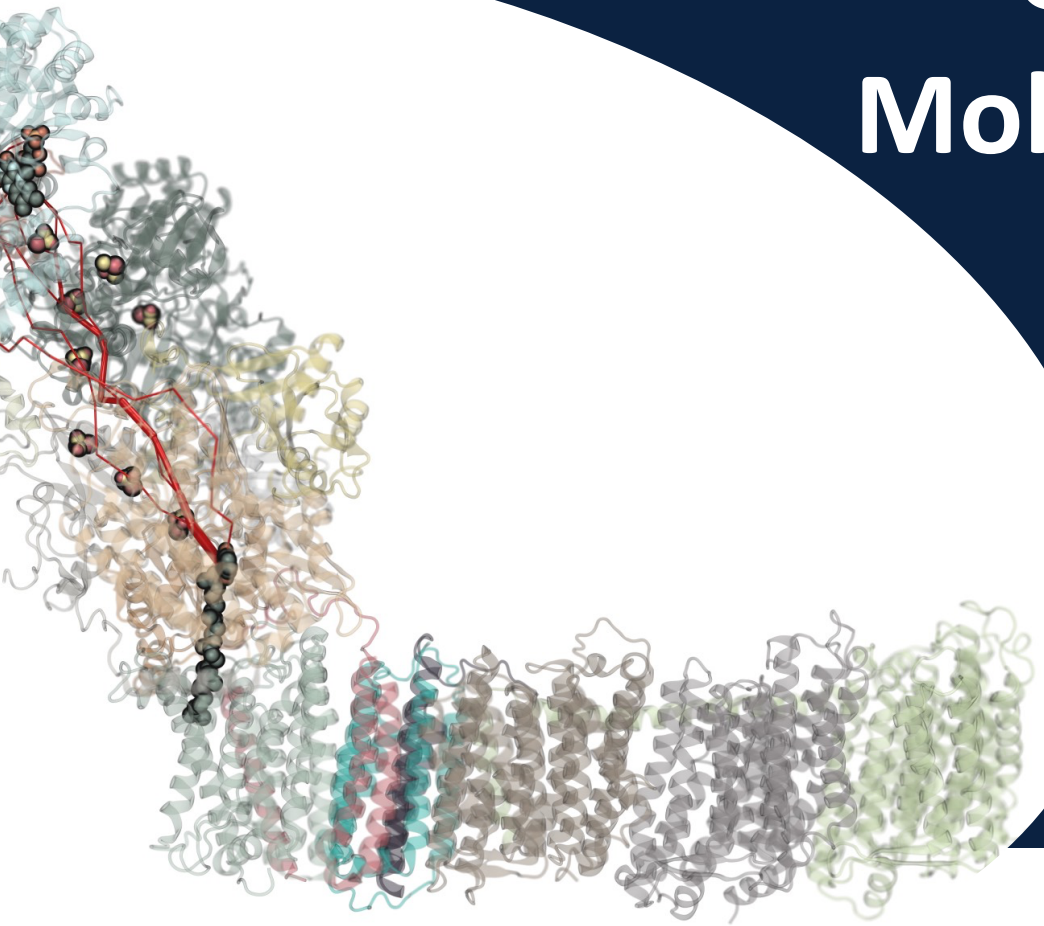
Virtual "Hands-on" Workshop on Computational Biophysics at ~~Pittsburgh, PA~~ *wherever you are*

QwikMD: Easy preparation of Molecular Dynamics Simulations



Rafael C. Bernardi

Department of Physics at Auburn University

NIH Center for Macromolecular Modeling and Bioinformatics

rcbernardi@auburn.edu

@rafaelcbernardi

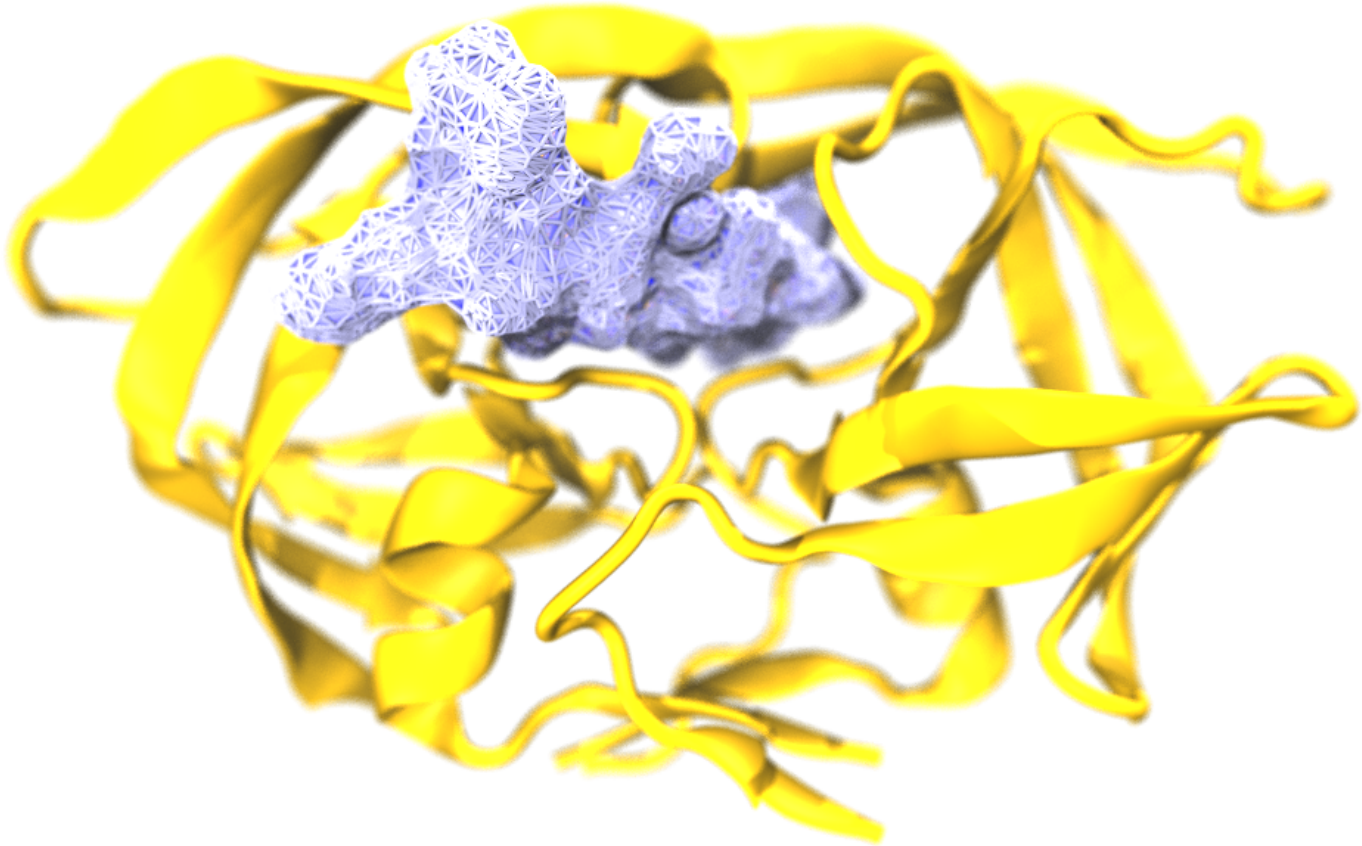
AUBURN UNIVERSITY

COLLEGE OF SCIENCES AND MATHEMATICS

www.ks.uiuc.edu/Research/qwikmd

Employing QwikMD, a user is able to prepare an MD simulation in just a few minutes, allowing studies of point mutations, partial deletions and even atomic force microscopy experiments.

QwikMD assists a new user in performing molecular dynamics (MD) simulations, while it also servers as a learning tool. Many "info buttons" provide the theoretical background underlying the MD procedures carried out in modern MD simulations.



JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

Rafael C. Bernardi
rcbernardi@auburn.edu

What is Molecular Dynamics?

"Certainly no subject or field is making more progress on so many fronts at the present moment than biology, and if we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that ***all things are made of atoms, and that everything that living things do can be understood in terms of the jigglings and wigglings of atoms****."*

Richard Feynman

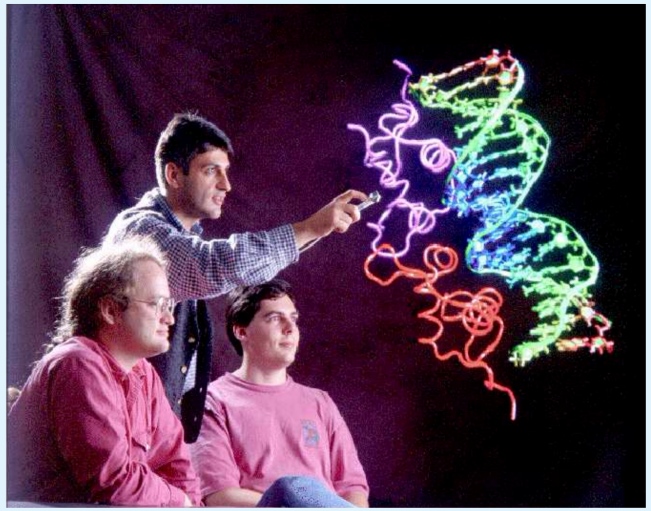
The Feynman Lectures on Physics: Mainly Mechanism, Radiation and Heat (1963)

Rafael C. Bernardi
rcbernardi@auburn.edu

Advances in MD are directly connected to advances in Structural Biology & Computer Hardware

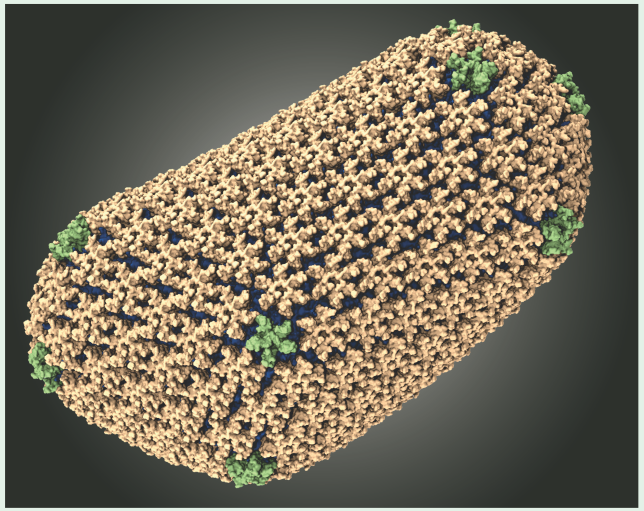
1958

Manual Construction of Structural Models



1996

Computer-aided Construction of Structural Models with Manual Positioning of Atoms



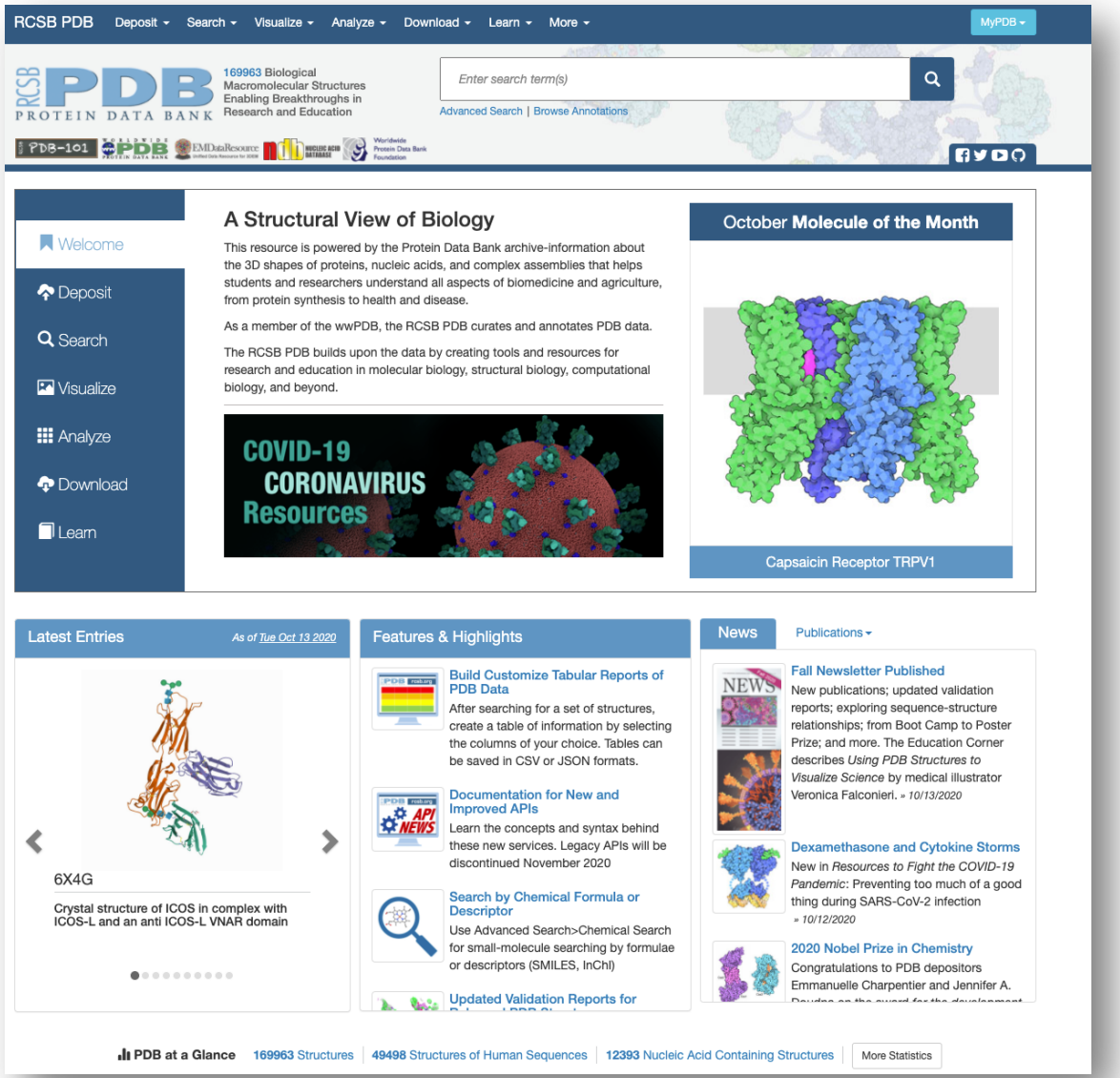
2013

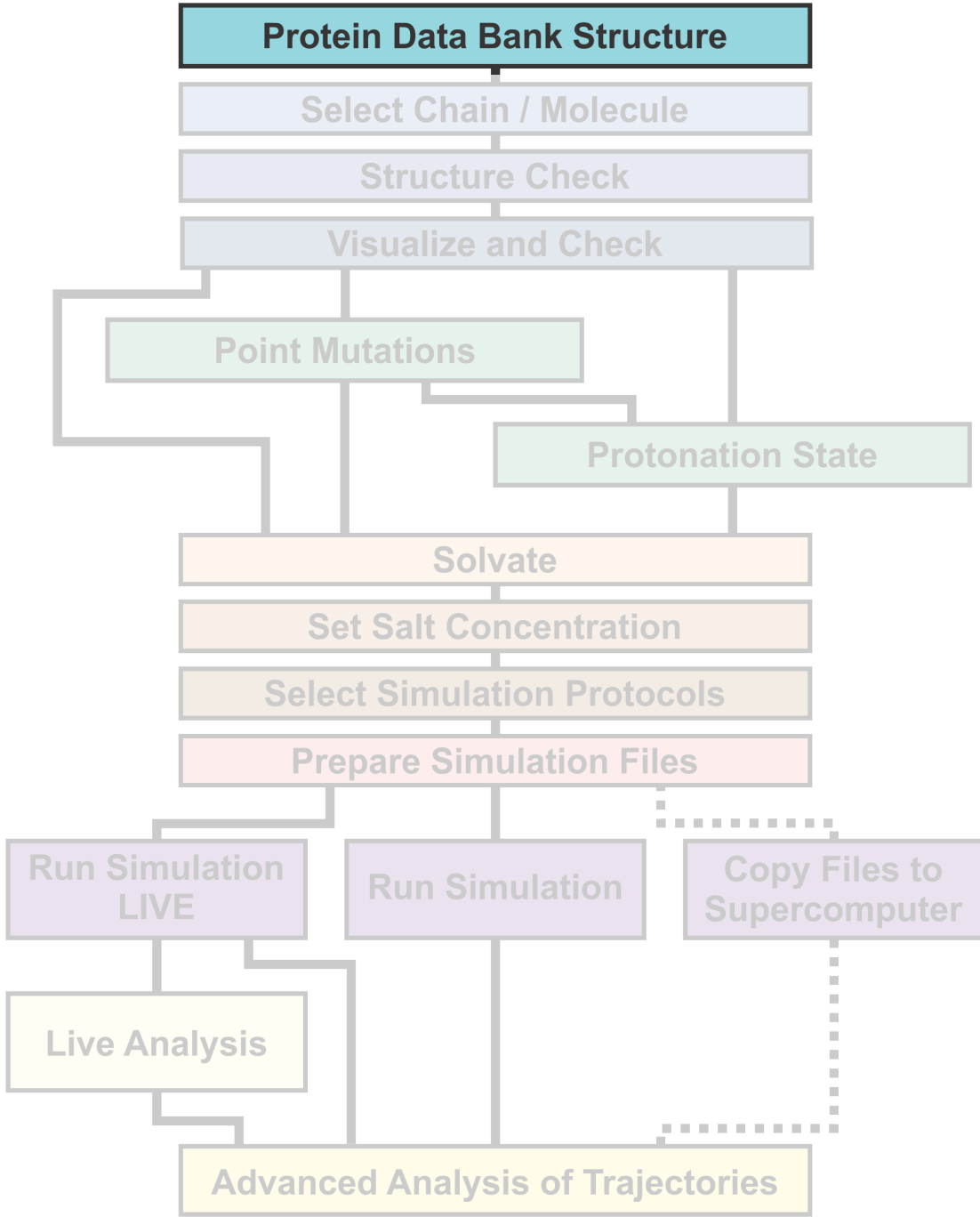
Computational Construction of Structural Models with Automated Positioning of Atoms

BC Goh, JA Hadden, RC Bernardi, et al.; **Computational Methodologies for Real-Space Structural Refinement of Large Macromolecular Complexes.** Annual Review of Biophysics, 2016

Rafael C. Bernardi
rcbernardi@auburn.edu

QwikMD: step-by-step

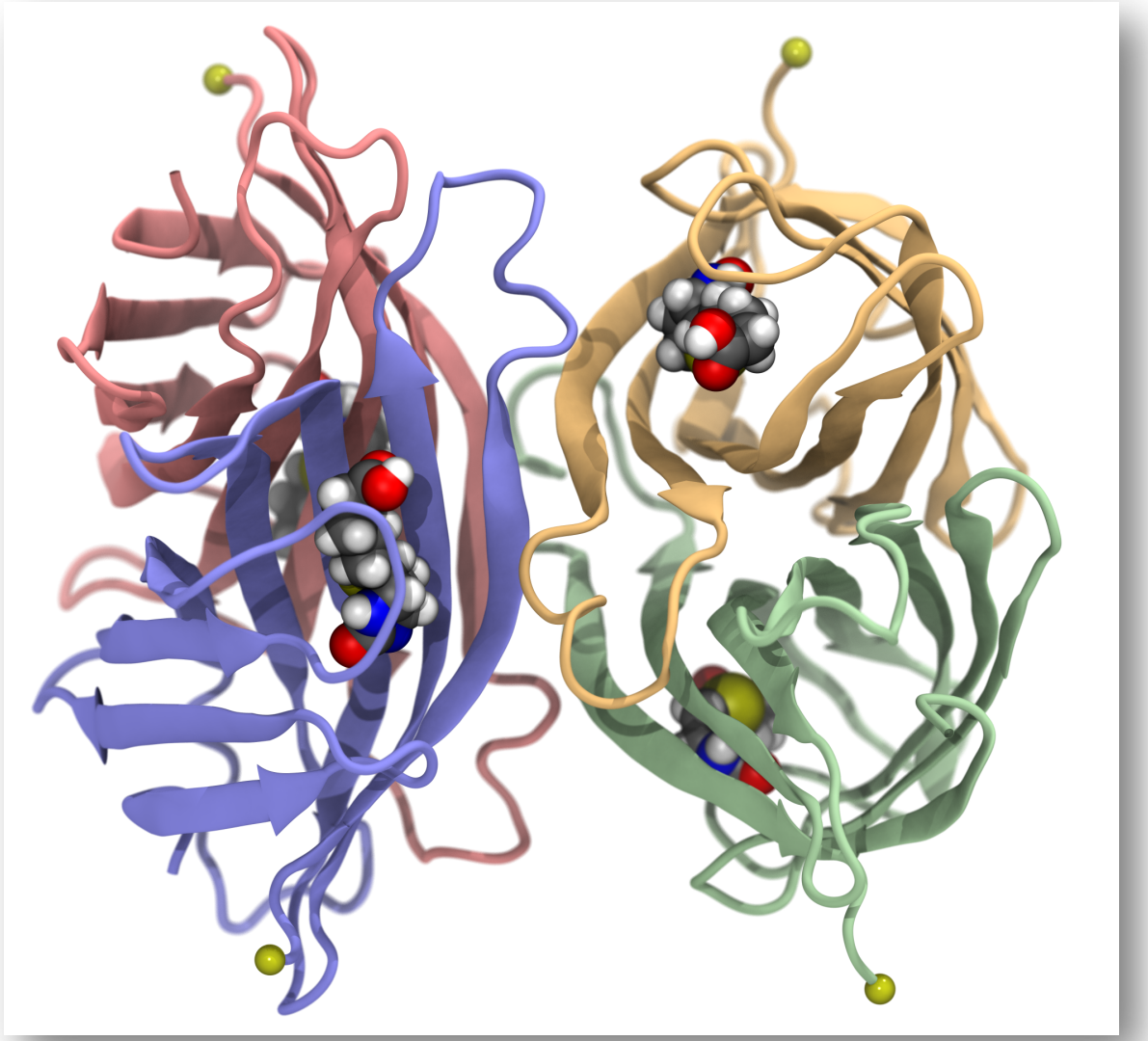


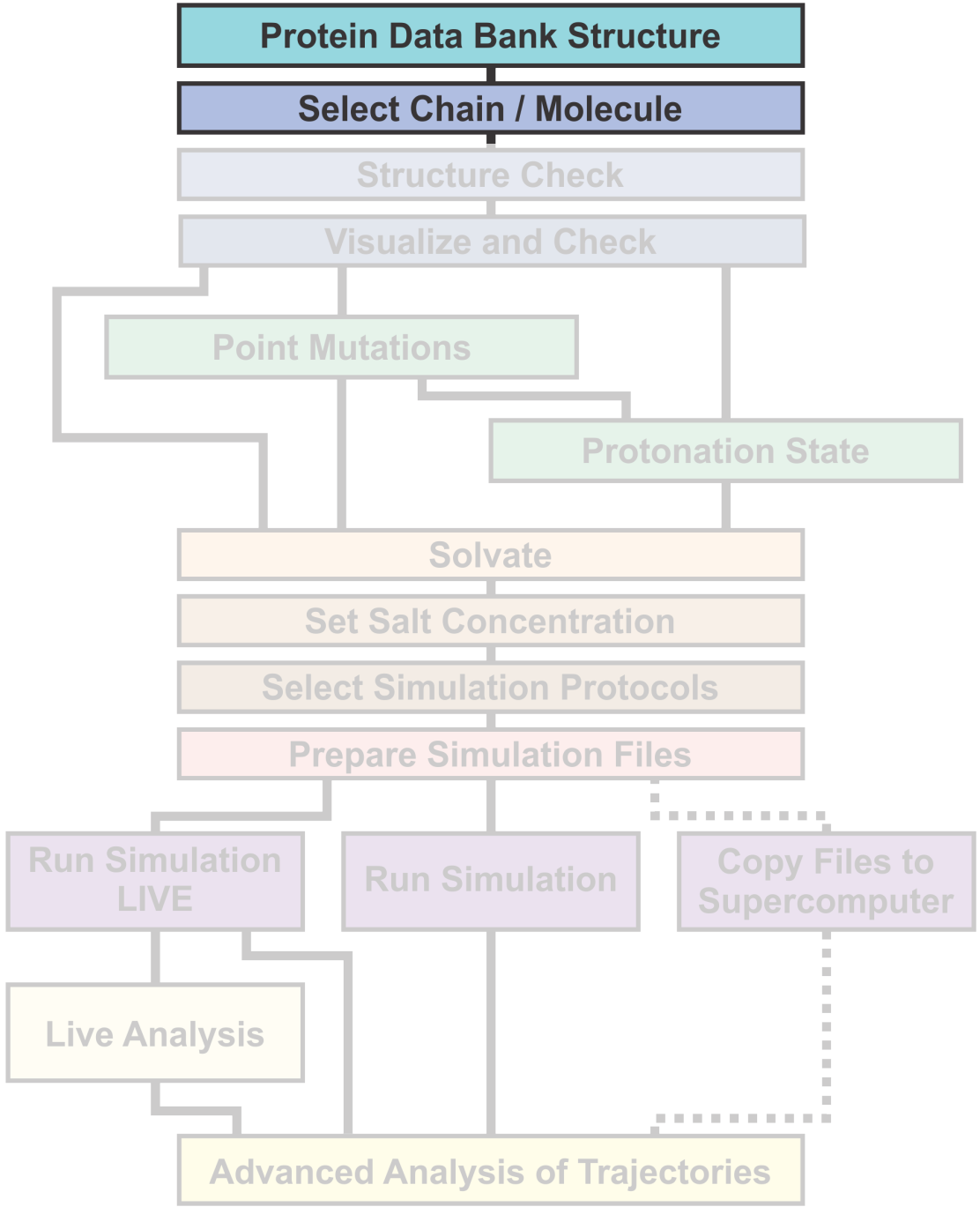


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

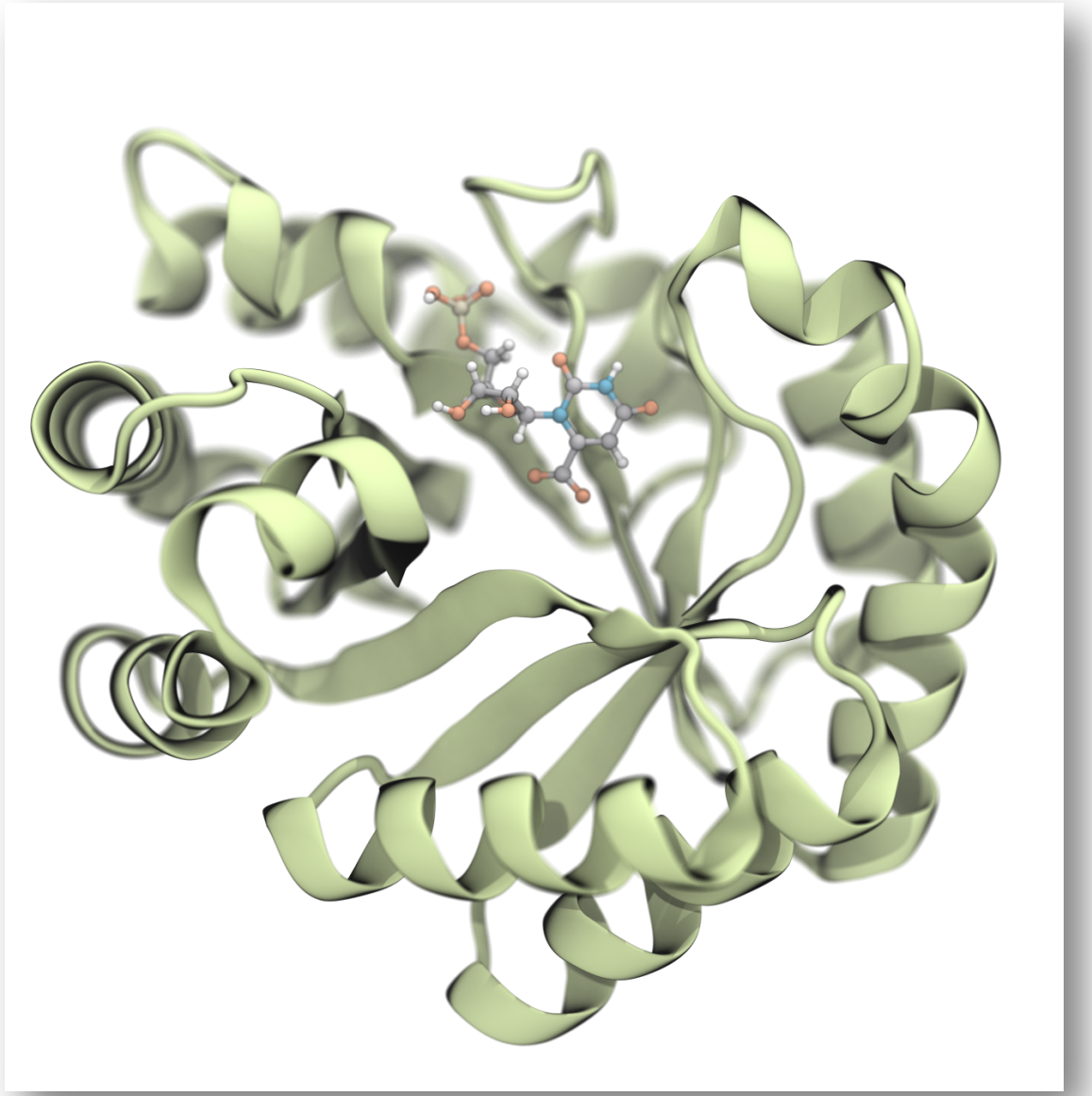


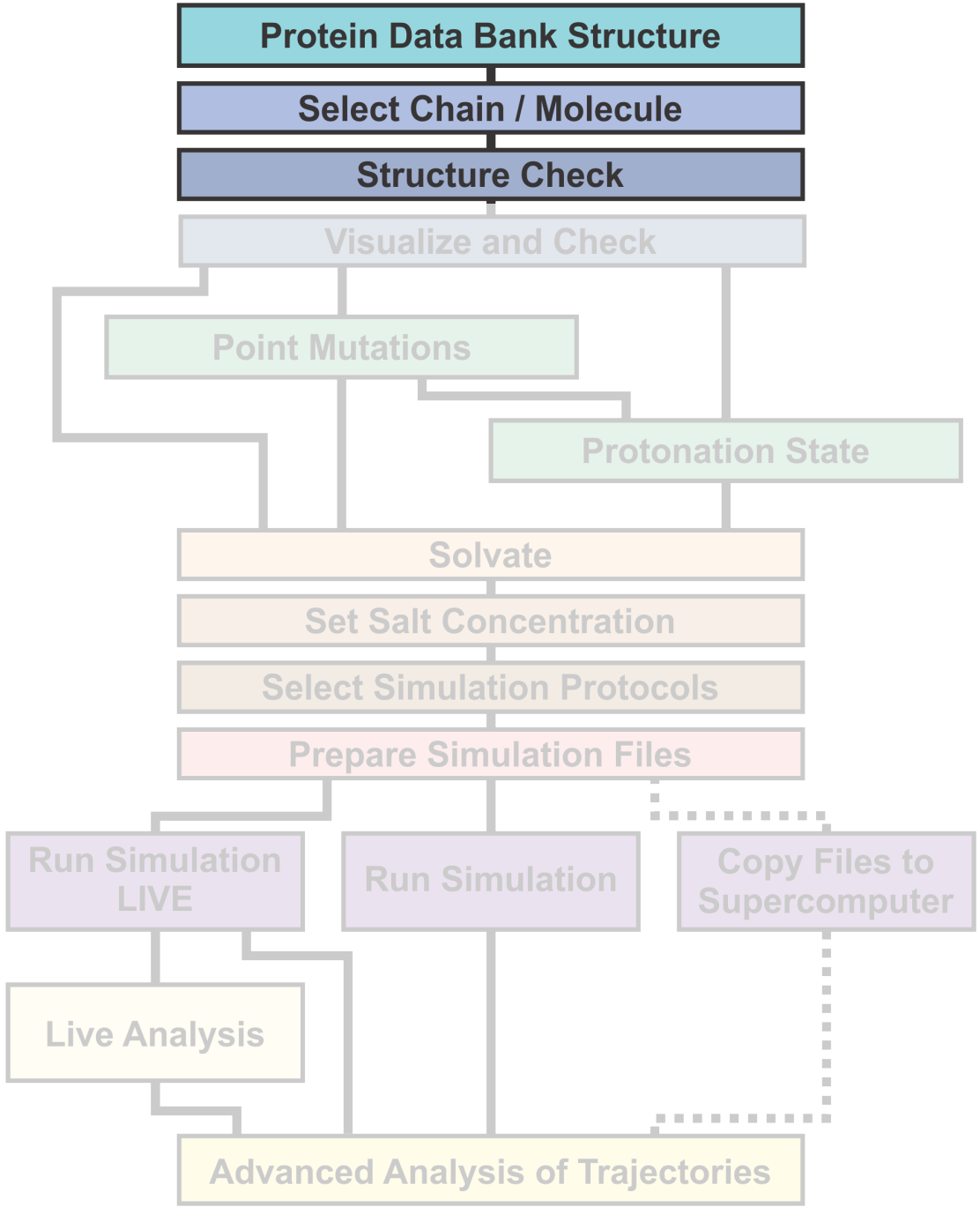


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

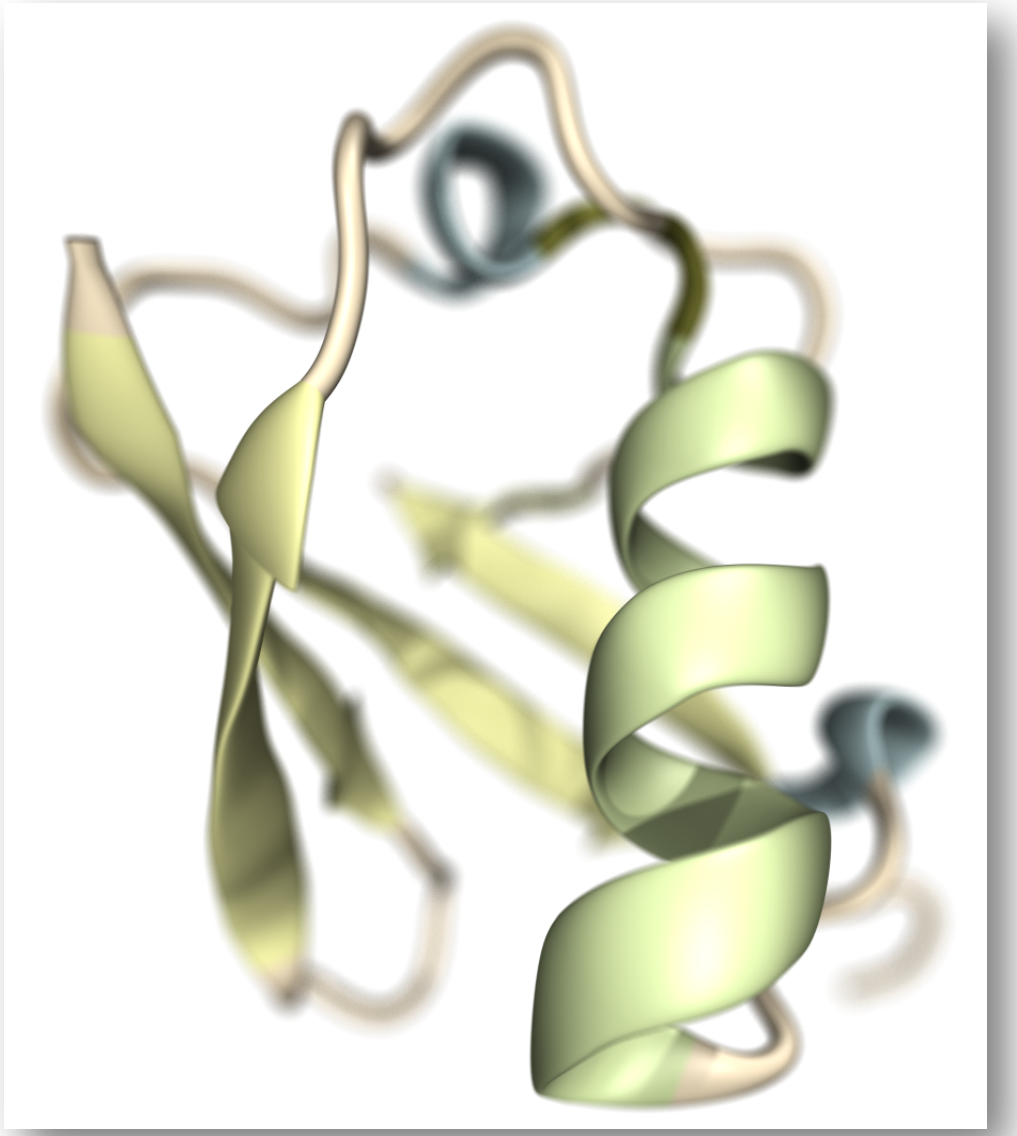


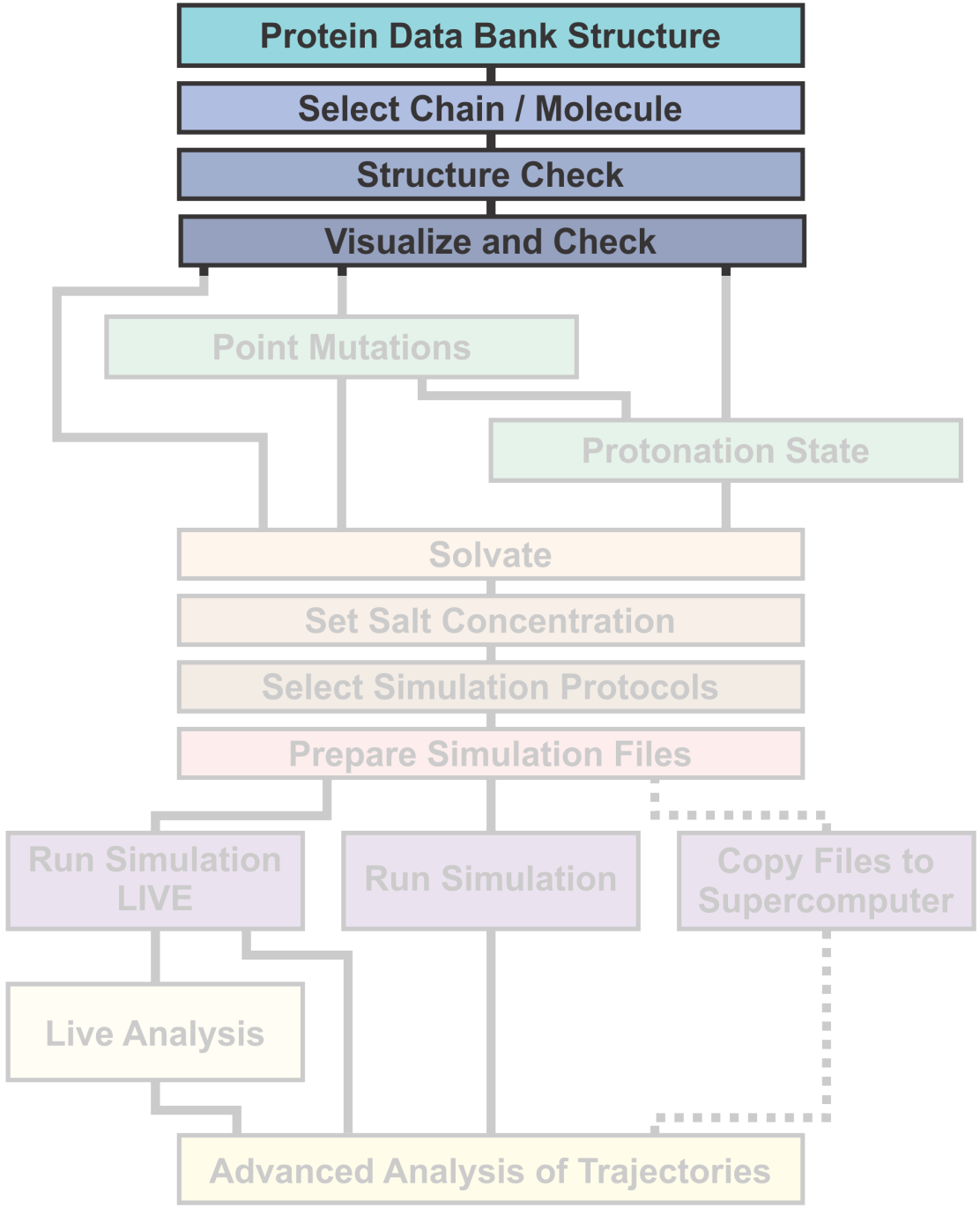


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

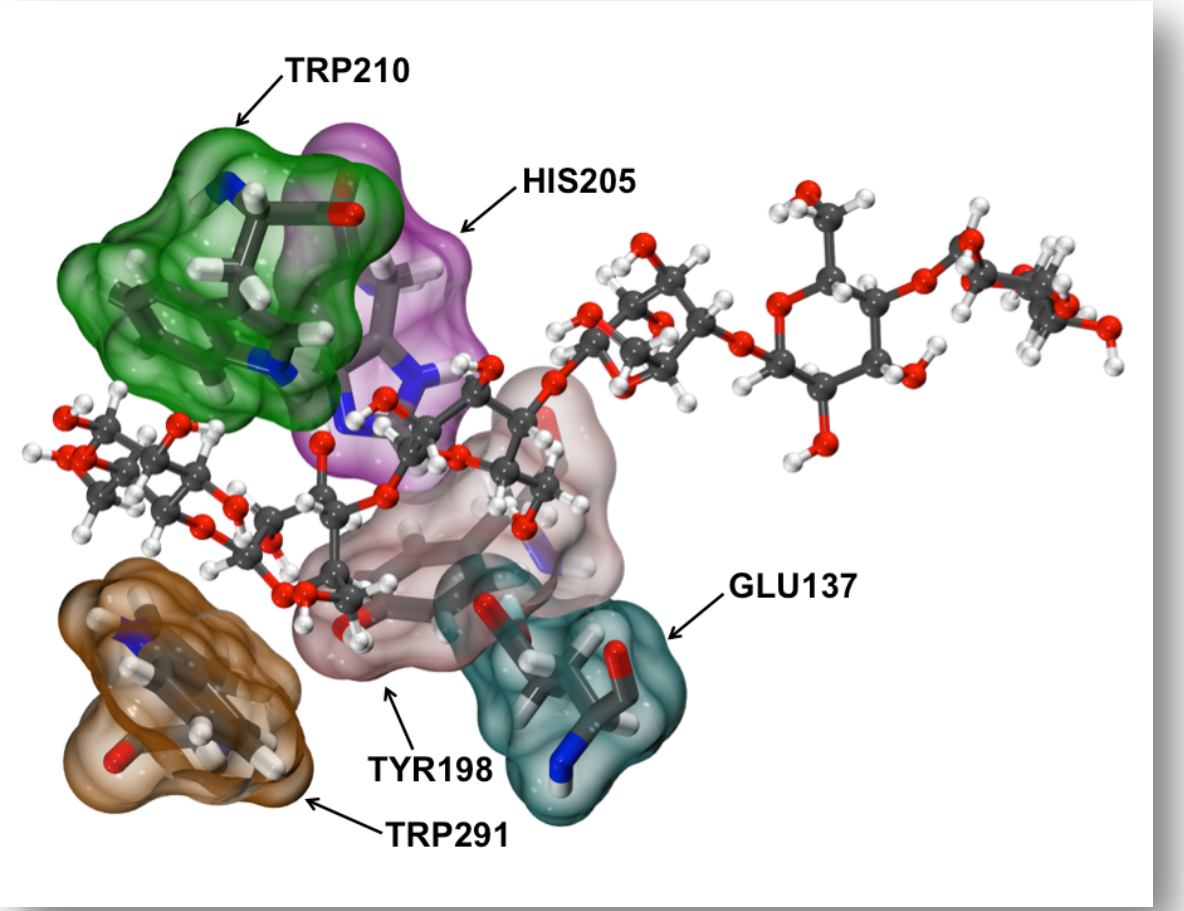


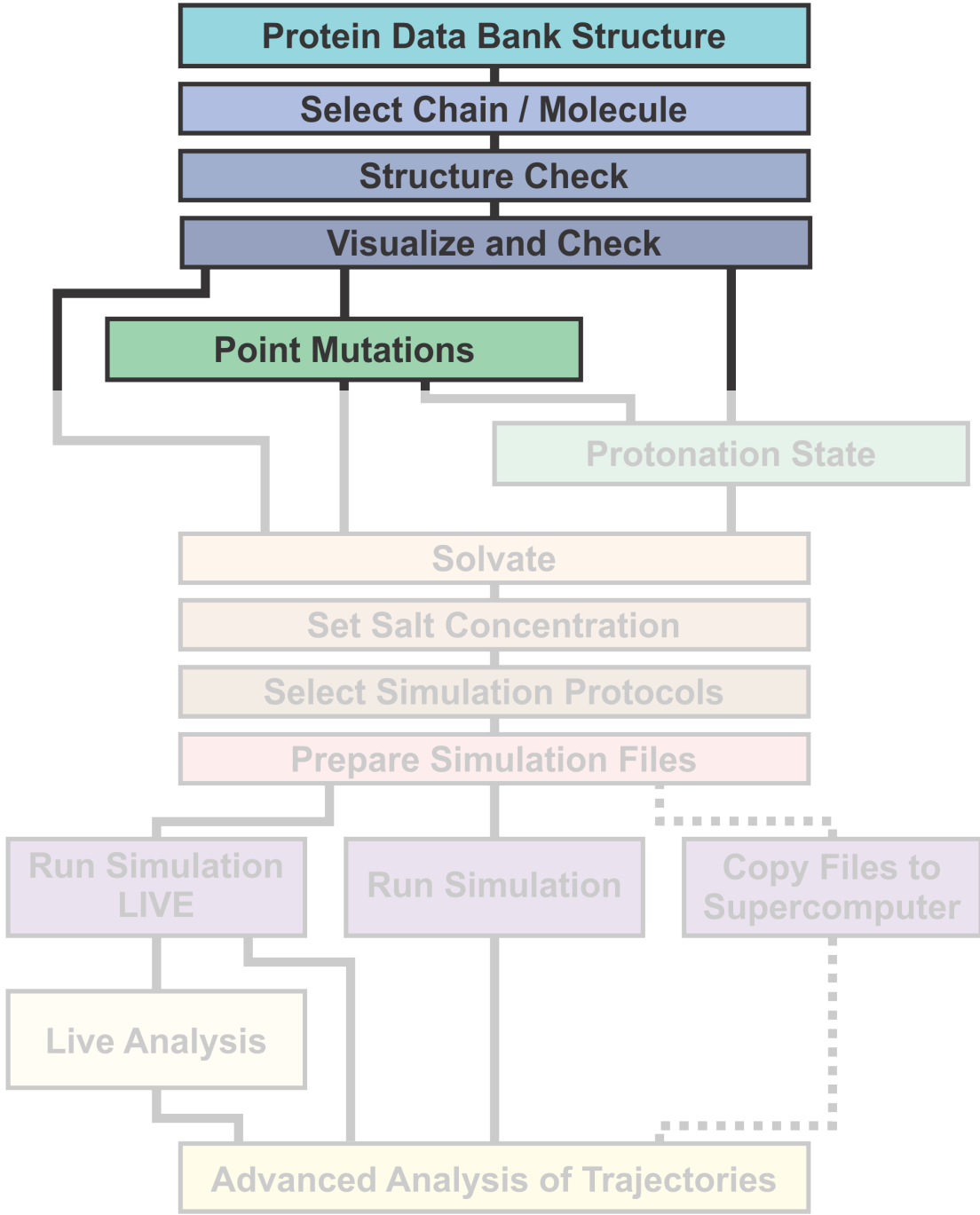


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

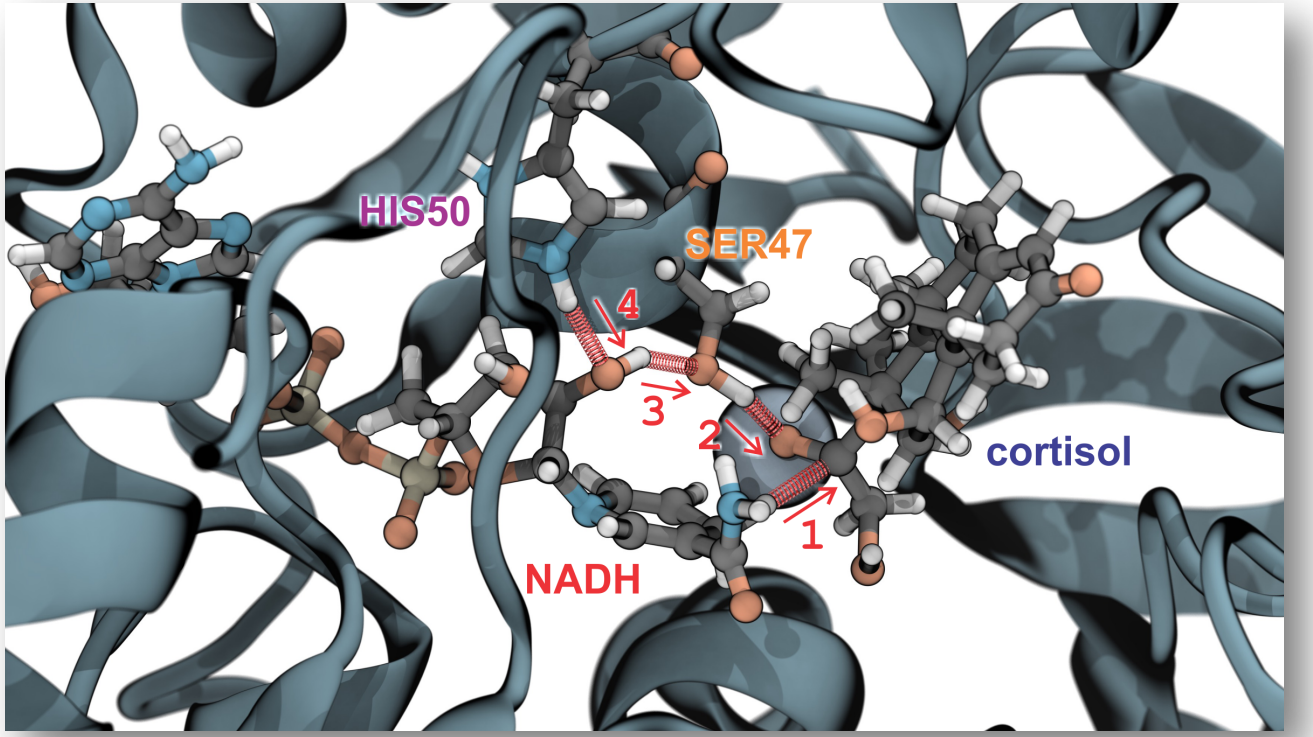


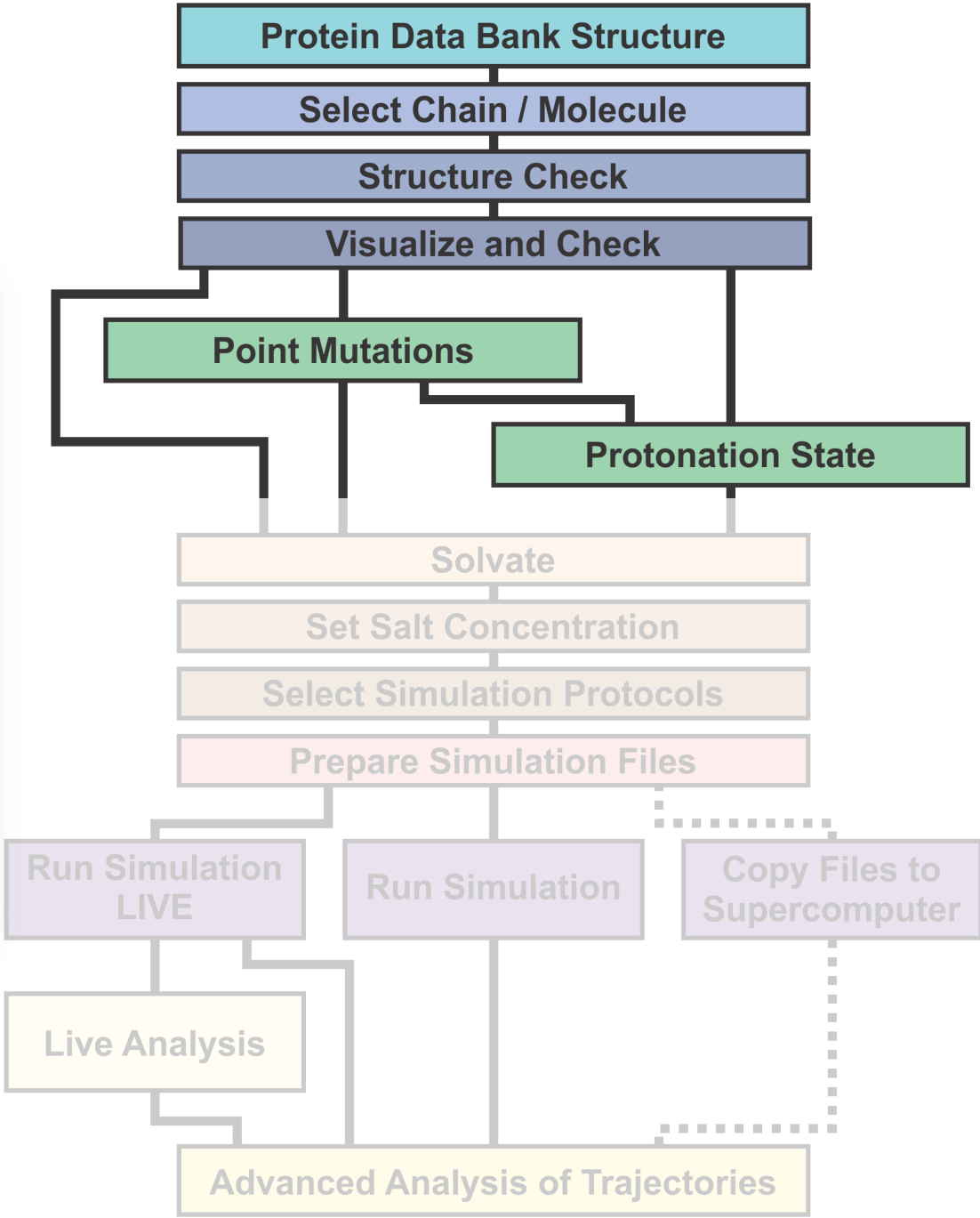


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step





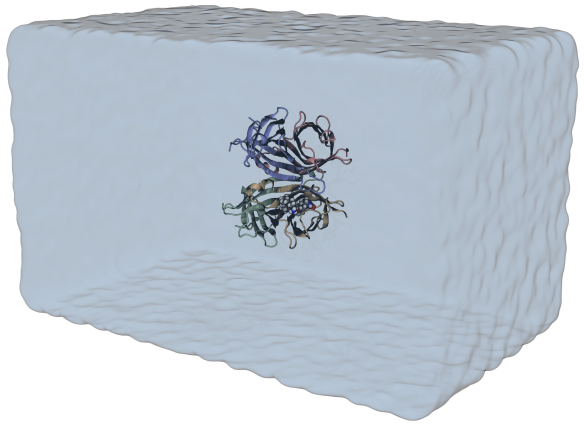
Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

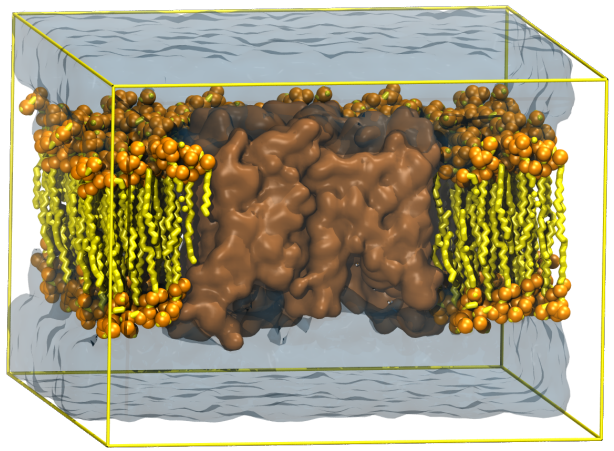
QwikMD: step-by-step

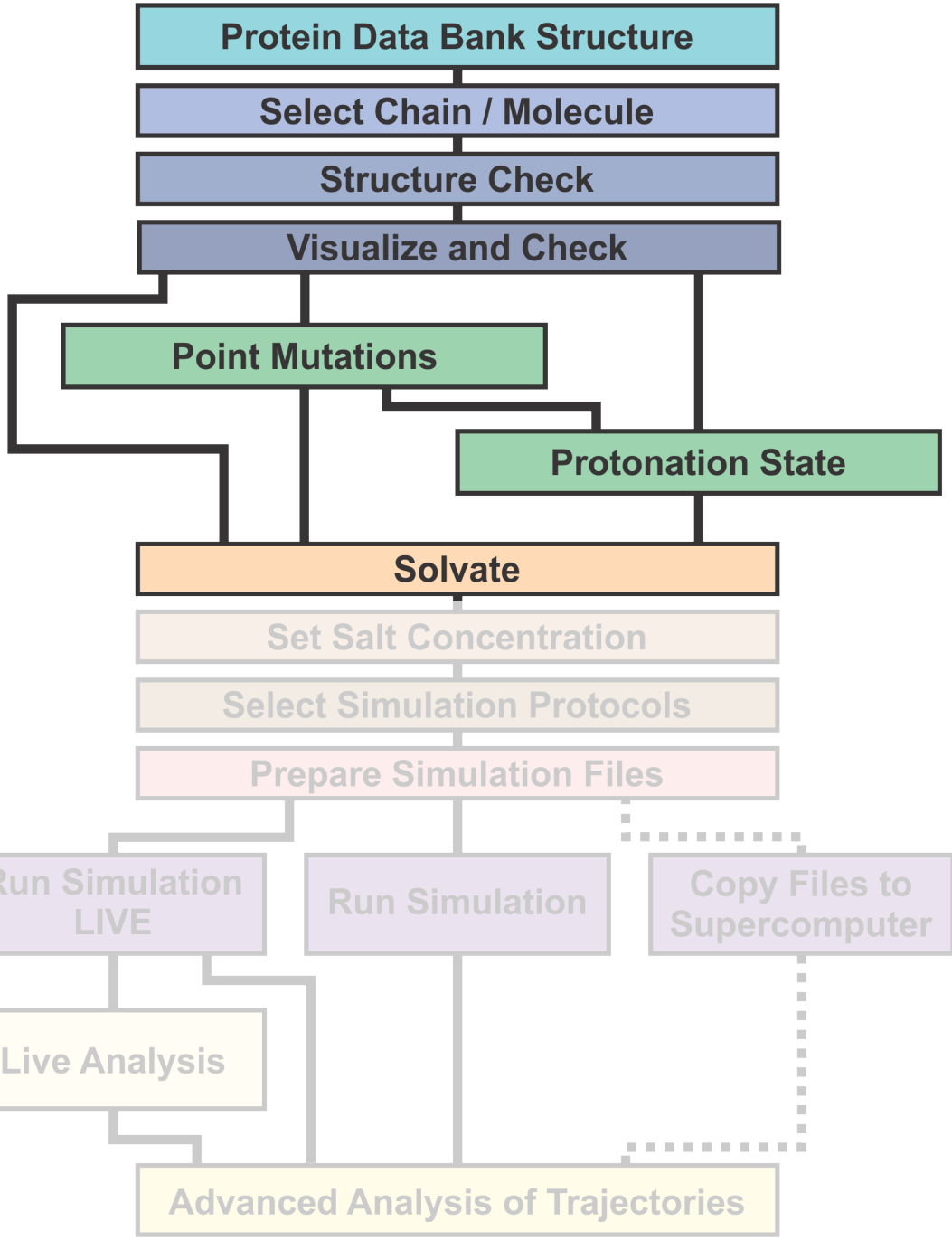
Vacuum / Implicit Solvent

Water Box



Membrane Environment

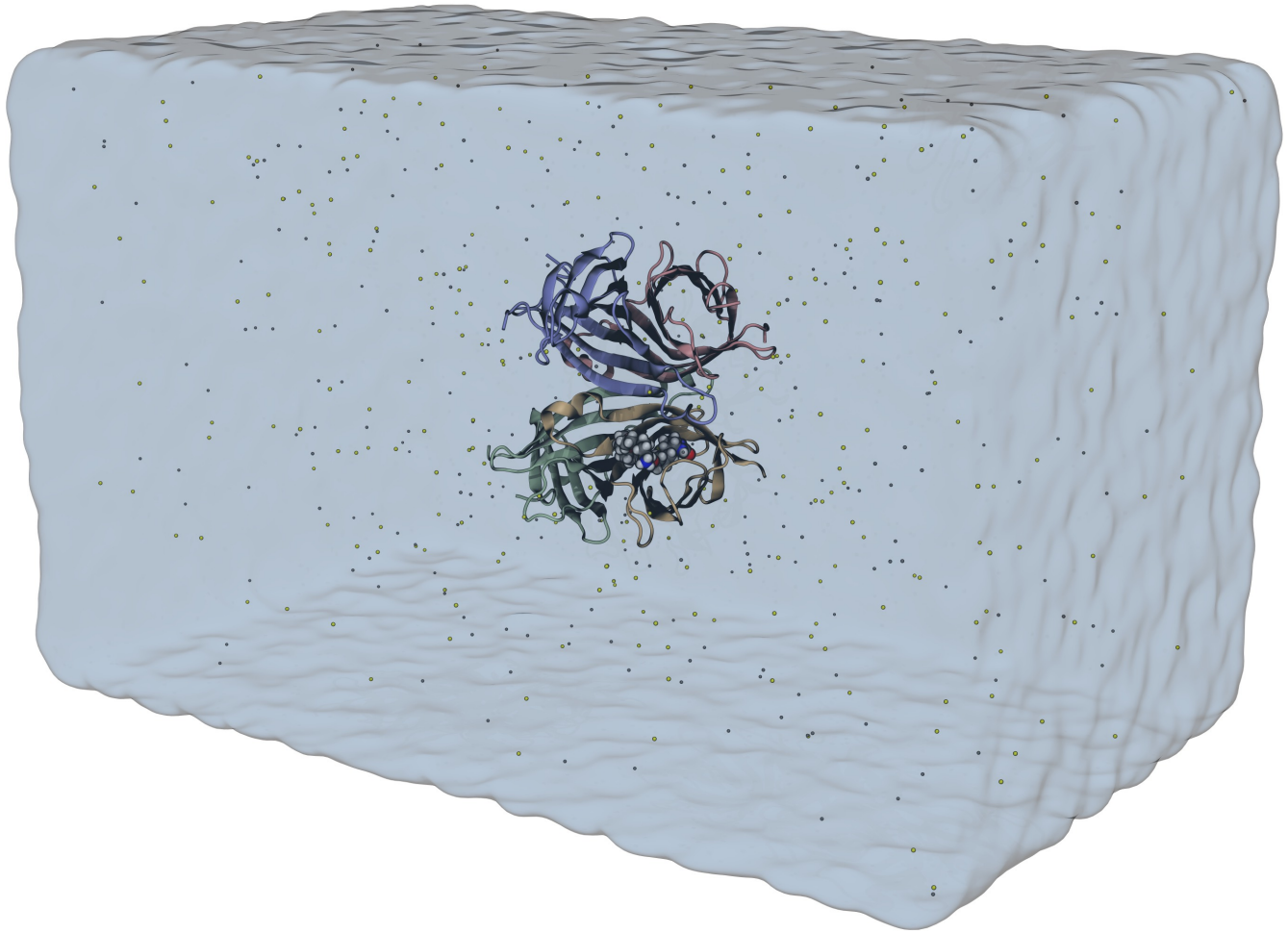


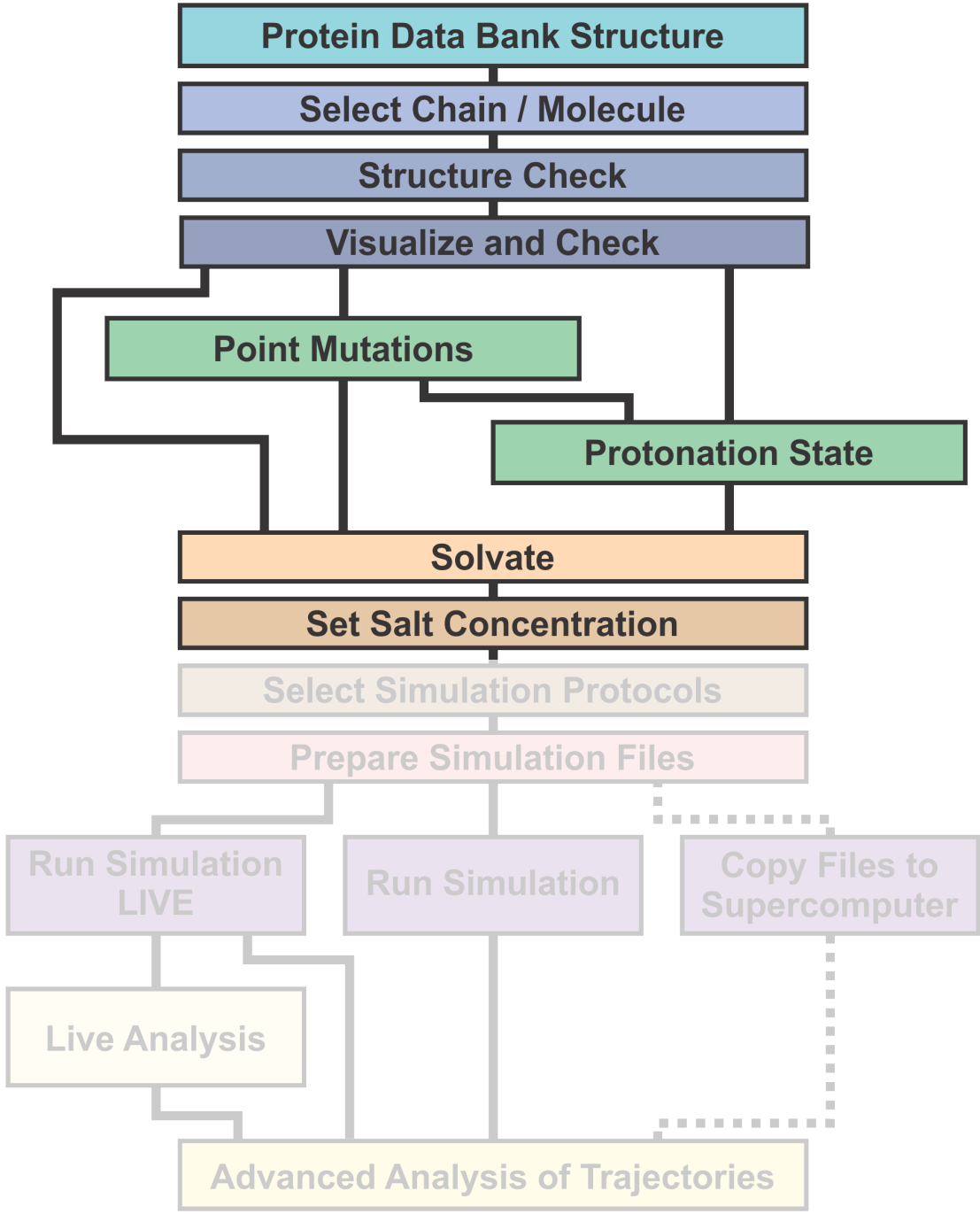


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step



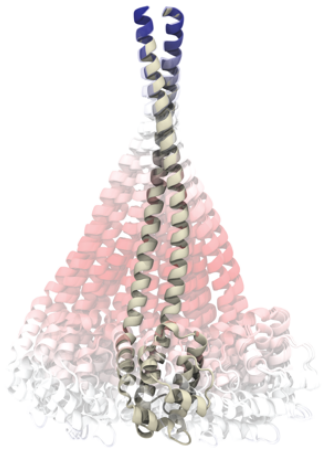


Rafael C. Bernardi
rcbernardi@auburn.edu

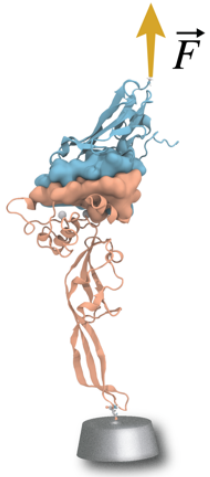
JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

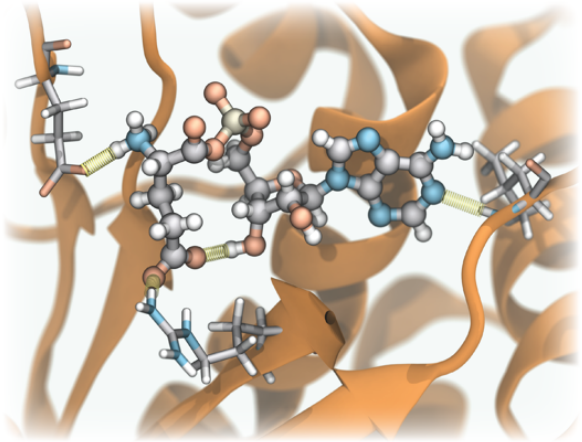
Molecular Dynamics



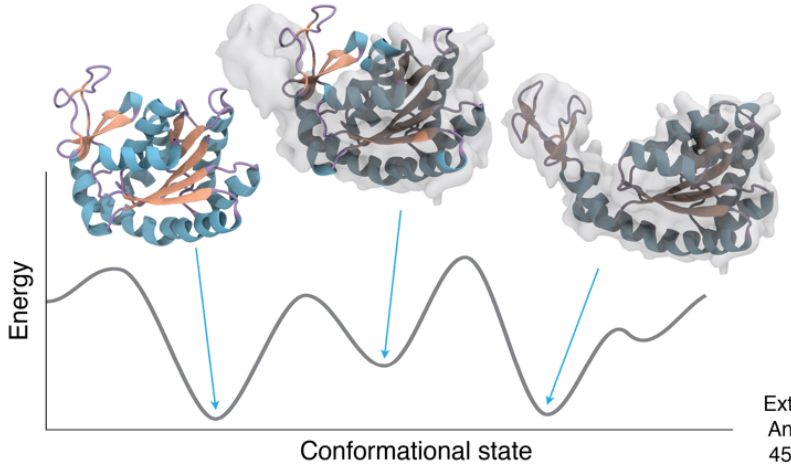
Steered MD



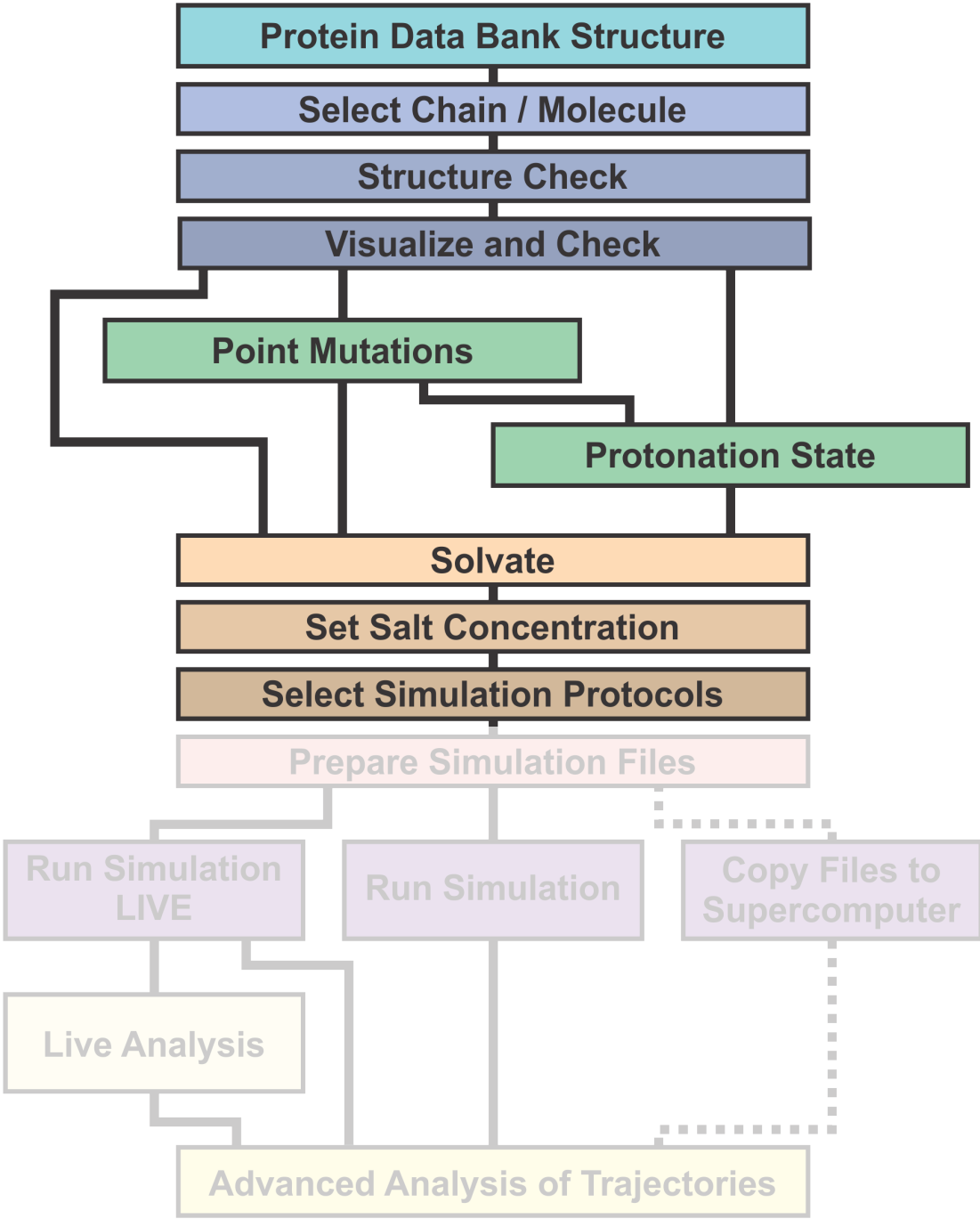
QM/MM *(New)*



Molecular Dynamics Flexible Fitting (MDFF)



Extracted from Goh BC, *et al.* Annu. Rev. Biophys. 2016. 45:253–78



Rafael C. Bernardi
rcbernardi@auburn.edu

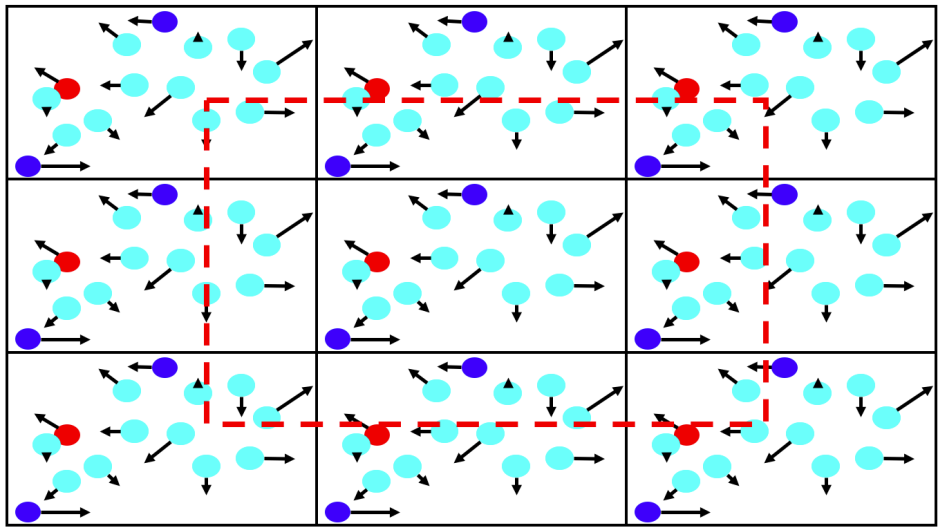
JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

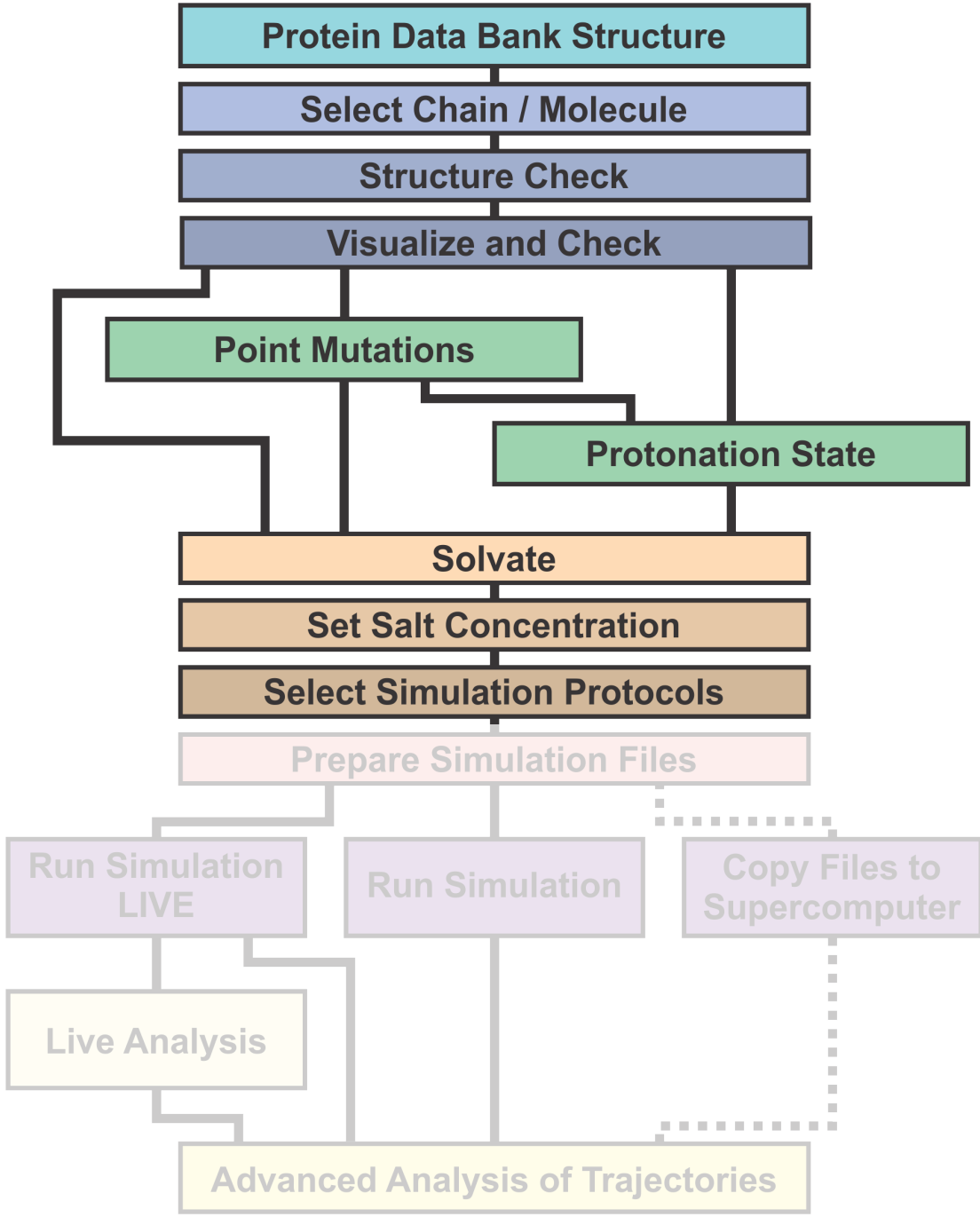
QwikMD: step-by-step

Molecular Dynamics Ensembles

- Constant energy, constant volume (NVE)
- Constant temperature, constant volume (NVT)
- Constant temperature, constant pressure (NPT)

Periodic Boundary Conditions





Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

All files are prepared in a stand-alone folder

The NAMD Configuration File:

Files needed:

```
structure          mypsf.psf
coordinates        mypdb.pdb
```

Define temperature

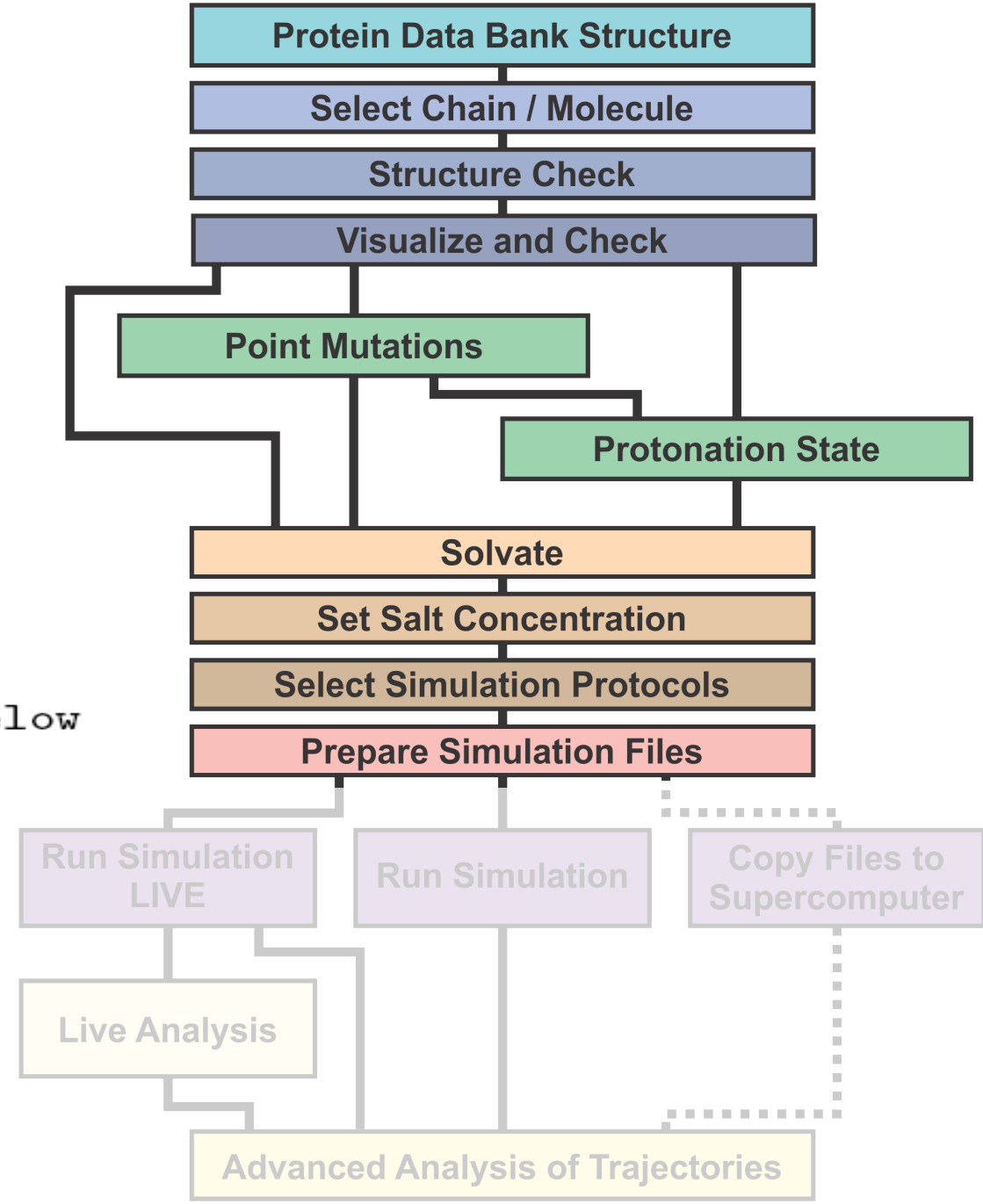
```
set temperature    310
  ;# target temperature used several times below
```

Starting simulation with random velocities

```
# starting from scratch
temperature         $temperature

        ;# initialize velocities randomly
```

...

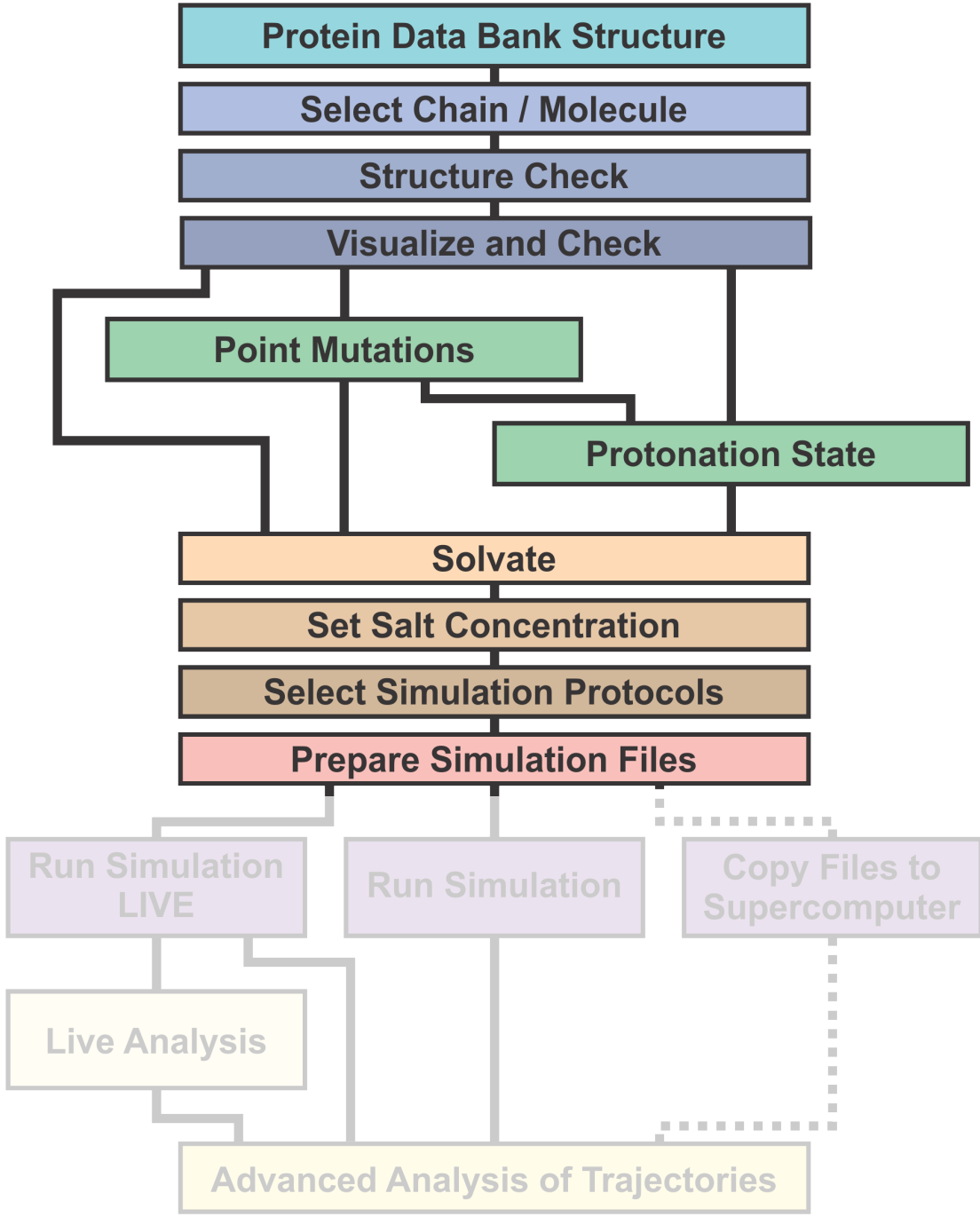


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

Everything that was done is saved in 2 log files



Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

Select: Easy Run or Advanced Run Analysis Tools can also be selected

Browse for a PDB file or type PDB code

In the structure manipulation window the QwikMD user can delete molecules or parts of a protein sequence; perform point mutations; change protonation states; check the structure; insert membrane model (Advanced mode only)

For structures solved by NMR, select the conformational state

Select the chains and type of molecule to be included in the simulation

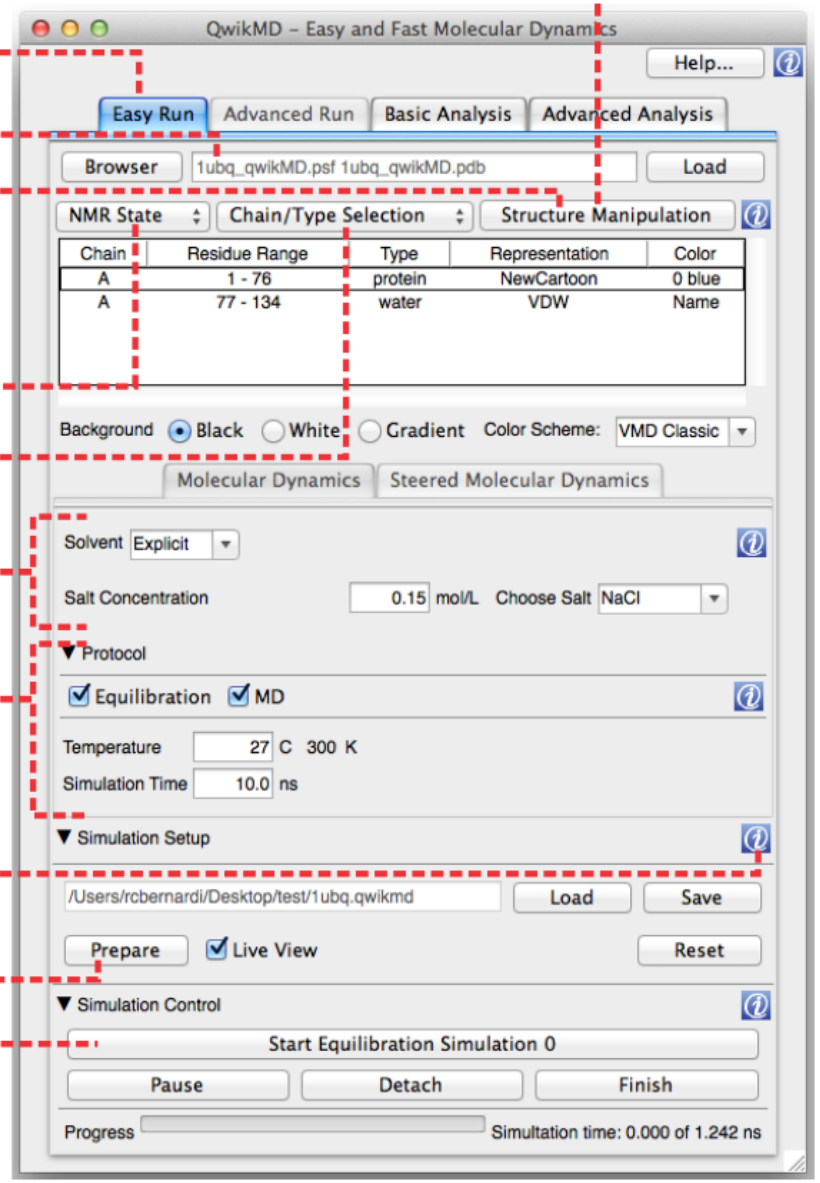
Select the environment: implicit or explicit solvent, and salt concentration

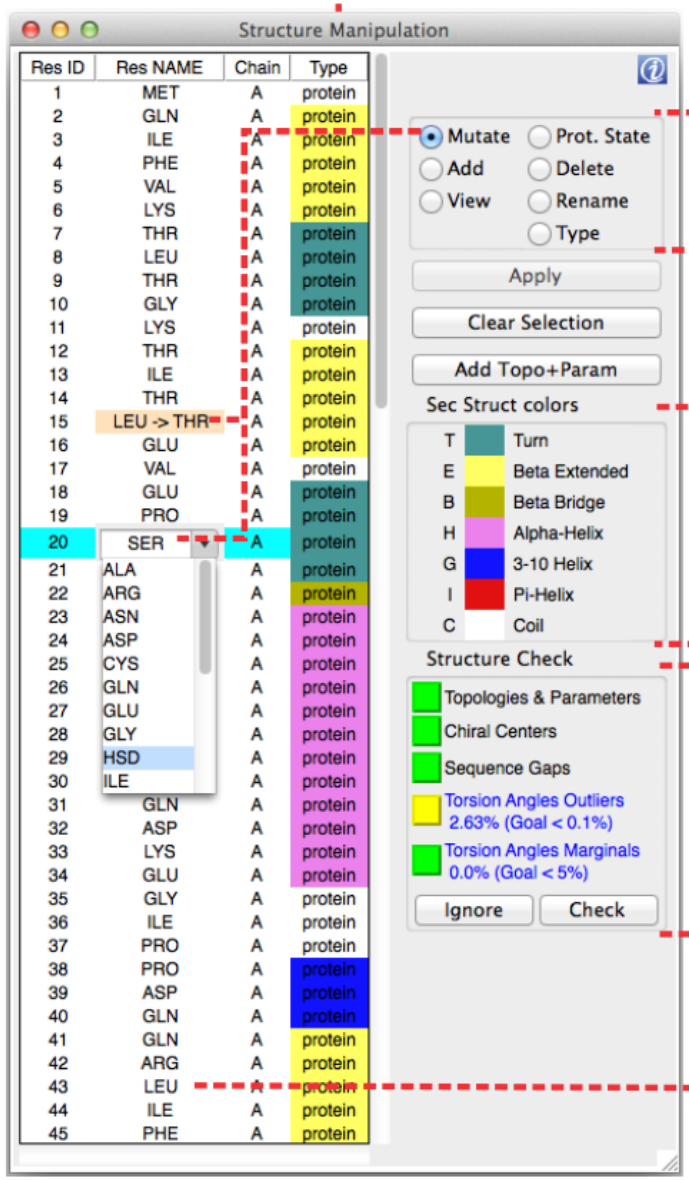
In the Protocol section the user selects temperature and duration of the simulation and also if an equilibration will be performed

"Info Buttons" provide the user with a variety of information, from protocols to a guidance on how to perform simulations and how to check results

When "Prepare" is clicked, QwikMD will invoke several scripts to perform all the operations set before, such as mutations, solvation, ...

Starts the simulation, either in "Live View" mode (if selected) or in "Background"





QwikMD user can easily perform point mutations. To do so, select "Mutate" and click on the amino acid from the sequence amino acid table. A list of all possible mutations will allow the user to select the desired mutation.

The list of amino acid in the protein sequence is colored according to the secondary structure.

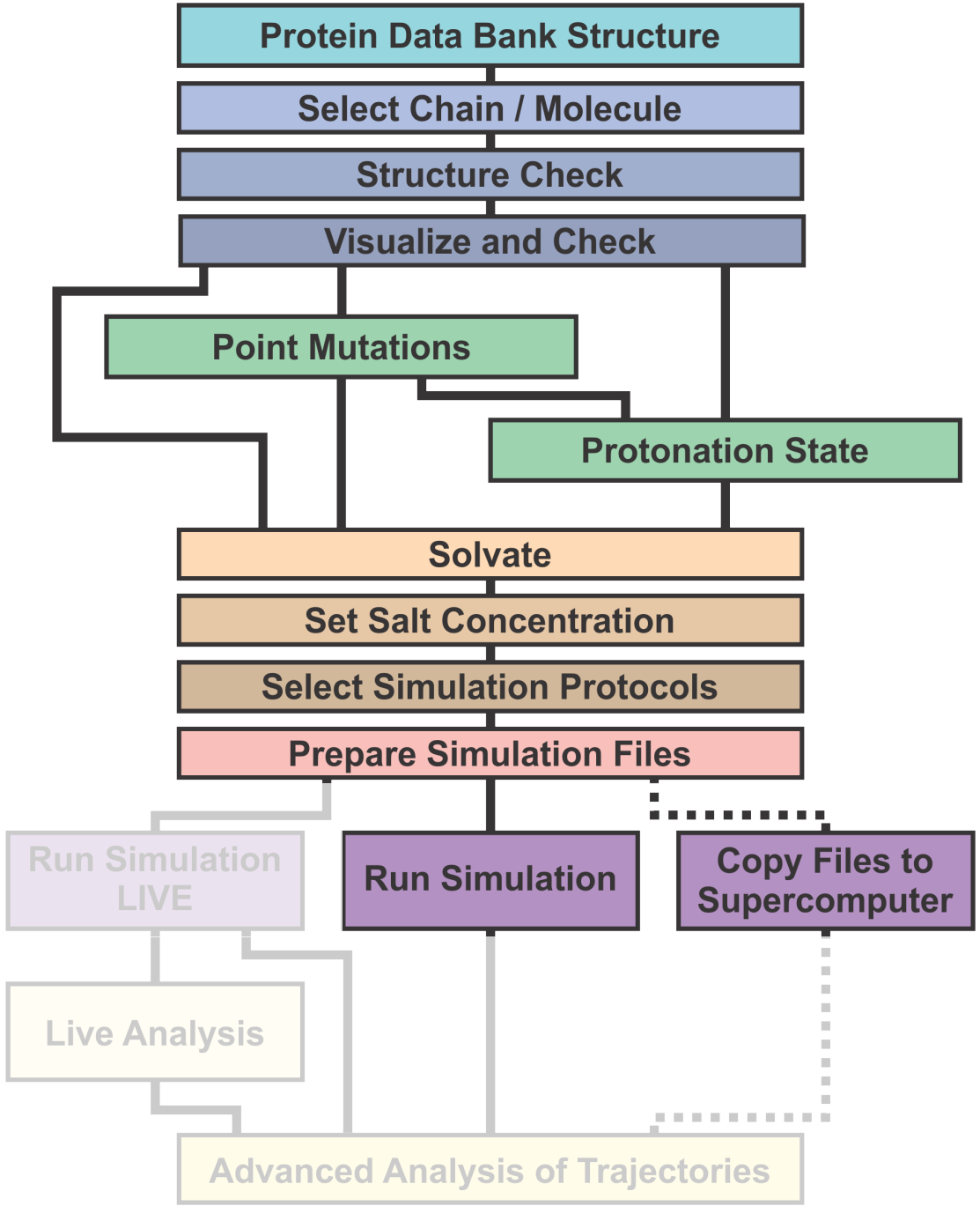
An automated check of the structure is performed when a PDB is loaded by QwikMD. If problems arise they will be marked in the "Structure Check" Tab. The user will be guided on how to fix the problems found.

All molecules of the system are presented in a list an can be separated by *type* or *chain*. The QwikMD user can easily delete parts of structure, change protonation states, perform point mutations, among other actions.

Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

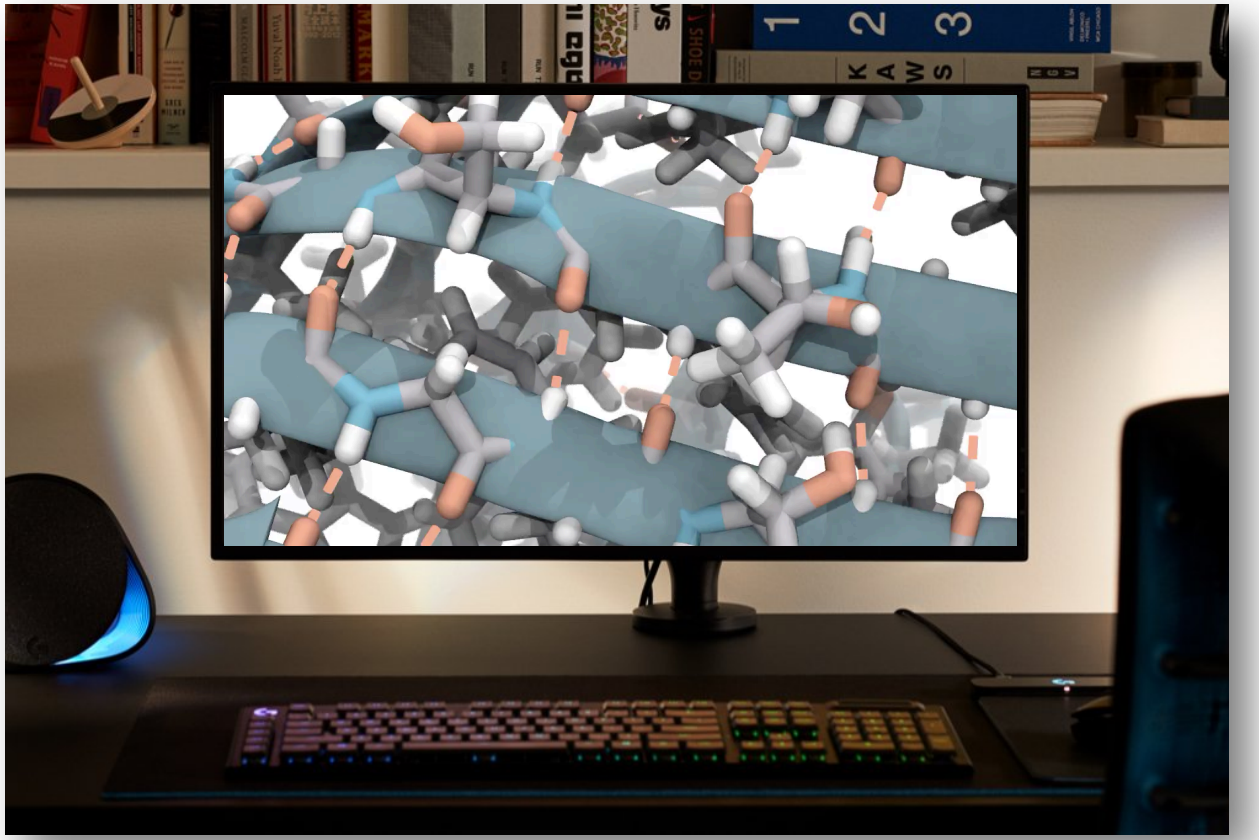
QwikMD: step-by-step

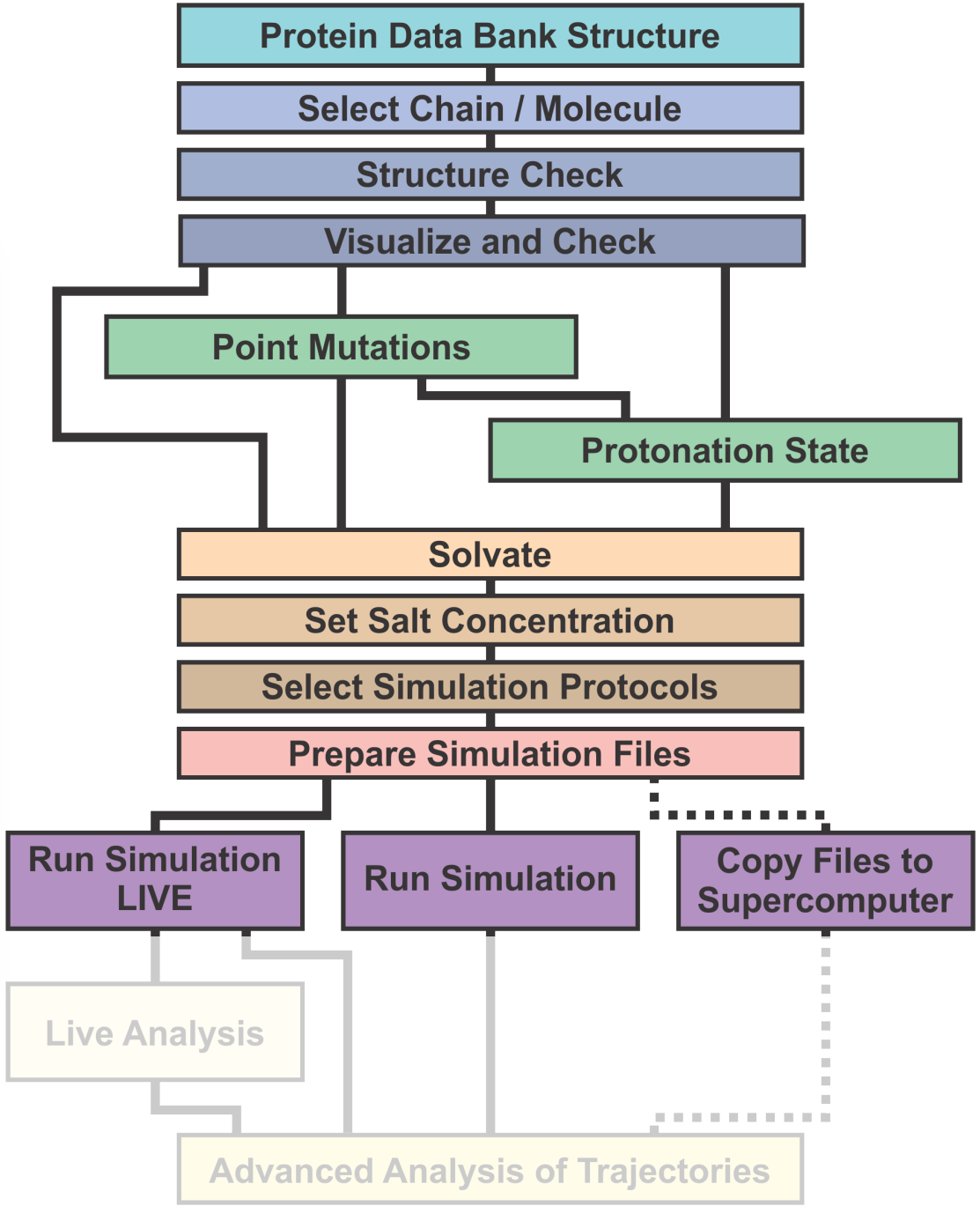


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

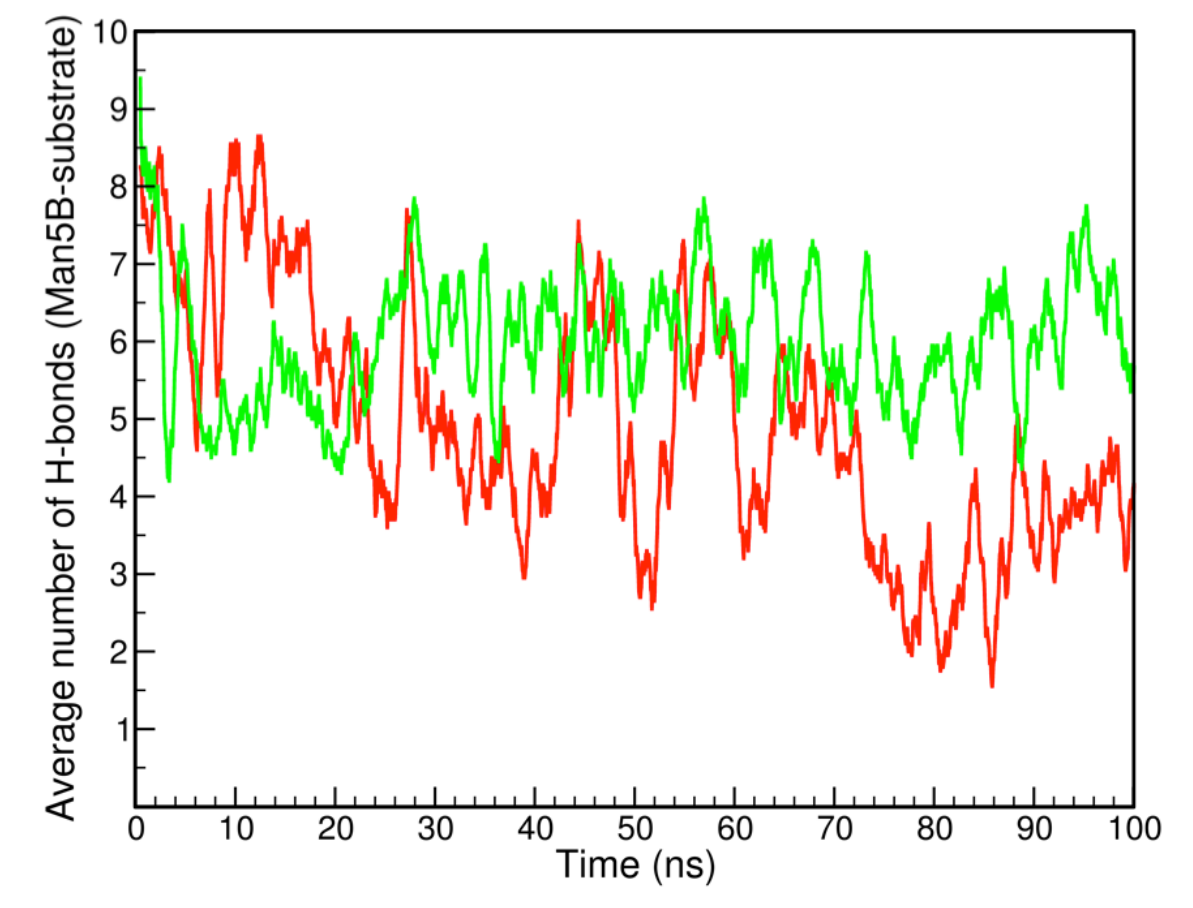


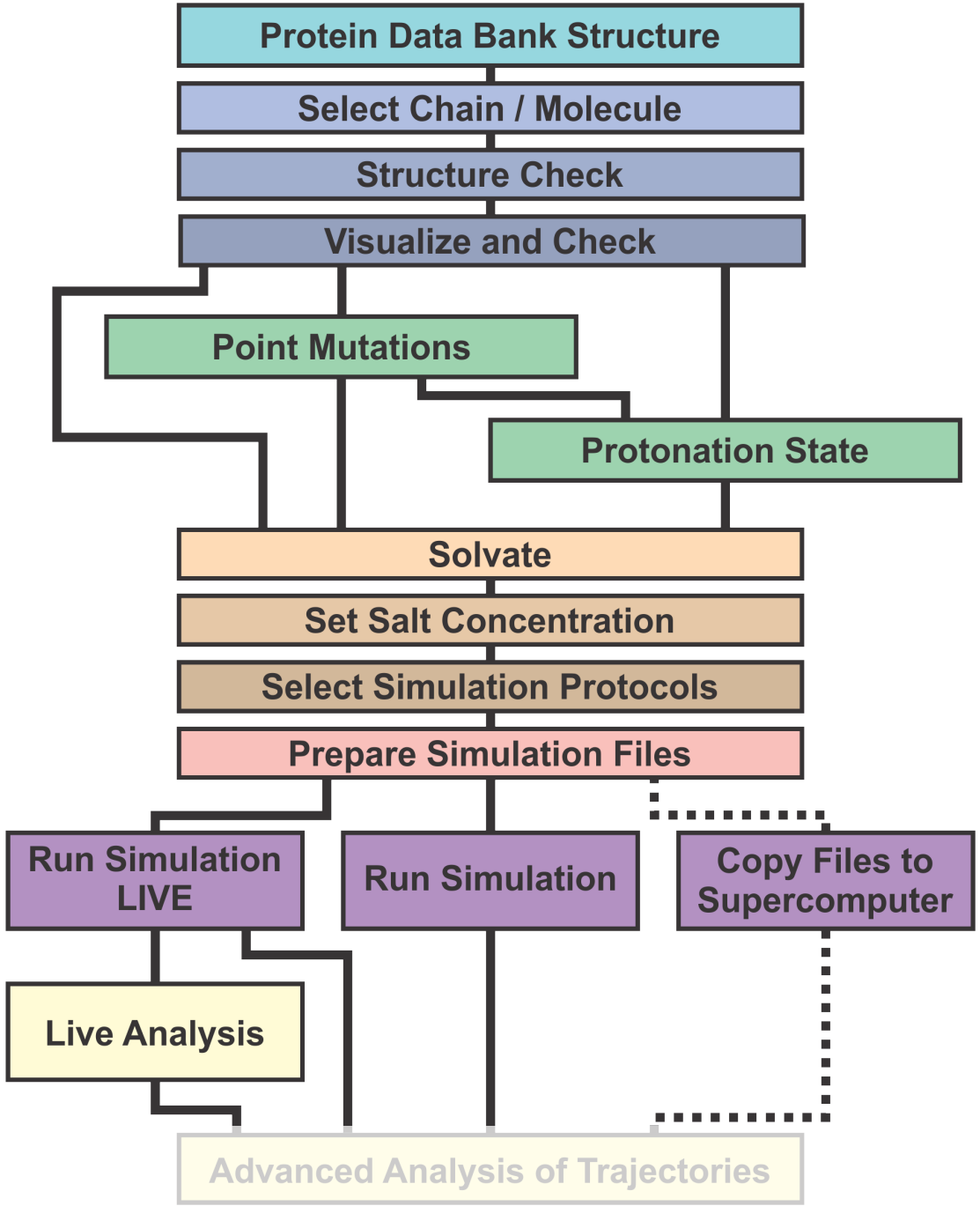


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

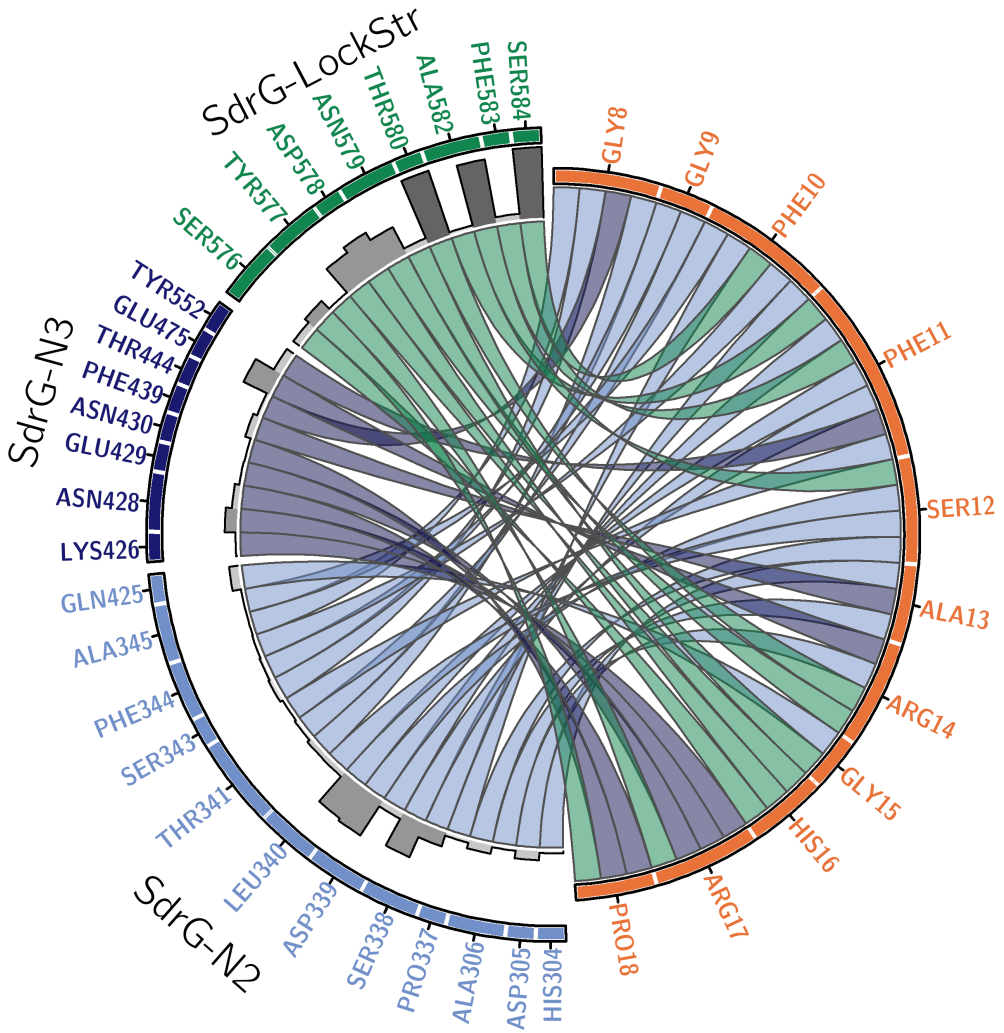


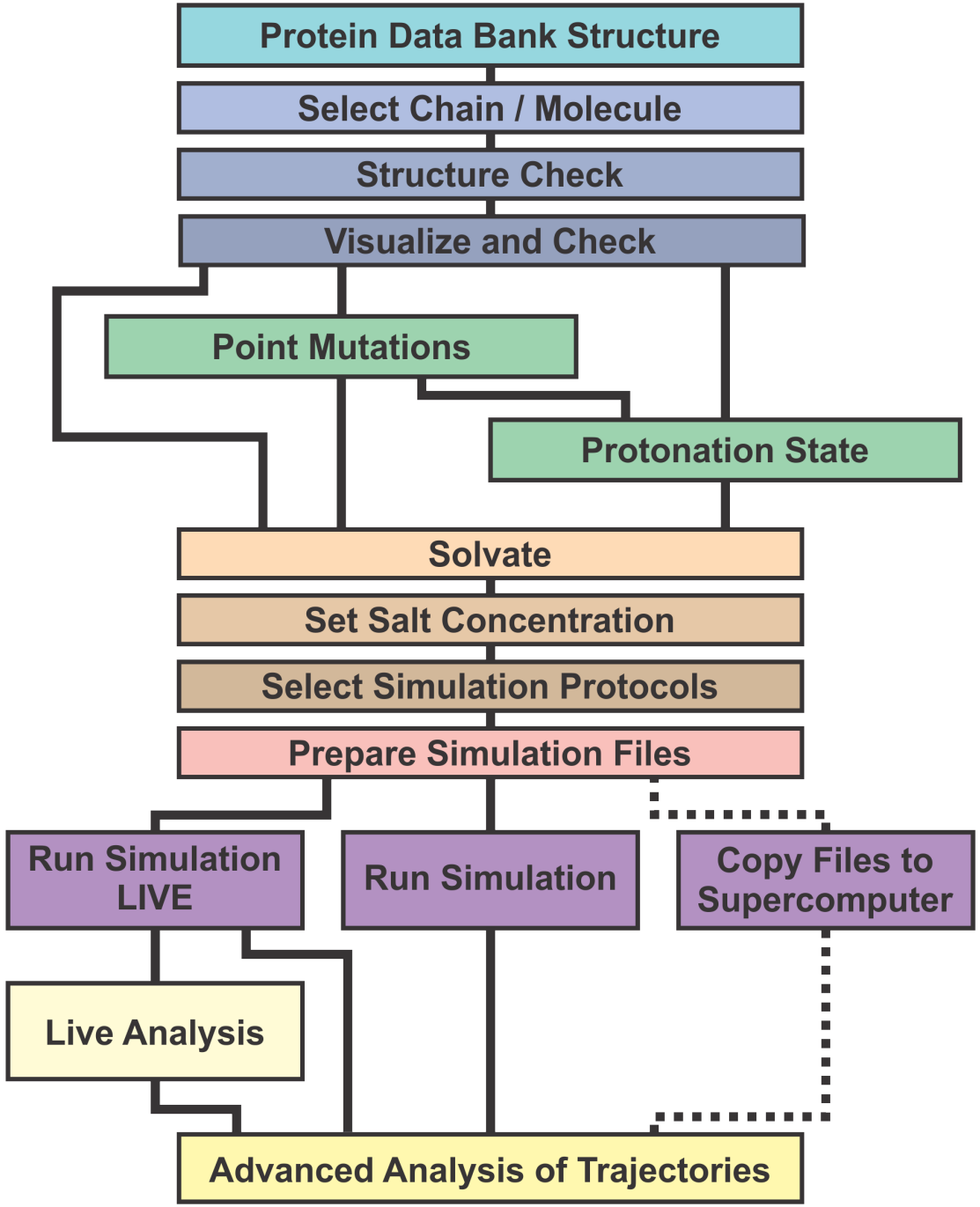


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step

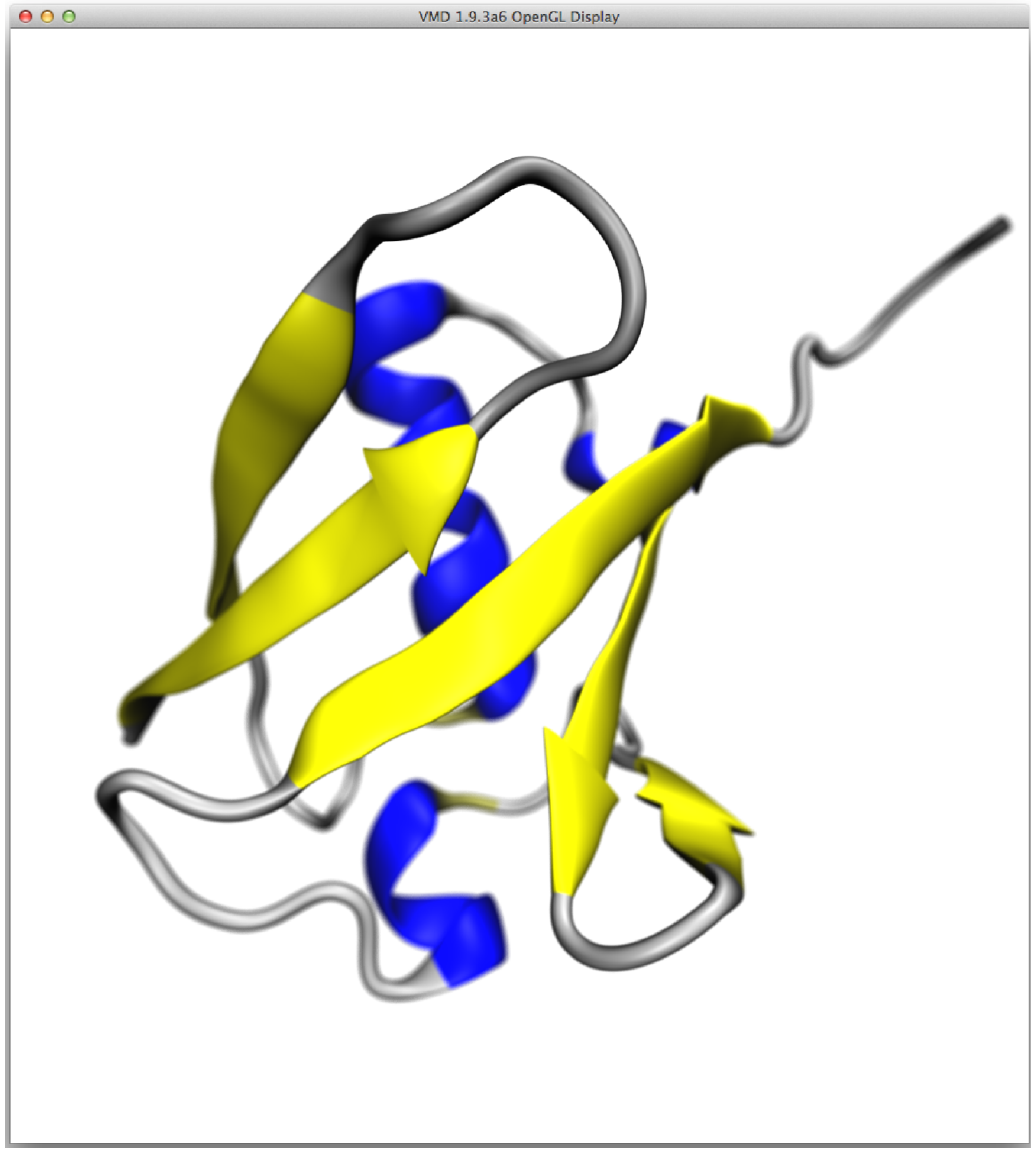


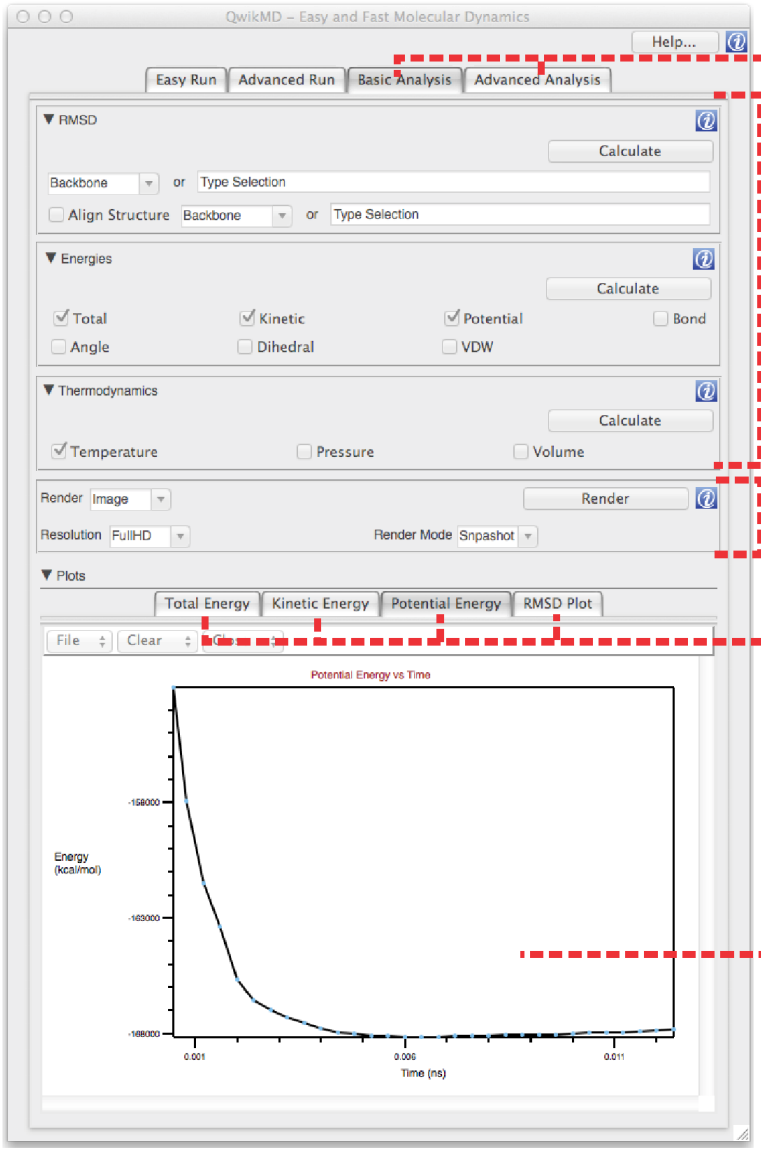


Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

QwikMD: step-by-step





QwikMD users can select between: (1) "Basic Analysis", which include most common analysis methods used to check how stable is the structure in the simulation; or (2) "Advanced Analysis", which includes several of the most used analysis tools in VMD, i.e., Hydrogen Bond count, and Solvent Accessible Surface Area (SASA).

Here the user can select the analysis to be performed when "Calculate" is clicked.

VMD is known for its structure image rendering capabilities. In QwikMD a quick-render tab allows for a fast high-quality rendering, employing the most used settings for shadows, colors, materials, ...

Multiple analysis can be performed at the same time. The resulting plots will be presented in different tabs.

In a simulation on *live view* mode the plot will be updated while the simulation is performed

Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

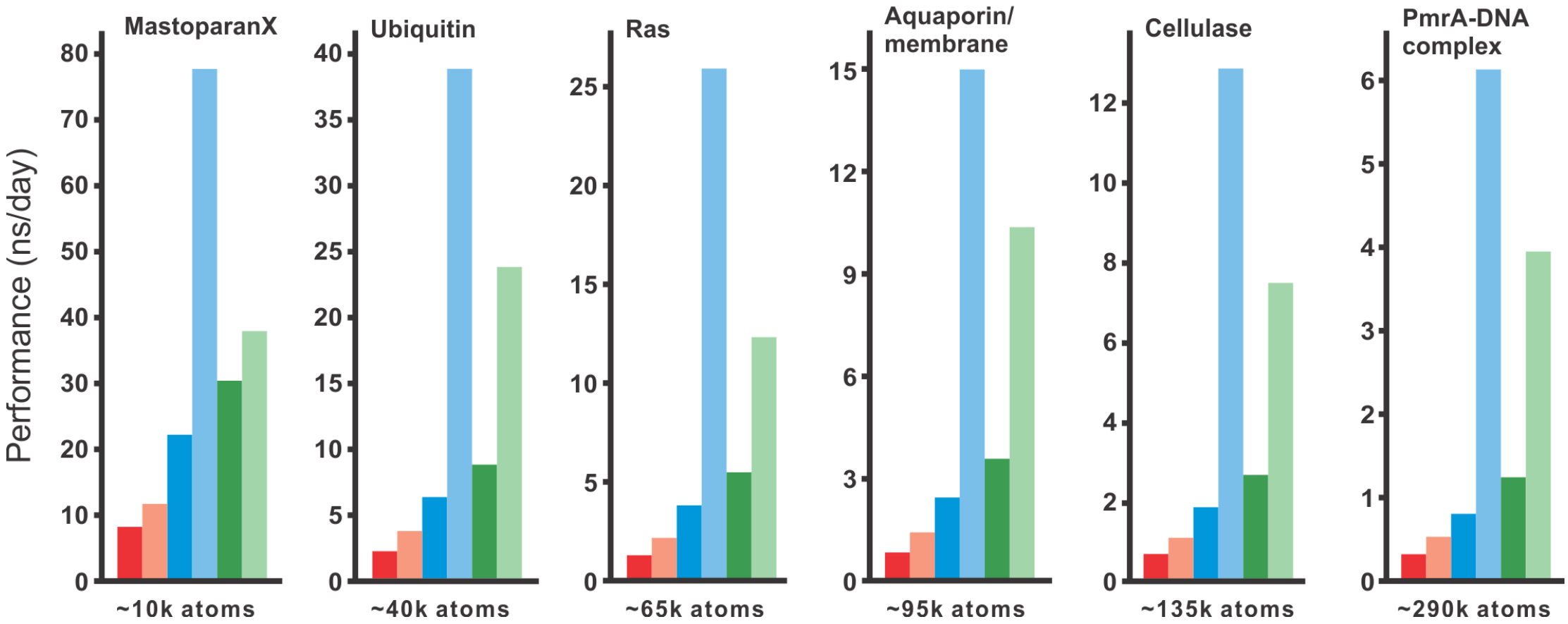
How much can I do with a Desktop computer?

CPU + GPU / CPU — **Laptop:** MacBook Pro (Late 2013 model) - Intel Core-i7 2.3 Ghz (4 CPU cores) - 16GB RAM - NVIDIA GeForce GT 750M

CPU + GPU / CPU — **Desktop:** Dual Intel E5-2650v2 2.6 Ghz (8 CPU cores each) - 64GB RAM - NVIDIA GeForce GTX Titan X

CPU + GPU / CPU — **Cloud:** G2.8 instance of the Amazon Elastic Compute Cloud
Cloud: C4.8 instance of the Amazon Elastic Compute Cloud

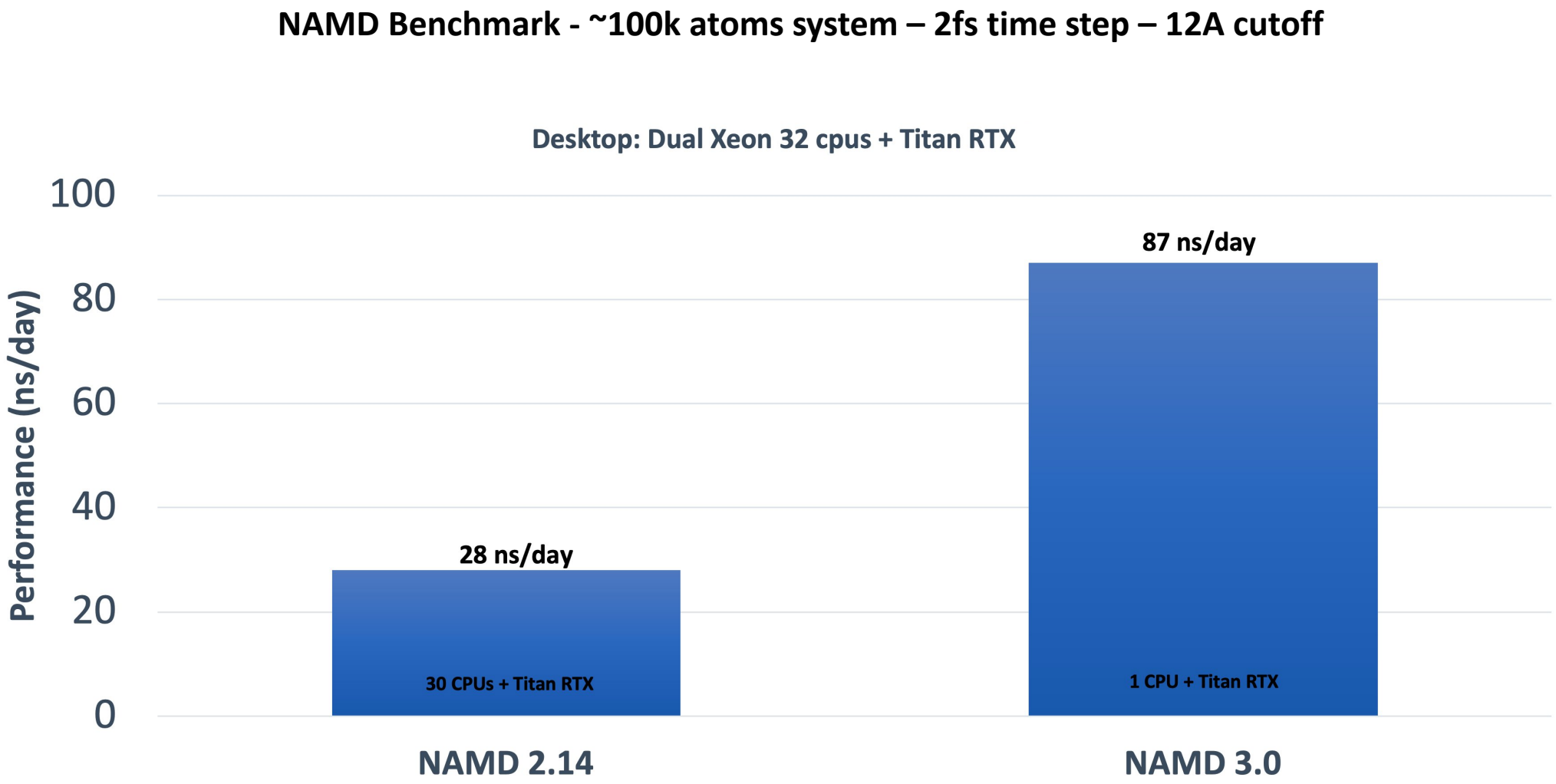
OLD BENCHMARKS



Rafael C. Bernardi
rcbernardi@auburn.edu

JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

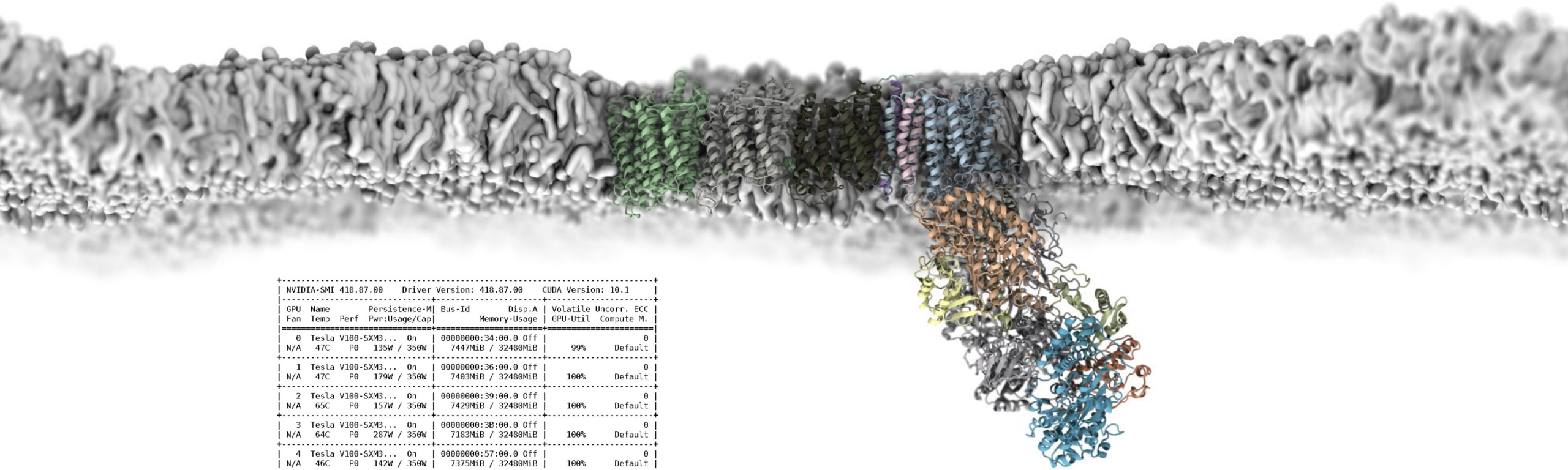
How much can I do with a Desktop computer?



Rafael C. Bernardi
rcbernardi@auburn.edu

JC Phillips, D Hardy, JDC Maia, JE Stone, JV Ribeiro, RC Bernardi, et al.; **Scalable Molecular Dynamics on CPU and GPU Architectures with NAMD**. JCP, 2020

DGX-2



```
+-----------------------------------------------------------------------------+
| NVIDIA-SMI 418.87.00    Driver Version: 418.87.00    CUDA Version: 10.1     |
|-------------------------------+----------------------+----------------------+
| GPU  Name        Persistence-M| Bus-Id        Disp.A | Volatile Uncorr. ECC |
| Fan  Temp  Perf  Pwr:Usage/Cap|         Memory-Usage | GPU-Util  Compute M. |
|===============================+======================+======================|
|   0  Tesla V100-SXM3...  On   | 00000000:34:00.0 Off |                    0 |
| N/A   47C    P0   135W / 350W |   7447MiB / 32480MiB |     99%      Default |
+-------------------------------+----------------------+----------------------+
|   1  Tesla V100-SXM3...  On   | 00000000:36:00.0 Off |                    0 |
| N/A   47C    P0   179W / 350W |   7403MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|   2  Tesla V100-SXM3...  On   | 00000000:39:00.0 Off |                    0 |
| N/A   65C    P0   157W / 350W |   7429MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|   3  Tesla V100-SXM3...  On   | 00000000:3B:00.0 Off |                    0 |
| N/A   64C    P0   287W / 350W |   7183MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|   4  Tesla V100-SXM3...  On   | 00000000:57:00.0 Off |                    0 |
| N/A   46C    P0   142W / 350W |   7375MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|   5  Tesla V100-SXM3...  On   | 00000000:59:00.0 Off |                    0 |
| N/A   63C    P0   179W / 350W |   7409MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|   6  Tesla V100-SXM3...  On   | 00000000:5C:00.0 Off |                    0 |
| N/A   47C    P0   151W / 350W |   7365MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|   7  Tesla V100-SXM3...  On   | 00000000:5E:00.0 Off |                    0 |
| N/A   62C    P0   167W / 350W |   7391MiB / 32480MiB |     99%      Default |
+-------------------------------+----------------------+----------------------+
|   8  Tesla V100-SXM3...  On   | 00000000:B7:00.0 Off |                    0 |
| N/A   47C    P0   169W / 350W |   7423MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|   9  Tesla V100-SXM3...  On   | 00000000:B9:00.0 Off |                    0 |
| N/A   47C    P0   186W / 350W |   7297MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|  10  Tesla V100-SXM3...  On   | 00000000:BC:00.0 Off |                    0 |
| N/A   60C    P0   189W / 350W |   7343MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|  11  Tesla V100-SXM3...  On   | 00000000:BE:00.0 Off |                    0 |
| N/A   62C    P0   167W / 350W |   7465MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|  12  Tesla V100-SXM3...  On   | 00000000:E0:00.0 Off |                    0 |
| N/A   45C    P0   157W / 350W |   7485MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|  13  Tesla V100-SXM3...  On   | 00000000:E2:00.0 Off |                    0 |
| N/A   47C    P0   183W / 350W |   7481MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|  14  Tesla V100-SXM3...  On   | 00000000:E5:00.0 Off |                    0 |
| N/A   59C    P0   131W / 350W |   7487MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
|  15  Tesla V100-SXM3...  On   | 00000000:E7:00.0 Off |                    0 |
| N/A   60C    P0   185W / 350W |   7495MiB / 32480MiB |    100%      Default |
+-------------------------------+----------------------+----------------------+
```

NAMD3 on the NVIDIA DGX-2

2.5 M atoms transmembrane complex

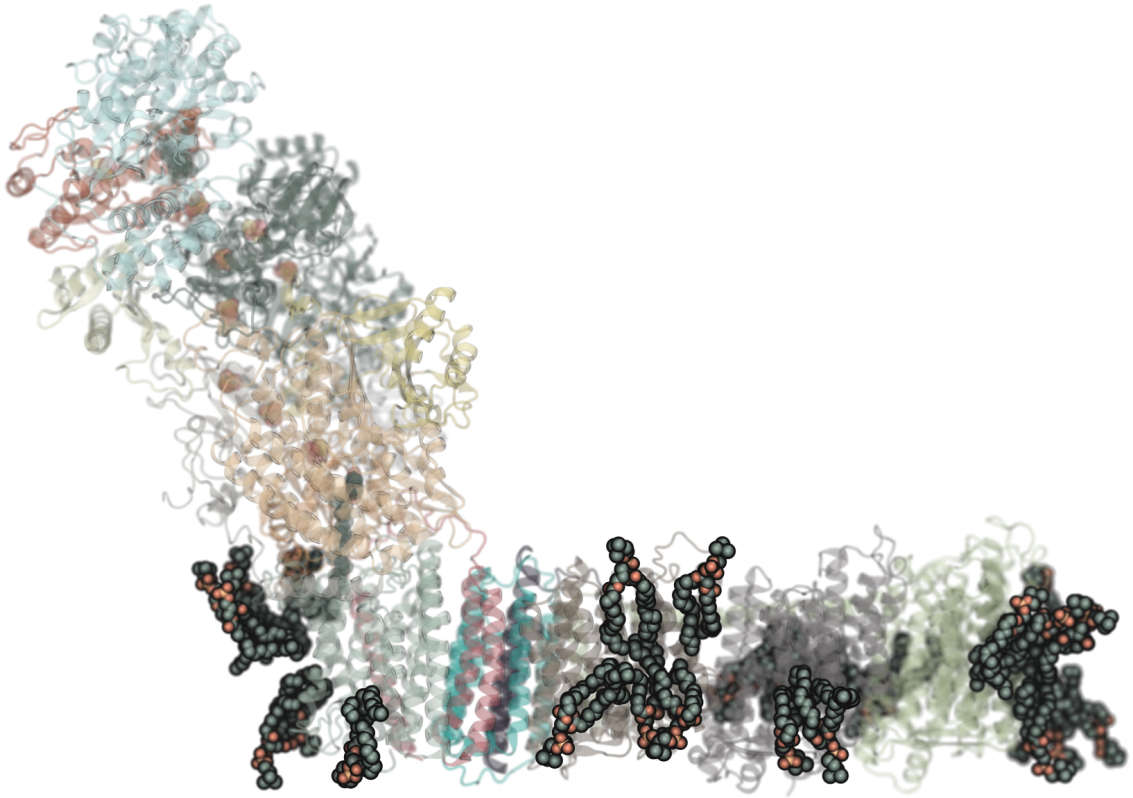
up to 130 ns/day with a 4fs timestep

Rafael C. Bernardi
rcbernardi@auburn.edu

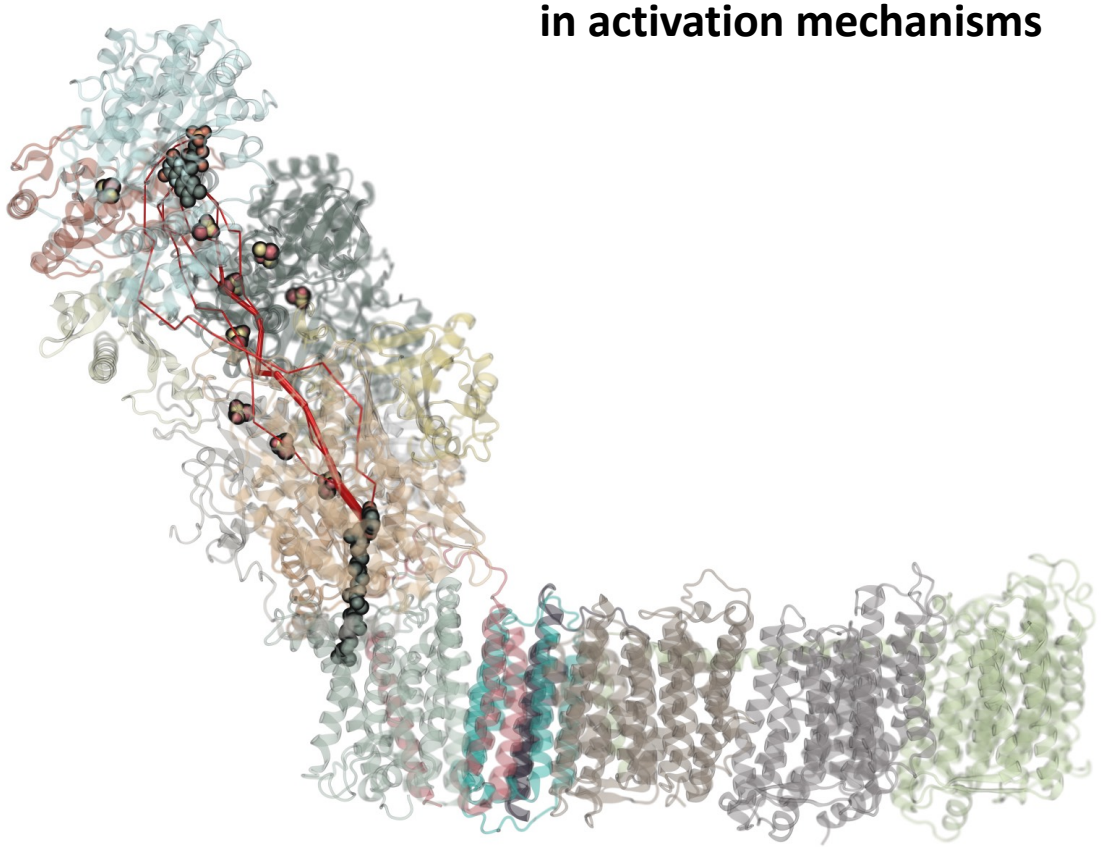
JC Phillips, D Hardy, JDC Maia, JE Stone, JV Ribeiro, RC Bernardi, et al.; **Scalable Molecular Dynamics on CPU and GPU Architectures with NAMD**. JCP, 2020

Why do I want all this computational power?

Study the stability of lipid/protein interaction



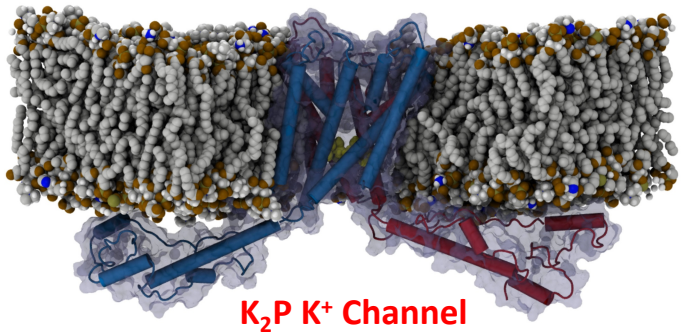
Study allosteric communication in activation mechanisms

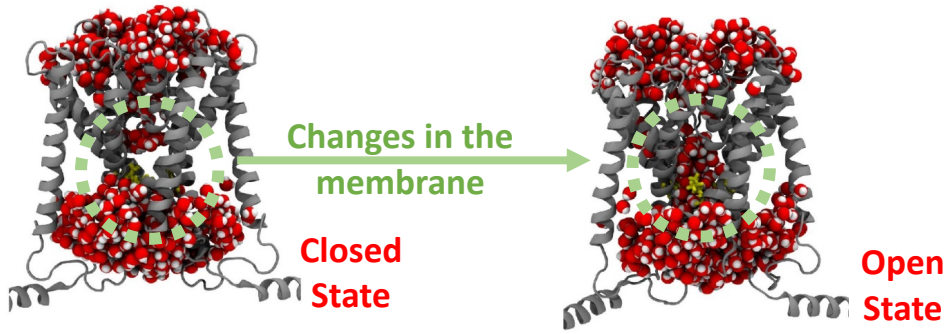


MCR Melo, RC Bernardi, et al.; **Generalized correlation-based dynamical network analysis: a new high-performance approach for identifying allosteric communications in molecular dynamics trajectories**. JCP, 2020

Why do I want all this computational power?

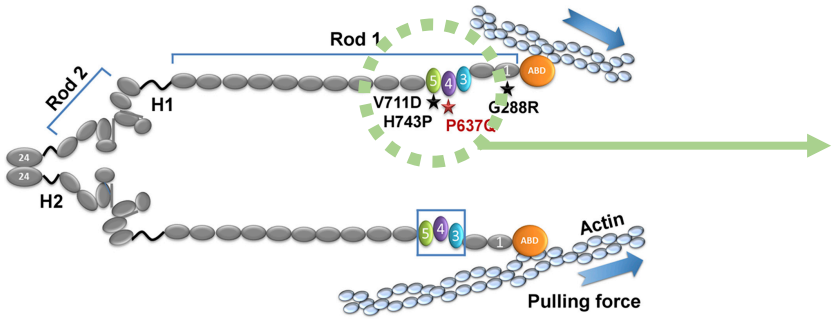
- **Mechanosensing activates signal transduction in neurons;**

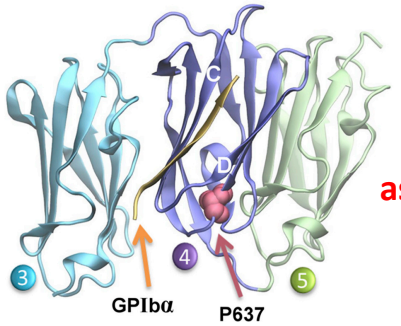




PhD Work
RC Bernardi, et. al.; Molecular Physics, 2009
RC Bernardi & PG Pascutti; JCTC, 2012

- **Mechanical stress alters Filamin affinity to molecules in the cytoplasm;**

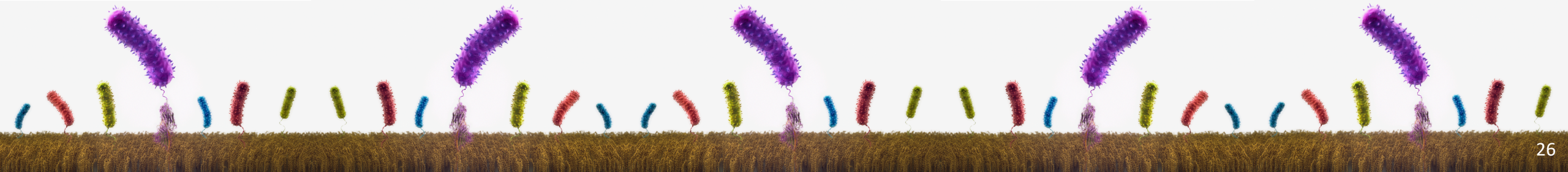




Mutations in Filamins are associated with genetic diseases

Collaboration with Ulla Pentikäinen
University of Jyväskylä, Finland
J Seppälä & RC Bernardi, et. al.; Scientific Reports, 2017
TJK Haataja & RC Bernardi, et. al.; Structure, 2019

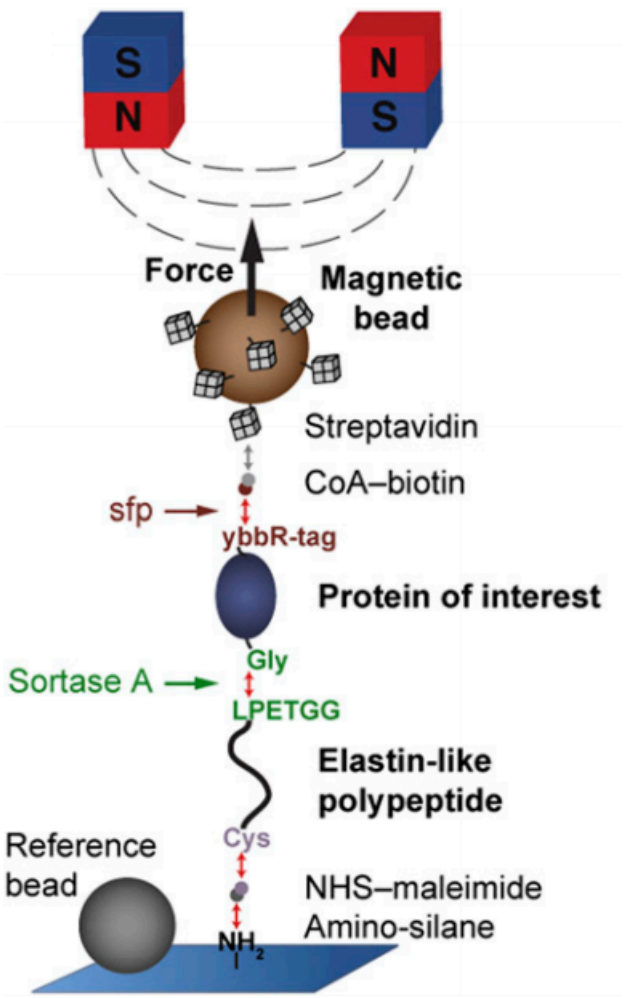
- **Bacteria adhesion is mostly regulated by mechanoactive proteins.**



How do we Measure Force?

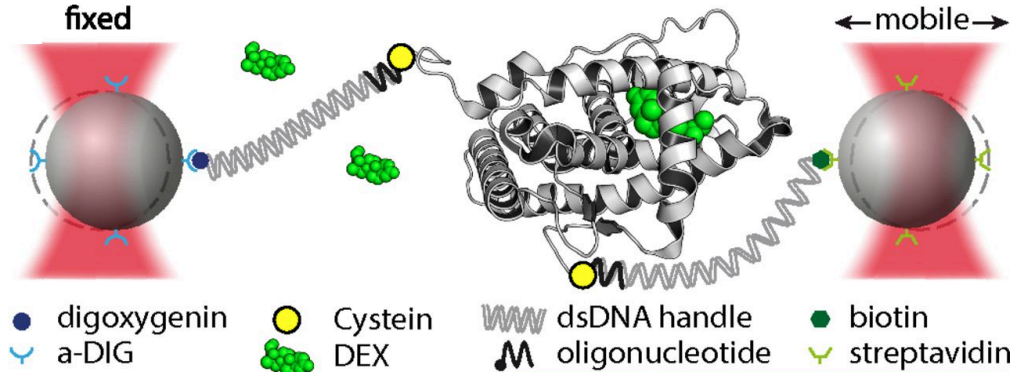
Single-Molecule Force Spectroscopy *in vitro*

Magnetic Tweezers



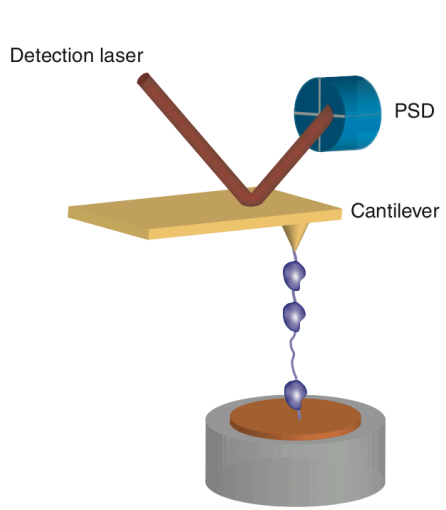
KC Neuman, et. al.; Nature Methdods, 2008
Sarkar, et.al.; Forntiers in Physics, 2016
A Löf, et. al.; PNAS, 2019

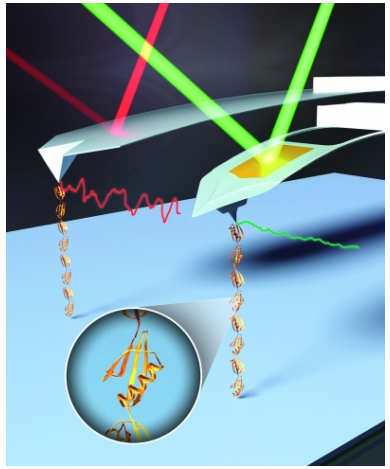
Optical Tweezers



KC Neuman, et. al.; Nature Methods, 2008
T Suren, et. al.; PNAS, 2018

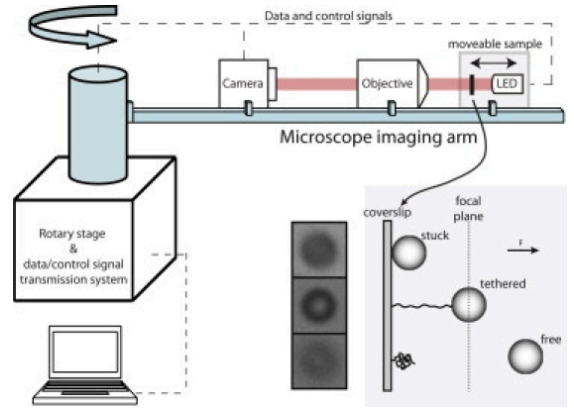
Atomic Force Microscope

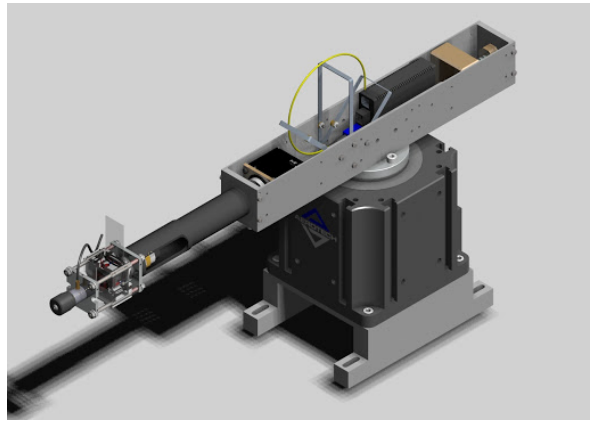




KC Neuman, et. al.; Nature Methods, 2008
MS Bull, et. al.; ACS NANO, 2014

Centrifugal Force Microscope





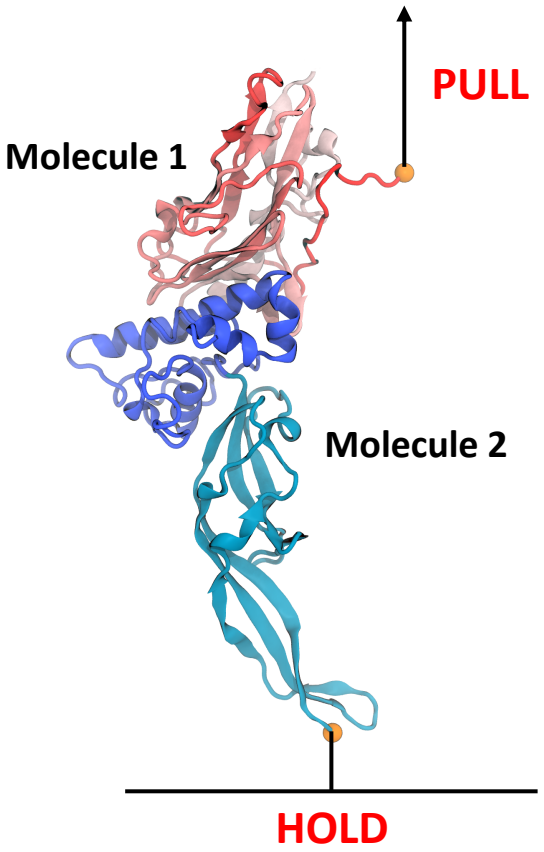
K Halvorsen & WP Wong; Biophysical Journal, 2010
D Yang, et. al.; Nature Communications, 2016

Rafael C. Bernardi
rcbernardi@auburn.edu

Single-Molecule Force Spectroscopy

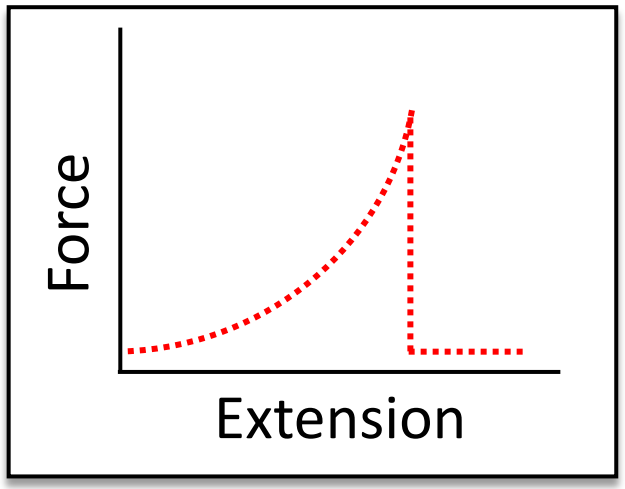
Computational Setup
in silico

Klaus Schulten
Univ. of Illinois



Pulling with a spring (Hooke's Law):

$$F = -k \cdot \Delta x$$



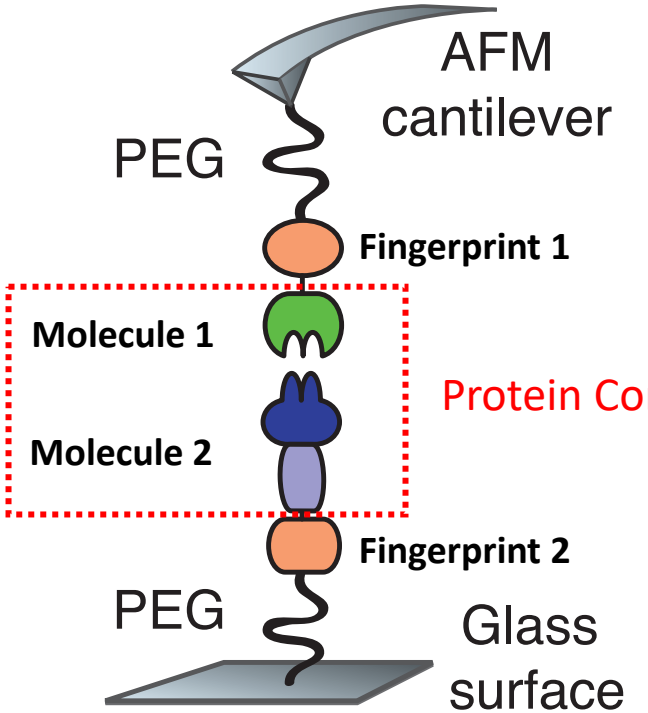
H Grubmüller, et. al.; Science, 1996
S Izrailev, et. al.; Biophysical Jounal, 1997

Experimental Setup
in vitro

Hermann Gaub (LMU)
Michael Nash (U Basel, ETH)

Single-Molecule Force Spectroscopy (SMFS)

- **Atomic Force Microscope**



Atomic Force Microscope (AFM)

Protein Complex of Interest

EL Florin, et. al.; Science, 1994
GU Lee, et. al.; Langmuir, 1994

Rafael C. Bernardi
rcbernardi@auburn.edu

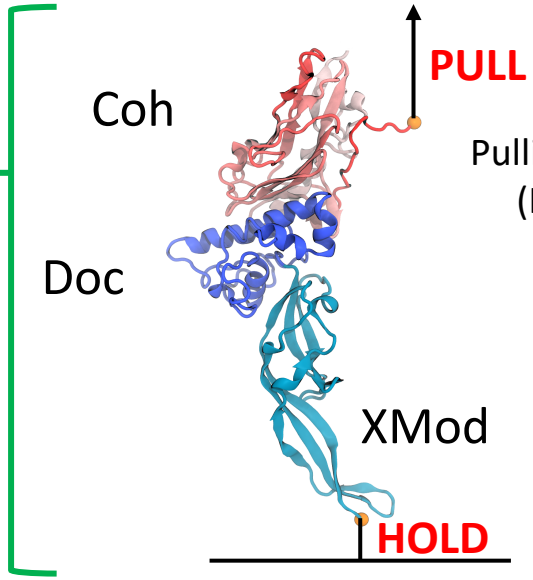
Steered Molecular Dynamics Simulations: *in silico* Single-Molecule Force Spectroscopy

Classical Mechanics (Newton Equations)

$$\vec{F}_i = -dV / d\vec{r}_i \quad \boxed{-k \cdot \Delta x}$$

$$\vec{a}_i = \vec{F}_i / m$$

$$\vec{s}_i = \vec{s}_{0i} + \vec{v}_i t + \frac{1}{2}\vec{a}_i t^2$$



Pulling with a spring (Hooke's Law):
$F = -k \cdot \Delta x$

H Grubmüller, et. al.; Science, 1996
S Izrailev, et. al.; Langmuir, 1997

$$V = V_{str} + V_{bend} + V_{tors} + V_{oop} + V_{vdW} + V_{es}$$

$$V_{es,ij} = Q_i Q_j / \varepsilon_r R_{ij}$$

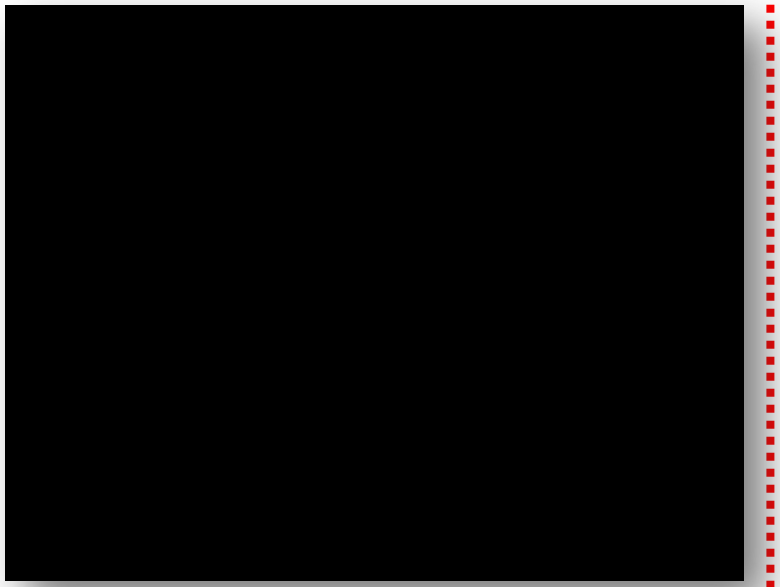
$$V_{vdW,ij} = \varepsilon_{IJ}\left[\left(\frac{R_{IJ}}{R_{ij}}\right)^{12} - 2\left(\frac{R_{IJ}}{R_{ij}}\right)^{6}\right]$$

$$V_{oop} = \frac{1}{2} k_{oop} \omega_{oop}^2$$

$$V_{tors,ijkl} = \frac{1}{2}\left[V_1(1+\cos\varphi) + V_2(1-\cos 2\varphi) + V_3(1+\cos 3\varphi) + \ldots\right]$$

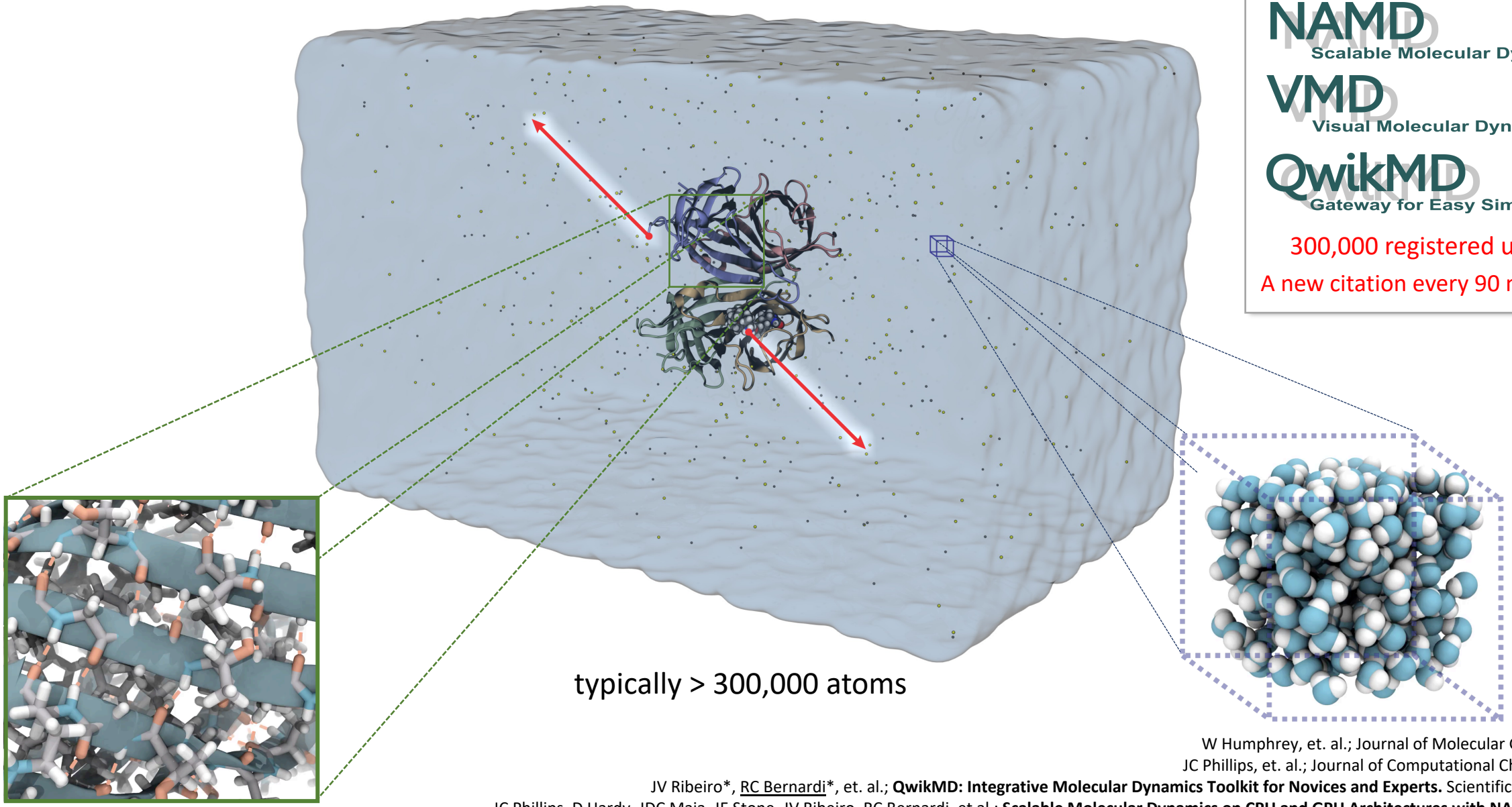
$$V_{bend,ijk} = \frac{1}{2} k_{IJK}\left(\theta_{ij} - \theta^0_{IJK}\right)^2$$

$$V_{str,ij} = \frac{1}{2} k_{IJ}\left(l_{ij} - l^0_{IJ}\right)^2$$



JC Phillips, D Hardy, JDC Maia, JE Stone, JV Ribeiro, RC Bernardi, et al.; **Scalable Molecular Dynamics on CPU and GPU Architectures with NAMD**. JCP, 2020

Steered Molecular Dynamics Simulations: *in silico* Single-Molecule Force Spectroscopy



typically > 300,000 atoms

NAMD
Scalable Molecular Dynamics

VMD
Visual Molecular Dynamics

QwikMD
Gateway for Easy Simulation

300,000 registered users;

A new citation every 90 minutes.

W Humphrey, et. al.; Journal of Molecular Graphics, 1996

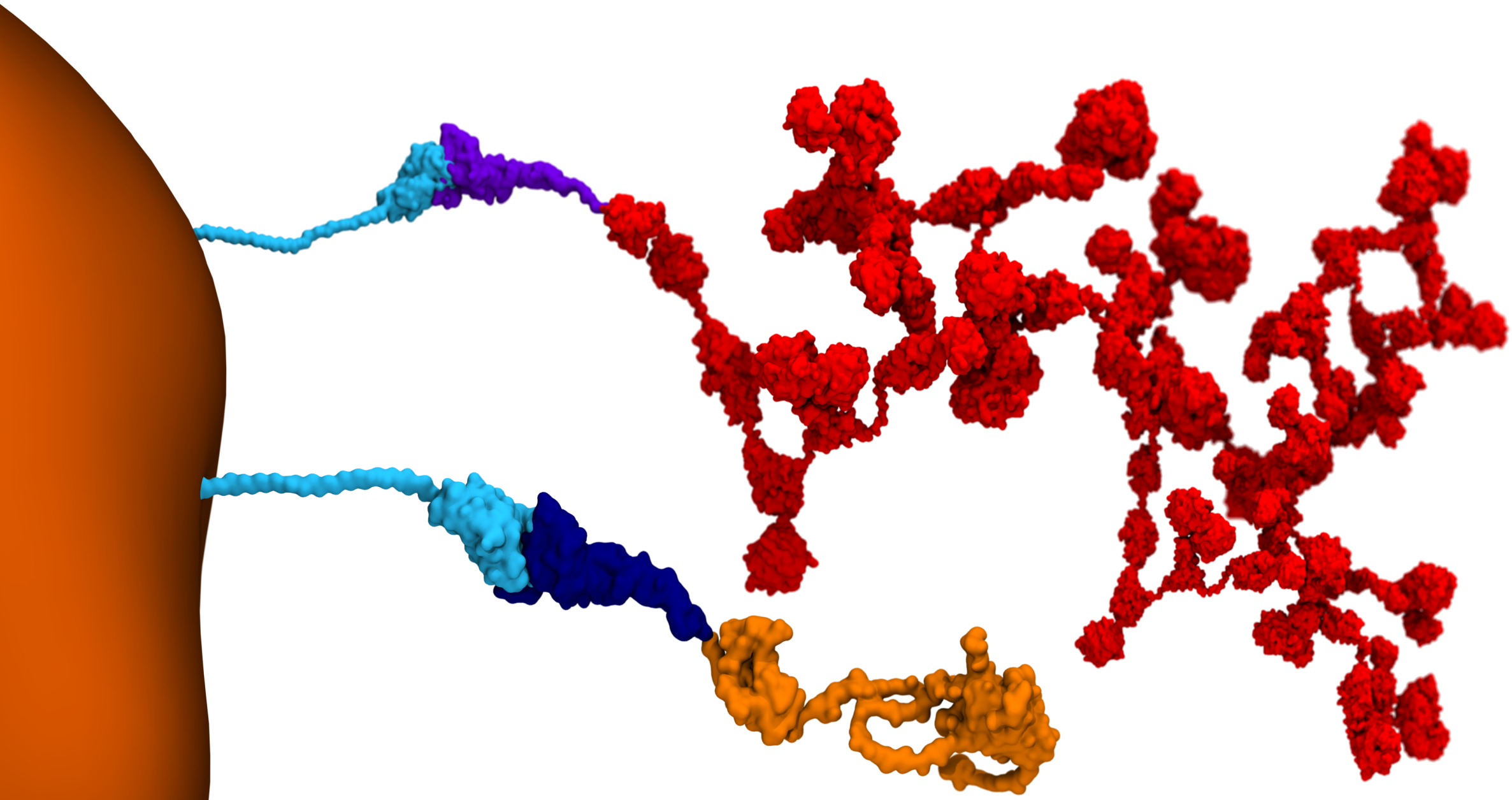
JC Phillips, et. al.; Journal of Computational Chemistry, 2005

JV Ribeiro*, RC Bernardi*, et. al.; **QwikMD: Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016

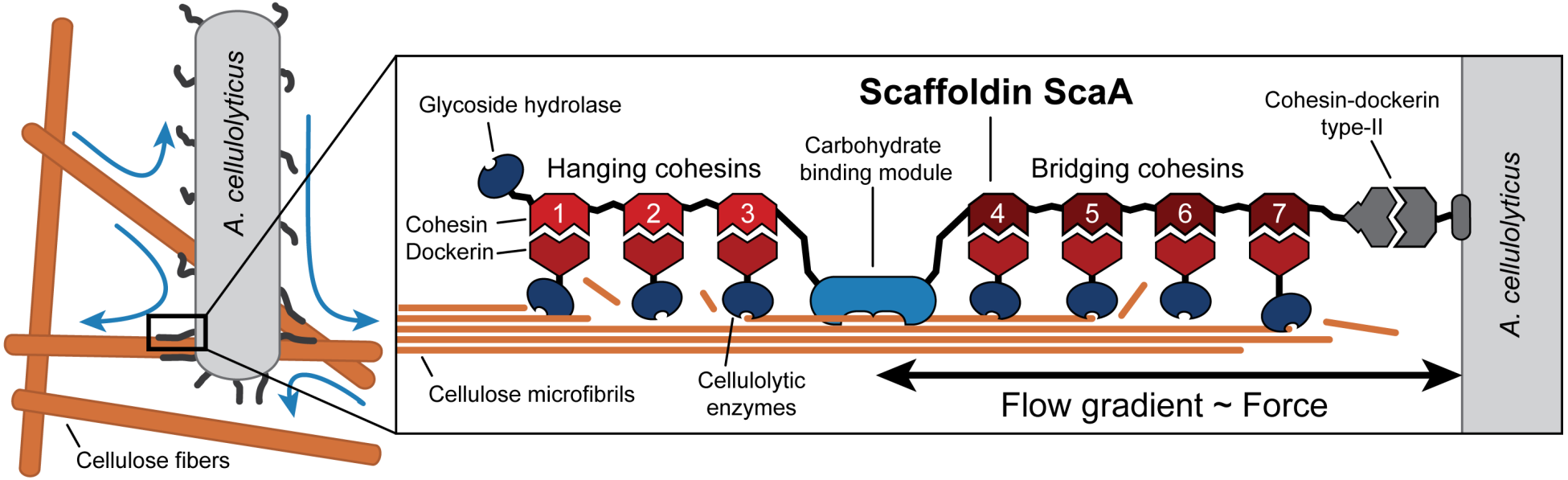
JC Phillips, D Hardy, JDC Maia, JE Stone, JV Ribeiro, RC Bernardi, et al.; **Scalable Molecular Dynamics on CPU and GPU Architectures with NAMD**. JCP, 2020

Rafael C. Bernardi
rcbernardi@auburn.edu

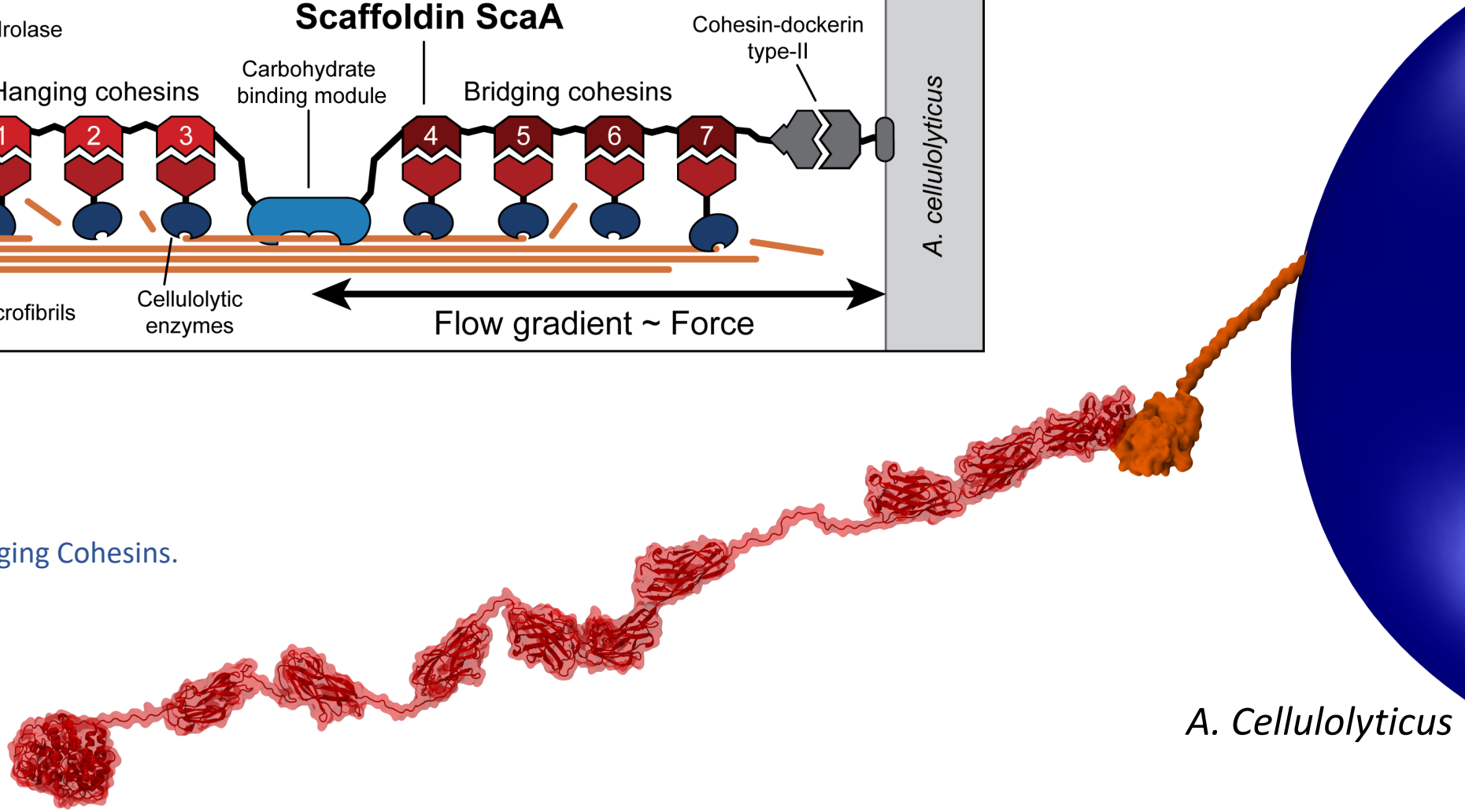
Cellulosomes are formed by cohesin:dockerin interactions



Are the cohesins in a scaffold different?

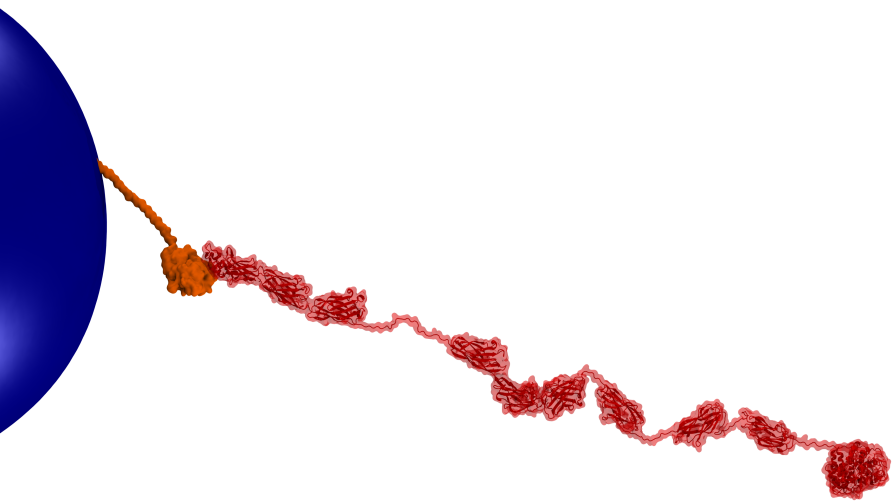


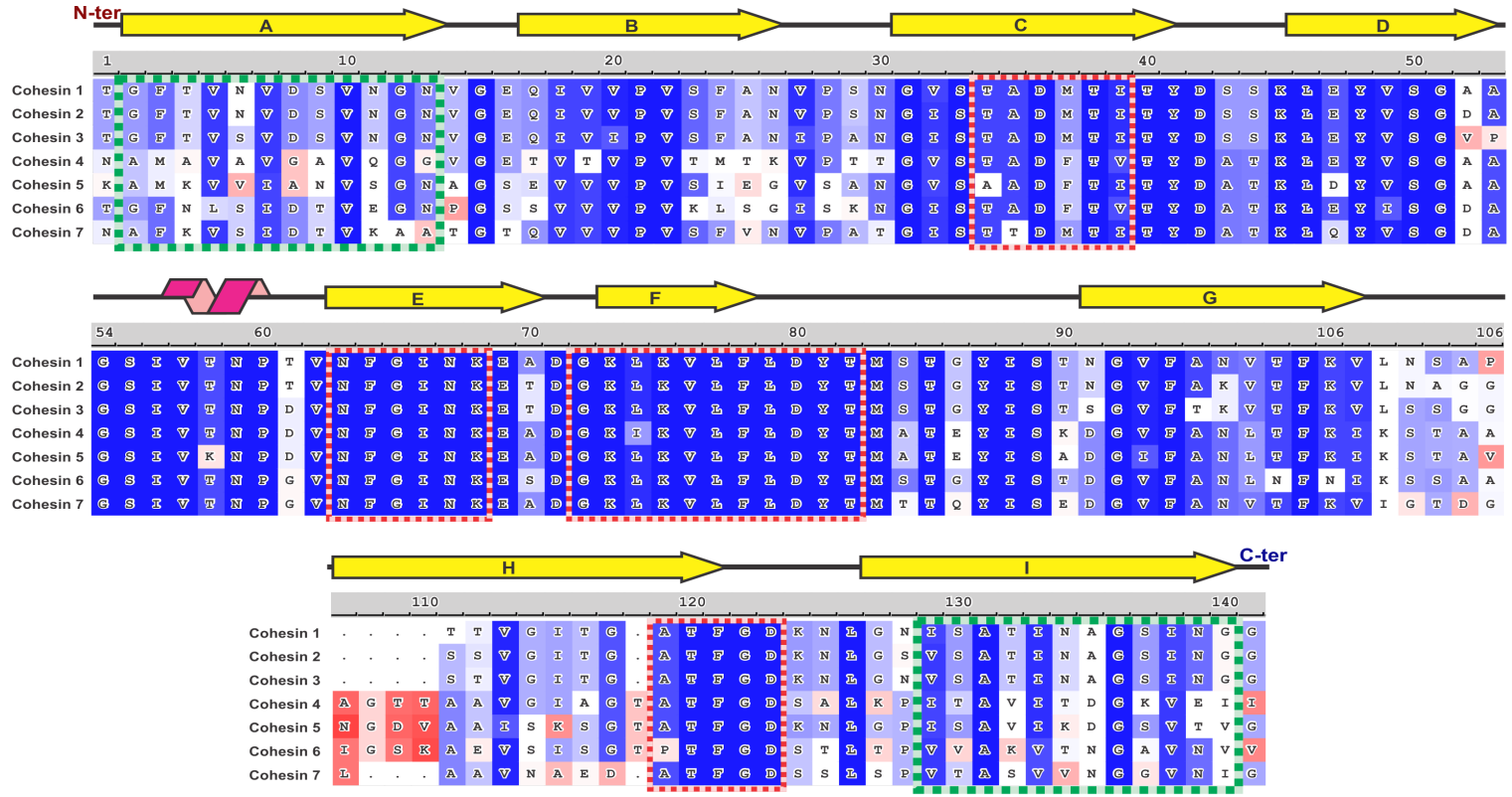
Bridging Cohesins are Stronger than Hanging Cohesins.
Proposed by *Valbuena, et. al. PNAS 2009*



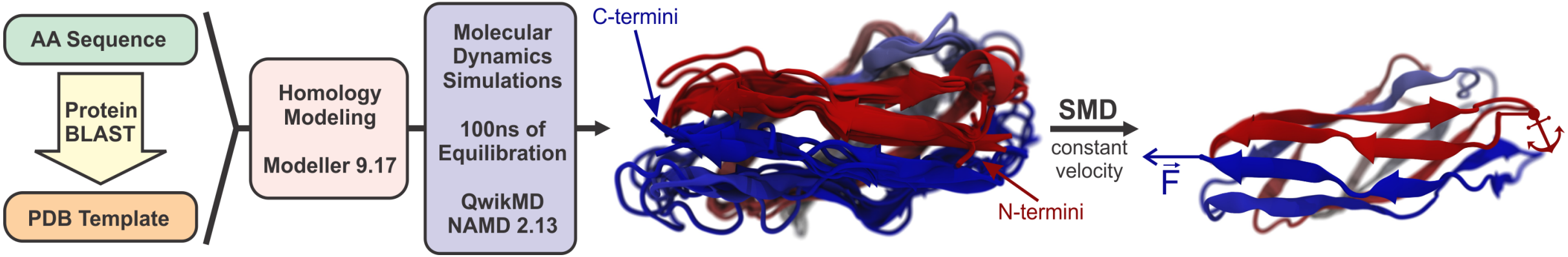
A. Cellulolyticus

Cohesins have high sequence similarity





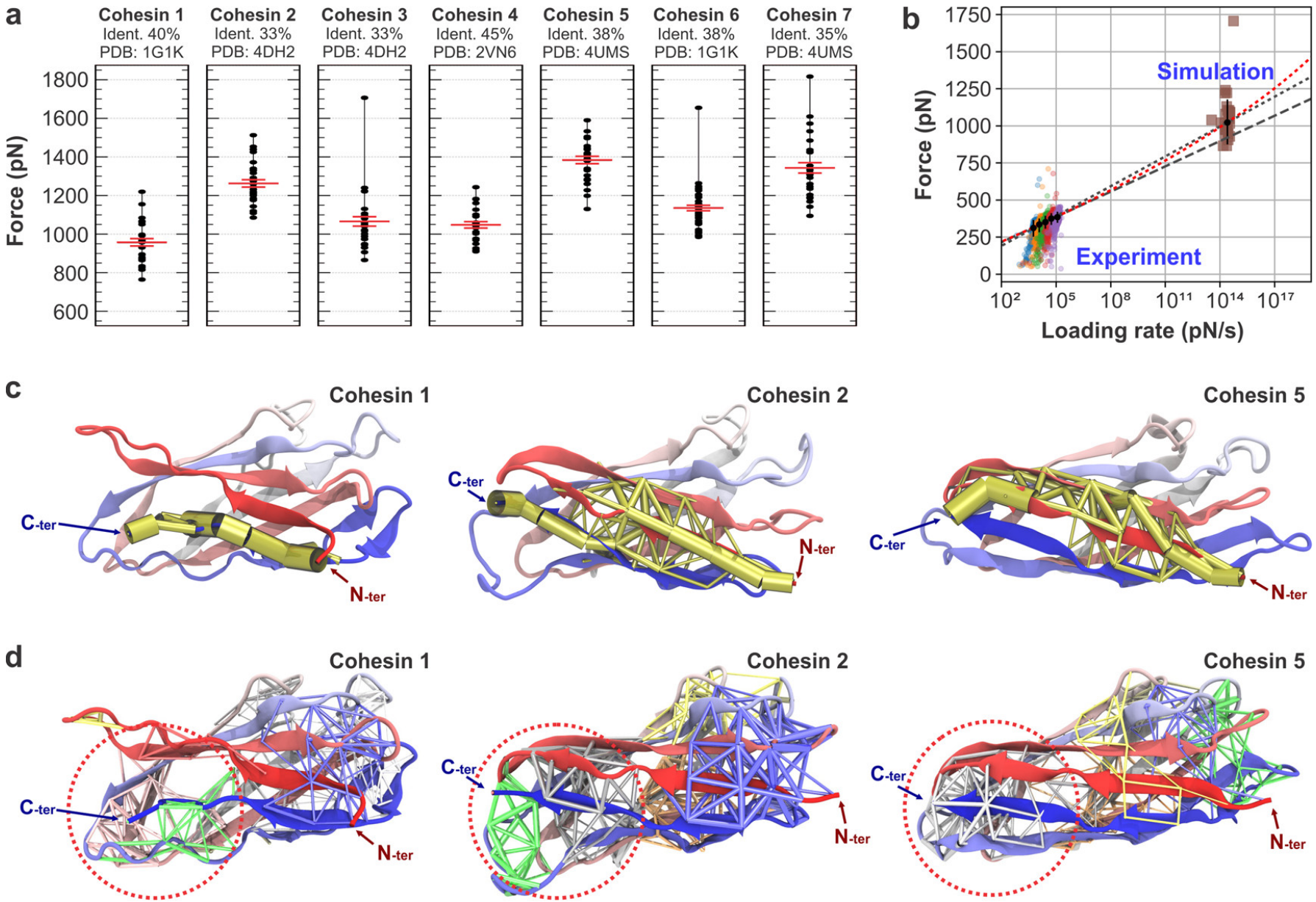
Modeling the Cohesins



Rafael C. Bernardi
rcbernardi@auburn.edu

T Verdorfer, RC Bernardi, et. al.; **Combining in Vitro and in Silico Single-Molecule Force Spectroscopy to Characterize and Tune Cellulosomal Scaffoldin Mechanics.** JACS, 2017

Can we trust a single MD trajectory?

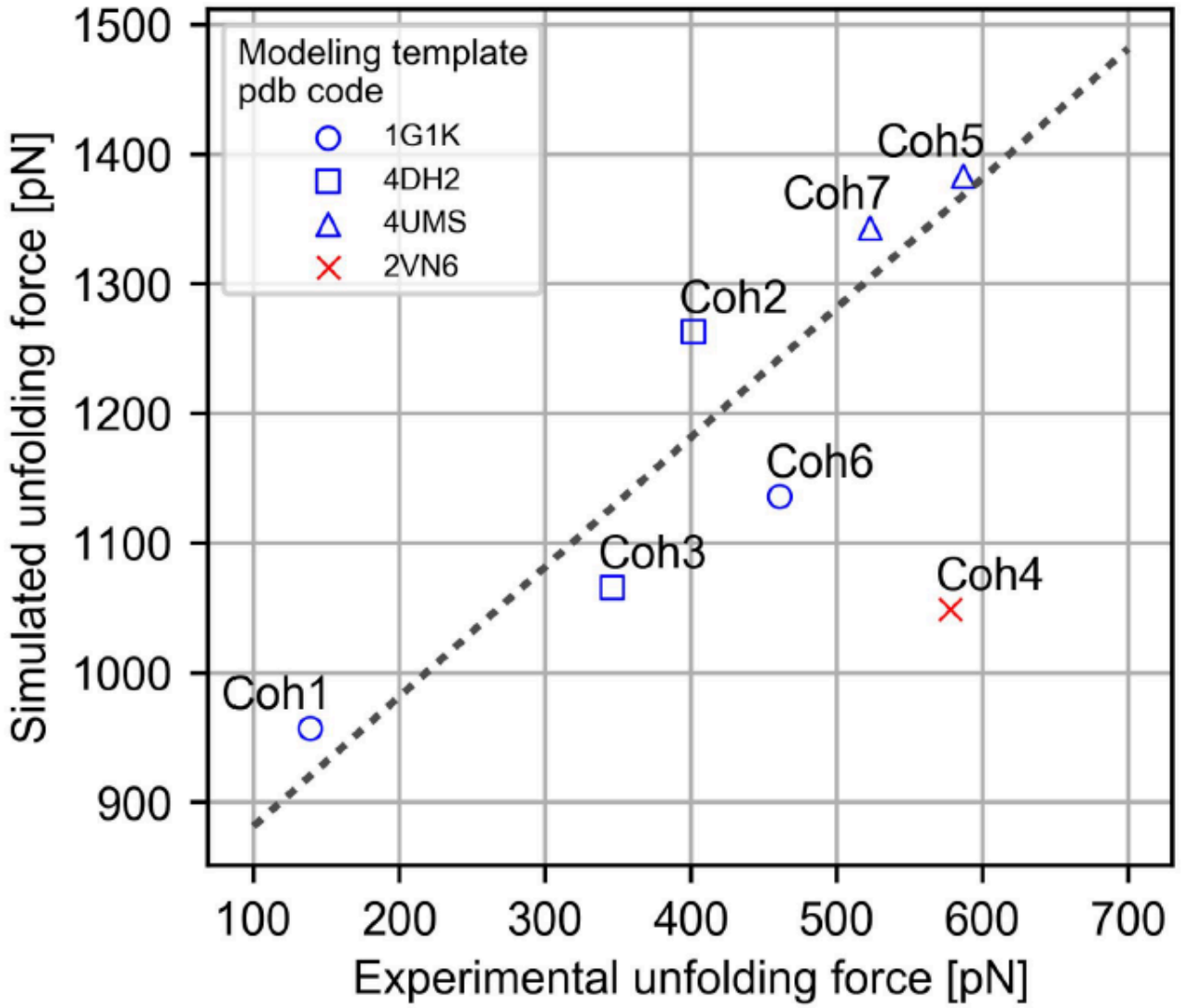


Rafael C. Bernardi
rcbernardi@auburn.edu

T Verdorfer, RC Bernardi, et. al.; **Combining in Vitro and in Silico Single-Molecule Force Spectroscopy to Characterize and Tune Cellulosomal Scaffoldin Mechanics.** JACS, 2017

Experiments vs. Simulations

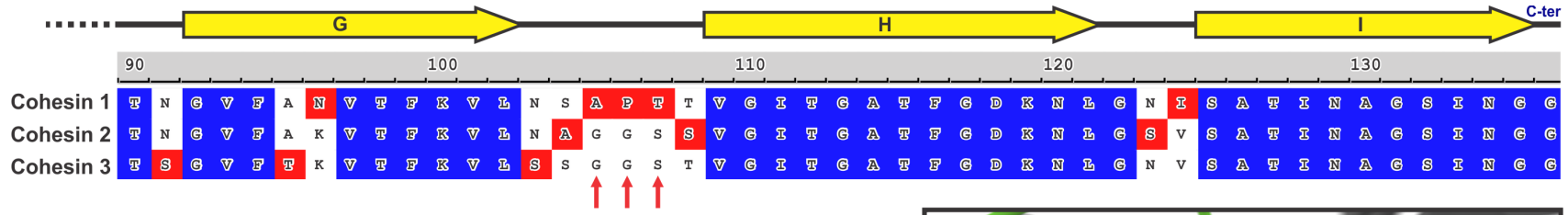
Simulations and Experiments agree extremely well, except for Cohesin 4.

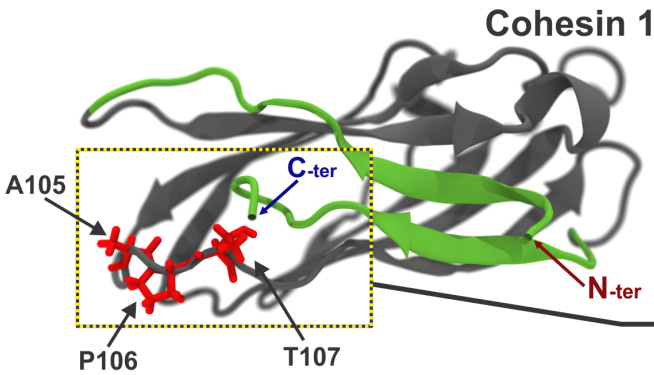


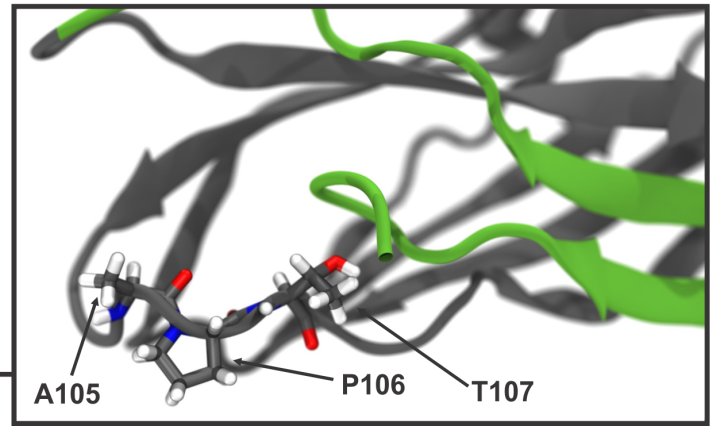
Rafael C. Bernardi
rcbernardi@auburn.edu

T Verdorfer, RC Bernardi, et. al.; **Combining in Vitro and in Silico Single-Molecule Force Spectroscopy to Characterize and Tune Cellulosomal Scaffoldin Mechanics.** JACS, 2017

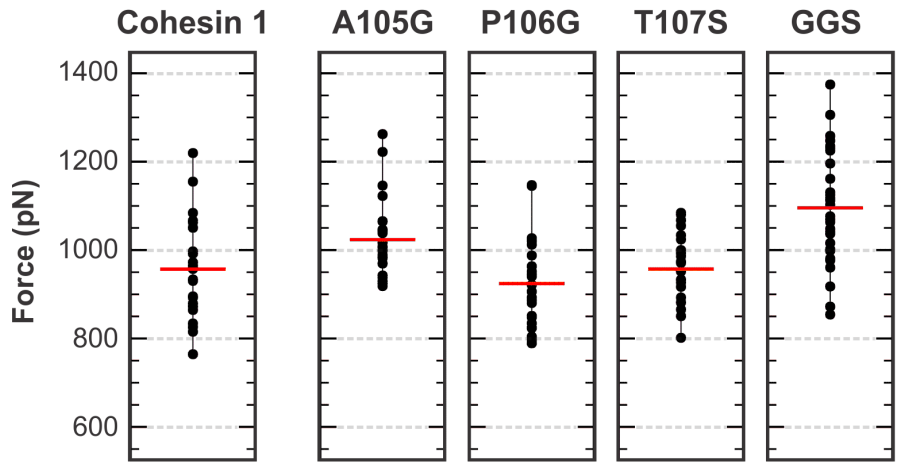
Engineering new cohesins

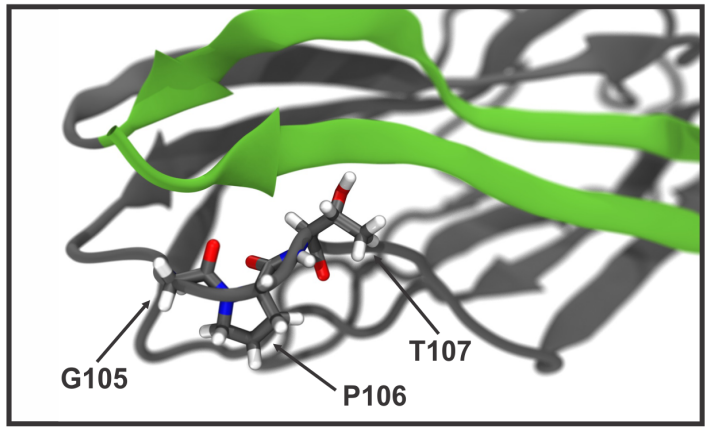






A105G Mutation

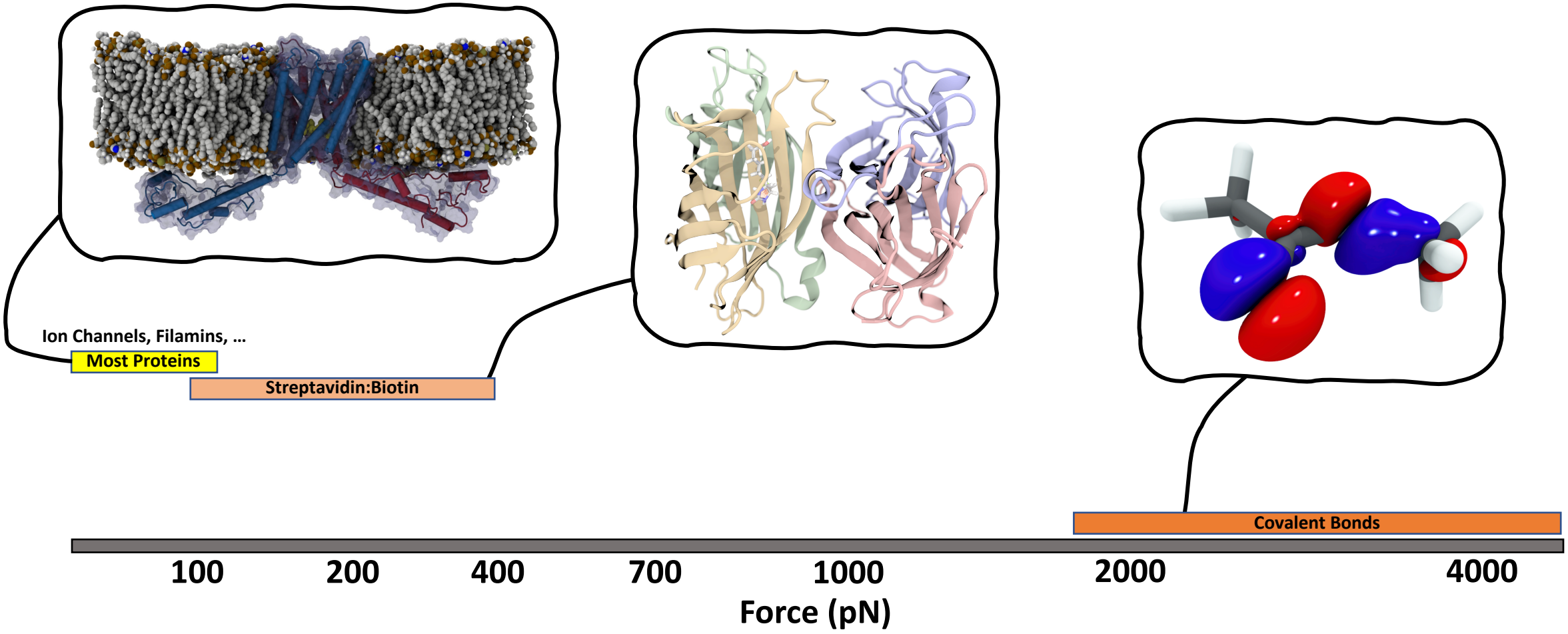




Rafael C. Bernardi
rcbernardi@auburn.edu

T Verdorfer, RC Bernardi, et. al.; **Combining in Vitro and in Silico Single-Molecule Force Spectroscopy to Characterize and Tune Cellulosomal Scaffoldin Mechanics.** JACS, 2017

Force Resilience in Biology: How were things until 2014?



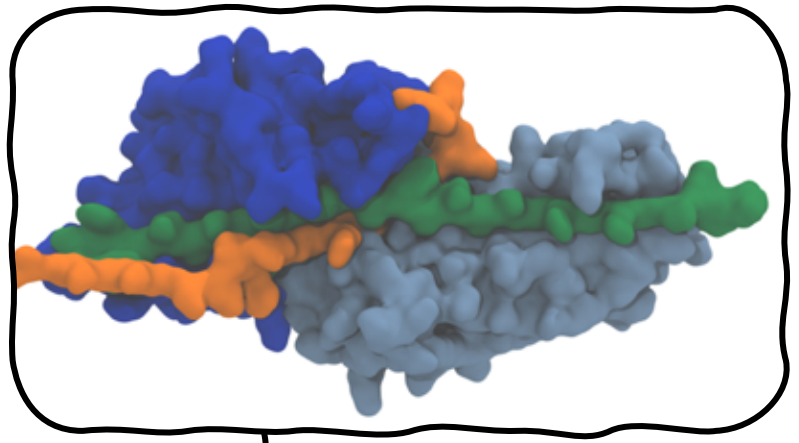
J Seppälä, RC Bernardi, et. al.; **Skeletal Dysplasia Mutations Effect on Human Filamins' Structure and Mechanosensing.** Scientific Reports, 2017

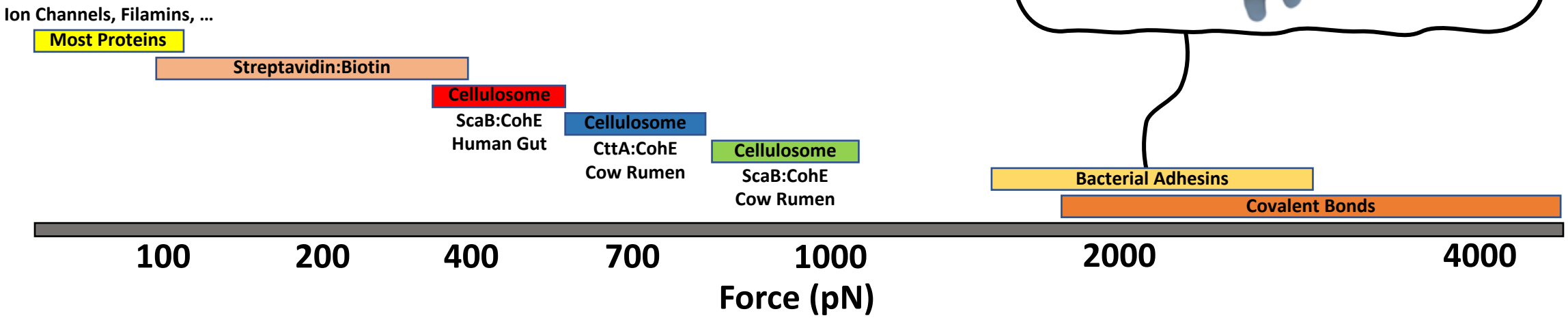
TJK Haataja, RC Bernardi, et. al.; **Non-syndromic Mitral Valve Dysplasia Mutation Changes the Force Resilience and Interaction of Human Filamin A.** Structure, 2019
SM Sedlak*, LC Schendel*, MCR Melo, DA Pippig, Z Luthey-Schulten, HE Gaub, RC Bernardi; **Direction Matters – Monovalent Streptavidin/Biotin Complex under Load.** Nano Letters, 2019

SM Sedlak*, LC Schendel*, HE Gaub, RC Bernardi; **Streptavidin/Biotin: Tethering Geometry Defines Unbinding Mechanics.** Science Advances, 2020

Force Resilience in Biology:

Mechanoactive bonds become ultrastable under mechanical stress





C Schoeler*, KH Malinowska*, RC Bernardi, et. al.; **Ultrastable cellulosome-adhesion complex tightens under load.** Nature Communications, 2014

C Schoeler*, RC Bernardi*, et. al.; **Mapping mechanical force propagation through biomolecular complexes.** Nano Letters, 2015

J Seppälä, RC Bernardi, et. al.; **Skeletal Dysplasia Mutations Effect on Human Filamins' Structure and Mechanosensing.** Scientific Reports, 2017

LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

TJK Haataja, RC Bernardi, et. al.; **Non-syndromic Mitral Valve Dysplasia Mutation Changes the Force Resilience and Interaction of Human Filamin A.** Structure, 2019

SM Sedlak*, LC Schendel*, MCR Melo, DA Pippig, Z Luthey-Schulten, HE Gaub, RC Bernardi; **Direction Matters – Monovalent Streptavidin/Biotin Complex under Load.** Nano Letters, 2019

RC Bernardi, et al.; **Mechanisms of Nanonewton Mechanostability in a Protein Complex Revealed by Molecular Dynamics Simulations and Single-Molecule Force Spectroscopy.** JACS, 2019

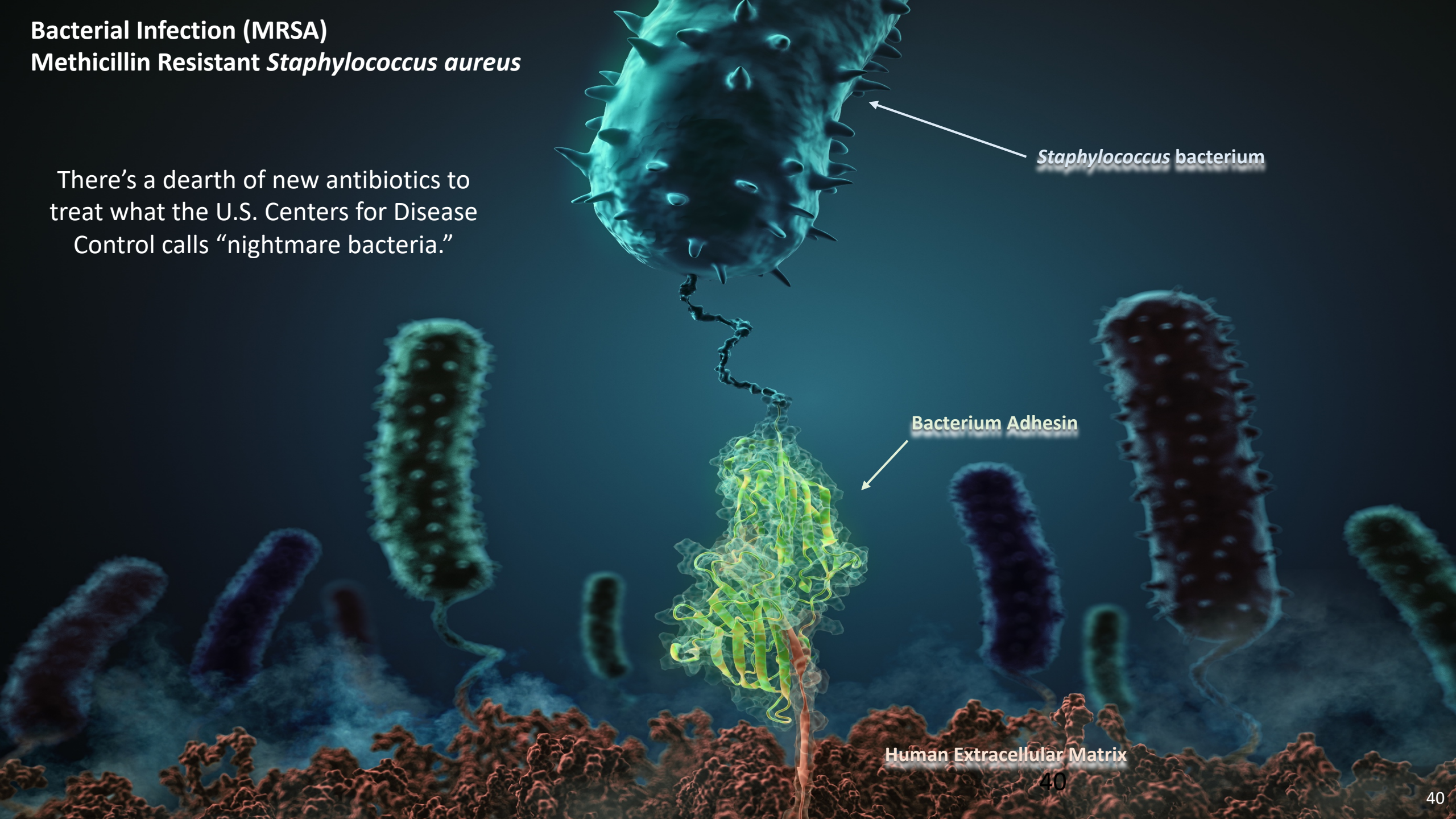
SM Sedlak*, LC Schendel*, HE Gaub, RC Bernardi; **Streptavidin/Biotin: Tethering Geometry Defines Unbinding Mechanics.** Science Advances, 2020

Z Liu, H Liu, AM Vera, RC Bernardi, et. al.; **High Force Catch Bond Mechanism of Bacterial Adhesion in the Human Gut.** Nature Communications, 2020

Rafael C. Bernardi
rcbernardi@auburn.edu

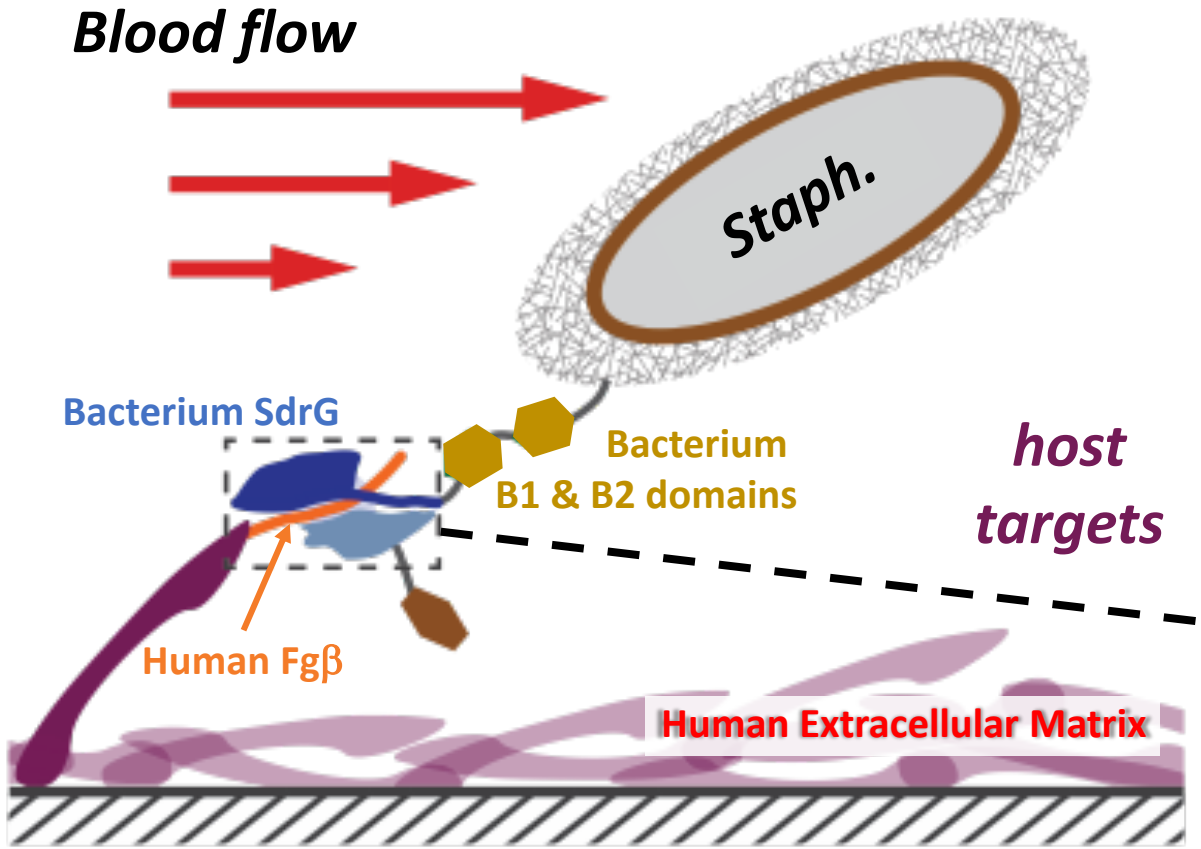
Bacterial Infection (MRSA)
Methicillin Resistant *Staphylococcus aureus*

There's a dearth of new antibiotics to treat what the U.S. Centers for Disease Control calls "nightmare bacteria."



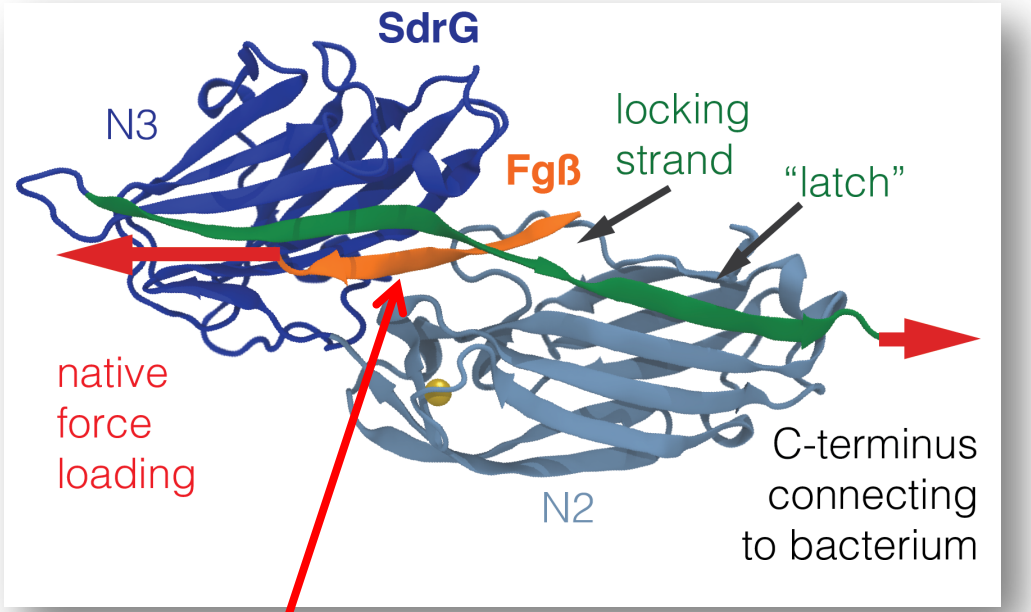
40

Staphylococcus epidermidis' Serine-aspartate repeat protein G (SdrG)



host targets

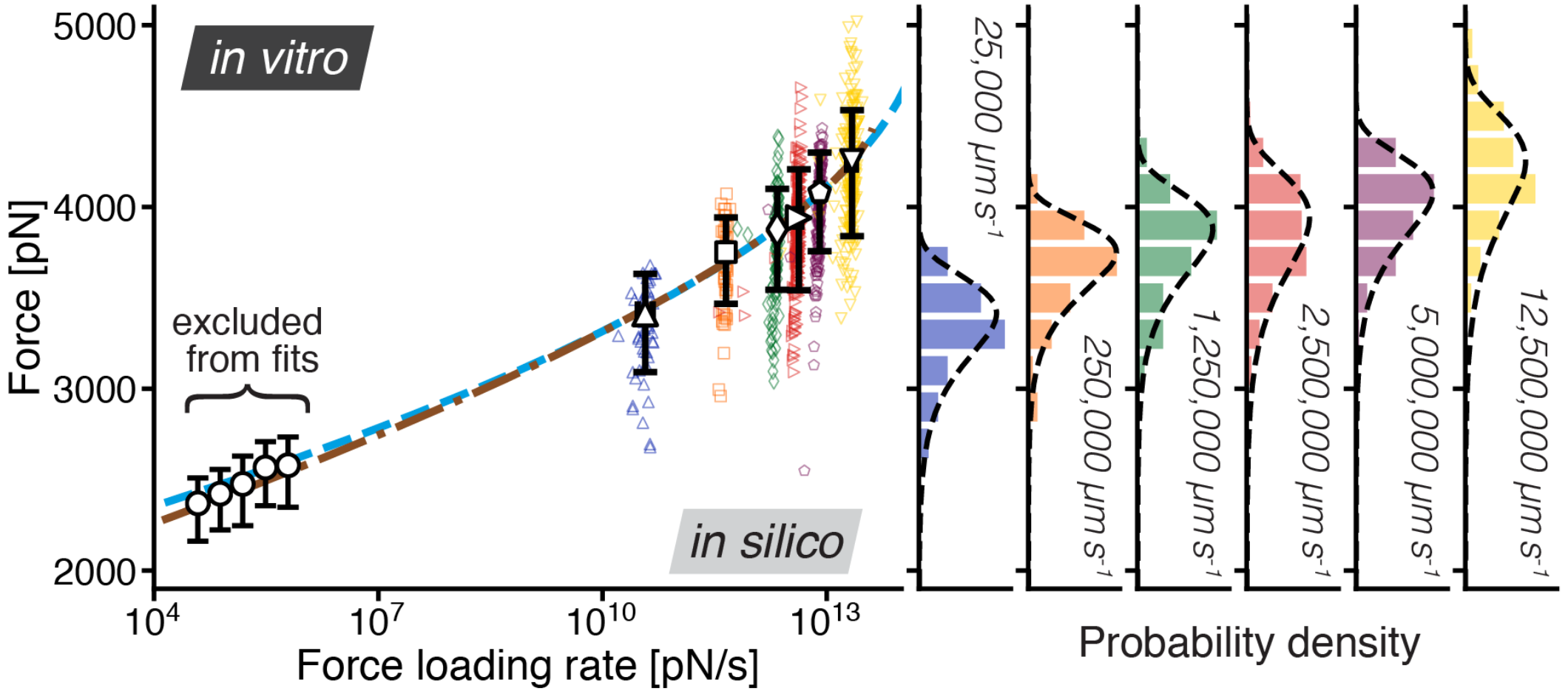
Targets Human's **Fibrinogen β (Fgβ)**



Thrombin Cleaves Fgβ at the same position

LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

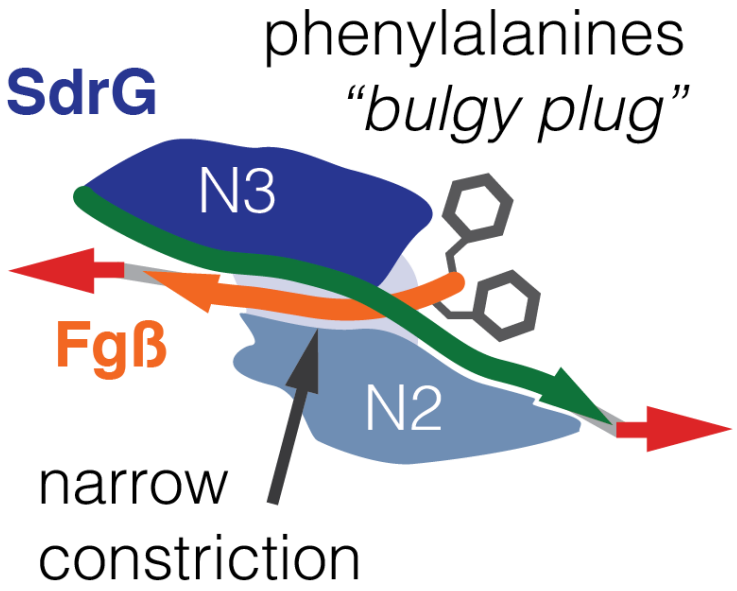
Dudko-Hummer-Szabo (DHS) Theory – Simulation and experiments agreement

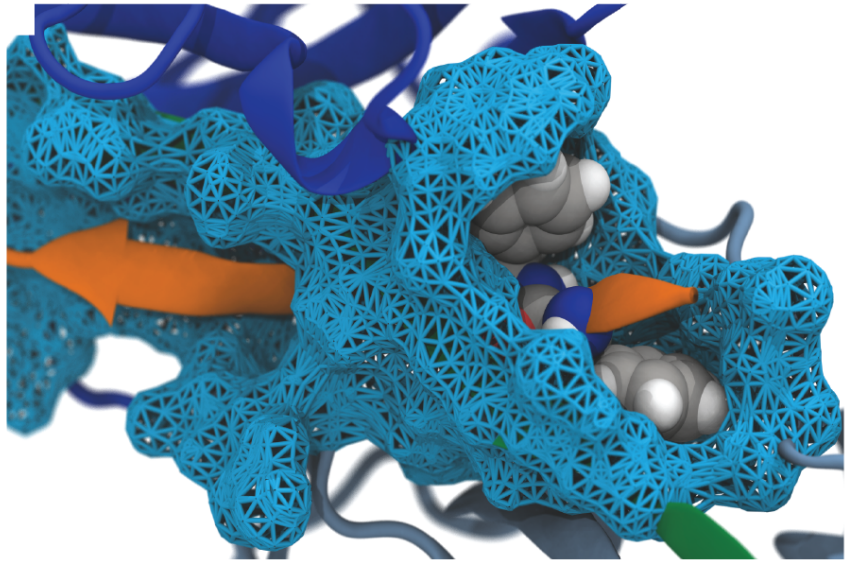


LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

Adhesion by Pathogenic Bacteria:

How a non-covalent bond is as strong as some covalent bonds?



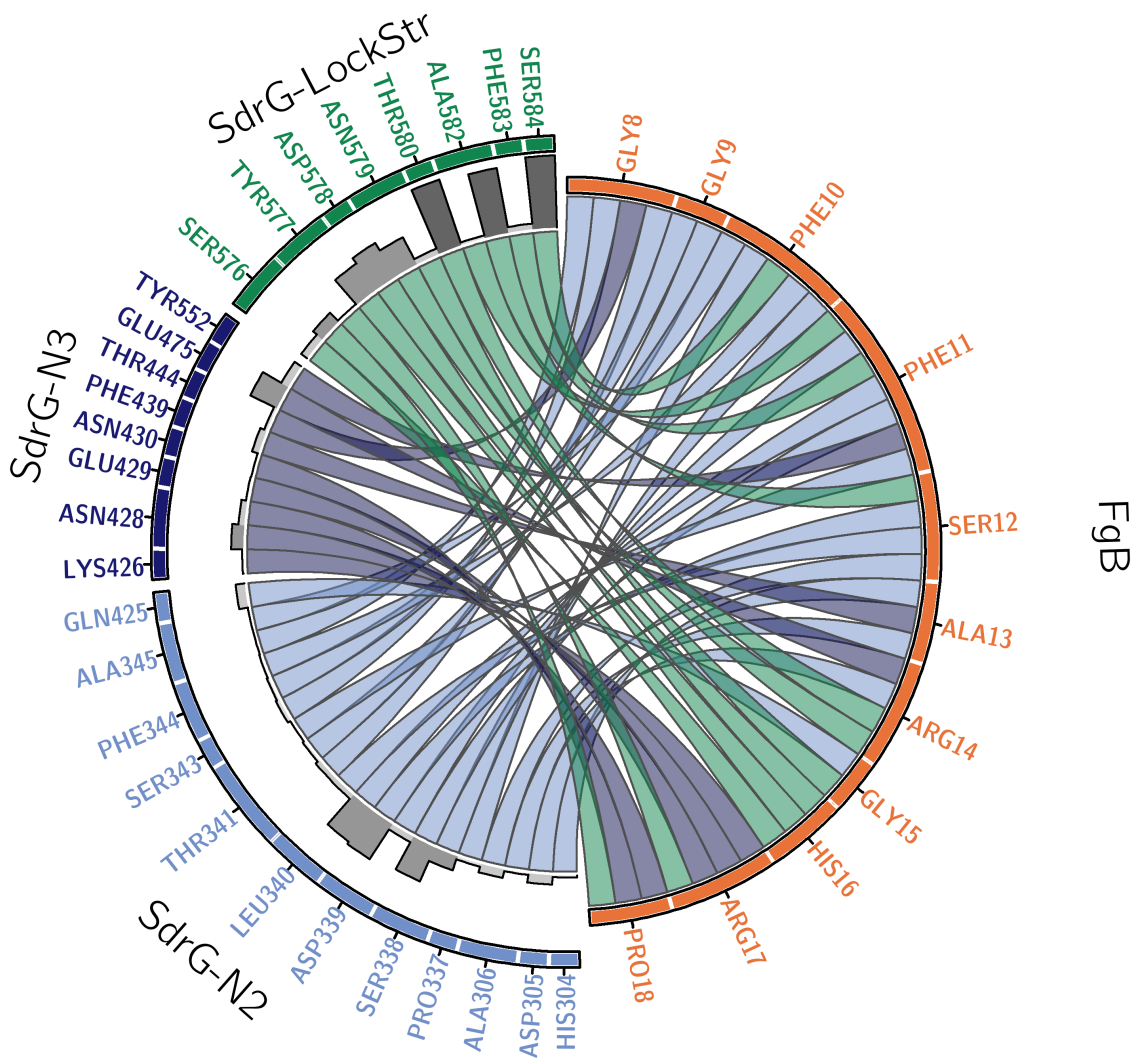


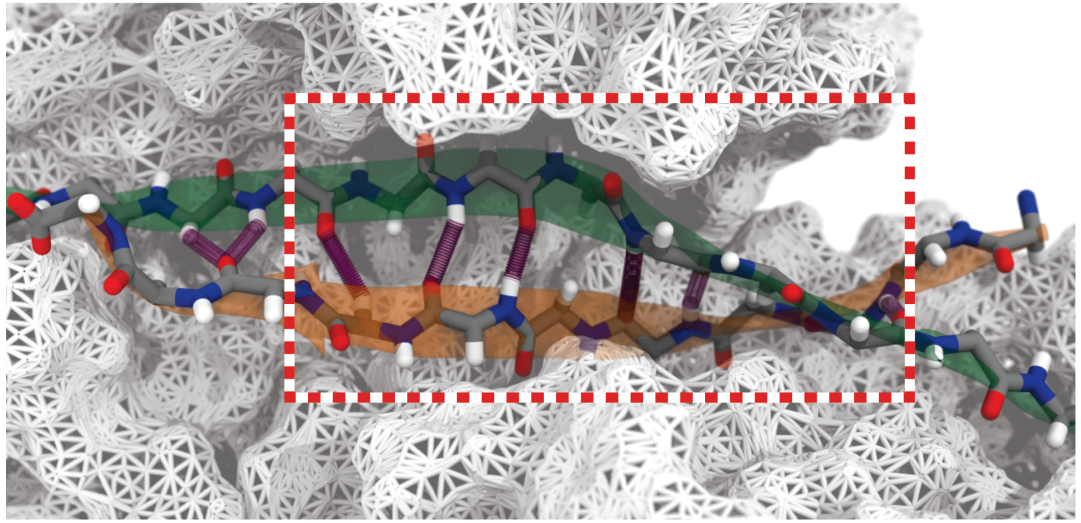
complex strength:		*in vitro*		*in silico*	
Fgß WT	G–FFSARG...	**100%**	2204 pN	**100%**	3362 pN
FgßF3	GFFFSARG...	101%	2236 pN	104%	3486 pN
FgßF1	G–AFSARG...	97%	2148 pN	92%	3082 pN
FgßF0	G–AASARG...	91%	1999 pN	82%	2758 pN

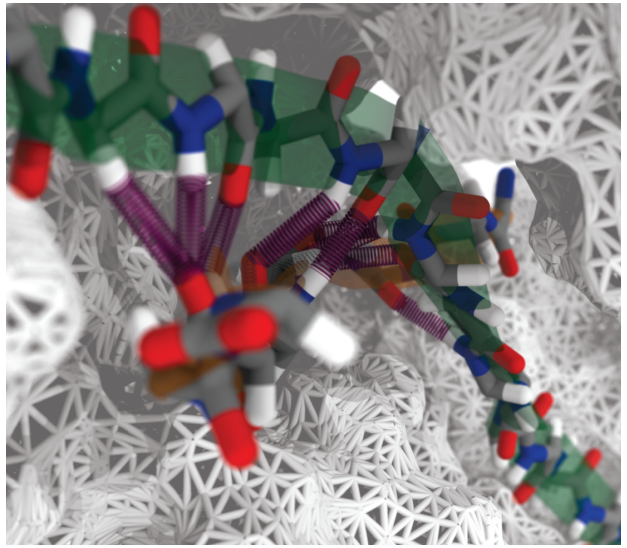
Rafael C. Bernardi
rcbernardi@auburn.edu

LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

Hydrogen Bond Network







A bond with a twist!

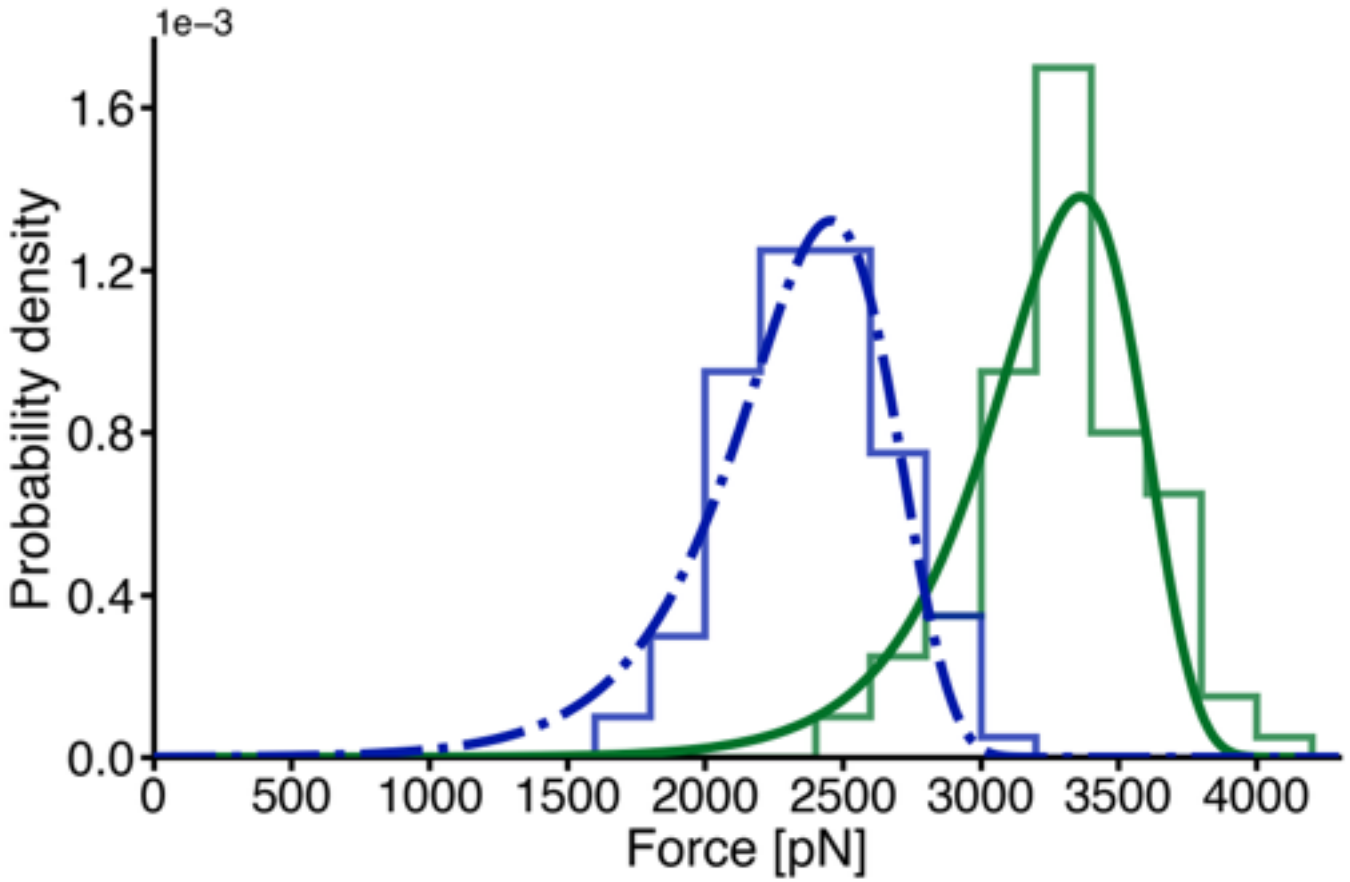
The corkscrew shape makes the complex hyperstable

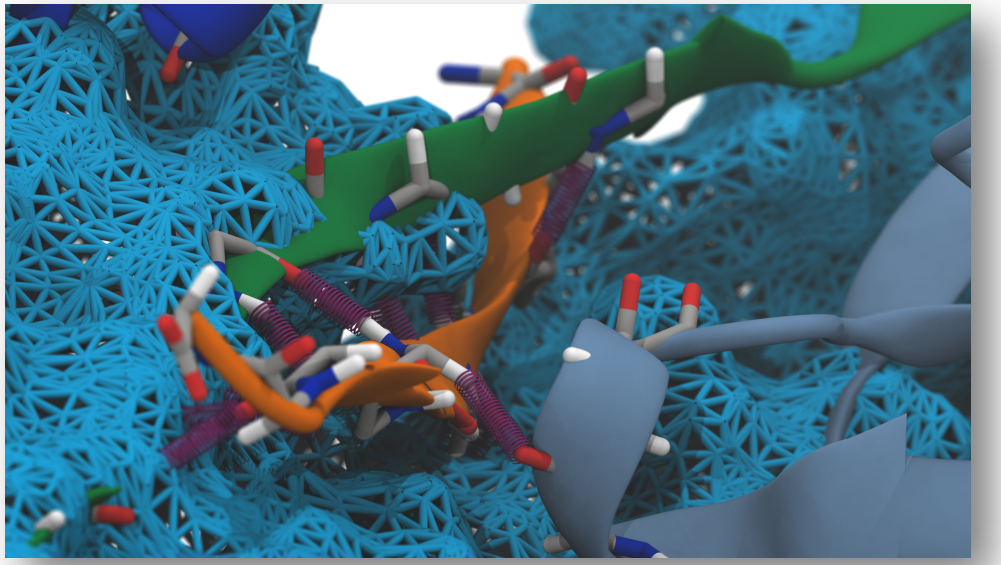
Rafael C. Bernardi
rcbernardi@auburn.edu

LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

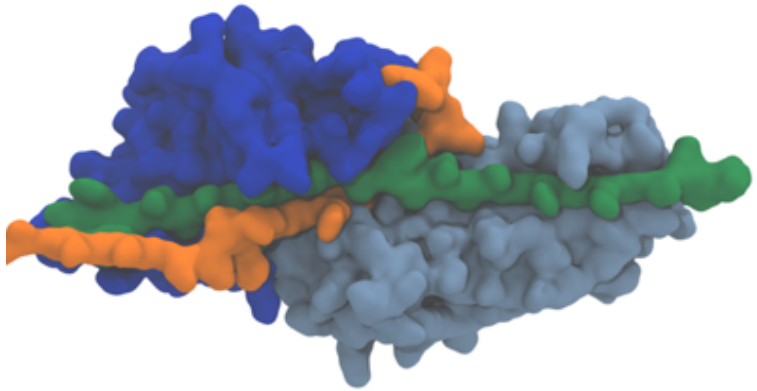
Side-chain Independence: Sequence Independence

Amino acid sequence is very important for binding affinity, but once it is bound even a polyglycine would become hyperstable





Strong Confinement

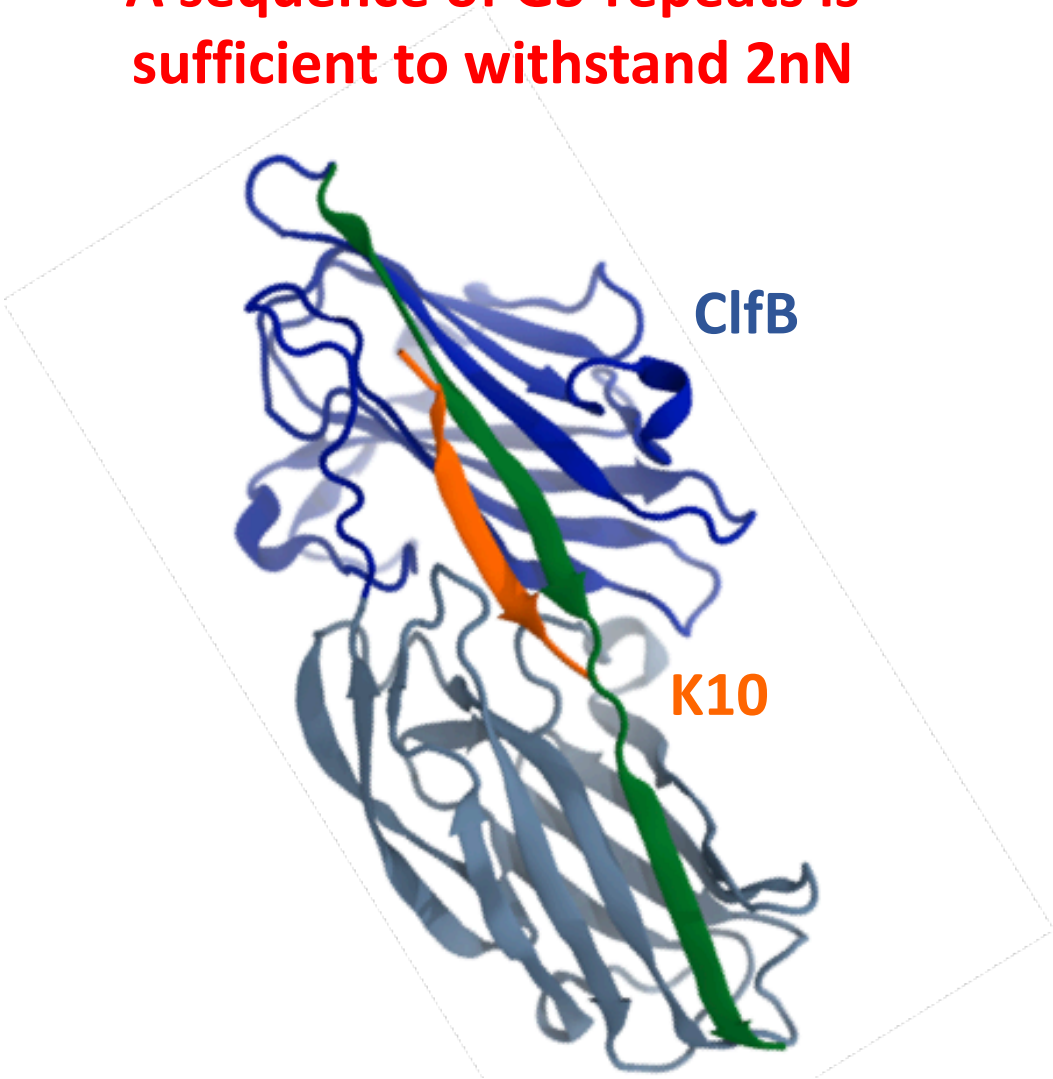


Rafael C. Bernardi
rcbernardi@auburn.edu

LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

Sequence Independence? Isn't it just a computer nonsense?

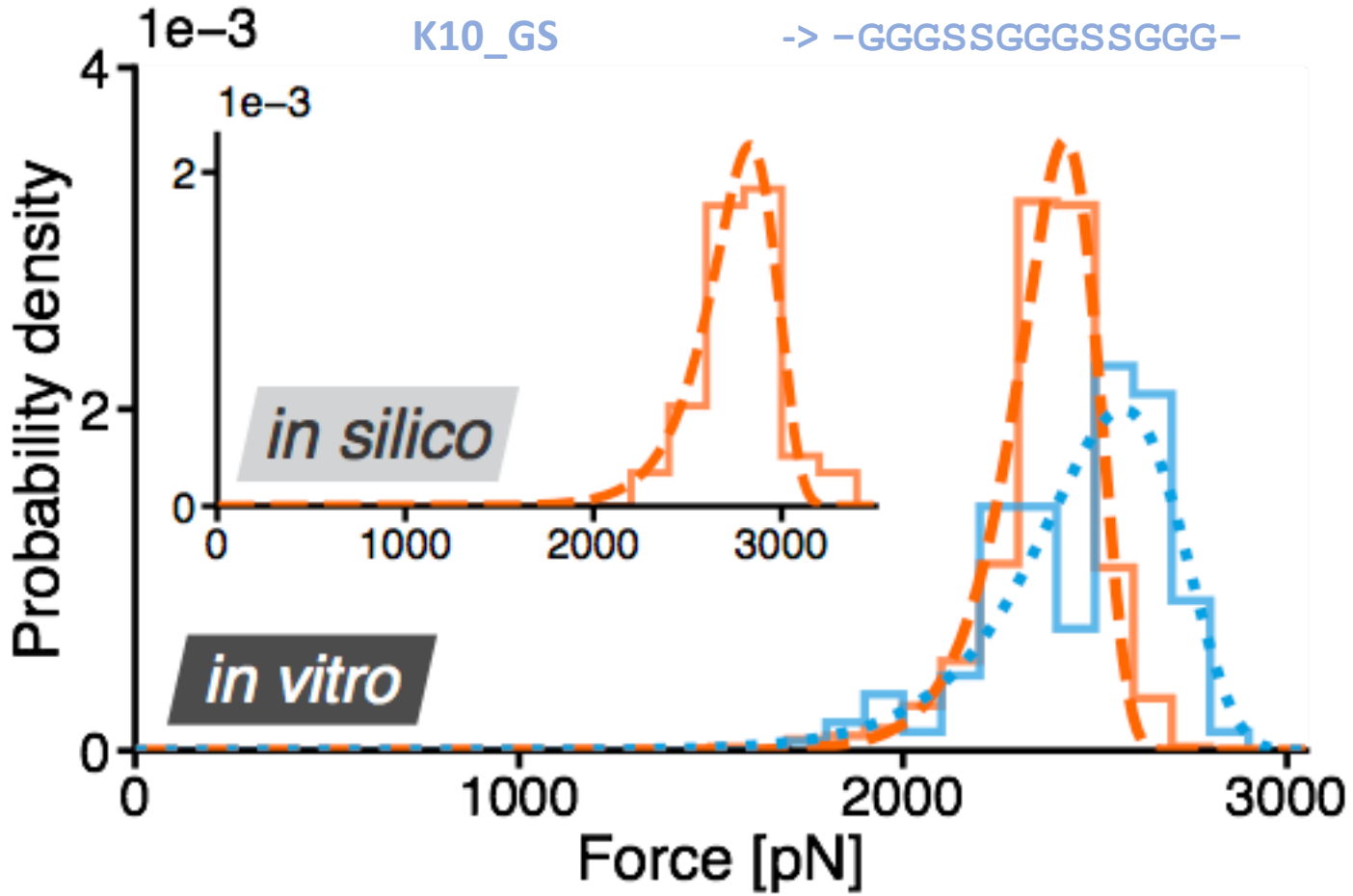
A sequence of GS-repeats is sufficient to withstand 2nN



ClfB from *S. aureus*, same Dock, Lock & Latch mechanism, binds C-Terminal peptides:

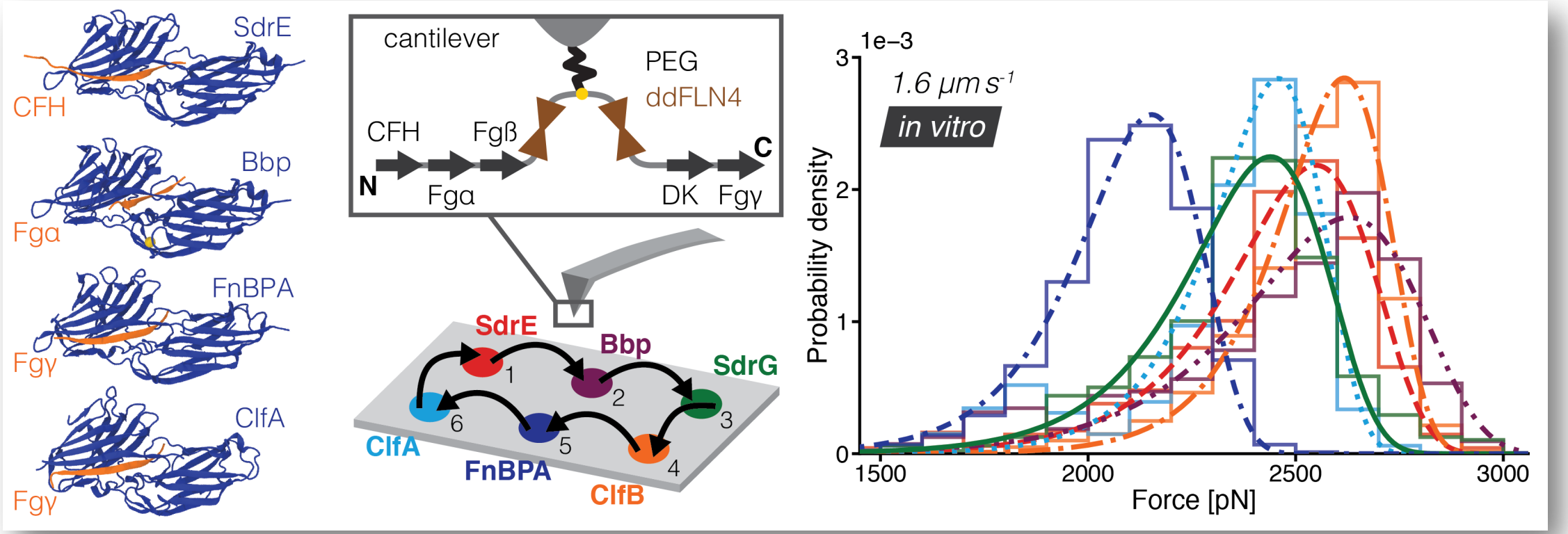
Keratin K10 -> YGGGSSGGGSSGGGH

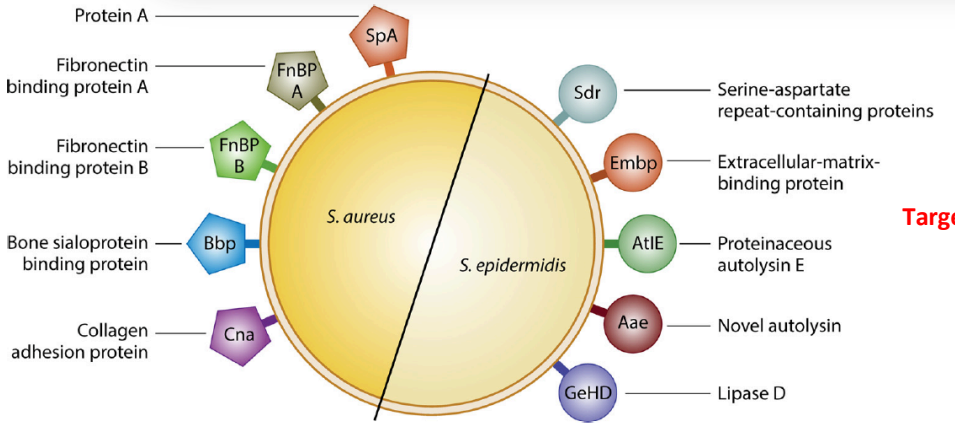
K10_GS -> −GGGSSGGGSSGGG−



LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

Sequence Independence: A Huge Evolutionary Advantage!





Targets include Fibrinogen (Fg, all chains), Keratin, Elastin, Complement Factor H, …

Evolution needs to find a better binder; mechanical resilience comes for free!

Rafael C. Bernardi
rcbernardi@auburn.edu

LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

And what now?

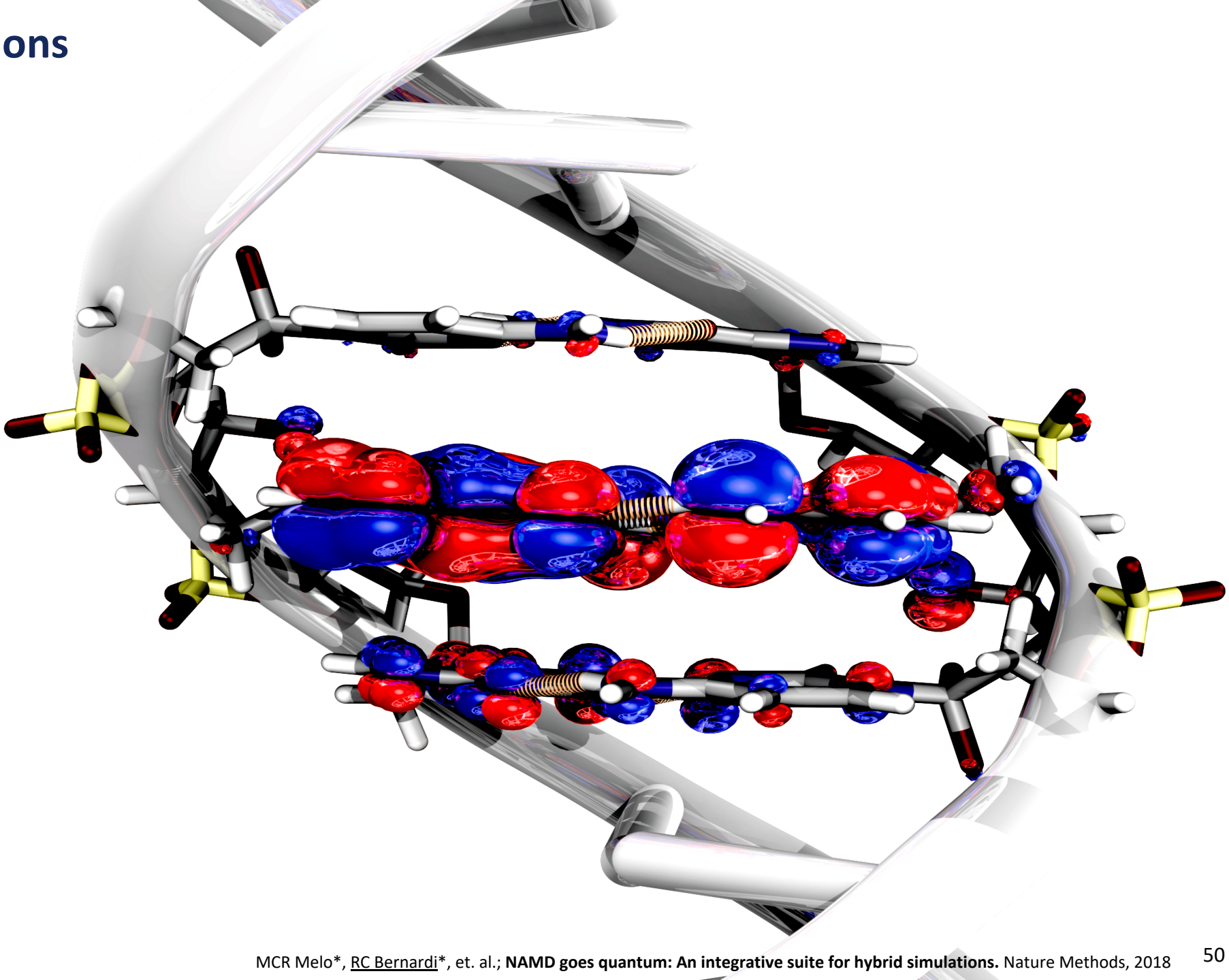
Can we design the perfect ligand?

LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018

What else can we do with QwikMD?

What if I don’t have Force Field parameters for my molecule?

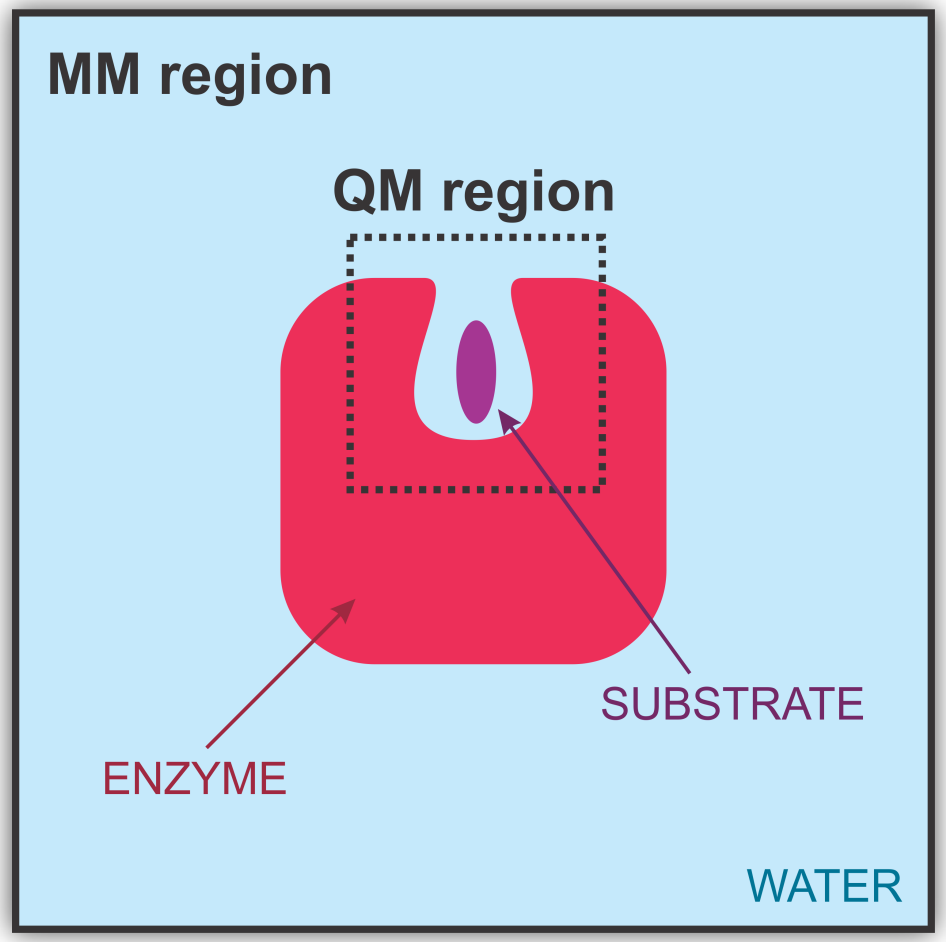
Hybrid QM/MM Simulations



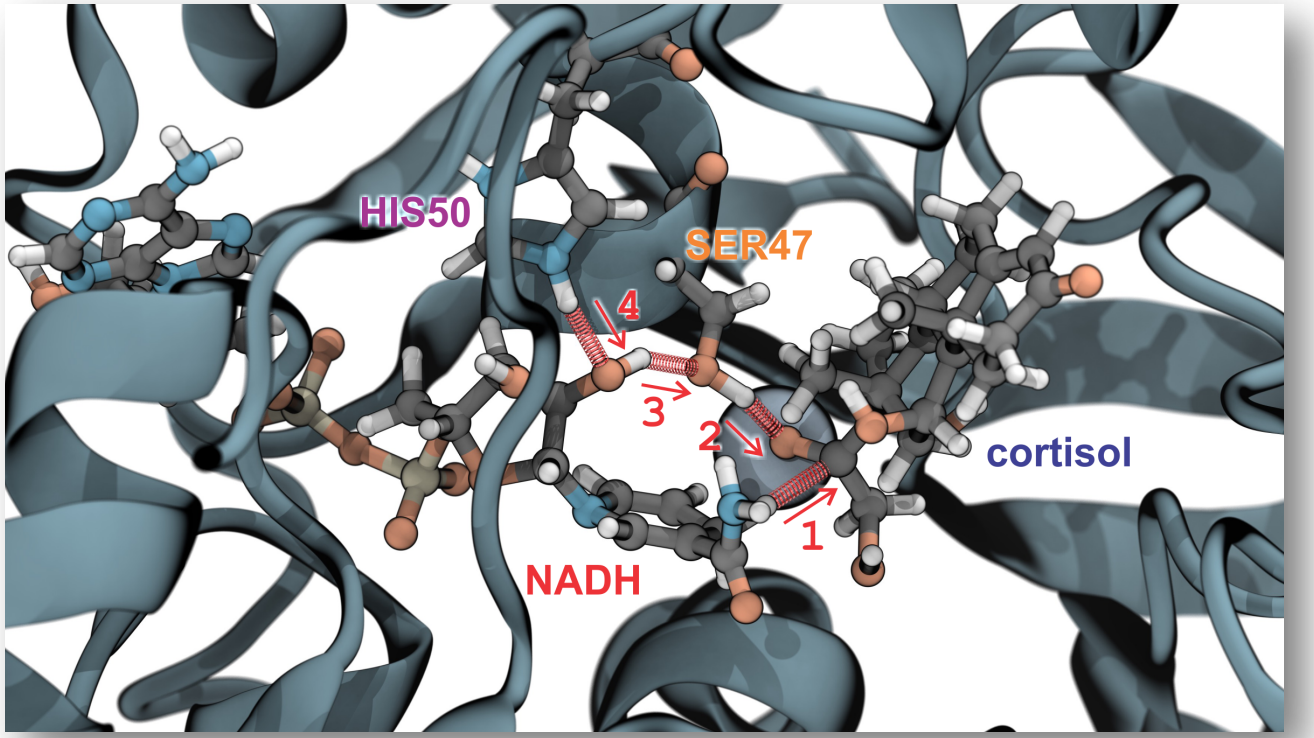
Rafael C. Bernardi
rcbernardi@auburn.edu

MCR Melo*, RC Bernardi*, et. al.; **NAMD goes quantum: An integrative suite for hybrid simulations.** Nature Methods, 2018

Hybrid QM/MM Simulations

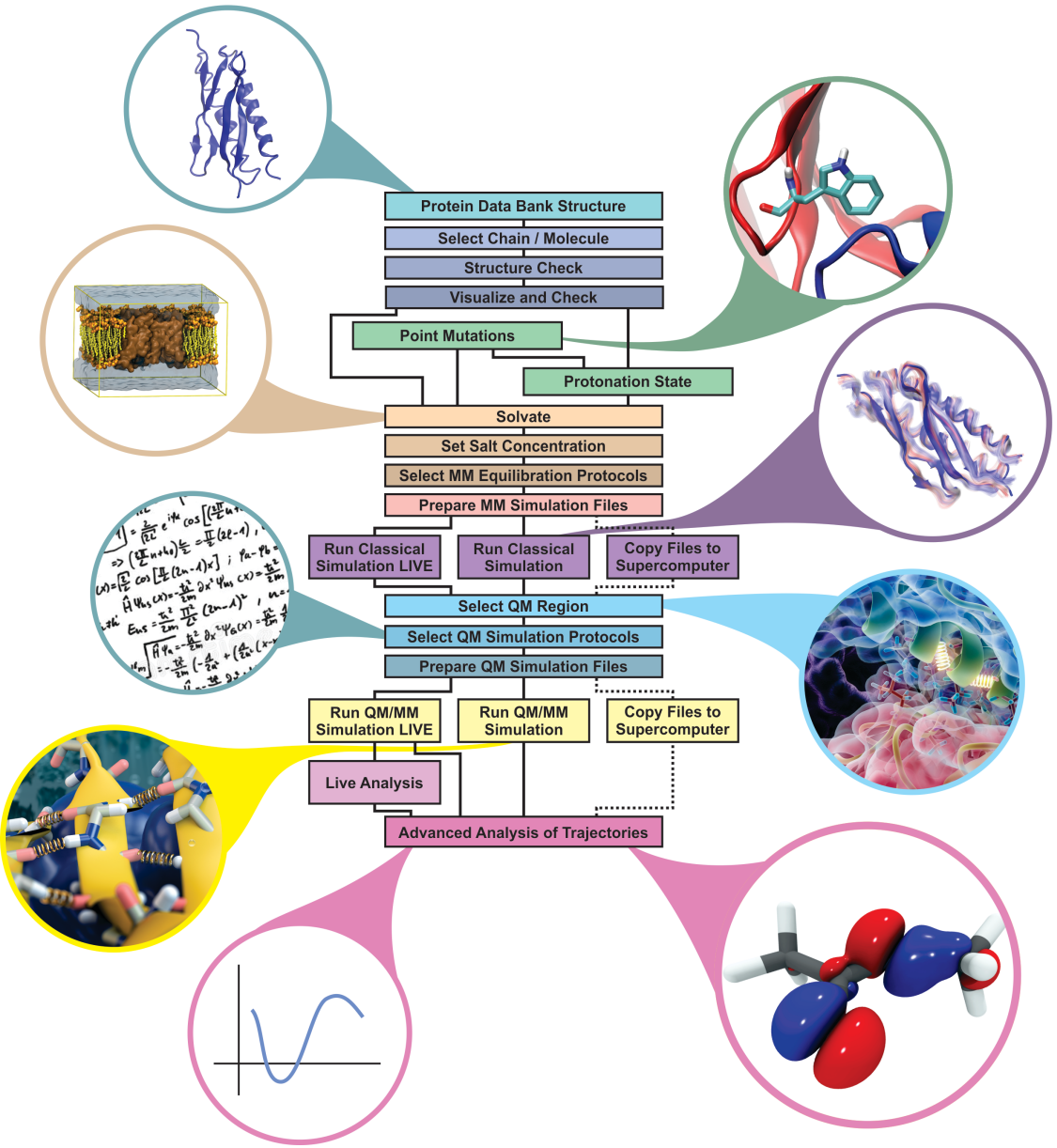


Chemical Reactions (bond breaking/forming)



MCR Melo*, RC Bernardi*, et. al.; **NAMD goes quantum: An integrative suite for hybrid simulations.** Nature Methods, 2018

Hybrid QM/MM Simulations with QwikMD



QM/MM available in the Advanced Run Tab

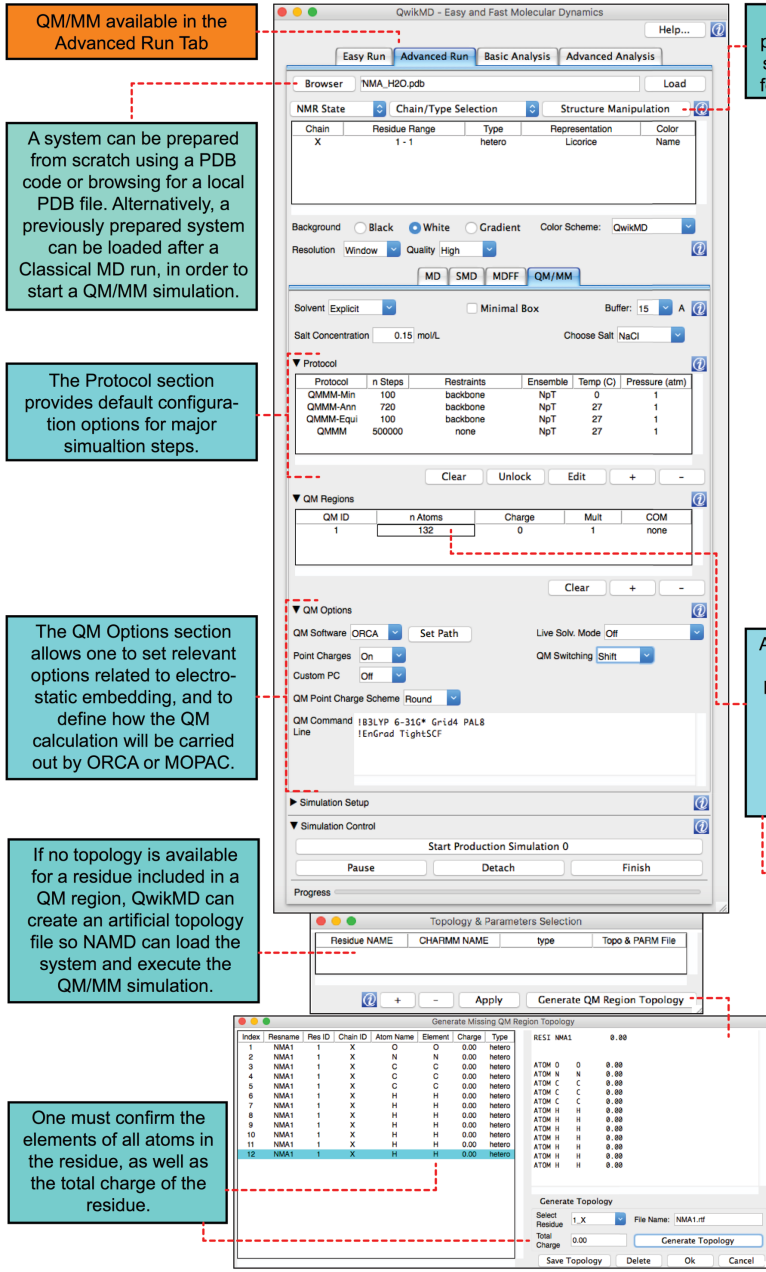
A system can be prepared from scratch using a PDB code or browsing for a local PDB file. Alternatively, a previously prepared system can be loaded after a Classical MD run, in order to start a QM/MM simulation.

The Protocol section provides default configuration options for major simualtion steps.

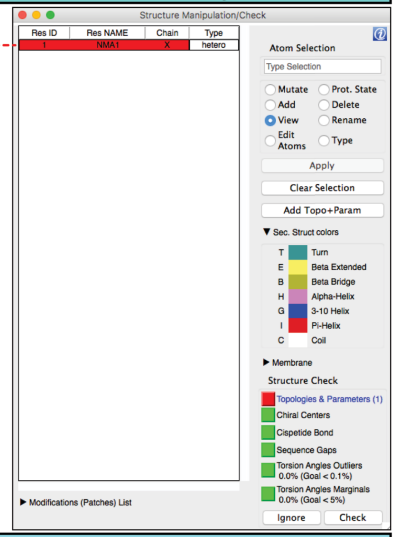
The QM Options section allows one to set relevant options related to electrostatic embedding, and to define how the QM calculation will be carried out by ORCA or MOPAC.

If no topology is available for a residue included in a QM region, QwikMD can create an artificial topology file so NAMD can load the system and execute the QM/MM simulation.

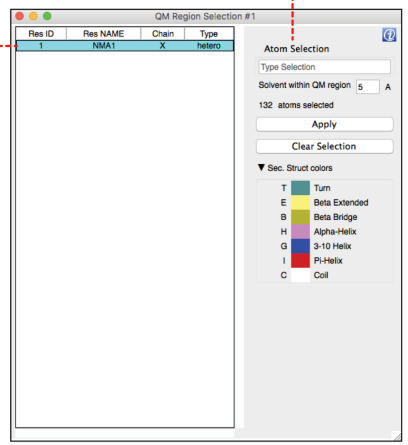
One must confirm the elements of all atoms in the residue, as well as the total charge of the residue.



The Structure Manipulation window allows one to perform mutations and other modifications to one's system, as well as selecting or creating topologies for new molecules, such as drugs and metabolites.



A QM region can be selected in any combination of three basic methods: a) Using the atomselect language and allowing QwikMD to select residues within a cutoff of your selection; b) Selecting residues from the list presented in the "Region Selection" window; c) Clicking on the residues themselves in the main VMD window, as one examines the structure being simulated.

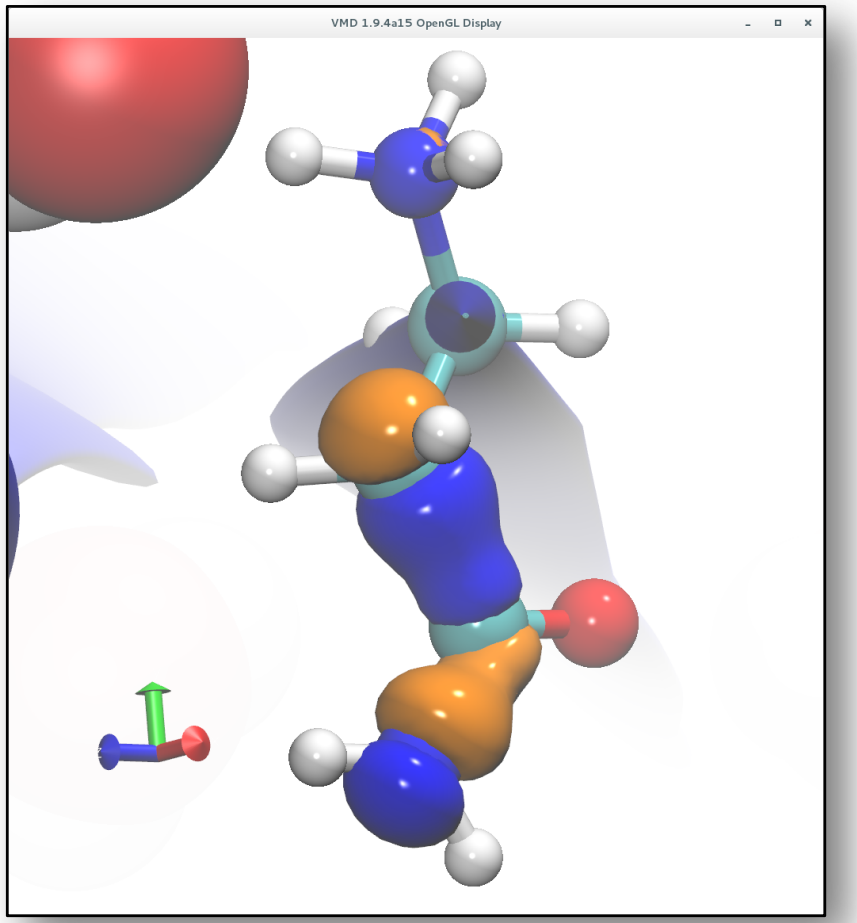


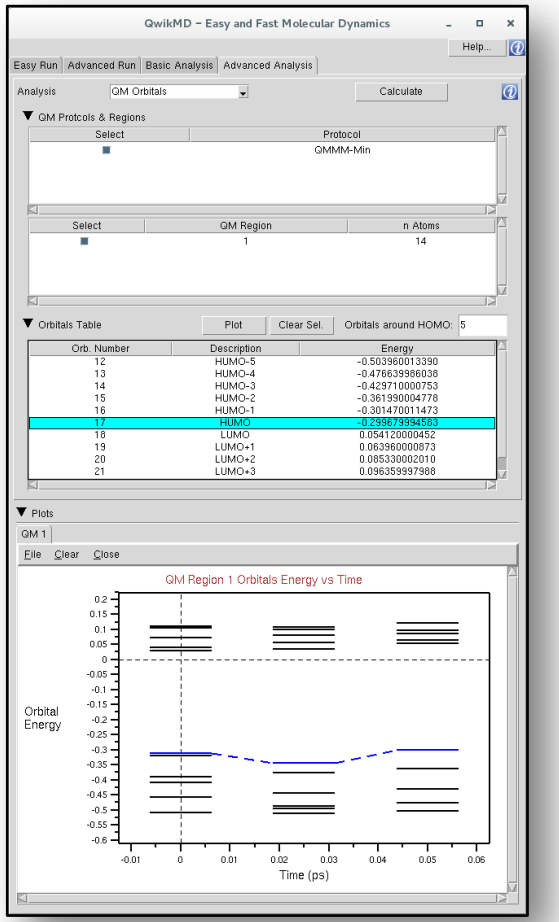
Rafael C. Bernardi
rcbernardi@auburn.edu

MCR Melo*, RC Bernardi*, et. al.; **NAMD goes quantum: An integrative suite for hybrid simulations.** Nature Methods, 2018

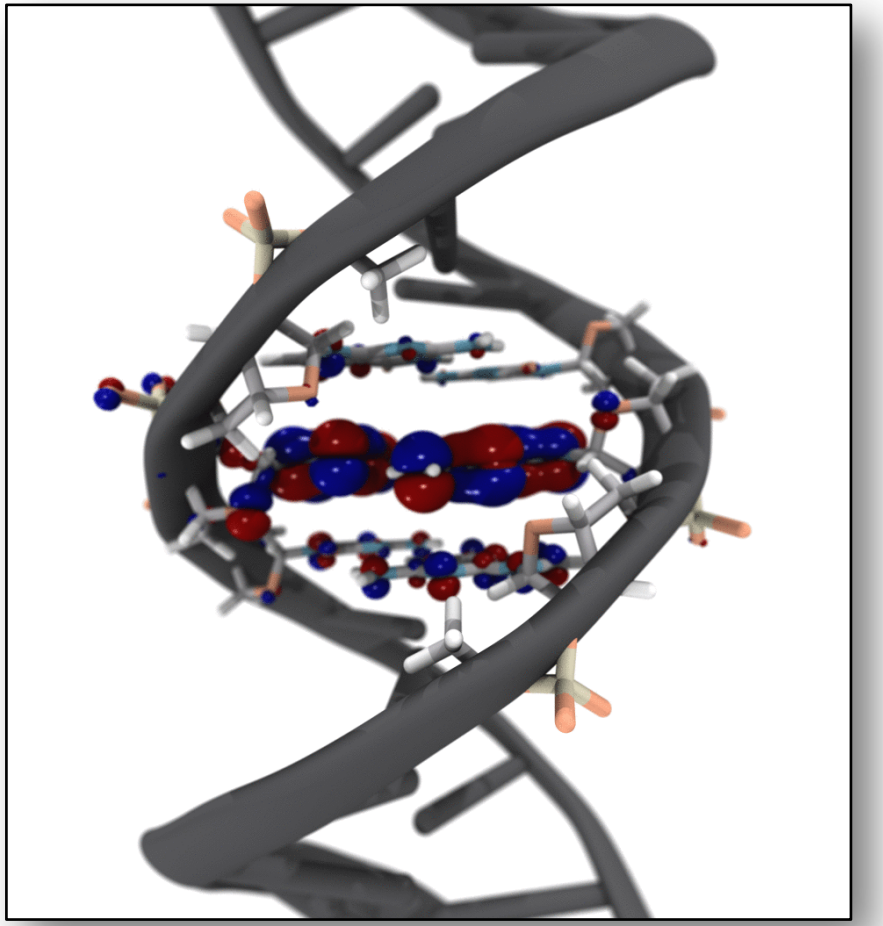
Hybrid QM/MM Simulations with QwikMD

Orbital Analysis and Visualization Tools allow for fast and easy study of molecular orbital properties.





GPU-accelerated rendering in VMD allows for fast publication-quality rendering.



Rafael C. Bernardi
rcbernardi@auburn.edu

MCR Melo*, RC Bernardi*, et. al.; **NAMD goes quantum: An integrative suite for hybrid simulations.** Nature Methods, 2018

NAMD goes quantum:
A new integrative suite for QM/MM simulations

Marcelo C. R. Melo[1], Rafael C. Bernardi[1], Till Rudack[1,2], Maximilian Scheurer[3], Christoph Riplinger[4], James C. Phillips[1], Julio D. C. Maia[5], Gerd B. Rocha[5], João V. Ribeiro[1], John E. Stone[1], Frank Neese[4], Klaus Schulten[1], Zaida Luthey-Schulten[1]

1. University of Illinois at Urbana-Champaign, USA
2. Ruhr-Universität Bochum, Germany
3. Heidelberg University, Germany
4. Max Planck Institut für Chemische Energiekonversion, Germany
5. Federal University of Paraíba, Brazil

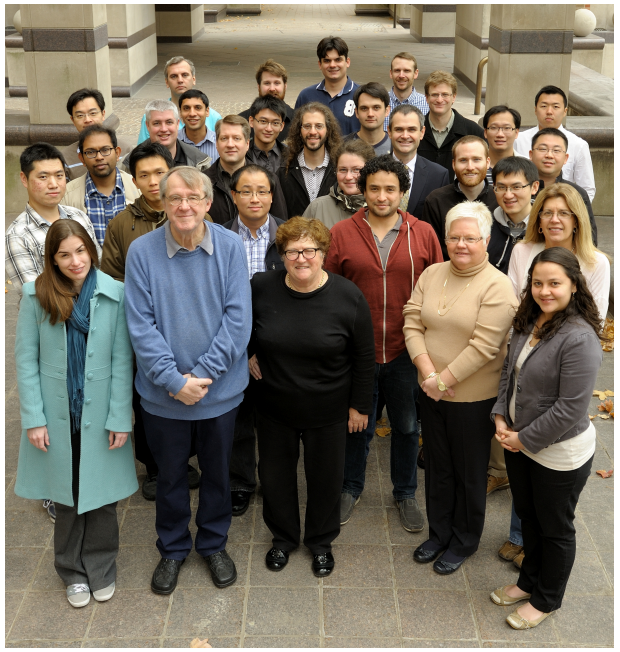
NIH Center for Macromolecular Modeling and Bioinformatics

Take home messages

- **QwikMD can assist the MD user from preparation of simulation all the way to analysis;**
- **Multiple Simulation Replicas are Necessary to have a Direct Comparison to Experiments (Wide Sampling Approach);**
- **In Biology, Force Resilience Depends on Force Application Geometry;**
- **Bonds Forming Contacts in Biomolecules can be Activated to Become as Strong as a Covalent Bond;**
- **Bacteria Adhesion Evolved so that their Mechanostability only Depends on Backbone:Backbone Interactions;**
- **Hybrid QM/MM simulations are now available in NAMD and QwikMD;**
- **Network Analysis can be used to calculate force propagation pathways and/or allosteric communications.**

C Schoeler*, KH Malinowska*, RC Bernardi, et. al.; **Ultrastable cellulosome-adhesion complex tightens under load.** Nature Communications, 2014
C Schoeler*, RC Bernardi*, et. al.; **Mapping mechanical force propagation through biomolecular complexes.** Nano Letters, 2015
JV Ribeiro*, RC Bernardi*, et al.; **QwikMD Integrative Molecular Dynamics Toolkit for Novices and Experts.** Scientific Reports, 2016
BC Goh, JA Hadden, RC Bernardi, et al.; **Computational Methodologies for Real-Space Structural Refinement of Large Macromolecular Complexes.** Annual Review of Biophysics, 2016
J Seppälä, RC Bernardi, et. al.; **Skeletal Dysplasia Mutations Effect on Human Filamins' Structure and Mechanosensing.** Scientific Reports, 2017
T Verdorfer, RC Bernardi, et. al.; **Combining in Vitro and in Silico Single-Molecule Force Spectroscopy to Characterize and Tune Cellulosomal Scaffoldin Mechanics.** JACS, 2017
M Scheurer, P Rodenkirch, M Siggel, RC Bernardi, et. al.; **PyContact: Rapid, customizable, and visual analysis of noncovalent interactions in MD simulations.** Biophysical Journal, 2018
MCR Melo*, RC Bernardi*, et. al.; **NAMD goes quantum: An integrative suite for hybrid simulations.** Nature Methods, 2018
LF Milles, K Schulten, HE Gaub, RC Bernardi; **Molecular mechanism of extreme mechanostability in a pathogen adhesin.** Science, 2018
TJK Haataja, RC Bernardi, et. al.; **Non-syndromic Mitral Valve Dysplasia Mutation Changes the Force Resilience and Interaction of Human Filamin A.** Structure, 2019
SM Sedlak*, LC Schendel*, MCR Melo, DA Pippig, Z Luthey-Schulten, HE Gaub, RC Bernardi; **Direction Matters – Monovalent Streptavidin/Biotin Complex under Load.** Nano Letters, 2019
RC Bernardi, et al.; **Mechanisms of Nanonewton Mechanostability in a Protein Complex Revealed by Molecular Dynamics Simulations and Single-Molecule Force Spectroscopy.** JACS, 2019
SM Sedlak*, LC Schendel*, HE Gaub, RC Bernardi; **Streptavidin/Biotin: Tethering Geometry Defines Unbinding Mechanics.** Science Advances, 2020
Z Liu, H Liu, AM Vera, RC Bernardi, et. al.; **High Force Catch Bond Mechanism of Bacterial Adhesion in the Human Gut.** Nature Communications, 2020
RC Bernardi, et al.; **Bacteria on steroids: the mechanism of an NADH-dependent dehydrogenase involved in the conversion of cortisol to androgen in the gut microbiome.** bioRxiv, 2020
MCR Melo, RC Bernardi, et al.; **Generalized correlation-based dynamical network analysis: a new high-performance approach for identifying allosteric communications in molecular dynamics trajectories**. JCP, 2020
JC Phillips, D Hardy, JDC Maia, JE Stone, JV Ribeiro, RC Bernardi, et al.; **Scalable Molecular Dynamics on CPU and GPU Architectures with NAMD**. JCP, 2020

Acknowledgments



University of Illinois at Urbana-Champaign

Beckman Institute

Prof. Klaus Schulten

Prof. Zan Luthey-Schulten (NAMD QM/MM, Network Analysis)

Prof. Emad Tajkhorshid (PyContact, NAMD, QMTools)

Dr. Marcelo Melo
(NAMD QM/MM, GSAFold, Machine Learning, Network Analysis)

Dr. Till Rudack
(NAMD QM/MM, QwikMD)

Dr. Jim Phillips
(NAMD QM/MM)

Dr. João Ribeiro
(QwikMD)

Dr. Mariano Spivak
(QMTools)

John Stone
(VMD QM/MM, QwikMD)

Julio Maia
(NAMD QM/MM, NAMD GPU)

Institute for Genomic Biology

Prof. Isaac Cann
(GH Enzymatic Mechanisms)

Prof. Jason Ridlon
(Human Gut Microbiome Enzymes)

Ludwig Maximilians University of Munich, Germany

Prof. Hermann Gaub (AFM-based SMFS)

Prof. Philip Tinnefeld (Human Gut Cellulosomes)

Dr. Lukas Milles (Bacteria Adhesion)

Dr. Constantin Schoeler (Cohesin:Dockerin)

Dr. Klara Malinowska (Cohesin:Dockerin)

Dr. Tobias Verdorfer (ScaA Cohesins)

Dr. Ellis Durner (ScaB Cohesin:Dockerin)

Dr. Steffen Sedlak (Streptavidin:Biotin)

Leonard Schendel (Streptavidin:Biotin)

University of Basel & ETH Zurich, Switzerland

Prof. Michael Nash (Cellulosome Mechanics)

Weizmann Institute, Israel

Prof. Ed Bayer (Cellulosome Mechanics/Structure)

University of Jyväskylä & University of Turku, Finland

Prof. Ulla Pentikäinen (Filamins)

University of Heidelberg, Germany

Maximilian Scheurer (QM/MM)

Max Planck Institute – Mülheim, Germany

Prof. Frank Neese (QM/MM)

Federal University of Paraíba, Brazil

Prof. Gerd Rocha (QM/MM)

Rafael C. Bernardi
rcbernardi@auburn.edu

Funding Support and Computational Resources provided by:

ENERGY BIOSCIENCES INSTITUTE · NATIONAL INSTITUTES OF HEALTH · NSF · U.S. DEPARTMENT OF ENERGY

Thank you!

AUBURN

UNIVERSITY

COLLEGE OF SCIENCES

AND MATHEMATICS

Department of Physics