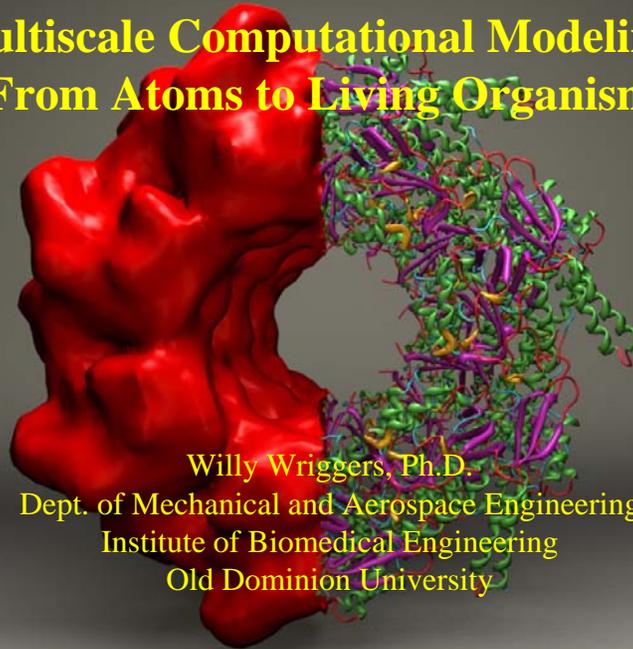


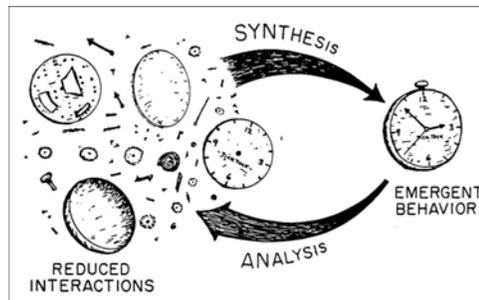
Multiscale Computational Modeling – From Atoms to Living Organisms



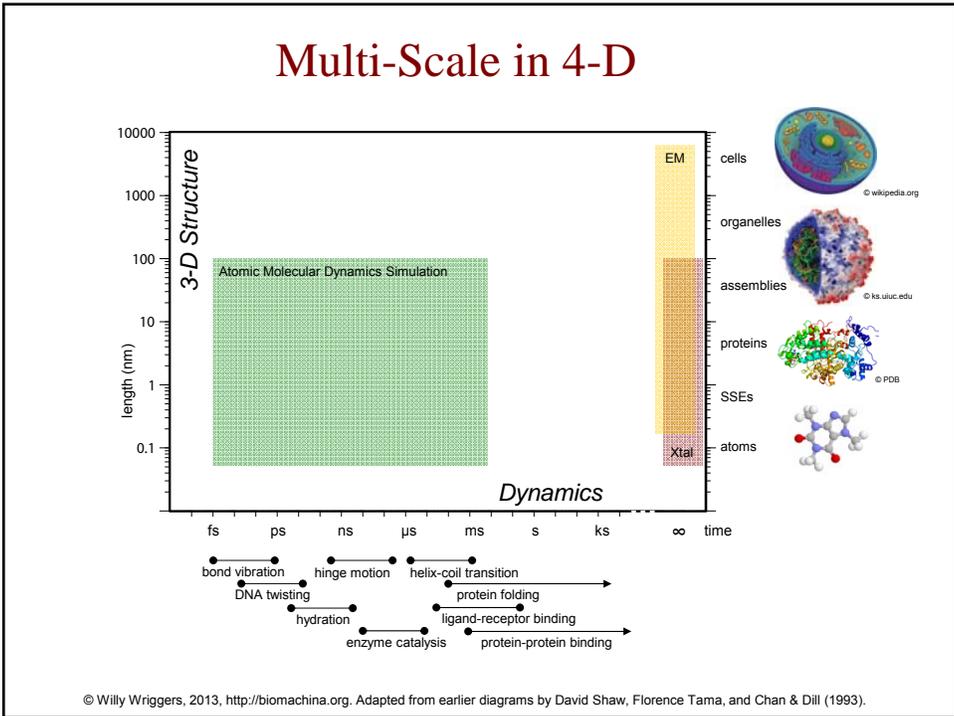
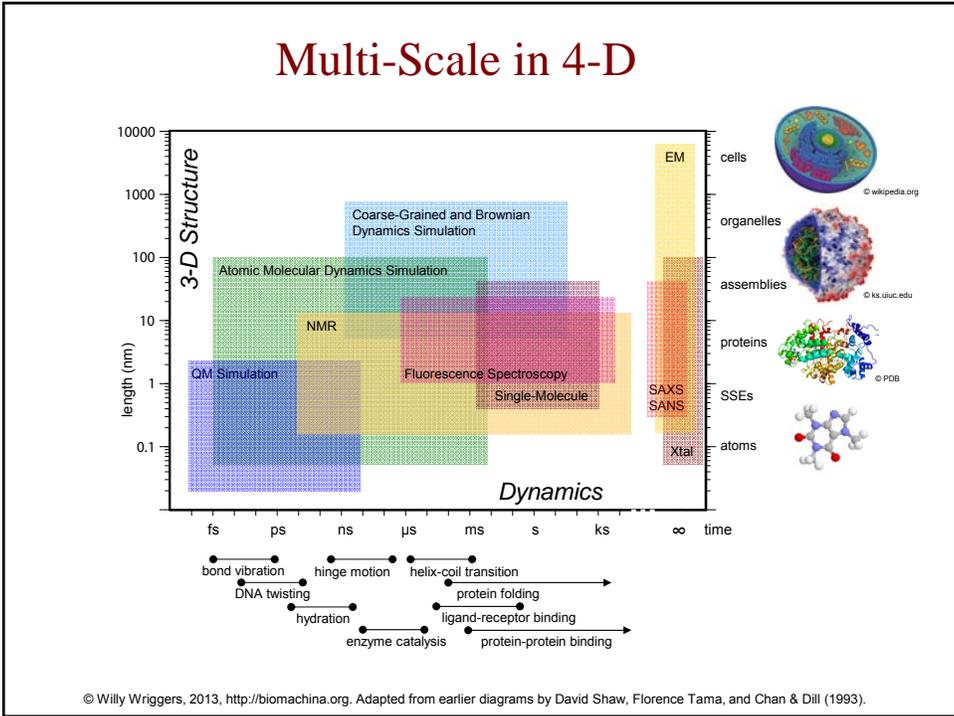
Willy Wriggers, Ph.D.
Dept. of Mechanical and Aerospace Engineering
Institute of Biomedical Engineering
Old Dominion University

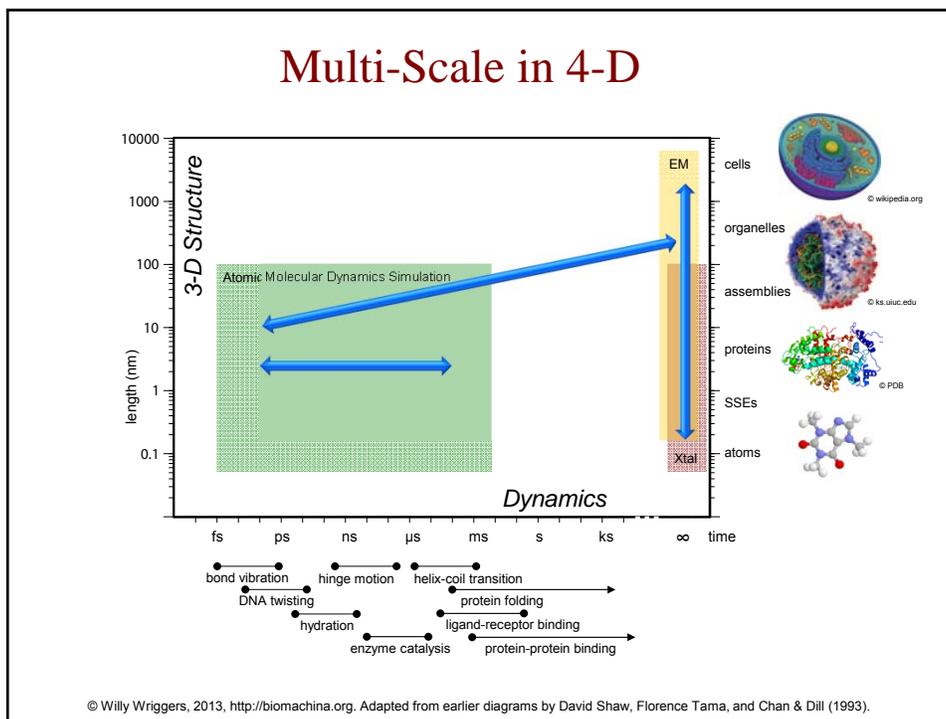
A “Systems” Strategy for Multi-Scale Discovery

- “Emergent Behavior” of Complex Systems (Lewes 1875)
- Concept known since Aristotle (antithesis to Constructionism)
- “The whole becomes not merely more, but different from the sum of its parts” (Anderson 1972)

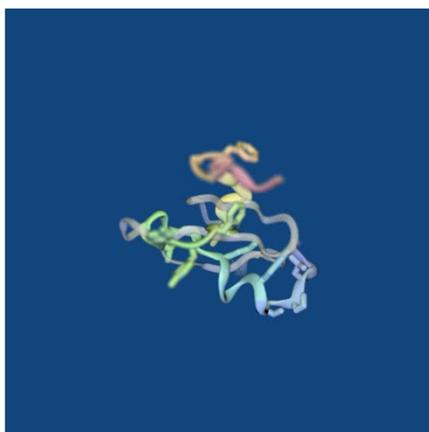


Jackson, Perspectives of Nonlinear Dynamics, Vol. II, 1990





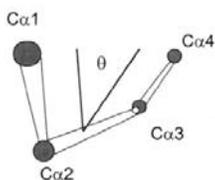
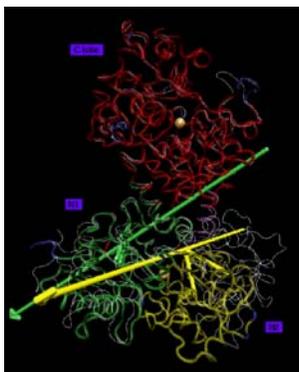
Emergence in the Time Domain



FIP35 folding:
Shaw et al., *Science* (2010) 330:341

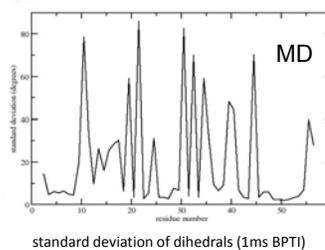
- We wish to map out regions (e.g. hinges, side-chain contacts) that are important for rare, collective motions.
- Such “emergent” collective motions may originate in fast, local degrees of freedom (e.g. bond distances, angles, torsions).
- How can we characterize slow (μs) timescale state changes (that are important for “emergent” function) using fast (ns) timescale fluctuations?

“Pivot Residue” Torsions Useful for Hinge Detection in PDB Structures



Wriggers and Schulten (1997)
Proteins: Structure, Function, and
Genetics 29:1-14

4-Cα pseudo-dihedrals:
Yan et al. (1999) J. Protein
Chemistry 18:807-811

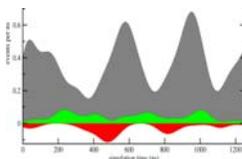
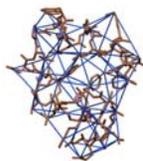


Assumption: Pivot residues are connected to rigid domains. This holds for *PDB* comparisons ... but *not* for *MD* (dominated by fast local fluctuations).

How to (Properly) Transform Time-Domain Data into Spatial Heat Maps

Time Series Data:

- $X(t)$: user-selected fast *local* variable, e.g. pivot dihedral angle
- $a(t)$: slow “activity” function (measuring *global* state changes)



TimeScapes

Wriggers et al., *J Chem Theory Comput* (2009)
5:2595

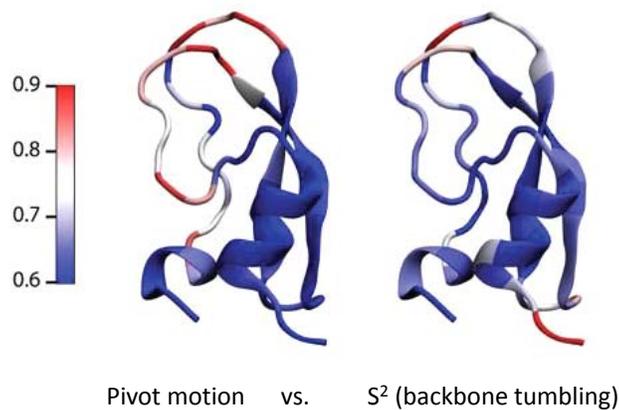
Statistical Characterization:
$$R_{Xa} = I \left(\left| \frac{\partial X(t)}{\partial t} \right| ; a(t) \right)$$

R_{Xa} : ranking coefficient, reports on relative *spatial importance of local changes* for global activity (heat map!)

I : Statistical Measure of Dependence, e.g.

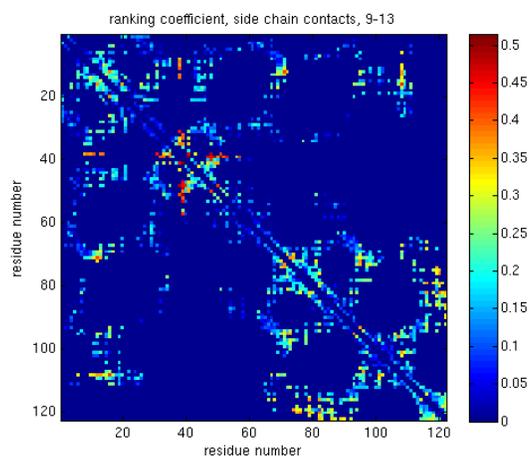
- Pearson Cross-Correlation (Shaw et al., *Science* 330:341, 2010)
- Mutual Information (Kovacs & Wriggers, *J Phys Chem B*, 2016)

Results: Pivot Residue Heat Map

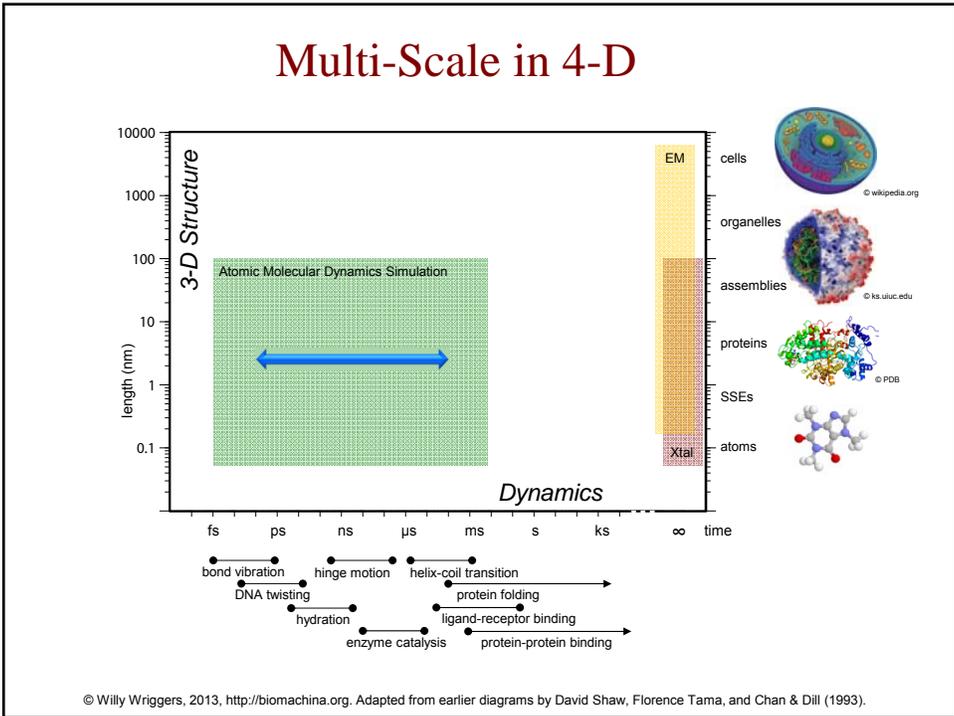
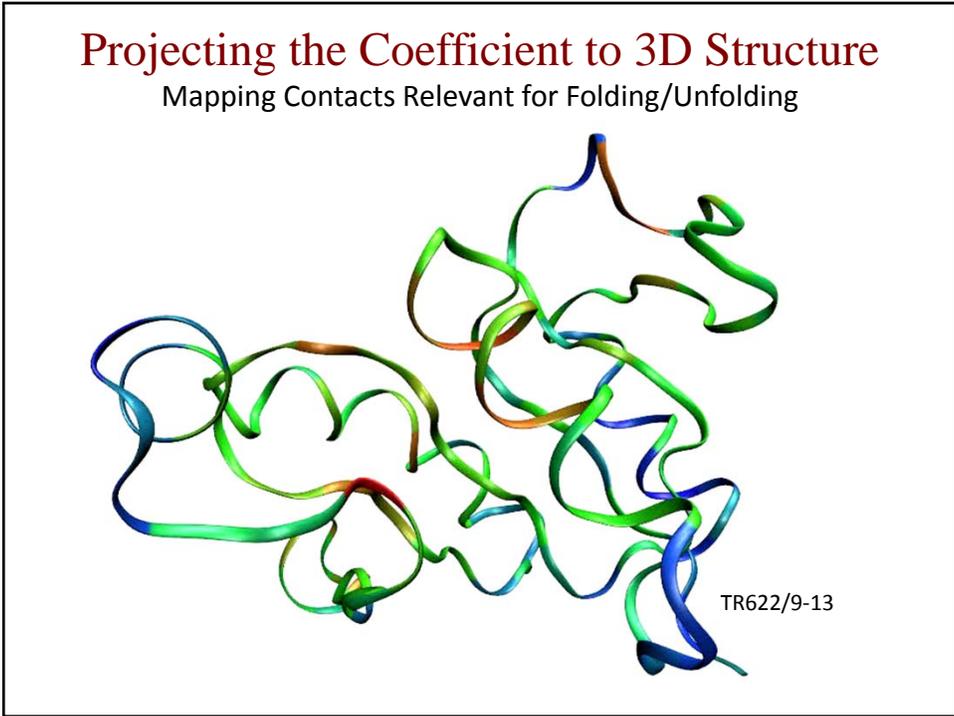


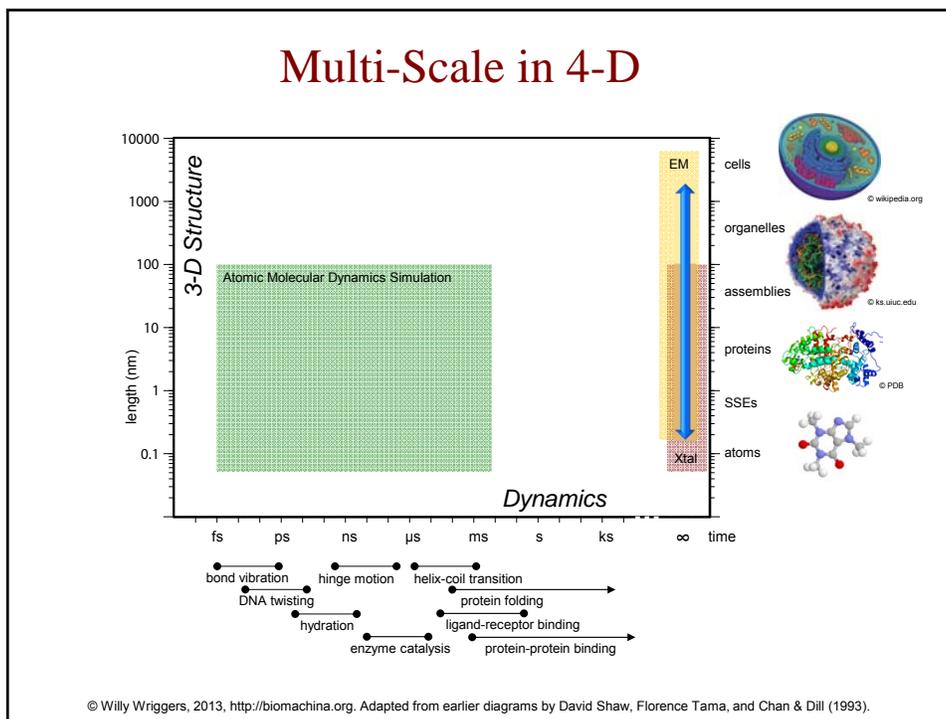
Shaw et al., *Science* (2010) 330:341

Results: Contact Heat Map

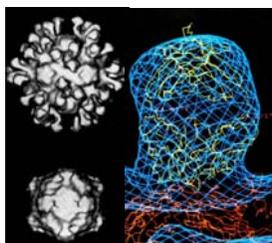


Contact coefficient measures the importance of residue-residue contacts for the global conformational change (e.g. folding/unfolding)





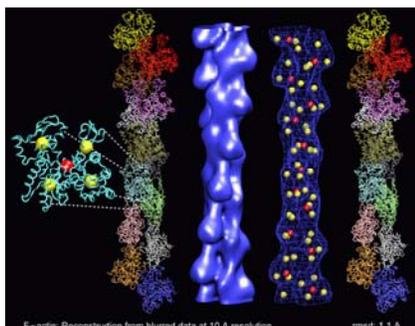
24 Years of Fitting in Electron Microscopy



Guoji Wang, Claudine Porta, Zhongguo Chen, Timothy S. Baker, John E. Johnson:

Identification of a Fab interaction footprint site on an icosahedral virus by cryoelectron microscopy and X-ray crystallography.

Nature (1992) 355:275



Willy Wriggers, Ronald A. Milligan, Klaus Schulten, and J. Andrew McCammon:

Self-Organizing Neural Networks Bridge the Biomolecular Resolution Gap.

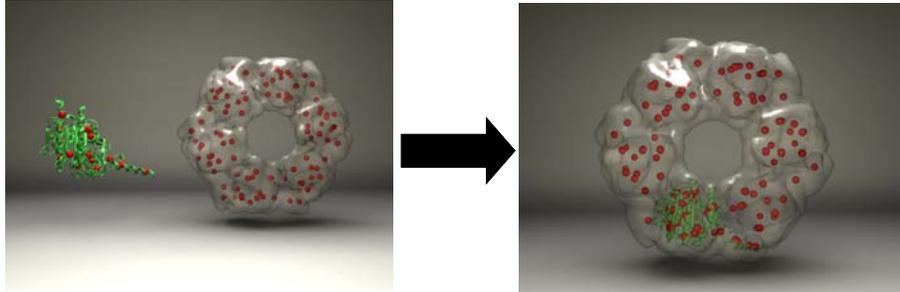
J Mol Biol (1998) 284:1247

Willy Wriggers, Ronald A. Milligan, and J. Andrew McCammon:

Situs: A Package for Docking Crystal Structures into Low-Resolution Maps from Electron Microscopy.

J Struct Biol (1999) 125:185

1999-2009: Fast “Point Cloud” Fitting



Simulated fiducials (*neural gas*, Martinetz & Schulten 1993), reduce complexity of search space.

Useful for:

- Rigid-body fitting
- Flexible fitting
- Interactive fitting / force feedback
- Building of deformable models

2002: Correlation Based Approach

1. 6D Search

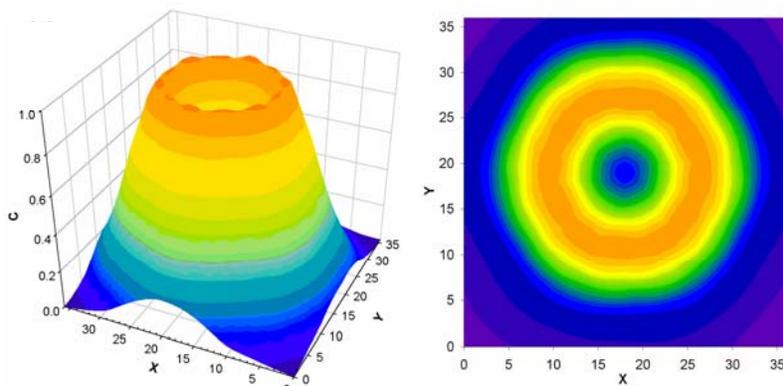
$$CC(R, T) = \int \rho_{\text{target}}(\mathbf{r}) \cdot \rho_{\sigma_{3D}}(R, \mathbf{r} + T) d^3\mathbf{r}$$

2. Find Peaks

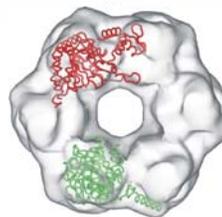
4. Output Results

3. Optimize Peaks

1. Correlation Landscape

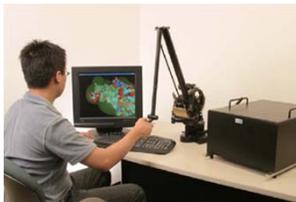


For resolutions below 10Å
interior detail is lost and
we cannot distinguish between
correct and spurious fits



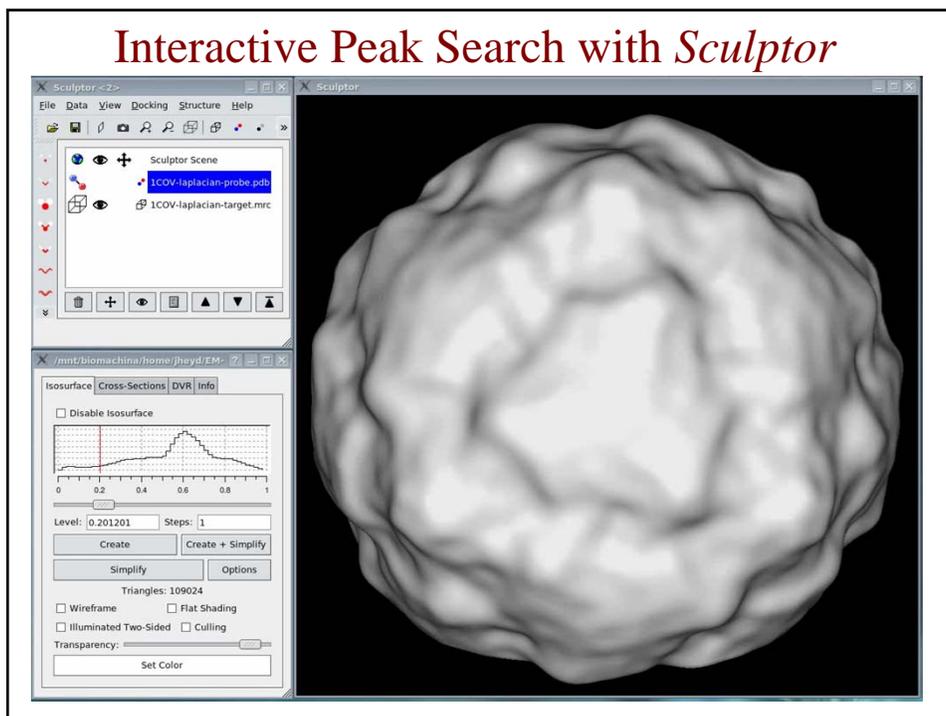
2. Interactive Peak Search

- Computer model augmented by reality (human expert)
- User guides model through the 6D search space supported by force-feedback
- Pre-computed cross-correlation as basis for force and torque calculation



- Can be combined with advanced virtual reality techniques (3D stereoscopic and tracked visual rendering)

Interactive Peak Search with *Sculptor*



3. Off-Lattice Refinement

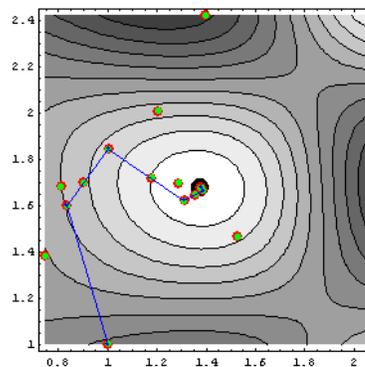
The exhaustive search is limited to a grid of points in the 6D search space

Improve the accuracy



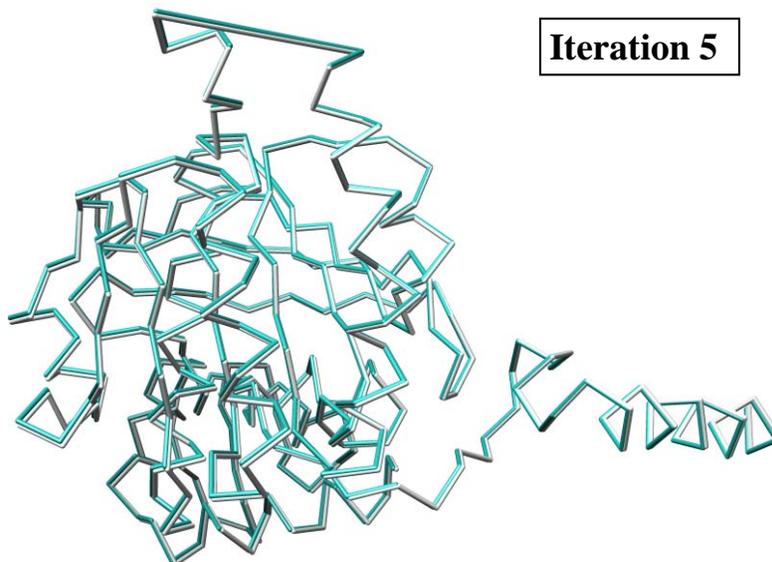
Off-lattice (6D) local maximization
of the correlation coefficient

(Powell conjugent gradient method)

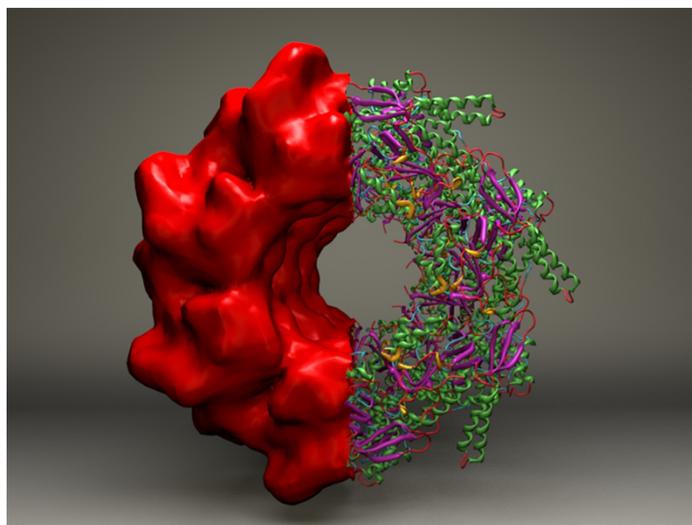


Off-Lattice Refinement: Example

Iteration 5



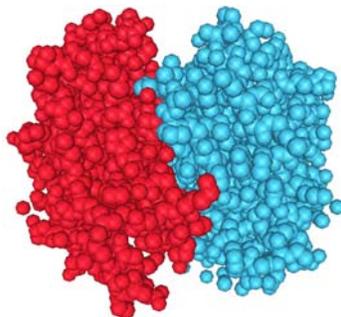
4. Molecular Visualization



Global illumination models are slow (ray tracing), but very accurate

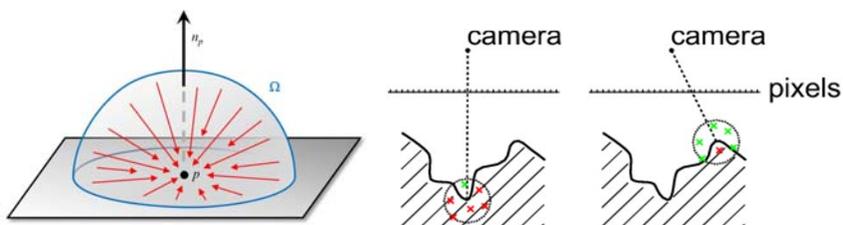
Interactive Molecular Rendering

- Typically only *local* lighting models
- Shading of each triangle determined without taking other triangles into account
- Flat appearance



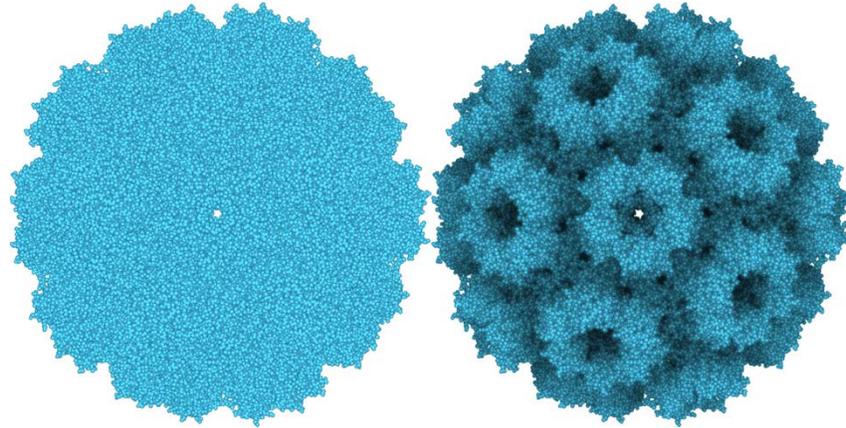
Screen Space Ambient Occlusion

- Developed by Vladimir Kajalin for the 2007 Windows game *Crysis*
- Creases, pockets, prevent triangles from receiving ambient light
- Screen-based ambient occlusion based on percentage of unoccupied samples in spherical template



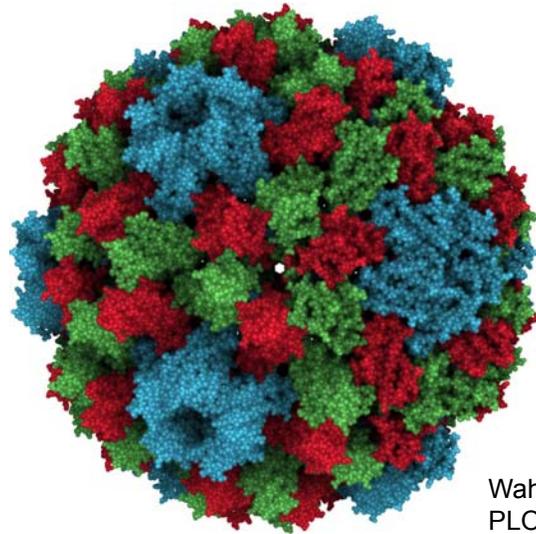
- Computed on GPU, scales with screen size
- Interactive on newer graphics cards

Ambient Occlusion in *Sculptor*



CCMV (PDB 1CWP)

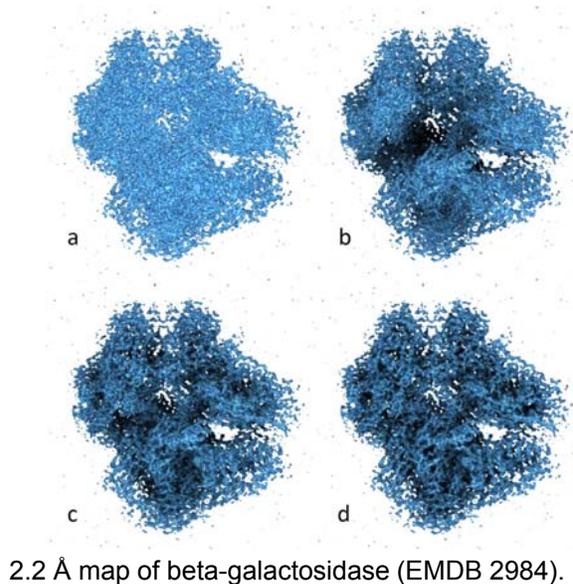
Unique User-Defined Template Radius



CCMV (PDB 1CWP)

Wahle & Wriggers
PLOS Comp. Biol.
(2015)

Unique User-Defined Template Radius

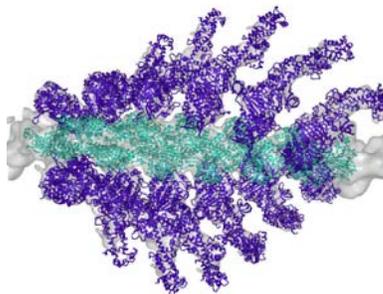


Wahle & Wriggers
PLOS Comp. Biol.
(2015)

Current Research: Simultaneous Multi-Fragment Refinement

- Powell conjugent gradient, 6N degrees of freedom
- What is the “systems behavior”? Fragments see each other (i.e avoid steric clashes) via normalization of cross correlation:

$$C(\mathbf{T}) = \frac{\int \rho_{\text{em}}(\mathbf{r}) \cdot \rho_{\text{calc}}(\mathbf{r} + \mathbf{T}) d^3 r}{\sqrt{\int \rho_{\text{em}}^2(\mathbf{r}) d^3 r} \sqrt{\int \rho_{\text{calc}}^2(\mathbf{r}) d^3 r}}$$

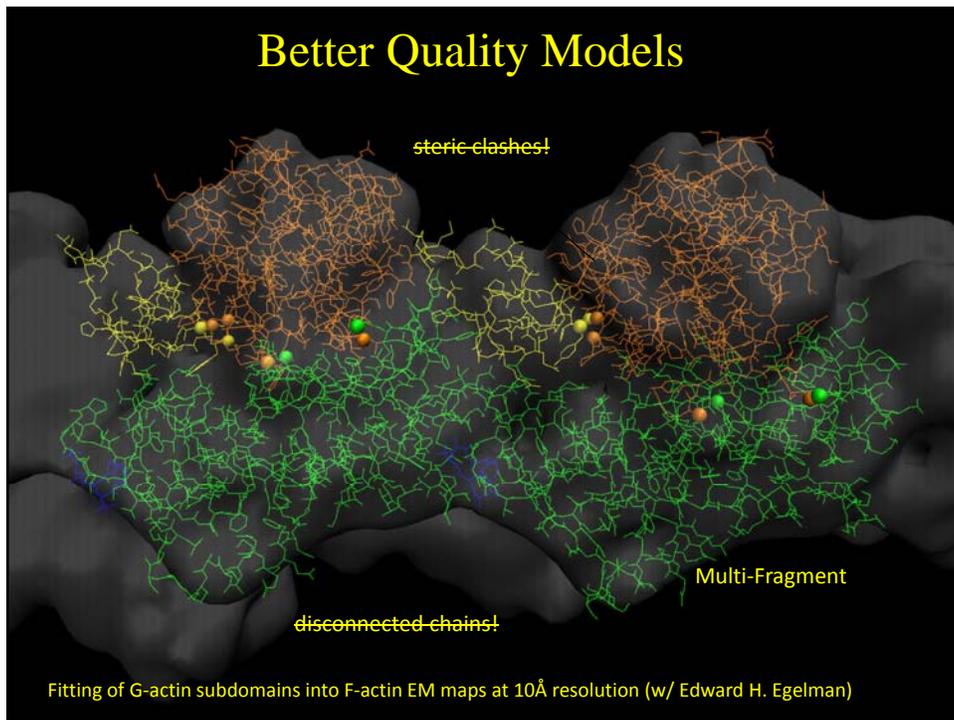
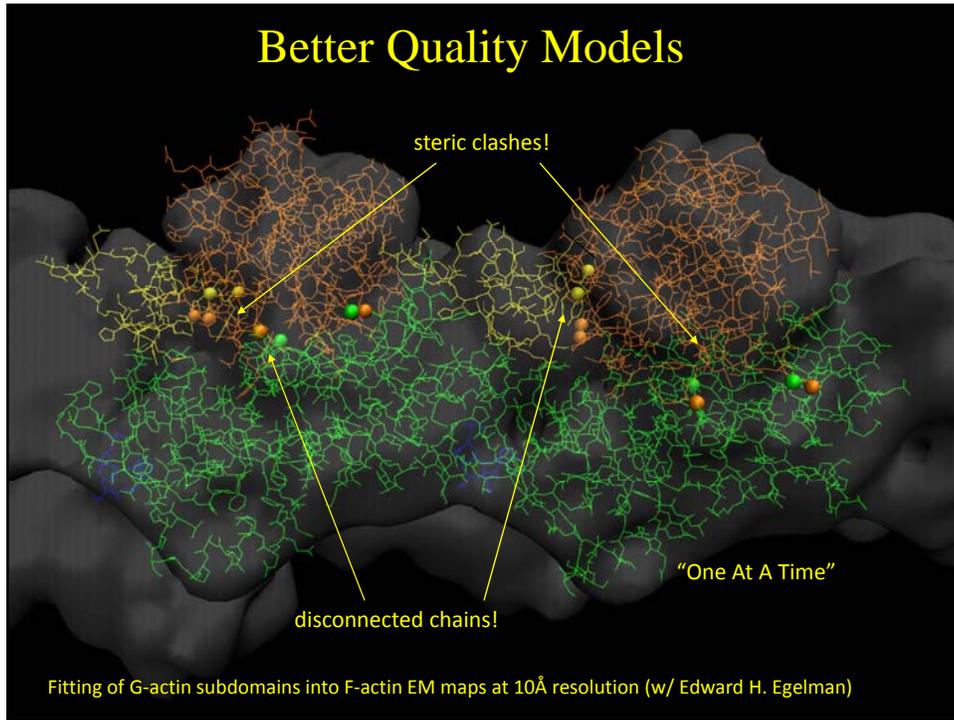


- Improved docking accuracy

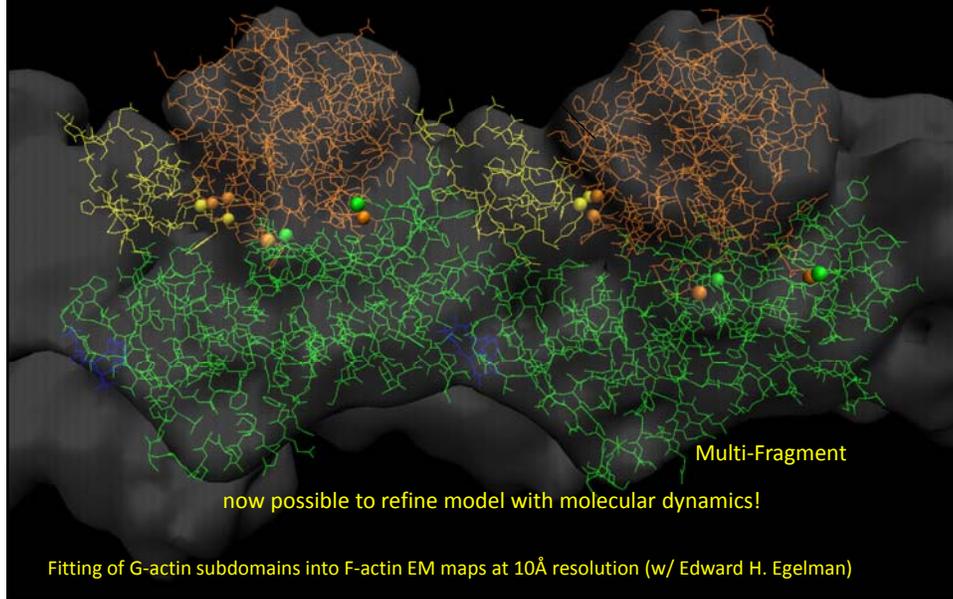
Birmanns et al., *J Struct Biol* (2011) 173:428

- Support of symmetry at each Powell step

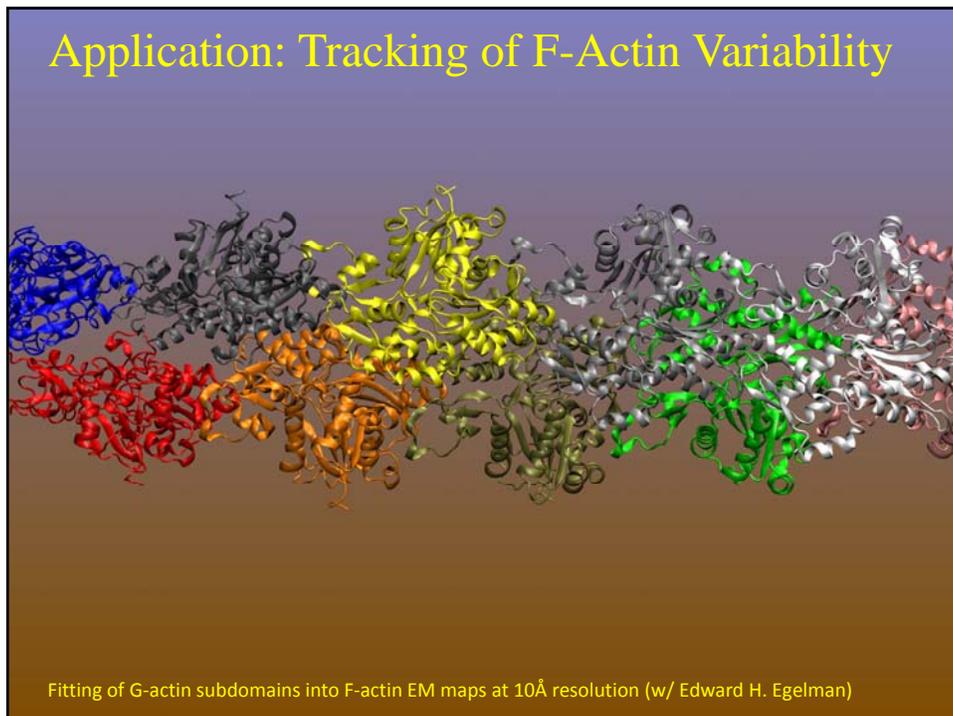
Wriggers, *Acta Cryst D* (2012) 68:344

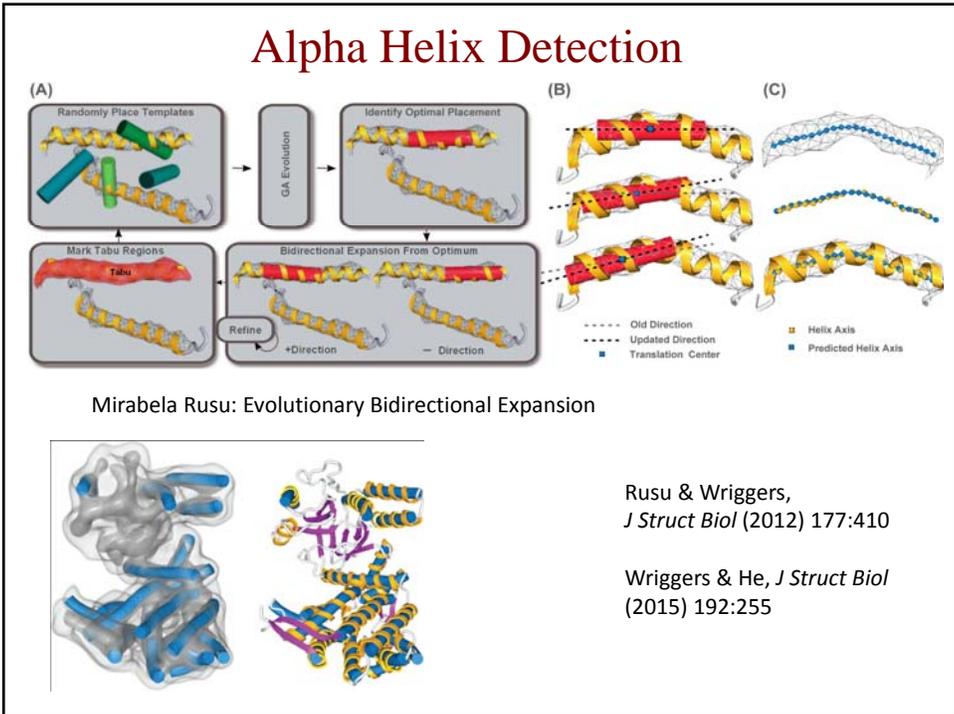
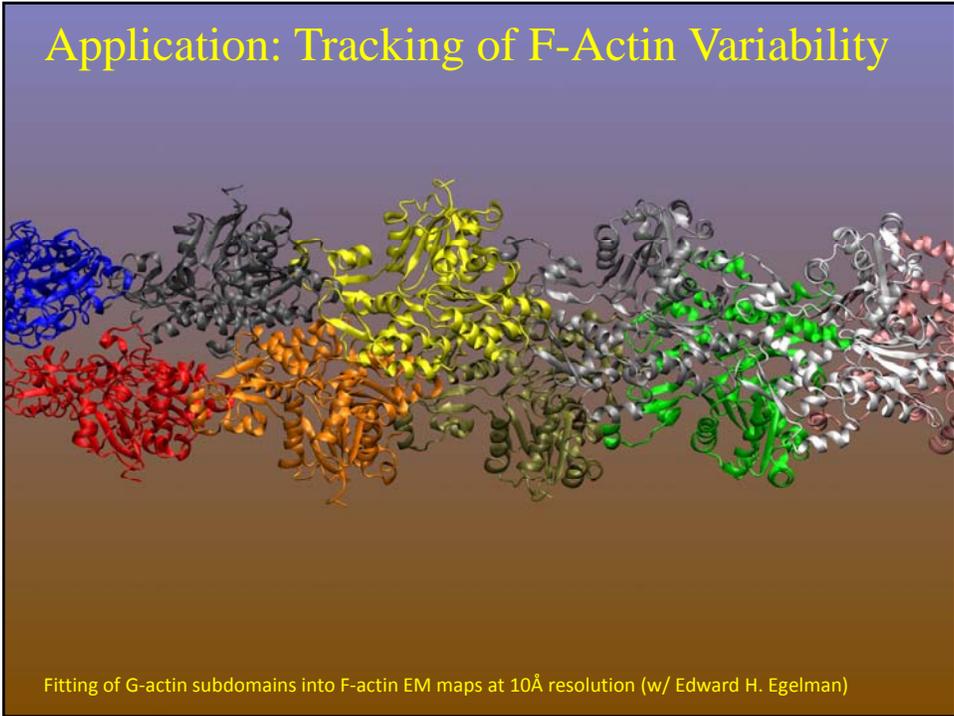


Better Quality Models

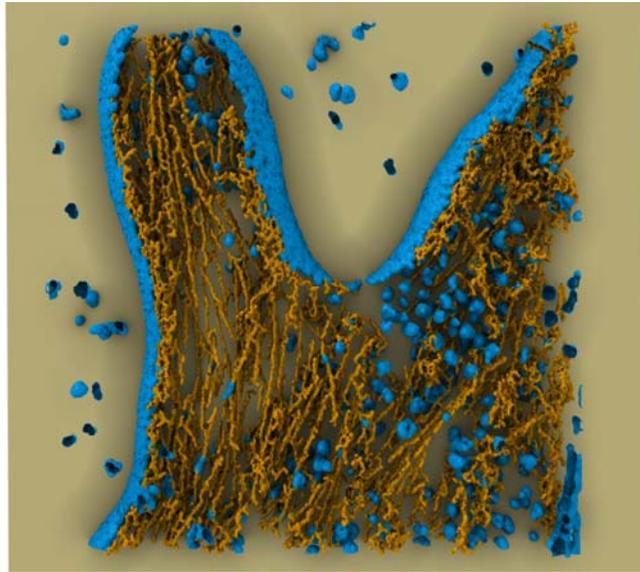


Application: Tracking of F-Actin Variability



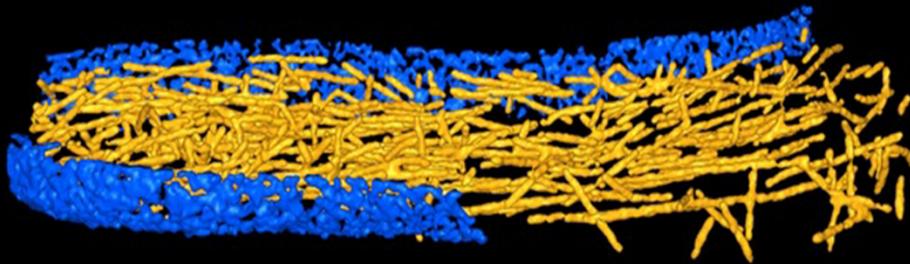


Tracing of Actin Networks in Filopodia

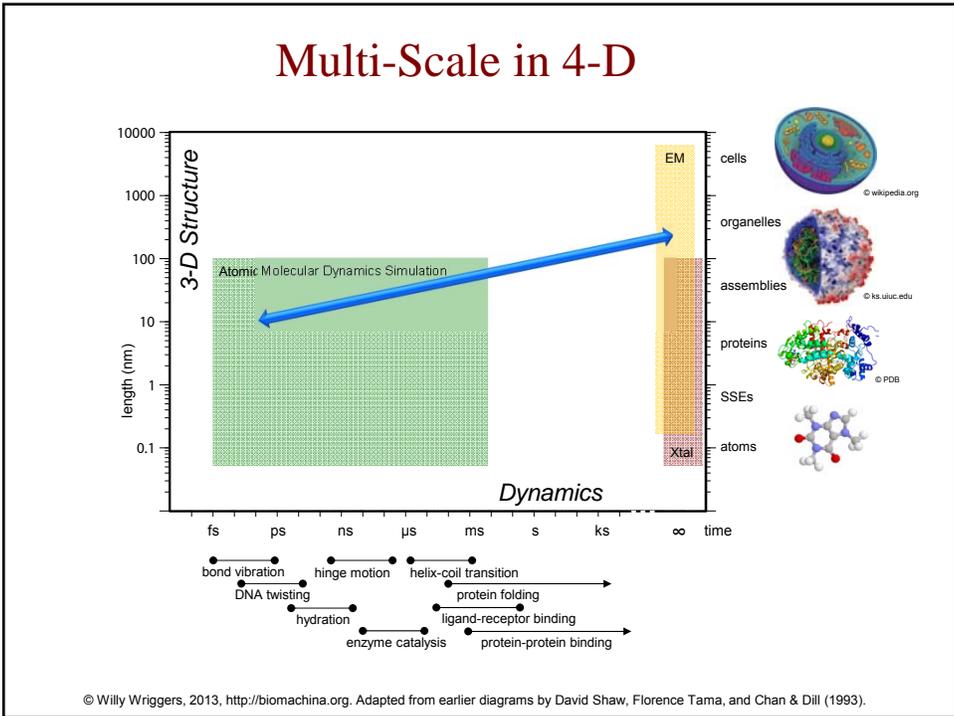
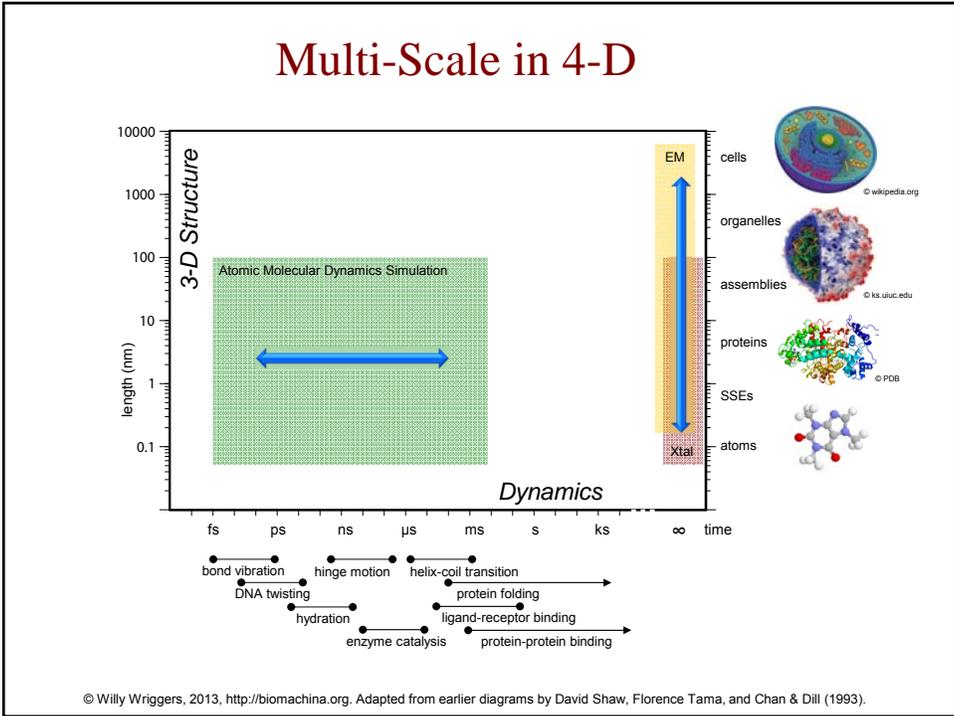


Dictyostelium filopodia (w/ Alexander Rigort, MPI Martinsried, Data by Ohad Medalia)

Tracing of Actin Networks in Filopodia



Rusu et al., *J Struct Biol* (2012) 178:121



Coarse-Grained Motion Model

Low Resolution



Modeling of tarantula myosin head dimers using simulated markers (with Raúl Padrón)

Motion Capture Network:

Darst et al., *PNAS* (2002) 99:4296

Wriggers et al., *Neurocomputing* (2004) 56:365

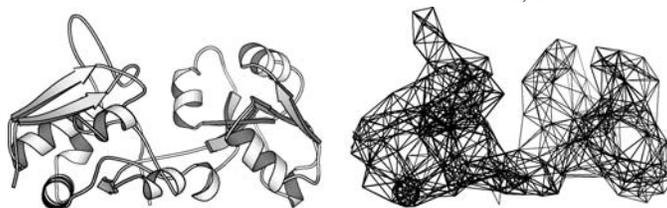
Alamo et al., *J Mol Biol* (2016) 428:1142

Elastic Network Model

Intermediate Resolution

Simplified force-field: no MD, already minimized

$$E(r_a, r_b) = \frac{C}{2} (|r_{a,b}| - |r_{a,b}^0|)^2 \quad E_p = \sum_{a,b} E(r_a, r_b)$$



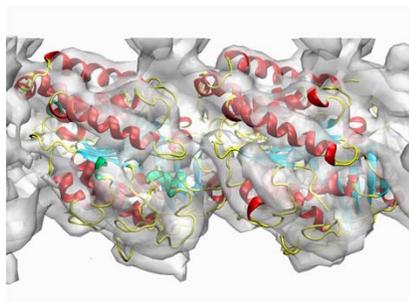
Possibility to include secondary structure constraints

Chacón et al., *J Mol Biol* (2003) 326:485

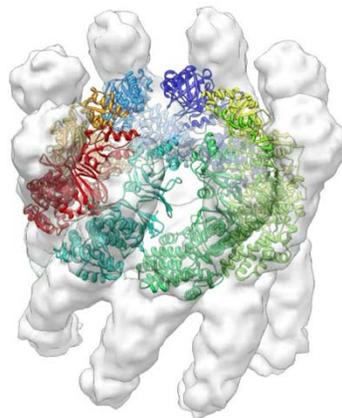
Stember & Wriggers, *J Chem Phys* (2009) 131:074112

Elastic Network Model

Intermediate Resolution



Tubulin (8.6 Å, 838 nodes, EMD 5223, PDB 1jff)

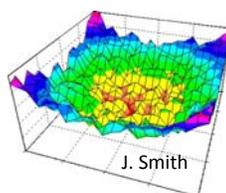


Thermosome (10 Å, 3836 nodes, EMD 1396, PDB 1a6d)

Refinement with iMod (Pablo Chacón):
López-Blanco et al., *Bioinformatics* (2011) 27:2843

Molecular Dynamics Model

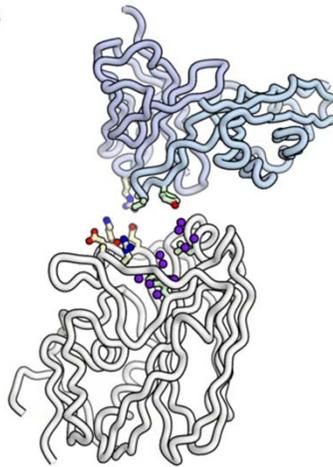
Atomic Resolution



- Sampling of the native state with unbiased MD is not (yet) routine.
- We use unbiased MD for generating an ensemble that contains few correct solutions among a large number of incorrect ones.
- Can we use low resolution data to “filter” the native state ensemble from unbiased long-time MD simulations?

Protein-Protein Binding Simulations

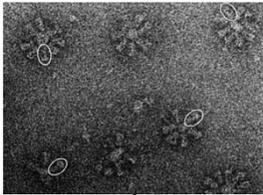
0.00us



Antibody CH65 spontaneously binds to hemagglutinin in MD simulations.

Schmidt et al.,
PNAS (2013)
110:264

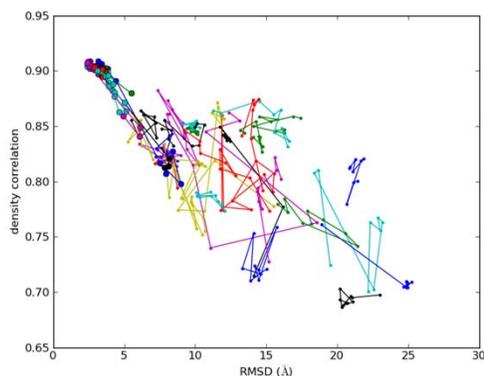
Epitope Mapping by EM and MD Binding Simulations



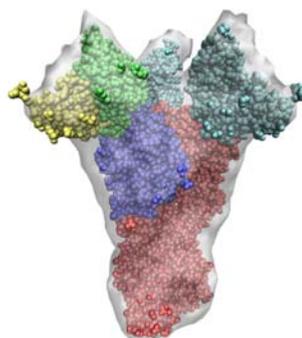
~11Å resolution

- Can we design immunogens that elicit epitope-specific antibodies?
 - Vaccines
- What are the immunogenic epitopes on the hemagglutinin surface? Need a structural model of complexes between hemagglutinin and antibodies (with Stephen Harrison and Niko Grigorieff)

Correlation with EM Density Selects Correct Complex Structures from Simulations



40 binding runs with different initial conditions
(by color)



Binding Simulations That Fit EM Data Have Correct Fab - HA Contacts

Binding Sims. Top 10

L:S92-D190

L:R29-E227

H:D107-Y95

L:R29-D225

H:D107-R226

H:Y109-T155

H:V106-V135

L:S92-N187

H:D107-S136

L:S92-G189

Complex Sims. Top 10

L:R29-E227

L:S92-D190

L:R29-D225

H:D107-Y95

H:V106-V135

H:Y109-T155

H:D107-R226

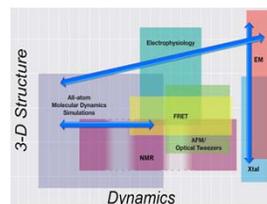
H:D107-S136

L:S92-N187

L:S92-G189

A “Systems” Strategy for Multi-Scale Discovery

Bridging between time and spatial scales often yields unexpected new insights



Bridging Approach	Motivation (Engineering)	Windfall (Research)
Temporal	Finding hinge residues	Functional annotation, mapping of hot spots
Spatial	Fitting of atomic structure to target EM map	Improved accuracy, support of symmetry, tracing α -helices, segmentation of tomograms
Spatio-temporal	Flexible fitting	Mapping of epitopes

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Mirabela Rusu

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John Heumann
Cailee Helmick

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Jing He
(Stephanie Zeil, Hussam Hallak, Kele McKaig)

D.E. Shaw Research, New York:

Paul Maragakis
Huafeng Xu

Experimental Collaborators:

Alexander Rigort & Wolfgang Baumeister
Edward Egelman & Vitold Galkin
Seth Darst, Joachim Frank, Ron Milligan
Raúl Padrón
Nikolaus Grigorieff & Stephen C. Harrison

Software: <http://biomachina.org>

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