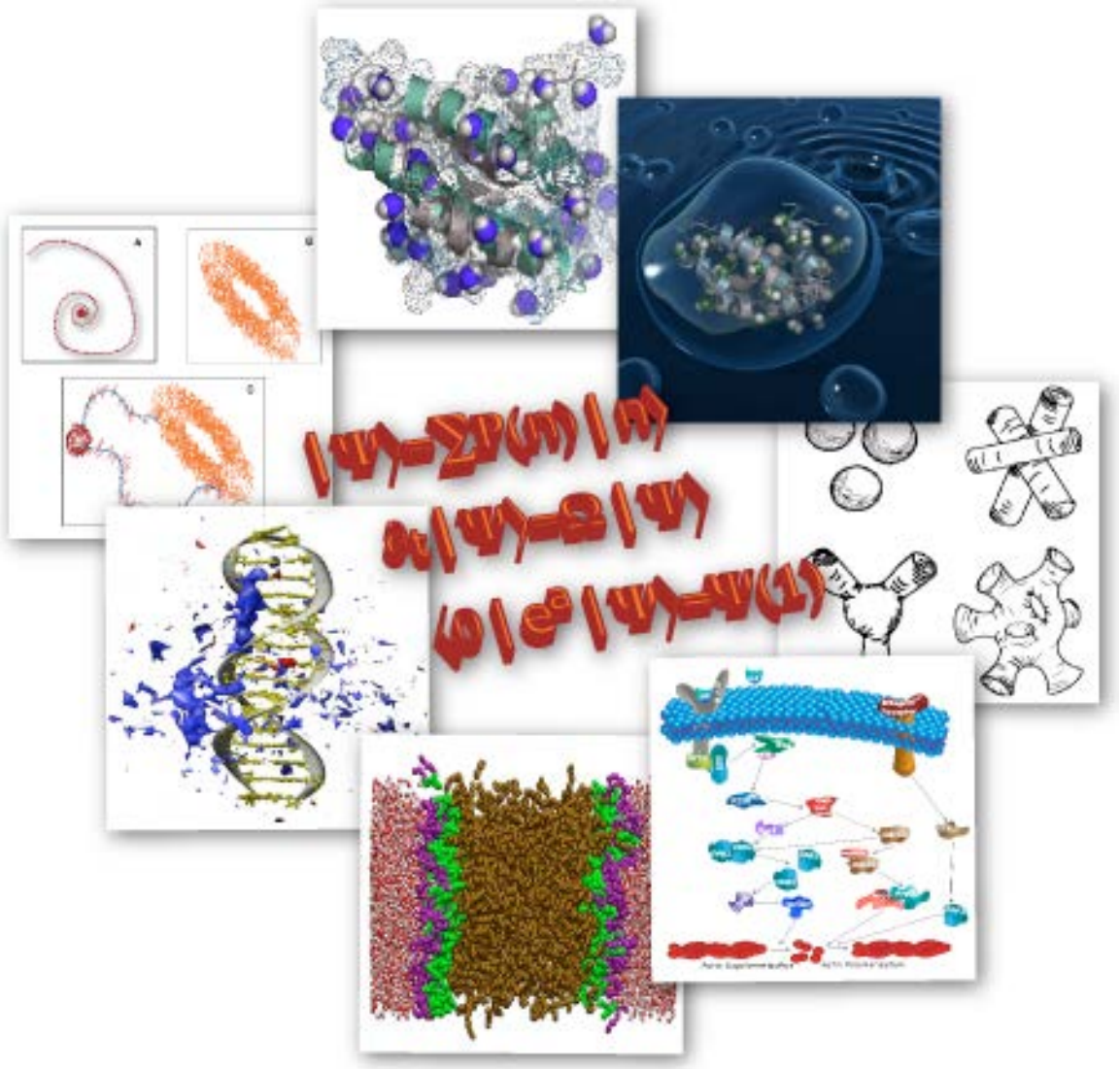
Modeling Biomolecular Structure and Dynamics by Blending Ideas from Machine Learning and Physics



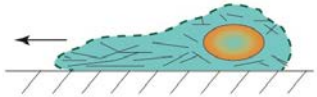
Department of Chemistry and Biochemistry

&

Institute for Physical Science and Technology

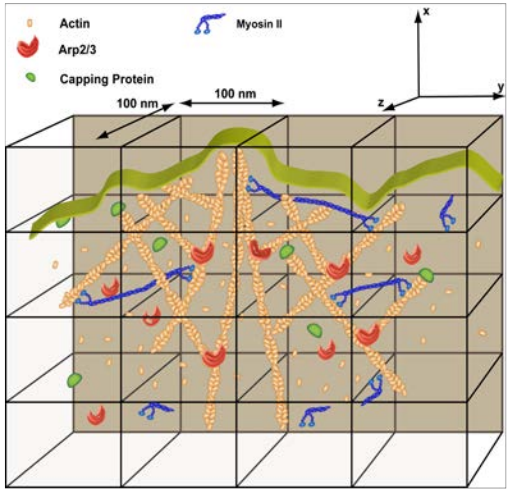
University of Maryland

Whole-Cell Modeling

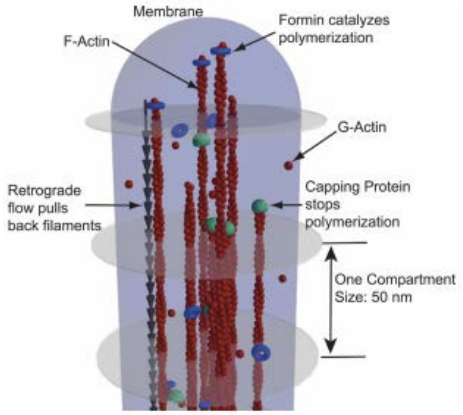


We study how cells move by creating stochastic models for the growth and retraction of lamellipodia and filopodia, which create and extend from the leading edge of a cell.

Modeling Actomyosin Networks, Lamellipodia Growth and Retraction



Modeling Filopodia Growth and Retraction



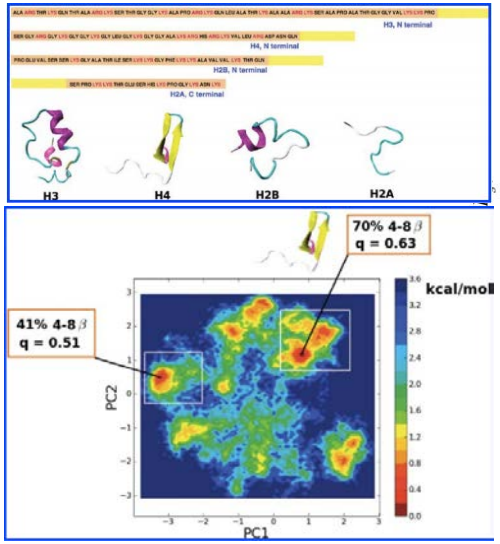
✏ **K. Popov, J. Komianos, G. A. Papoian, PLOS Comp Bio, 2016, DOI:10.1371/journal.pcbi.1004877**

Chromatin and Histone Dynamics

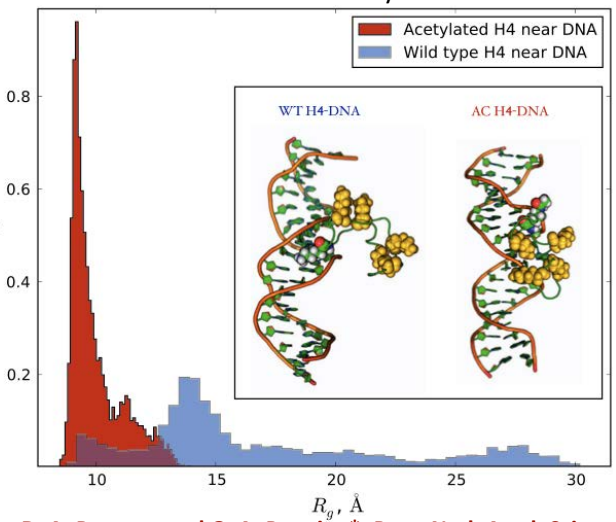
We study the structure and dynamics of chromatin: the DNA-protein complex within the nucleus. We model modified histone tails as well as entire nucleosomes using all atom simulations.

D. A. Potoyan and G. A. Papoian; JACS; 2011, 133, 7405-7415.

Histone Energy Landscapes



The Effects of Histone Acetylation

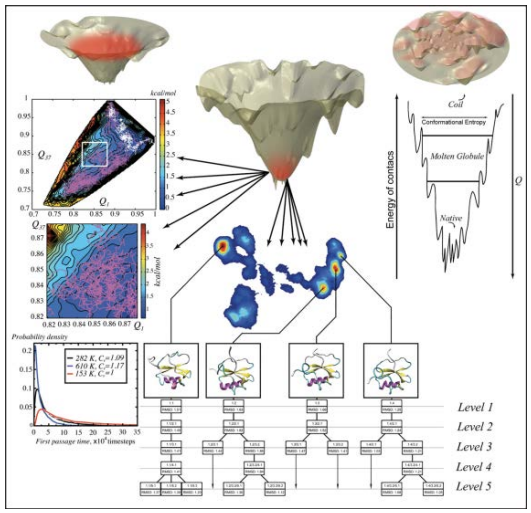


D. A. Potoyan and G. A. Papoian*; Proc. Natl. Acad. Sci. USA; 2012, 109, 17857-17862.

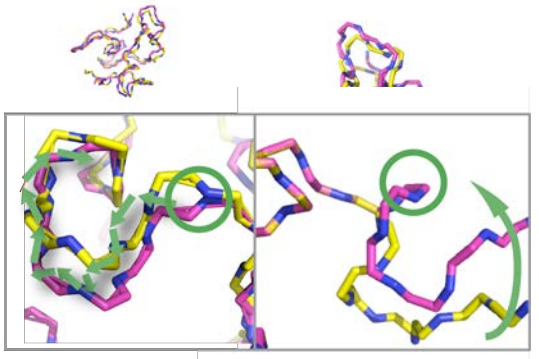
Protein Dynamics

We study the structure and dynamics of folded and unfolded proteins using Energy Landscape theory, examining different possible conformations and better understanding internal friction.

Protein Dynamics, Free Energy Landscapes and Calculations



Unfolded Protein Dynamics



- Compact state
- Local rearrangements
- Viscosity independent

- Swollen state
- Global rearrangements
- Viscosity dependent

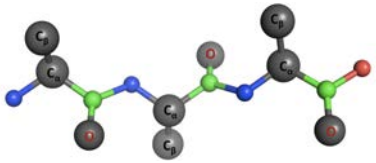
P. I. Zhuravlev, C. K. Materese and G. A. Papoian; J. Phys. Chem. B (Feature Article; July 2 2009 Journal Cover); 2009, 113, 8800

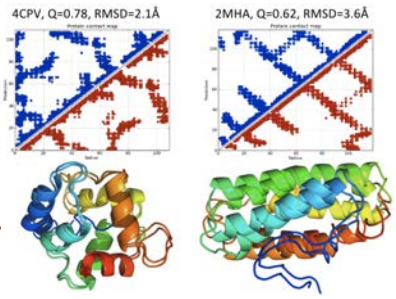
Protein and DNA Coarse Graining

We continue to improve our coarse-grained force fields to predict protein and DNA structure, which draw from physically motivated terms as well as a bioinformatical term.

A. Davtyan, W. Zheng, N. Schafer, C. Clementi, P. G. Wolynes and G. A. Papoian, JPCB, (2012), 116, 8494

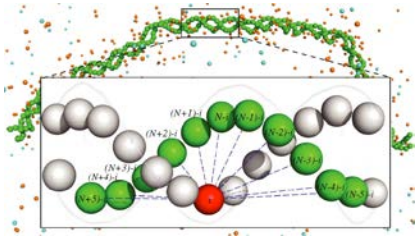
Coarse-grained Force Fields and Protein Folding Prediction





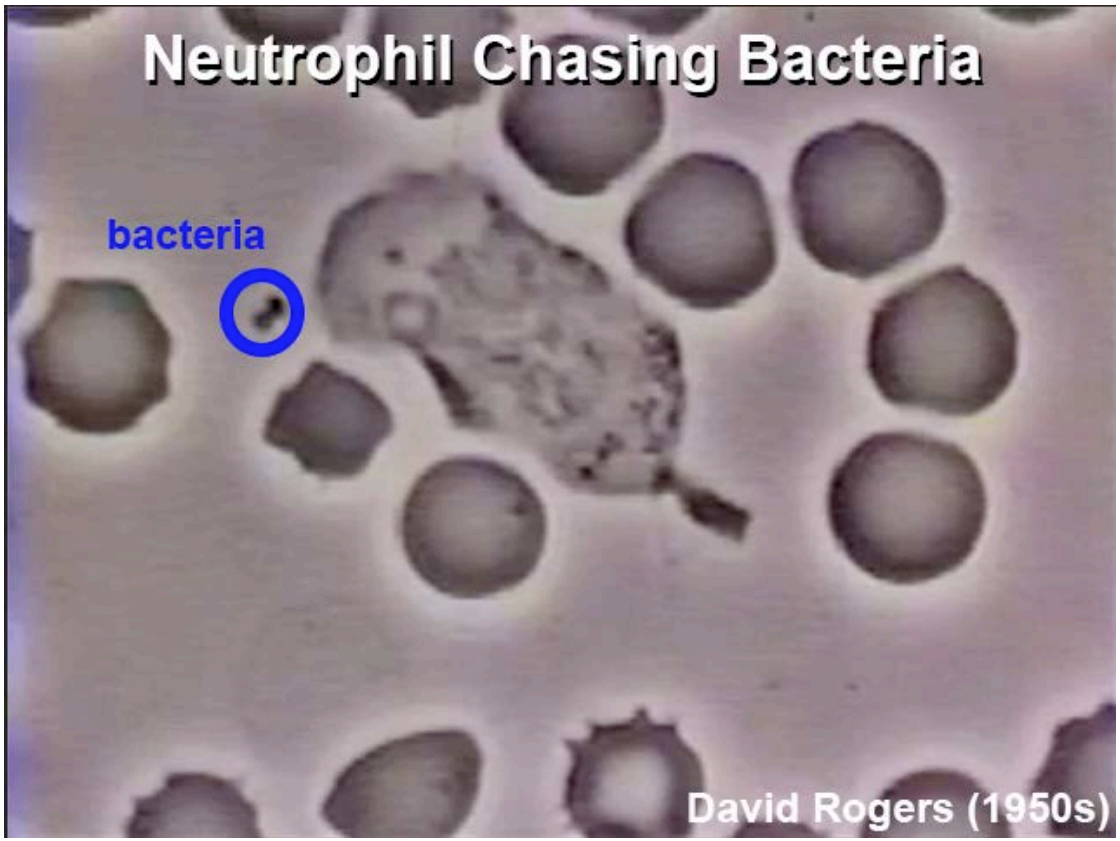
Predicting Ubiquitin Dimerization

Coarse-grained DNA Force Fields



A. Savelyev and G. A. Papoian; Proc. Natl. Acad. Sci. USA; 2010, 107, 20340–5.

The most famous video in biology

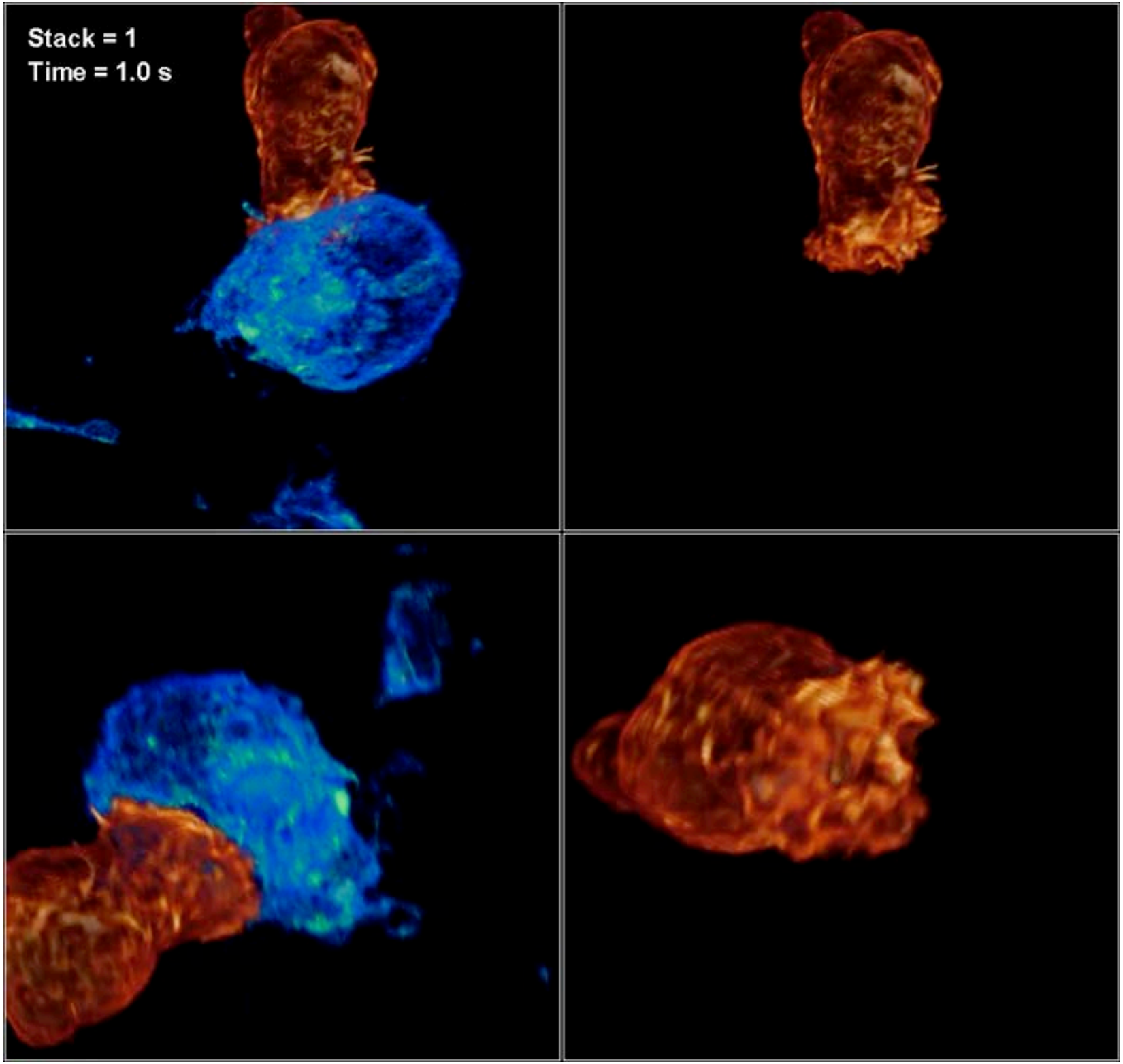


This video is taken from a 16-mm movie made in the **1950s** by the late **David Rogers** at Vanderbilt University. It was given to Thomas P. Stossel via Dr. Victor Najjar, Professor Emeritus at Tufts University Medical School and a former colleague of Rogers.

Hill, M.A. 2017 Embryology Movie - Neutrophil chasing bacteria.

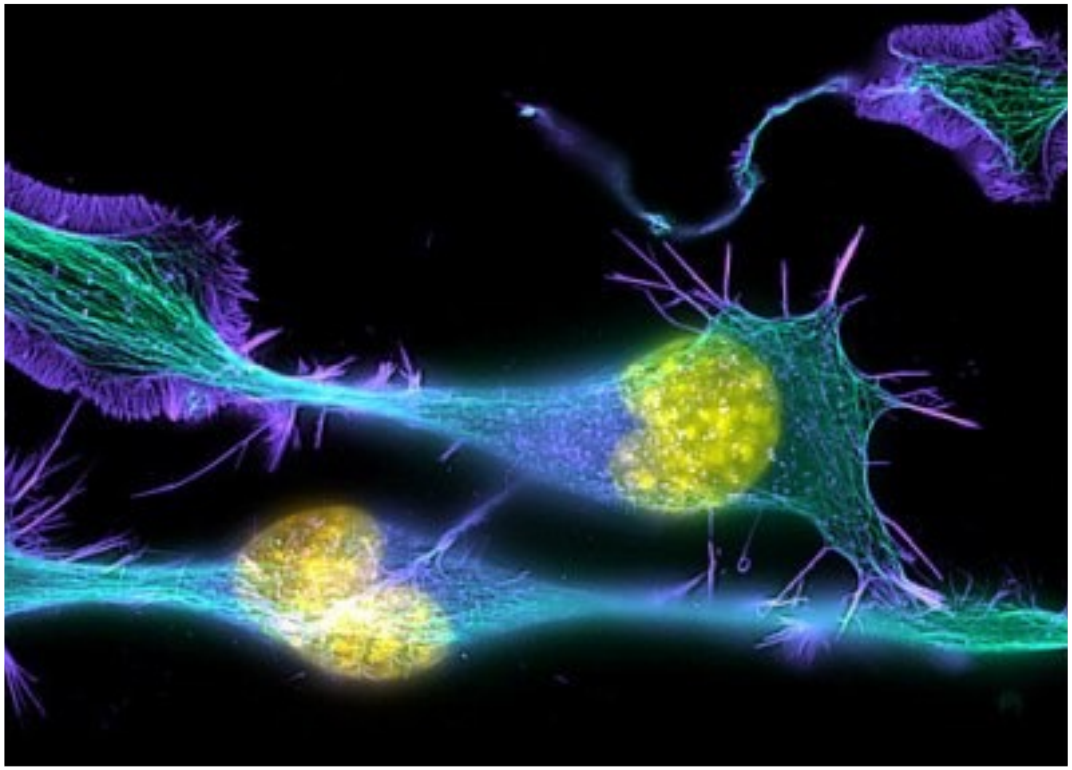
Richard Feynman: What I cannot create, I do not understand

... or to add a modern twist: What I cannot simulate, I do not understand


Stack = 1
Time = 1.0 s

The Actin Cytoskeletal Network

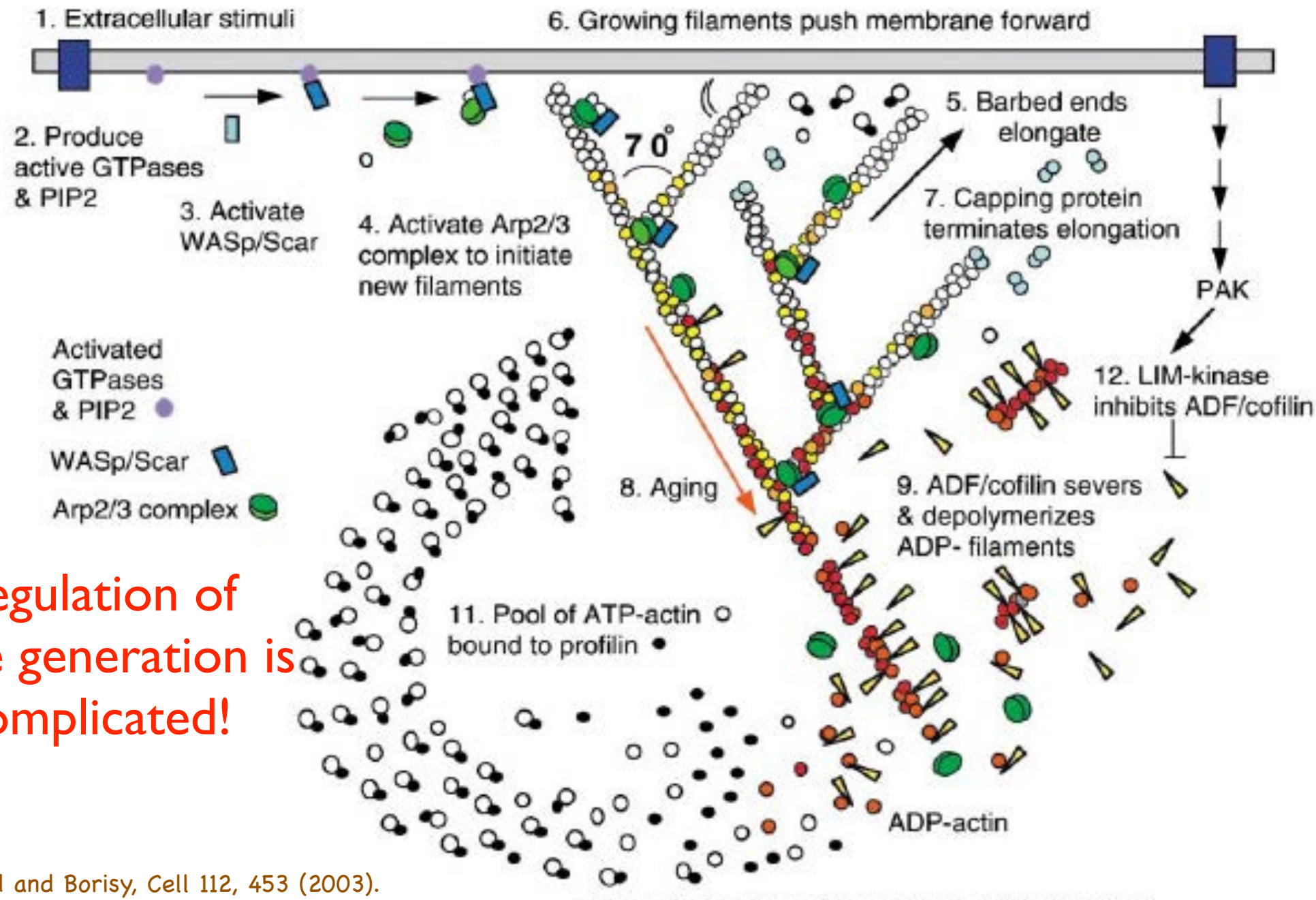
- A biological **active matter** system
- Driven by consumption of energy, transferred into mechanical work
- Crucial role in many aspects of cell shape, function, and dynamics
- Many constituents that create **collective, emergent behavior**



A growing neural dendrite
actin (purple), microtubules (green)

Neurodevelopment 2014

Dendritic nucleation/Array treadmilling model

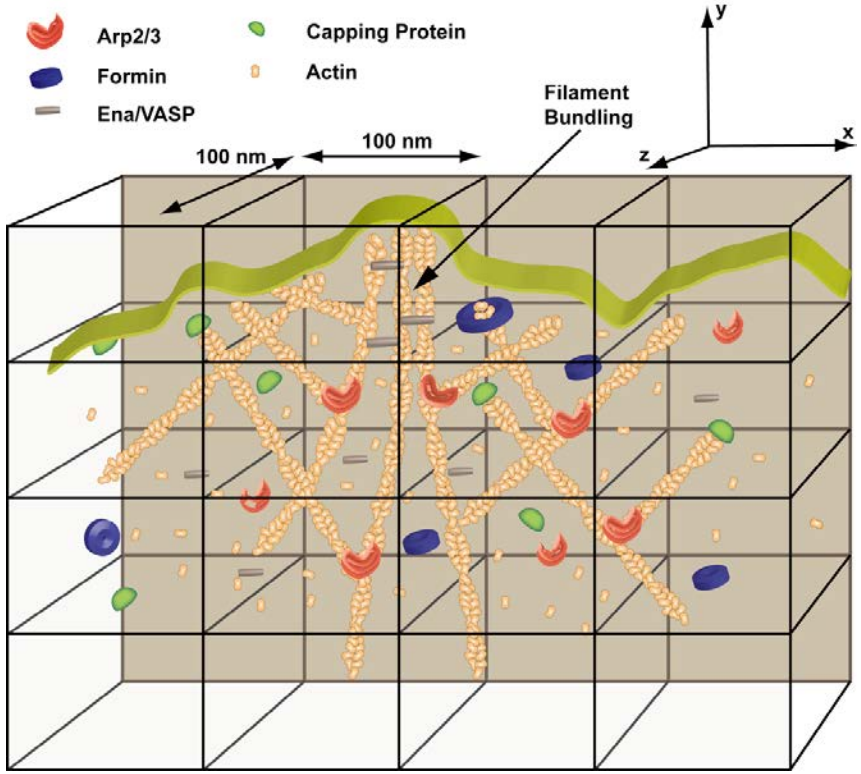


Regulation of force generation is complicated!

- Pollard and Borisy, Cell 112, 453 (2003).
- T.D Pollard, L Blanchoin, R.D Mullins Annu. Rev. Biophys. Biomol. Struct., 545-576 (2000)

MEDYAN: Mechanochemical Dynamics of Active Networks

- 3D simulation region is divided into compartments.
- Diffusion (Actin, Capping protein, Arp2/3) between compartments.
- Chemical reactions in compartments:
  - Polymerization, Depolymerization, Capping, Branching...
- Monte Carlo algorithm to generate stochastic trajectories

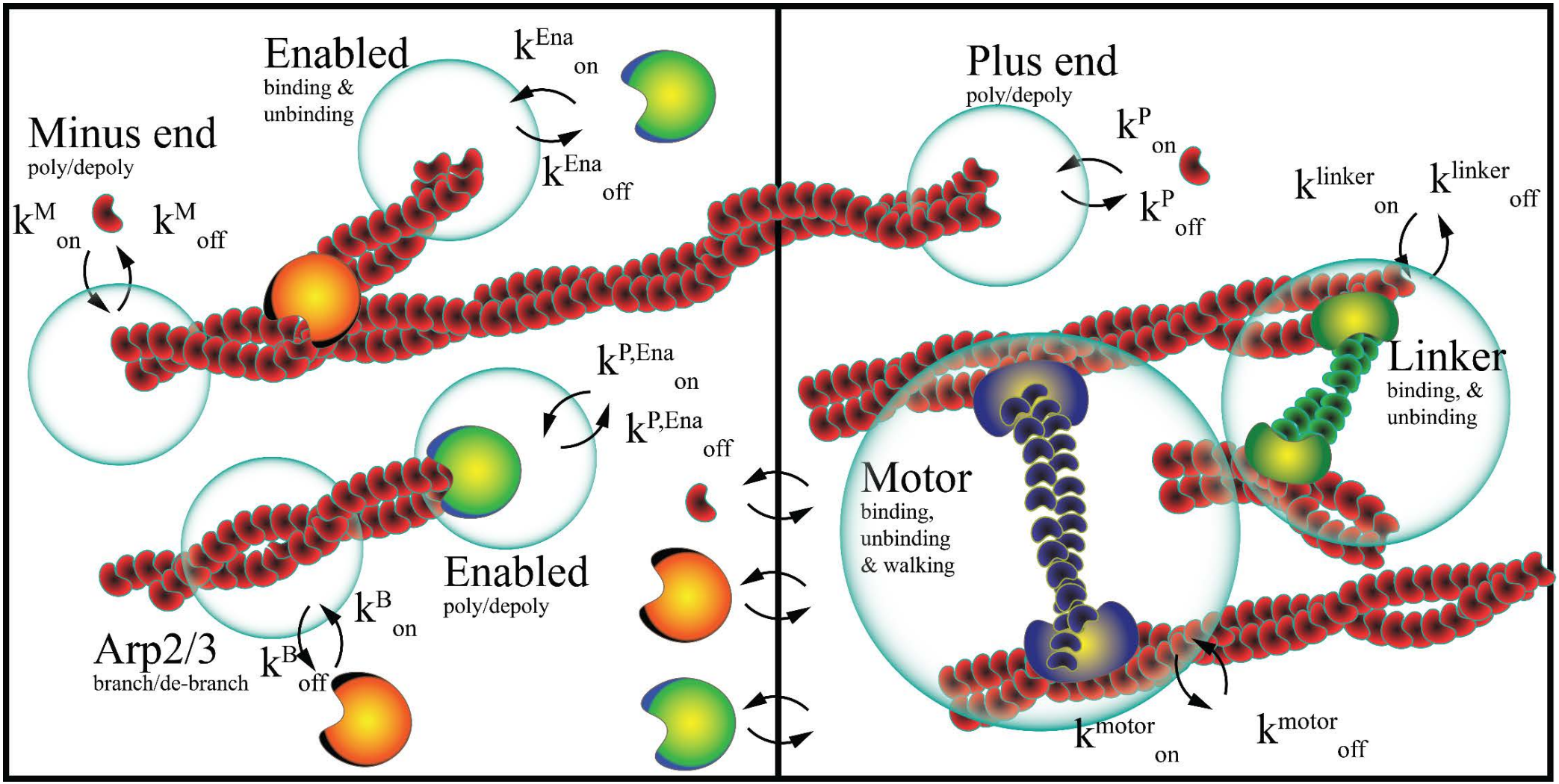


✏ K. Popov, J. Komianos, G. A. Papoian, **PLOS Comp Bio**, *2016*, DOI:10.1371/journal.pcbi.1004877

✏ L. Hu and G. A. Papoian, **Biophys. J.**; *2010*, 98,1375

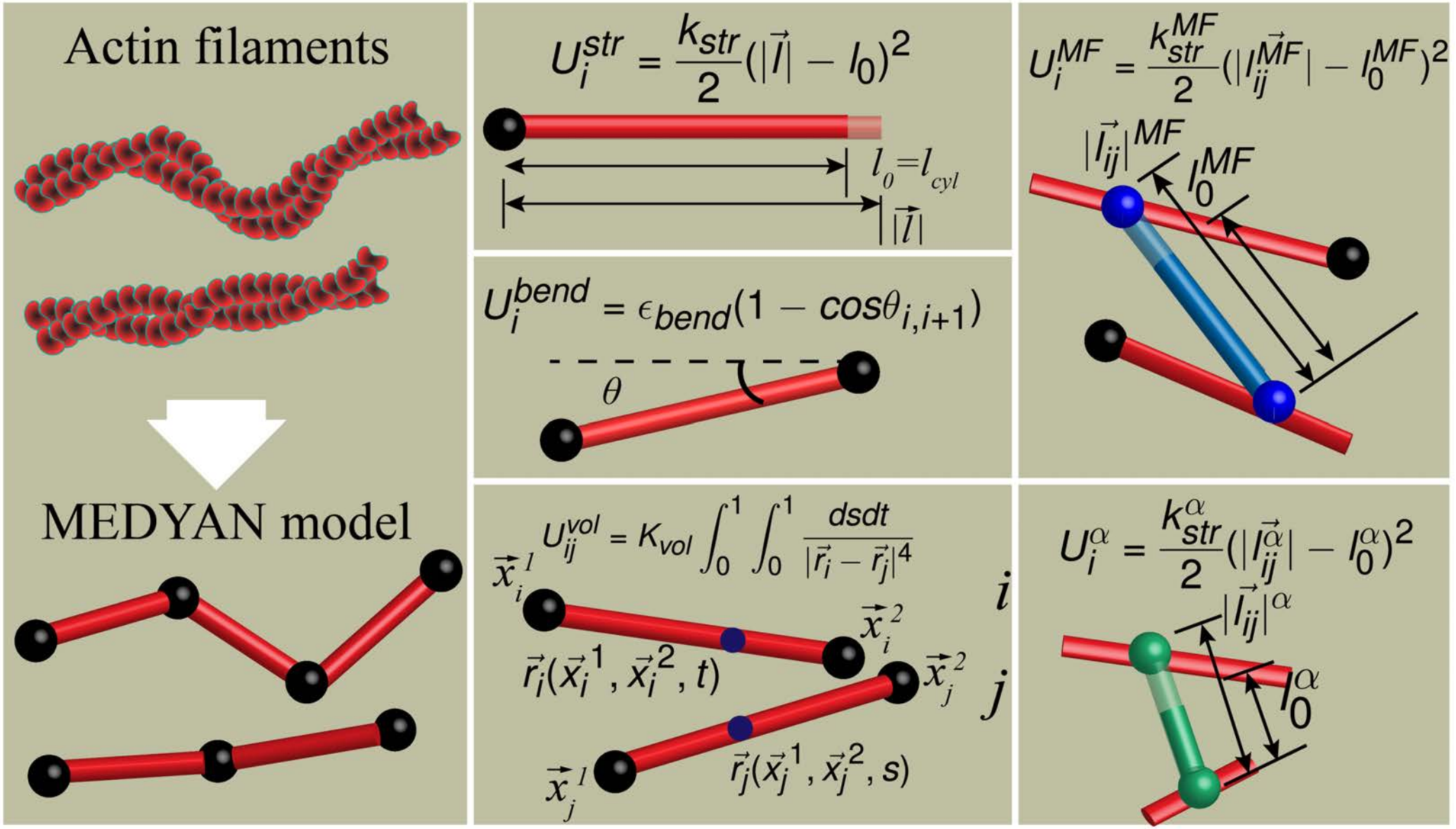
✏ L. Hu and G. A. Papoian, **J. Phys.: Condens. Matter**; *2011*, 23, 374101

Spatially resolved chemistry

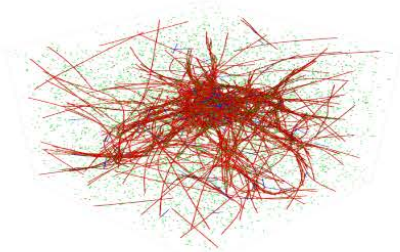


✏ K. Popov, J. Komianos, G. A. Papoian, PLOS Comp Bio, 2016, DOI:10.1371/journal.pcbi.1004877

MEDYAN: Mechanics



http://medyan.org

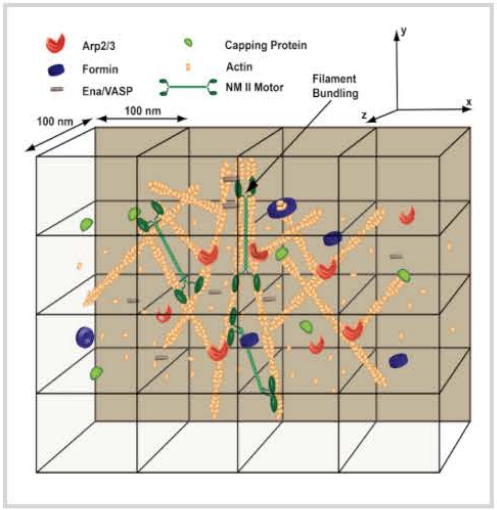


Home Documentation Download Publications Gallery Contact

MEDYAN - Mechanochemical Dynamics of Active Networks

Welcome to the webpage of the *MEDYAN*, an efficient and scalable computational model for mechanochemical simulations of active matter networks created by the Papoian lab at the University of Maryland. This webpage contains documentation and examples for the *MEDYAN* software package, which is implemented in C++. The source code for this package is downloadable for scientific use.

Background



The cell cytoskeleton plays a key role in human biology and disease, contributing ubiquitously to such important processes as embryonic development, wound repair and cancer metastasis. The Papoian laboratory is interested in gaining deeper understanding of the physical chemistry behind these complex, far-from-equilibrium mechanochemical processes.

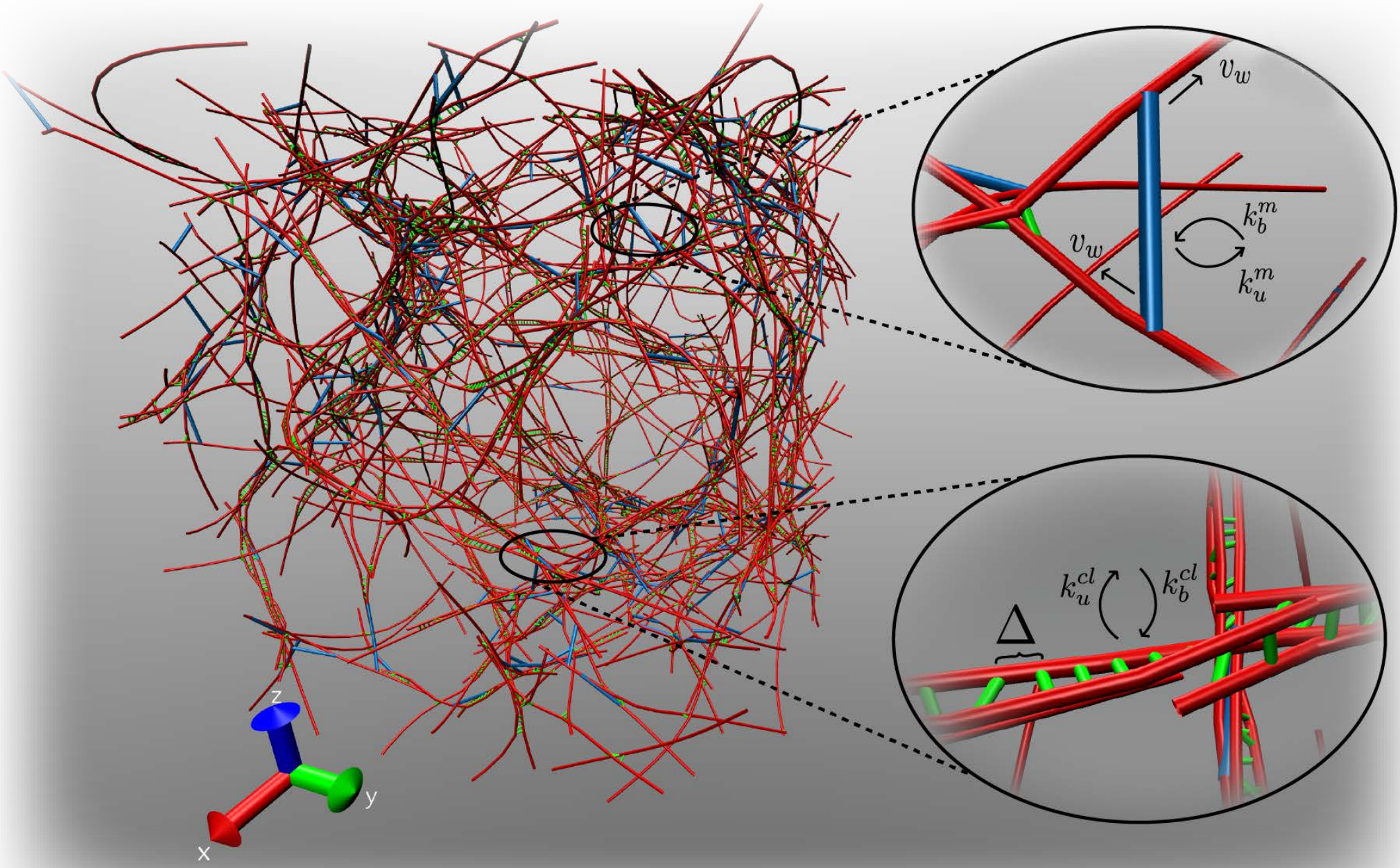
Read more

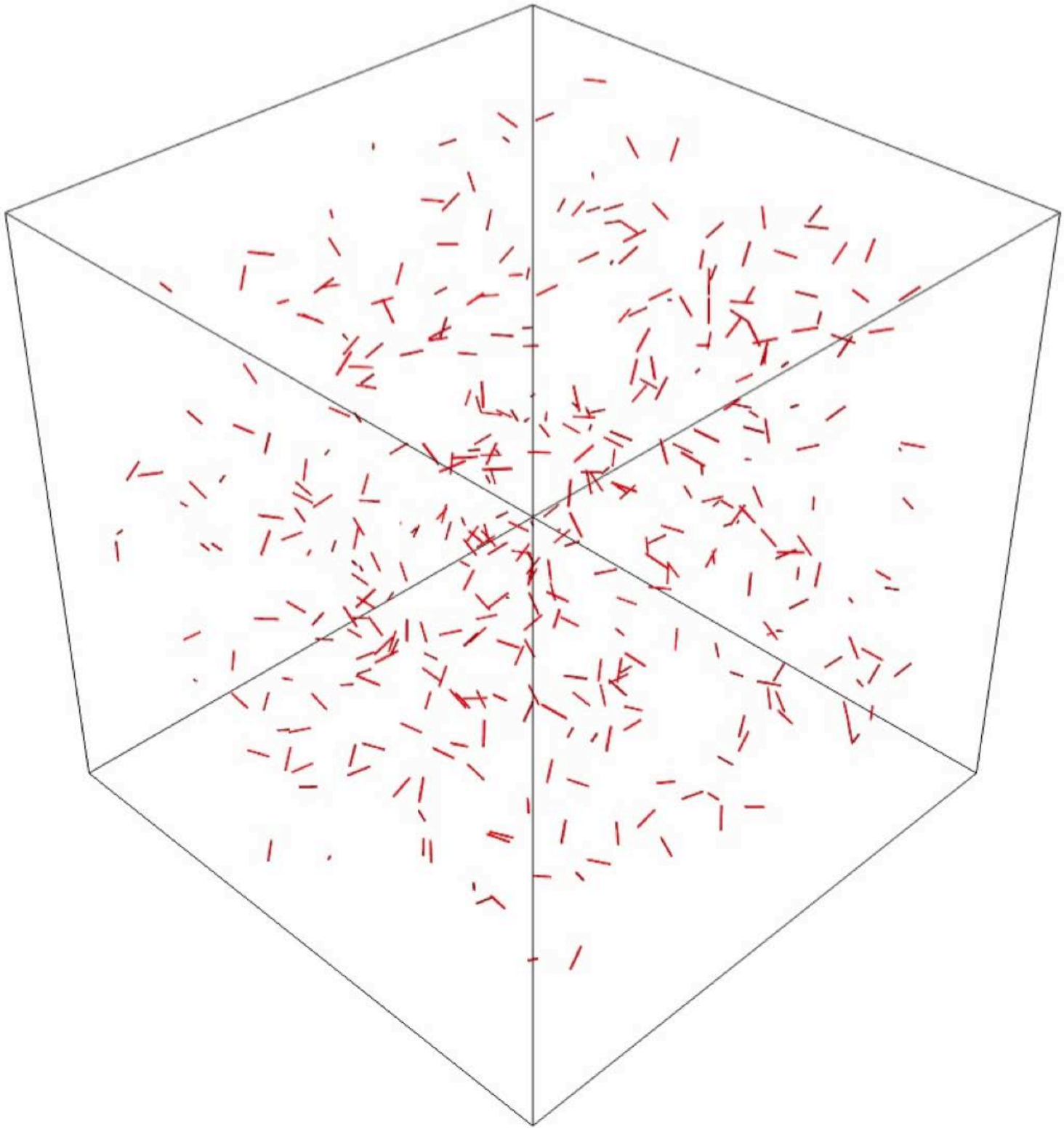
Latest news

April 2016 - Our paper titled *"MEDYAN: Mechanochemical Simulations of Contraction and Polarity Alignment in Actomyosin Networks"* was accepted in PLoS Computational Biology.

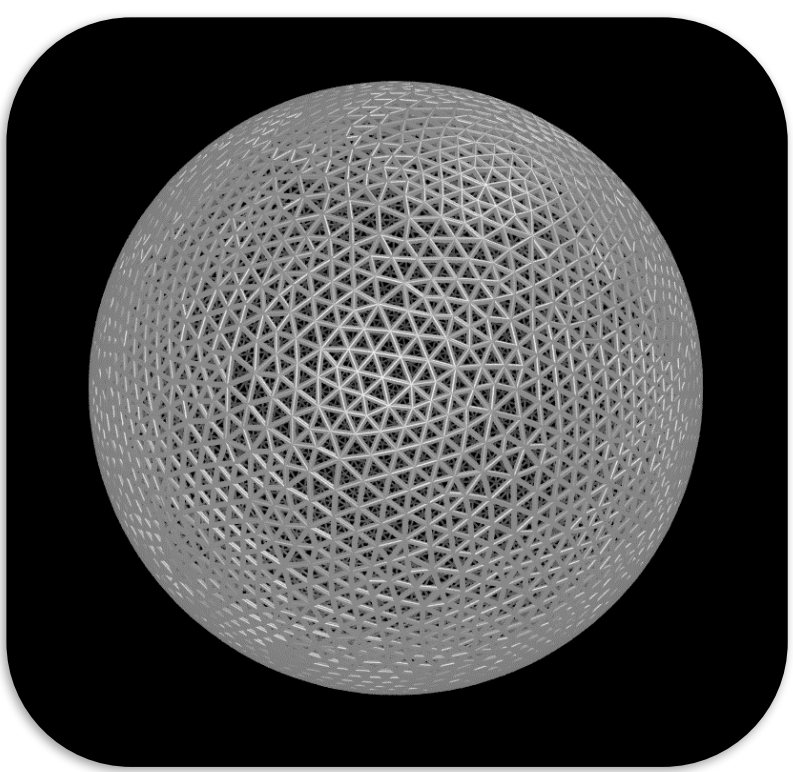
Funding sources

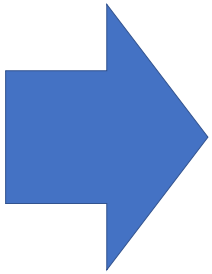
A Simulation Trajectory Snapshot

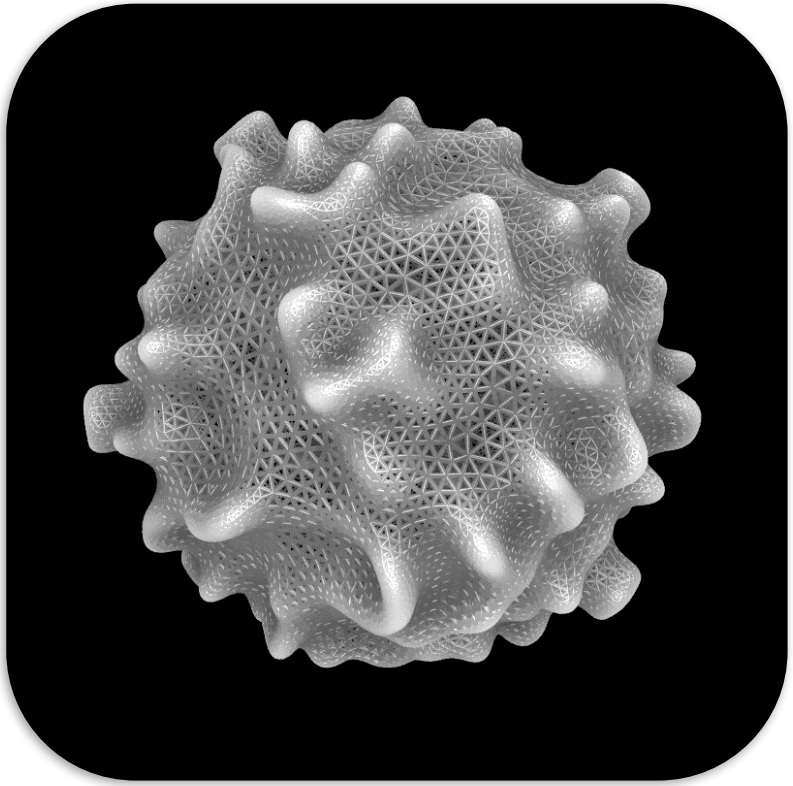




Membrane crumpling in hyperosmotic solution







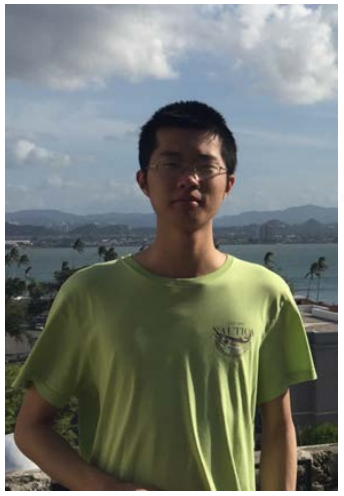
Tension: $F = k_s/(2A_0)(A - A_0)^2$

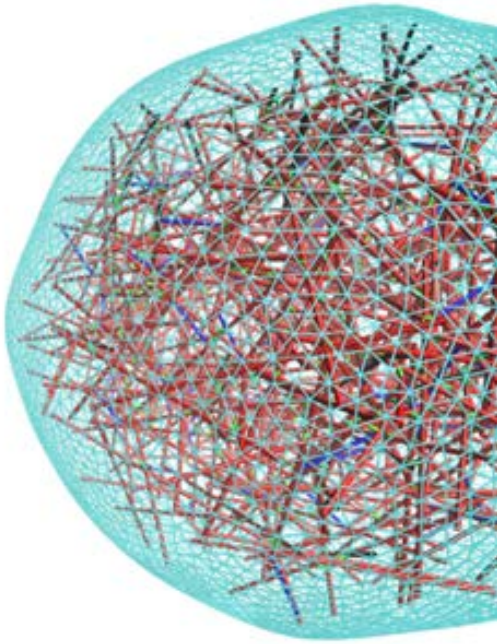
Bending: $F = \int 2k_b(H - c_0)^2 dA$

Volume Conservation: $F = k_V/(2V_0)(V - V_0)^2$

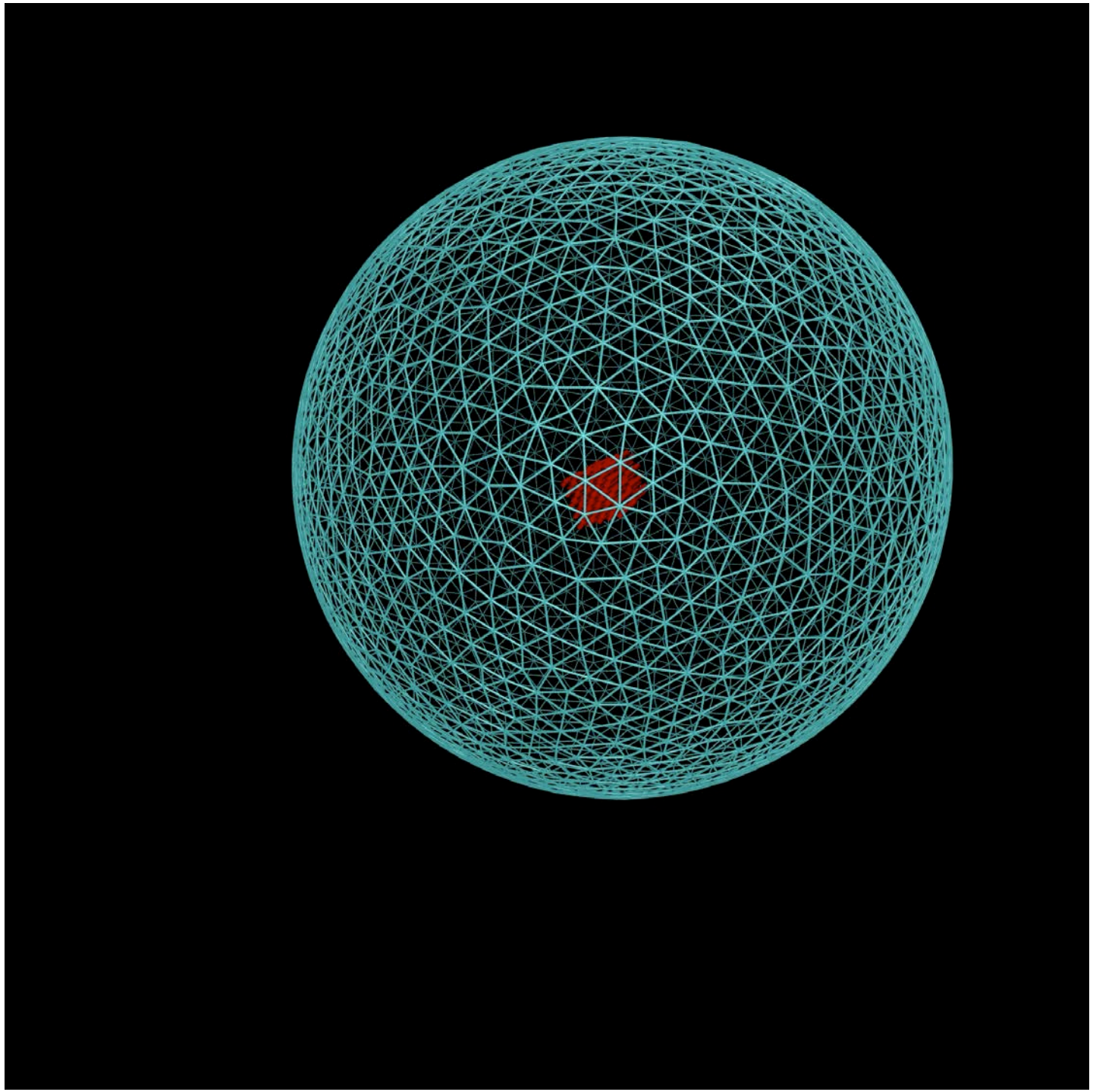
Volume Exclusion: $F = k_{vol} \int dA/|r_b - r_p|^4$

- Haoran Ni

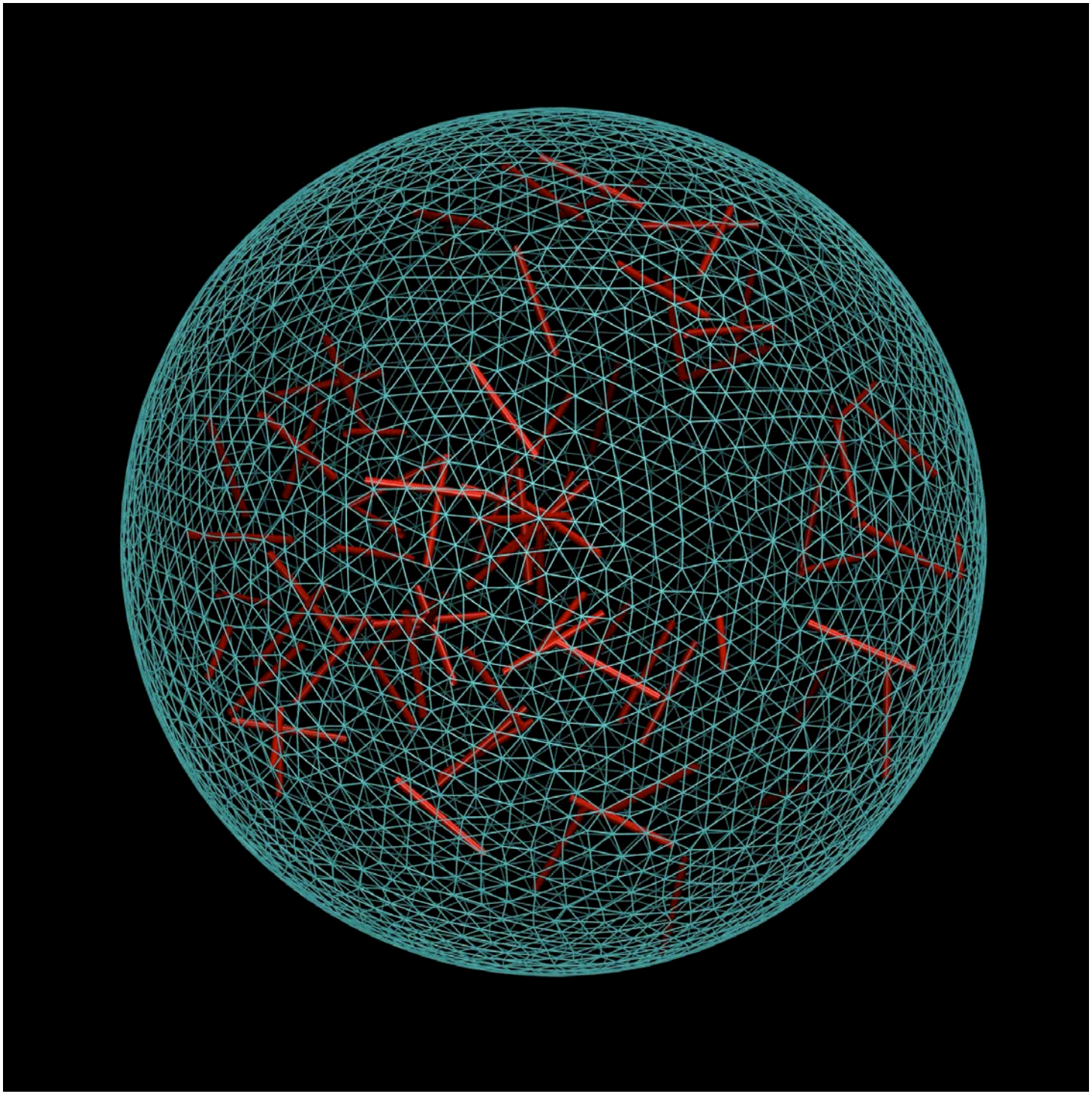




Towards Simulating a Whole Cell



Towards Simulating a Whole Cell



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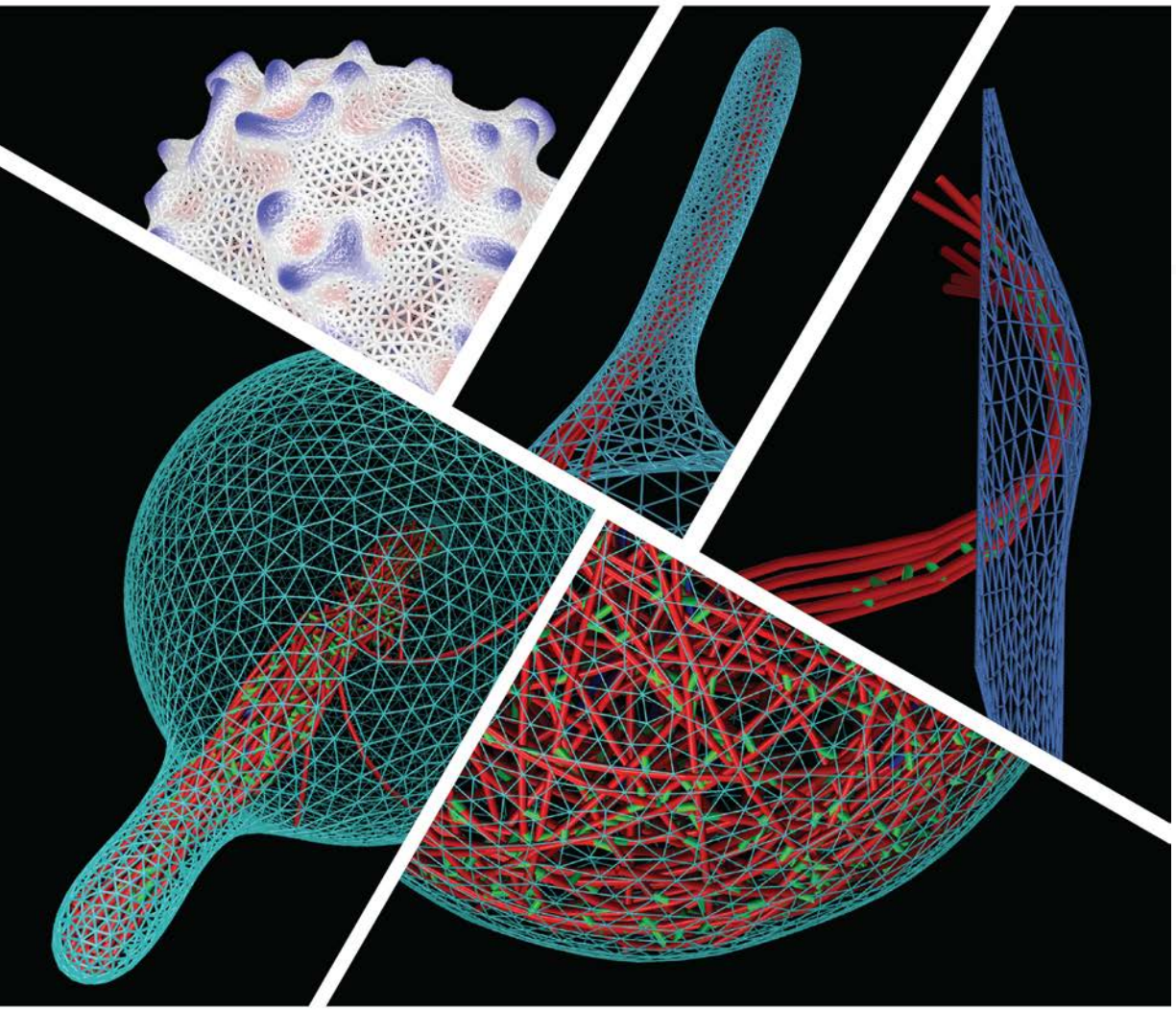


THE JOURNAL OF PHYSICAL CHEMISTRY B
A JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/JPCB

Article

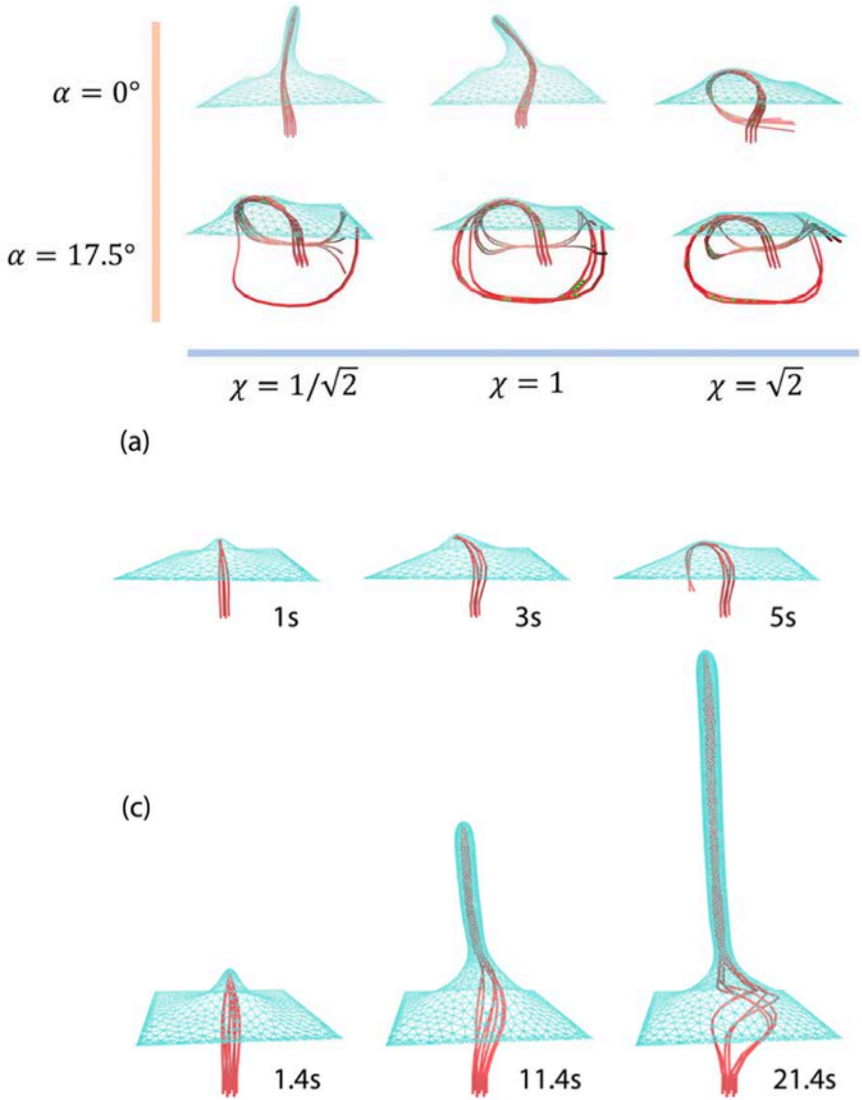
Membrane-MEDYAN: Simulating Deformable Vesicles Containing Complex Cytoskeletal Networks

Published as part of The Journal of Physical Chemistry virtual special issue "Dave Thirumalai Festschrift".

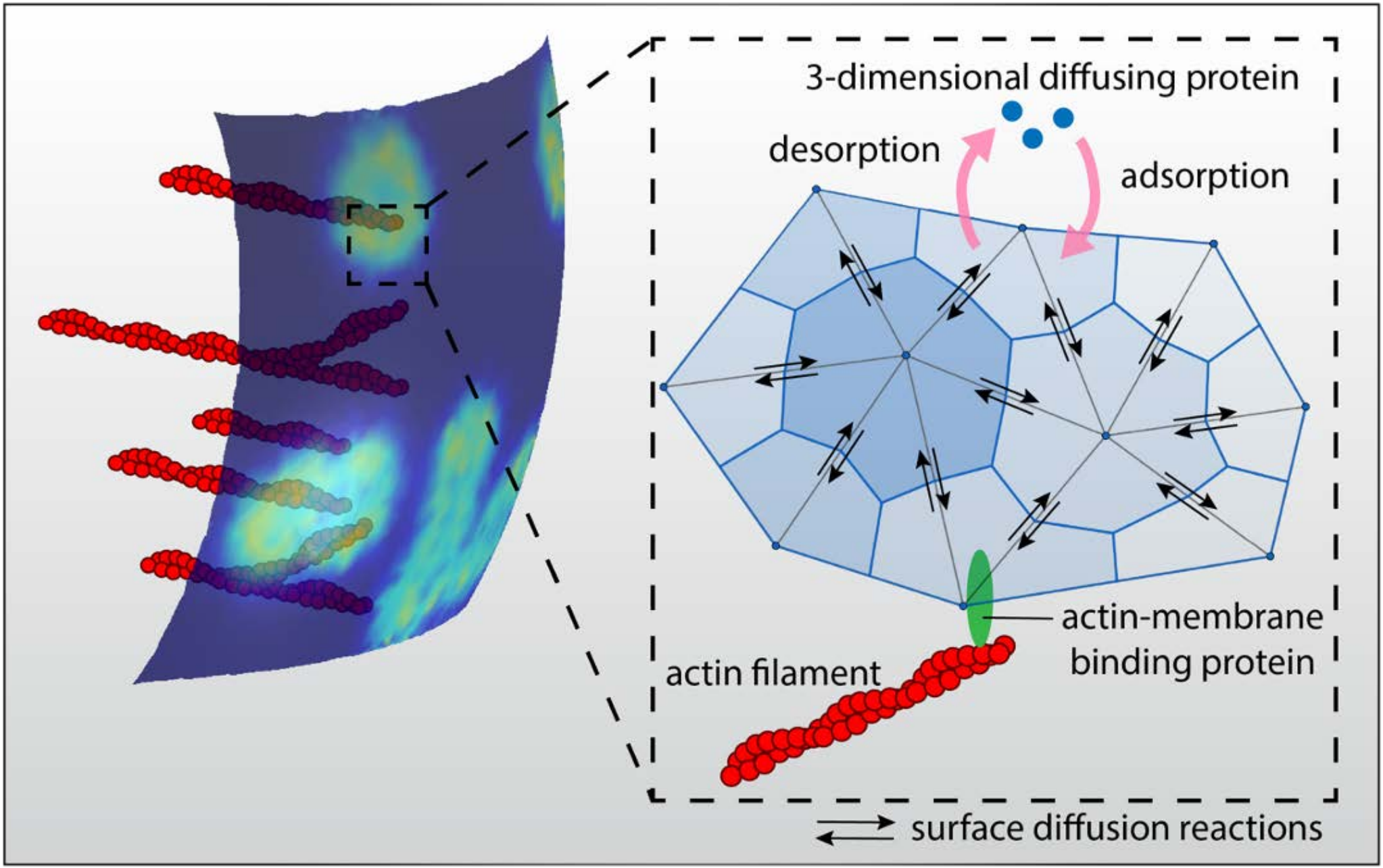
Haoran Ni and Garegin A. Papoian*

Cite This: *J. Phys. Chem. B* 2021, 125, 10710–10719

Read Online



Surface Reaction-Diffusion: Receptor Signaling & Clustering



PNAS Proceedings of the National Academy of Sciences of the United States of America

Keyword, Author,

Home | Articles | Front Matter | News | Podcasts | Authors

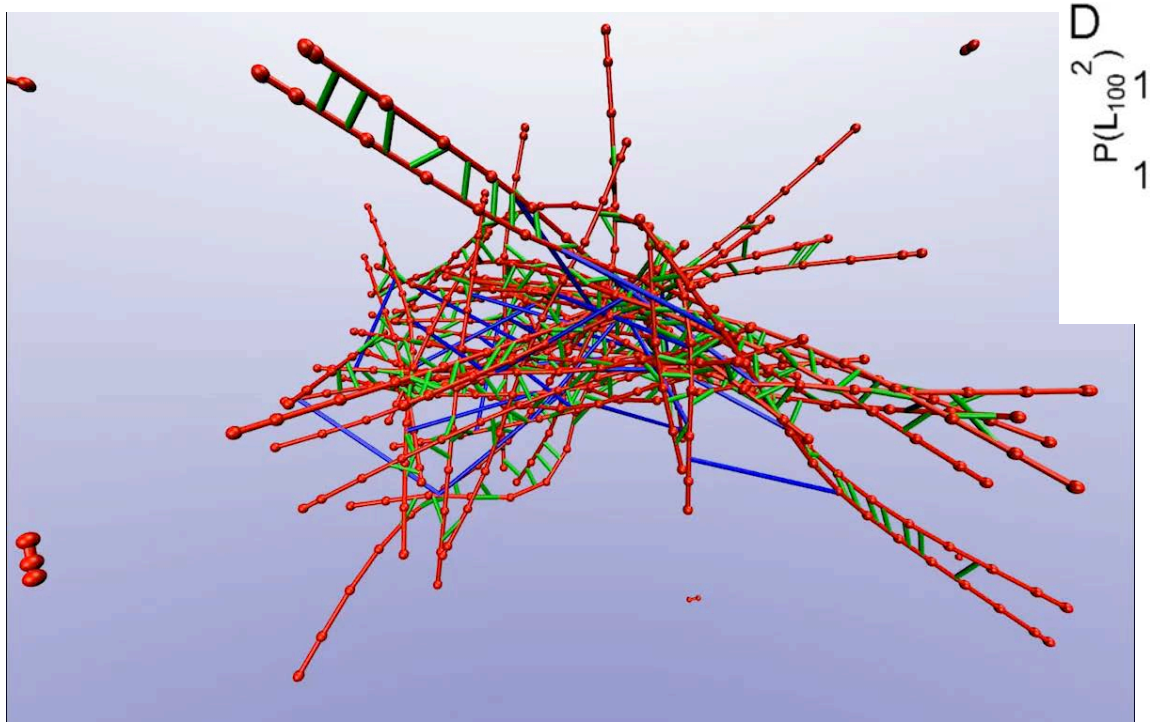
RESEARCH ARTICLE

Understanding cytoskeletal avalanches using mechanical stability analysis

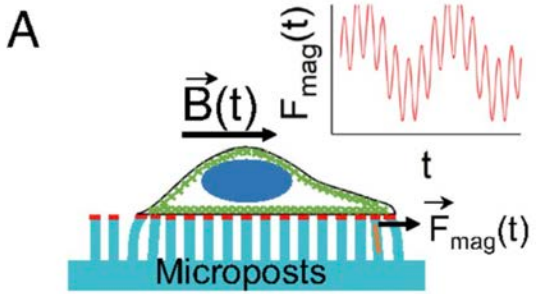
Carlos Floyd, Herbert Levine, Christopher Jarzynski, and Garegin A. Papoian

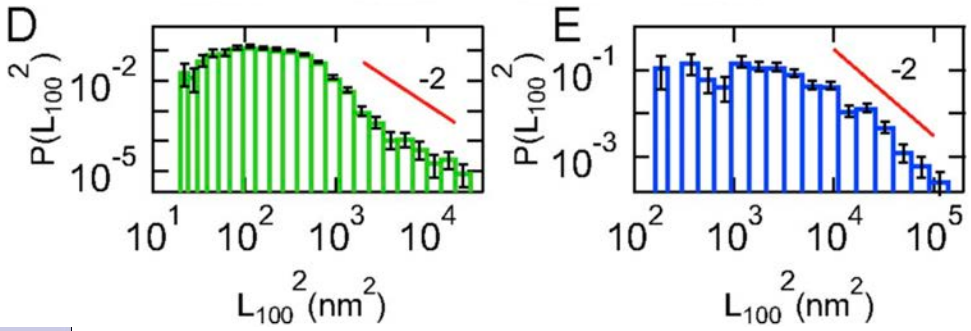
+ See all authors and affiliations

PNAS October 12, 2021 118 (41) e2110239118; https://doi.org/10.1073/pnas.2110239118



- *In vivo* studies of cytoskeletal motions reveal **heavy-tailed distributions of event sizes** - similar to Gutenberg-Richter law
- "Cytoquakes" have been introduced as **large, sudden events** in cytoskeletal dynamics

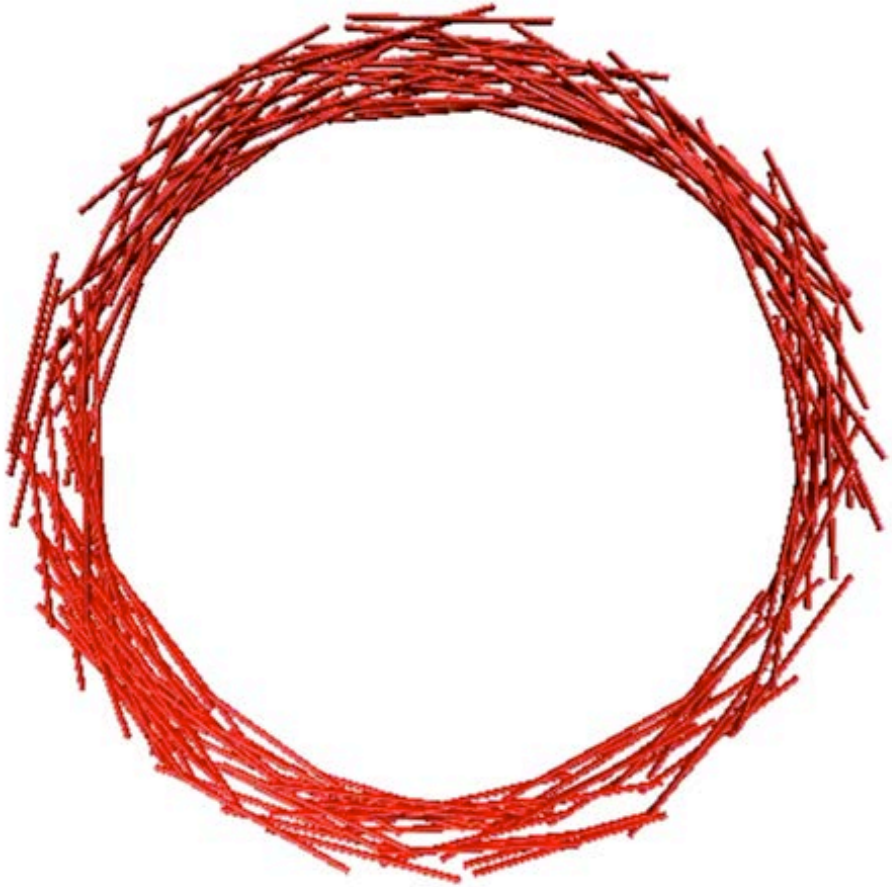




Shi, Y., et al., *PNAS (2019)*

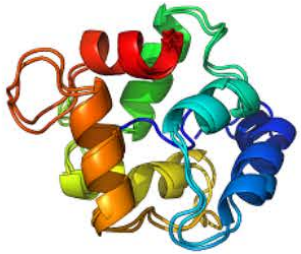
Cal Floyd will talk about this work on Friday

Upregulating Myosin Activity



Qin Ni

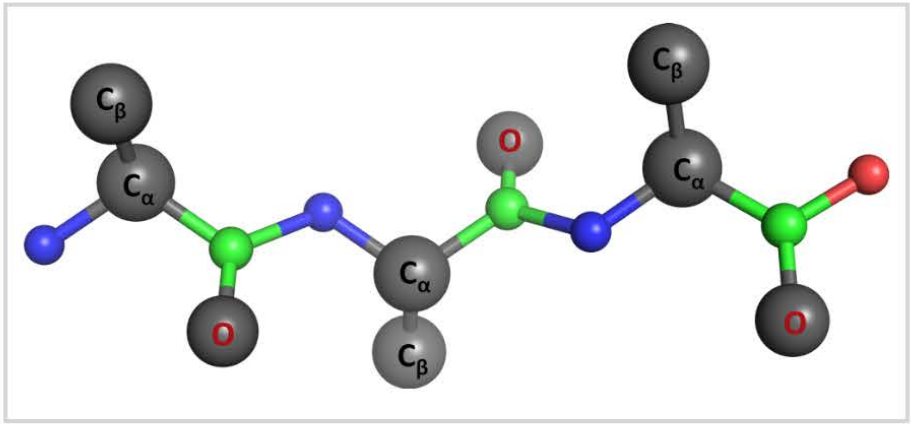
http://awsem-md.org



AWSEM - Associative Memory, Water Mediated, Structure and Energy Model

Welcome to the webpage of *AWSEM-MD*, a coarse-grained protein simulation package that is being developed and maintained by the Papoian lab at the University of Maryland and the Wolynes lab at Rice University. This webpage contains documentation and examples for the *AWSEM* software package, which is implemented as a package for the LAMMPS Molecular Dynamics Program. The source code for this package is downloadable for scientific use.

Background

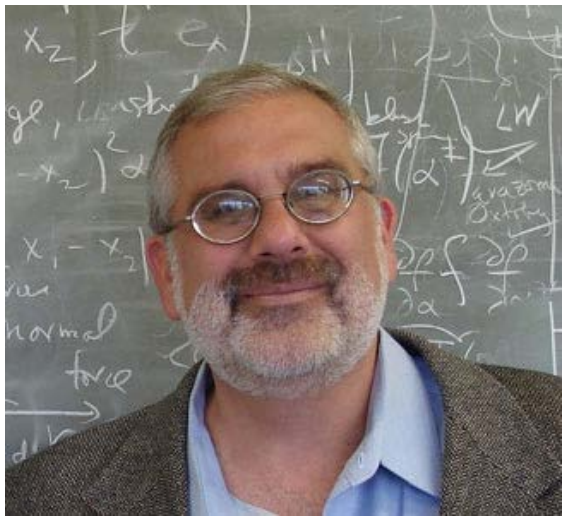


Proteins and other biomolecules can be simulated on a computer primarily in two ways: relying either on atomistic or coarse-grained force fields. The latter approaches, which enable treating large systems at long timescales, come in with rather broad variety of choices, compared with the atomistic models. In particular, many useful coarse-grained protein force fields require prior knowledge of the native structure for the specific protein target, often with the stated goal of simulating protein folding kinetics and dynamics. These methods, however, cannot be used when the target protein structure is unknown or non-native interactions play a significant role. To address such problems, several coarse-grained protein force fields have been developed in the last 30 years or so that allow de novo structure prediction even in the absence of sequence homology. The AWSEM potential is a prominent member of this latter group, where various research groups have successfully demonstrated its broad applications in monomeric protein structure prediction, binding predictions of dimers and multimeric assemblies, folding of membrane proteins, and structural and kinetic studies of protein-DNA complexes. AWSEM naturally covers the whole spectrum between native-structure-based and de novo methods, and can be used both with the knowledge of native structures, and without such explicit knowledge. In the latter case it relies solely on sequence information. Because AWSEM's potential is analytical and differentiable, it is currently implemented as a molecular dynamics algorithm (AWSEM-MD).

Acknowledgments

Invented AMH (1989)

- Prof. Peter Wolynes



Wrote AWSEM-MD in C++ (2011)

- Dr. Aram Davtyan

Currently a postdoc at
CTBP at Rice University

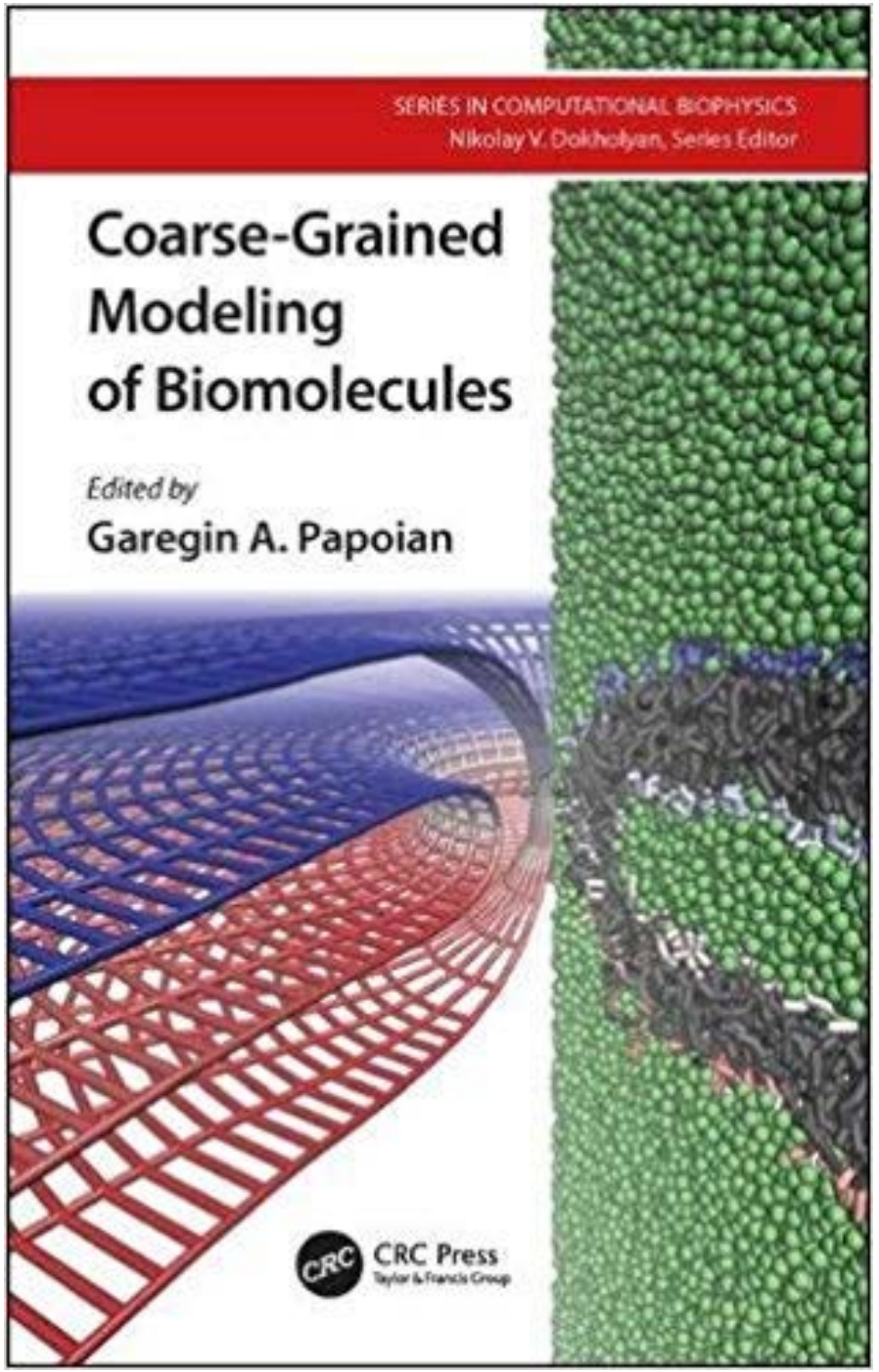
The AWSEM Collaboration

- Dr. Nick Schafer

- Dr. Weihua Zheng

Title: Coarse-Grained Modeling of Biomolecules

- To be Published this Fall (2017)
- Some of the FFs:
  - **Proteins:**
    - UNRES
    - AWSEM
    - Elastic network models
    - Go models
  - **DNA:**
    - Various strategies
    - Nucleosomes
  - **Polymer coarse-graining**
    - Genome modeling
  - **Coarse-grained methodologies**



AWSEM-MD

From Neural Networks to Protein Structure Prediction and Functional Dynamics of Complex Biomolecular Assemblies

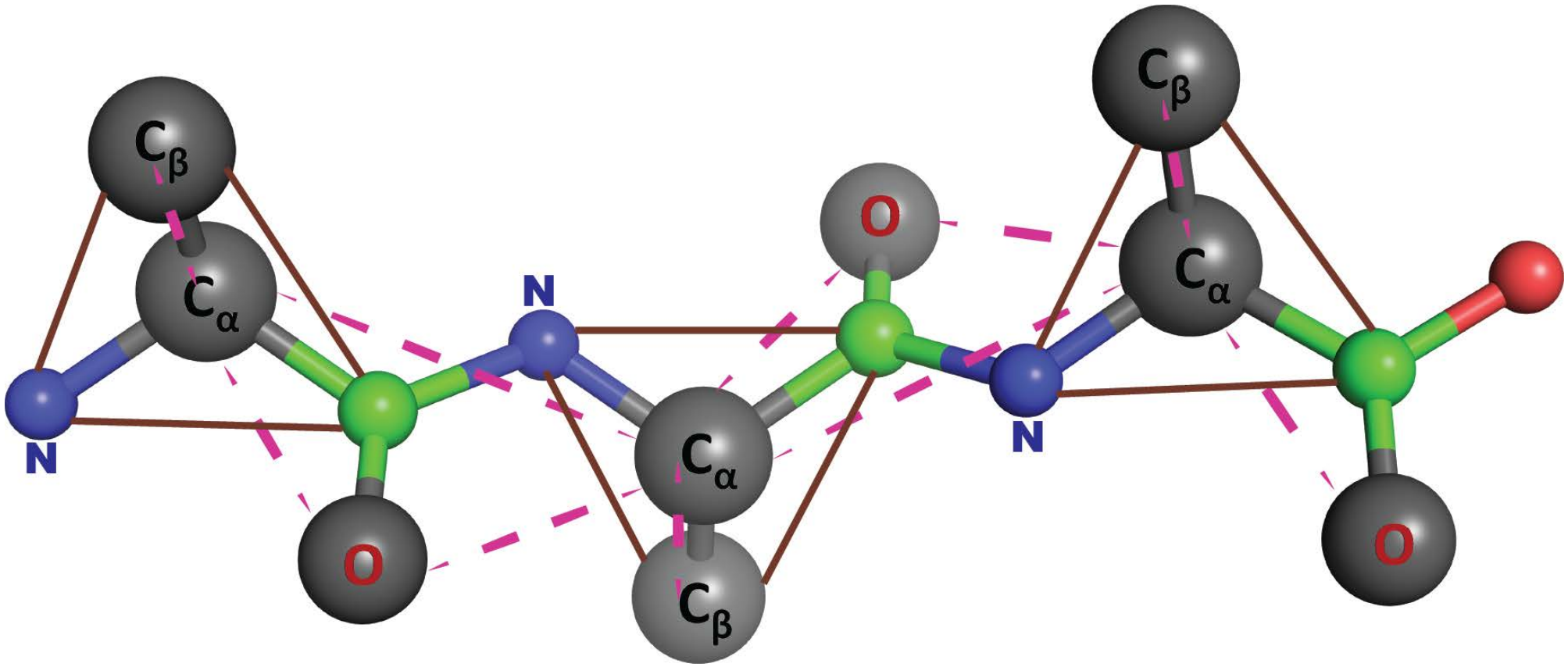
Garegin A. Papoian, and Peter G. Wolynes

CONTENTS

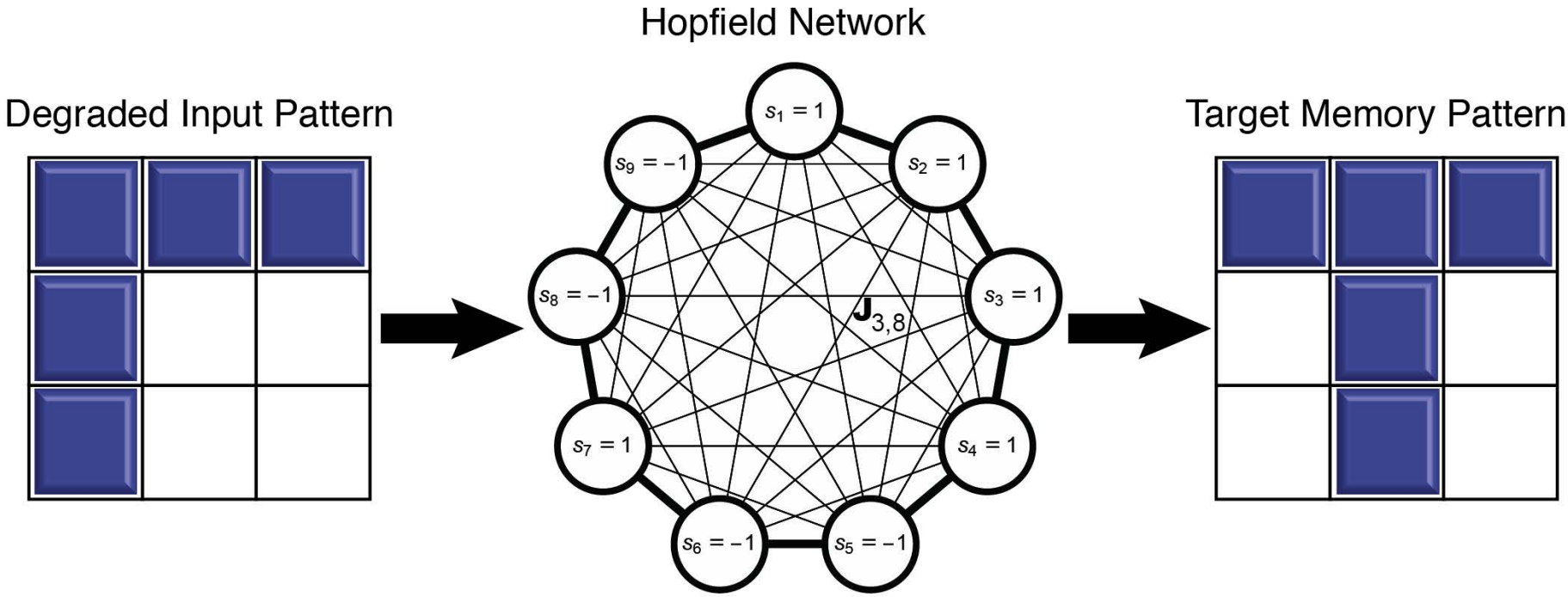
4.1 INTRODUCTION

Proteins come in a myriad of shapes, exposing specific chemically hetero-

AWSEM's Backbone Model



AMH's Neural Network Origins



$$\mathcal{H}^{\text{str}-\text{seq}} = -\sum_{\mu}\sum_{m,n}\sum_{i\neq j}\gamma_{ij}^{\mu}(q_i, q_j, q_i^{\mu}, q_j^{\mu})\theta(r_{ij} - r_{ij}^{\mu}),$$

where, $\theta(r_{ij} - r_{ij}^{\mu}) = 1$ if $r_{ij} \approx r_{ij}^{\mu}$ and,

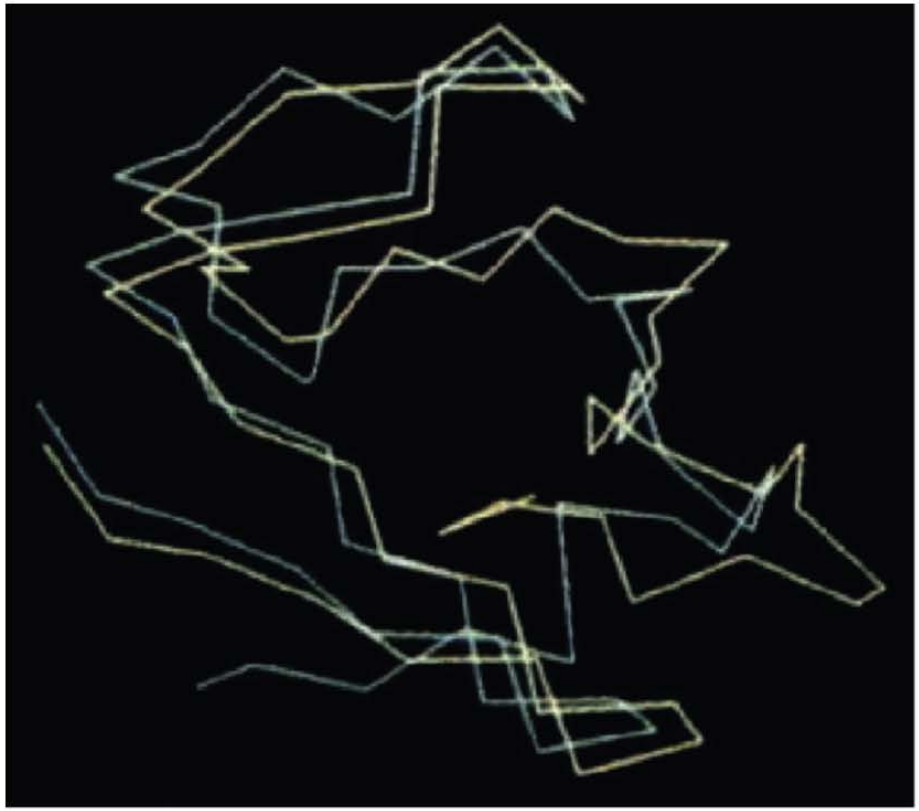
$$\gamma_{ij}^{\mu}(q_i, q_j, q_i^{\mu}, q_j^{\mu}) \equiv q_i^{\mu} q_j^{\mu} q_i q_j + q_i^{\mu} q_i + q_j^{\mu} q_j$$

Associated Memory Hamiltonians (AMH) for Protein Structure Prediction are Introduced

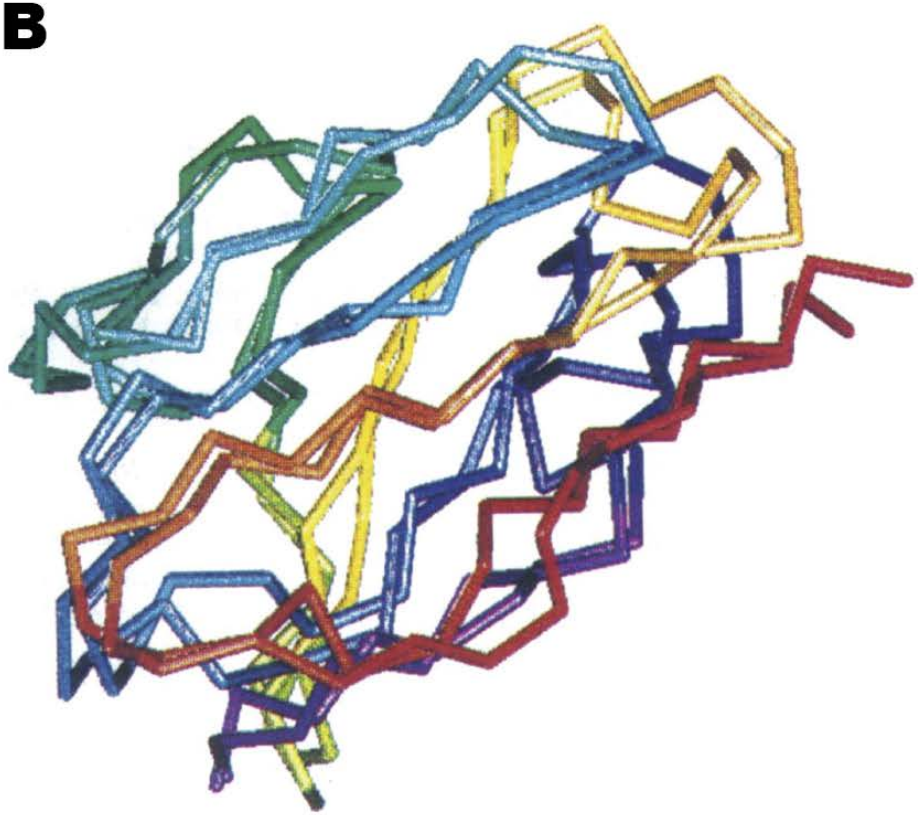
Friedrichs & Wolynes, Science, 1989

Goldstein et al, PNAS, 1992

A



B



The AWSEM Hamiltonian

$$\mathcal{H}^{\mathrm{AWSEM}} = \mathcal{H}^{\mathrm{bb}} + \mathcal{H}^{\mathrm{AM}} + \mathcal{H}^{\mathrm{PMF}}$$

where,

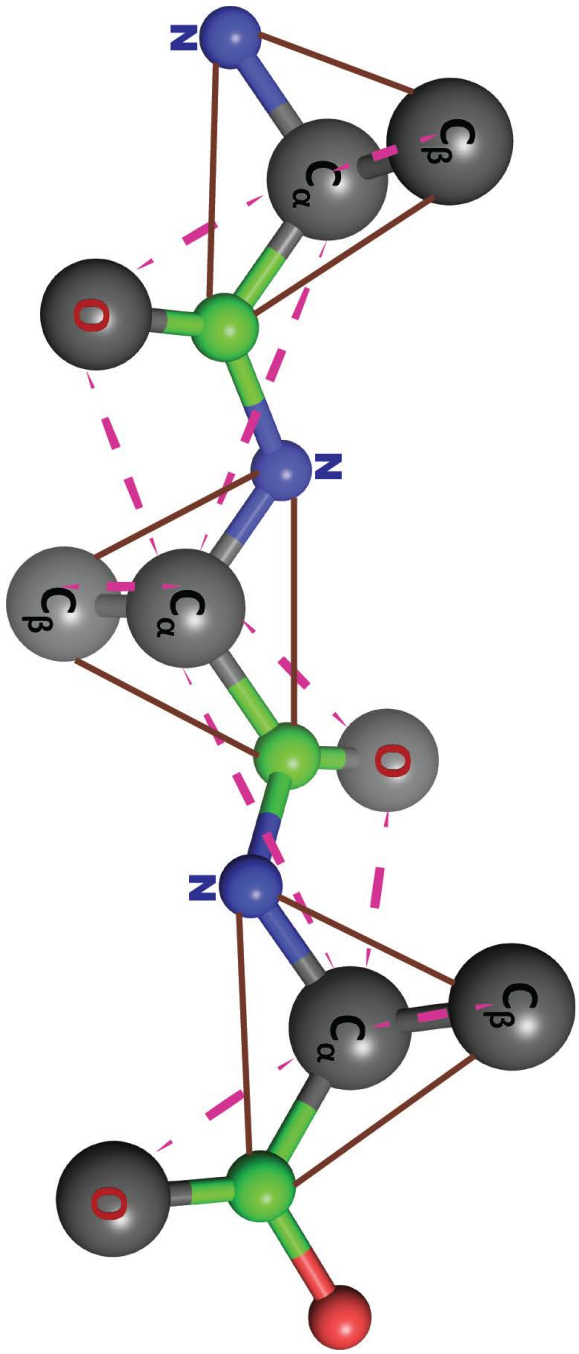
$$\mathcal{H}^{\mathrm{FM}} = -\sum_{\mu}\sum_{i\neq j}\theta(r_{ij} - r_{ij}^{\mu})$$ Hopfield-like

$$V_{\mathrm{backbone}} = V_{\mathrm{con}} + V_{\mathrm{chain}} + V_{\chi} + V_{\mathrm{rama}} + V_{\mathrm{excl}}$$

Example of a backbone term, V_{χ}, to maintain chirality of the peptide groups:

$$V_{\chi} = \lambda_{\chi}\sum_{i=2}^{N-1}(\chi_i - \chi_0)^2$$

and $$\chi_i = \left(\mathbf{r}_{C_i'C_{\alpha_i}} \times \mathbf{r}_{C_{\alpha_i}N_i}\right)\cdot \mathbf{r}_{C_{\alpha_i}C_{\beta_i}}$$



✏ Davtyan, Schafer, Zheng, Clementi, Wolynes, Papoian, J. Chem Phys B, 2012, 116, 1709-1715

Coarse-Grained Modeling with Physical Bioinformatics

✏ G. A. Papoian and P. G. Wolynes, **Biopolymes**, 68, (2003), 333-349.

✏ G. A. Papoian, J. Ulander and P. G. Wolynes, **J. Am. Chem. Soc.**, 125, (2003), 9170-9178.

Coupling of Binding & Folding

Extending Protein Folding Models into Binding

Folding Potentials Fail in Wet Interfaces

Hypothesis: Hydrophilic Interactions are Specifically Mediated through Water

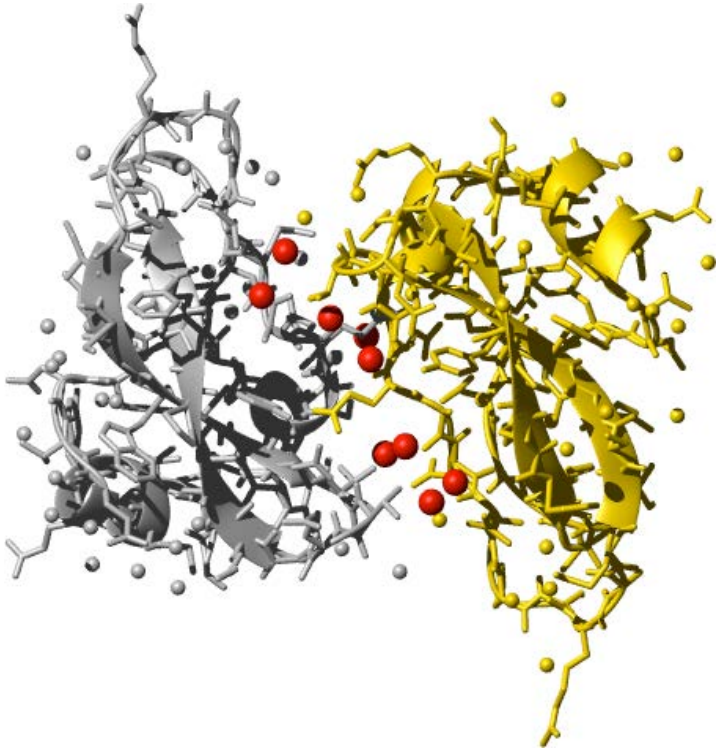
Deriving Binding Potentials

Bioinformatics: Parameter Learning & Validation

✏ PNAS, 101, (2004), 3352-3357
✏ JACS, 128, (2006), 5168-5178
✏ JMB 367, (2007), 262-274
✏ Methods, 52, (2010), 84–90

Water in protein folding

Knowledge-Based Optimization of Direct and Water-Mediated Binding Pair-Potentials



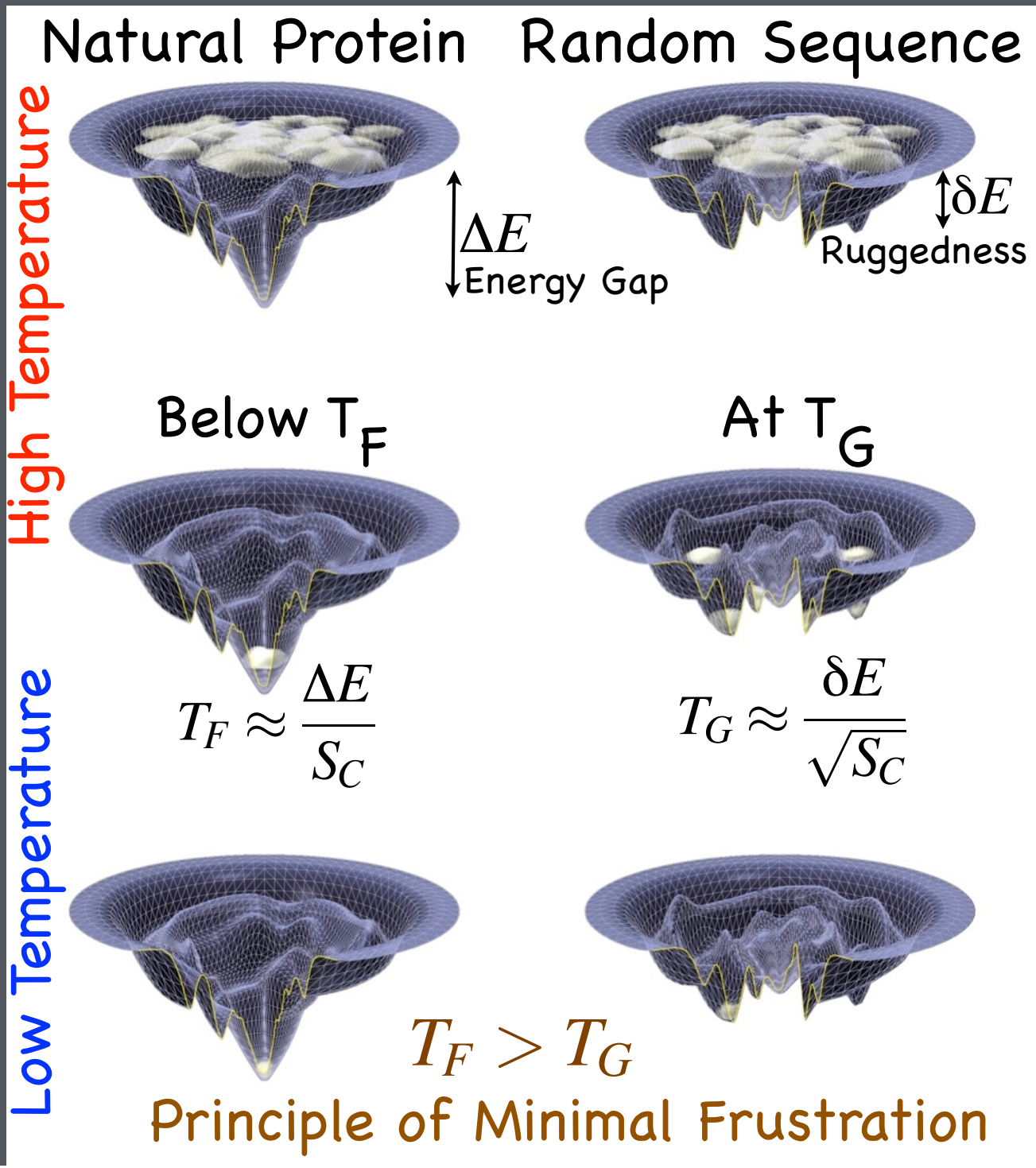
Defining Contacts:

Direct – d < 6.5 Å between C-β atoms.

Water-Mediated – 7.8 Å < d < 9.5 Å between C-β atoms, with the constraint that both residues are at least partially water-exposed.

✏ Papoian, Ulander and Wolynes, **J. Am. Chem. Soc.**, 125, (**2003**), 9170-9178.
✏ Papoian, Ulander, Eastwood, Luthey-Schulten, and Wolynes, **PNAS**, 101, (**2004**), 3352-3357
✏ Davtyan, Schafer, Zheng, Clementi, Wolynes, Papoian, **J. Chem Phys B**, 116, (**2012**), 1709–1715

Optimization: Using Energy Landscape Theory of Protein Folding



- **Denatured Ensemble:**
  - **Large Structural Entropy**
  - **Energetic Ruggedness**

Principle of Minimal Frustration

Maximize T_f/T_g

J. N. Onuchic, P. G. Wolynes, Z. Luthey-Schulten, N. D. Socci, PNAS, 92, (1995), 3626

THE JOURNAL OF PHYSICAL CHEMISTRY B

Article

pubs.acs.org/JPCB

AWSEM-MD: Protein Structure Prediction Using Coarse-Grained Physical Potentials and Bioinformatically Based Local Structure Biasing

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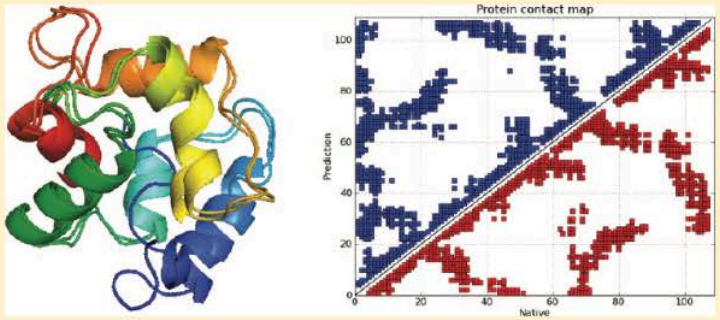
[†]Department of Chemistry and Biochemistry and Institute for Physical Science and Technology, University of Maryland, College Park, Maryland 20742, United States

[‡]Department of Chemistry, Rice University, Houston, Texas 77251, United States

[§]Center for Theoretical Biological Physics, University of California in San Diego, La Jolla, California 92093, United States

Supporting Information

ABSTRACT: The associative memory, water mediated, structure and energy model (AWSEM) is a coarse-grained protein force field. AWSEM contains physically motivated terms, such as hydrogen bonding, as well as a bioinformatically based local structure biasing term, which efficiently takes into account many-body effects that are modulated by the local sequence. When combined with appropriate local or global alignments to choose memories, AWSEM can be used to perform *de novo* protein structure prediction. Herein we present structure prediction results for a particular choice of local sequence alignment method based on short residue sequences called fragments. We demonstrate the model's structure prediction capabilities for three levels of global homology between the target sequence and those proteins used for local structure biasing, all of which assume that the structure of the target sequence is not known. When there are no homologues in the database of structures used for local structure biasing, AWSEM calculations produce structural predictions that are somewhat improved compared with prior works using related approaches. The inclusion of a small number of structures from homologous sequences improves structure prediction only marginally, but when the fragment search is restricted to only homologous sequences, AWSEM can perform high resolution structure prediction and can be used for kinetics and dynamics studies.

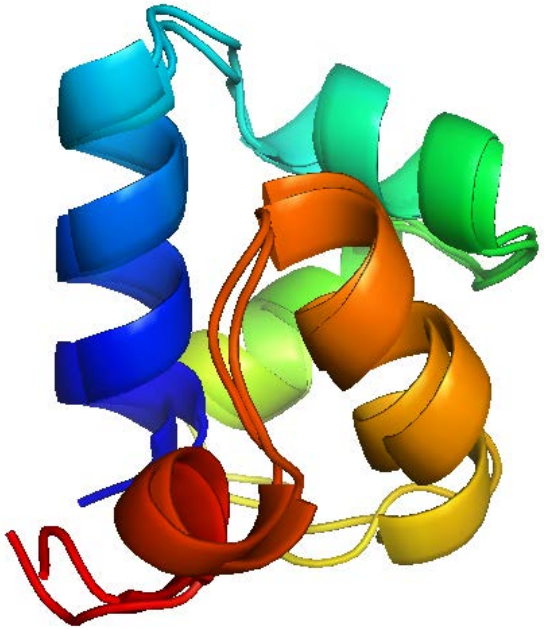


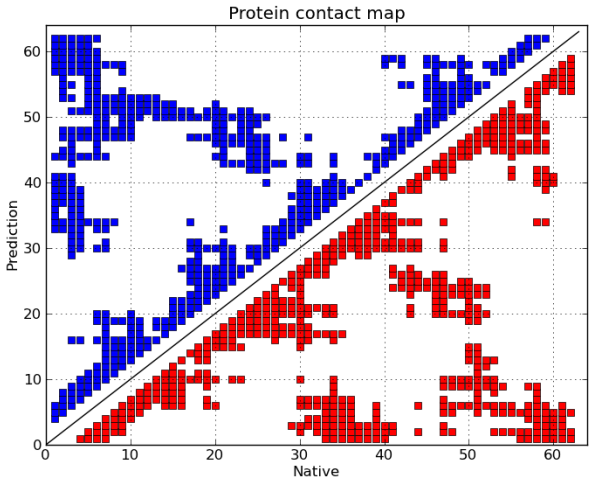
INTRODUCTION

were predicted by Pauling and Kauzmann before crystal structure determination of proteins.[3,4] It has turned out that

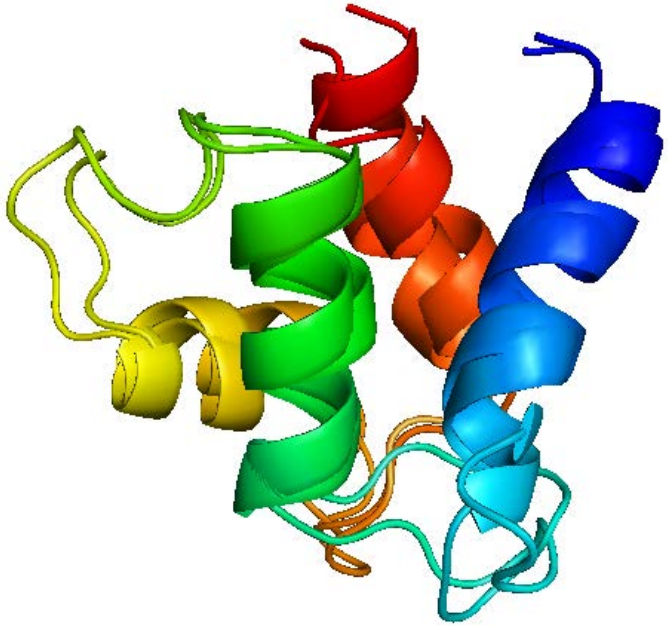
High Resolution "Blind" Predictions for Some Proteins

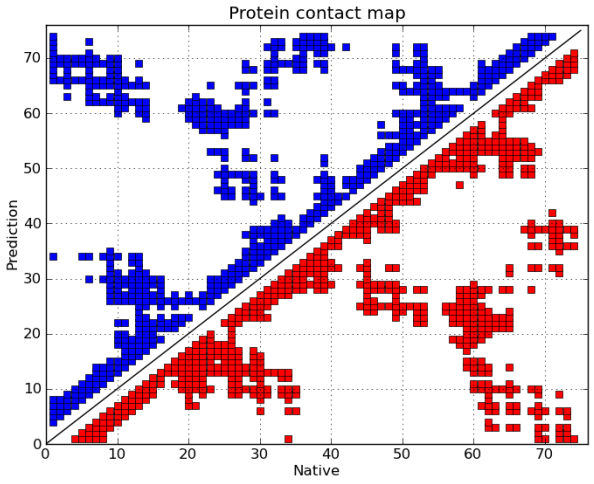
1R69
(RMSD 1.6 Å)





3ICB
(RMSD 2.4 Å)





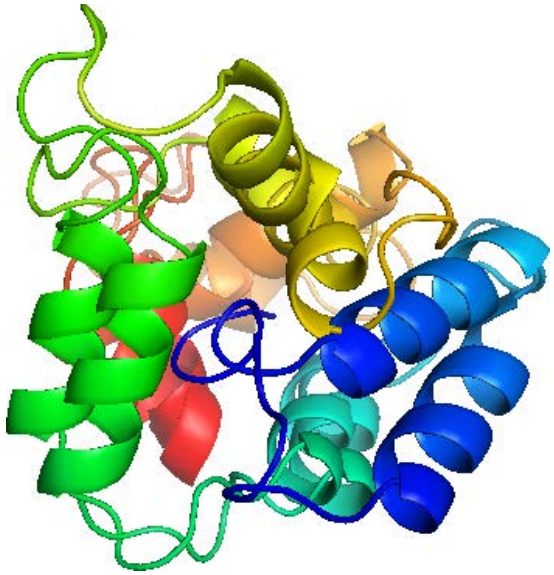
Some Historical References (AMH & AMW)

- Friedrichs & Wolynes, Science 1989, 246, 371
- Sasai, Wolynes, PRL 1990, 65, 2740
- Papoian, Ulander, Eastwood, Luthey-Schulten, Wolynes, PNAS, 2004, 101, 3352

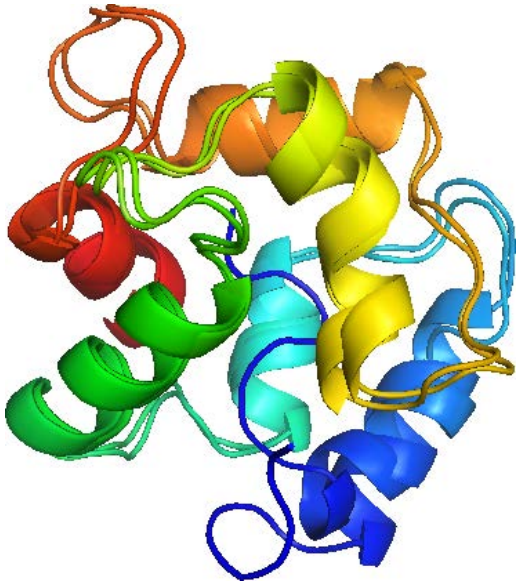
✏ Davtyan, Schafer, Zheng, Clementi, Wolynes, Papoian, J. Chem Phys B, 116, 1709-1715

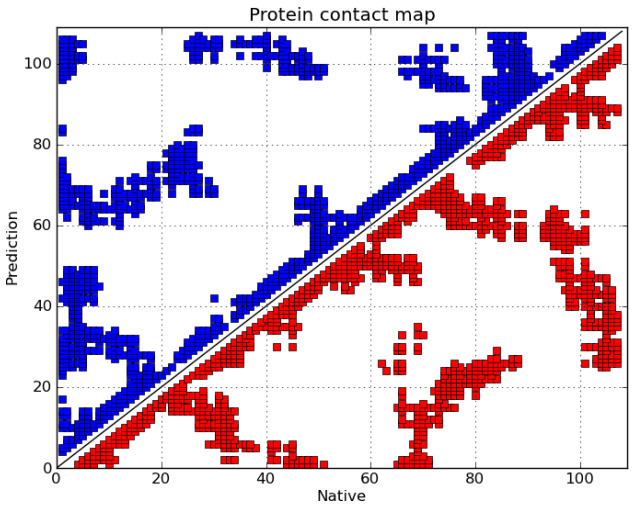
Globally Homologous Proteins can be Used as Fragment Memories

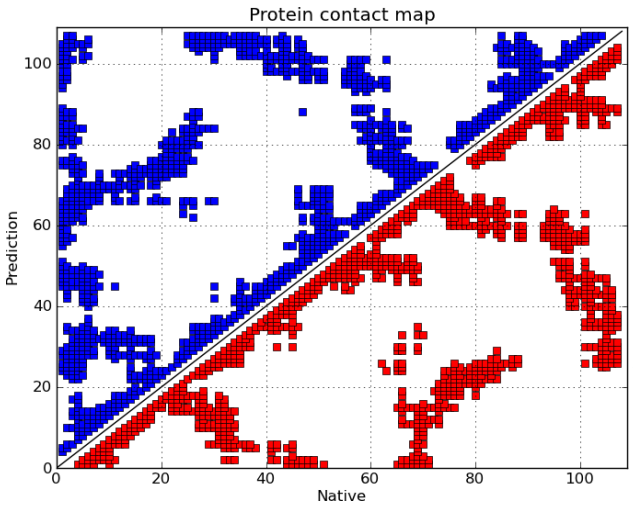
4CPV
(RMSD 5.8 Å)



4CPV
(RMSD 1.3 Å)



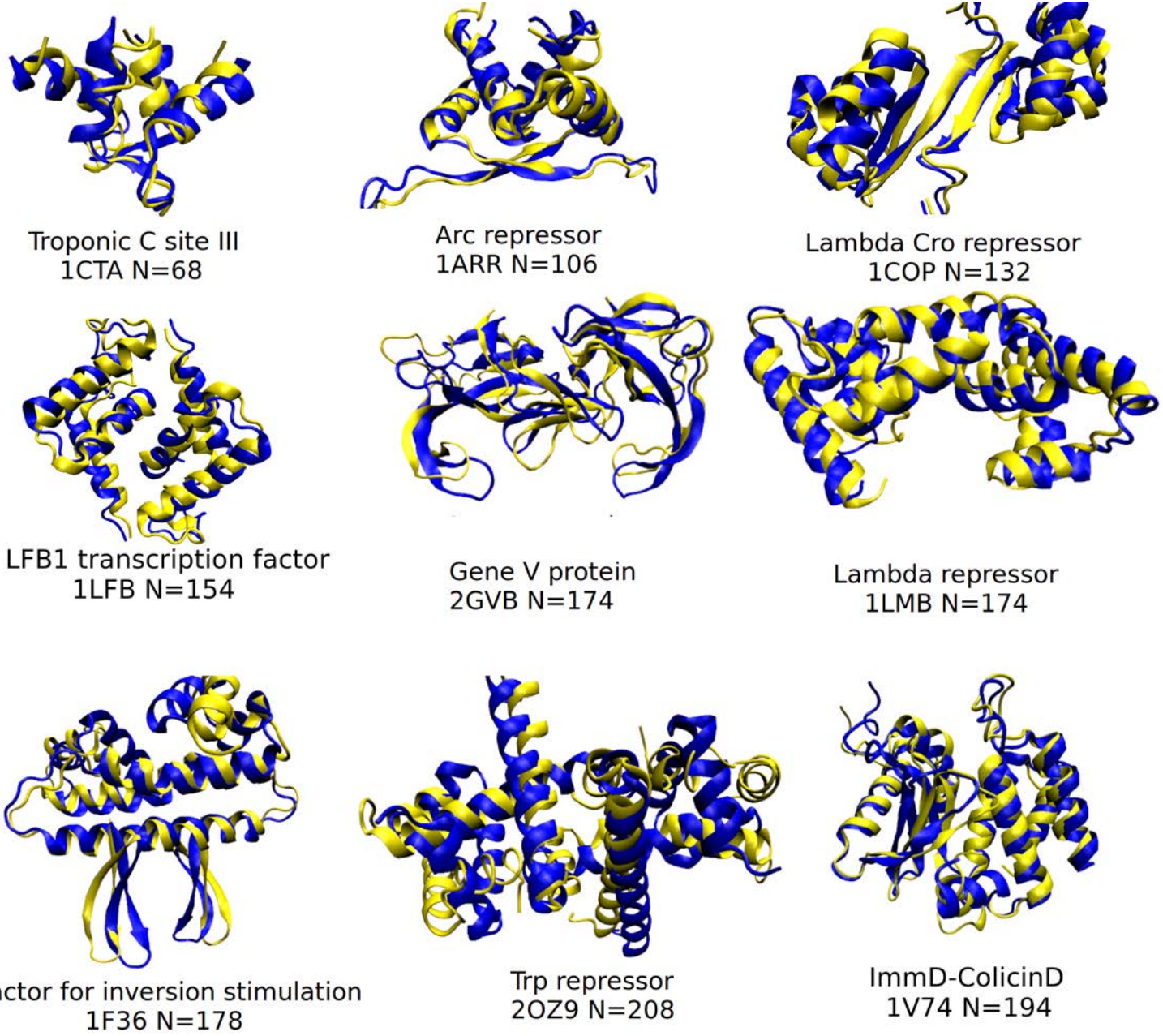




- For larger proteins, the prediction is often relatively low resolution when no homologues are included as fragment memories
- When even distant homologues are included, nearly atomic resolution predictions can be made
- Hence, AWSEM-MD may be used instead of Gō-models in many cases

✏ Davtyan, Schafer, Zheng, Clementi, Wolynes, Papoian, J. Chem Phys B, 116, 1709-1715

AWSEM-MD: Binding of Homo- and Heterodimers



✏ Zheng, Schafer, Davtyan, Papoian, Wolynes, **Proc Natl Acad Sci USA**, (2012), 109, 19244-19429

Additional Developments

- **AWSEM-IDP**
  - Added a new potential to better better control the radius of gyration of the protein chain; atomistic or experimental memories; fine-tuning of the AWSEM potential

✏ **Wu, Wolynes, Papoian, 2018, JPCB, DOI: 10.1021/acs.jpcb.8b05791**

- **AAWSEM**
  - Use atomistic simulations to generate fragment libraries, hence, removing the need to rely on a structural database

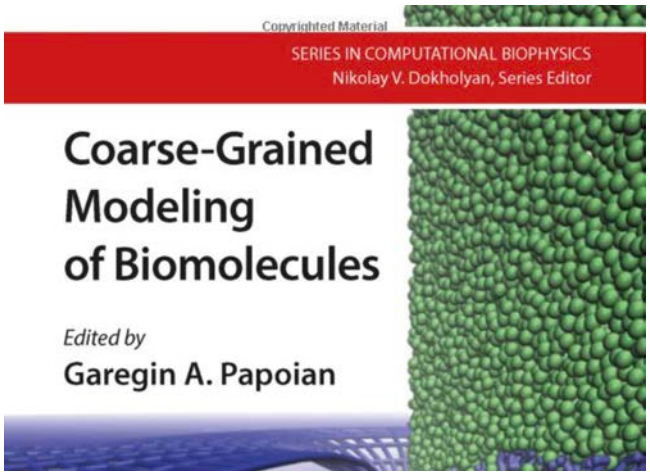
✏ **Chen, Lin, Lu, Onuchic, Wolynes JPCB, 2017, 121, 3473**

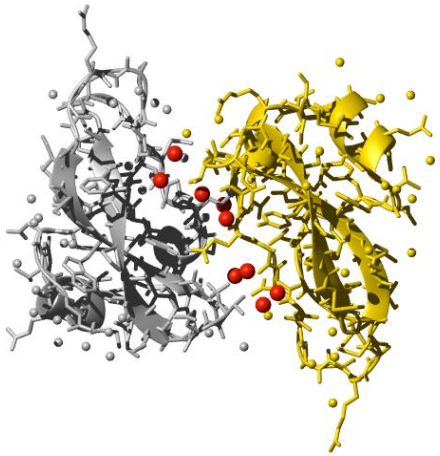
- **AWSEM-ER**
  - Added a biasing pairwise potential, which is determined from the correlations between co-evolution of sequence pairs.

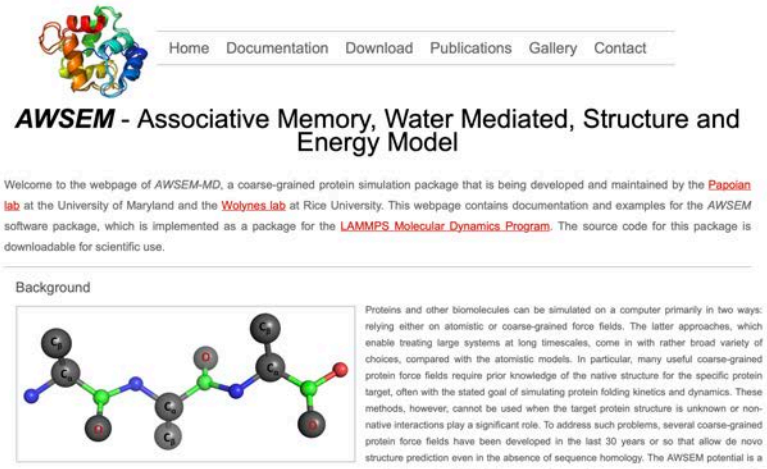
✏ **Sirovetz, Schafer, Wolynes, Proteins, 2017, DOI: 10.1002/prot.25367**

Intrinsically Disordered Proteins (IDPs): A Challenging Frontier

Type	Method	Advantage	Limitation
Experimental	NMR	Detailed local structure	Ensemble averaging
	SAXS	Overall shape and size	
Computational	All-atom MD	Precise structural & dynamic information	Accuracy issues Major sampling issues
	Coarse-grained MD	Broad conformational exploration	Major accuracy issues





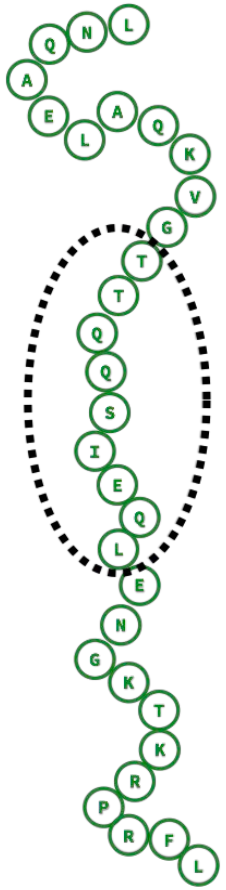


✏ Papoian, Ulander, Eastwood, Luthey-Schulten, and Wolynes, **PNAS**, 101, (**2004**), 3352-3357
✏ Davtyan, Schafer, Zheng, Clementi, Wolynes, Papoian, **J. Chem Phys B**, 116, (**2012**), 1709–1715

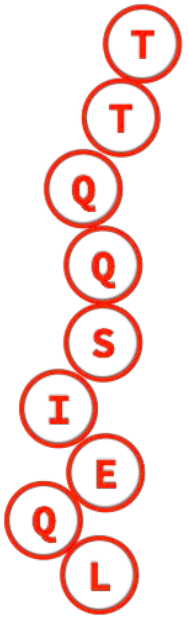
AWSEM-IDP

$$V_{total_{IDP}} = V_{backbone} + V_{contact} + V_{burial} + V'_{Hbond} + V'_{FM} + V''_{Rg}$$

Target sequence **Local segment** **Fragment memories**

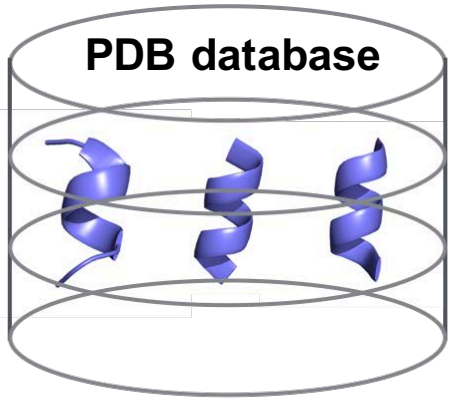


Locate local fragments



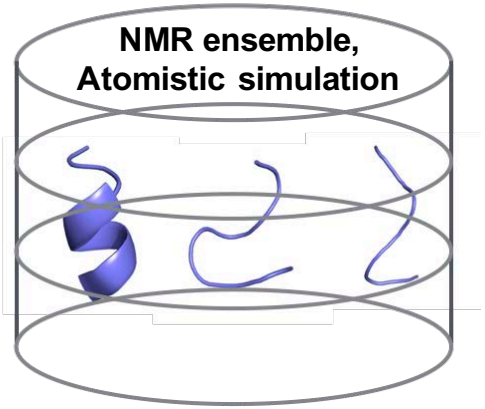
AWSEM

Find homologous structures from PDB



AWSEM-IDP

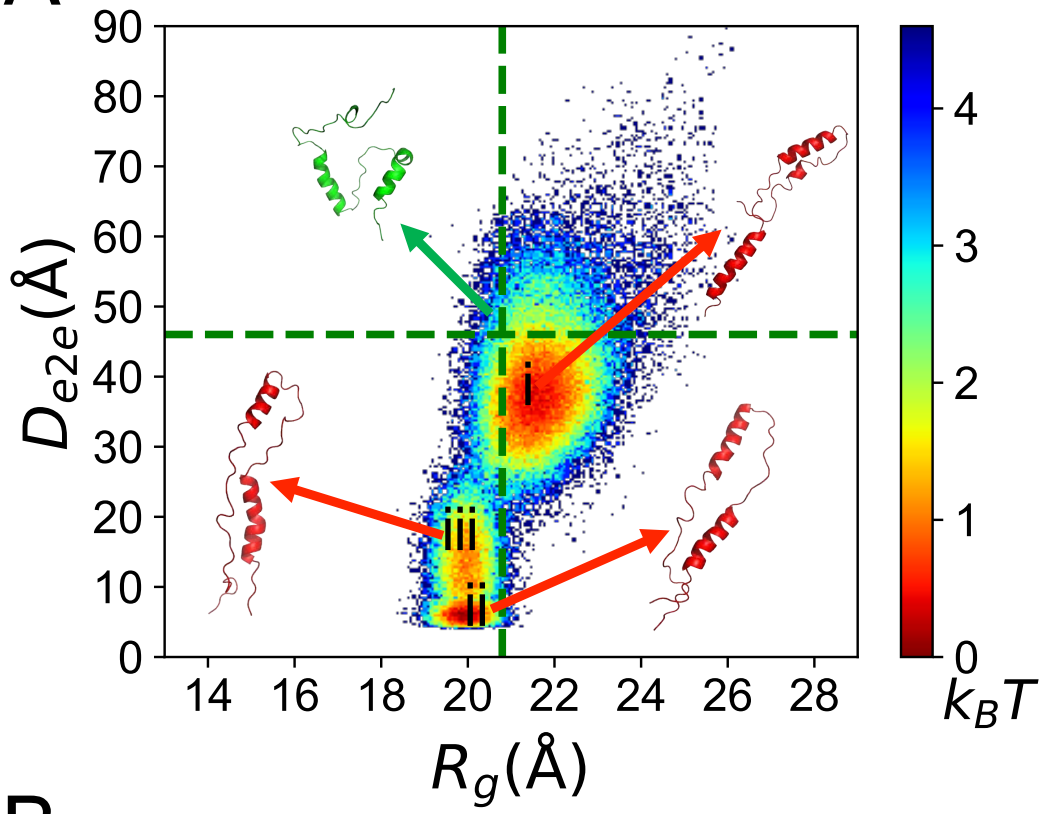
Find IDP ensembles from experiments or simulations



✏ Hao Wu et el

PaaaA2

A



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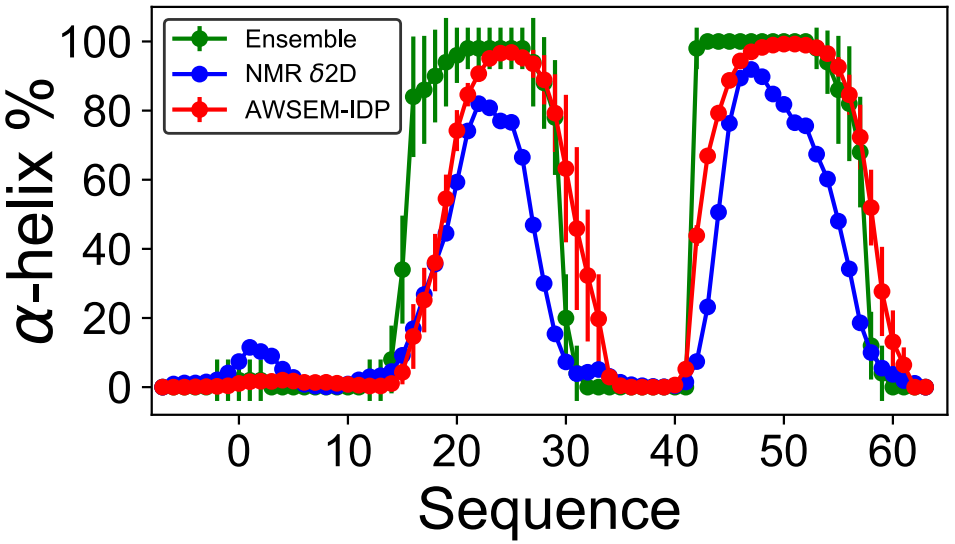


- Green - experimental
- Red - AWSEM-IDP
- **The key idea:** Reproduce statistical distributions of important physical observables (order paramaters most pertinent to the IDPs)

✏ Hao Wu et al

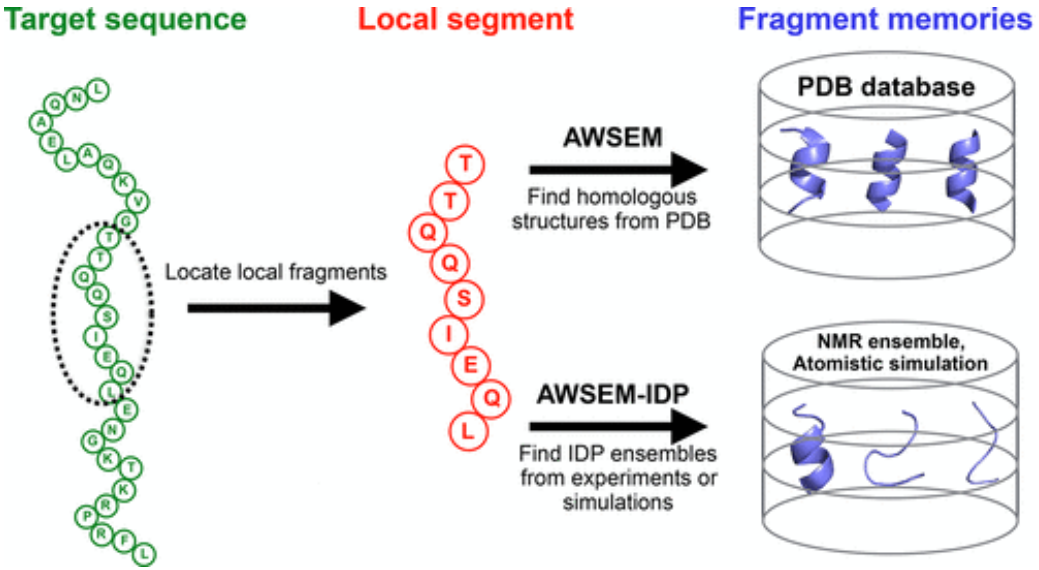
IDP Modeling Powered by Experimental Data

THE JOURNAL OF PHYSICAL CHEMISTRY B
Article
Cite This: J. Phys. Chem. B 2018, 122, 11115−11125
pubs.acs.org/JPCB

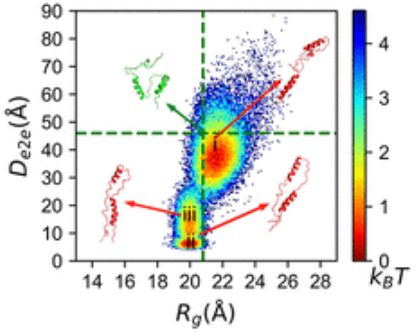
IDP: PaaA2

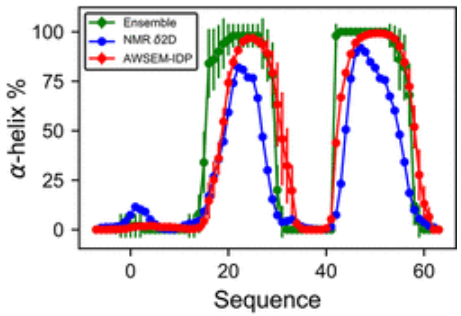
AWSEM-IDP: A Coarse-Grained Force Field for Intrinsically Disordered Proteins

Hao Wu,[†] Peter G. Wolynes,[‡] and Garegin A. Papoian*[,†,§]

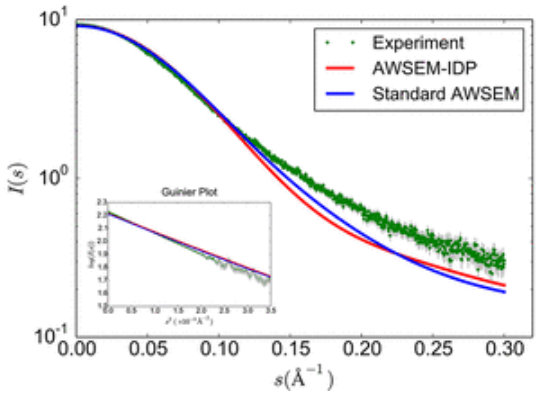


Comparison with NMR

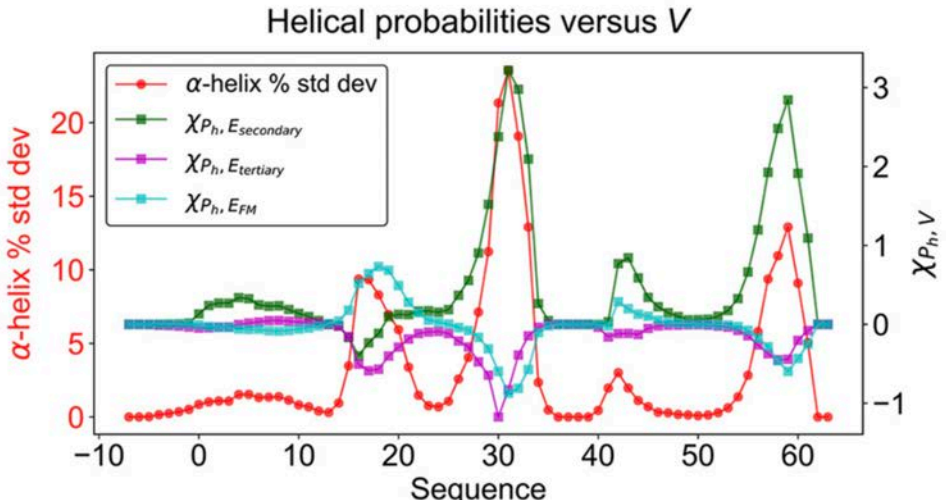


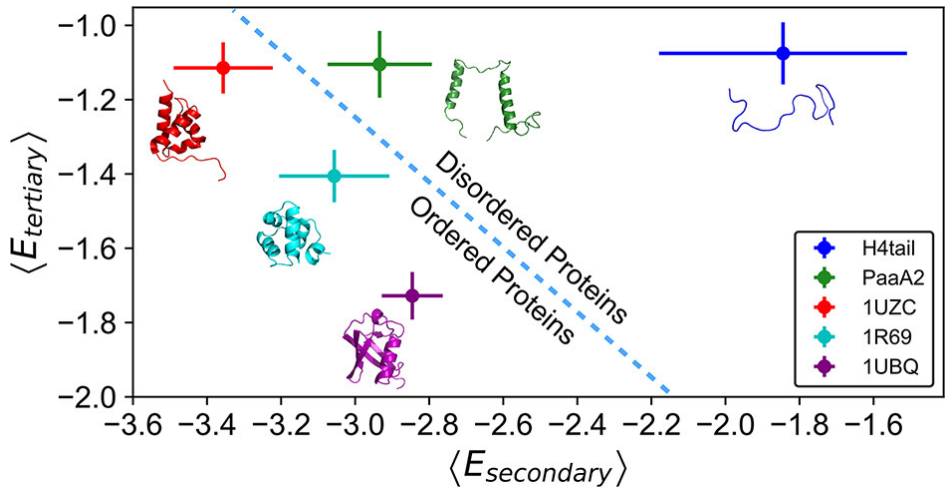


Comparison with SAX

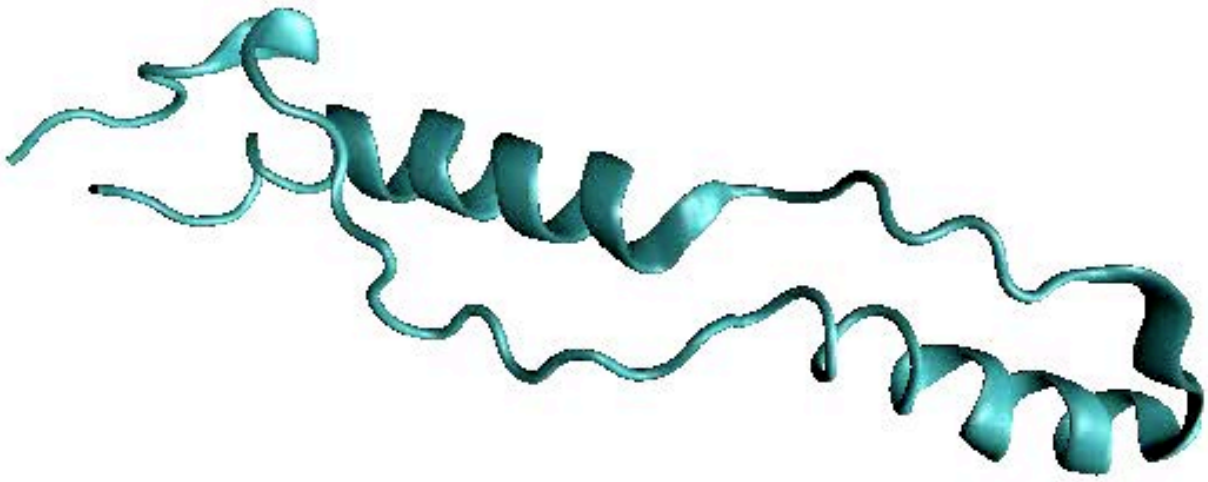


Small force field errors can lead to large structural changes!





PaaaA2



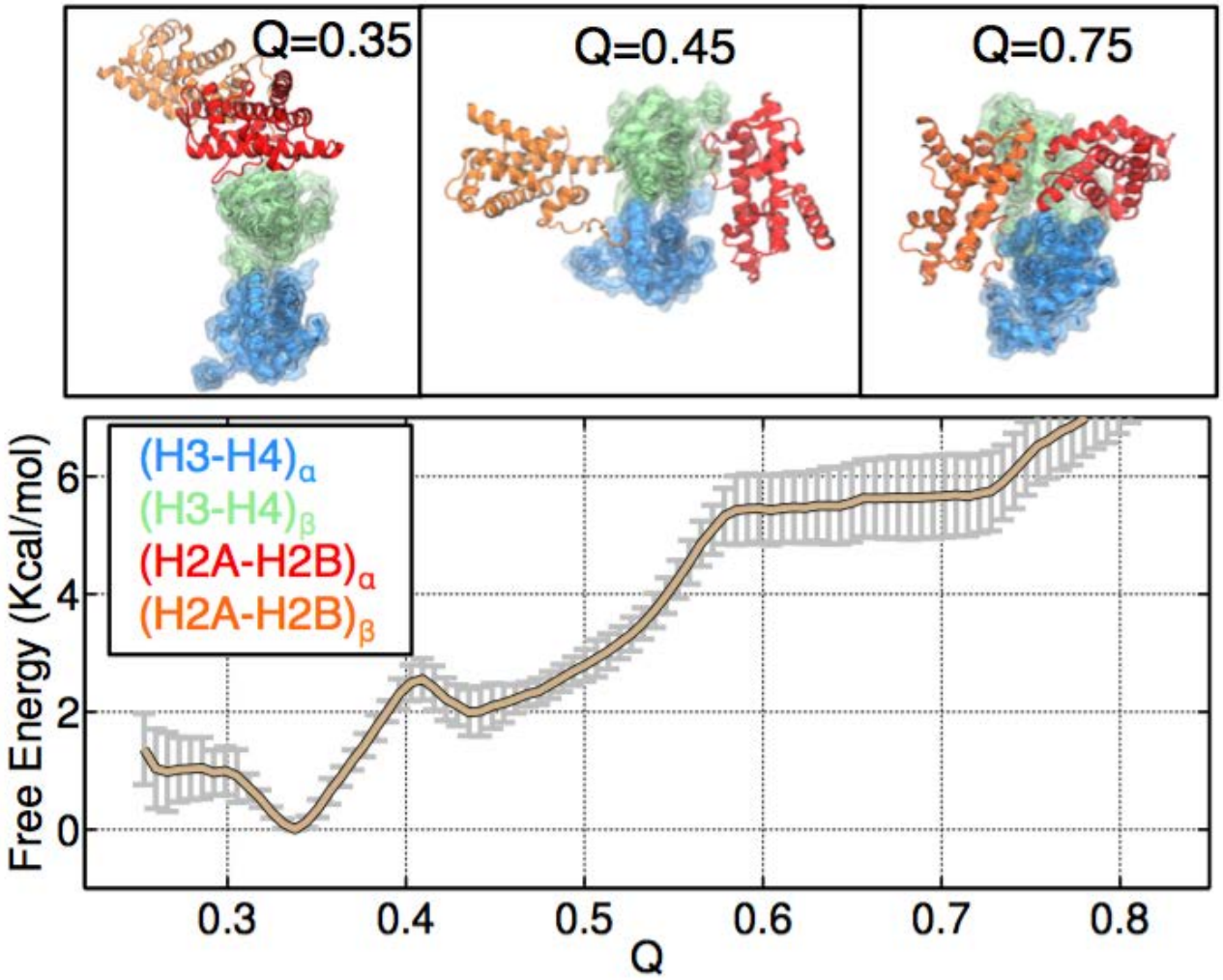
Chaperone HJURP Stabilizes CENP-A/H4

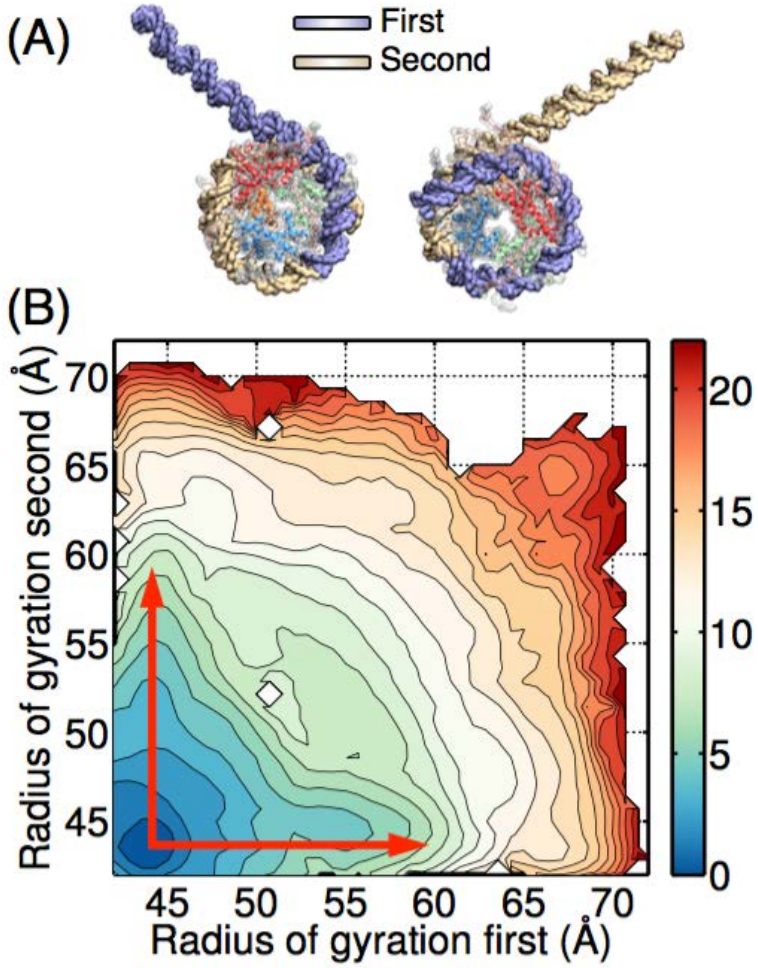
- H4 histone serves as a reinforcing structural element within the histone core
  - Evolutionarily highly conserved
  - No histone variant
- CENP-A/H4 dimer is significantly more dynamic than its canonical counterpart H3/H4
- HJURP stabilizes the CENP-A/H4 dimer by forming a specific electrostatic interaction network
- Structural distributions obtained from AWSEM and explicit-solvent atomistic simulations were largely in agreement!

✏ H. Zhao, D. Winogradoff, M. Bui, Y. Dalal, G. A. Papoian, JACS, (2016), 138, 13207

Exploring the Free Energy Landscape of Nucleosomes Using AWSEM-MD

✏ B. Zhang, W. Zheng, G. A. Papoian, and P. G. Wolynes, JACS, (2016), v 138, pp 8126-8133

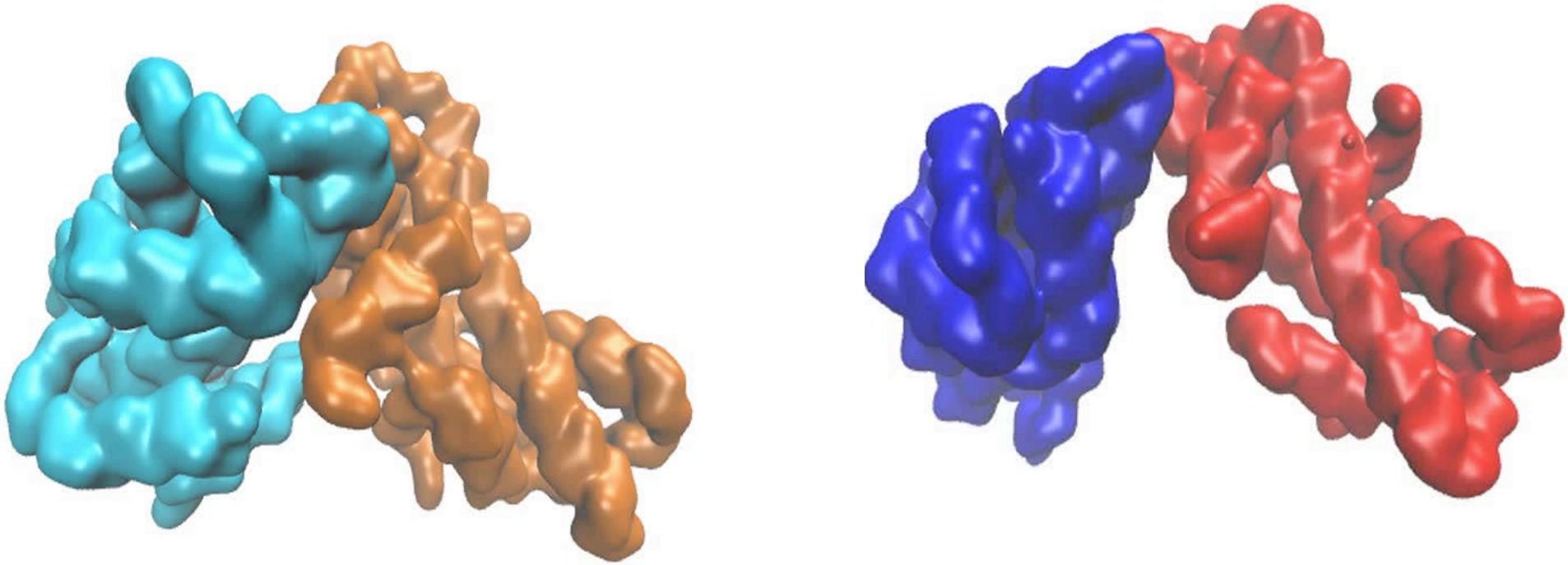




H3/H4 Tetramer Swivels Around the Central Interface

CENP-A/H4

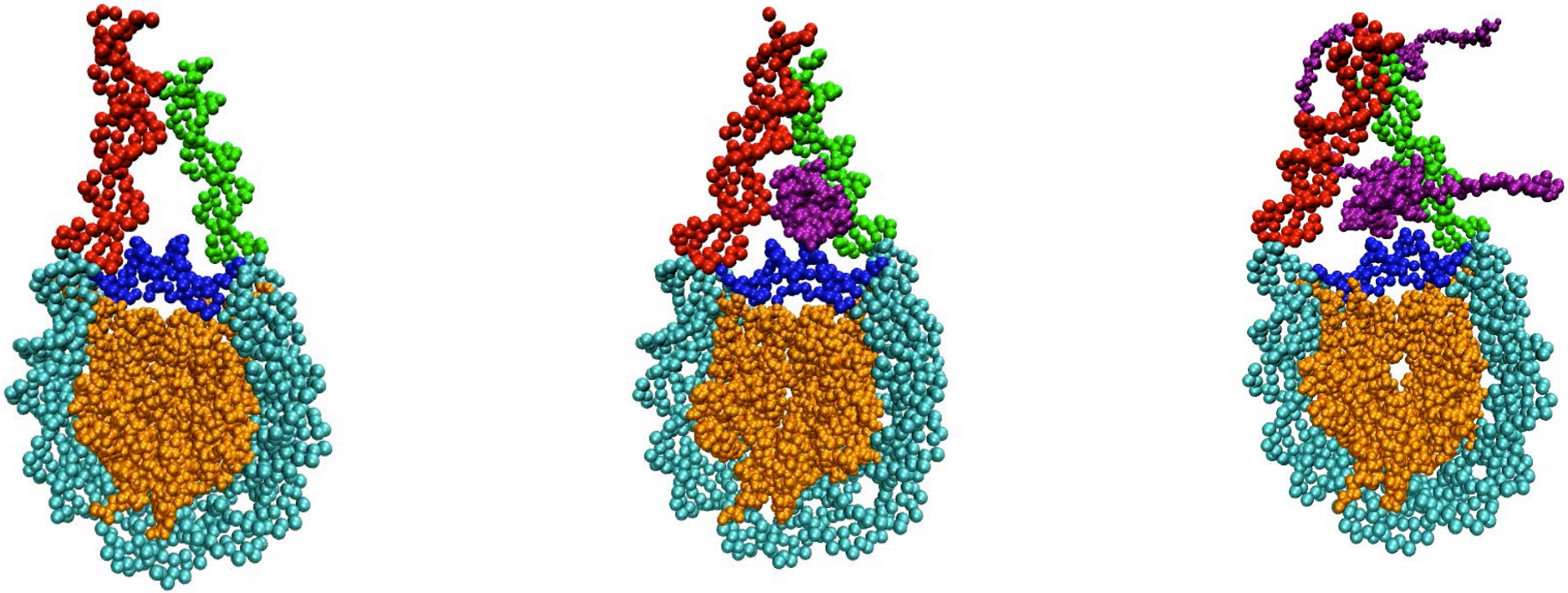
H3/H4



✏ H. Zhao, D. Winogradoff, Y. Dalal, G. A. Papoian, Biophysical J, (2019), in press

Simulations of H1-Nucleosome Complex by AWSEM-3SPN2.c

color code: histone core/nucleosomal DNA/H1/dyad DNA/linker DNA1/linker DNA2



- A hybrid force field ***AWSEM-IDP:3SPN2*** to model H1 globular domain, disordered tails and DNA.
- Studied three systems: “noH1”, “GH1”, “fullH1” to highlight the functions of different H1 domains.
- 50 independent 60ns (~3μs in total) MD simulations for each system.

Biophysical Journal
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Minimal Cylinder Analysis Reveals the Mechanical Properties of Oncogenic Nucleosomes

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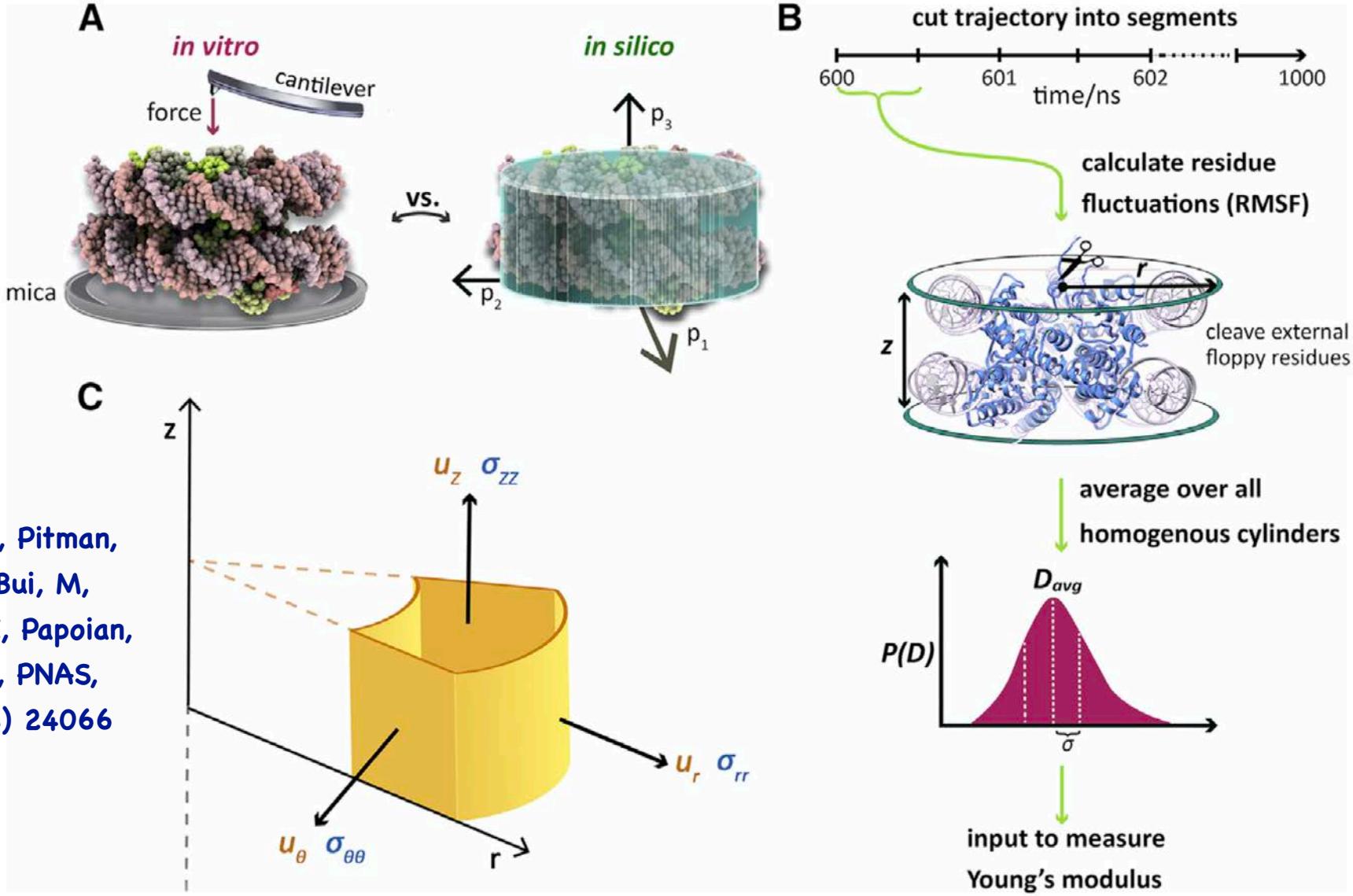
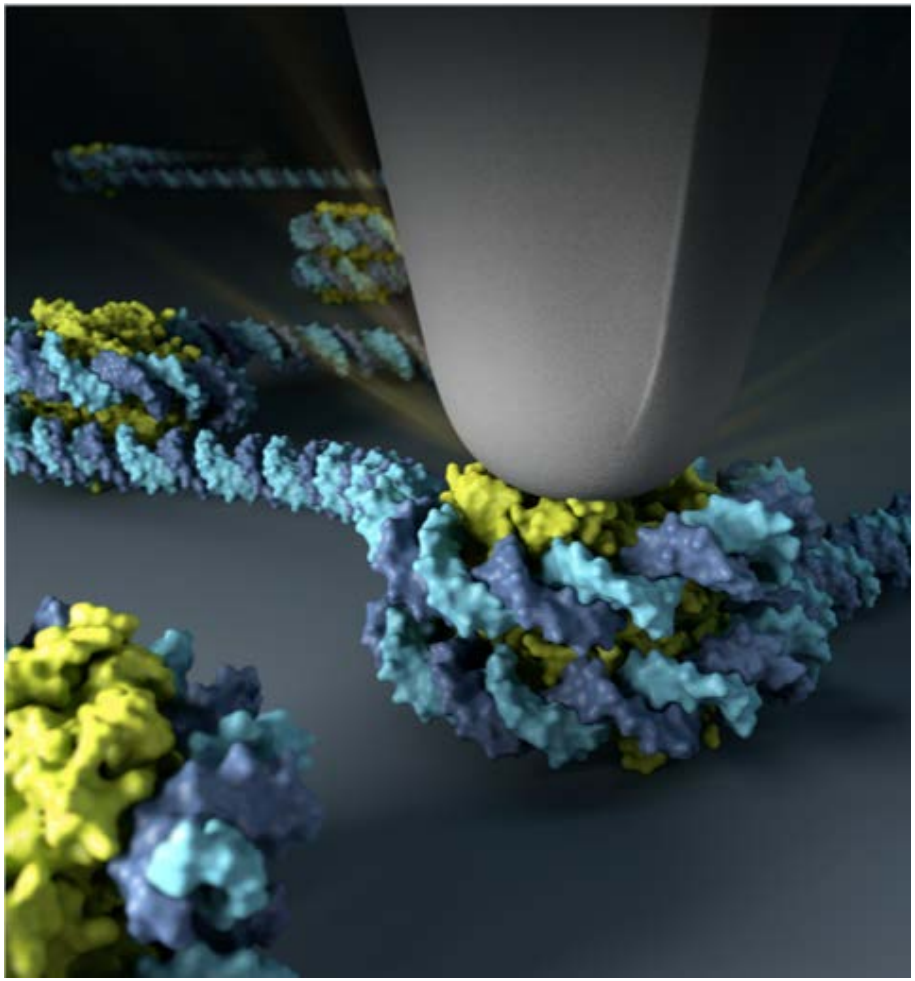
ABSTRACT Histone variants
widely accepted as a paradigm
erties. Here, we present a new

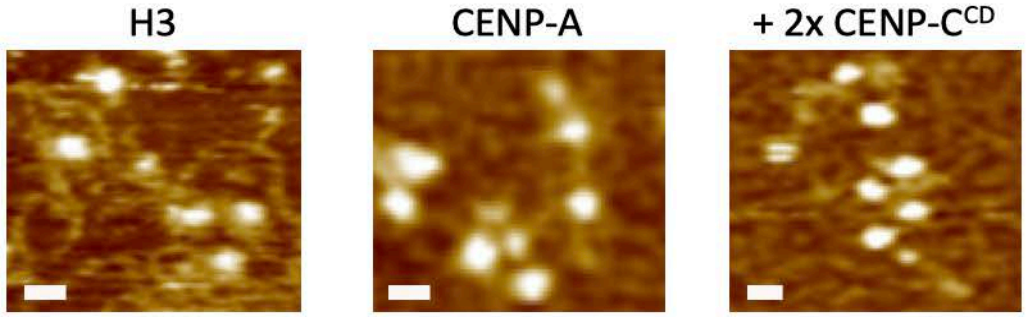
$$E = \frac{k_b T(1 - \nu - 2\nu^2)}{V\left(\varepsilon_{zz}^2 - \nu\varepsilon_{zz}^2 + 2\varepsilon_{rr}^2 + 4\nu\varepsilon_{zz}\varepsilon_{rr}\right)}. \quad (6)$$

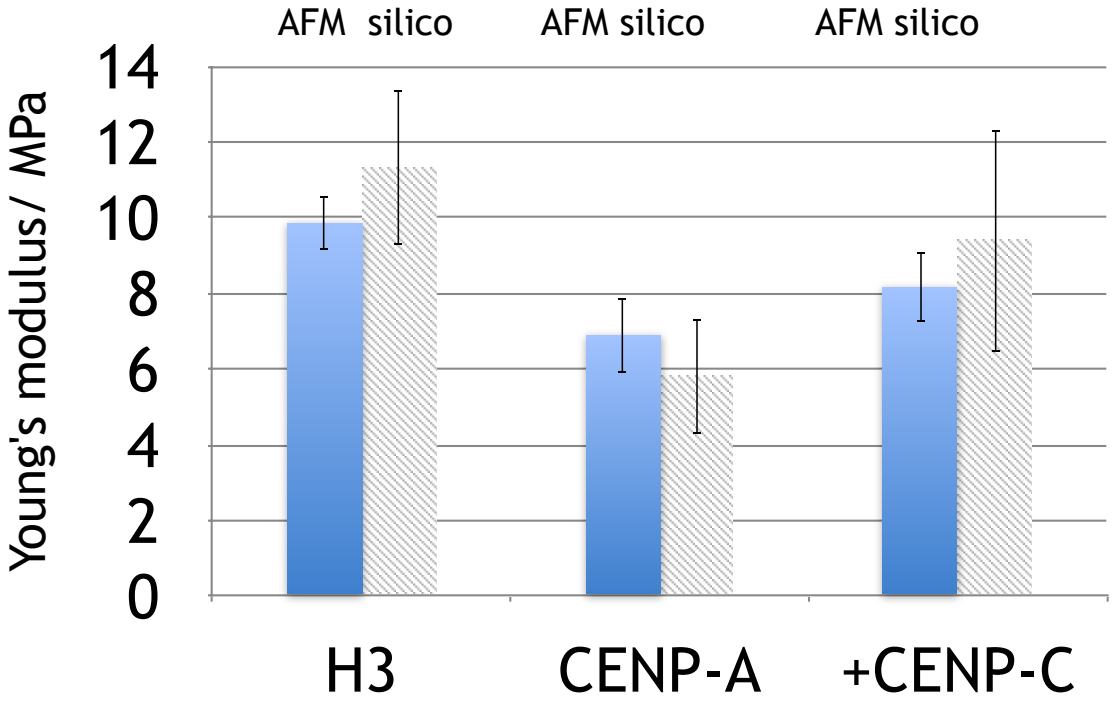


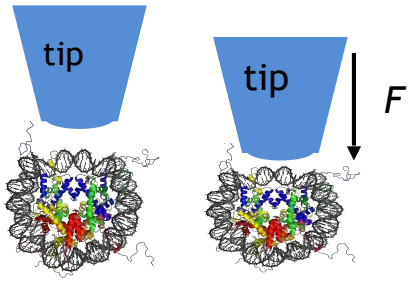
✏ Melters, D, Pitman, M , Rakshit, Bui, M, Dimitriadis, E, Papoian, G.A., Dalal, Y, PNAS, 2019, 116 (48) 24066

CENP-C Rigidifies CENP-A *in vitro*









✏ Melters, D, Pitman, M , Rakshit, Bui, M, Dimitriadis, E, Papoian, G.A., Dalal, Y, PNAS, 2019, 116 (48) 24066

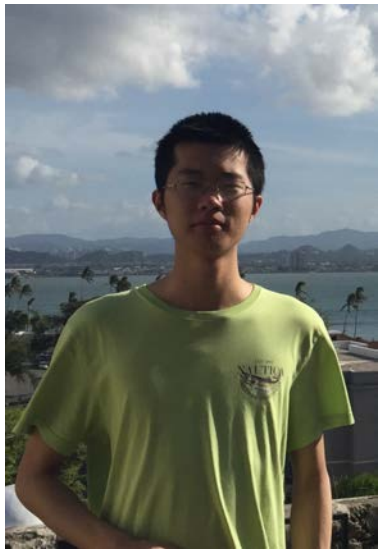
In vitro work: Tatini Rakshit

Acknowledgments

James Komianos

Aravind Chandrasekaran

Qin Ni



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NSF CHEMISTRY: CTMC
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Carlos Floyd

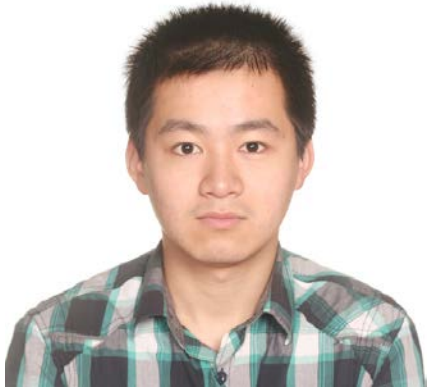
Radek Erban

Arpita Upadhyaya

Acknowledgments

- Mary Pitman (UMD)

- Haiqing Zhao (Columbia University)



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