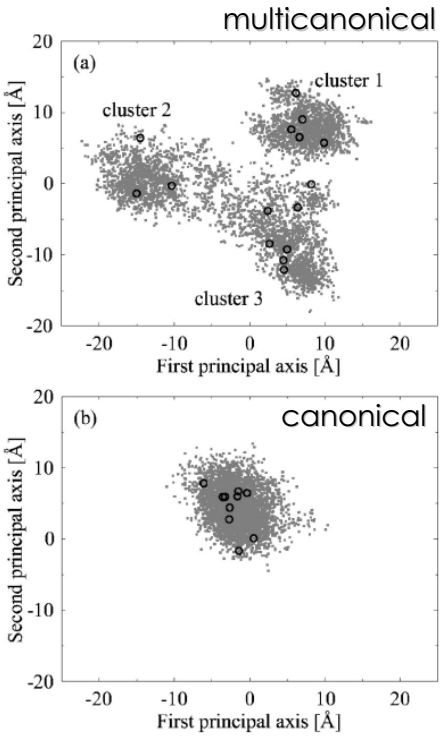
$$P_{canonical} \sim \Omega(E) e^{-\beta E}$$

$$P_{canonical} \sim P_{mult} e^{W-\beta E}$$



Multicanonical MD Simulation of Chymotrypsin Inhibitor 2

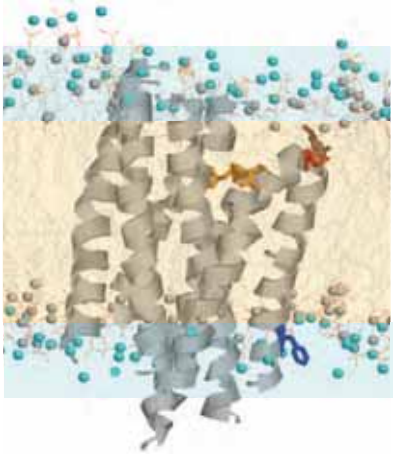


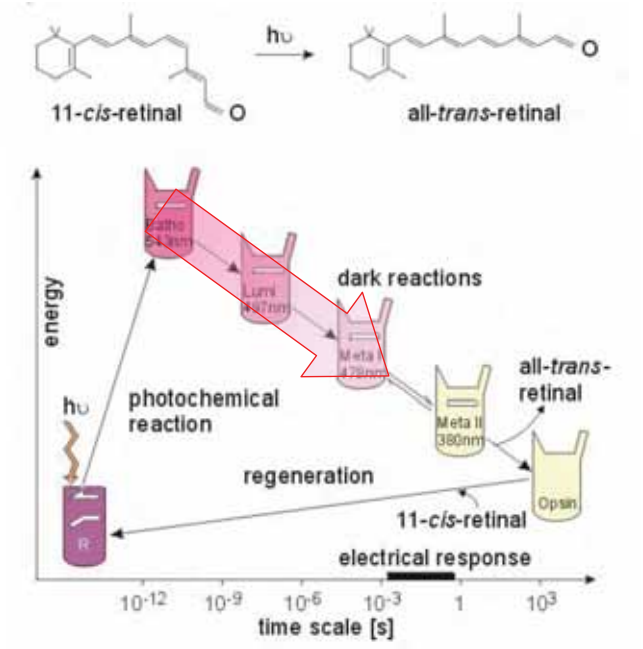


Rhodopsin Photocycle

~1μs MD simulation of ~50,000 atoms

Blue Matter/Blue Gene





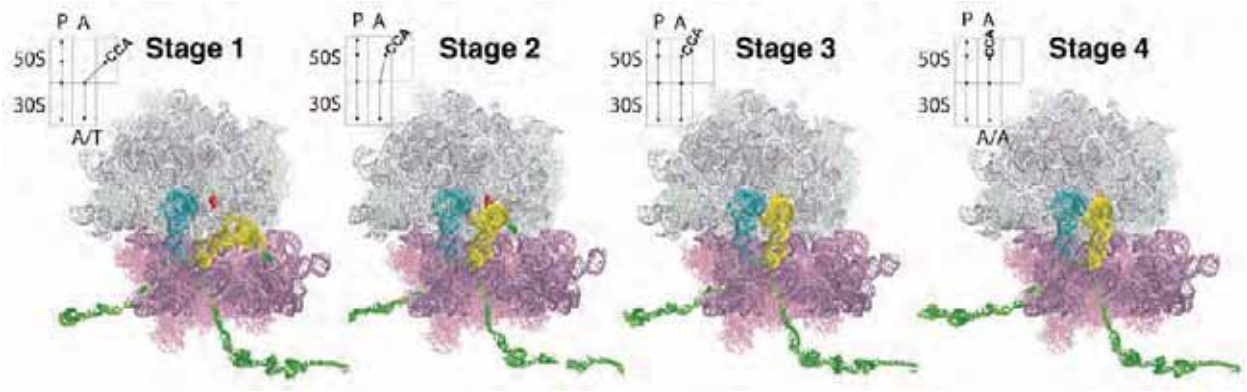
MC Pitman, A Grossfield, SE Feller, Annual Meeting of Biophysical Society, 2006

Ribosome

2.64 x 10^6 atoms 20 ns About 10^6 computer hours

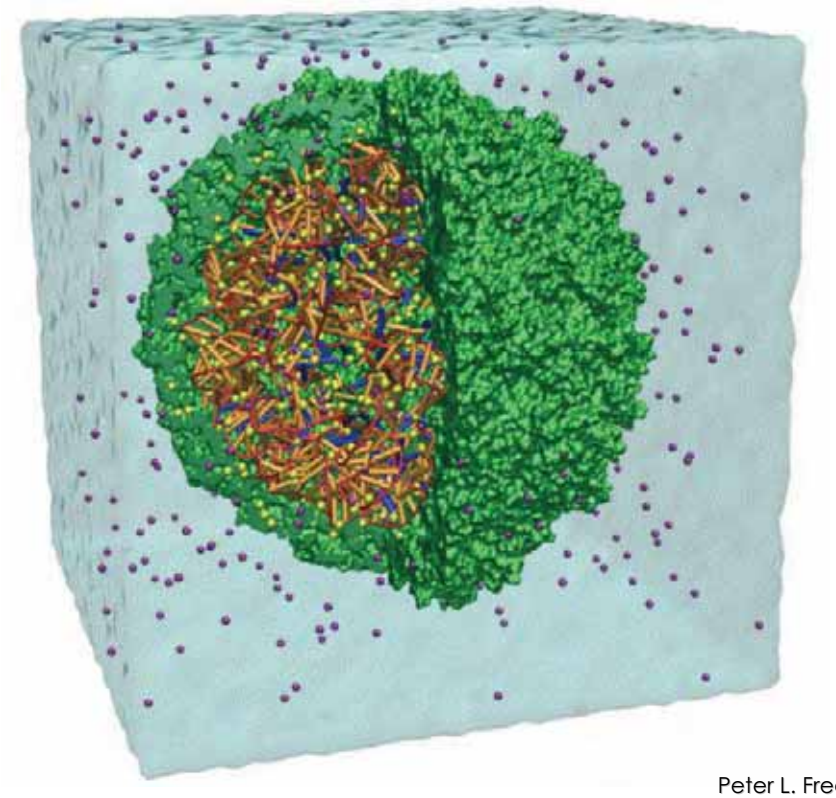
ASCI Q at Los Alamos National Laboratory

the movement inside the ribosome of the aminoacyl-tRNA from the partially bound "A/T" state to the fully bound "A/A" state.



KY Sanbonmatsu, S Joseph, and C-S Tung, *Proc Natl Acad Sci U S A*. **102**,15854-9 (2005).

Satellite Tobacco Mosaic Virus



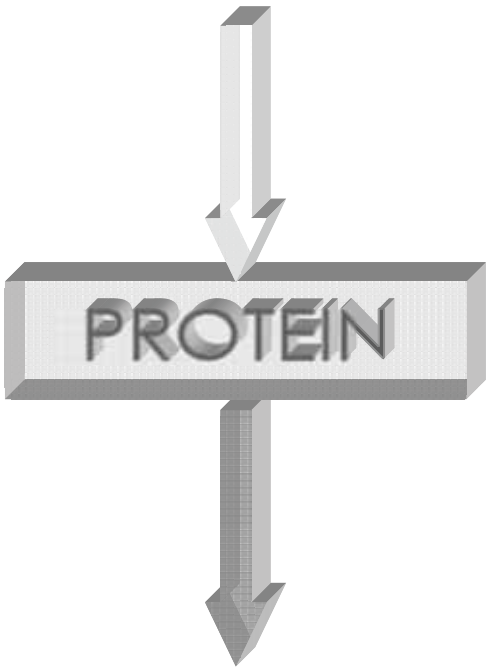
1.07×10^6 atoms 53 ns

256 Altix nodes at NCSA

The simulation is the first to capture a whole biological organism in such intricate molecular detail.

Peter L. Freddolino, et al., *Structure* **14**, 437-49 (2006).

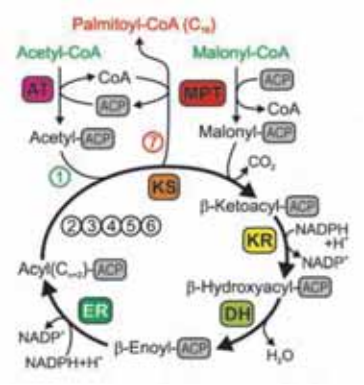
Context

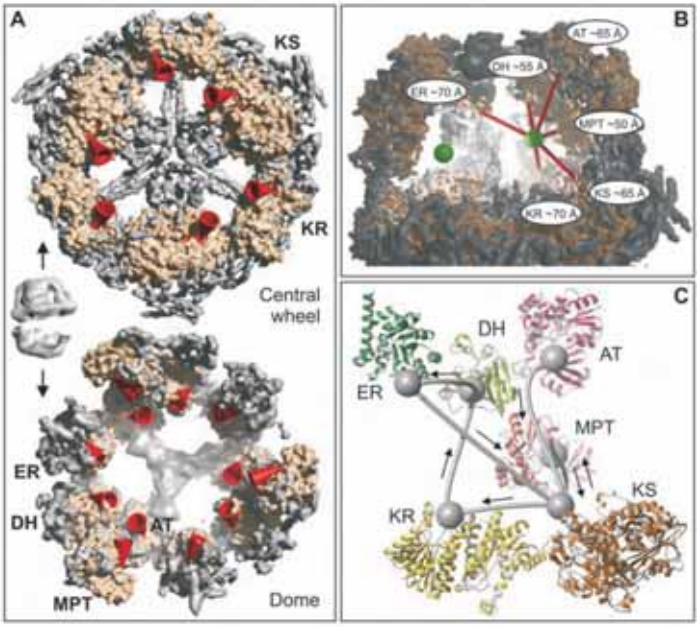


Network = Binary Relation

Context

Fatty Acid Synthesis





Jenni S, et al. *Science* **311**, 1263 (2006)

Context

高次機能は離合集散を繰り返す多数タンパク質からなる超分子複合体によって担われている

そのような超分子複合体の立体構造は
結晶学的には解析不能である

要素となるタンパク質の多くは
個別に立体構造が解かれている

細胞生物学の課題

Folding

Sequence

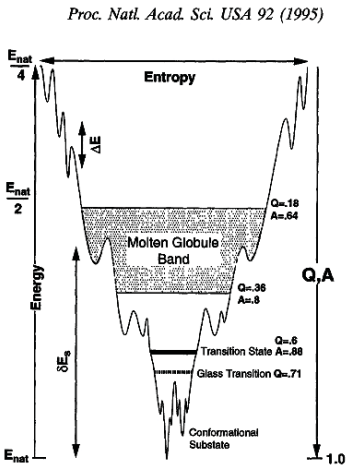
Folding

3D structure

Response

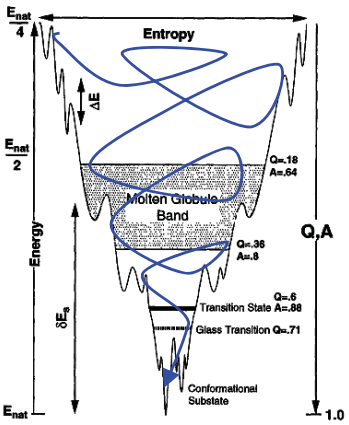
Molecular function

Cellular function

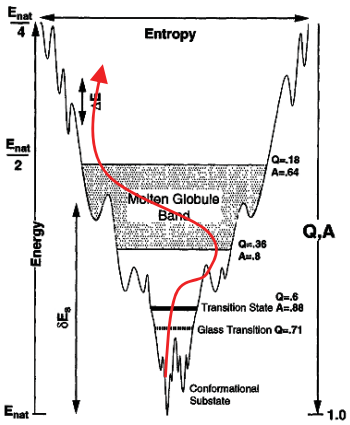


シミュレーションの時間内に生起するFolding

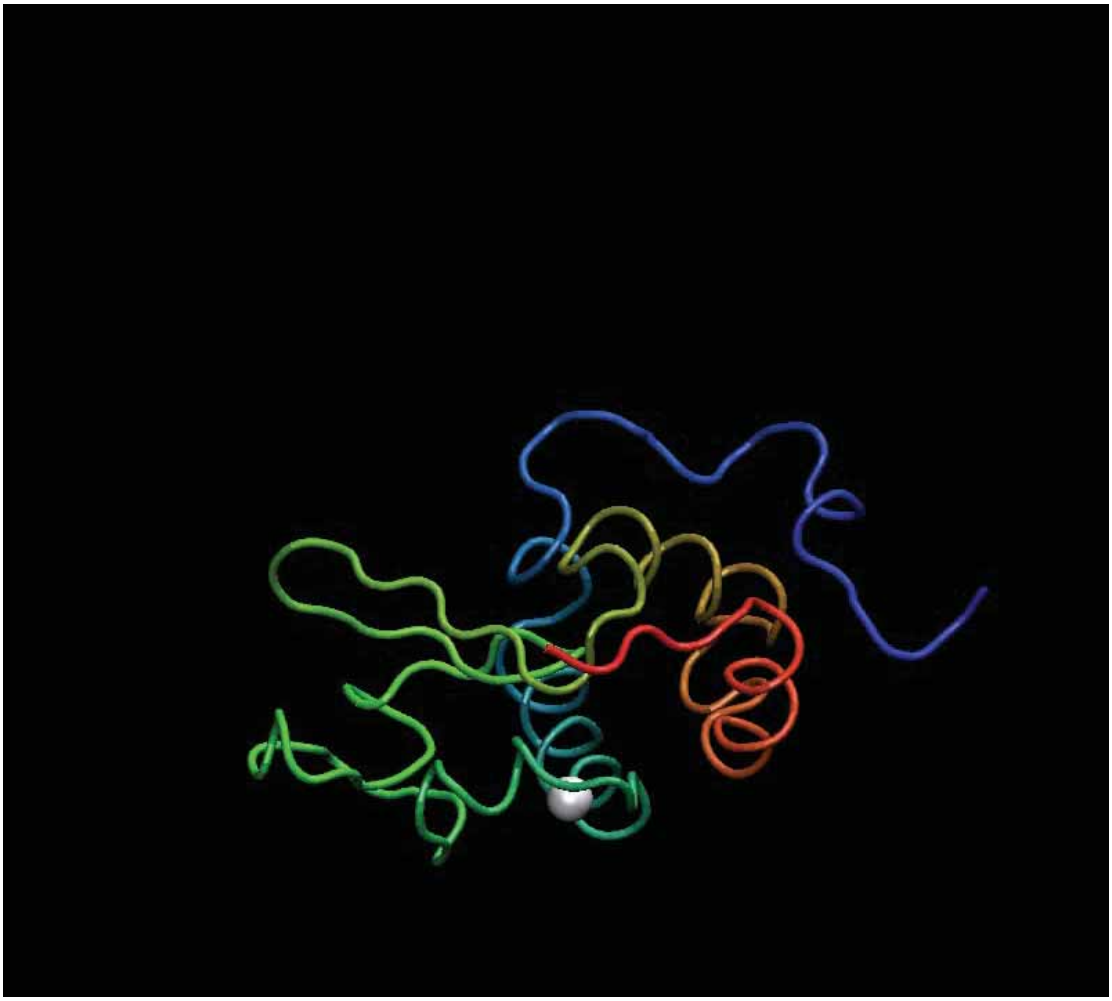
Unfolding simulation of α-lactalbumin at high temperature



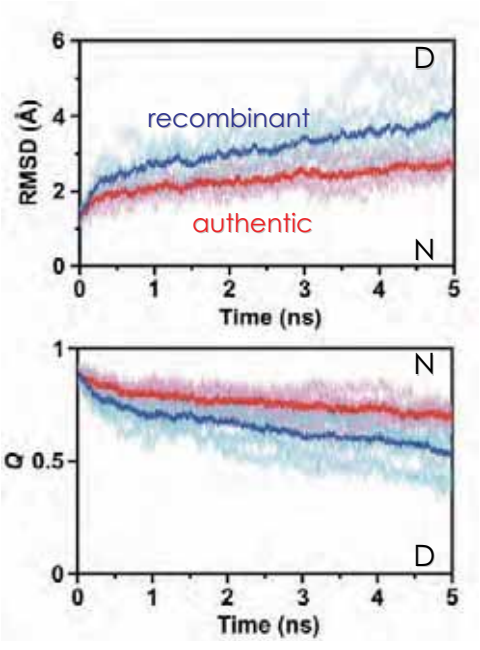
Folding



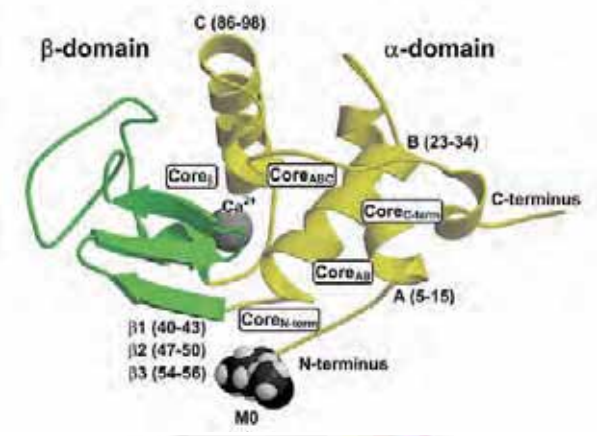
Unfolding

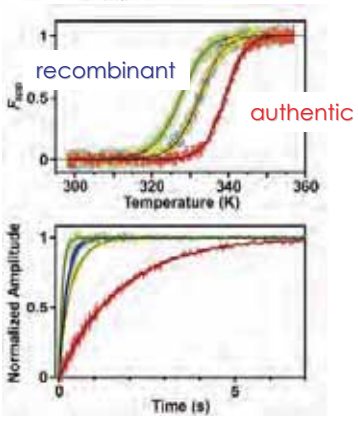


Results



The initial stage of unfolding
before reaching the transition state





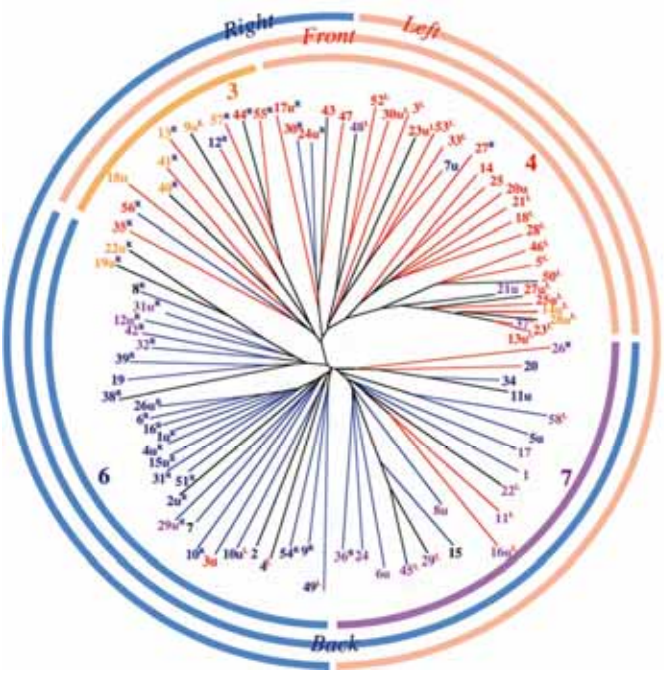
Folding of a Miniprotein

Trp-Cage (20 residues)

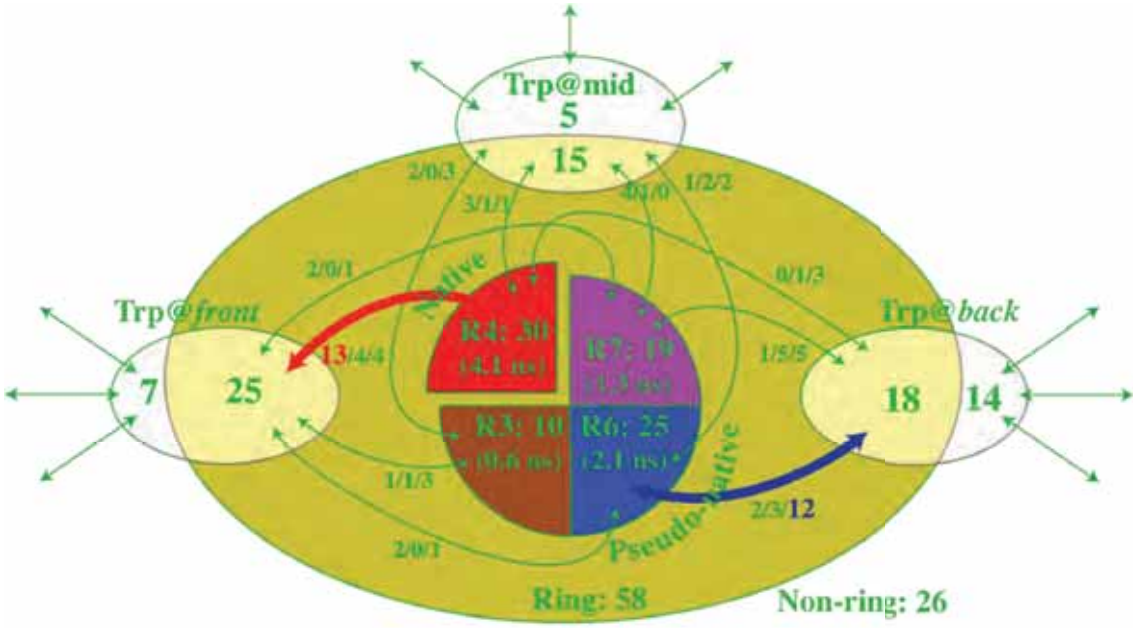
10 ms MD (200 x 50 ns)
by Titech Grid (800 CPU)

58 folding
31 unfolding

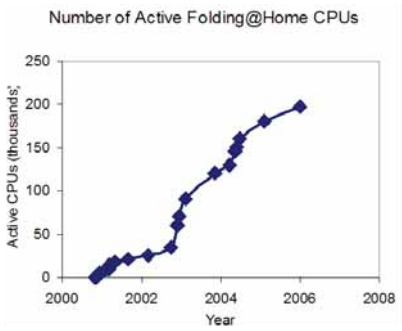
Phylogeny of Trajectories

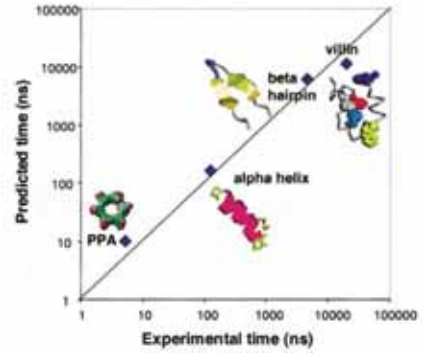


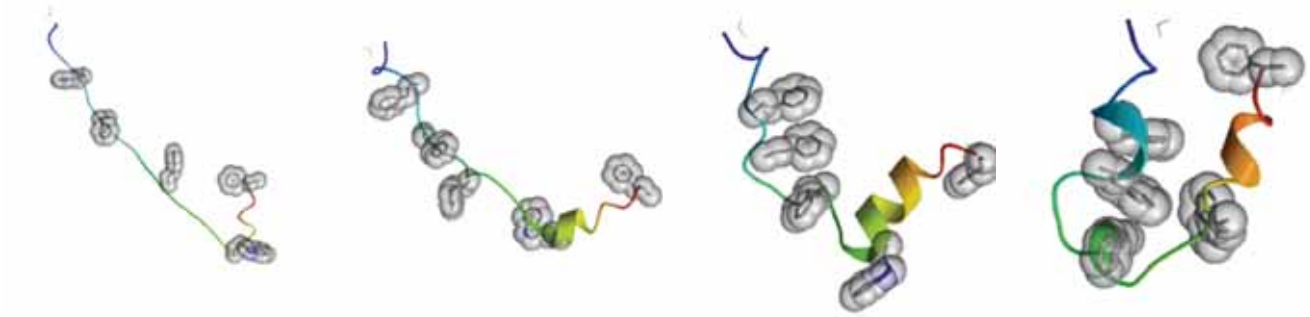
False Funnel



Folding@home distributed computing







Villin Headpiece (36 residues)

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