



# *Biomolecular Simulation*

## *Aspirations, Limitations and Prospects*

Sarah Anne Harris  
University of Leeds

Computational

In pursuit of an accurate spatial and temporal model of biomolecules at the atomistic level: a perspective on computer simulation

← as a biophysical tool

Alan Gray, Oliver G. Harlen, Sarah A. Harris, Syma Khalid, Yuk Ming Leung, Richard Lonsdale, Adrian J. Mulholland, Arwen R. Pearson, Daniel J. Read and Robin A. Richardson

*Acta Cryst.* (2015). D71, 162–172

# *Current State of the Art*

Quantum  
mechanics

Atomistic  
MD

Coarse-  
grained MD

Dissipative  
particle  
dynamics,  
Lattice  
Boltzmann

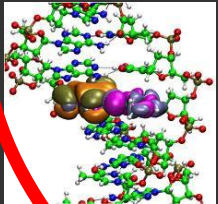
Finite  
element  
analysis

CCPBioSim

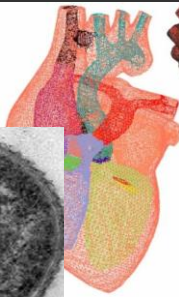
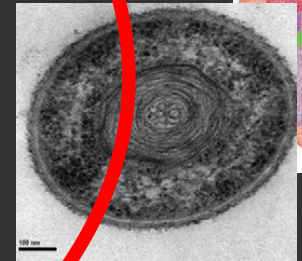
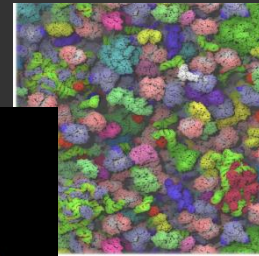
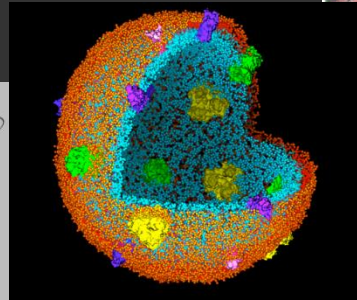
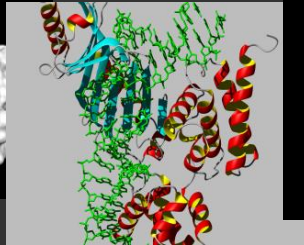
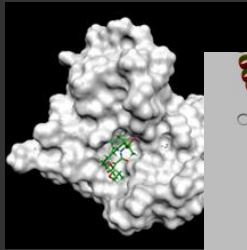
Accuracy

Size/  
timescale

100 atoms



10,000 atoms/ $\mu$ s  
1 million atoms/ns



Photosynthesis  
Enzyme  
catalysis

Molecular  
recognition

Cytoplasmic  
crowding,  
supermolecular  
structures

Cells,  
biological  
tissues, organs

# Biological Structural Databases

## The Protein Data Bank (PDB)



RCSB Protein Data Bank - RCSB PDB - Windows Internet Explorer

http://www.pdb.org/home/home.do

Search: Everything | Author | Macromolecule | Sequence | Ligand

g. PDB ID, molecule name, author

Search History, Previous Results

Customize This Page

Available on the App Store

PDB-101

Structural View of Biology

Molecule of the Month: Actinomycin

Many antibiotics have been found by studying the constant warfare between bacteria and fungi, and isolating the toxic molecules that they build to protect themselves. Actinomycin is the first natural antibiotic discovered that has anti-cancer activity. It was discovered in the bacterium Streptomyces antibioticus in 1940. Unfortunately, it is too toxic for general use, killing cancer cells but also poisoning the patient, but

RCSB PDB News

Weekly | Quarterly | Yearly

2013-04-09

Visit the RCSB PDB at NSTA

Build DNA models and more at the 2013 meeting of the National Science Teachers Association in San Antonio, TX. more

Atomistic co-ordinates

## The EM Data Bank (EMDB)



Home : EMDatabank - Windows Internet Explorer

http://www.emdatabank.org/

2013-04-10 : 1826 EMDB map entries, 555 PDB coordinate entries

EMDatabank

Unified Data Resource for 3DEM

One-stop shop for 3DEM deposition and retrieval

Home | About | Deposit | Search | Tools | Events | News | Links | Help

Unified Data Resource for 3-Dimensional Electron Microscopy

EMDatabank is a unified global portal for deposition and retrieval of 3DEM density maps, atomic models, and associated metadata, as well as a resource for news, events, software tools, data standards, validation methods for the 3DEM community.

Recently released entries

2345

PDBe | RCSB

March 27, 2013 RELEASED ON April 10, 2013 singleParticle 44.0A NEW

The electron microscopy reconstruction of the tripod of lactococcal phage Tuc2009.

News

Announcement: EMDB header format update

On 16 January 2013, the EMDB archive plans to adopt an updated format, v.1.9.0, for the entry header file (XML file associated with each map). This means that EMDB header files distributed from wwPDB partner sites will conform to the 1.9.0 format, and EMDatabank deposition/annotation/search services will start using this format. Read more...

EMDatabank September News

Changes to FTP access for map data: reminder

As we announced early in the year, the EMDB map archive is now distributed alongside the PDB archive by all three wwPDB partner sites. To

Volumetric data

Data standardisation and validation  
SAS-DataBank?

# *Successes*

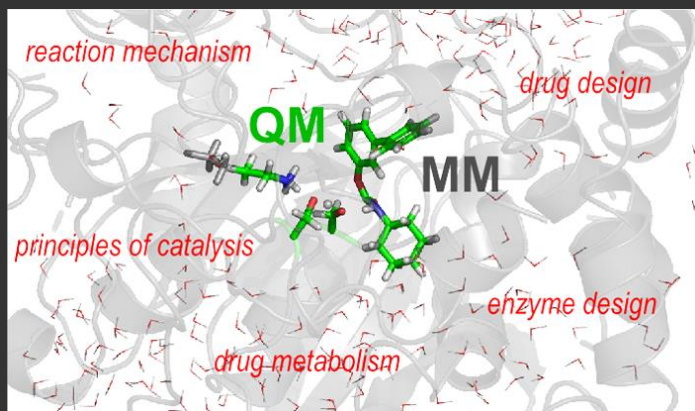
Well established software & visualisation tools  
(GROMACS/AMBER/NAMD/DL\_POLY)  
(VMD/PYMOL/CHIMERA)

Ubiquitous in pharmaceutical industry (High  
throughput screening)

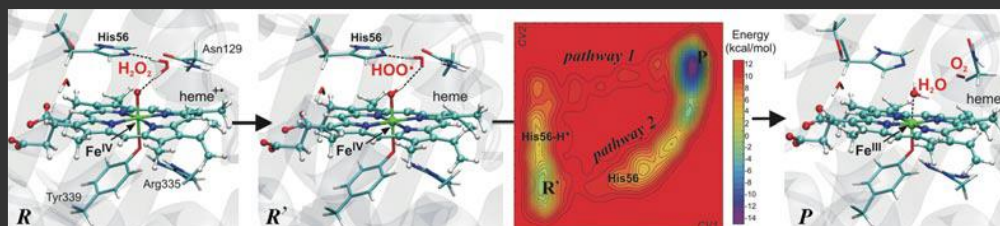
Reasonable parallelisation/porting to GPU

Nobel prizes in 2013

# *PDB: QM, QM-MM, MD, Coarse-grained*



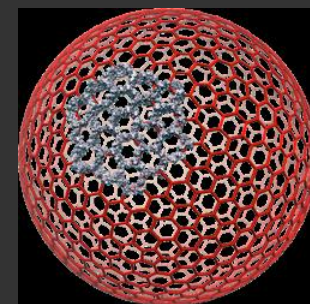
Van der Kamp & Mulholland, Biochemistry (2013)



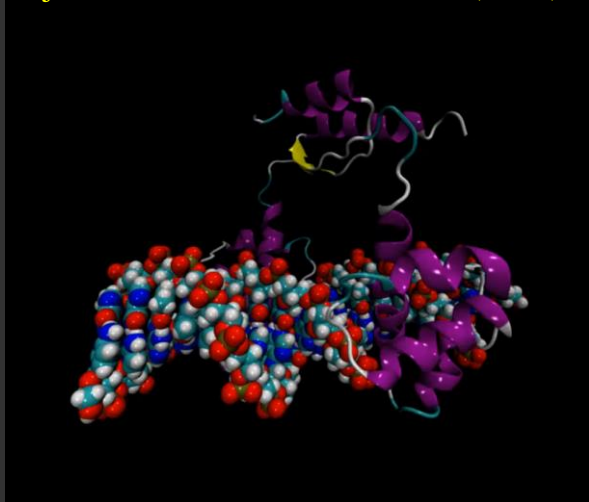
## Molecular mechanisms of catalase reaction with metadynamics

Barducci et al WIRES 2011

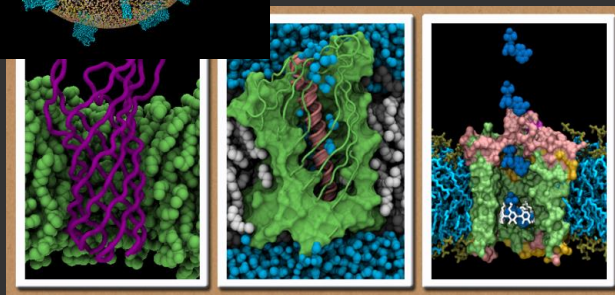
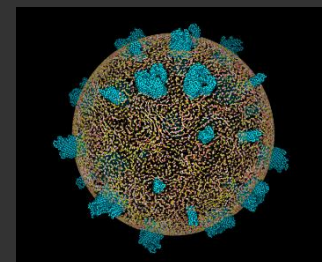
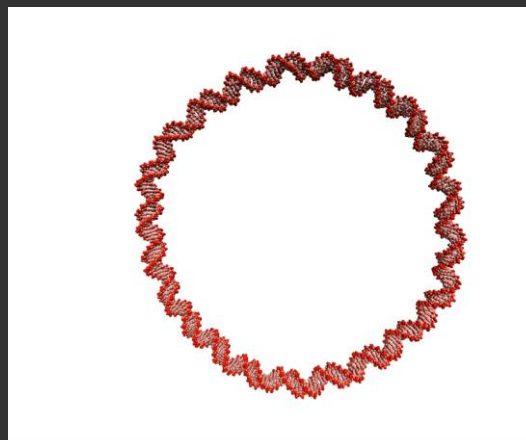
Paper Self-Assembling Cages from Coiled-Coil Peptide Modules (Science 2013)



Rajasekar et al, Nucleic Acids Res. (2016)



Noy et al, Biophys J, 2017





# *Challenges*

Connecting with experimental data (limitations in accessible length/time-scales)

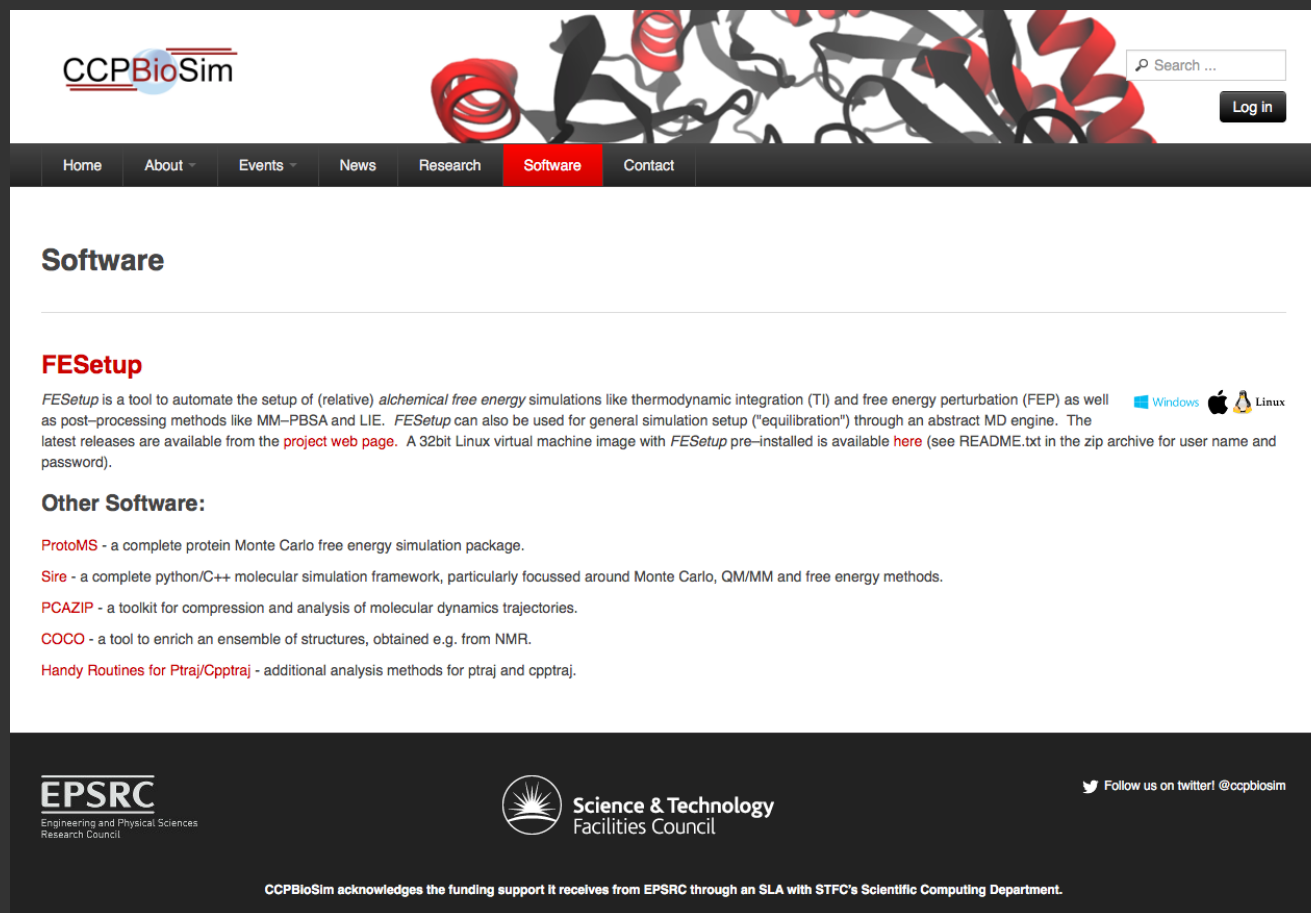
Method validation (eg forcefields)

Software usability/avoiding the “black box”

Exploiting hardware (e.g. GPUs/parallelisation)

Enhanced sampling/multi-scale approaches are required ~ need for method development at all stages

# Method and Software Development



The screenshot shows the CCPBioSim website. The header features the CCPBioSim logo, a search bar, and a 'Log in' button. A navigation menu includes links for Home, About, Events, News, Research, Software (highlighted in red), and Contact. The main content area is titled 'Software' and features a section for 'FESetup'. This section describes FESetup as a tool for automating the setup of (relative) alchemical free energy simulations, including thermodynamic integration (TI) and free energy perturbation (FEP), as well as post-processing methods like MM-PBSA and LIE. It also mentions that FESetup can be used for general simulation setup ('equilibration') through an abstract MD engine. The latest releases are available from the project web page, and a 32bit Linux virtual machine image with FESetup pre-installed is available here (see README.txt in the zip archive for user name and password). Below this, there is a section for 'Other Software:' listing several tools: ProtoMS (a complete protein Monte Carlo free energy simulation package), Sire (a complete python/C++ molecular simulation framework), PCAZIP (a toolkit for compression and analysis of molecular dynamics trajectories), COCO (a tool to enrich an ensemble of structures), and Handy Routines for Ptraj/Cpptraj (additional analysis methods for ptraj and cpptraj). The footer contains logos for EPSRC (Engineering and Physical Sciences Research Council) and the Science & Technology Facilities Council, along with a Twitter follow link @ccpbiosim. A disclaimer at the bottom states that CCPBioSim acknowledges funding support from EPSRC through an SLA with STFC's Scientific Computing Department.

CCPBioSim

Search ...

Log in

Home About Events News Research **Software** Contact

## Software

### FESetup

*FESetup* is a tool to automate the setup of (relative) *alchemical free energy* simulations like thermodynamic integration (TI) and free energy perturbation (FEP) as well as post-processing methods like MM-PBSA and LIE. *FESetup* can also be used for general simulation setup ("equilibration") through an abstract MD engine. The latest releases are available from the [project web page](#). A 32bit Linux virtual machine image with *FESetup* pre-installed is available [here](#) (see README.txt in the zip archive for user name and password).

Windows Apple Linux

### Other Software:

**ProtoMS** - a complete protein Monte Carlo free energy simulation package.


**Sire** - a complete python/C++ molecular simulation framework, particularly focussed around Monte Carlo, QM/MM and free energy methods.

**PCAZIP** - a toolkit for compression and analysis of molecular dynamics trajectories.

**COCO** - a tool to enrich an ensemble of structures, obtained e.g. from NMR.

**Handy Routines for Ptraj/Cpptraj** - additional analysis methods for ptraj and cpptraj.

**EPSRC**  
Engineering and Physical Sciences  
Research Council

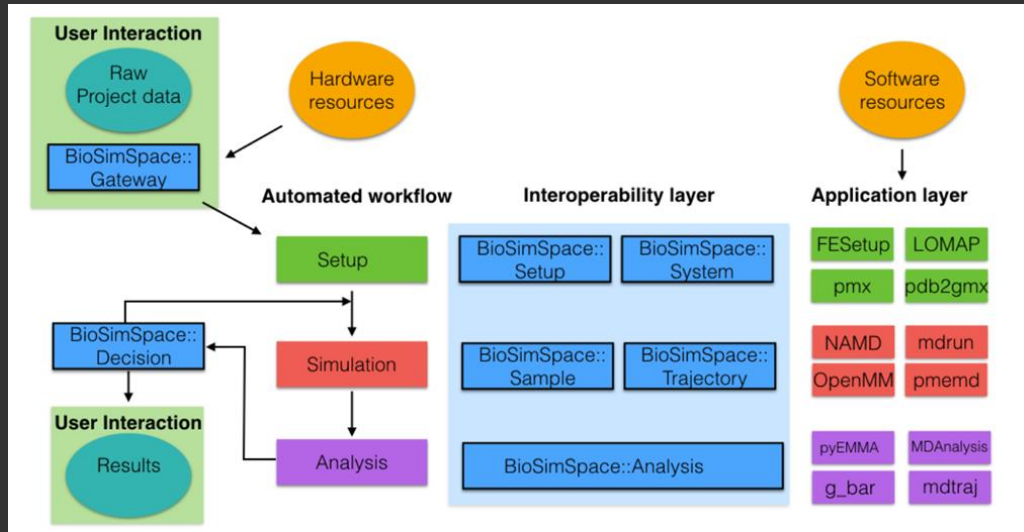
 **Science & Technology  
Facilities Council**

Follow us on twitter! @ccpbiosim

CCPBioSim acknowledges the funding support it receives from EPSRC through an SLA with STFC's Scientific Computing Department.

New and old methods need to reach our community e.g.  
workshops/conferences/online tools

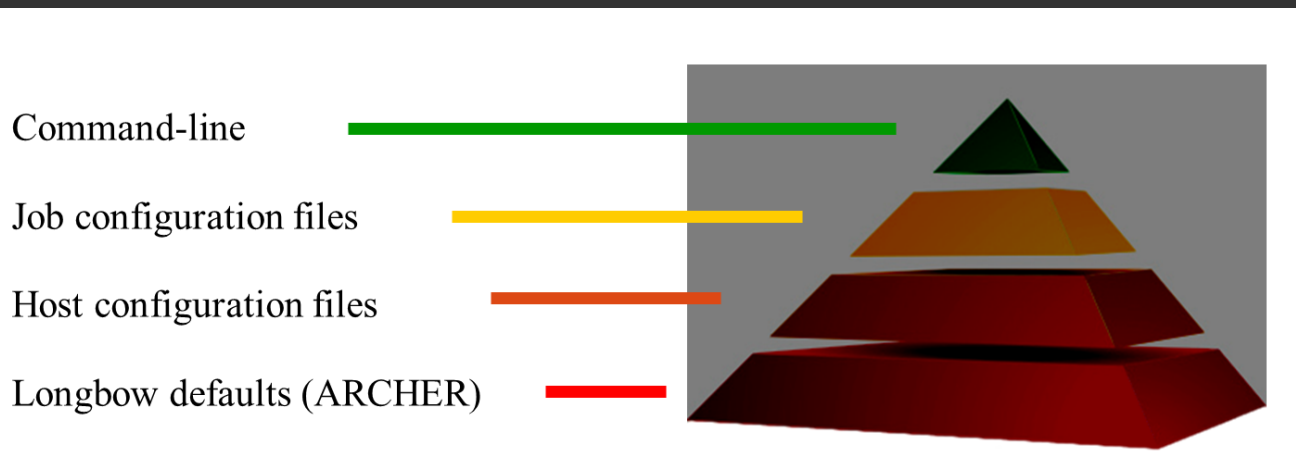
# Software Flagship: BioSimSpace



Python translation layer  
to allow tools  
communicate

Easier to write robust and  
reusable workflow  
components

**Longbow:** Submission and retrieval of multiple HPC jobs





# *Training*

[http://www.ccpbiosim.ac.uk/events/  
workshop-course-material](http://www.ccpbiosim.ac.uk/events/workshop-course-material)

Collaborations with other CCPs to understand scientific challenges and share resources and expertise

# *Collaborative Conferences*

Two way street – Complementary Methods CCP4 2014

CCPN/CCPBioSim Joint Conference 2016

2nd Conference on Multiscale Modelling of Condensed Phase and Biological Systems - CCPBioSim & CCP5 2016

Multiscale Modelling of Condensed Phase and Biological Systems 2014

Collaborations with other CCPs to understand scientific challenges and share resources and expertise

Essential to avoid duplication of effort.

Annual grand CCP meeting? Grand CCP science challenge?

*The Future....*

Computation for Biomolecular Cryo-Electron  
Microscopy and Tomography

Thursday 13 July 2017 - Workshops  
- on Wednesday 13 September 2017 - Conferences

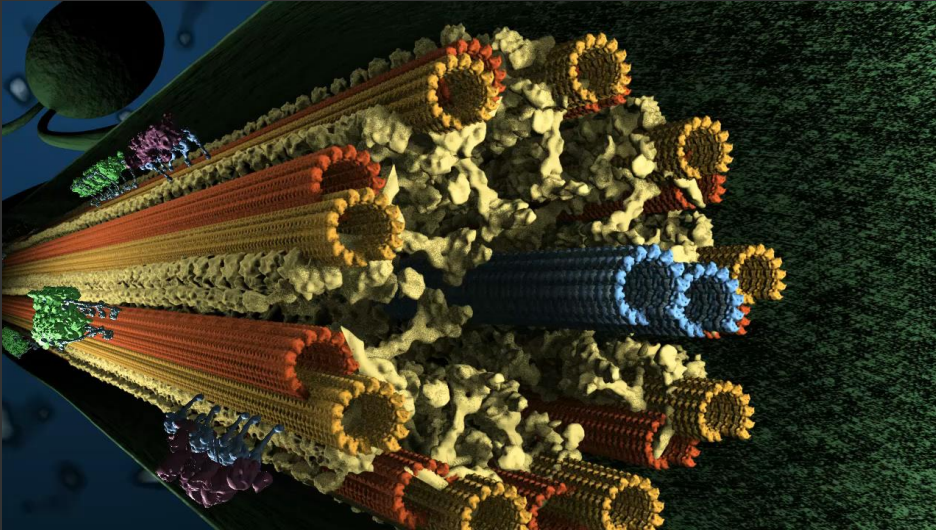
5th Annual CCP-BioSim Conference: Frontiers  
of Biomolecular Simulation

Wednesday 13 September 2017 - Conferences

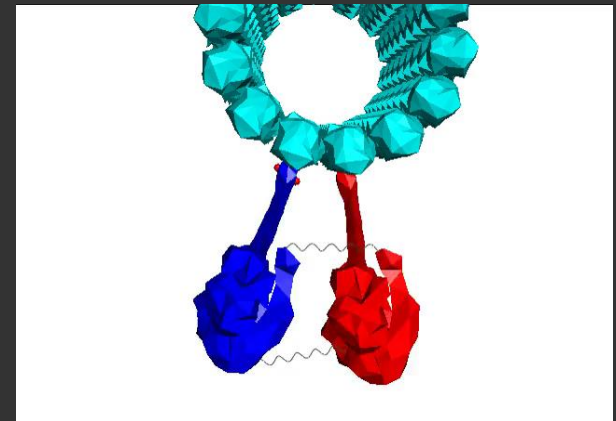
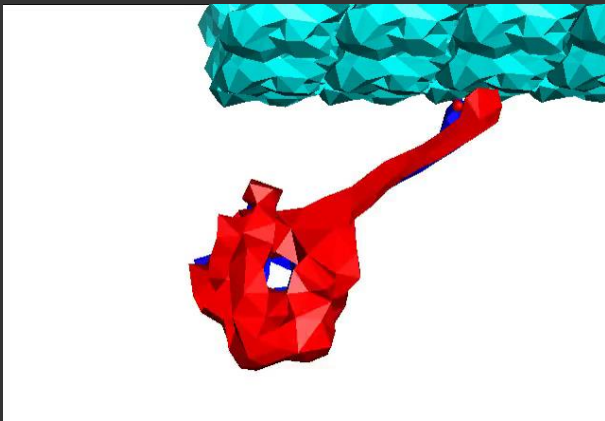
**All Welcome!**

# *EMDB: Towards Ultra-structure ~ FFEA*

Animation by Bara Malkova for Pagino group



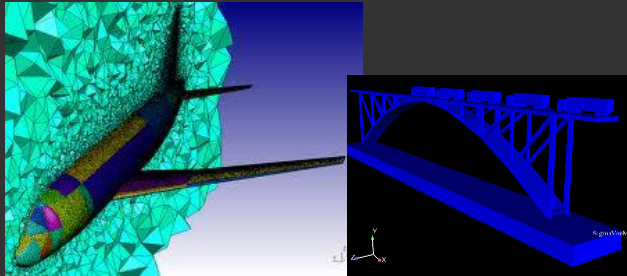
What is the effect of the strength of the interaction between the monomers?



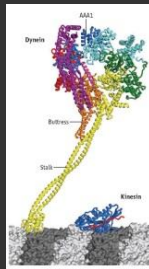
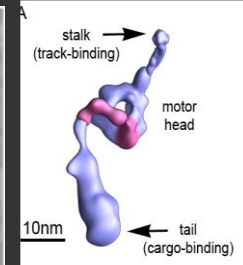
*Fluctuating Finite Element Analysis (FFEA)*

# *Fluctuating Finite Element Analysis (FFEA)*

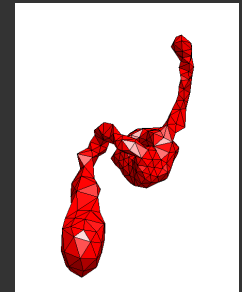
Finite element analysis describes the shape of a complex object using a 3D mesh.



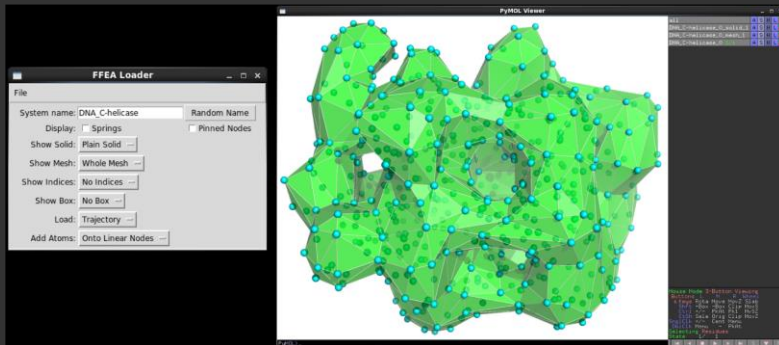
EMDB/PDB file



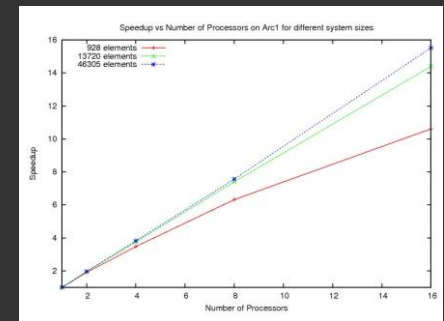
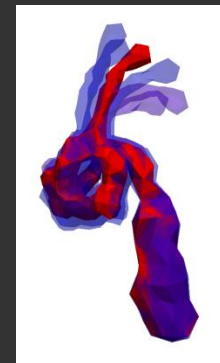
Generate mesh



Assign material parameters



FFEA



Analyse trajectory

Code uses shared  
memory parallelisation