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Flexible Docking

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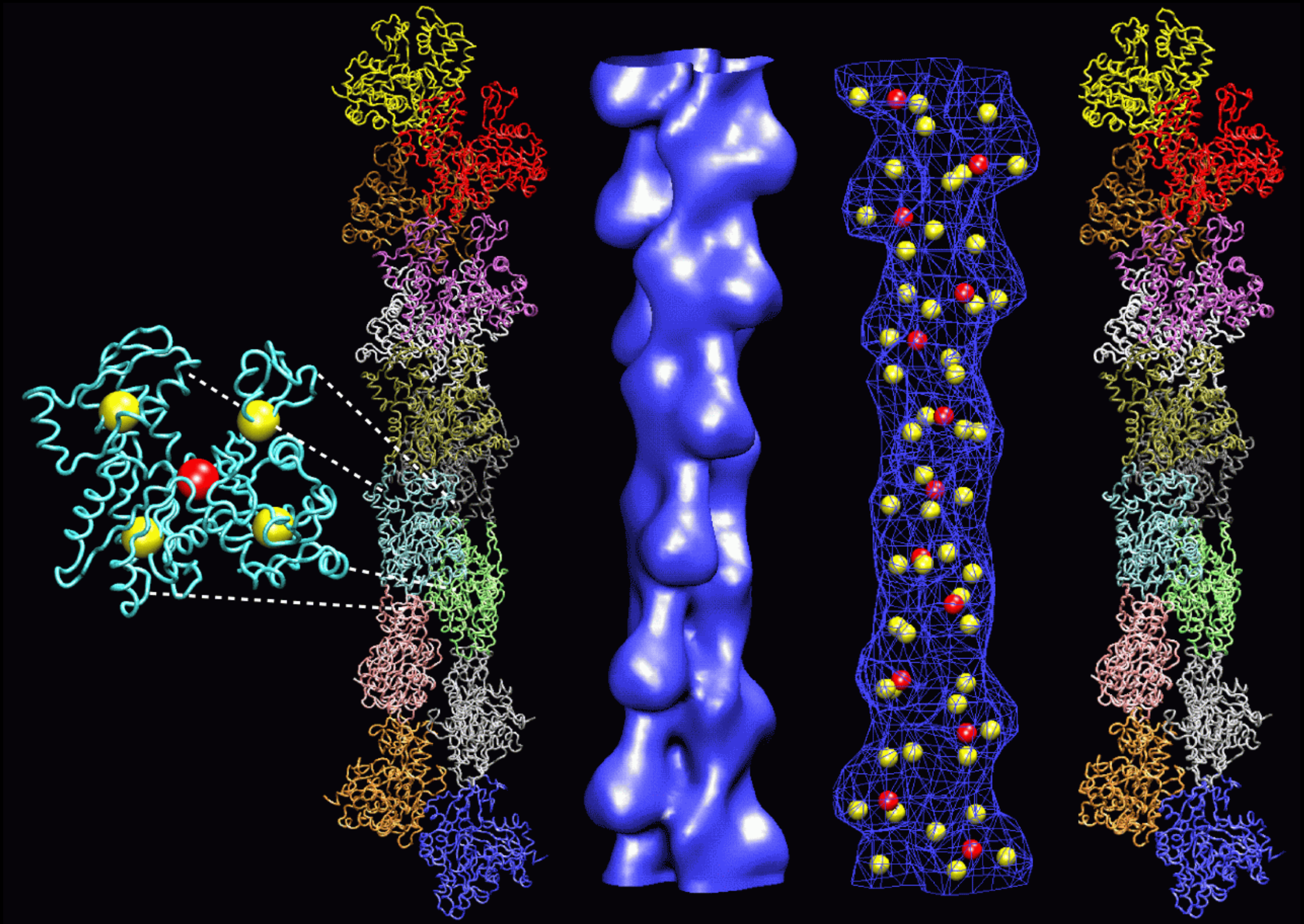
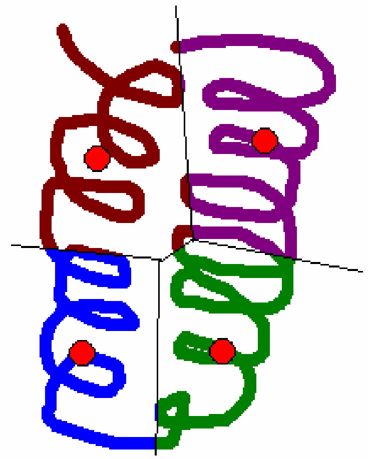
“Simulated Markers”



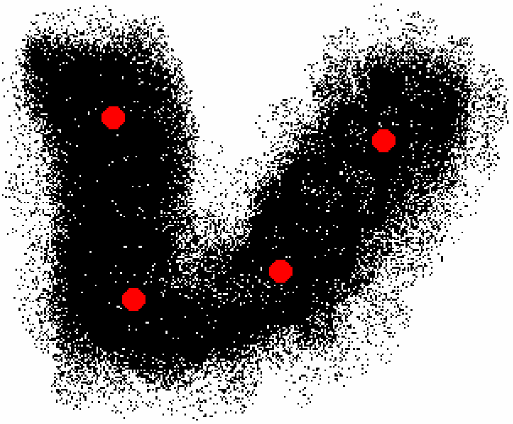
Actin filament: Reconstruction from EM data at 20Å resolution rmsd: 1.1Å

Application in Flexible Fitting

Xtal
structure



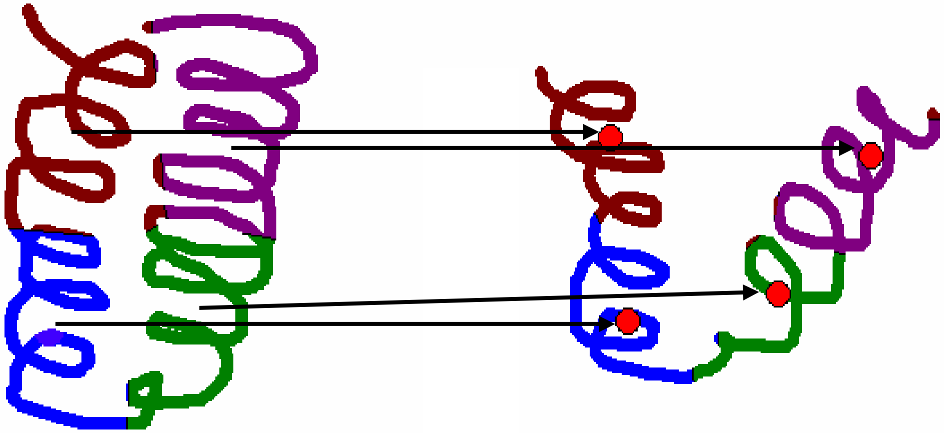
$w_j^{(h)}$



$w_j^{(l)}$

3D EM
reconstruction

constrain
centroids



molecular
dynamics
simulation

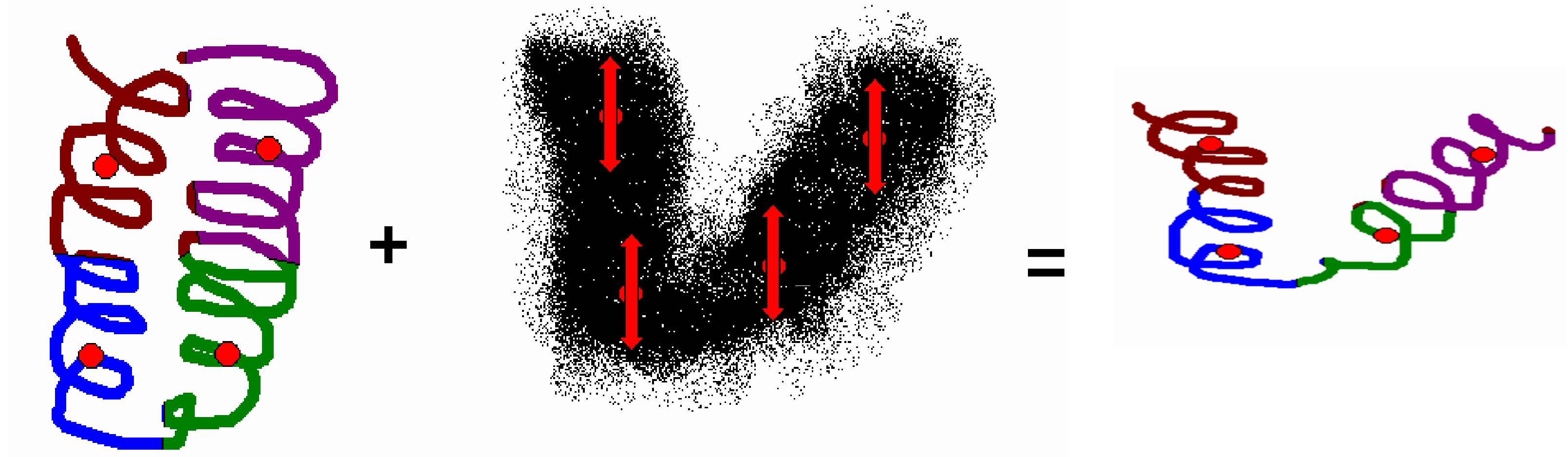
Stereochemical Quality of Flexible Fitting

The atomic model has many more degrees of freedom than there are independent pieces of information in the EM map. Hence, there is the danger that over fitting distorts the structure

How can over fitting be avoided? Reduce noise by eliminating “inessential” degrees of freedom!…

Skeletons Limit the Effect of Noise:

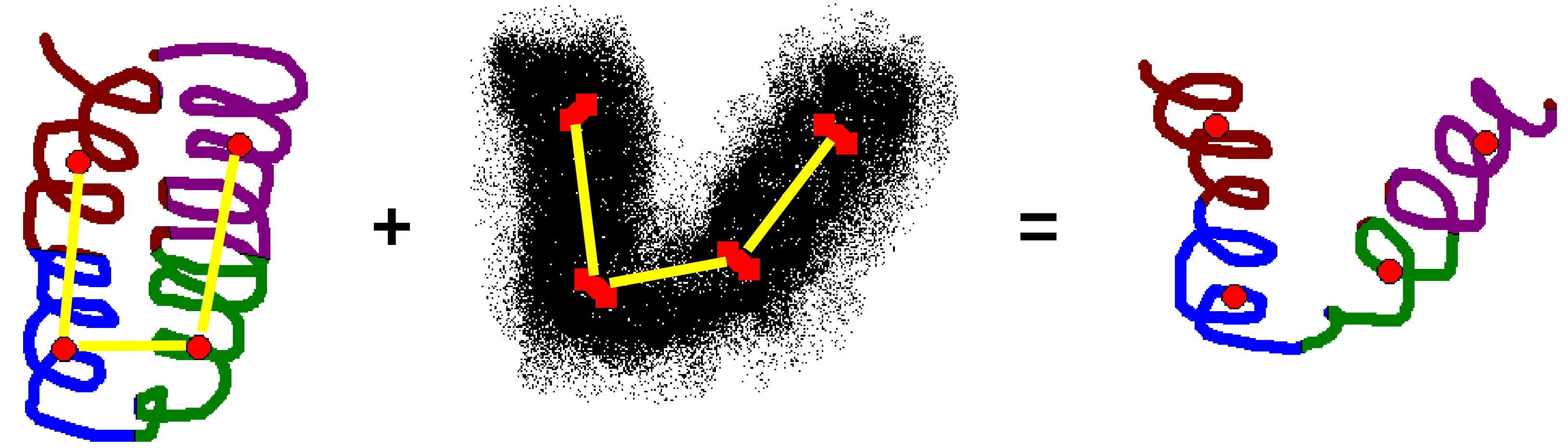
freezing inessential degrees of freedom:



unrestrained markers

exp. and meth. uncertainty

distortion

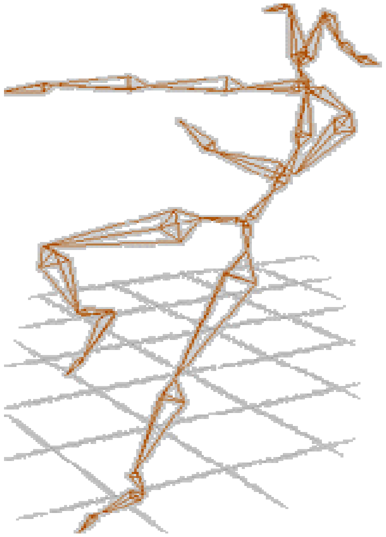


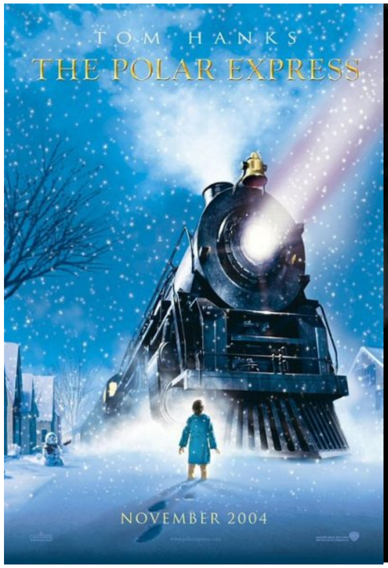
skeleton

distance constraints

less distortion

Fitting Skeletons: Motion Capture



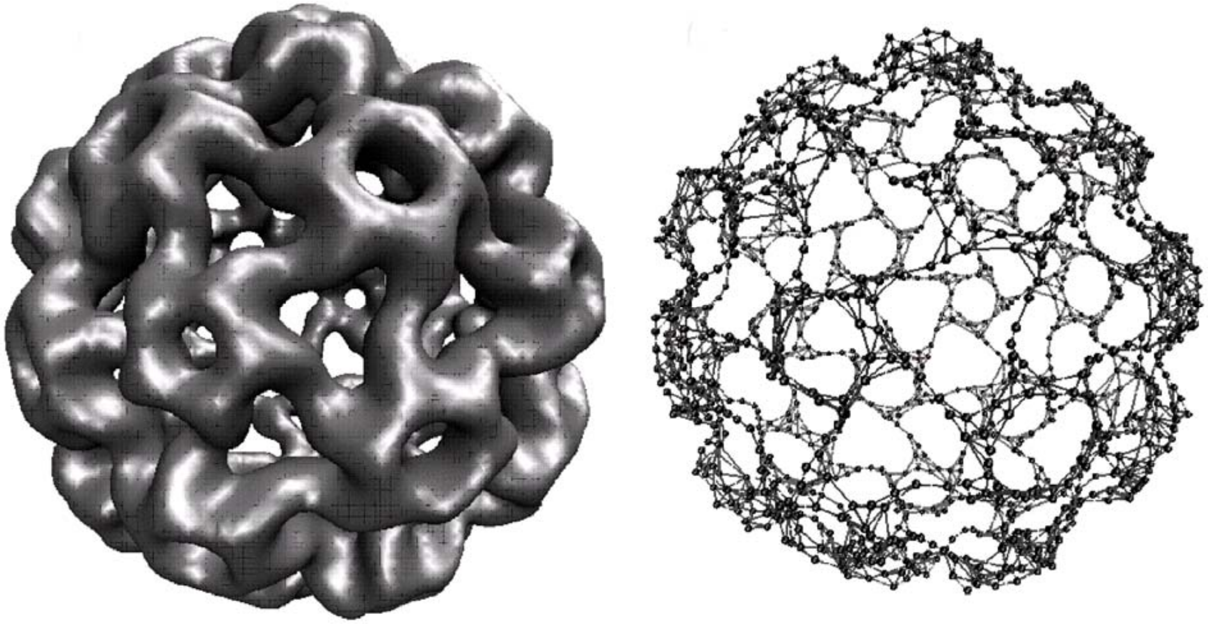


Motion Capture Network

Topology Representing Neural Network
(Martinetz and Schulten, 1993)

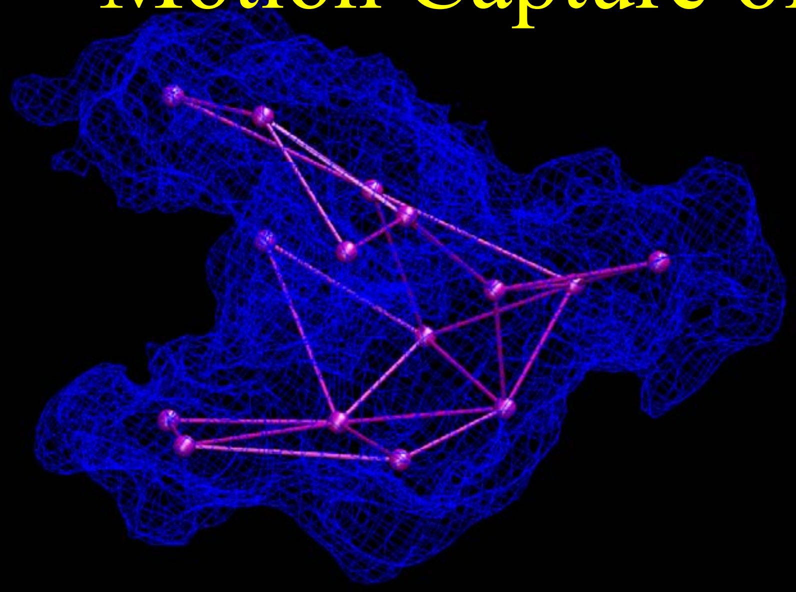
+

SHAKE Distance Constraints
(van Gunsteren, 1977)

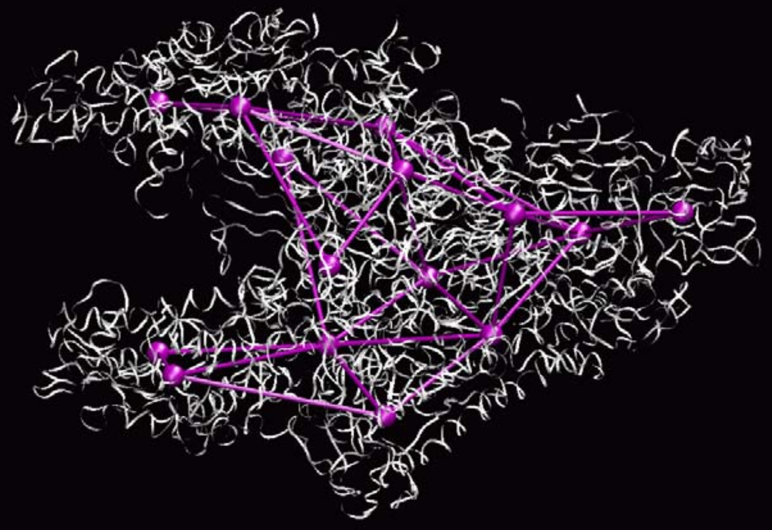


Neurocomputing (2004) 56:365

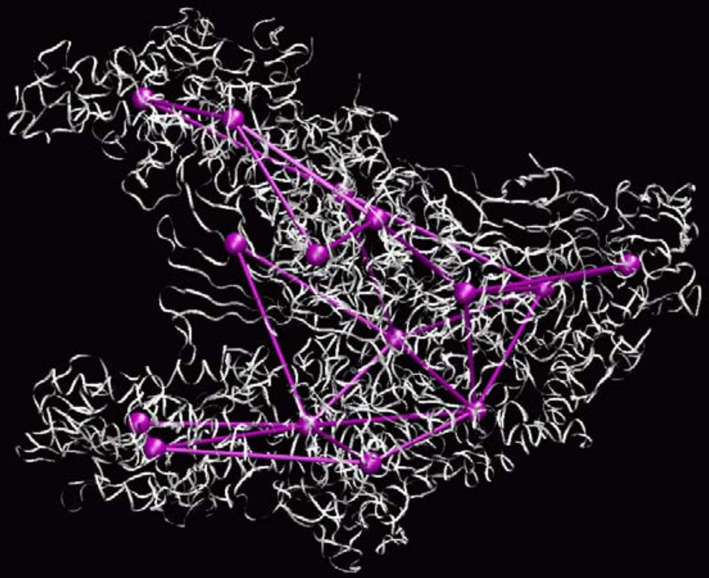
Motion Capture of RNA Polymerase



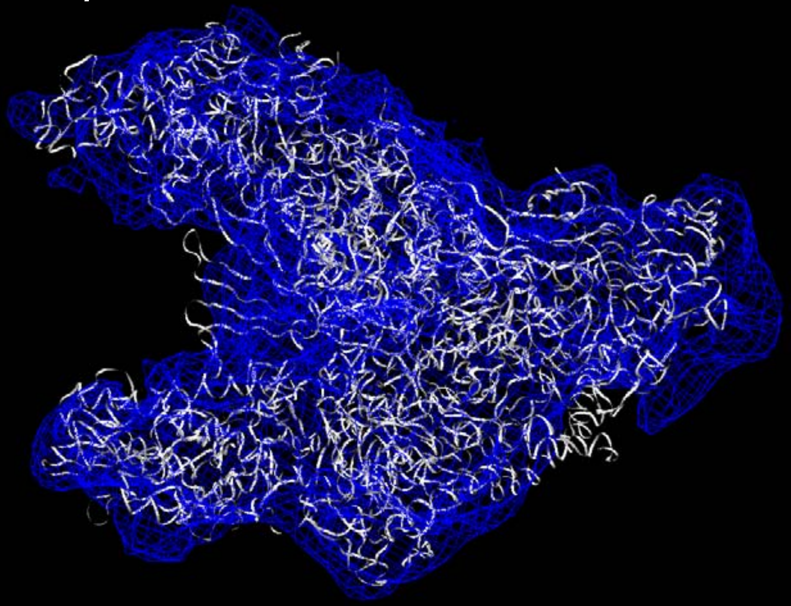
Taq-like single molecule map



Taq RNAP x-tal structure

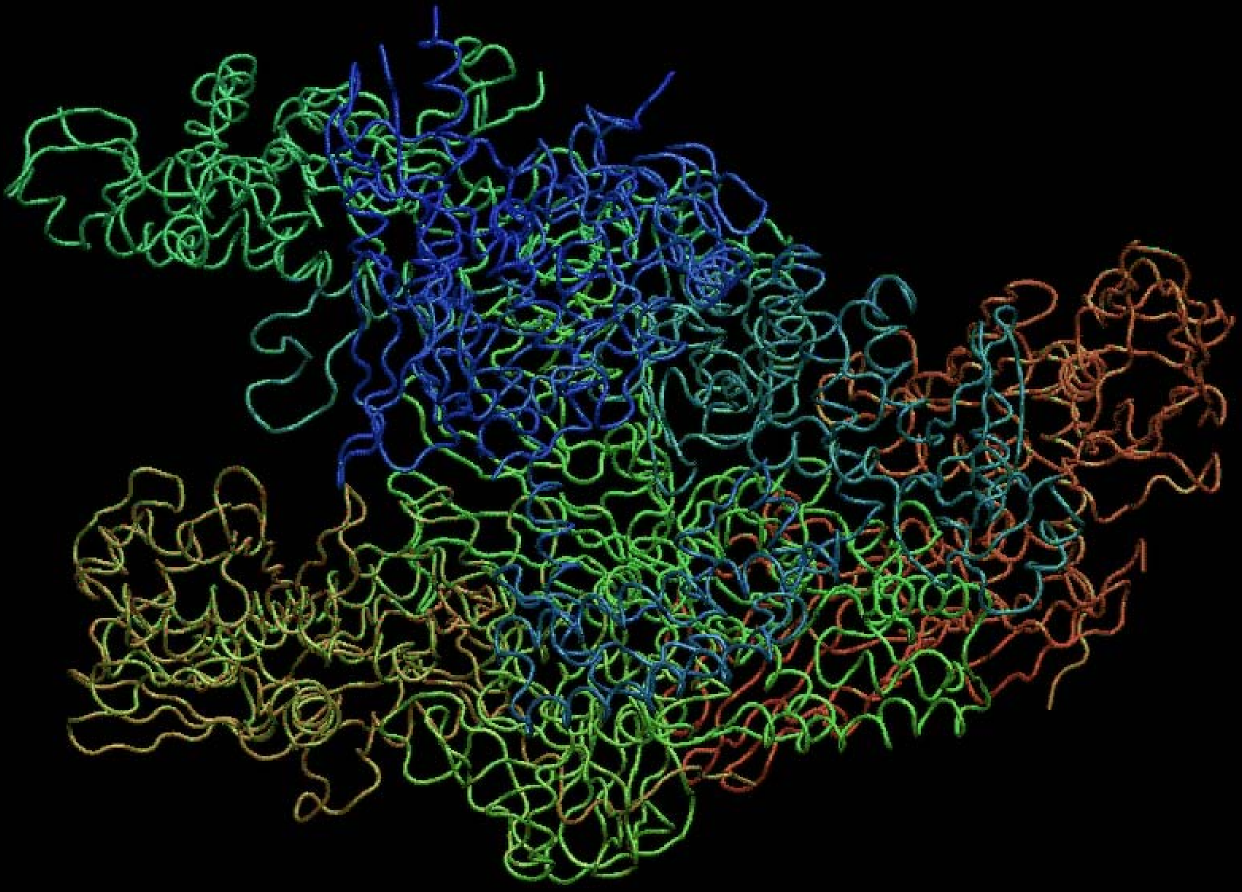


flexible fitting (15 vectors)



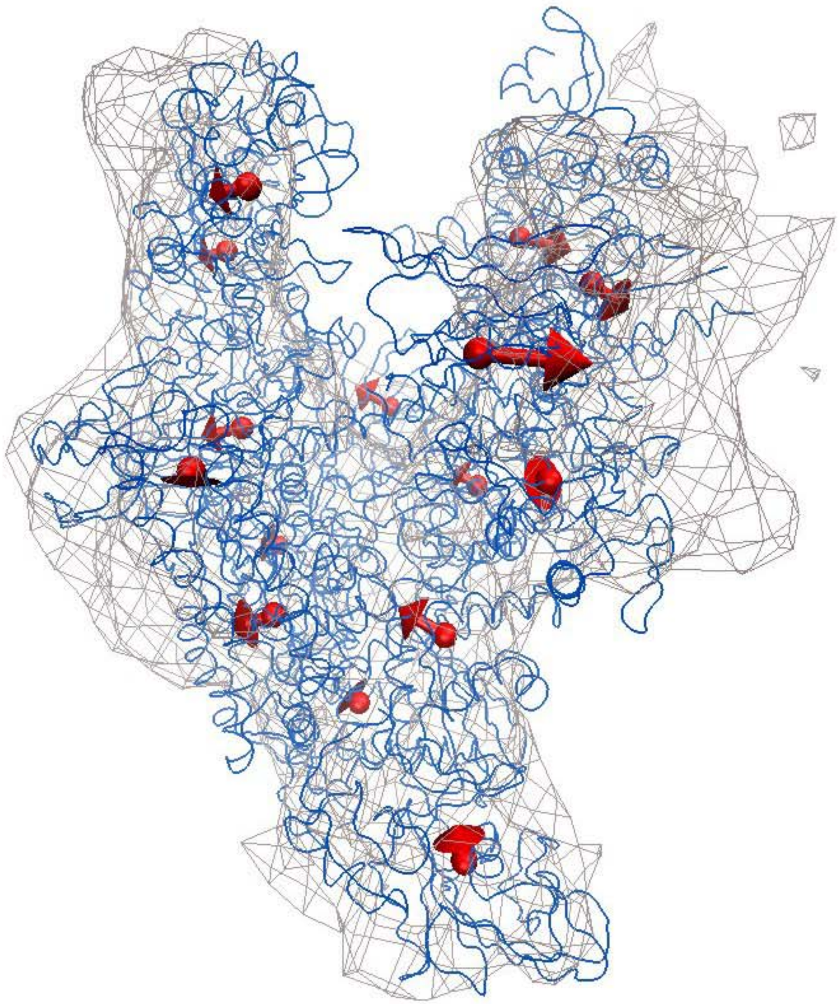
final result

Domain Motions

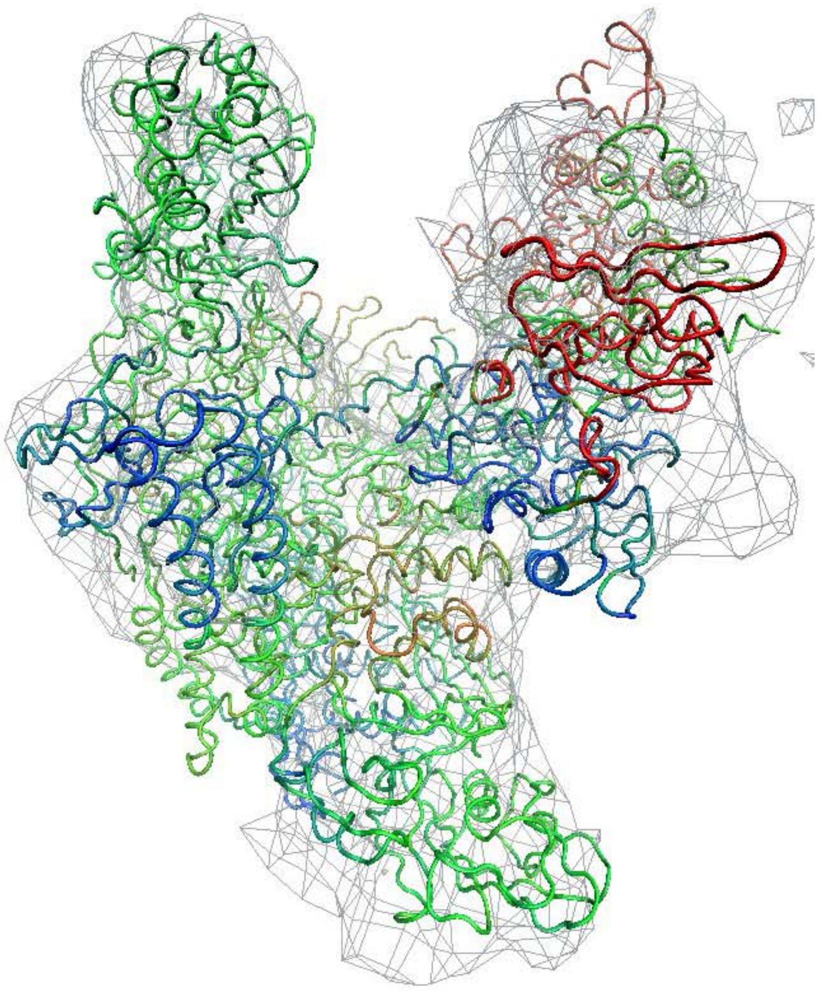


Flexing of the RNAP “jaws” suggests a jaw-closing in presence of DNA
PNAS (2002) 99:4296
Cell (2003) 114:335

What Information is Used?



Displacements



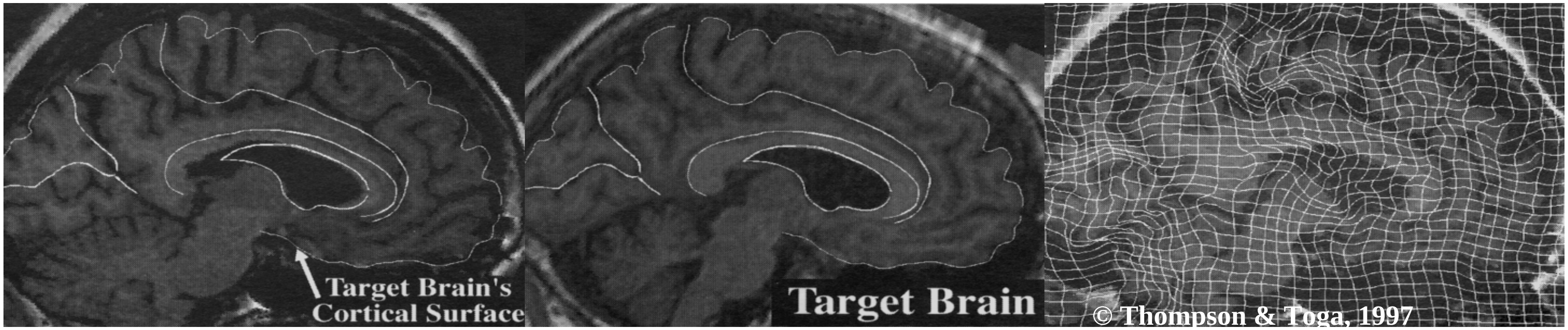
Molecular Dynamics

Molecular Dynamics vs. Interpolation

MD simulation requires an expert user and hours of preparation. We know a sparse estimation of the displacement field at markers. Can we extend the sparse estimate to the full space by an inexpensive interpolation?

Interpolation Pros:

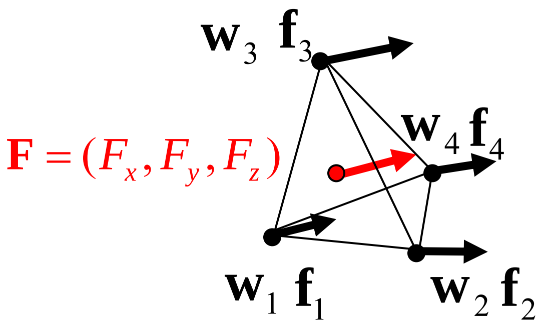
- Ease of use / implementation
- Detailed mass rearrangement plan.
- Linear or nonlinear registration of features
- Used in neuroscience and machine vision:



© Thompson & Toga, 1997

(i) Piecewise-Linear Inter- / Extrapolation

For each probe position find 4 closest vectors.



Ansatz: $F_x(x,y,z) = ax + by + cz + d$

$$F_x(\mathbf{w}_1) = f_{1,x},$$
$$F_x(\mathbf{w}_2) = f_{2,x},$$
$$F_x(\mathbf{w}_3) = f_{3,x},$$
$$F_x(\mathbf{w}_4) = f_{4,x} \quad \text{(similar for } F_y, F_z\text{)}.$$

Cramer's rule:

$$a = \frac{\begin{vmatrix} f_{1,x} & w_{1,y} & w_{1,z} & 1 \\ f_{2,x} & w_{2,y} & w_{2,z} & 1 \\ f_{3,x} & w_{3,y} & w_{3,z} & 1 \\ f_{4,x} & w_{4,y} & w_{4,z} & 1 \end{vmatrix}}{D}, \quad b = \frac{\begin{vmatrix} w_{1,x} & f_{1,y} & w_{1,z} & 1 \\ w_{2,x} & f_{2,y} & w_{2,z} & 1 \\ w_{3,x} & f_{3,y} & w_{3,z} & 1 \\ w_{4,x} & f_{4,y} & w_{4,z} & 1 \end{vmatrix}}{D}, \ \cdots, \quad D = \begin{vmatrix} w_{1,x} & w_{1,y} & w_{1,z} & 1 \\ w_{2,x} & w_{2,y} & w_{2,z} & 1 \\ w_{3,x} & w_{3,y} & w_{3,z} & 1 \\ w_{4,x} & w_{4,y} & w_{4,z} & 1 \end{vmatrix}$$

(ii) Non-Linear Kernel Interpolation

Consider all k vectors and interpolation kernel function $U(r)$.

Ansatz:

$$F_x(x,y,z) = a_1 + a_x x + a_y y + a_z z + \sum_{k=1}^{k} b_i \cdot U\left(\left|\mathbf{w}_i - (x,y,z)\right|\right)$$

$$F_x(\mathbf{w}_i) = f_{i,x}, \ \forall i \quad \text{(similar for } F_y, F_z\text{)}.$$

Solve :

$$\mathrm{L}^{-1}(f_{1,x},\cdots,f_{k,x},0,0,0,0) = (b_1,\cdots,b_k,a_1,a_x,a_y,a_z)^{\mathrm{T}},$$

$$\text{where} \quad \mathbf{L} = \left(\begin{array}{c|c} \mathbf{P} & \mathbf{Q} \\ \hline \mathbf{Q}^{\mathrm{T}} & \mathbf{0} \end{array}\right), \quad \mathbf{Q} = \begin{pmatrix} 1 & w_{1,x} & w_{1,y} & w_{1,z} \\ \cdots & \cdots & \cdots & \cdots \\ 1 & w_{k,x} & w_{k,y} & w_{k,z} \end{pmatrix}, \ k \times 4,$$

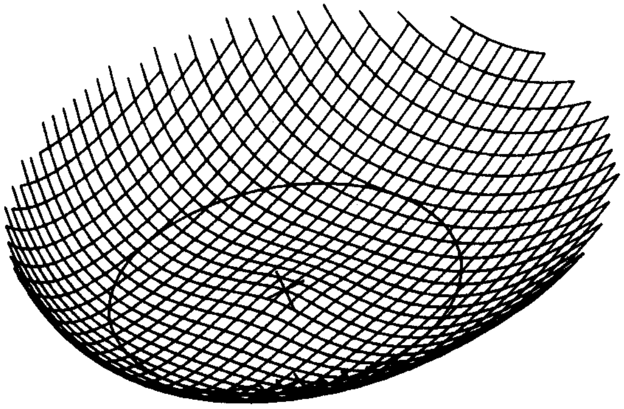
$$\mathbf{P} = \begin{pmatrix} 0 & U(w_{12}) & \cdots & U(w_{1k}) \\ U(w_{21}) & 0 & \cdots & U(w_{2k}) \\ \cdots & \cdots & \cdots & \cdots \\ U(w_{k1}) & U(w_{k2}) & \cdots & 0 \end{pmatrix}, \ k \times k.$$

Bookstein "Thin-Plate" Splines

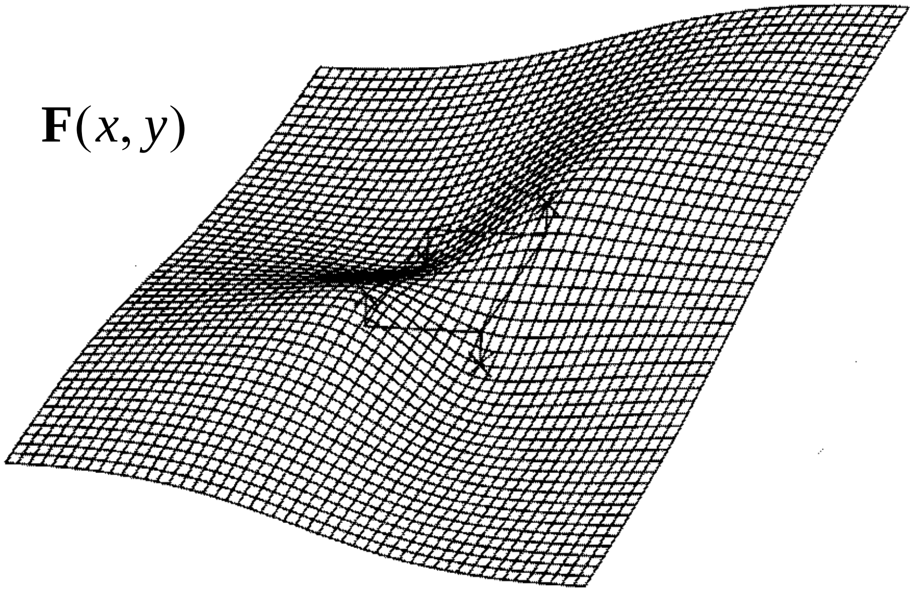
- kernel function $U(r)$ is principal solution of biharmonic equation that arises in elasticity theory of thin plates:

$$\boxed{\Delta^2 U(r) = \nabla^4 U(r) = \delta(r).}$$

- variational principle: $U(r)$ minimizes the bending energy (not shown).
- 1D: $U(r) = |r^3|$ (cubic spline)
- 2D: $U(r) = r^2 \log r^2$
- 3D: $U(r) = |r|$

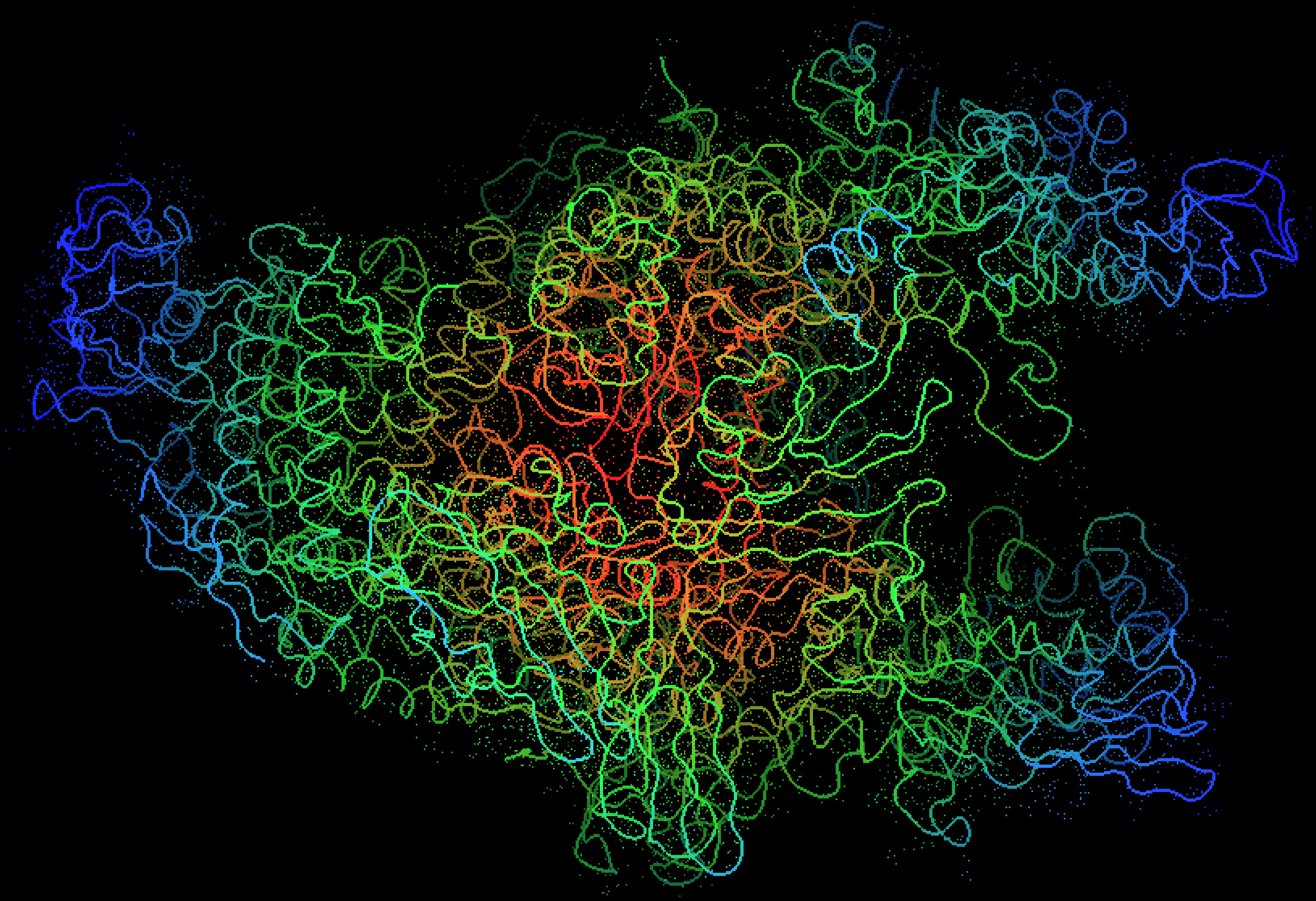


2D: $U(r)$

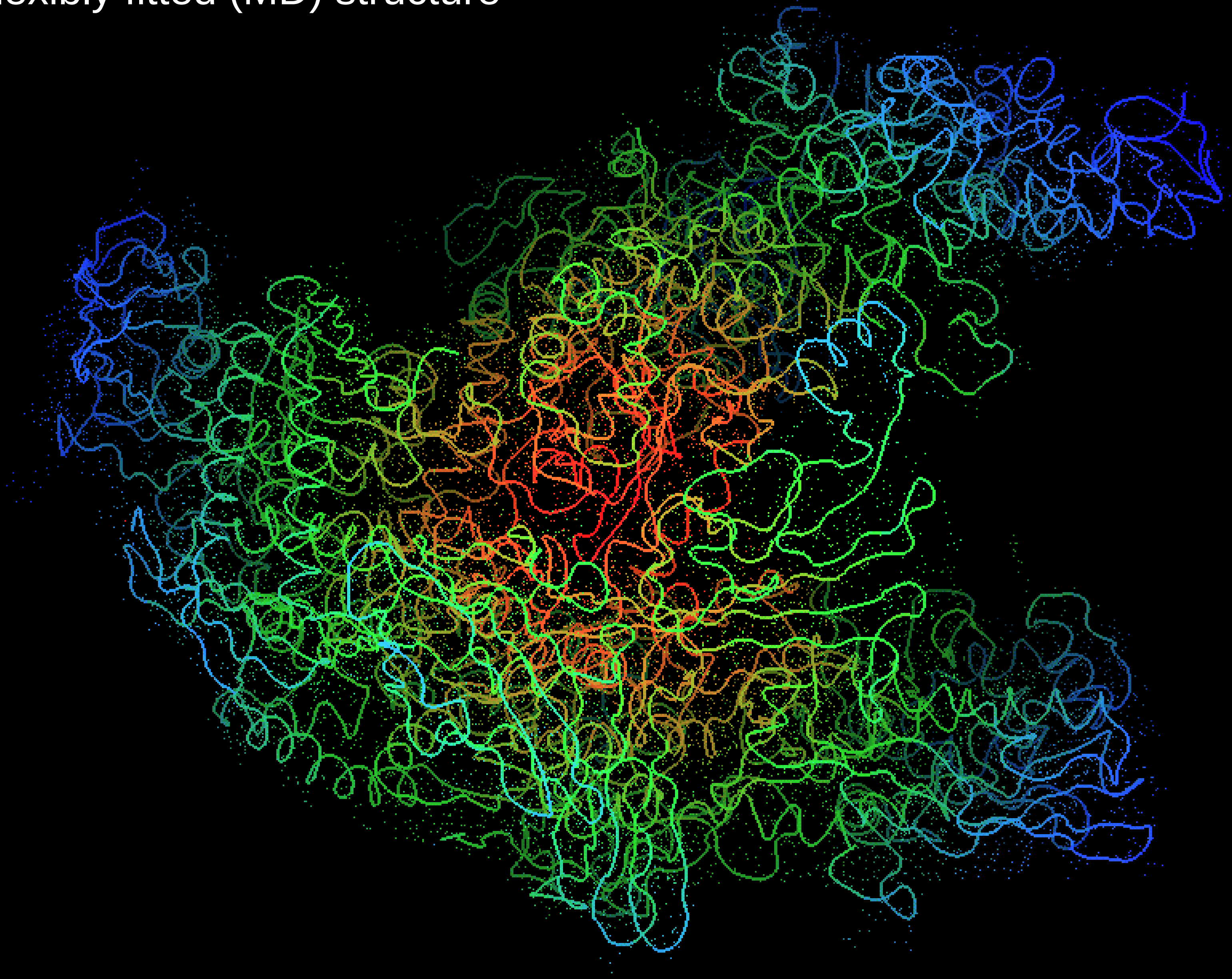


$\mathbf{F}(x, y)$

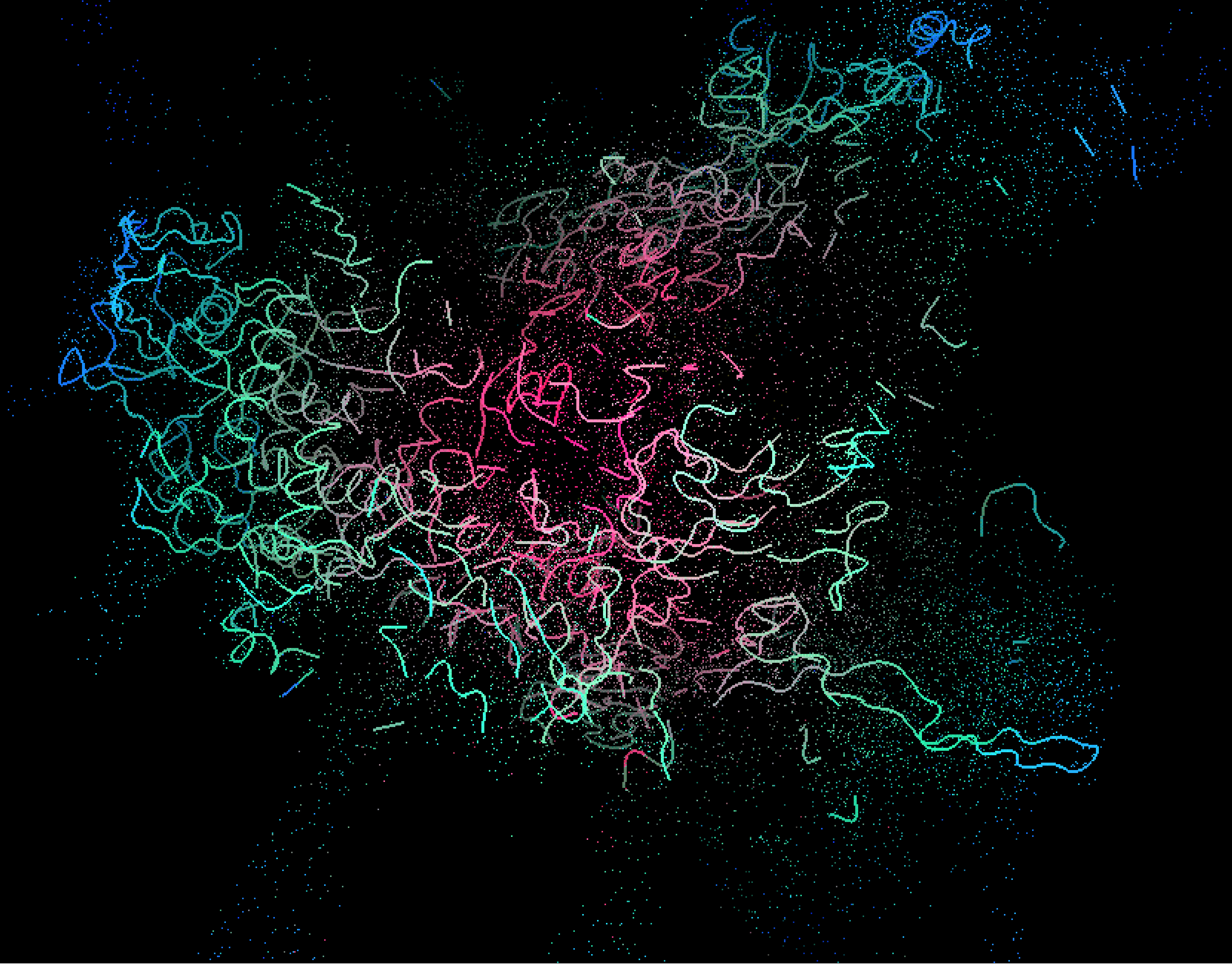
Taq RNAP x-tal structure



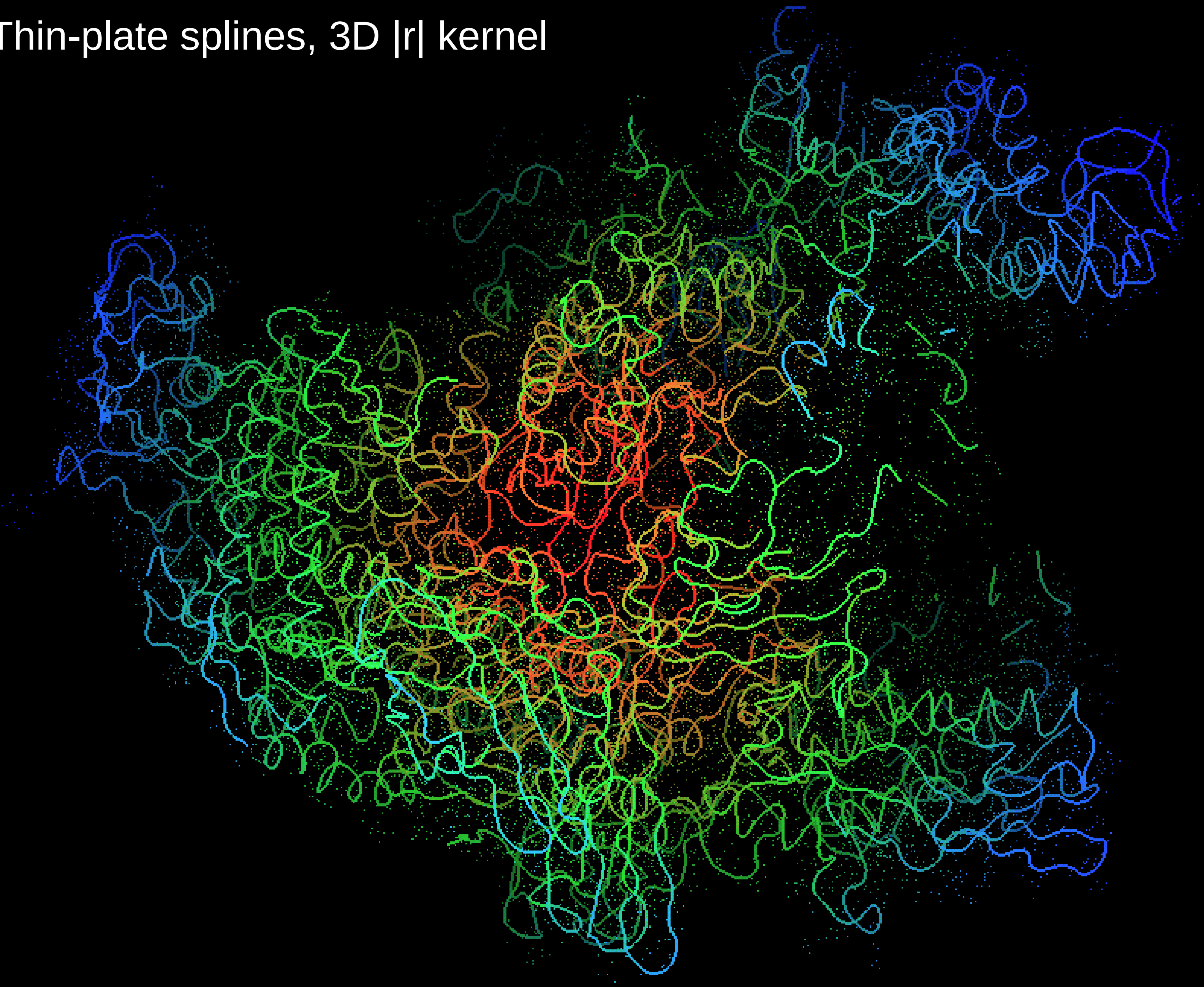
Flexibly fitted (MD) structure



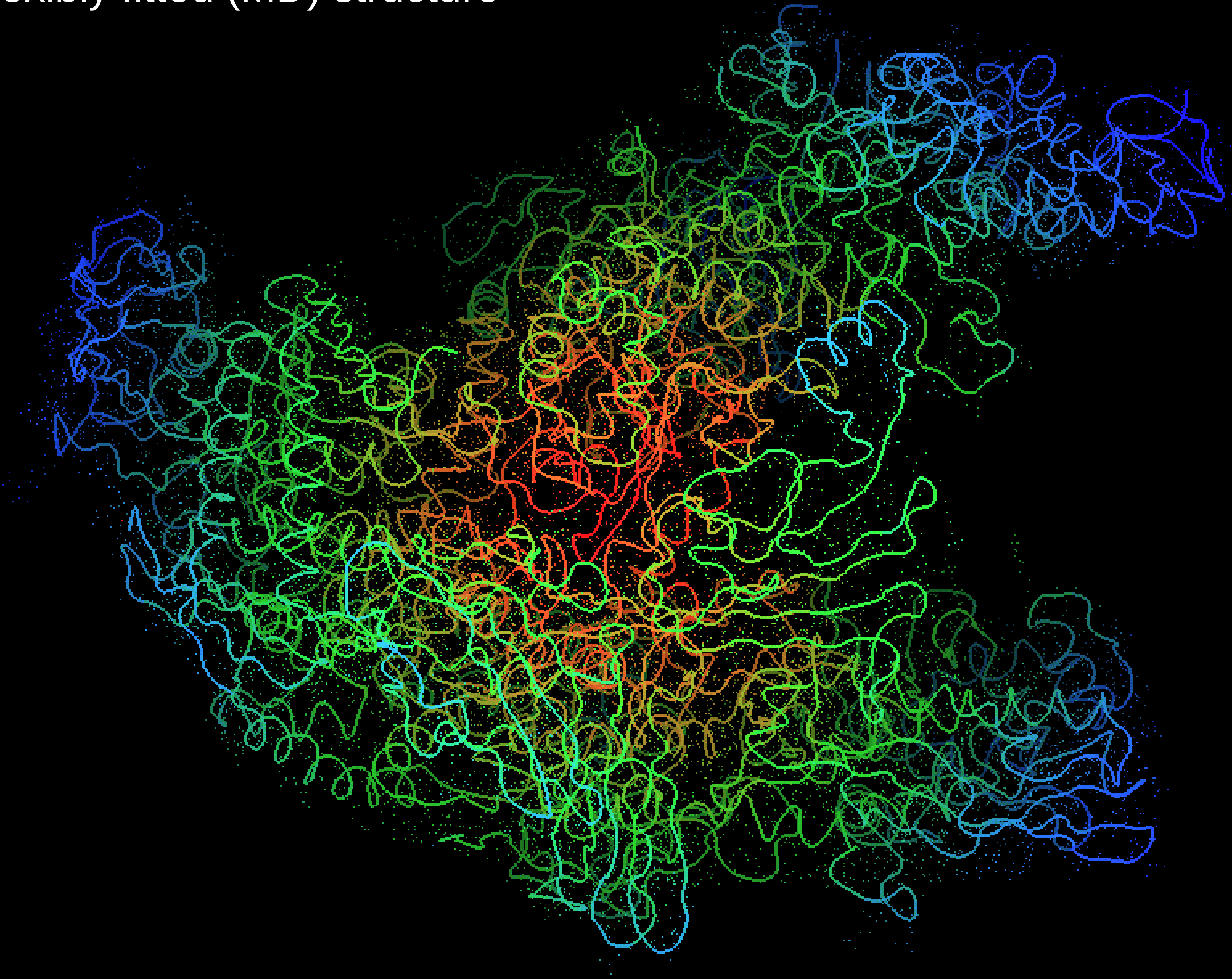
Piecewise-linear inter- / extrapolation



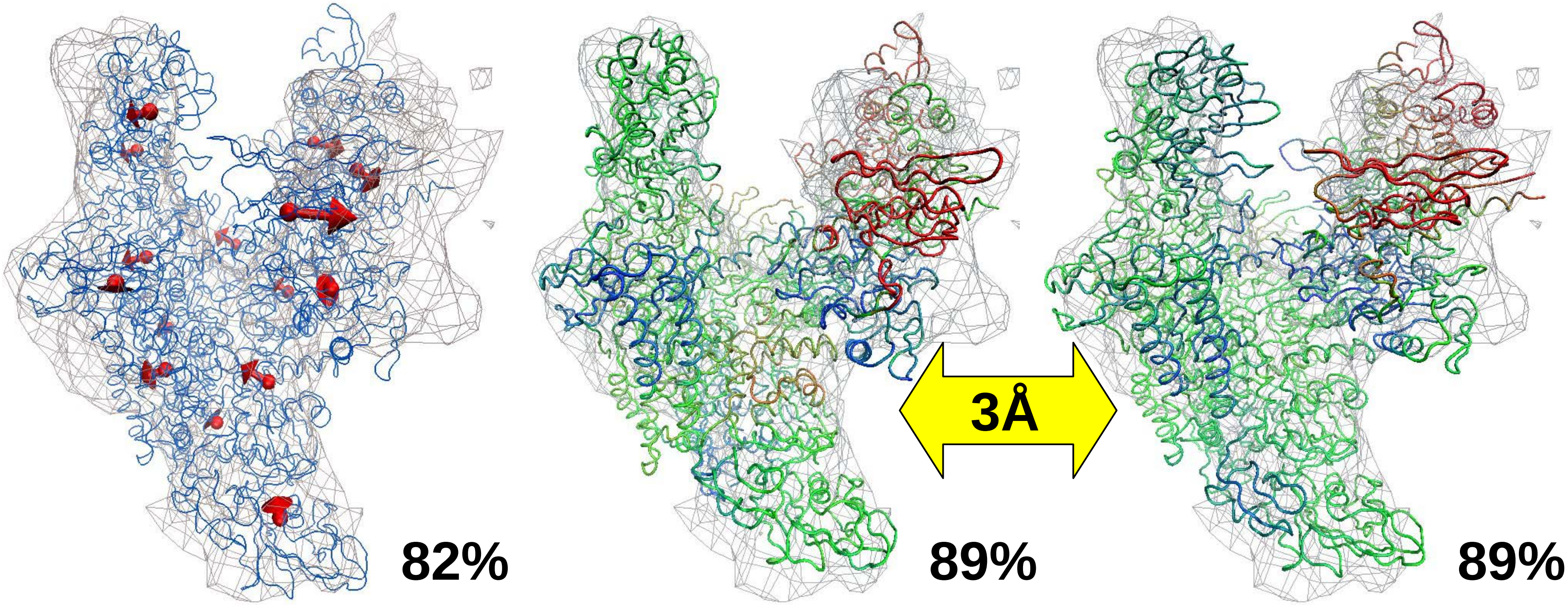
Thin-plate splines, 3D |r| kernel



Flexibly fitted (MD) structure



MD vs. Thin Plate Splines

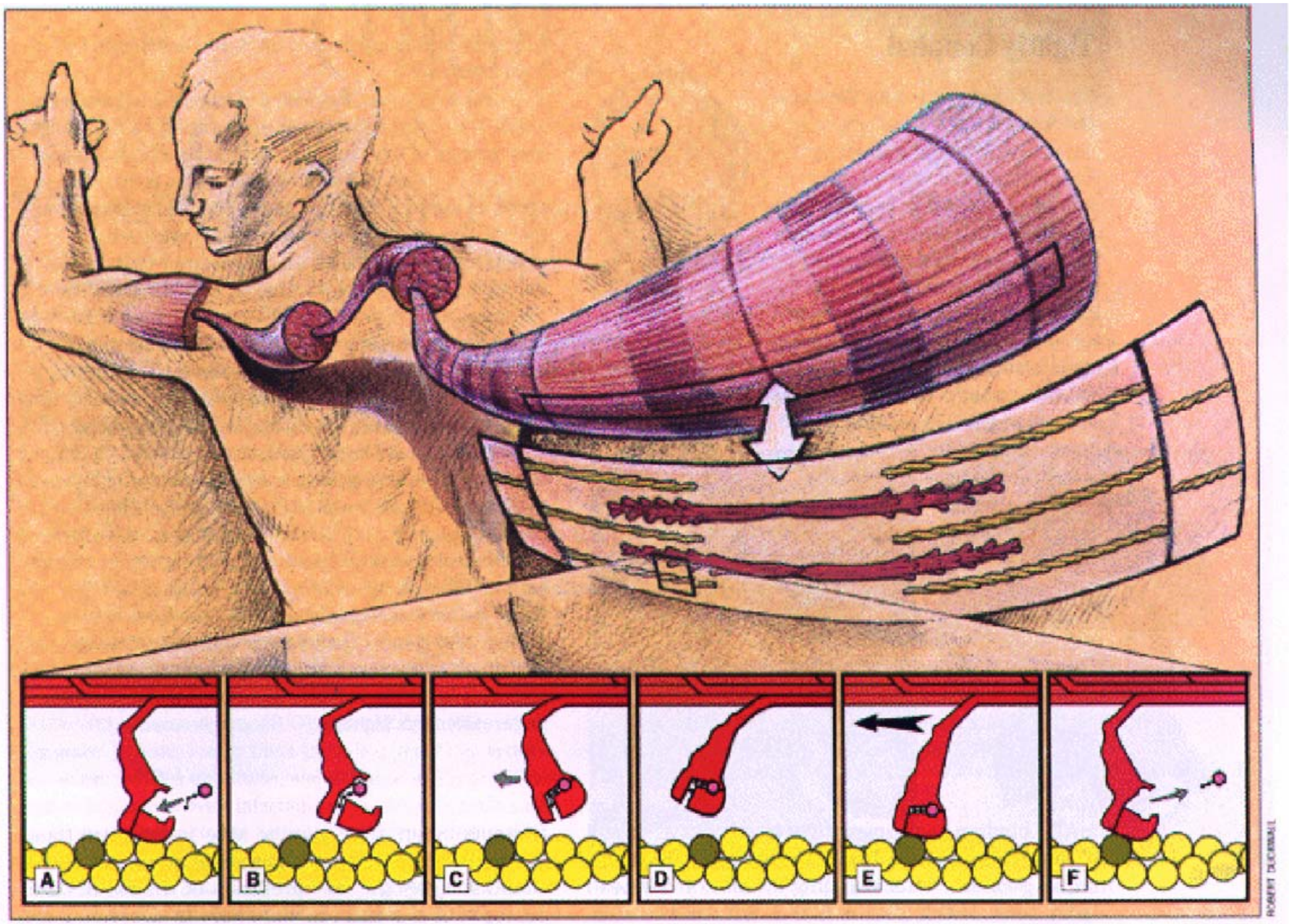


Displacements Molecular Dynamics Thin-Plate Splines

How do we know MD is really better?

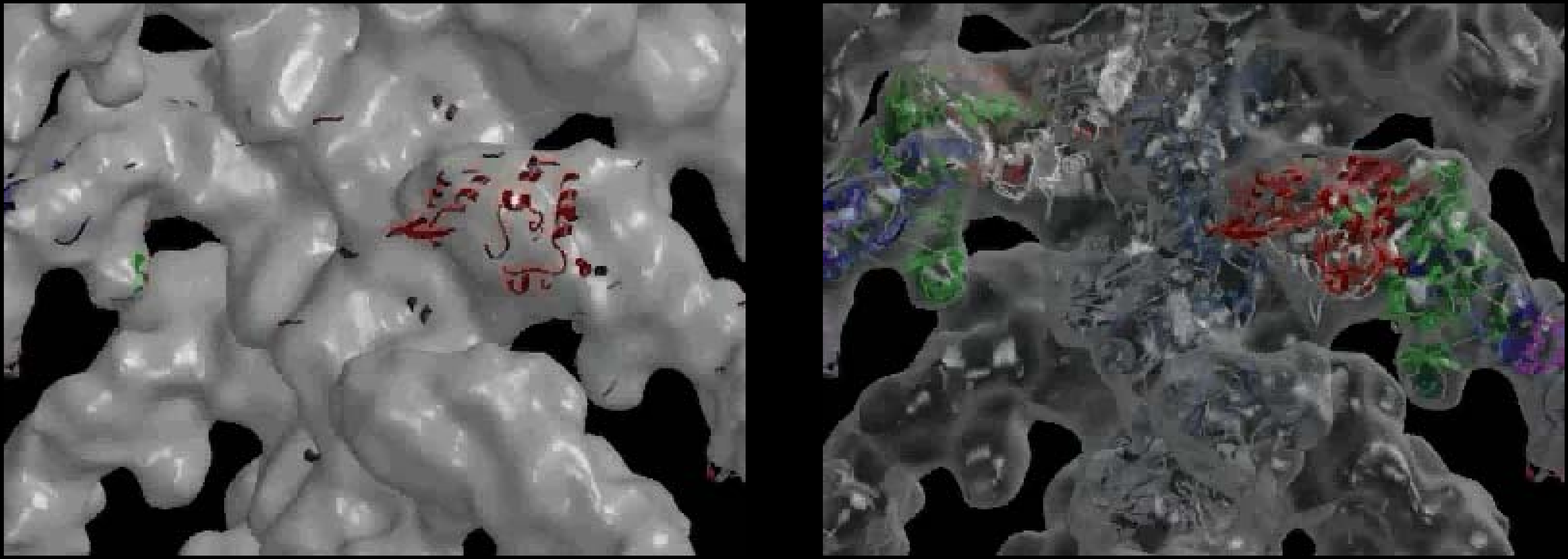
Structure (2004) 12:1

Validation Example: Muscle Contraction



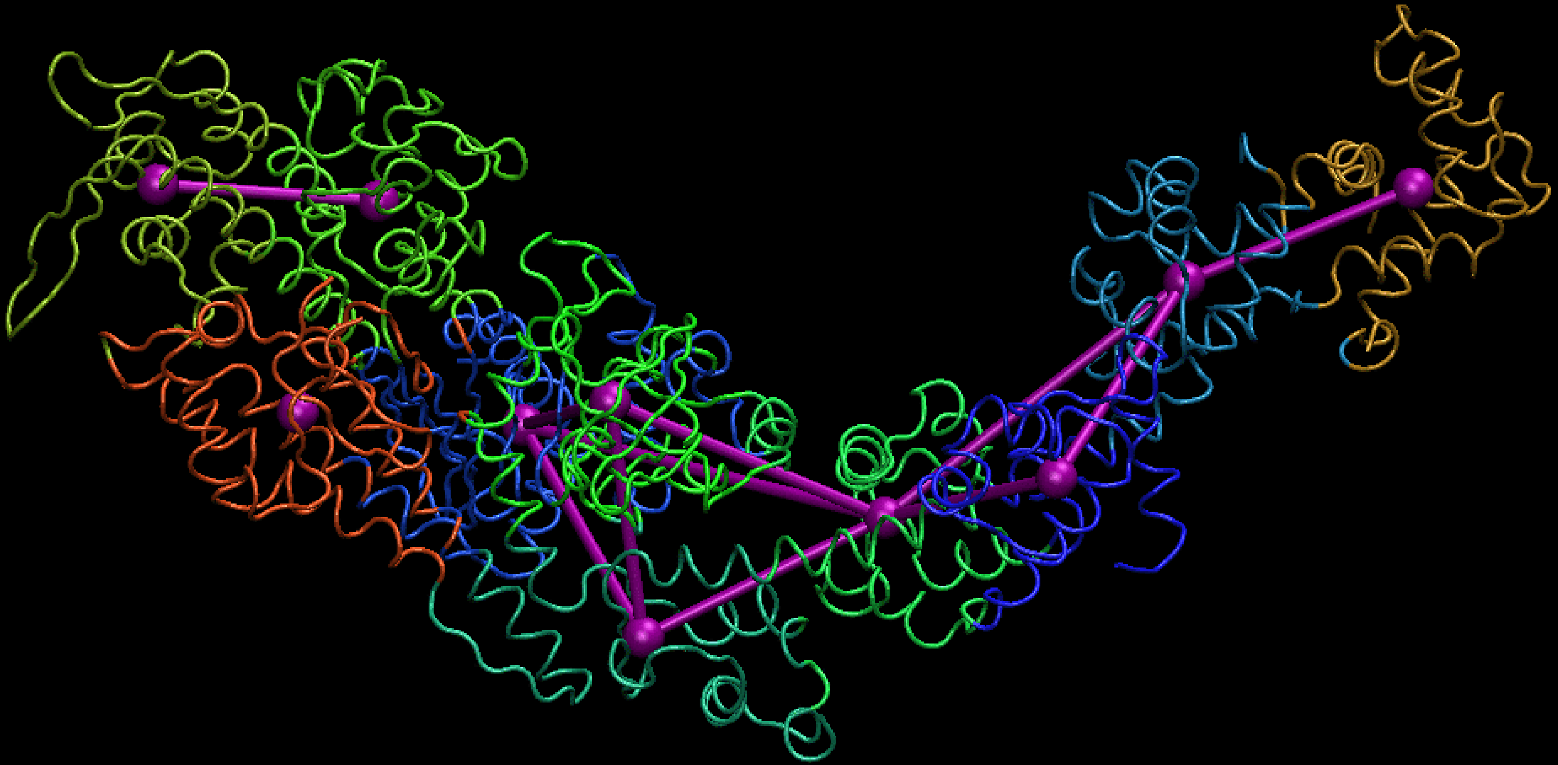
A Hierarchy of Muscle Structure, J. NIH Res. 1993

Acto-Myosin (II) Complex at 14Å

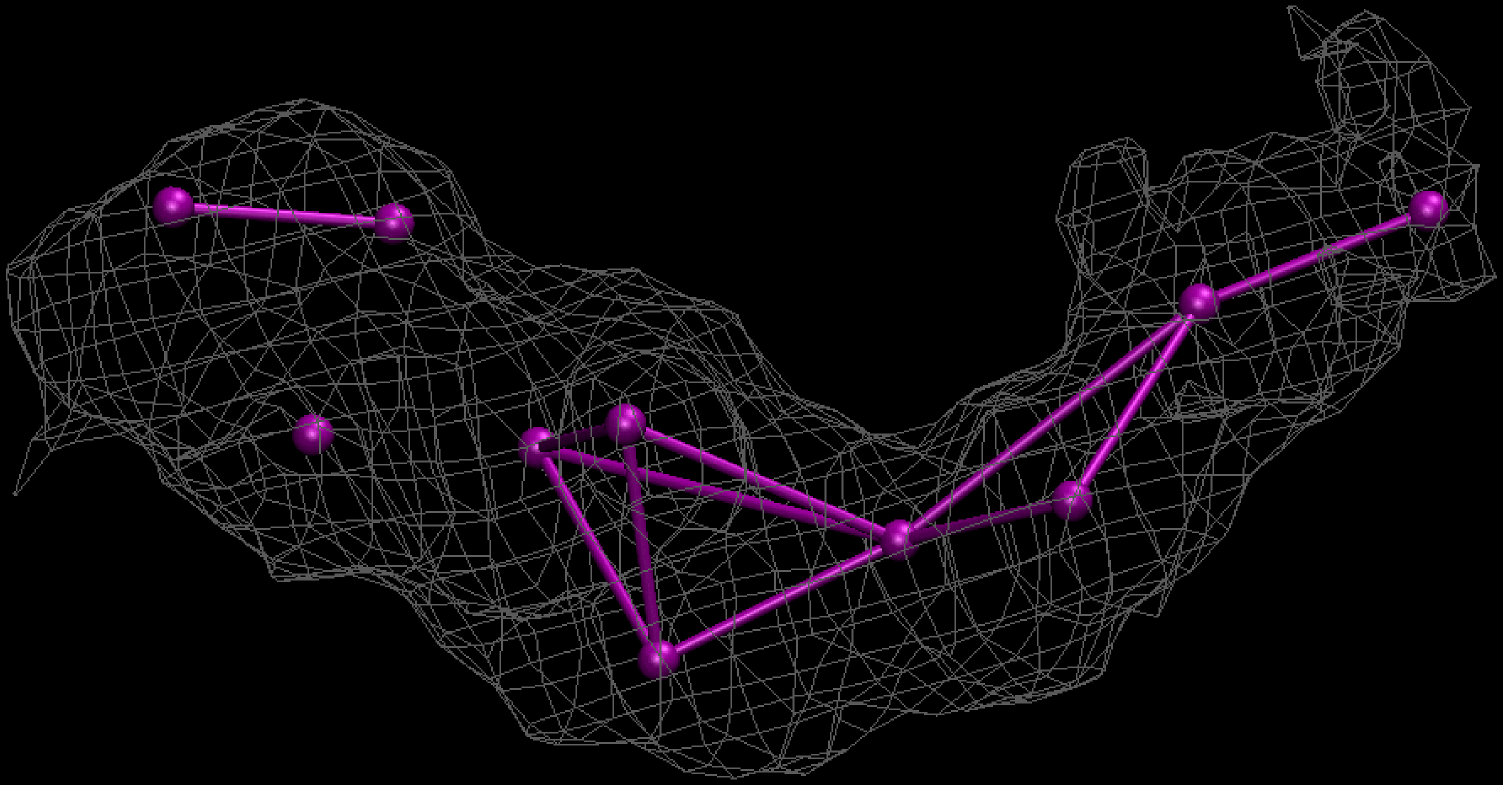


R. Schröder et al., *Nature* (2003) 425:423

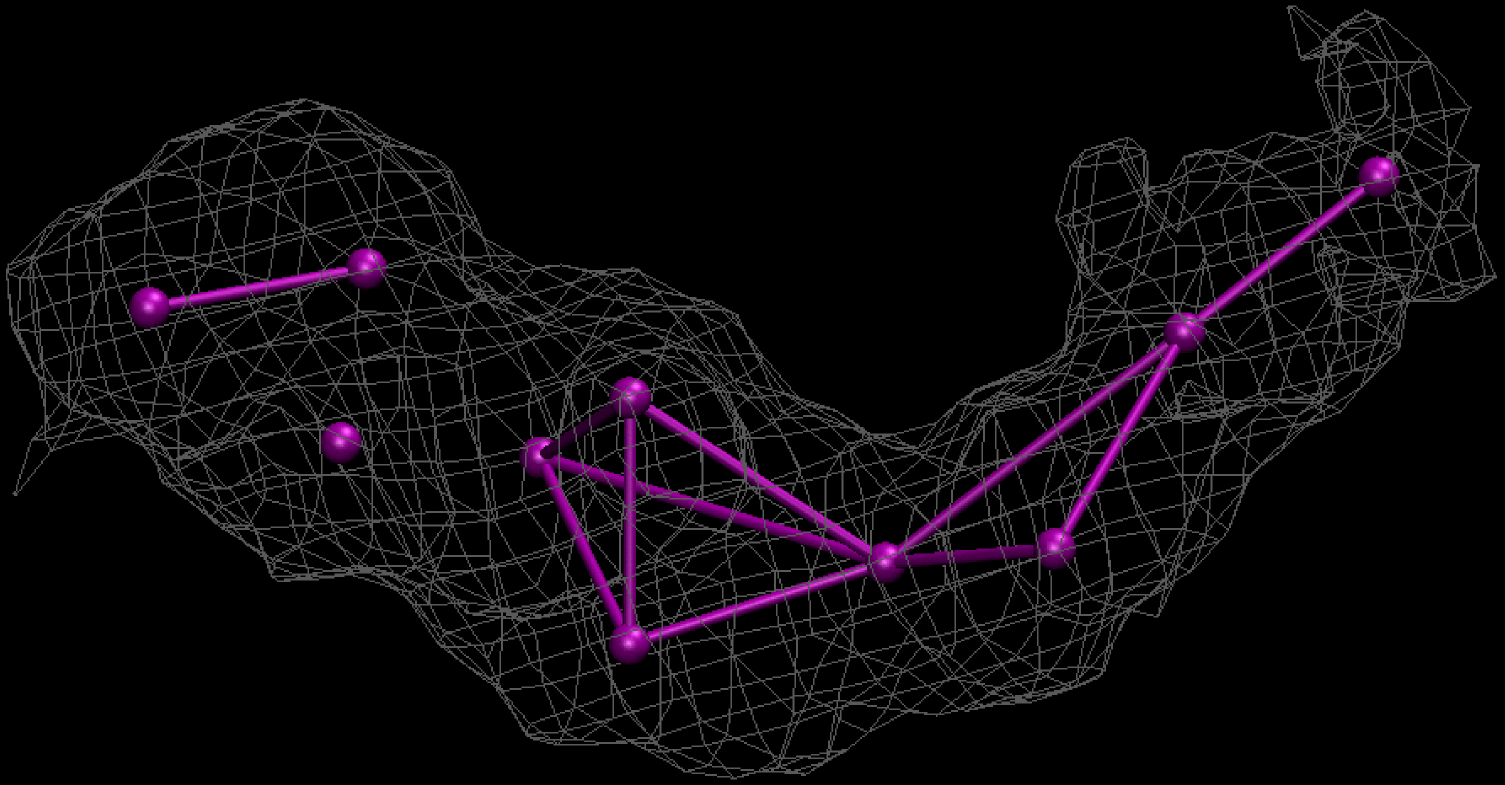
Flexing of Myosin II



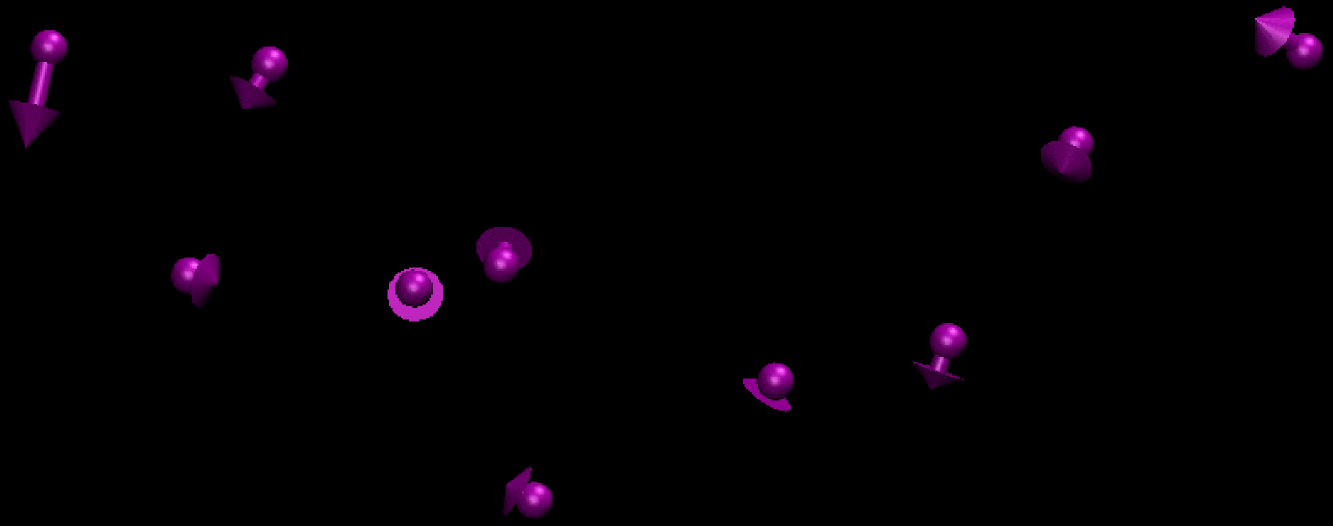
Flexing of Myosin II



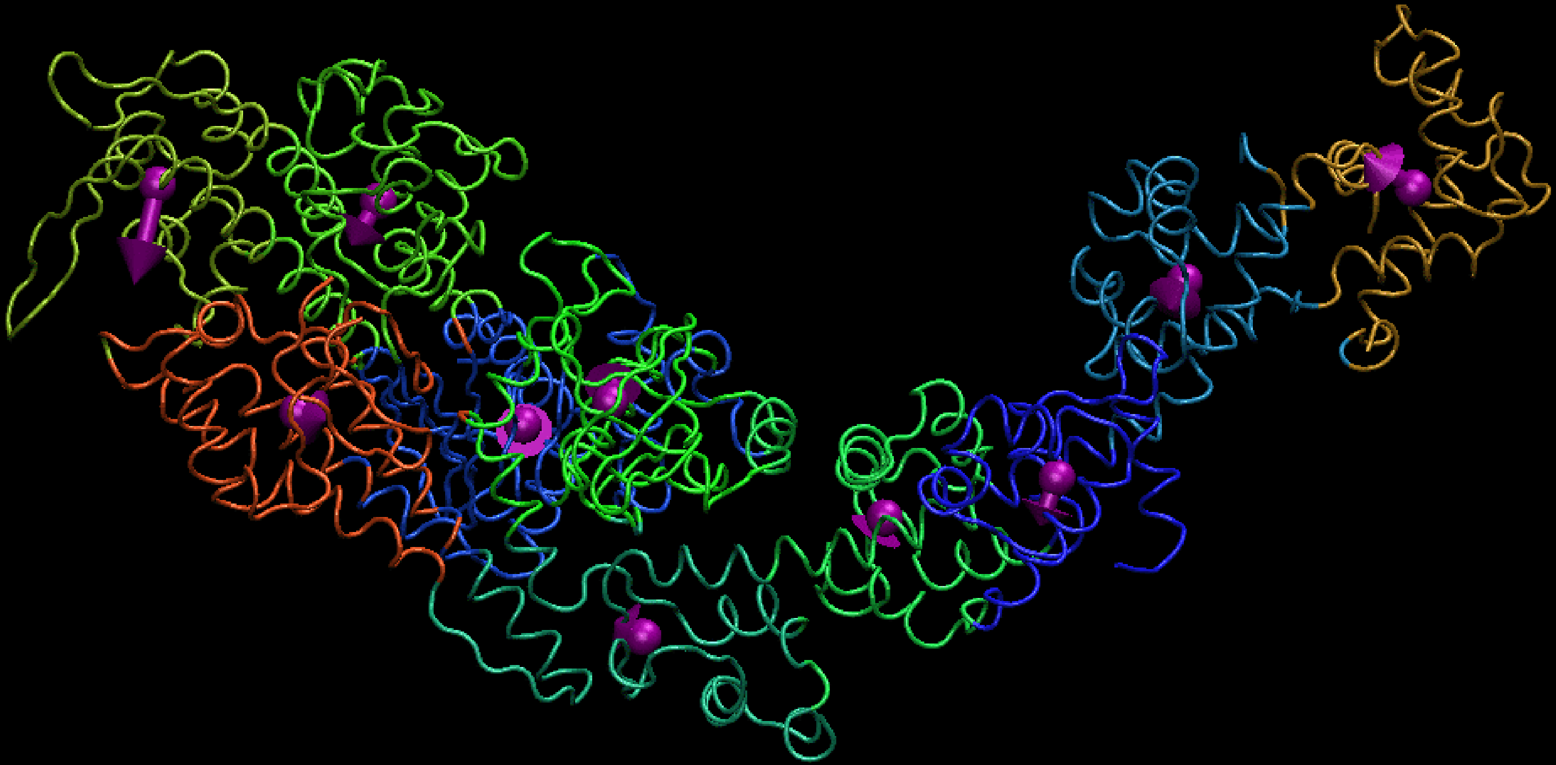
Flexing of Myosin II



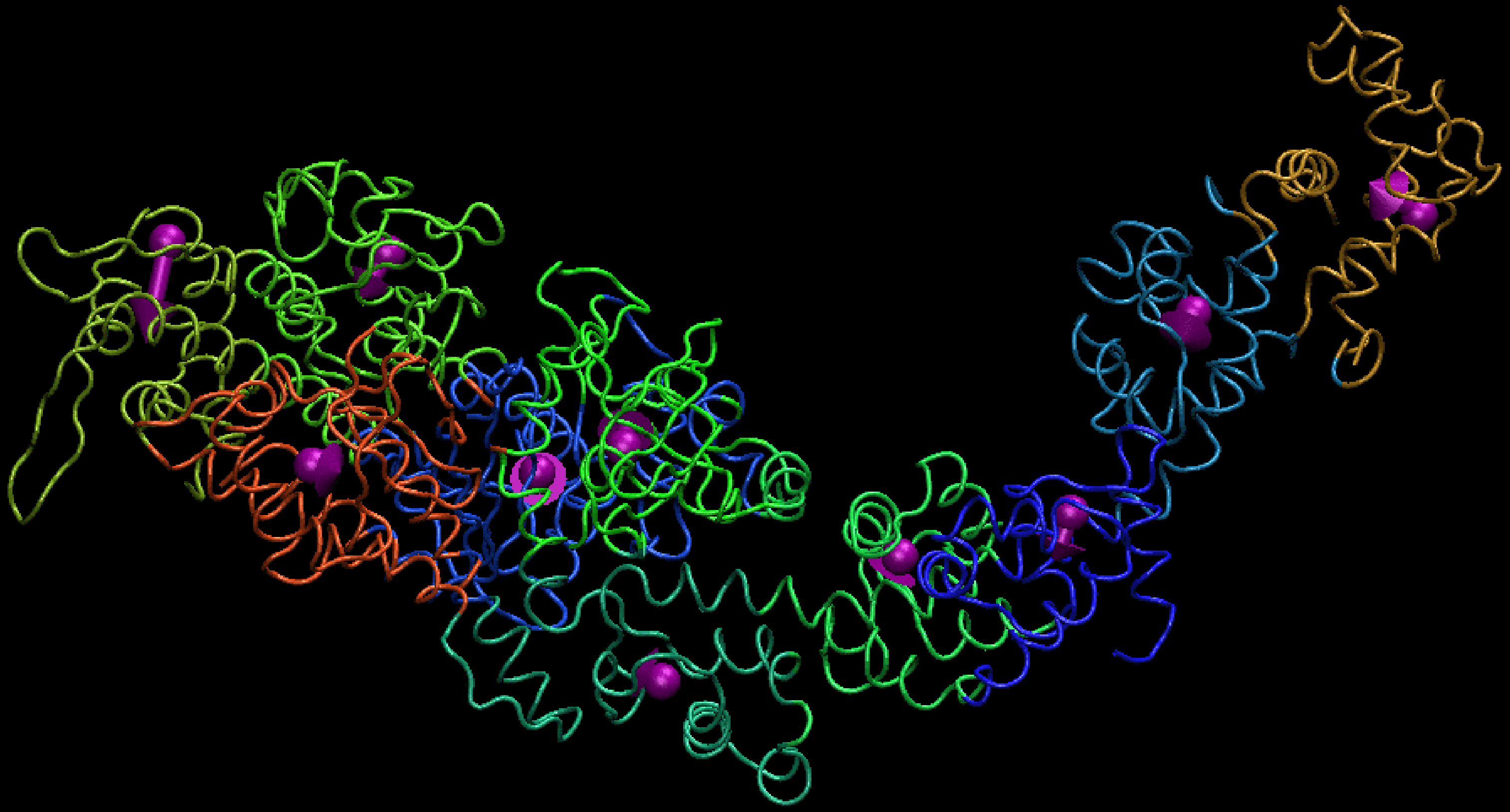
Flexing of Myosin II



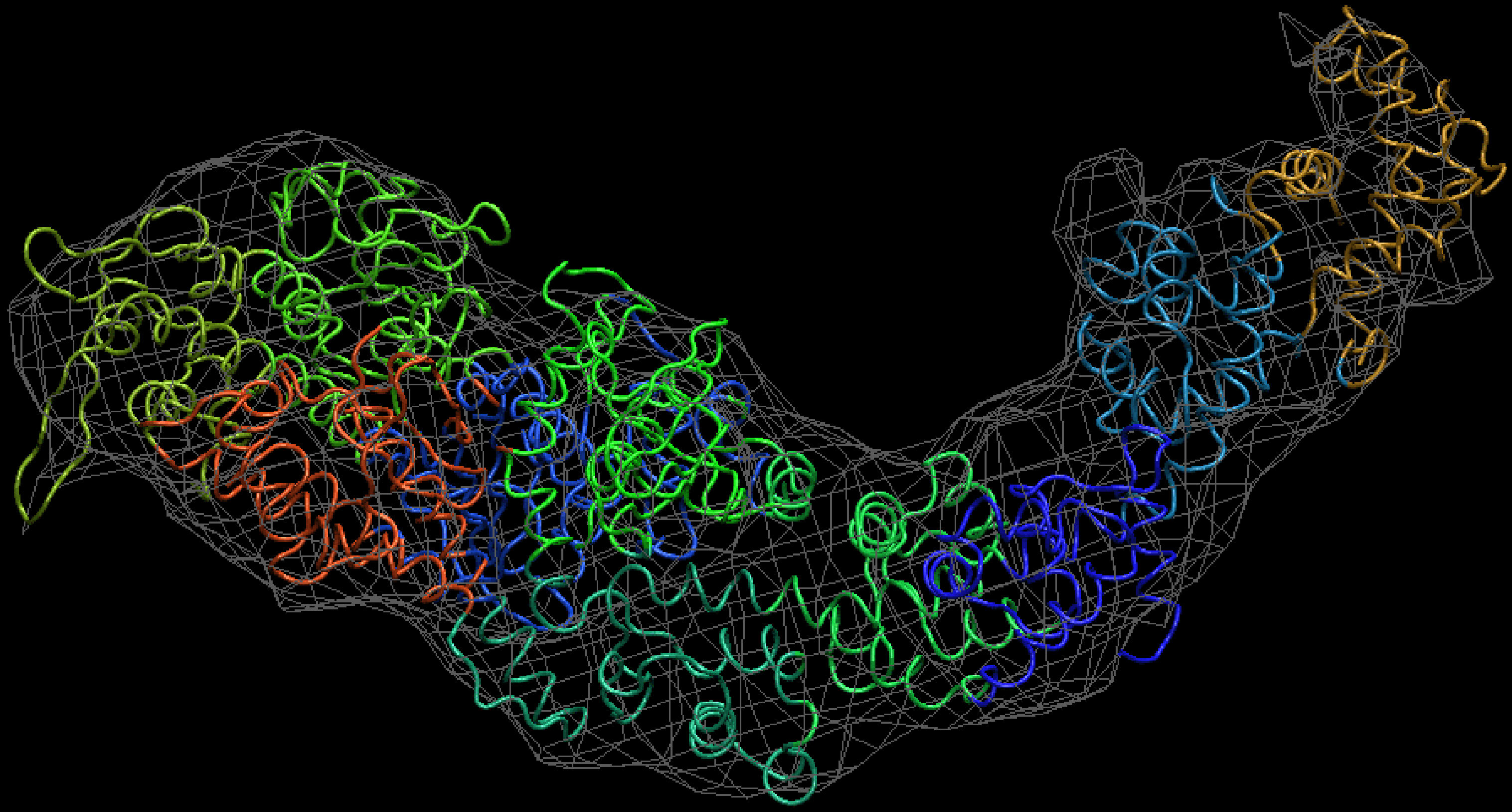
Flexing of Myosin II



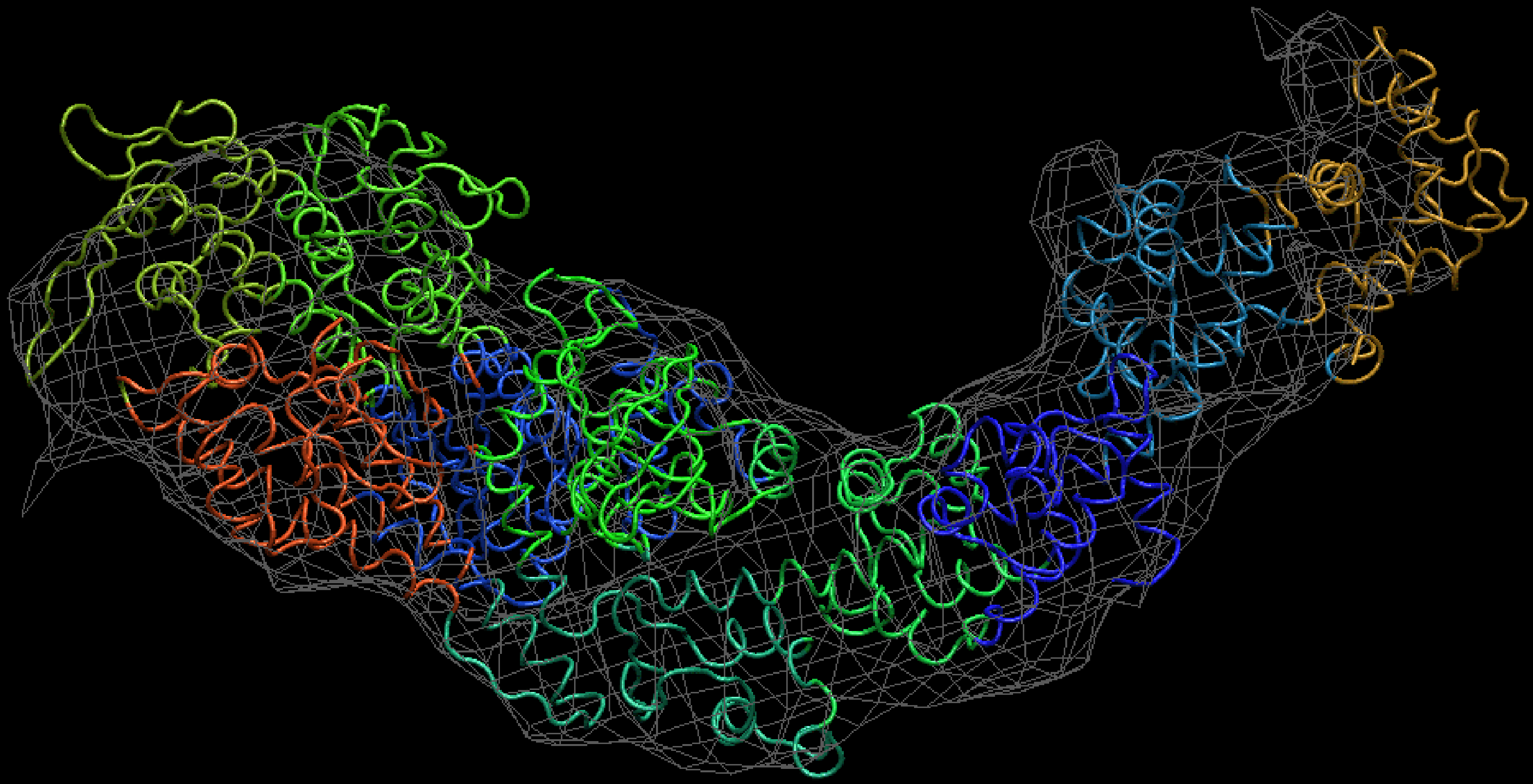
Flexing of Myosin II



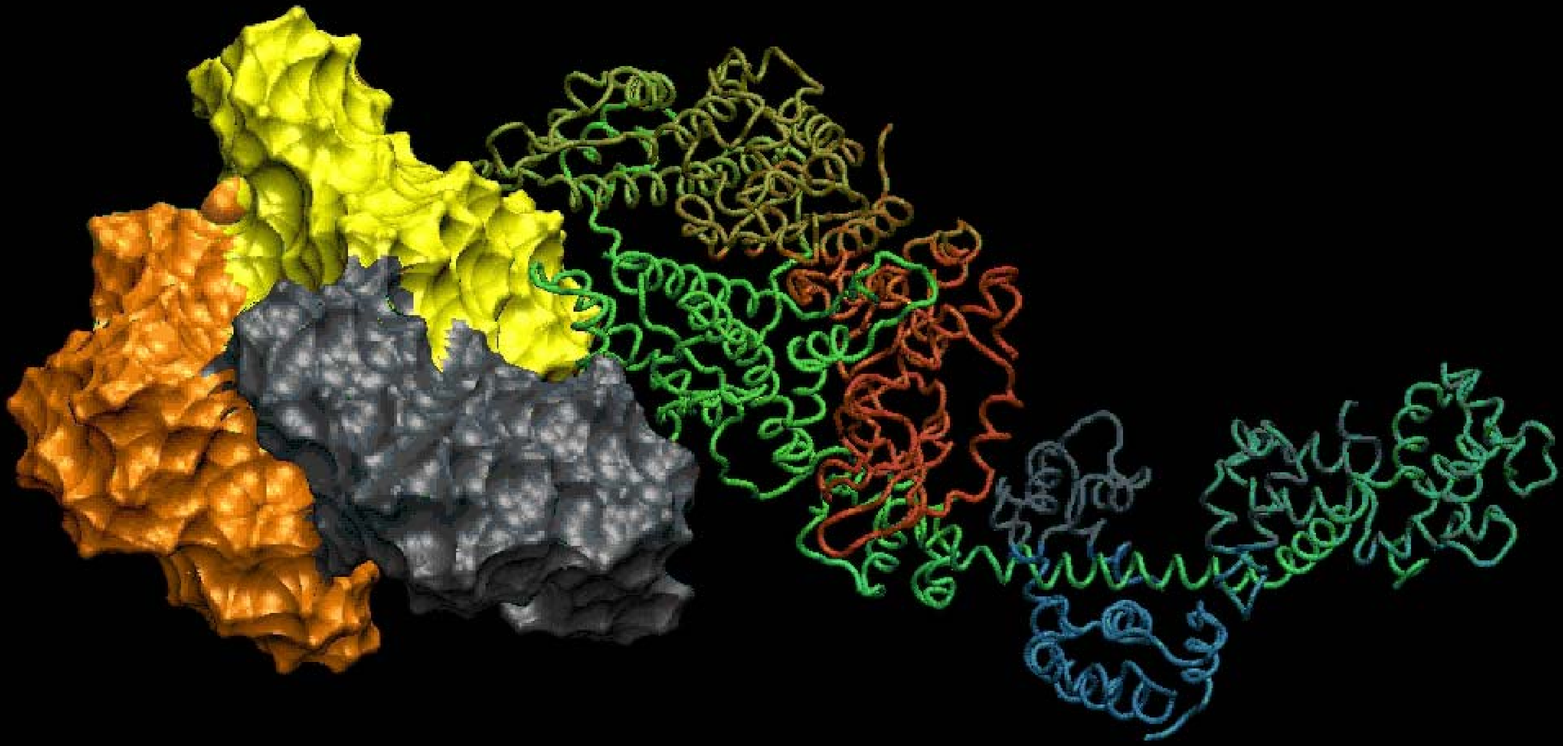
Flexing of Myosin II



Flexing of Myosin II



Improved Actin Binding Surface



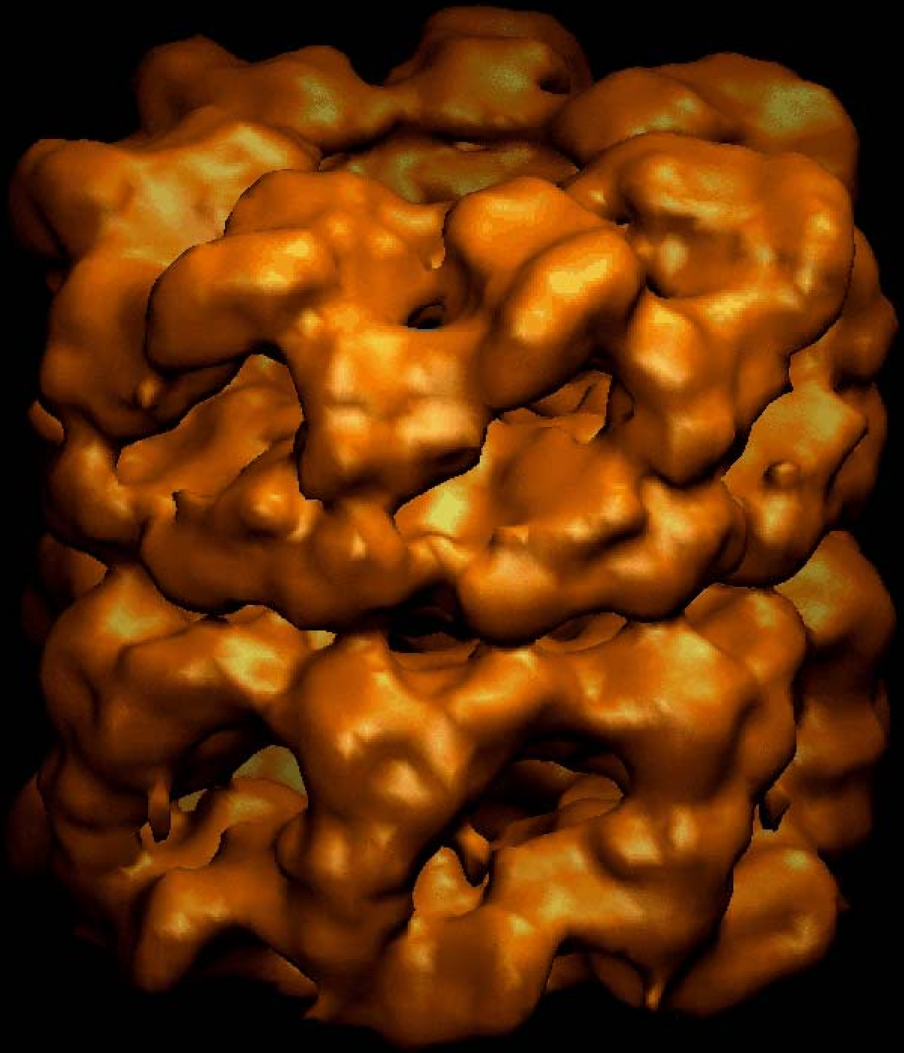
Cleft closure induced by actin binding

Myosin Flexing Validation Results:

- Agreement (~2Å rmsd) between flexed myosin II and myosin V too close to be coincidental.
- MD flexible fitting reproduces entire allosteric mechanism (cleft closure, beta sheet twist, etc).
- Mechanism only partially observed with rigid-body fitting.
- Since myosin V was not used for modeling, this validates technique.

GroEL Chaperonin

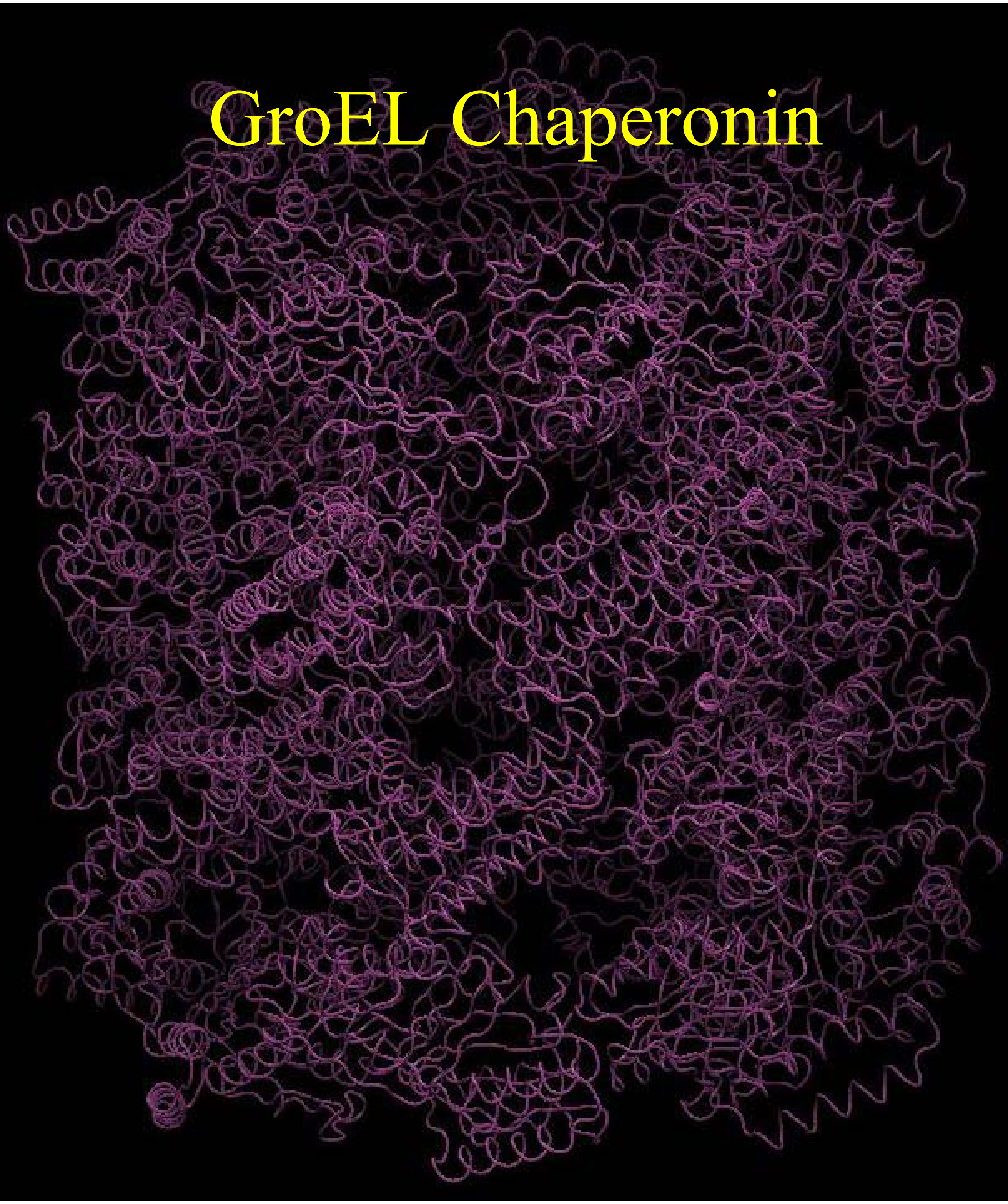
Dalia Segal,
Sharon Wolf,
Amnon Horovitz,
Weizmann
Institute, Israel



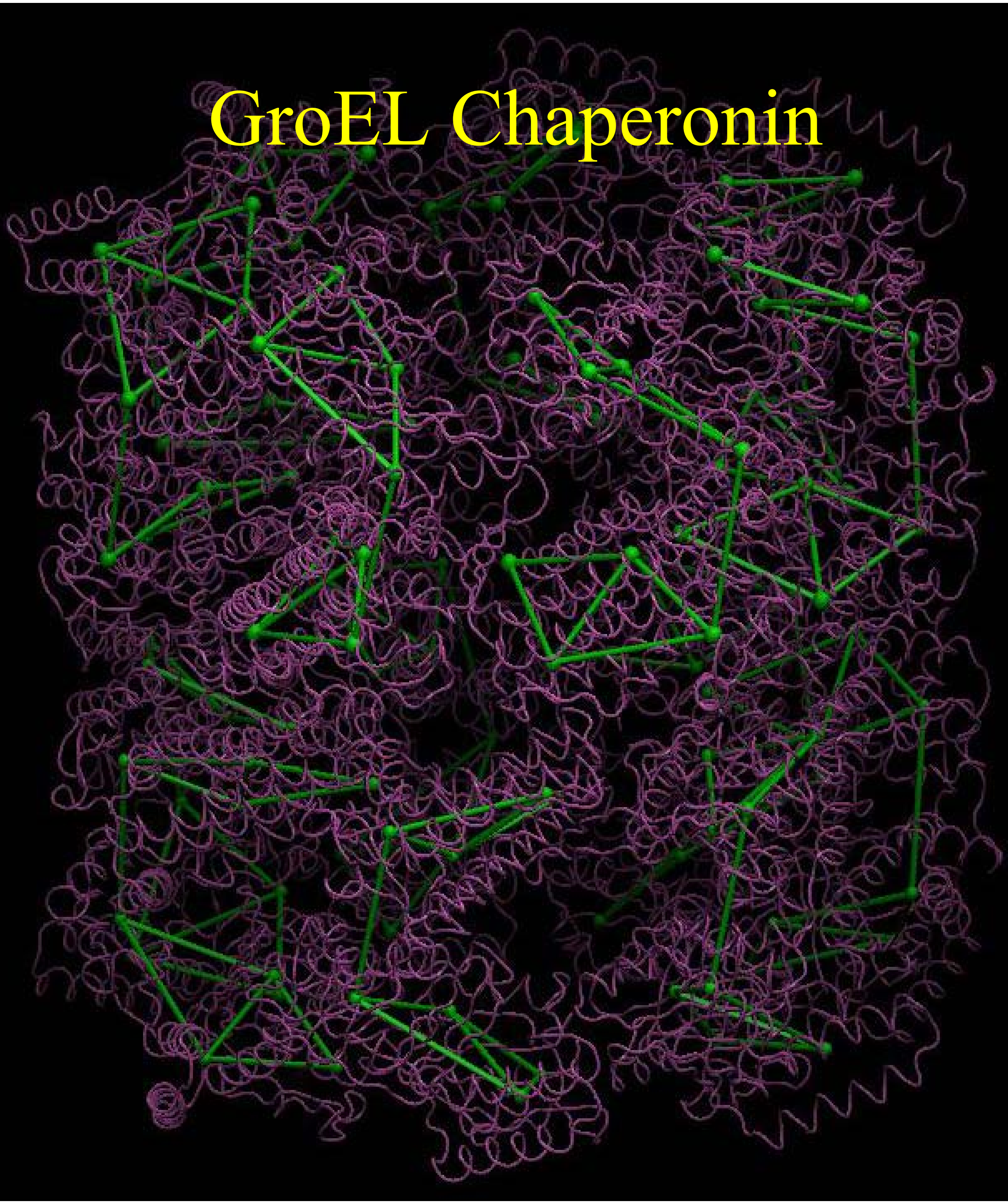
resolution ~14Å
wild type
(Sabil et al.)

& mutant

GroEL Chaperonin



GroEL Chaperonin



GroEL Chaperonin

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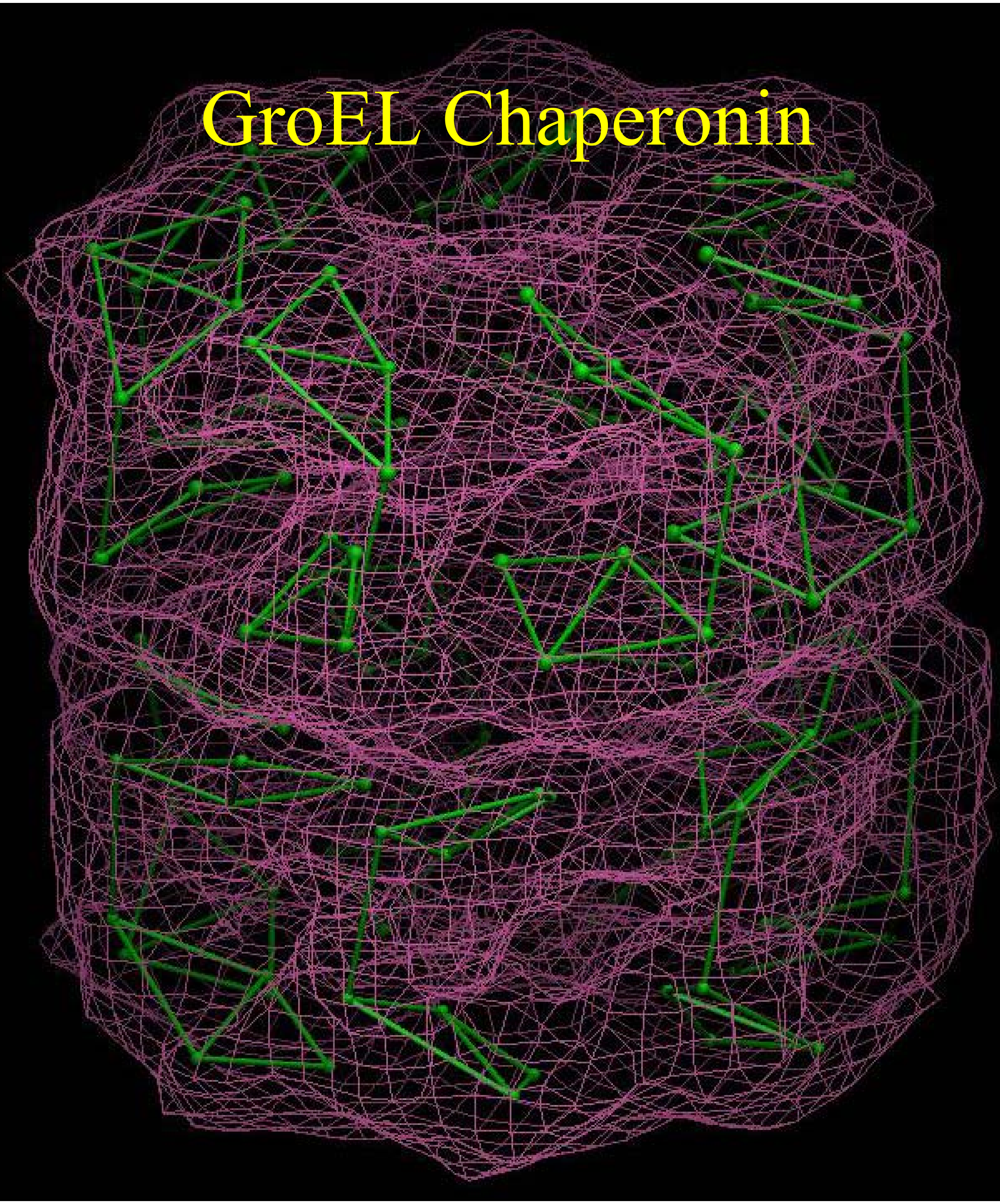

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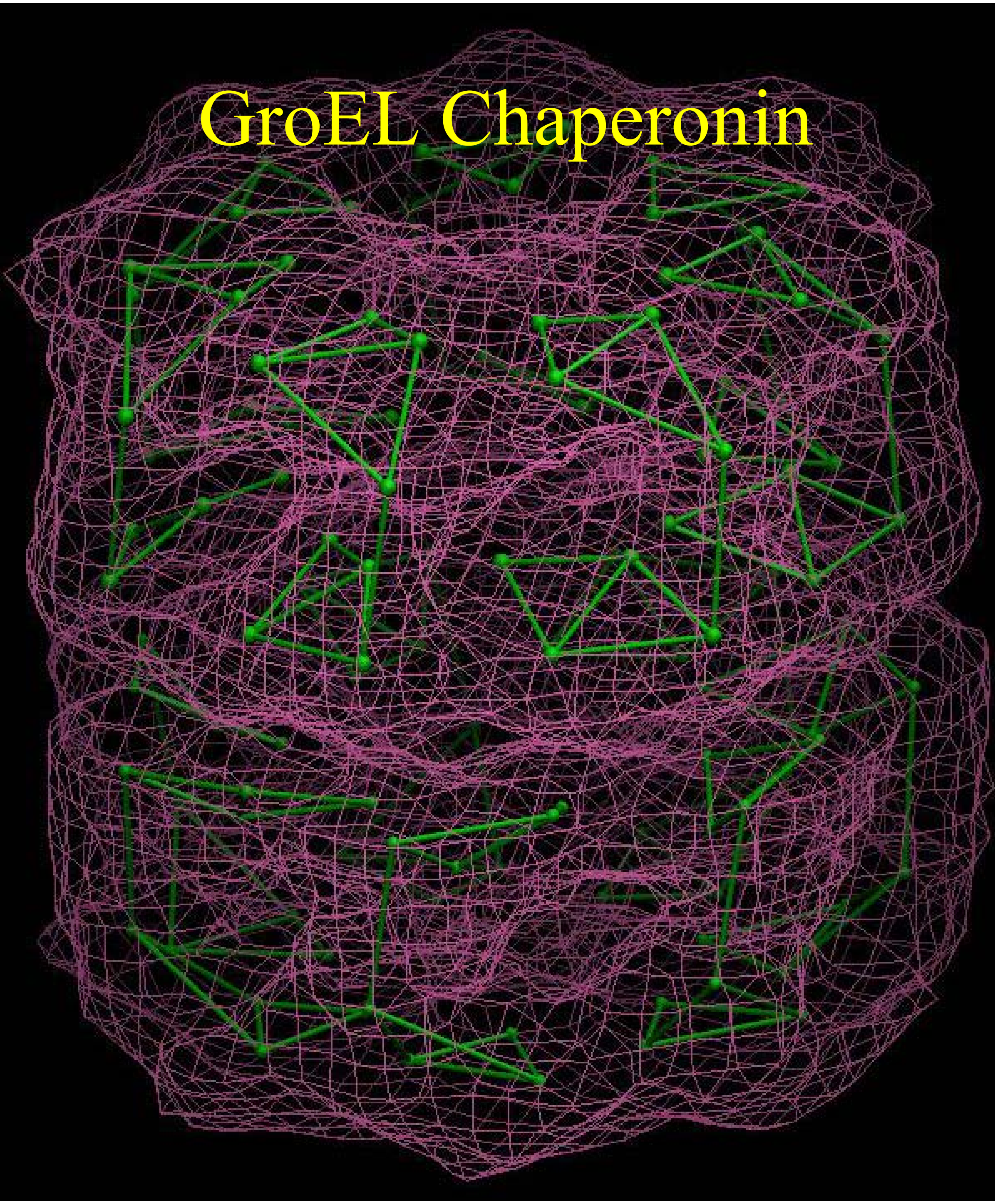

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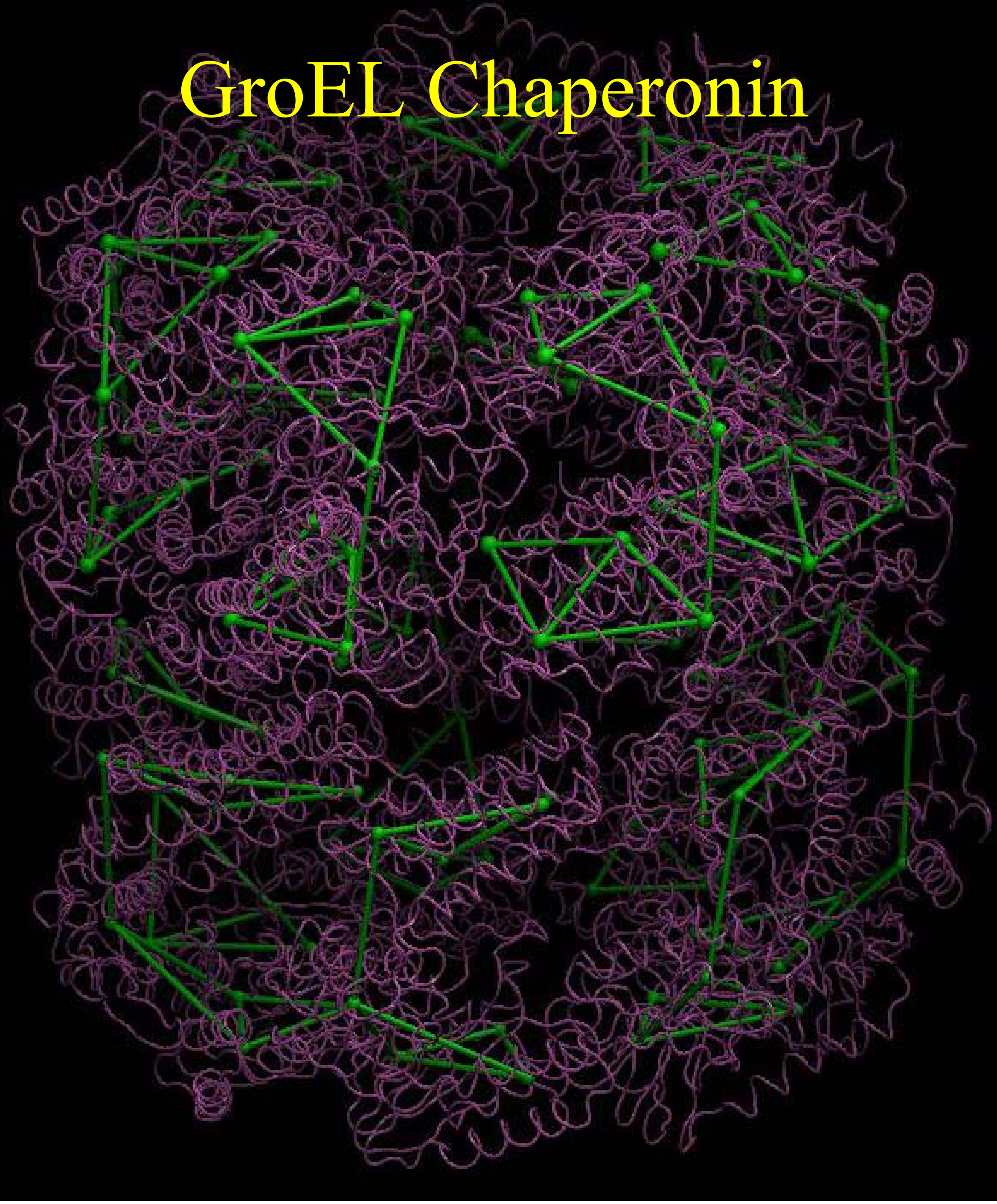
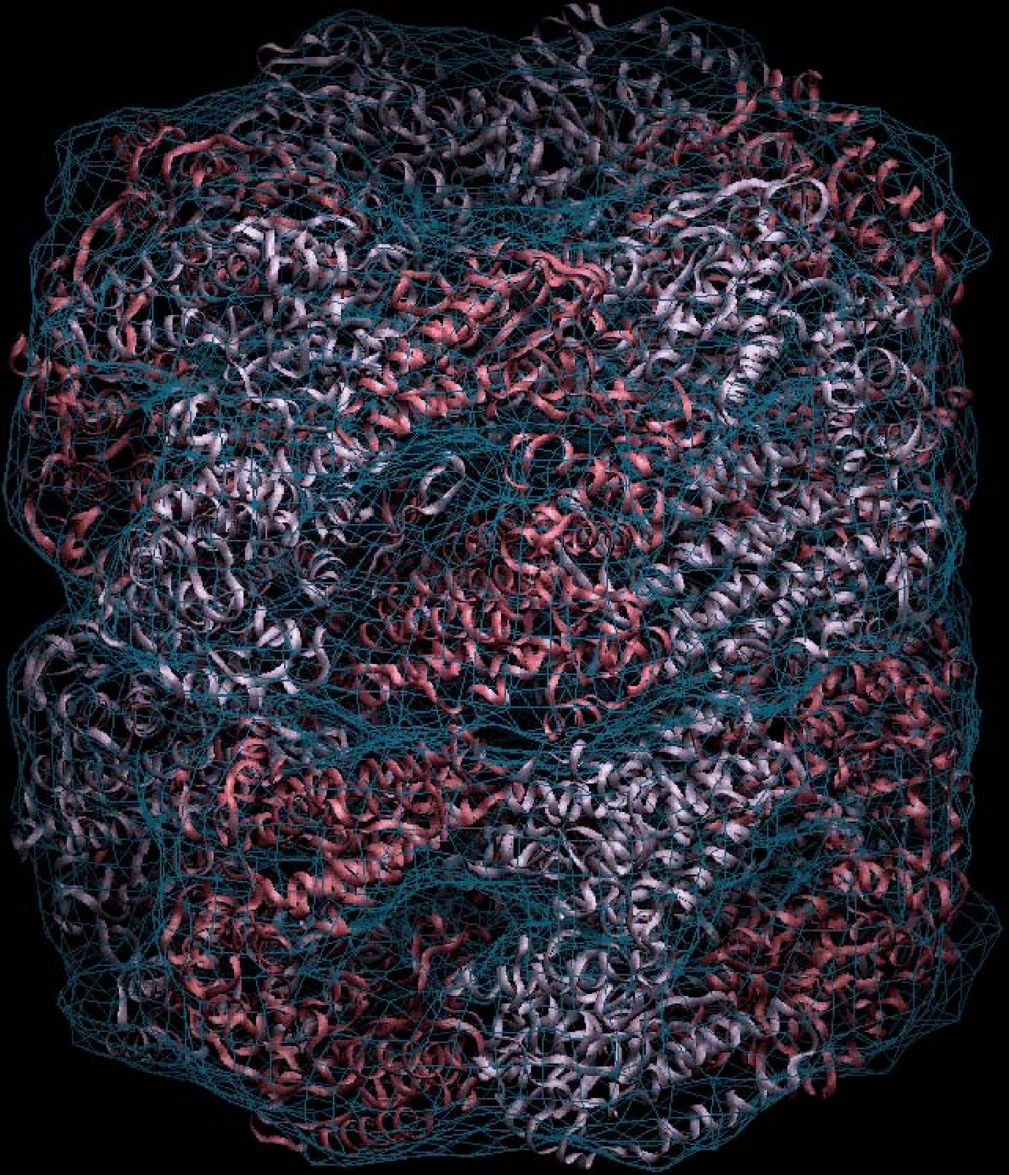


GroEL Chaperonin



Critical Assessment of MD Flexing

EM / Xtal Data	Resolution	Source	Precision (rmsd)
Myosin 2 Myosin 5	14Å	Schröder 2003	**2.0Å**
GroEL EM / Xtal WT	13Å	Saibil 2001	**3.0Å**
GroEL EM / Xtal WT	11A	Ludtke 2003	**2.5Å**
GroEL EM / Xtal WT	6Å	Ludtke 2004	**2.0Å**
simulated EM / Xtal WT	6-14Å	simulated	**<1.0Å**

Resources and Further Reading

WWW:
http://situs.biomachina.org
http://http://situs.biomachina.org/tutorial_flex.html

Papers:
Willy Wriggers and Pablo Chacón. Structure, 2001, Vol. 9, pp. 779-788.
Willy Wriggers et al. Neurocomputing, 2004, Vol. 56, pp. 365-379.

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