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

$w_j^{(h)}$

constrain centroids

molecular dynamics simulation

3D EM reconstruction
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
Flexing of the RNAP “jaws” suggests a jaw-closing in presence of DNA

*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: \( F_x(x, y, z) = ax + by + cz + d \)
\( F_x(w_1) = f_{1,x}, \)
\( F_x(w_2) = f_{2,x}, \)
\( F_x(w_3) = f_{3,x}, \)
\( F_x(w_4) = f_{4,x} \) (similar for \( F_y, F_z \)).

Cramer’s rule:

\[
\begin{vmatrix}
 f_{1,x} & w_{1,y} & w_{1,z} & 1 \\
 f_{2,x} & w_{2,y} & w_{2,z} & 1 \\
 f_{3,x} & w_{3,y} & w_{3,z} & 1 \\
 f_{4,x} & w_{4,y} & w_{4,z} & 1 \\
\end{vmatrix}
\]
\[
\begin{vmatrix}
 w_{1,x} & f_{1,y} & w_{1,z} & 1 \\
 w_{2,x} & f_{2,y} & w_{2,z} & 1 \\
 w_{3,x} & f_{3,y} & w_{3,z} & 1 \\
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 w_{3,x} & w_{3,y} & w_{3,z} & 1 \\
 w_{4,x} & w_{4,y} & w_{4,z} & 1 \\
\end{vmatrix}
\]

\( a = \frac{D}{D}, \quad b = \frac{D}{D}, \quad \ldots, \quad D = \begin{vmatrix}
 w_{1,x} & w_{1,y} & w_{1,z} & 1 \\
 w_{2,x} & w_{2,y} & w_{2,z} & 1 \\
 w_{3,x} & w_{3,y} & w_{3,z} & 1 \\
 w_{4,x} & w_{4,y} & w_{4,z} & 1 \\
\end{vmatrix} \)
(ii) Non-Linear Kernel Interpolation

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

Ansatz:

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

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

Solve :

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

where

$$L = \begin{pmatrix} P & Q \\ Q^T & 0 \end{pmatrix}, \quad Q = \begin{pmatrix} 1 & w_{1,x} & w_{1,y} & w_{1,z} \\ \cdots & \cdots & \cdots & \cdots \\ 1 & w_{k,x} & w_{k,y} & w_{k,z} \end{pmatrix}, \quad k \times 4,$$

$$P = \begin{pmatrix} 0 & U(w_{12}) & \cdots & U(w_{1k}) \\ U(w_{21}) & 0 & \cdots & U(w_{2k}) \\ \cdots & \cdots & \cdots & \cdots \\ U(w_{k1}) & U(w_{k2}) & \cdots & 0 \end{pmatrix}, \quad k \times k.$$
• kernel function $U(r)$ is principal solution of biharmonic equation that arises in elasticity theory of thin plates:

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

• 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: $U(r)$

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

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
## Critical Assessment of MD Flexing

<table>
<thead>
<tr>
<th>EM / Xtal Data</th>
<th>Resolution</th>
<th>Source</th>
<th>Precision (rmsd)</th>
</tr>
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<tbody>
<tr>
<td>Myosin 2</td>
<td>14Å</td>
<td>Schröder 2003</td>
<td>2.0Å</td>
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<tr>
<td>Myosin 5</td>
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<tr>
<td>GroEL EM /</td>
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<td>Saibil 2001</td>
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<tr>
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<tr>
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<tr>
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<td>Ludtke 2004</td>
<td>2.0Å</td>
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<tr>
<td>Xtal WT</td>
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<tr>
<td>simulated EM</td>
<td>6-14Å</td>
<td>simulated</td>
<td>&lt;1.0Å</td>
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<tr>
<td>Xtal WT</td>
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Resources and Further Reading

WWW:
http://situs.biomachina.org

Papers:

Acknowledgements:
Mirabela Rusu

Collaborators:
Seth Darst (Rockefeller University)
Rasmus Schröder (Max-Planck Inst. Biophysics, Frankfurt)
Dalia Segal, Sharon Wolf, Amnon Horovitz (Weizmann Institute, Israel)