Multi-scale Modelling of Molecular Motors with Fluctuating Finite Element Analysis

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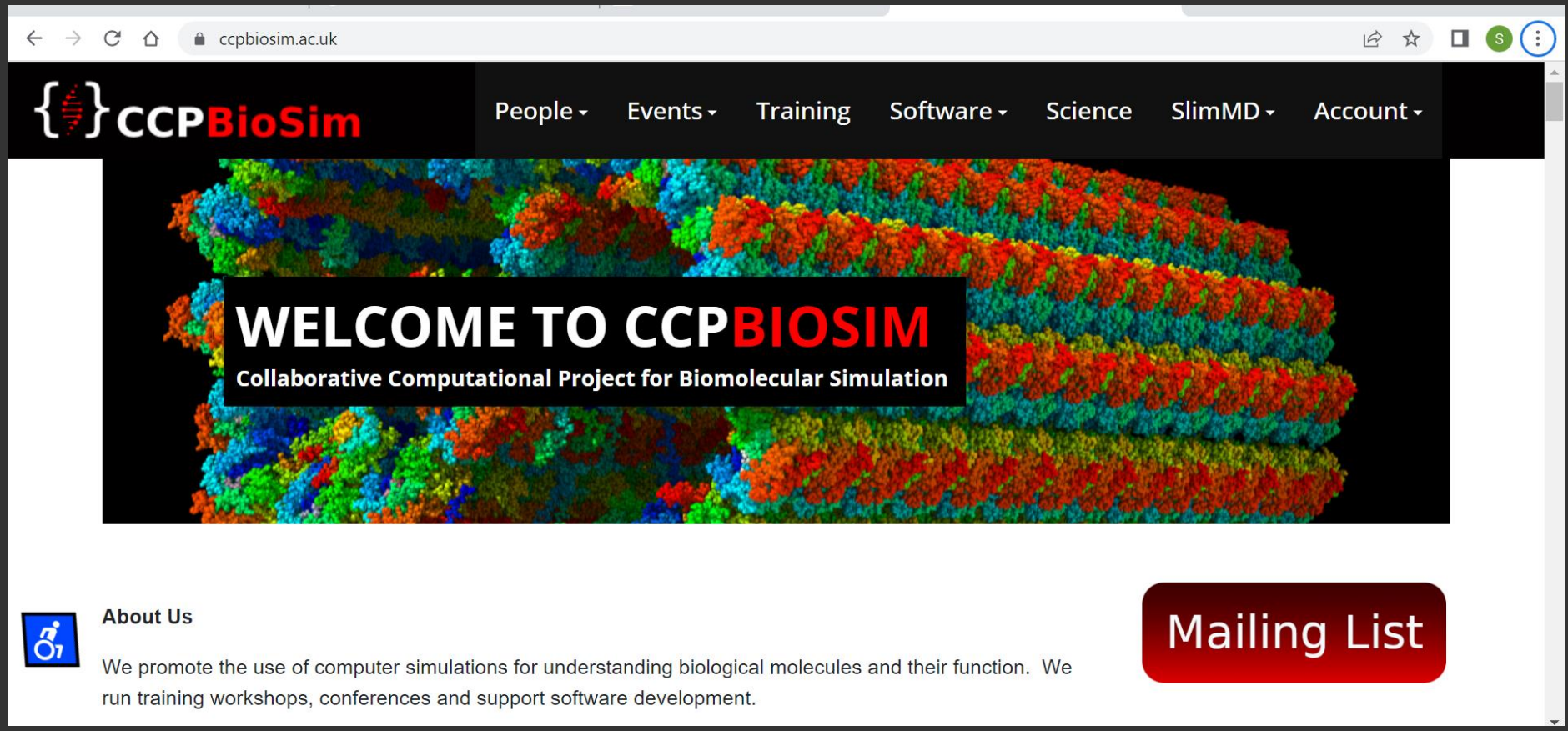
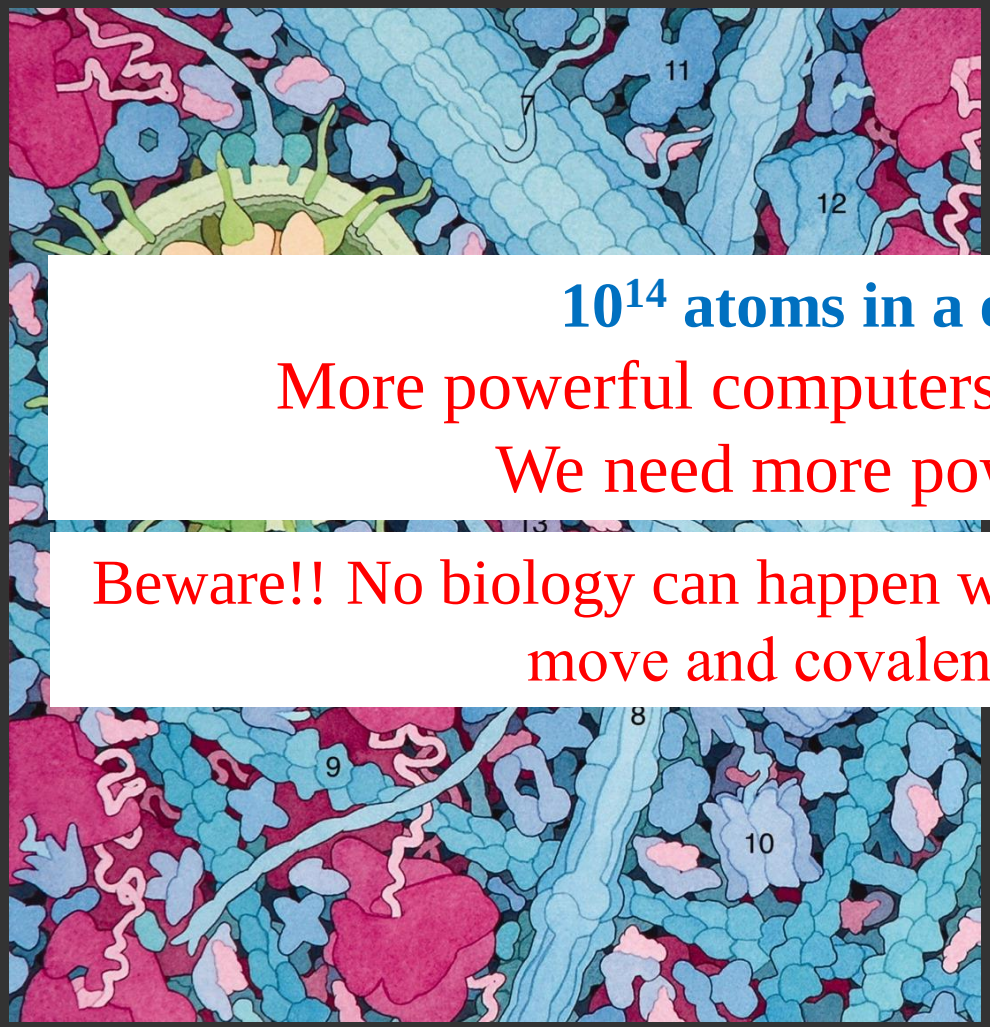
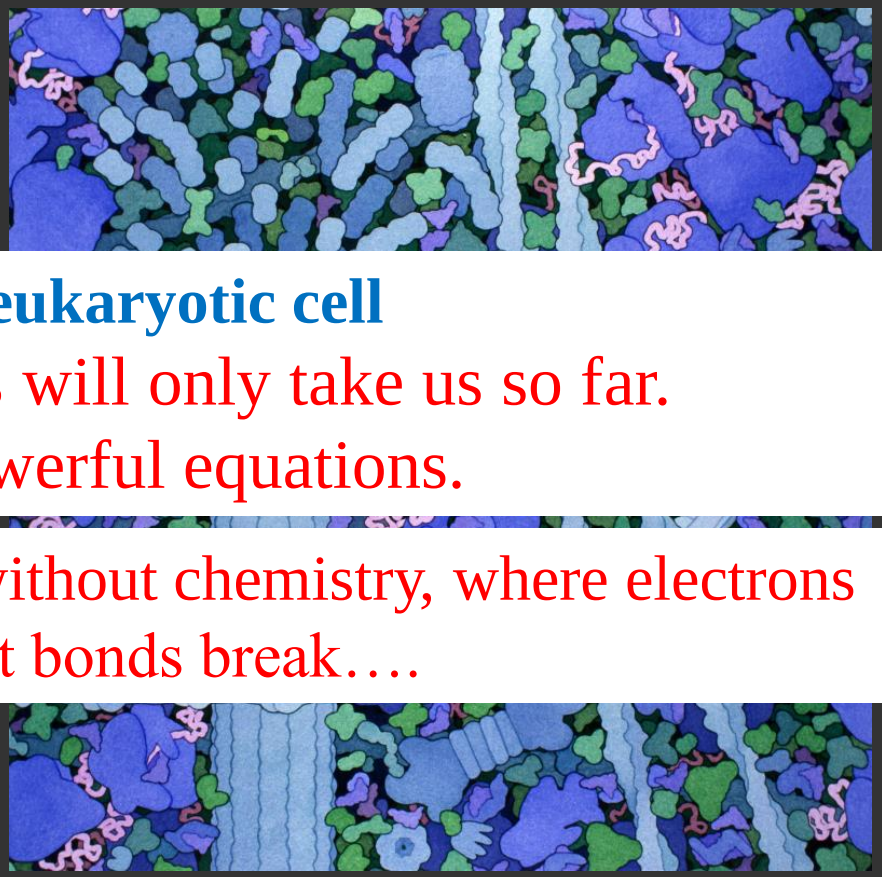
CCPBioSim Network – Please join us!!

https://www.ccpbiosim.ac.uk/



The Cytoplasm is Packed with Motors





10^{14} atoms in a eukaryotic cell

More powerful computers will only take us so far.

We need more powerful equations.

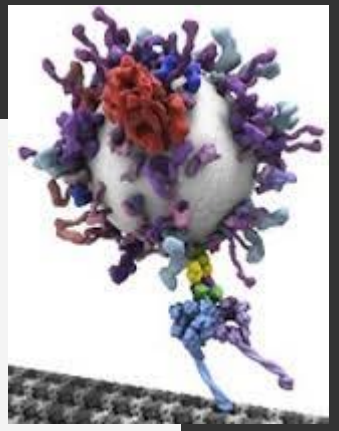
Beware!! No biology can happen without chemistry, where electrons move and covalent bonds break….

Transport of a vesicle through the cytoplasm. (1) SNARE; (2) vacuolar ATPase; (3) golgin; (4) Rab; (5) kinesin; (6) microtubule; (7) MAP; (8) intermediate filament; (9) actin; (10) TRiC/CCT chaperonin; (11) fatty acid synthase; (12) calcium/calmodul independent protein kinase II; (13) caspase 7 and XIAP

Eukaryotic Cell Panorama, Goodsell 2011: doi.org/10.1002/bmb.20494

Cytoplasmic Dynein Walking

Cytoplasmic dynein transports cargo along microtubules (towards the cell center!)



HARVARD MEDICAL SCHOOL

The Axoneme ~ A Macromolecular Machine

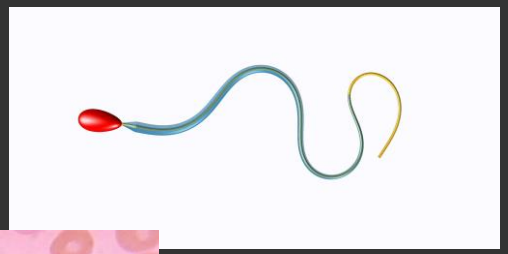
16 dyneins in 96nm repeat; 9 MT doublets

50-100×96nm = 5-10μm length

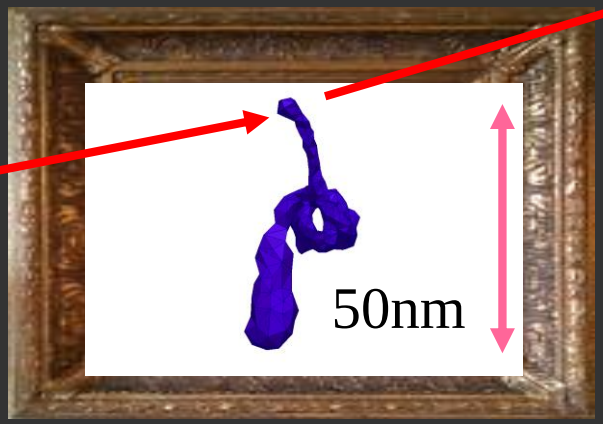
6×10^8 atoms (non solvent)

Hermes Gadelha, York

Sperm



Trypanosomes

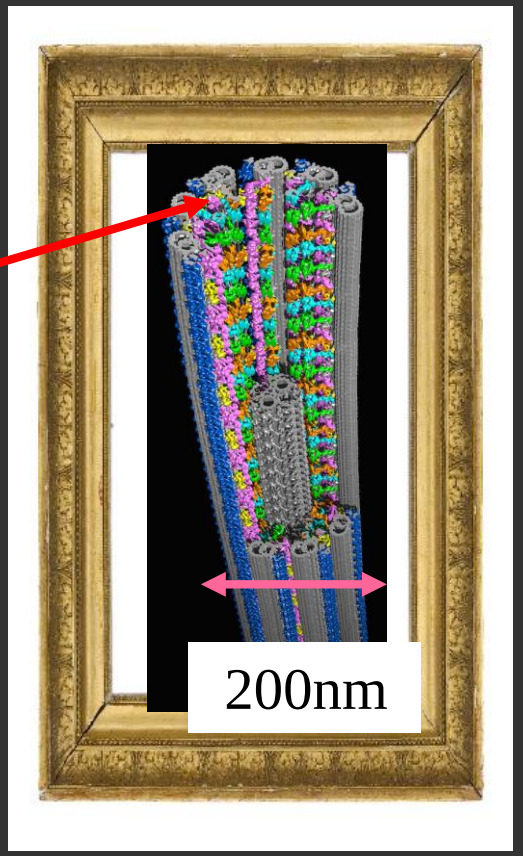


Dynein Motor

~1 million atoms in water (no tail)

10nm

Dynein MTBD

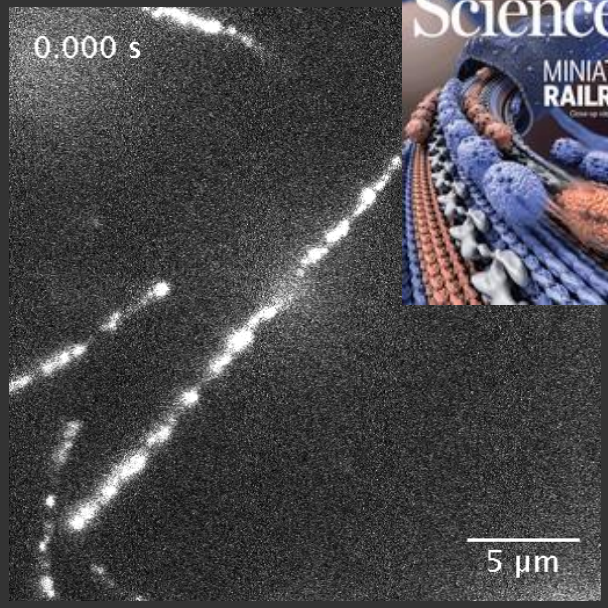


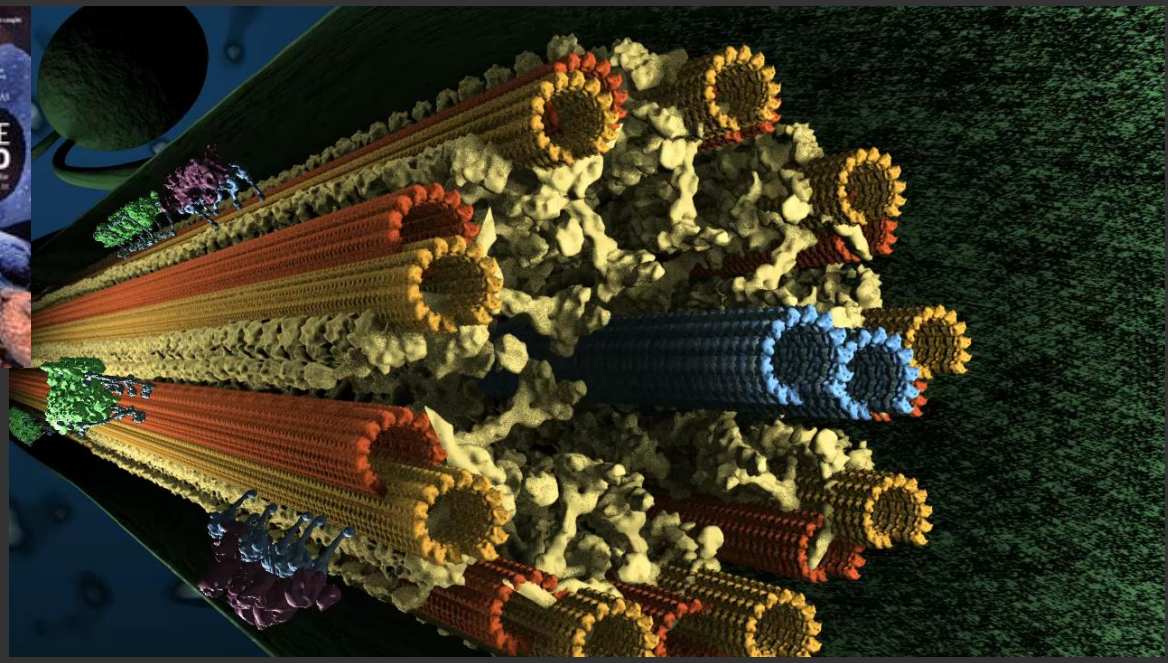
Cryo-ET Nicastro lab

Axoneme

Constructing the Axoneme: An Animation

TIRF microscopy of GFP labelled IFT trains in Chlamydomonas flagella attached to a coverslip. After 8 sec the movement is stopped by glutaraldehyde fixation.



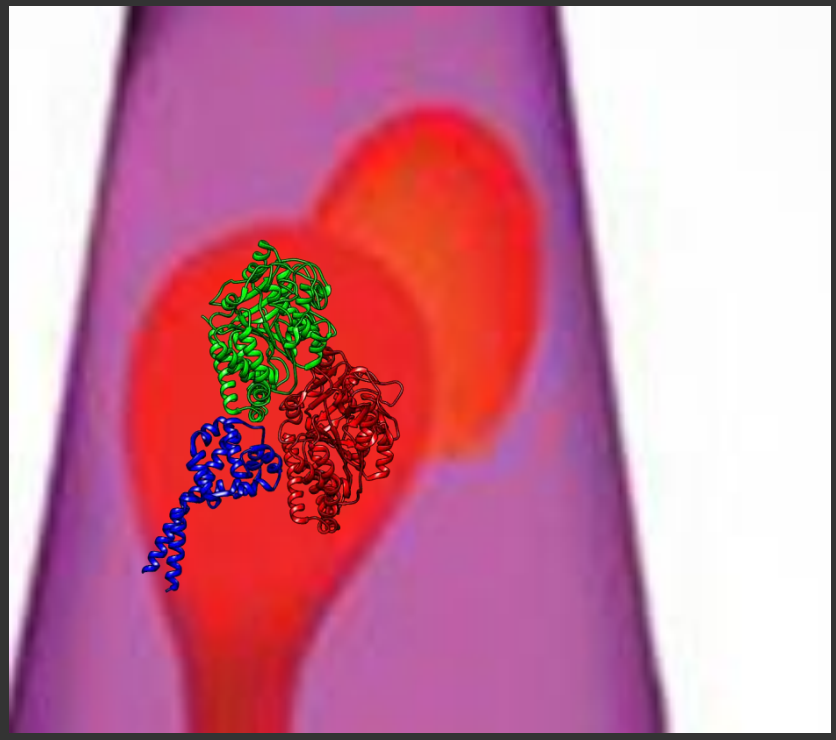


Animation by Bara Malkova for Pigino group

https://www.mpi-cbg.de/en/research-groups/current-groups/gaia-pigino/gallery/

Nicastro axoneme movie: https://www.youtube.com/watch?v=9nZYlyFGm50

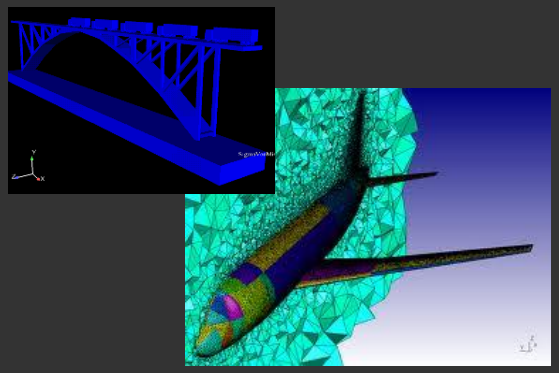
A New Mechanics for Soft Matter: FFEA



Fluctuating Finite Element Analysis (FFEA): proteins are continuum viscoelastic solids experiencing thermal noise

Fluctuating-Finite Element Analysis (FFEA)

FEA describes the shape of a complex object using a 3D mesh.



To model protein dynamics, FFEA includes a thermal noise term.

Change of momentum

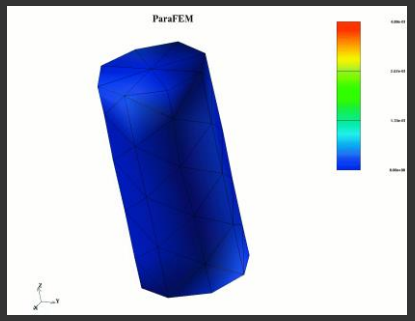
$$\rho \frac{D\mathbf{u}}{Dt} = \nabla \cdot \left(\boldsymbol{\sigma}^{e} + \boldsymbol{\sigma}^{v} + \boldsymbol{\sigma}^{t} \right)$$

Thermal noise
New in FFEA

Viscous dissipation
"Liquid"-like

Elastic stresses
"Solid"-like

A fluctuating "jelly" model of a protein



FFEA is a new *continuum* method for bio-simulation appropriate for length-scales between 10 and 500nm (and larger)

Oliver, Read, Harlen, Harris *J. Comp. Phys* (2013) 239, 147.

FFEA Simulation Workflow

Volumetric Mesh generation from cryo-ET is non-trivial!

EMDB/PDB file

↓

Generate mesh

↓

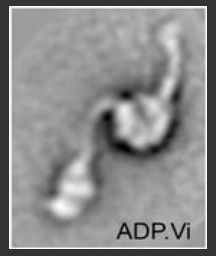
Assign material parameters & protein-protein interactions

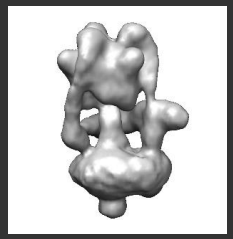
↓

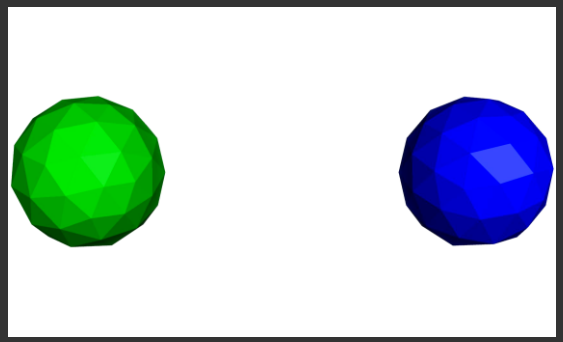
FFEA

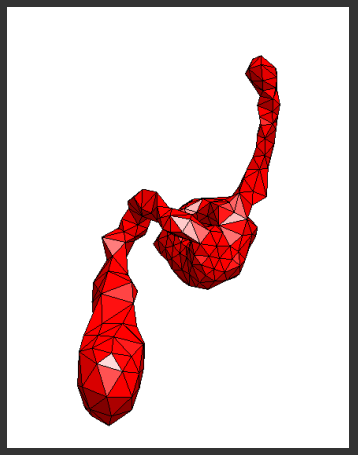
↓

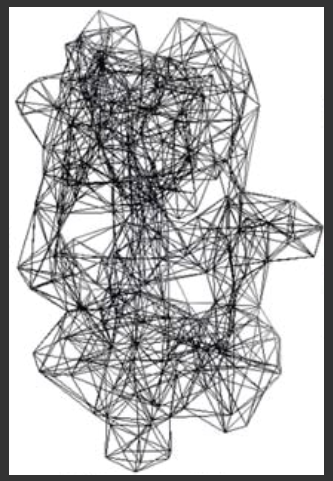
Analyse trajectory



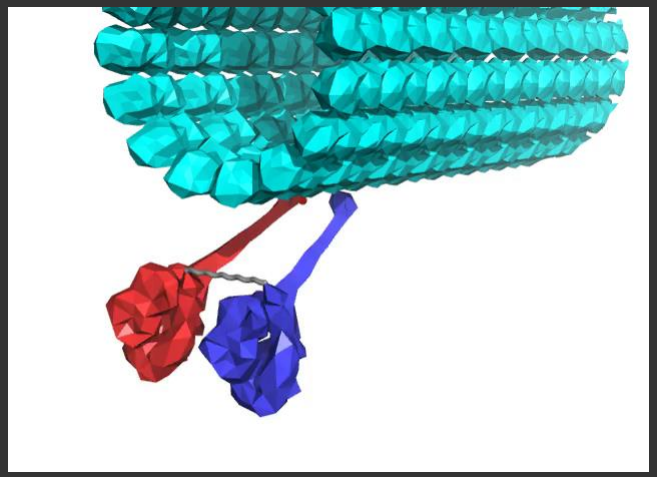


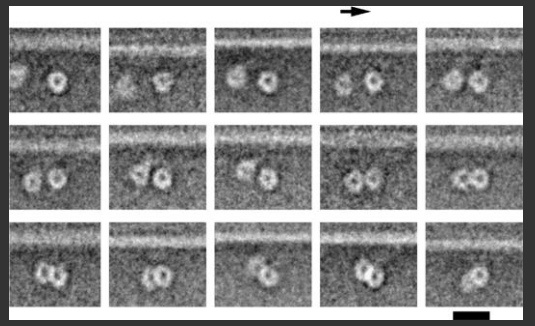






Richardson *et al*, Proteins, 2014

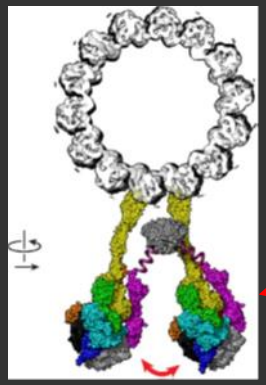




Imai *et al* Nat Comm 2015

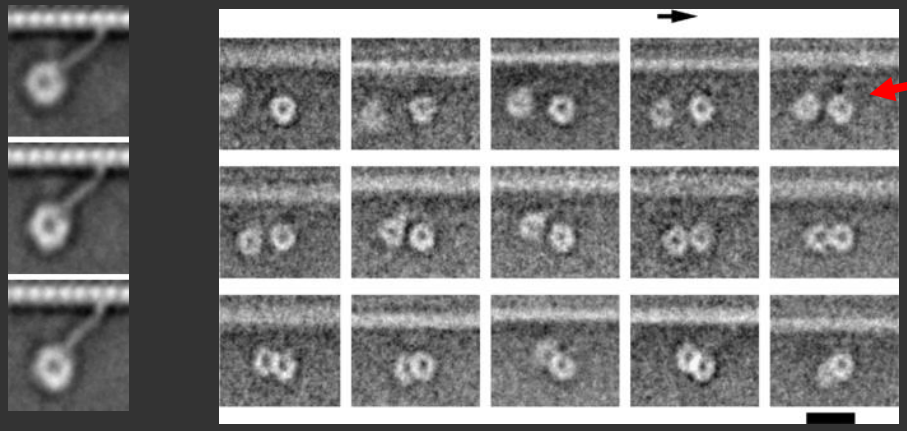
Cryo-EM of Cytoplasmic Dynein

Cryo-EM of truncated cytoplasmic dynein shows the static conformations that dynein adopts while walking.



X-ray crystal structure

Kon et al NSMB 2011/Nature 2012

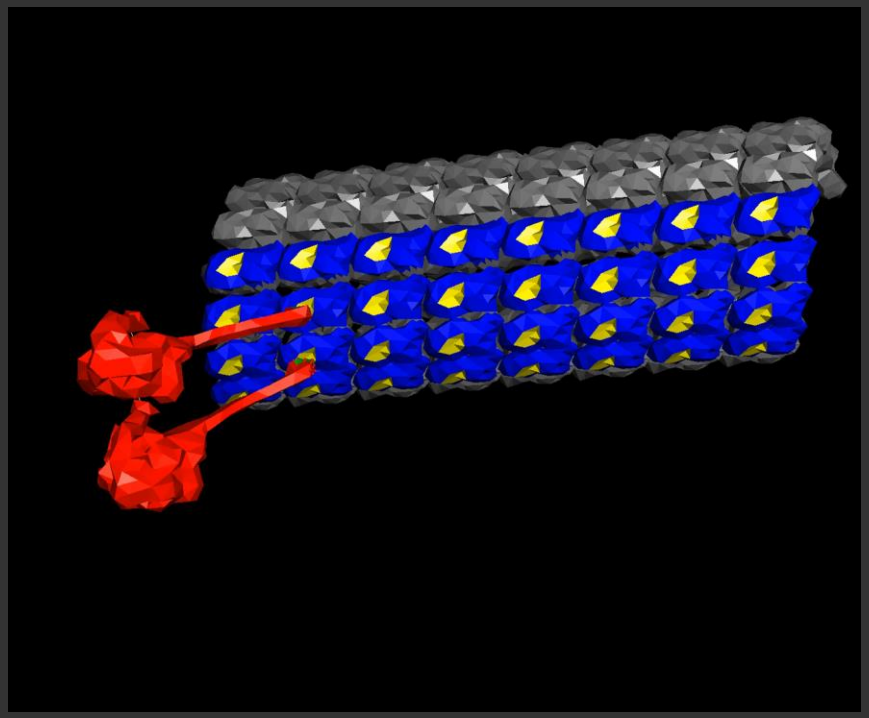


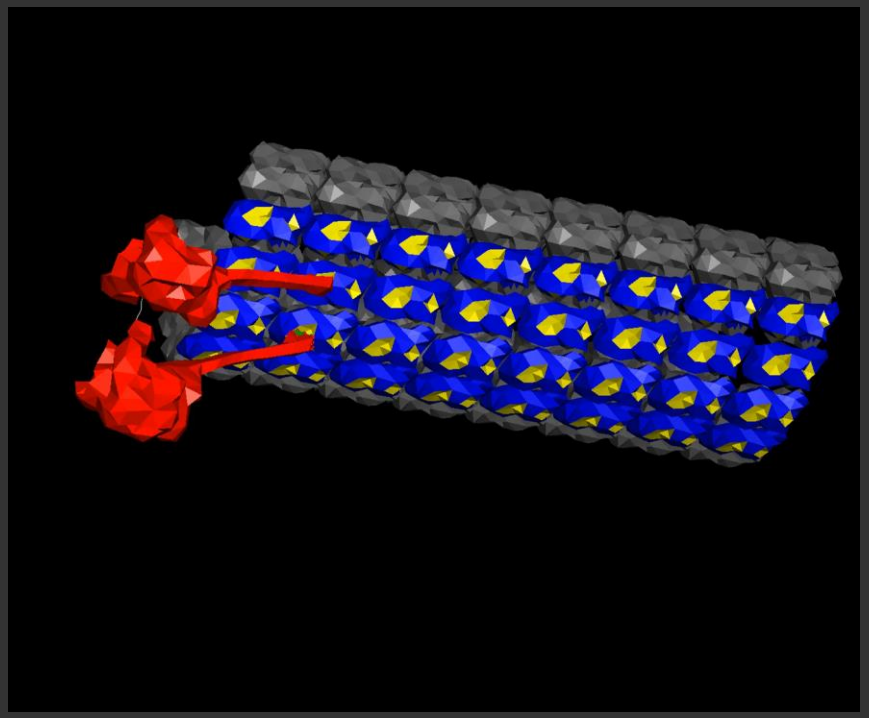
Dimers dissociate during walking

Imai *et al* Nat Comm 2015

Can we use FFEA to turn these static picture into a mechanical model of dynein walking?

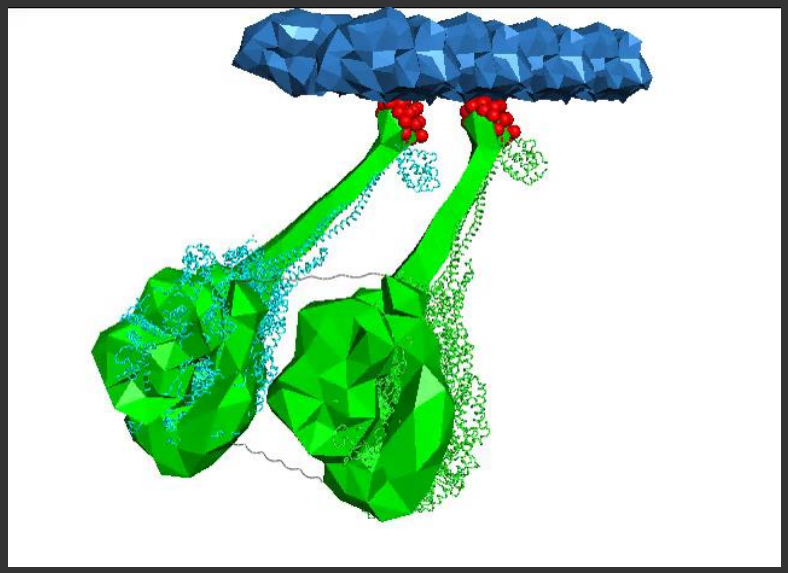
Apply a weakly attractive potential (blue) and strongly attractive (yellow) for the specific motor binding sites
FFEA over ~μs timescales

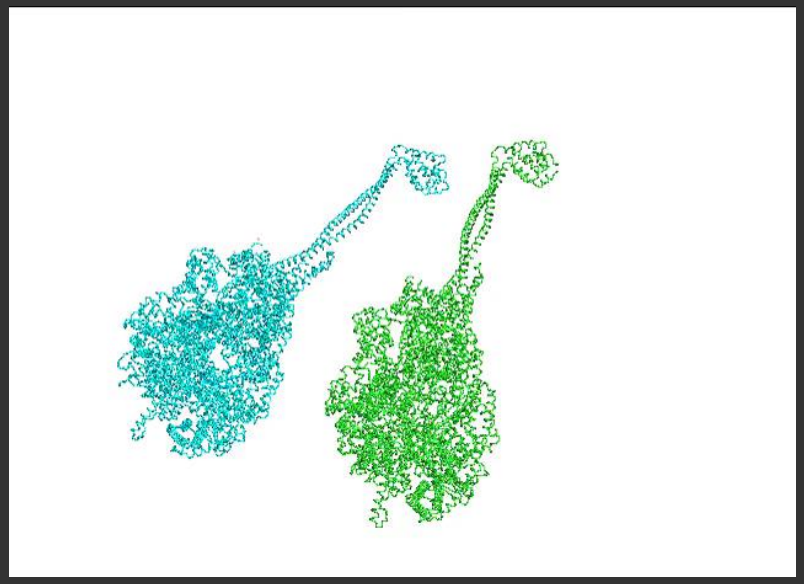




FFEA shows motor processivity is only achievable with a weak non-specific potential

From FFEA to Atomistic Models





FFEA models can be mapped back onto atomistic co-ordinates

Can make point mutations/add ligands etc, re-parameterise, assess effect on mesoscale!!

Atomistic MD of dynein monomer: 980 265 atoms, 53 443 in dynein

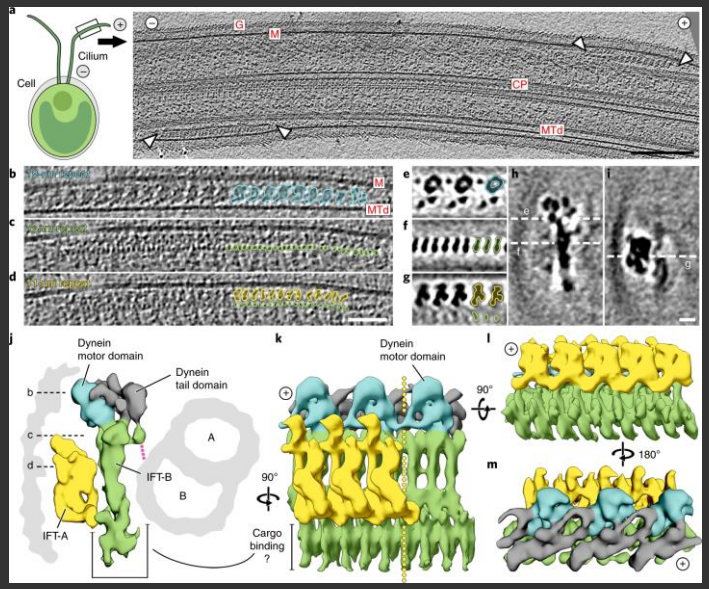
See Kamiya et al, PEDS, 2016

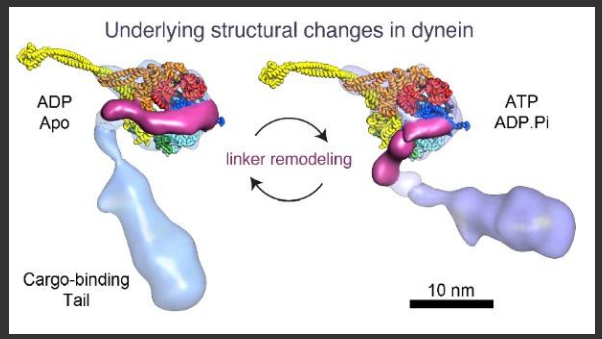
(Dimer 1 636 455 total, 106,886 in dynein)

From cryo-ET to FFEA models

How can we construct hierarchical dynamic models of subcellular structures?

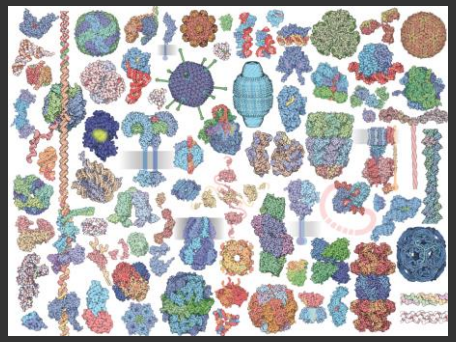
Pigino lab: NCB 2018





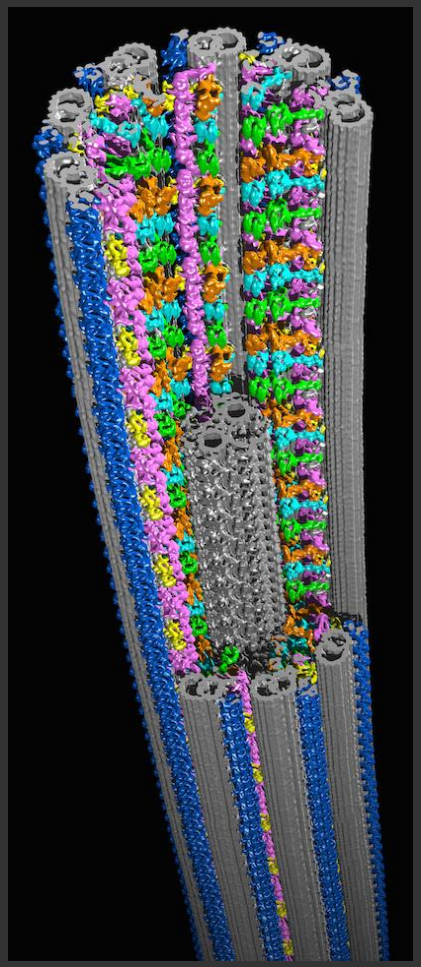
Roberts *et al*, *Structure* (2012), 20 1670

Identify molecular components



Assign multiple conformers

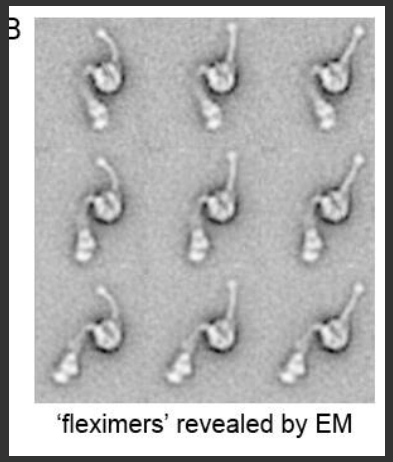
Automatic mesh generation

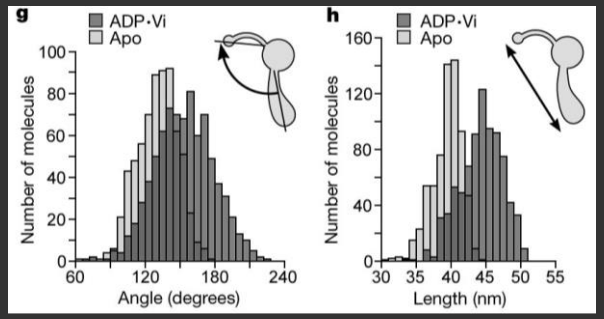


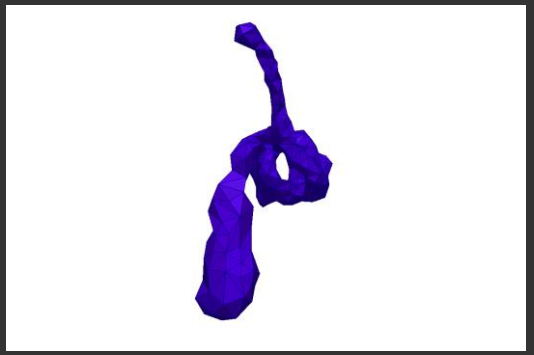
Nicastro lab

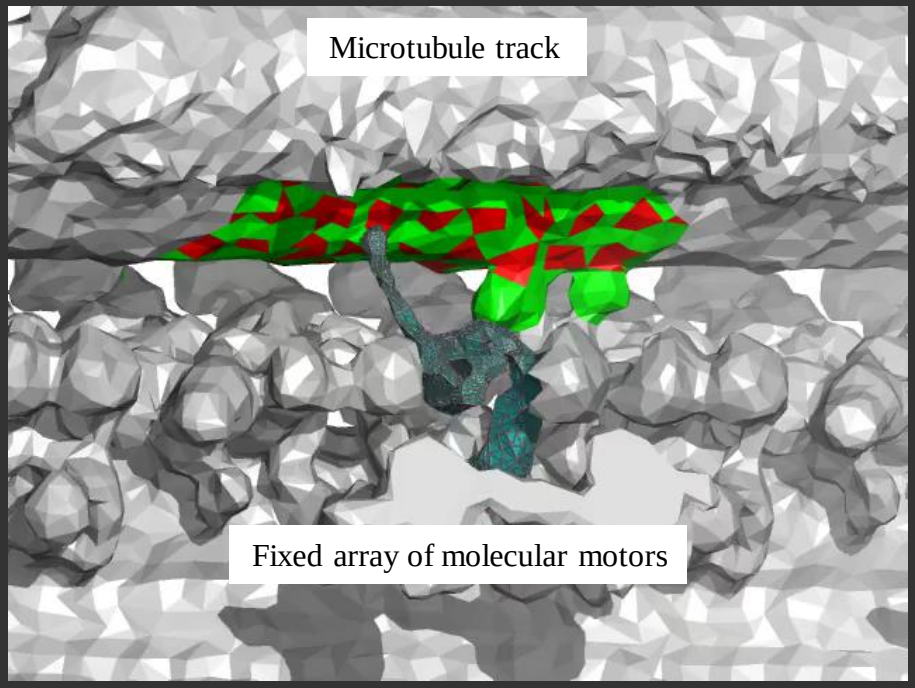
Assign material parameters:
i) Experimental data ii) MD simulations

(Hanson, Methods 2020; Richardson QRB 2020)



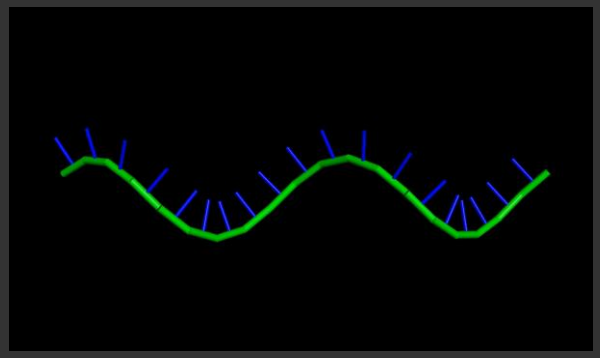




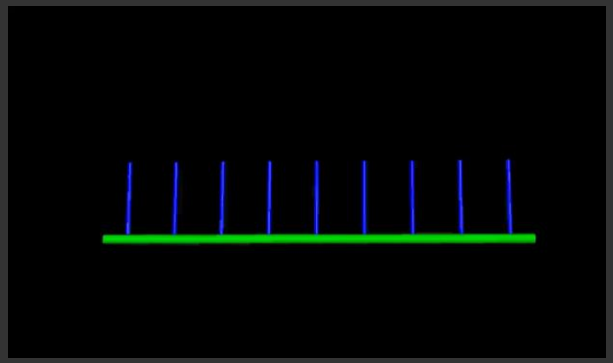


FFEA with Rods

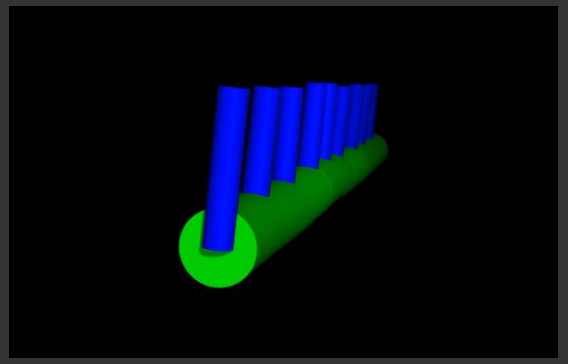
Twist

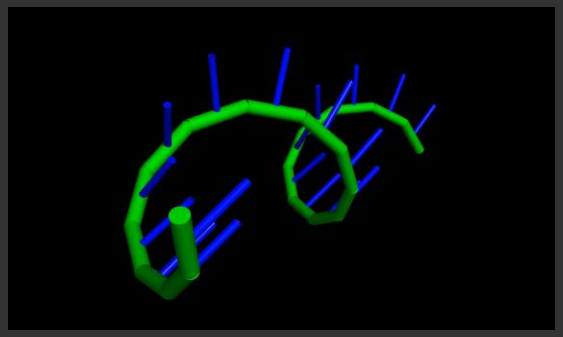


Hinge

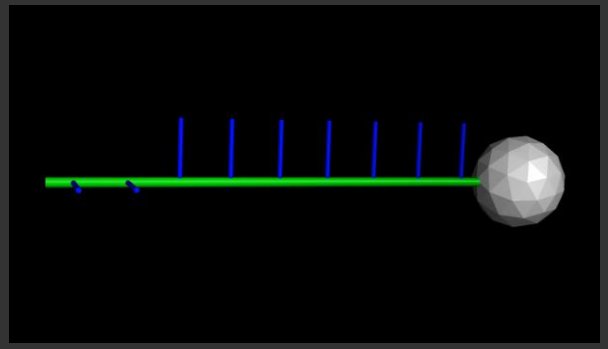


Wobble





Rods+blobs

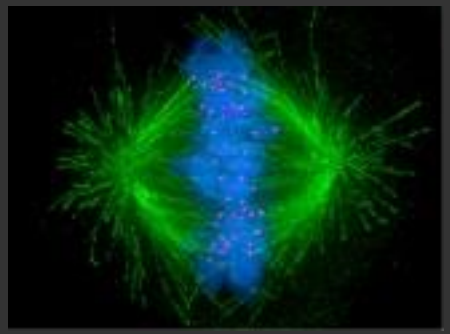


Long objects are inefficient for tetrahedral meshing

Welch et al Soft Matter 2020 "KOBRA: a fluctuating elastic rod model for slender biological macromolecules"

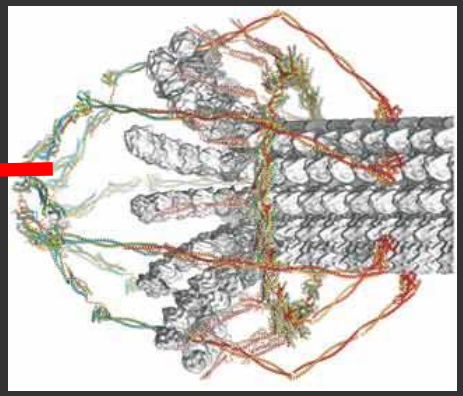
We are also intending to include 2D sheets (e.g. for membrane modelling)

Simulations of the Kinetochore Lateral Attachment with FFEA



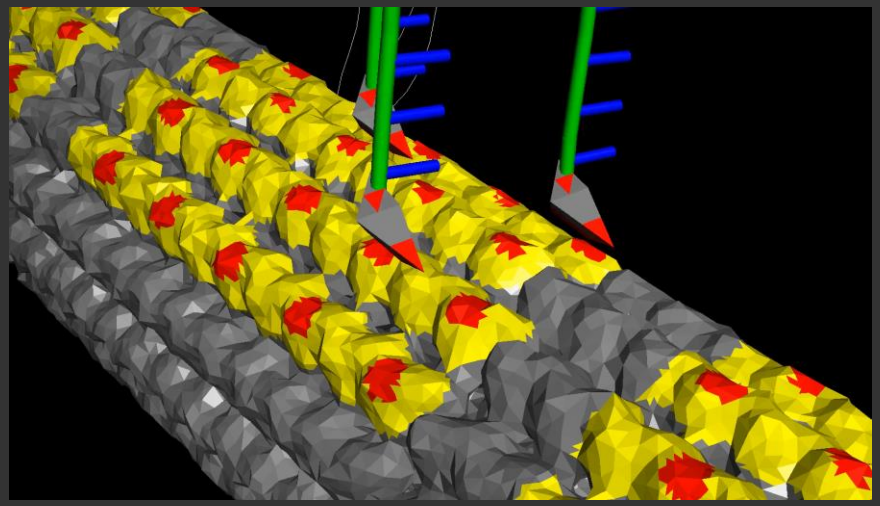
Microtubules green, chromosomes (DNA) in blue (Eva nogales)

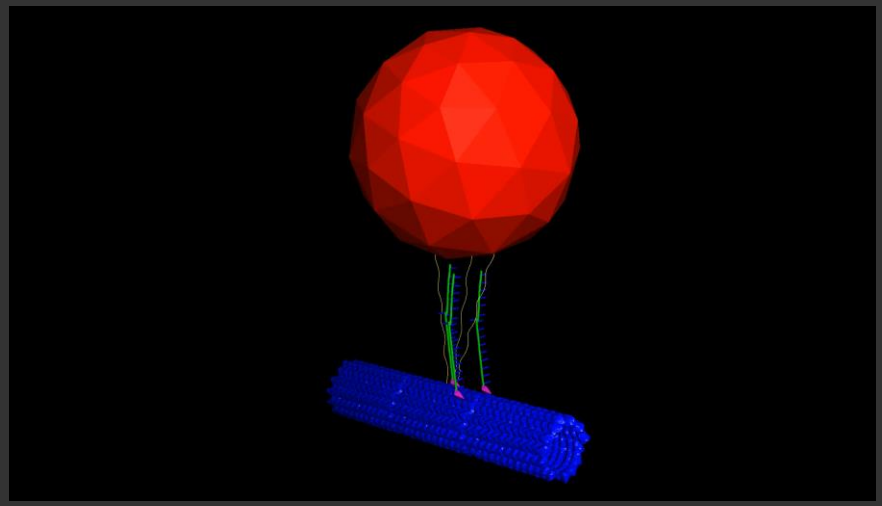
DNA



The Kinetochore

Jenni & Harrison, Science, 2018





Modelling Philosophy

Experiment

Simulation

Data Analysis

http://ffea.bitbucket.io/

Solernou et al, PLoS Comp. Bio 2018

FFEA Funding ~ EPSRC/BBSRC