Physicist's Understanding of Molecular Machines

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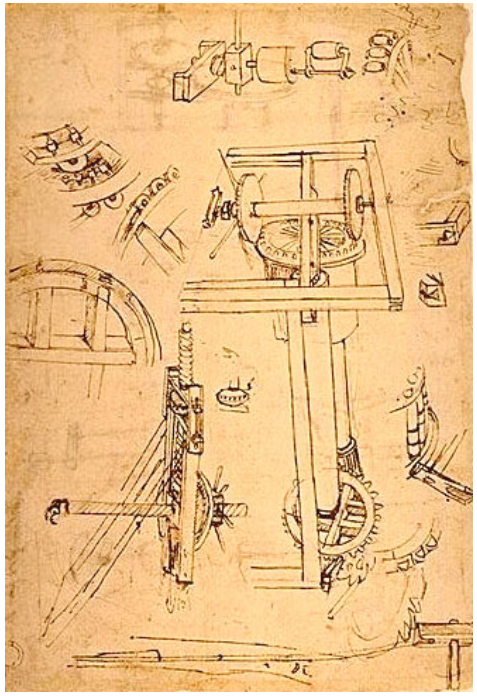
Gerhard Ertl,

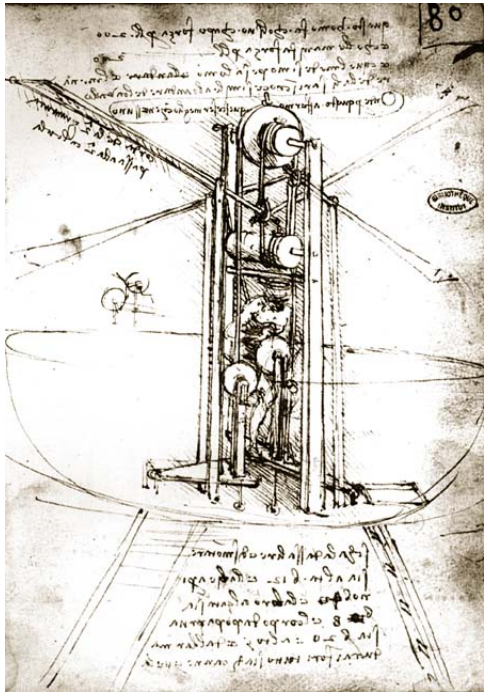
Nobel Prize 2007

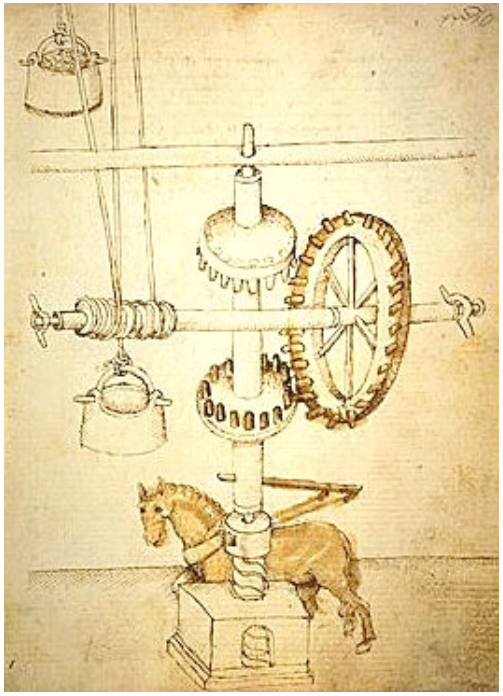
Japan Prize 1992

Zur Anzeige wird der QuickTime™
Dekompressor „“
benötigt.

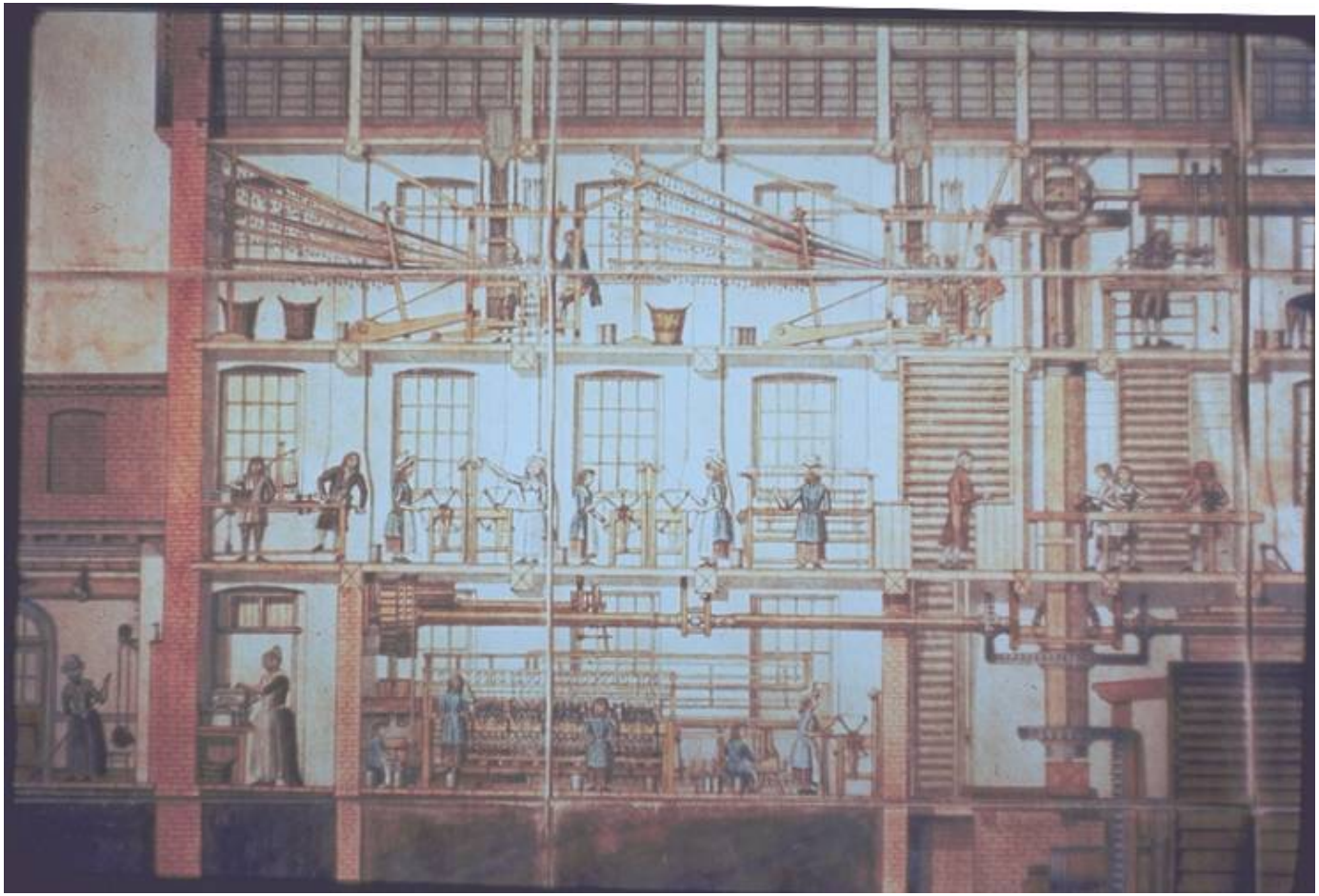
ChemPhysChem **10**, 86 (2009)



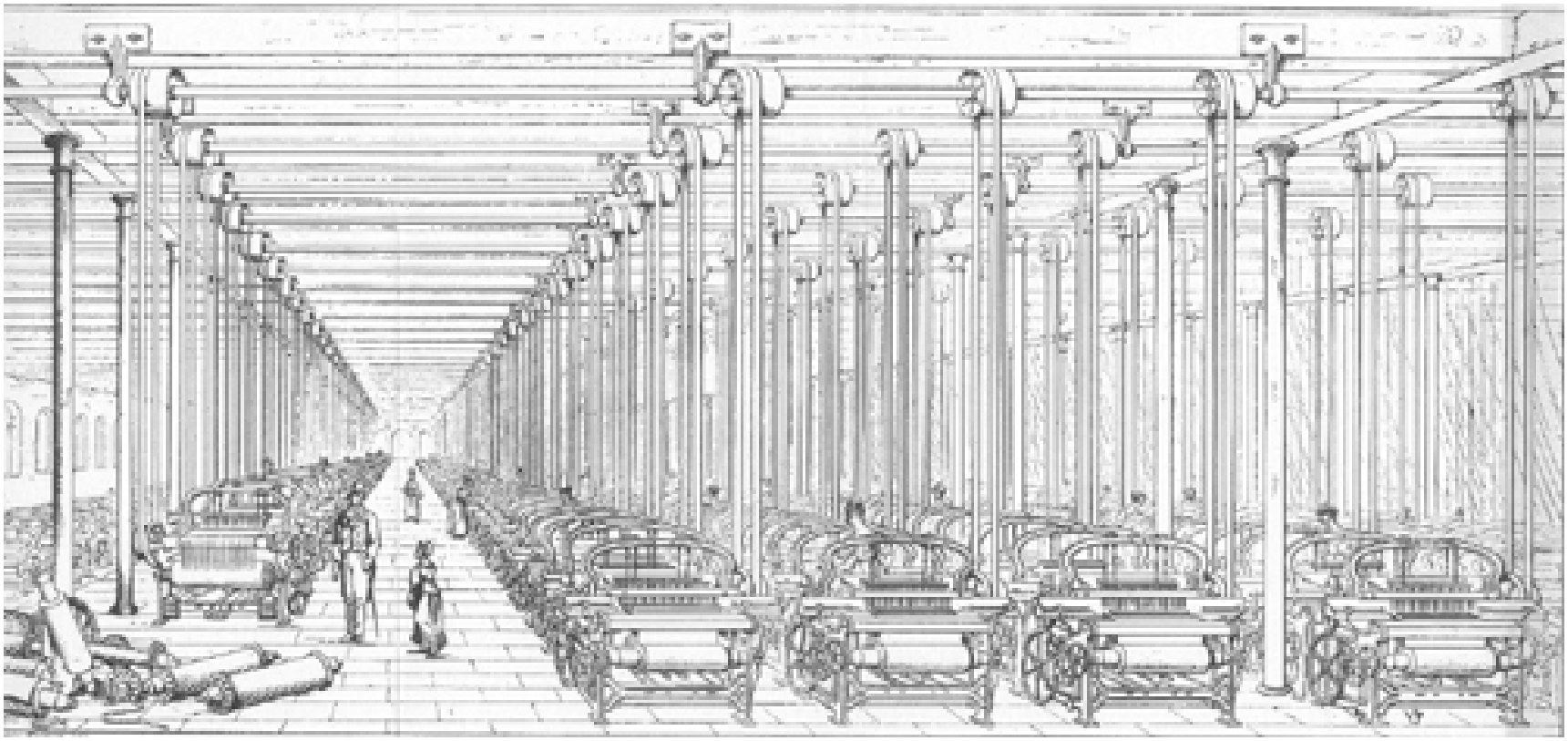




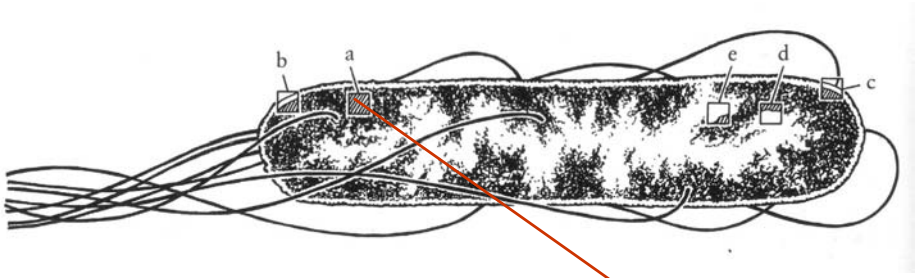
Drawings of machines, Leonardo da Vinci



A factory in England

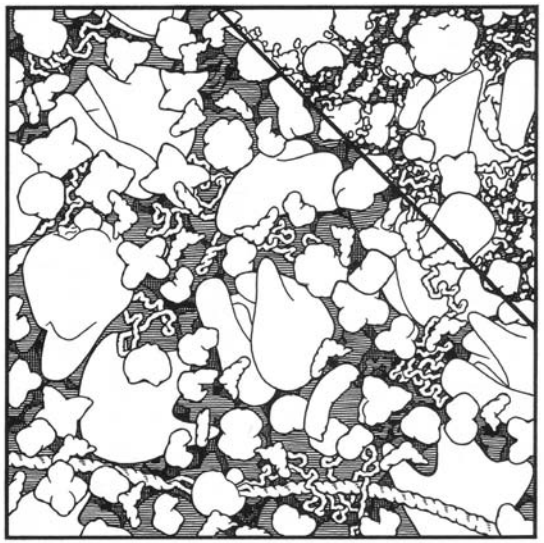


Bacterium *E. coli*



0.5 μm

A factory of single-molecule nanoscale machines: motors, ion pumps, enzymes,... Many thousands of such machines are packed inside a volume of about 1 μm^3. The factory is self-regulated and is able to reproduce itself.



100 nm

Most of the molecular machines are proteins and their molecular structures and equilibrium conformations are known. Full molecular dynamics simulations of such molecules, using modern computers, are however only possible for very short times of about a picosecond, whereas one operation cycle of a protein machine usually takes a millisecond or even longer....

Therefore, physicists studying molecular machines are currently divided into two communities.

In the first community, detailed molecular structures and chemical properties of particular machines are discussed - but the analysis is restricted to static patterns or short-time behaviour.

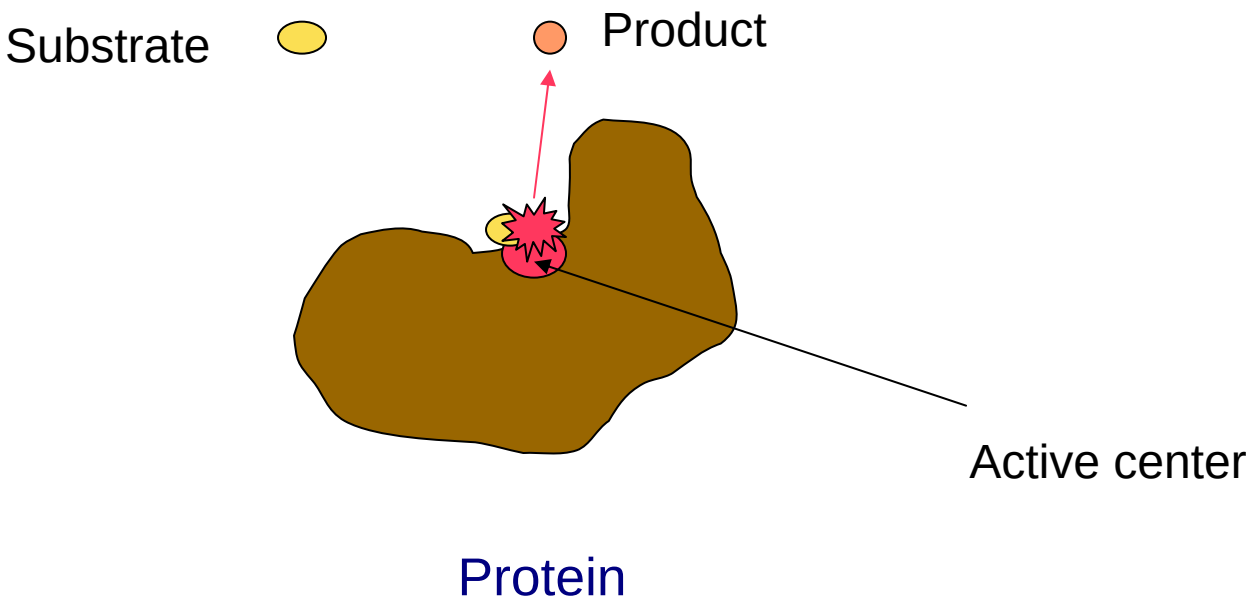
In the second community, abstract models of molecular machines (ratchets, etc.) are only considered.

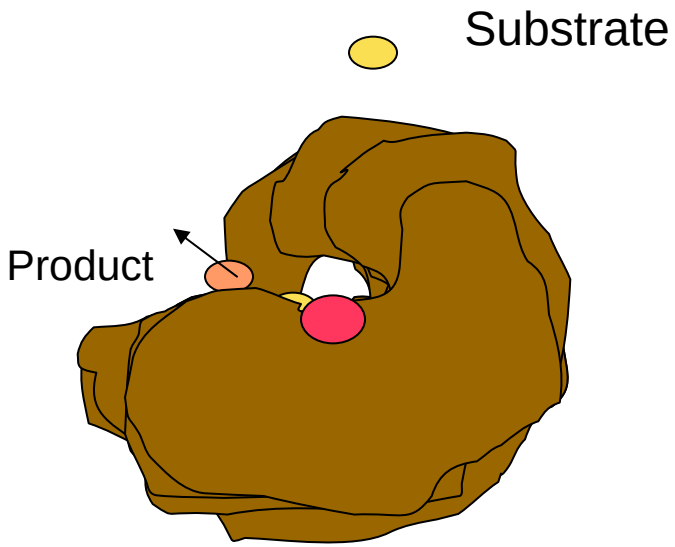
There is a gap between these two approaches which must be bridged.

Biological systems usually have hierarchical organization. While each individual unit may possess great internal complexity, the units interact as if they were relatively simple objects with only a few essential state variables. This ensures robust and predictable operation of such systems.

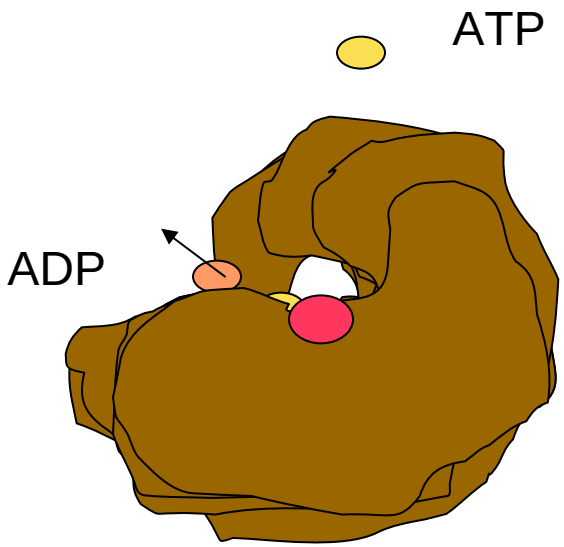
It should be therefore expected that the internal complexity of protein machines is not fully reflected in their operation and very simple - but not abstract - models are sufficient to describe their cycles.

Enzymes are single-molecule catalysts





Ordered internal mechanical motions inside turnover cycles. These motions represent conformational relaxation processes. Energy is supplied with the ligand (the substrate particle).



All molecular motors are enzymes catalyzing the reaction ATP -> ADP. However, this reaction is only used to generate internal mechanical motions and to produce work.

QuickTime™ and a
Keine decompressor
are needed to see this picture.

Molecular motor
Kinesin

QuickTime™ and a
Keine decompressor
are needed to see this picture.

Molecular motor
Myosin

QuickTime™ and a
H.264 decompressor
are needed to see this picture.

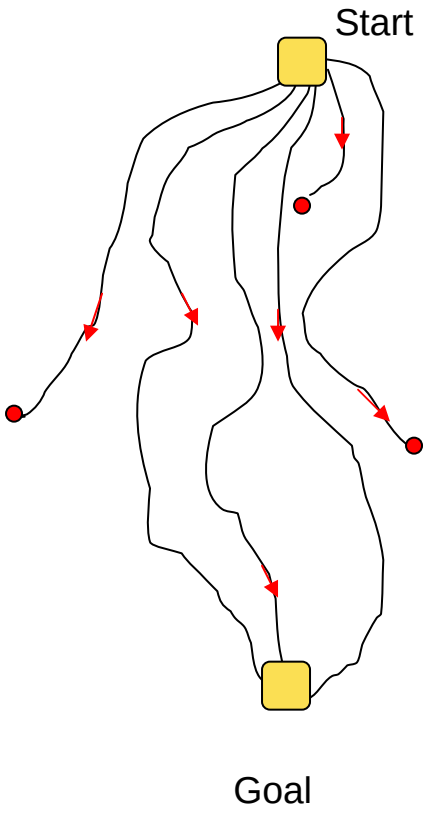
Hepatitis Virus C (HVC) Helicase
splits DNA into two strands

Protein machines

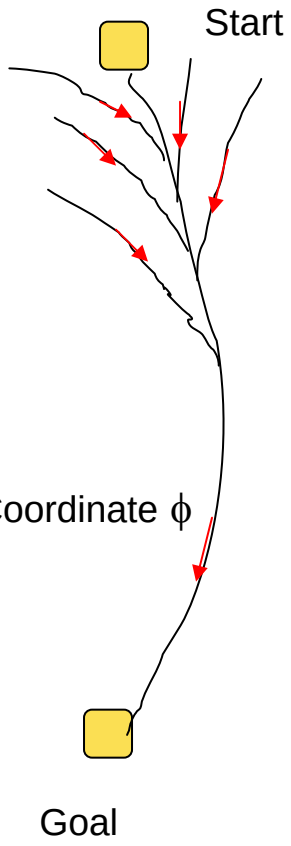
- Energy is supplied in discrete portions, by binding of a ligand (e.g., ATP)
- Subsequent internal motions are relaxation processes of the protein-ligand complex and of the free protein after ligand conversion into a product and the product release
- These conformational motions are used in molecular motors to produce mechanical work
- In enzymes, they are used to facilitate chemical reaction events.

If a protein is able to operate as a machine, conformational relaxation in this molecule should follow a well-defined path, robust against pertubations.

Special energy landscapes: a long, deep and narrow valley leading to the equilibrium state. This valley is approached starting from various initial conditions. The mechanical coordinate of the machine is the coordinate along the bottom of this energy valley.



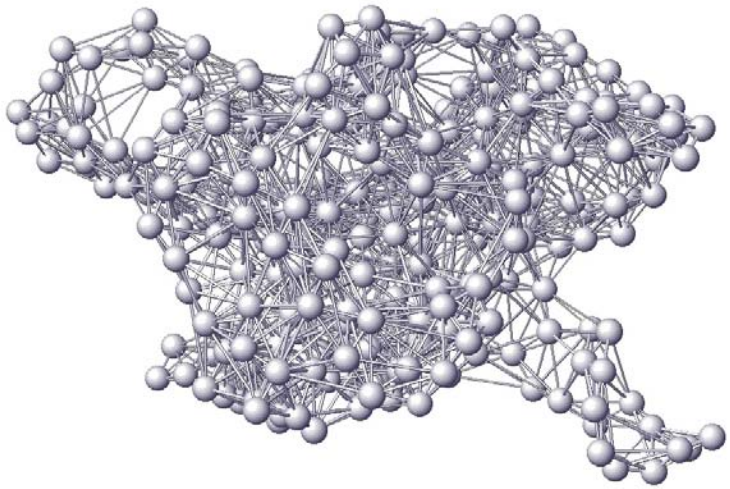
Ragged slope



Narrow deep valley

Elastic networks

$$E = \frac{1}{2}\kappa \sum_{i,\,j=1}^{N} A_{ij}\left(d_{ij} - d_{ij}^{0}\right)^{2}$$



Two particles *i* and *j* are connected by an elastic string, if at equilibrium distance between them is shorter than the cut-off length l_0

$$A_{ij} = 1, \text{ if } d_{ij}^{0} < l_0;\ A_{ij} = 0 \text{ otherwise}$$

Relaxation dynamics of networks

$$\frac{d\mathbf{R}_i}{dt} = -\Gamma \frac{\partial E}{\partial \mathbf{R}_i}$$

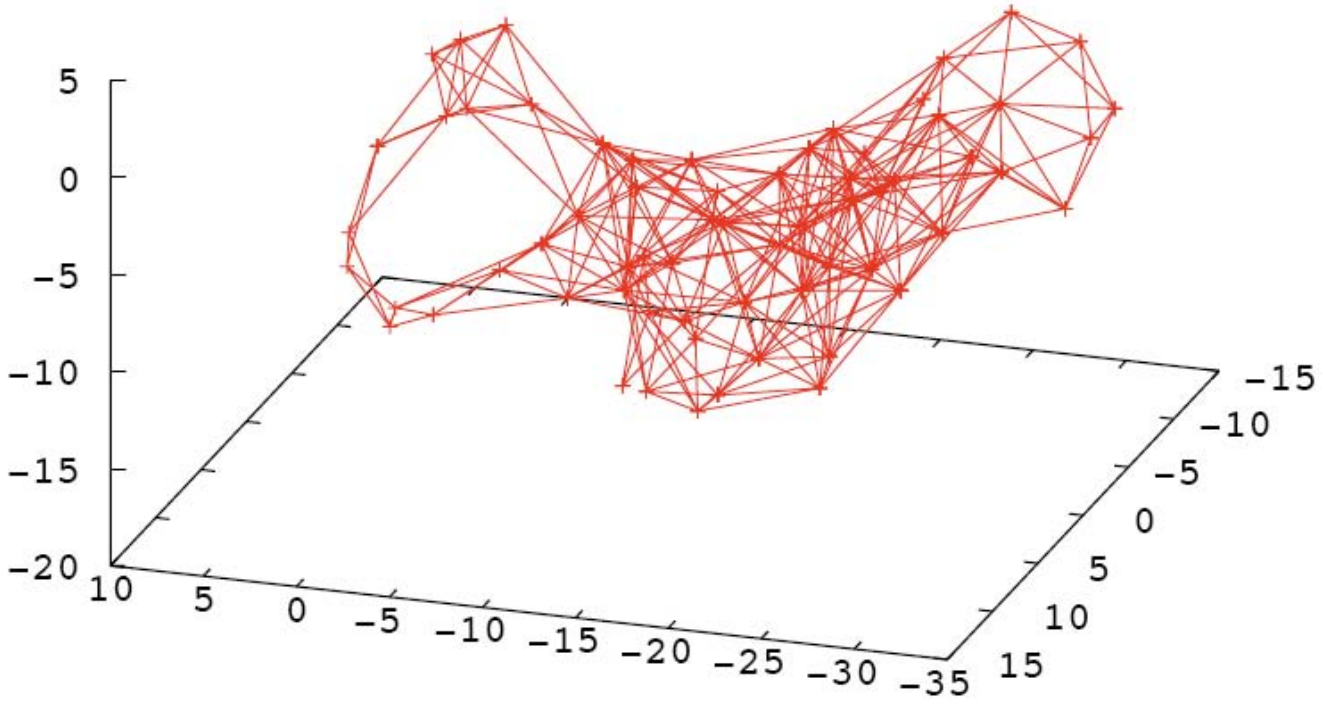
$$\frac{d\mathbf{R}_i}{dt} = -\sum_{j=1}^{N} K \sum_{j=1}^{N} A_{ij} \frac{\mathbf{R}_i - \mathbf{R}_j}{|\mathbf{R}_i - \mathbf{R}_j|} \left(|\mathbf{R}_i - \mathbf{R}_j| - |\mathbf{R}_i^{(0)} - \mathbf{R}_j^{(0)}| \right)$$

$R_i^{(0)}$: Equilibrium positions of particles

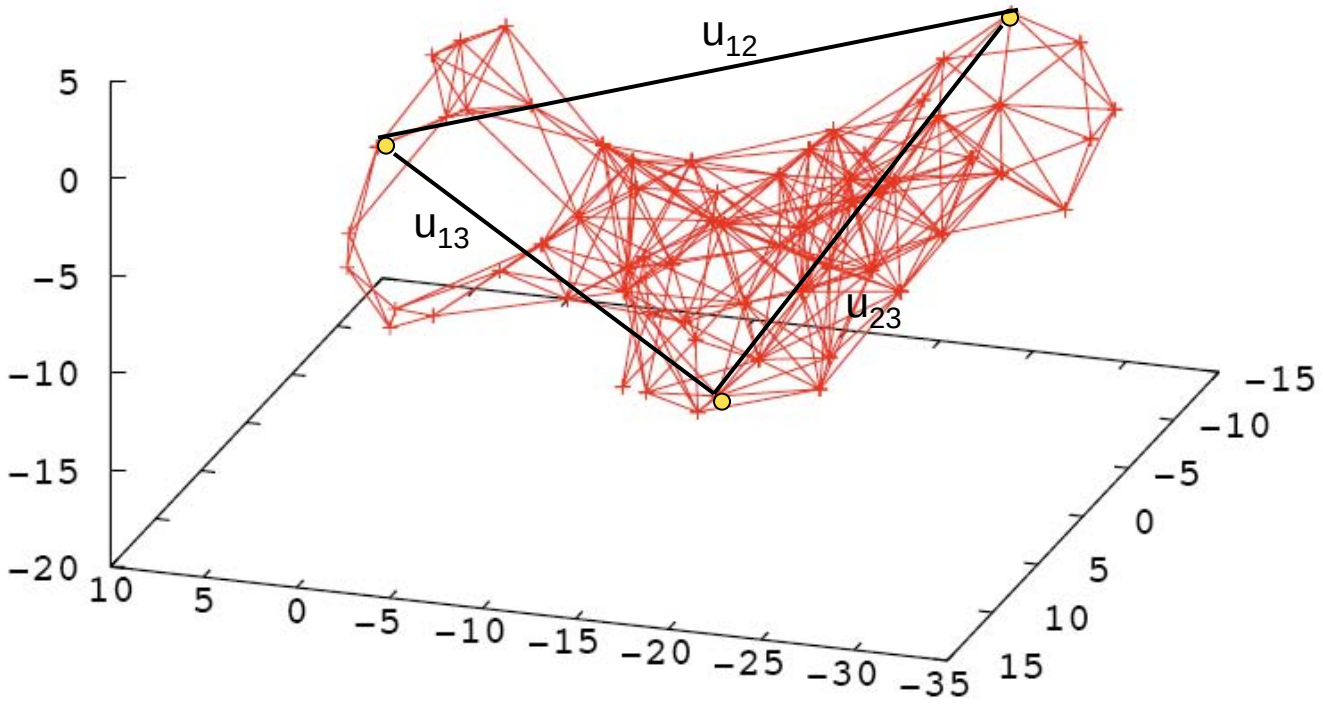
$$d_{ij} = |\mathbf{R}_i - \mathbf{R}_j| = \sqrt{(X_i - X_j)^2 + (Y_i - Y_j)^2 + (Z_i - Z_j)^2}$$

This relaxation dynamics is nonlinear.

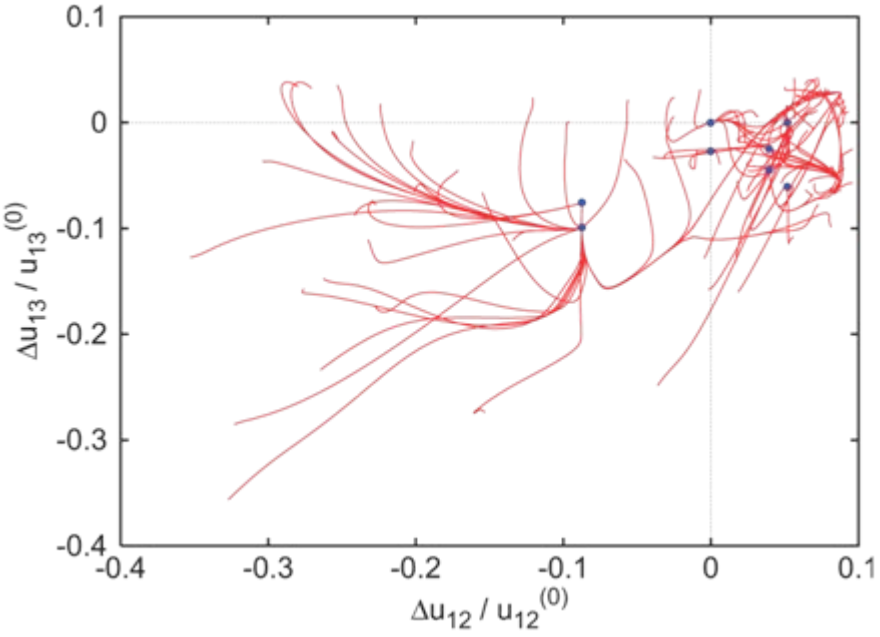
Random elastic networks

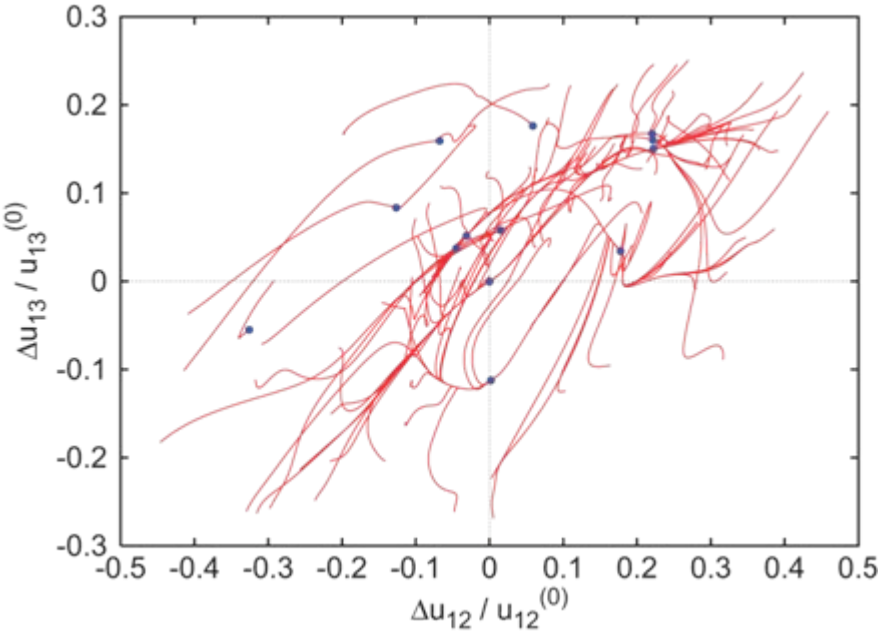


Random elastic networks



Relaxation trajectories of random networks





Initial states are prepared by applying random forces to all network nodes

Random elastic networks cannot be used to construct machines!

Linearized equations

$$\mathbf{r_i} = \mathbf{R_i} - \mathbf{R}_i^{(0)}$$

$$\frac{d\mathbf{r_i}}{dt} = -\sum_{j=1}^{N} A_{ij} \frac{\mathbf{R}_i^{(0)} - \mathbf{R}_j^{(0)}}{\left|\mathbf{R}_i^{(0)} - \mathbf{R}_j^{(0)}\right|^2} \left[\left(\mathbf{R}_i^{(0)} - \mathbf{R}_j^{(0)}\right)\left(\mathbf{r}_i - \mathbf{r}_j\right)\right]$$

$$\ddot{\mathbf{r}}_i = -\sum_{j=1}^{N} \Lambda_{ij} \mathbf{r}_j$$

Normal relaxation modes

$$\dot{\mathbf{r}}_i = -\sum_{j=1}^{N} \Lambda_{ij} \mathbf{r}_j$$

$$\Lambda \mathbf{e}^{(\alpha)} = \lambda_\alpha \mathbf{e}^{(\alpha)}$$

General solution is given by a superposition of normal relaxation modes

$$\mathbf{r}_i(t) = \sum_\alpha k_\alpha e^{-\lambda_\alpha t} \mathbf{e}_i^{(\alpha)}$$

Soft relaxation modes

Soft mode: $\lambda_1 << \lambda_t$

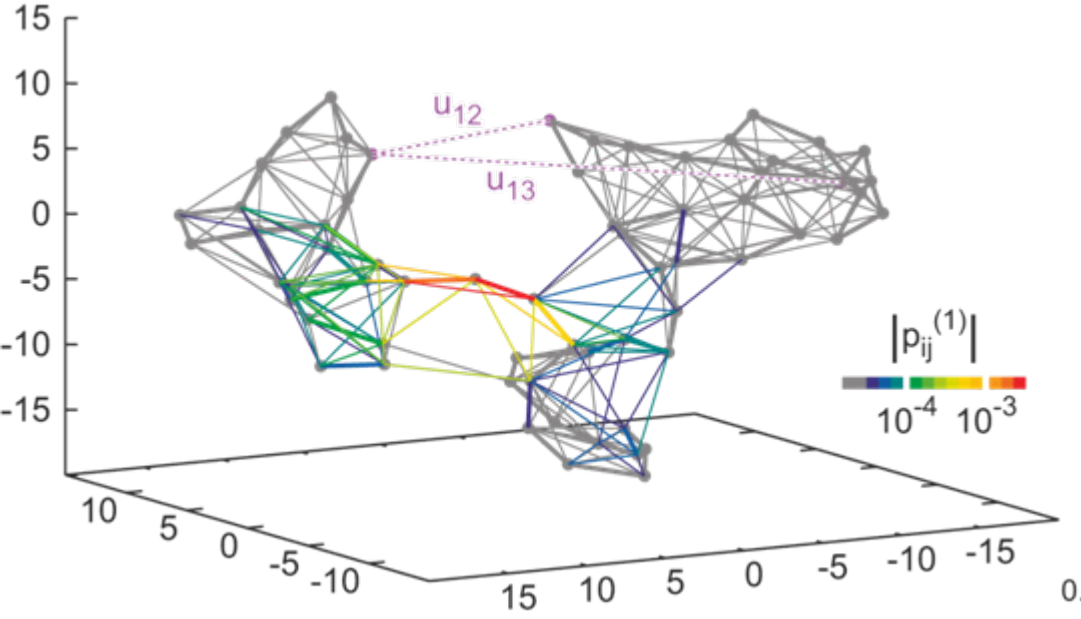
After a transient, relaxation dynamics gets reduced to a low-dimensional manifold spanned by soft modes. If there is only one soft mode, the asymptotic motion is characterized by a single coordinate.

We need elastic networks with soft modes!

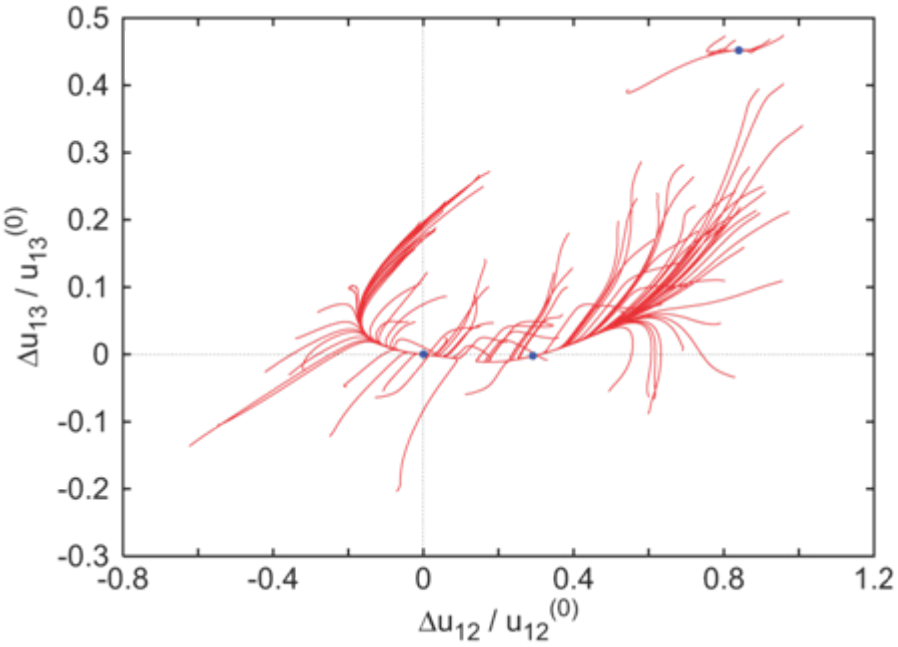
Evolutionary construction of networks with a soft mode

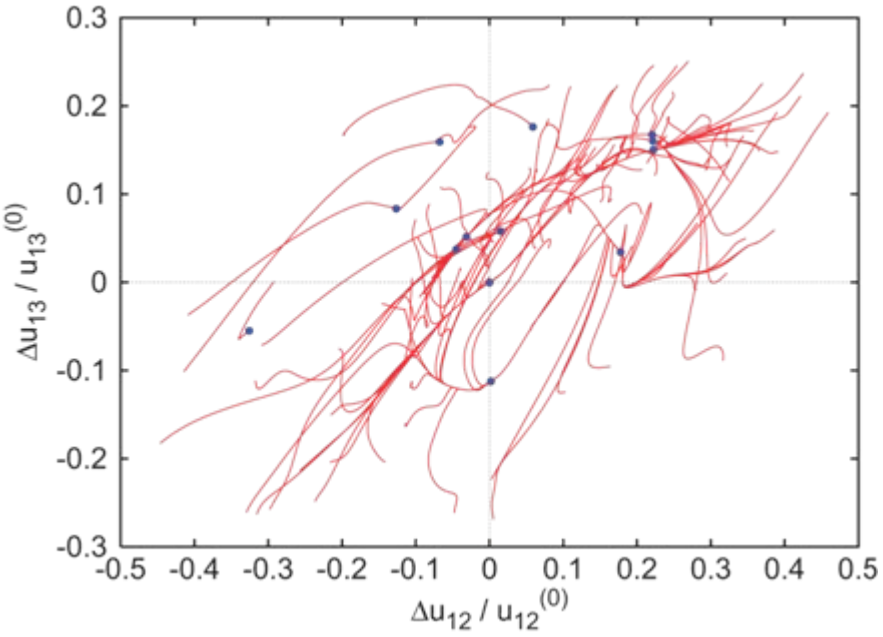
Maximization of the spectral gap $g = \log(\lambda_2 / \lambda_1)$

1. Apply a structural mutation (change of the equilibrium position of a particle).
2. Determine spectral gaps g and g´ of the networks before and after the mutation.
3. If $\Delta g = g' - g > 0$, always accept the mutation.
4. If $\Delta g < 0$, accept with probability $\exp(\Delta g / \theta)$.



Designed elastic network with a soft mode





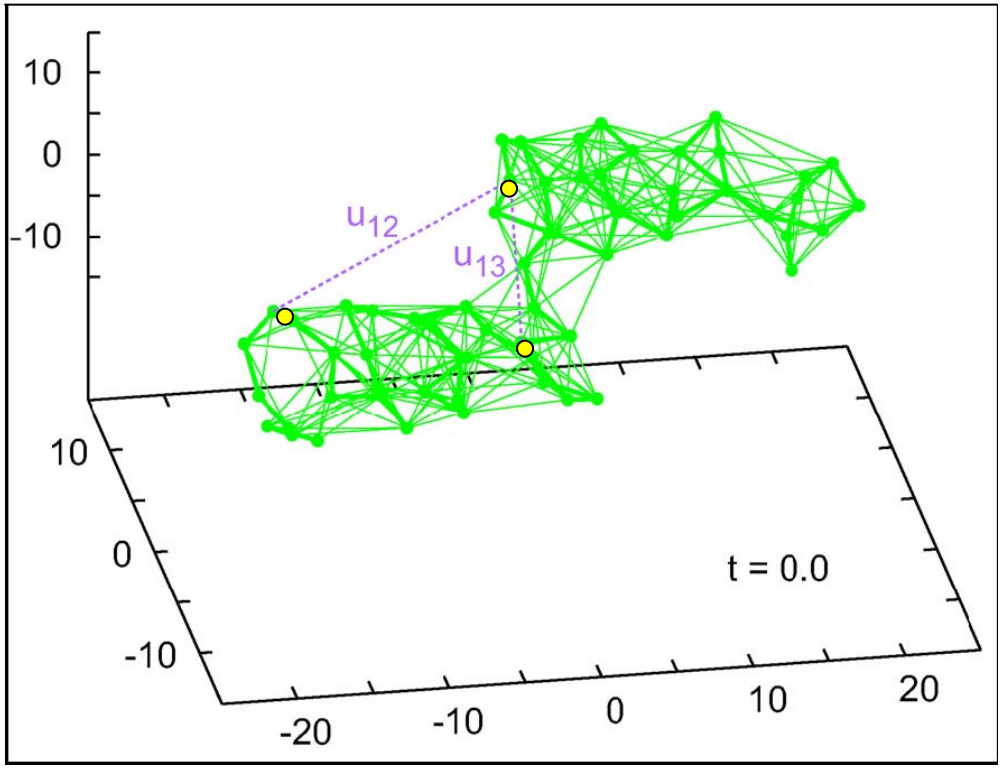
Random network

Designed machine

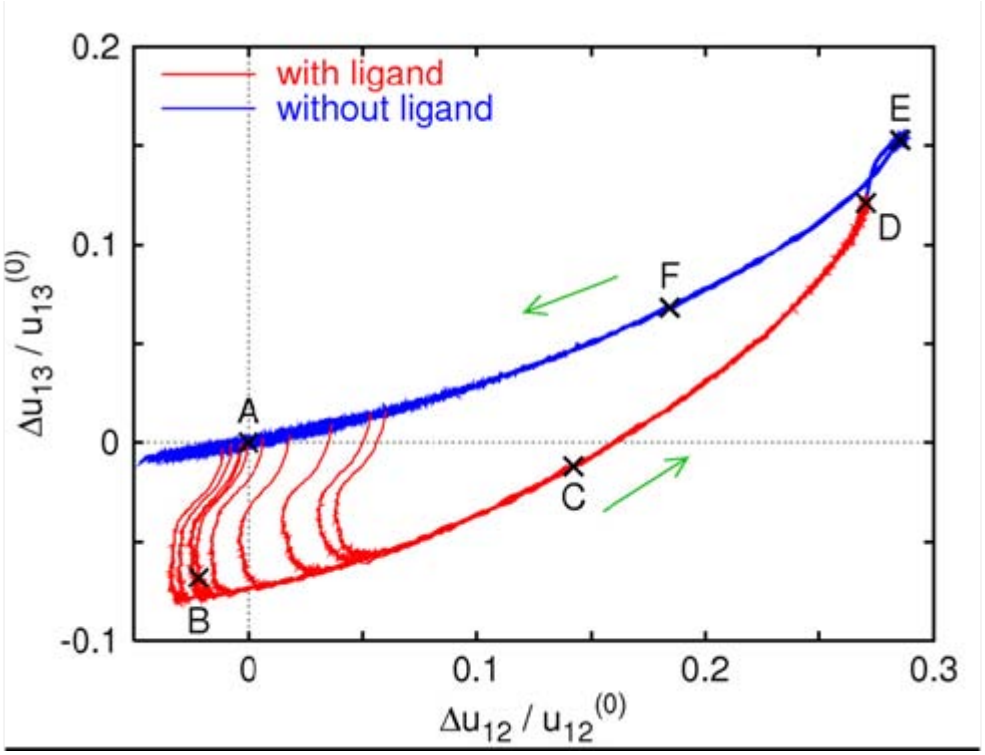
QuickTime™ and a
H.264 decompressor
are needed to see this picture.

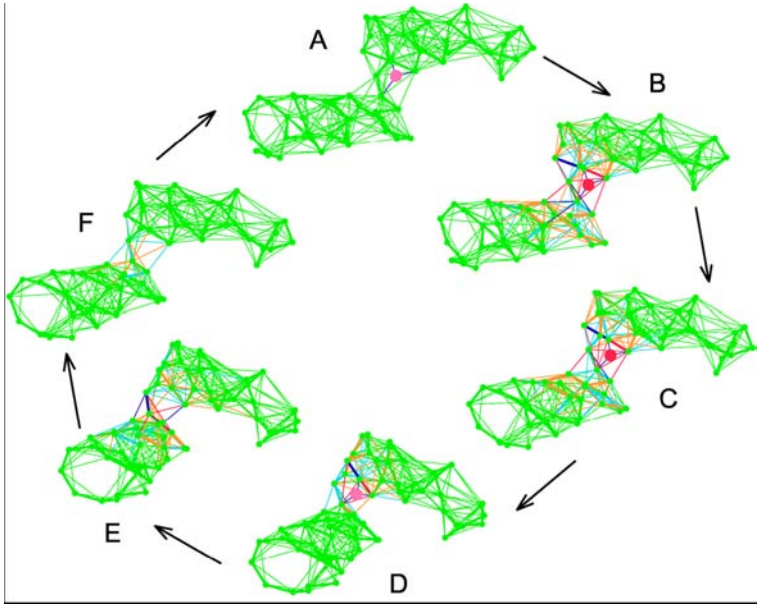
The cycle begins when an additional particle (ligand) is added to the network. The additional links are initially stretched -> energy is supplied. The complex relaxes to its equilibrium state. Then, „reaction“ occurs and the additional particle is removed. The network returns to its initial equilibrium state, completing the cycle.

Y. Togashi & AM „Nonlinear relaxation dynamics in elastic networks and design principles of molecular machines“ *PNAS* **104**, 8697 (2007)


10
0
-10
u_{12}
u_{13}
10
0
-10
t = 0.0
-20
-10
0
10
20

Cycles of artificial machine

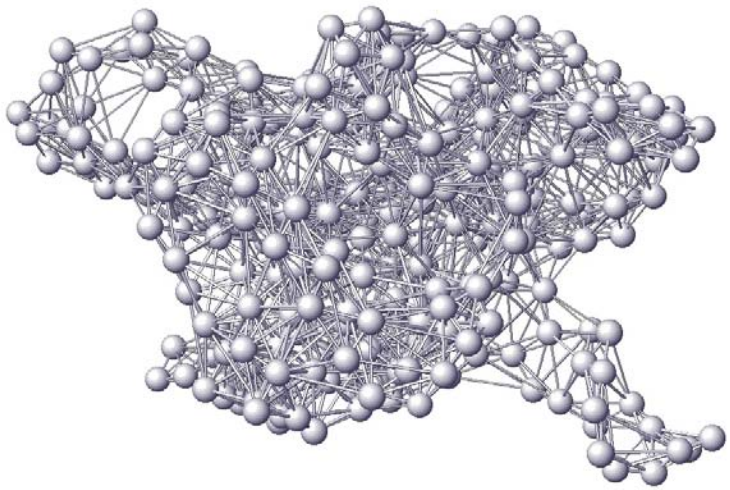




Binding of ligands is stochastic. Noise is added to the equations of motion of the particles.

Elastic networks of proteins

$$E = \frac{1}{2}\kappa \sum_{i,j=1}^{N} A_{ij}\left(d_{ij} - d_{ij}^{0}\right)^2$$



Kinesin

Two particles *i* and *j* are connected by an elastic string, if at equilibrium distance between them is shorter than the cut-off length l_0

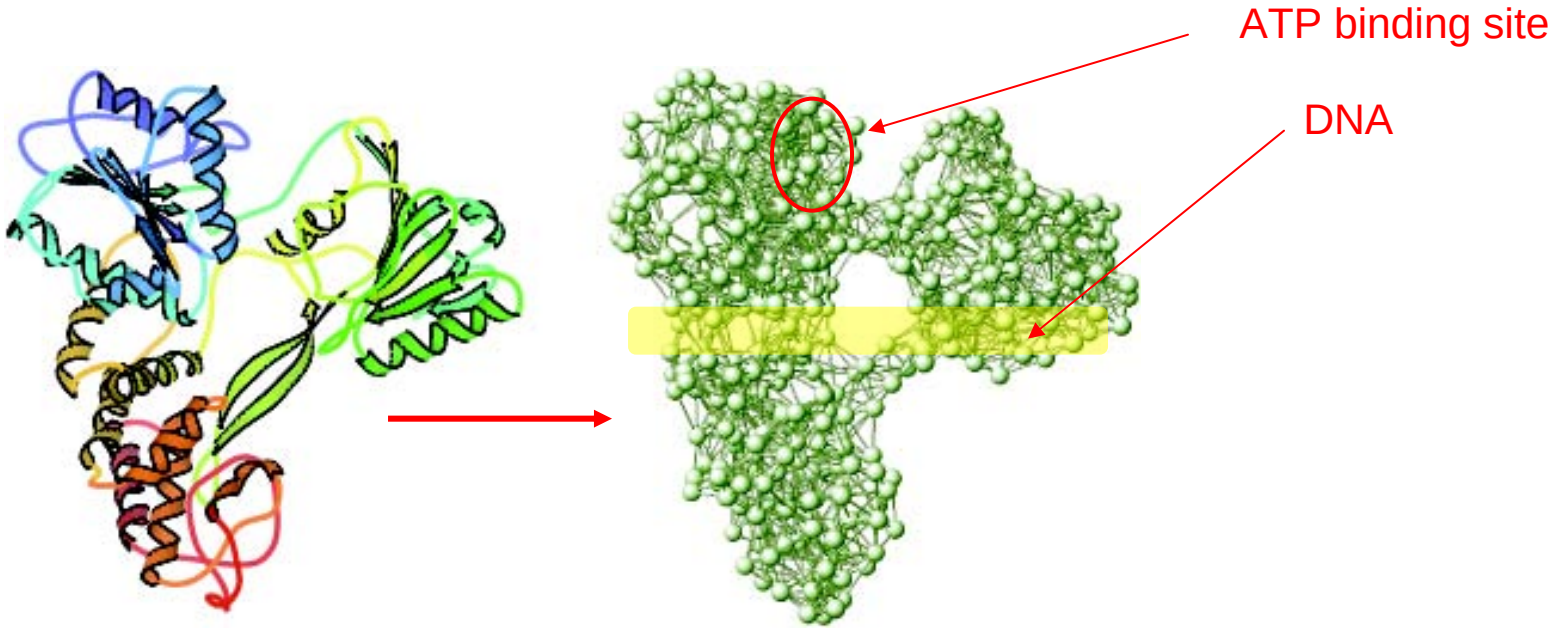
$$A_{ij} = 1, \text{ if } d_{ij}^{0} < l_0; \; A_{ij} = 0 \text{ otherwise}$$

Each particle corresponds to an atomic group (residue) in a protein. Equilibrium positions $\mathbf{R}_i^{(0)}$ of these particles are taken from the Protein Data Bank.

$$d_{ij}^{0} = \left|\mathbf{R}_i^{(0)} - \mathbf{R}_j^{(0)}\right|$$

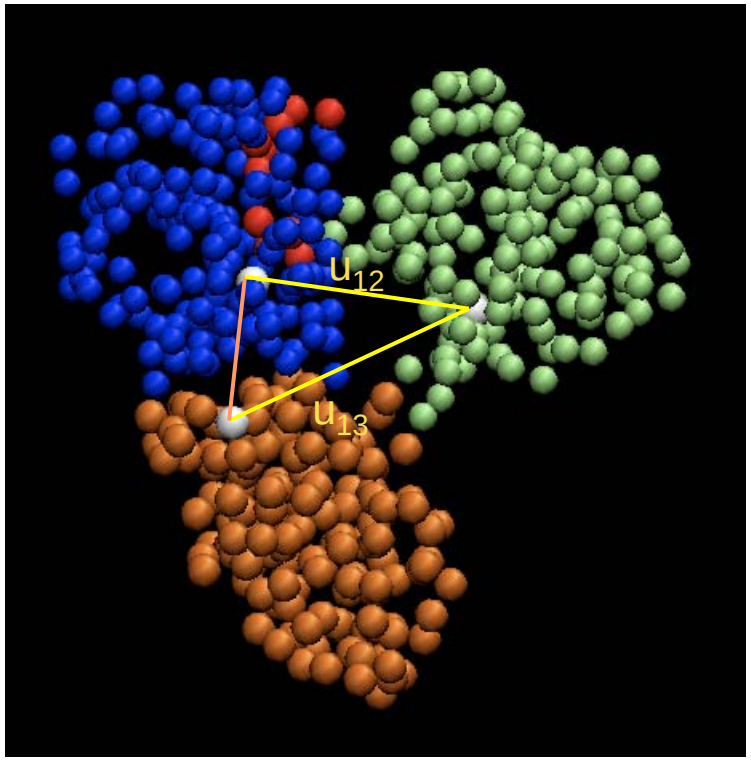
M. Tirion, *Phys. Rev. Lett.* **77**, 1905 (1996)

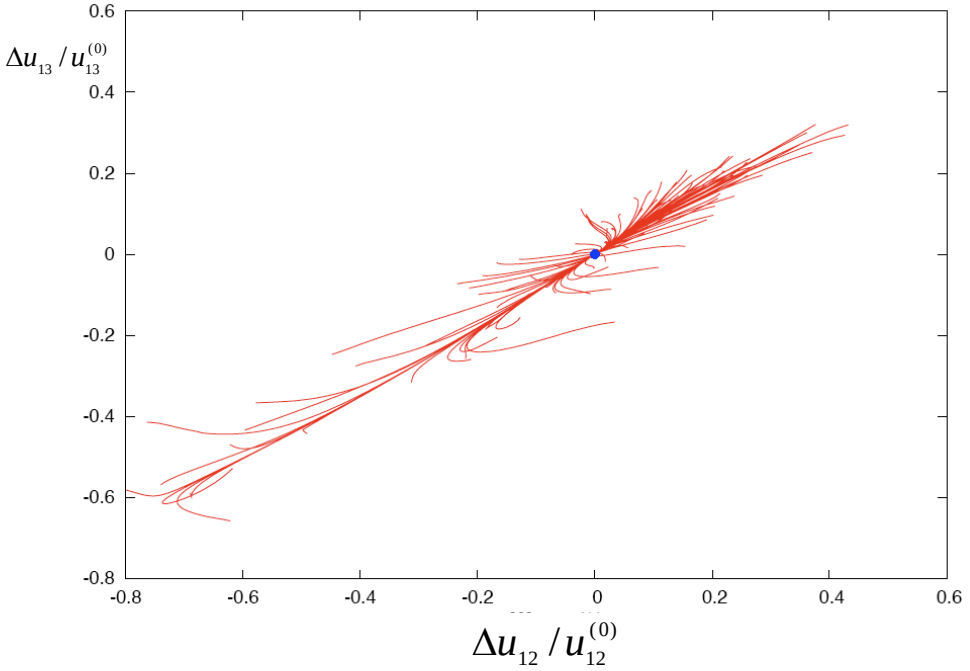
Elastic network of HVC helicase



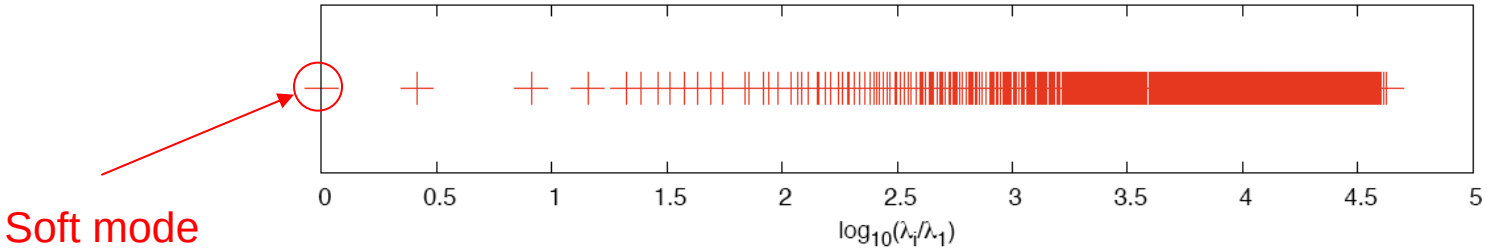
QuickTime™ and a
H.264 decompressor
are needed to see this picture.

HVC Helicase: nonliear ordered responses to random global perturbations



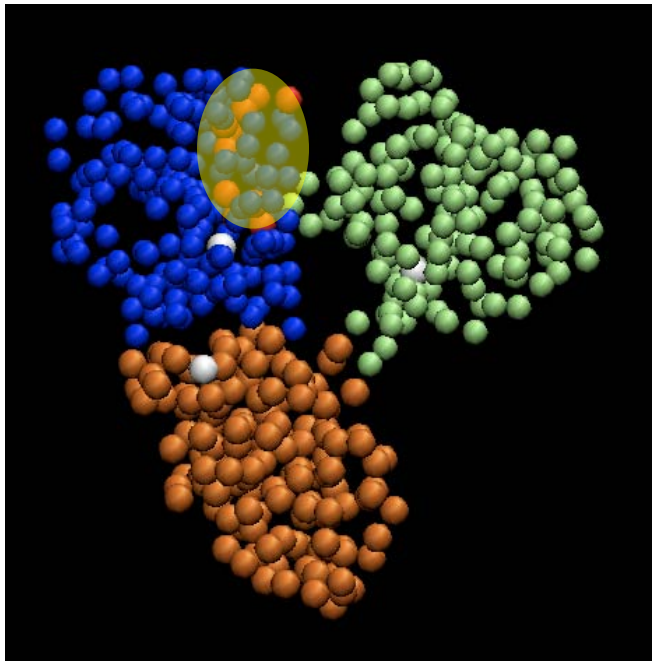


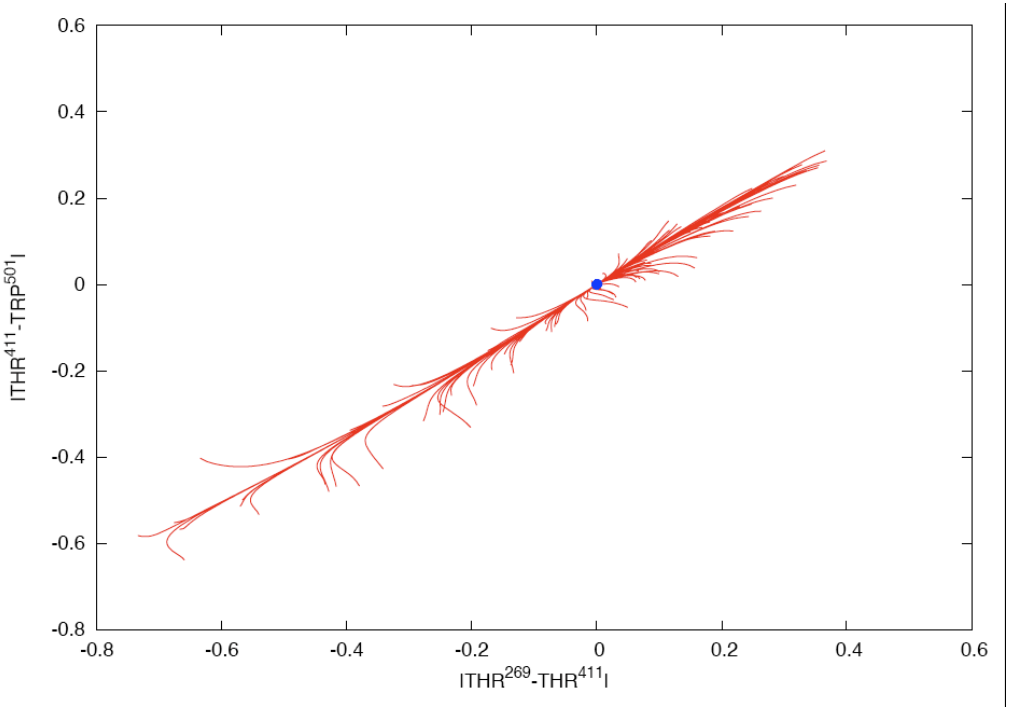
100 relaxation trajectories starting from different global distributed perturbations (without unfolding)



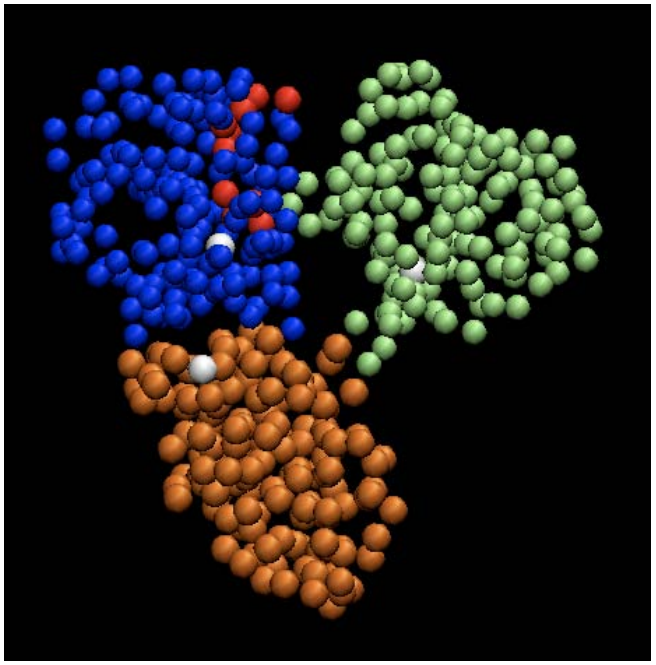
Soft mode

HVC Helicase: responses to random *local* perturbations around the ATP binding site





Random contracting forces are applied only within the ATP binding site



QuickTime™ and a
None decompressor
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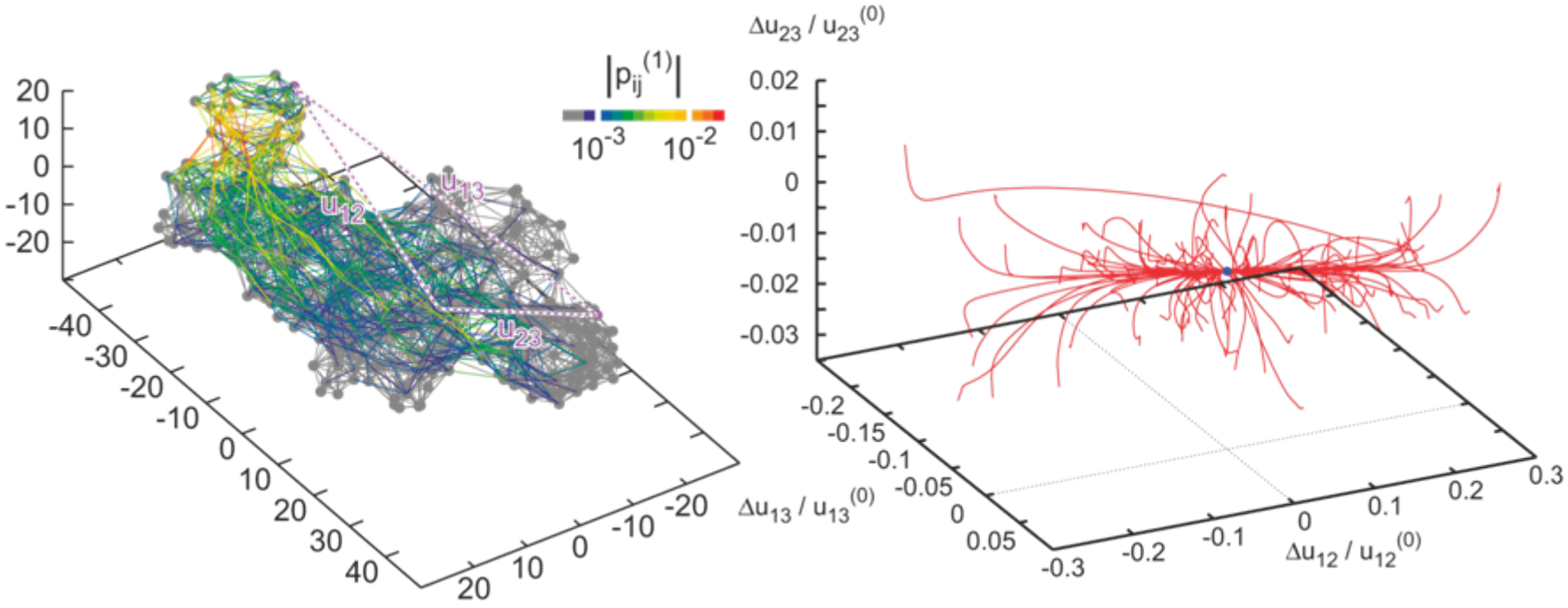
QuickTime™ and a
H.264 decompressor
are needed to see this picture.

H. Flechsig & AM, 2008

F1-ATPase (single β-unit)



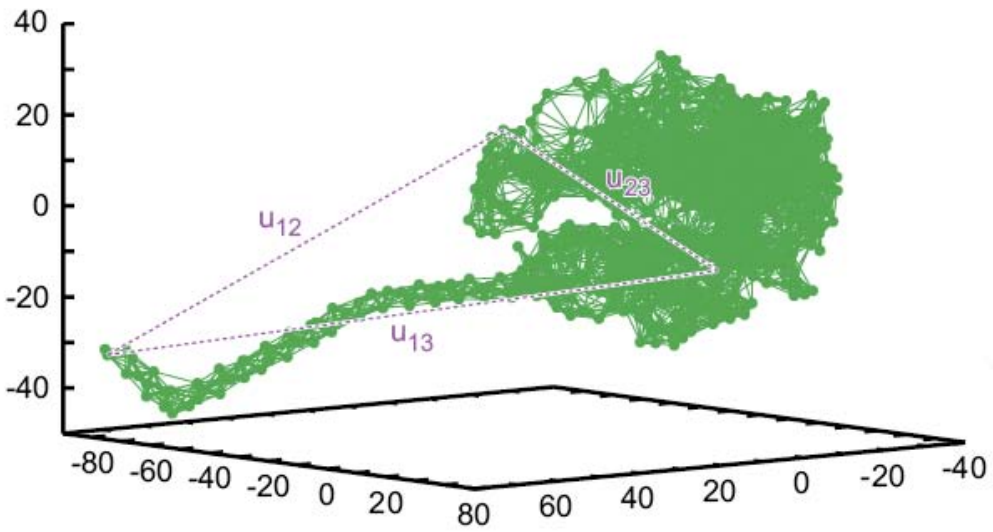
Initial states are prepared by applying random static forces to *all* particles,

$$\frac{1}{N}\sum_{i=1}^{N}|\mathbf{F}_i| = f$$

100 nonlinear relaxation trajectories starting from different initial conditions (without unfolding)

Y. Togashi & AM, *PNAS* **104**, 8697 (2007)

Elastic network of Myosin II



QuickTime™ and a
YUV420 codec decompressor
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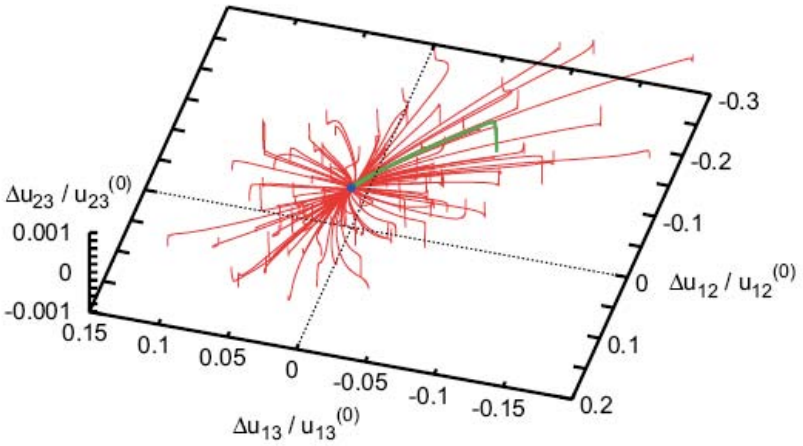
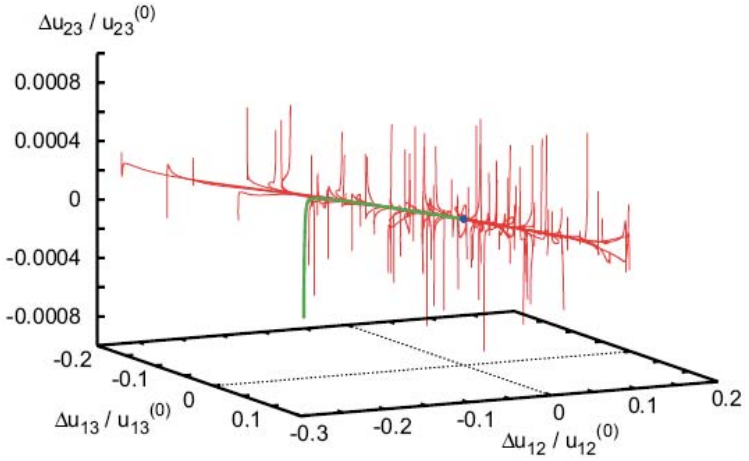
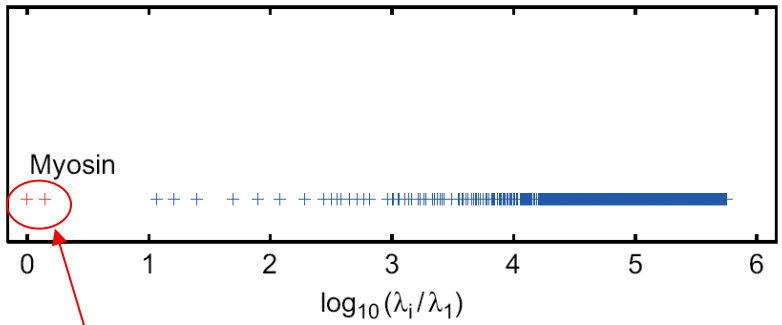
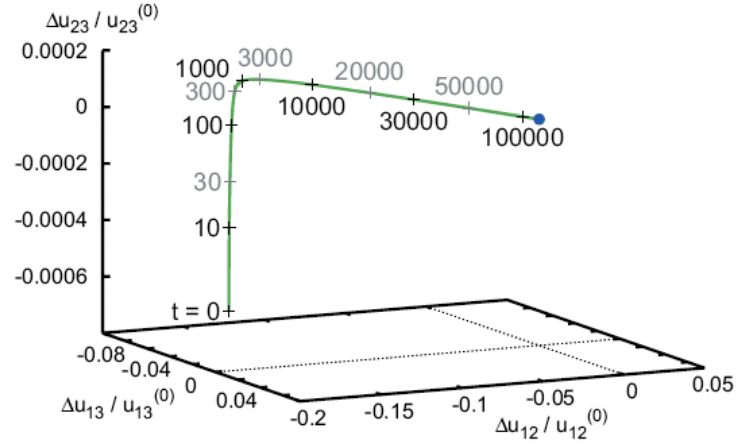


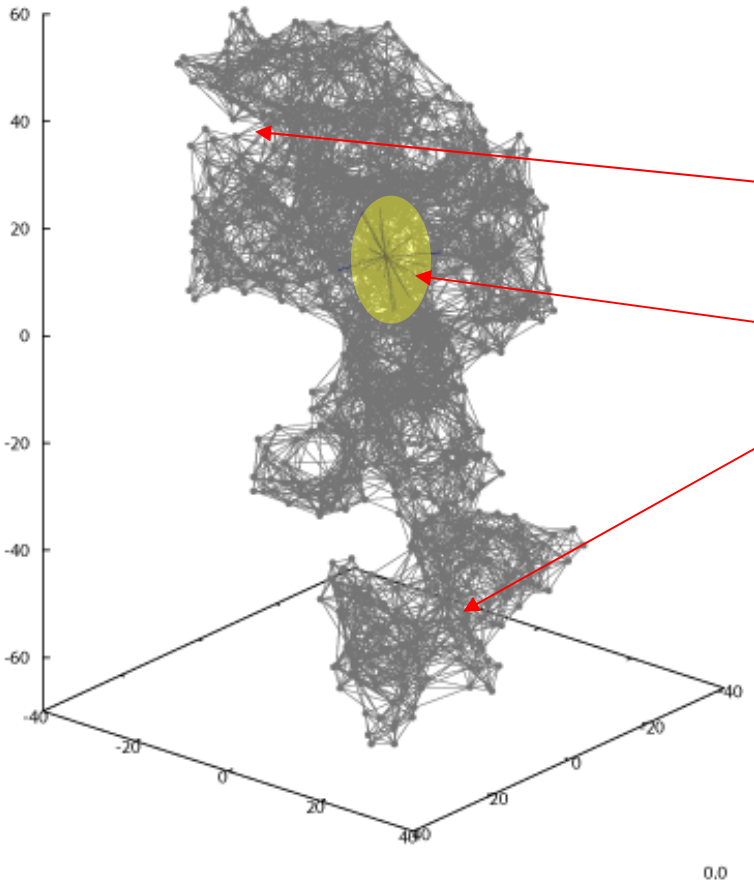


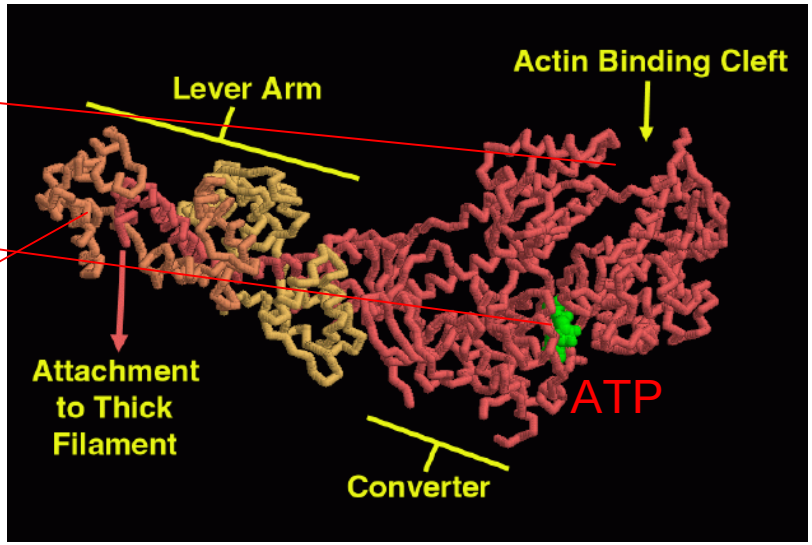


Two soft modes



Myosin II



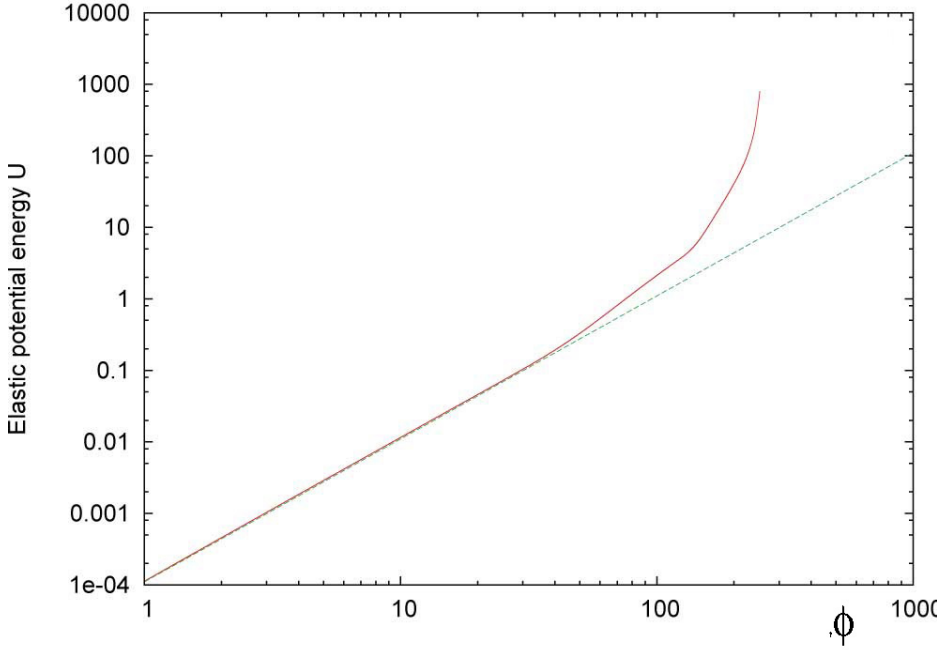


Y. Togashi & AM, 2008

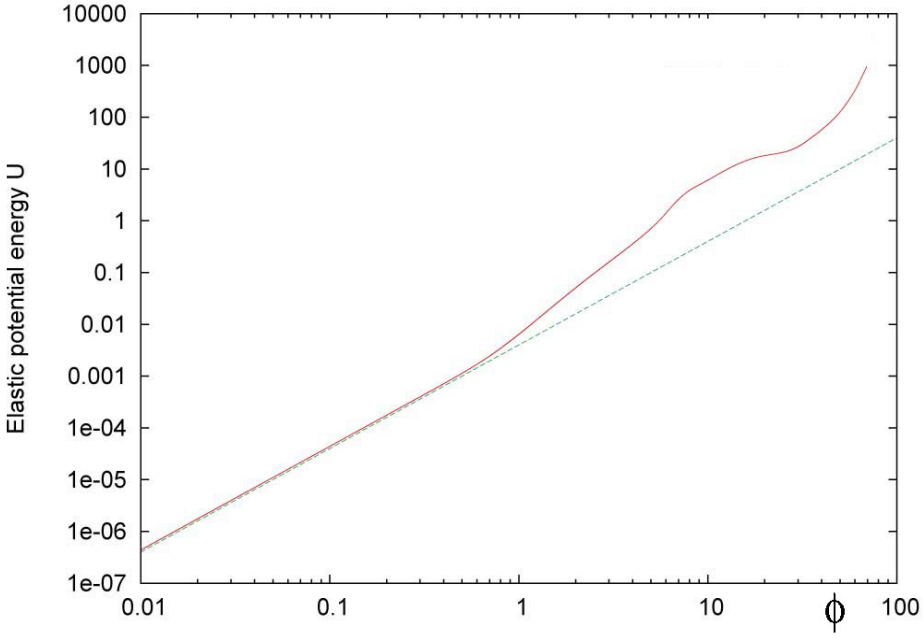
Nonlinear response of the elastic network of myosin to the introduction of a *fictitios* ligand into the ATP binding pocket and conformational relaxation after the removal of the ligand.

Mechanical coordinates of two molecular motors

$$\frac{d\phi}{dt} = -\frac{\partial U}{\partial \phi}$$



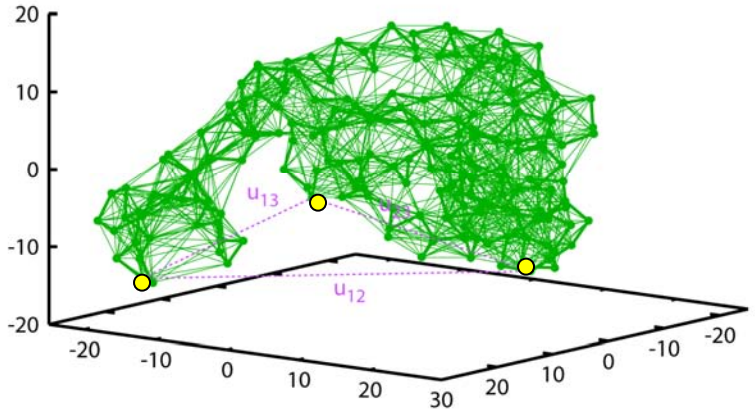
Myosin V

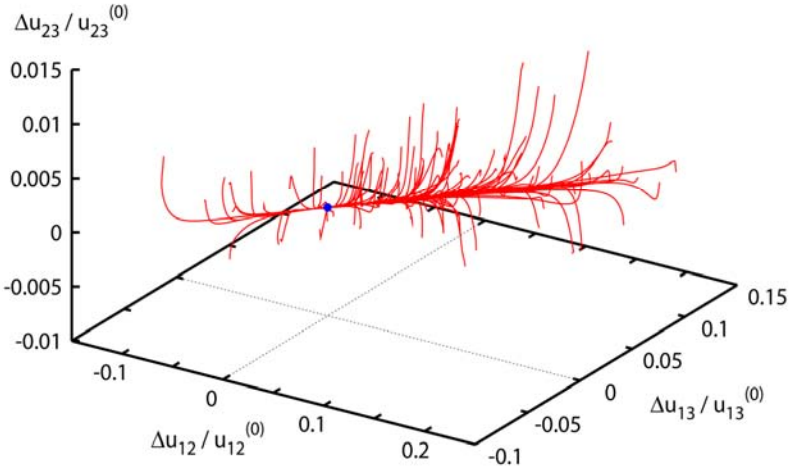


Kinesin

In contrast to myosin, slow conformational motions in kinesin are strongly non-harmonical

Enzyme Adenylate Kinase

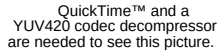


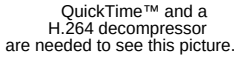


Relaxation trajectories starting from 100 different initial conditions, prepared by applying random static forces to all nodes

Full cycles, including solvent hydrodynamics...

„Multiparticle collision dynamics“





Artificial designed machine

A. Cressman, Y.Togashi, AM, and R.Kapral „Mesoscale modeling of molecular machines: Cyclic dynamics and hydrodynamical fluctuations“ *Phys. Rev.* **E77**, 050901(R) (2008)

Real protein machine
Adenylate Kinase

C. Echeveria, Y. Togashi, AM & R. Kapral, 2008

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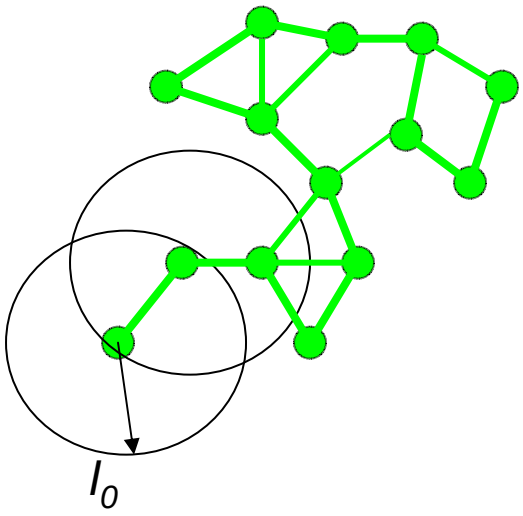
Dr. Yuichi Togashi

Prof. Raymond Kapral

Dr. Carlos Echeveria

Andrew Cressman

Random elastic networks



N = 64