Biosimulation for drug discovery across multiple length-scales – from enzymes to organs

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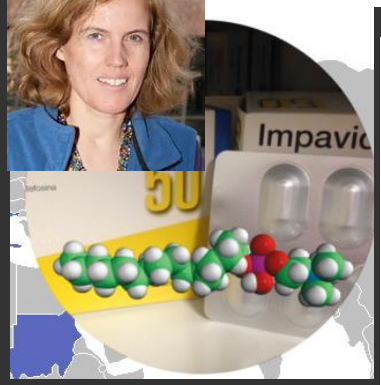
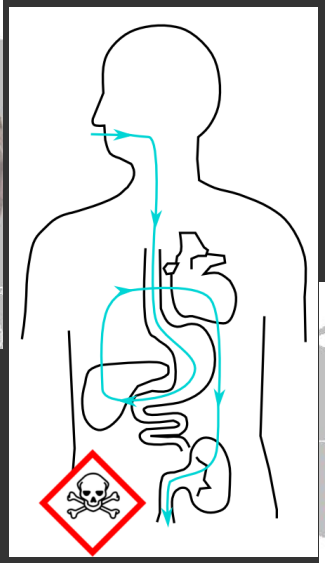
Visit your "in silico GP"

Rebecca Wade, HITS, Heidelberg



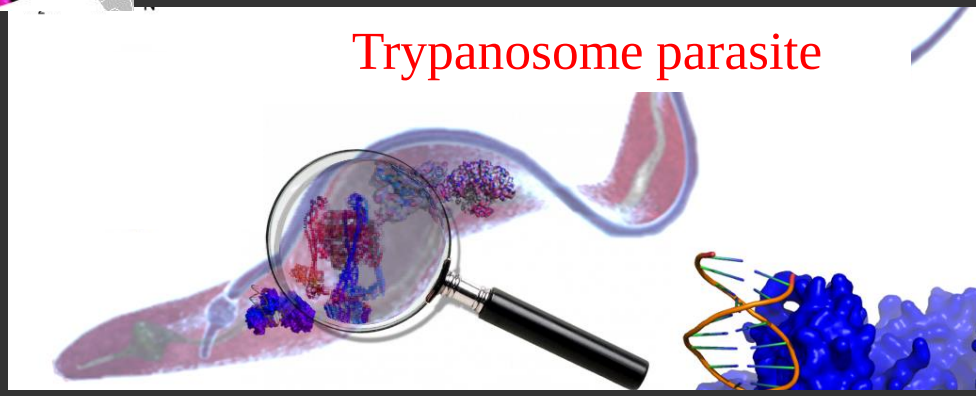


Medication against neglected parasitic tropical diseases.

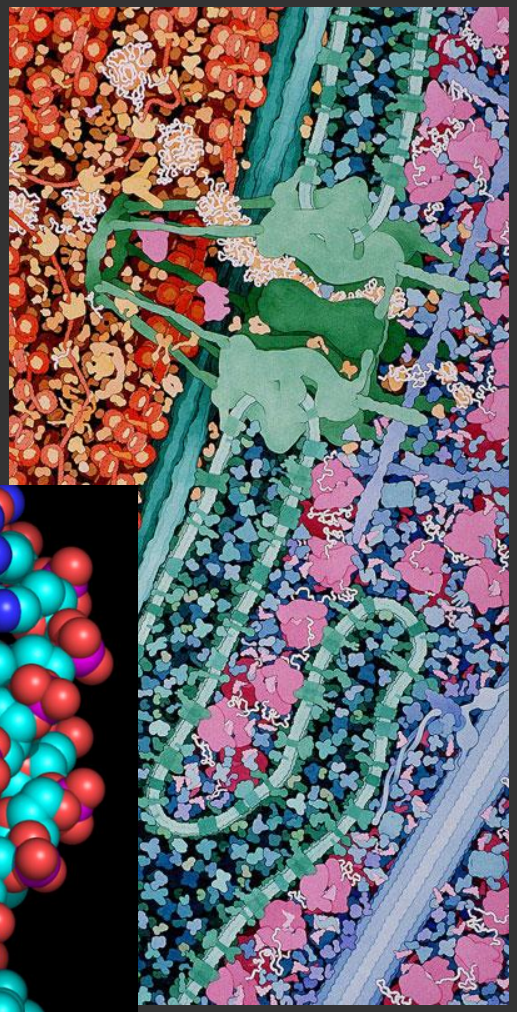
Simulate the drug from intake to action at target to elimination

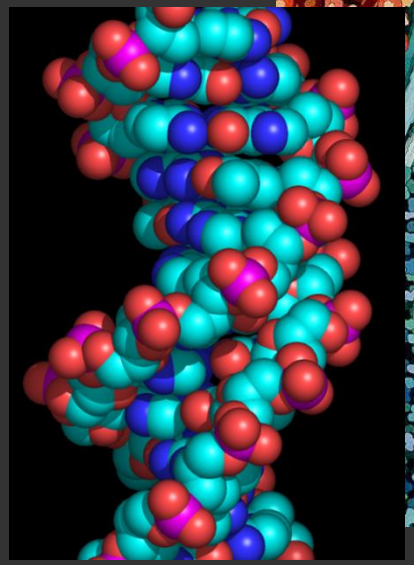
Consider host (human) and parasite from the atomistic level upwards

Trypanosome parasite



Molecular Biology





2nm = 2×10^{-9} m = 0.0000002 cm

Human cell: >10µm

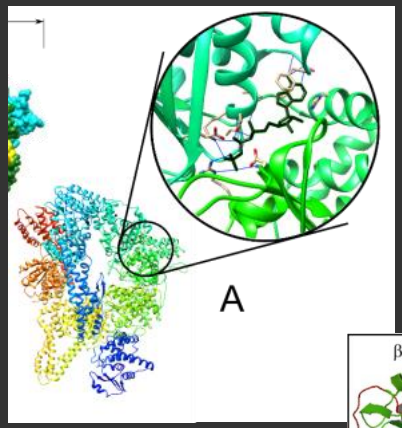
Human genome: 3 billion (3000 Mb/ 3×10^{9}) base pairs 3m long

Ribosome (makes proteins from RNA): 30nm

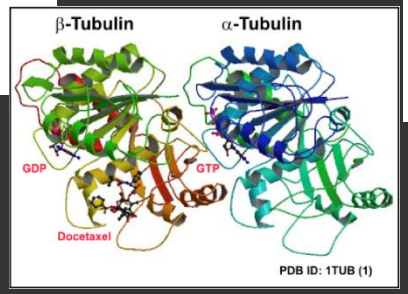
Hormone molecule/ Antibiotics/ Other drugs: 1-5nm

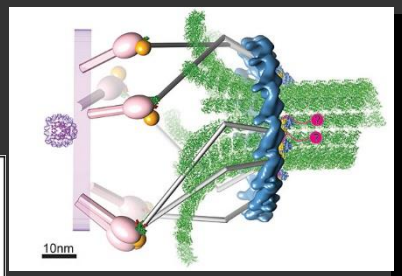
Time and length-scales in Cell Divison

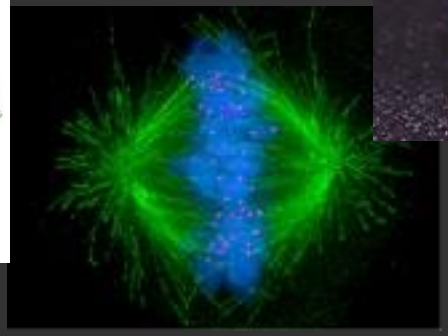
Quantum	Atomic	Molecular	Cellular	Macroscopic
100 atoms, 1nm,100fs	10,000 atoms 10nm,100µs	100nm, ms	10^{14} atoms, 1µm, 30 mins	1m 100 years



Unseen







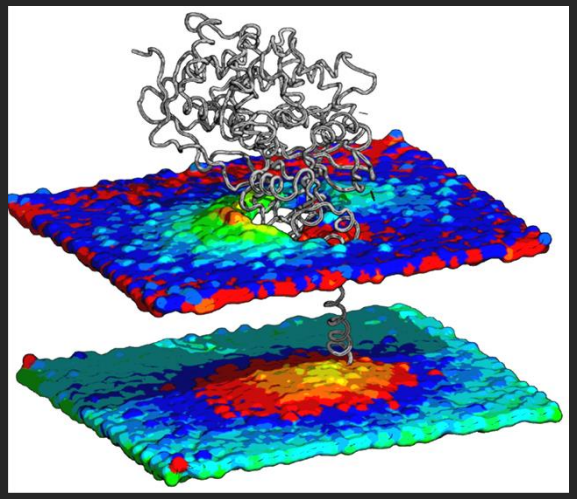
Microtubules green, chromosomes (DNA) in blue (Eva nogales)

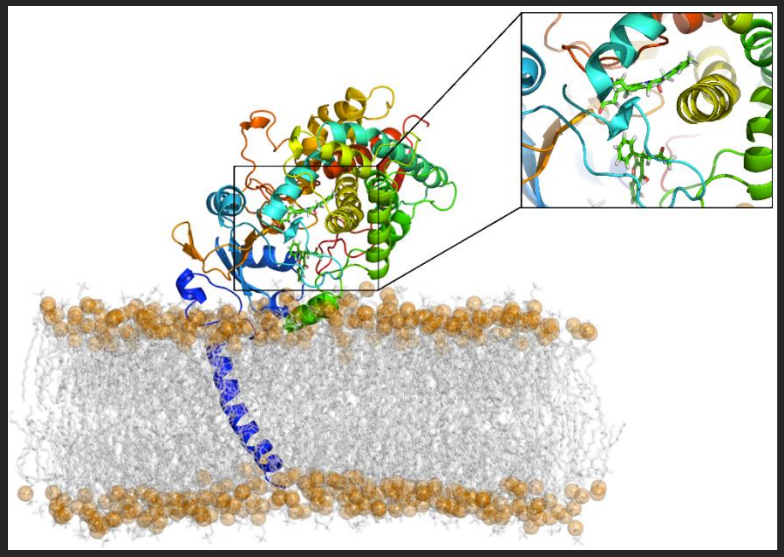
Burning fuel (ATP hydrolysis)	Molecular recognition	Molecular self-assembly	Cell division	Tissue/organ growth

Multiscale Modelling of CYP450 drug metabolism

- **Coarse-grained MD**
  - Build model of protein in the membrane
  - Study orientation of protein in membrane
- **Atomistic MD**
  - Relaxation
  - Explore conformations of protein and binding modes of drugs
- **QM/MM**
  - Model reactions of drugs in P450s
  - (e.g. Lonsdale *et al*. *JACS* 2013; PLoS *Comp. Biol*. 2014)
  - Amaro and Mulholland, *Nature Reviews Chemistry* 2018

CCPBioSim

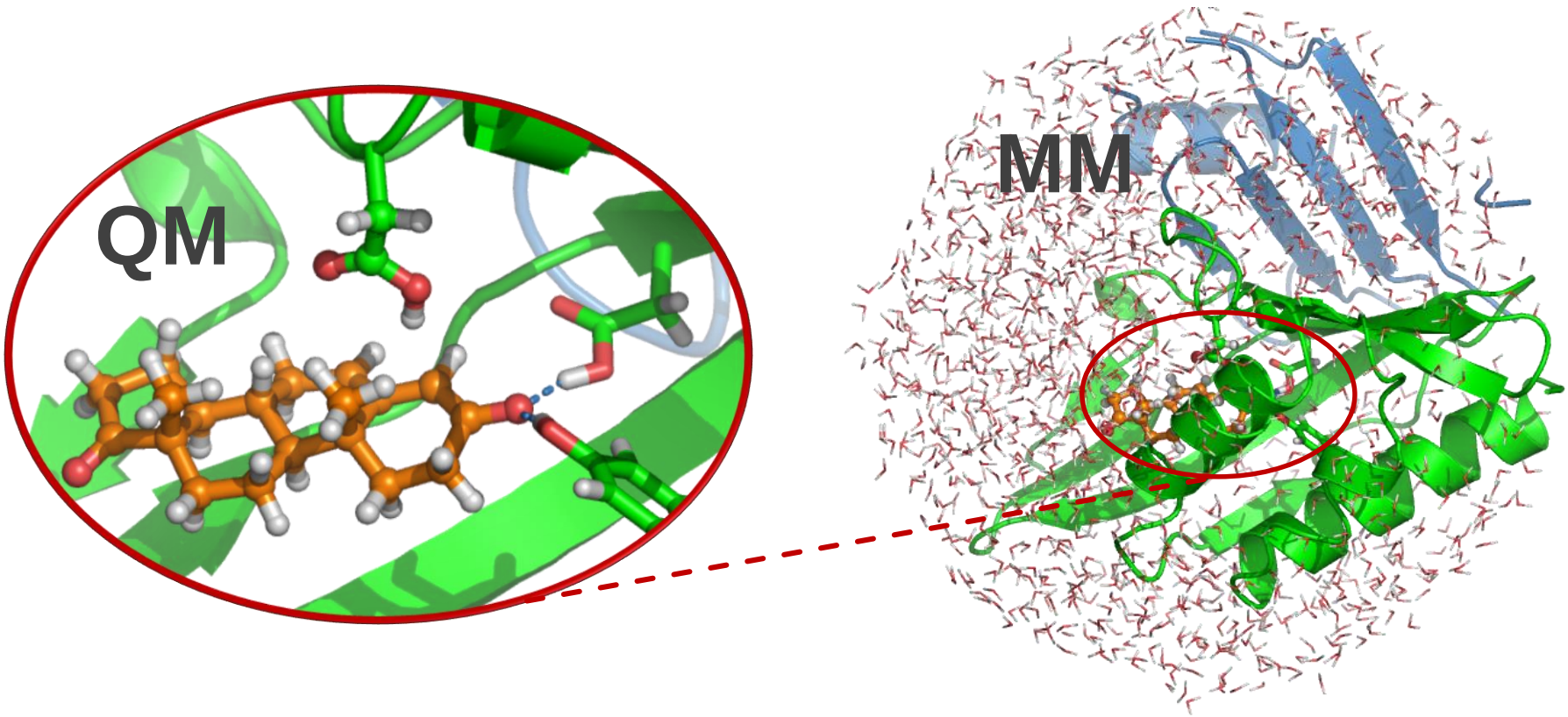




Scripts will be available on ccpbiosim.ac.uk

QM/MM Enzyme Reaction Modelling

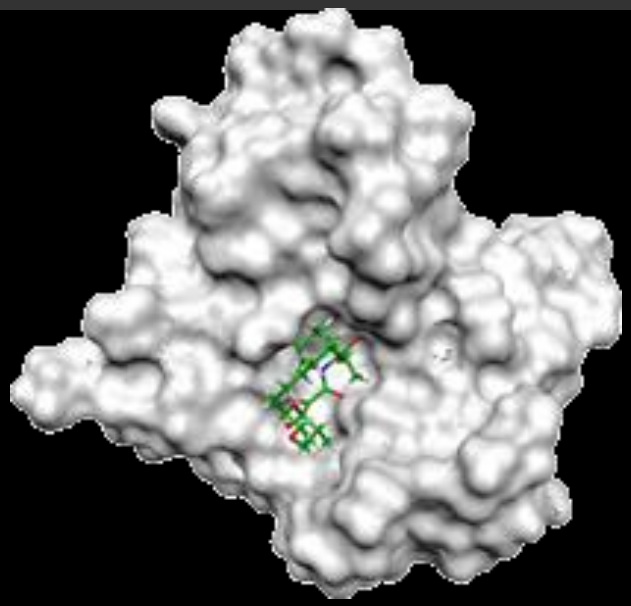
Use QM only for region where bonding changes, and molecular mechanics (MM) for the surroundings



QM/MM for enzymes: Van der Kamp, Mulholland (2013) *Biochem 52: 2708*

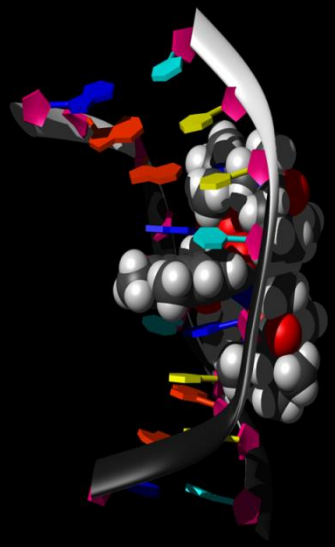
Molecular Recognition and Drug Design

Molecular recognition uses shape and chemical complementarity to convey metabolic information



Amprenavir/HIV protease

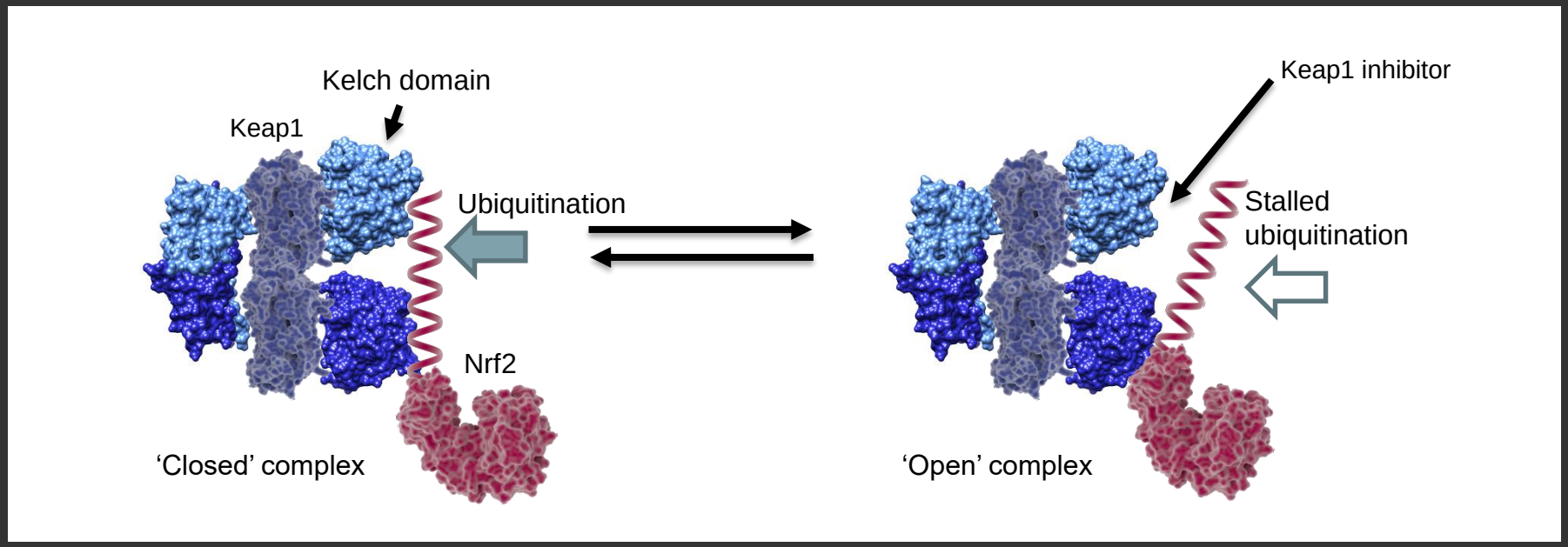
Actinomycin D/ DNA



But biomolecules (and the solvent) are always moving….

Inhibition of the Keap1-Nrf2 Interaction

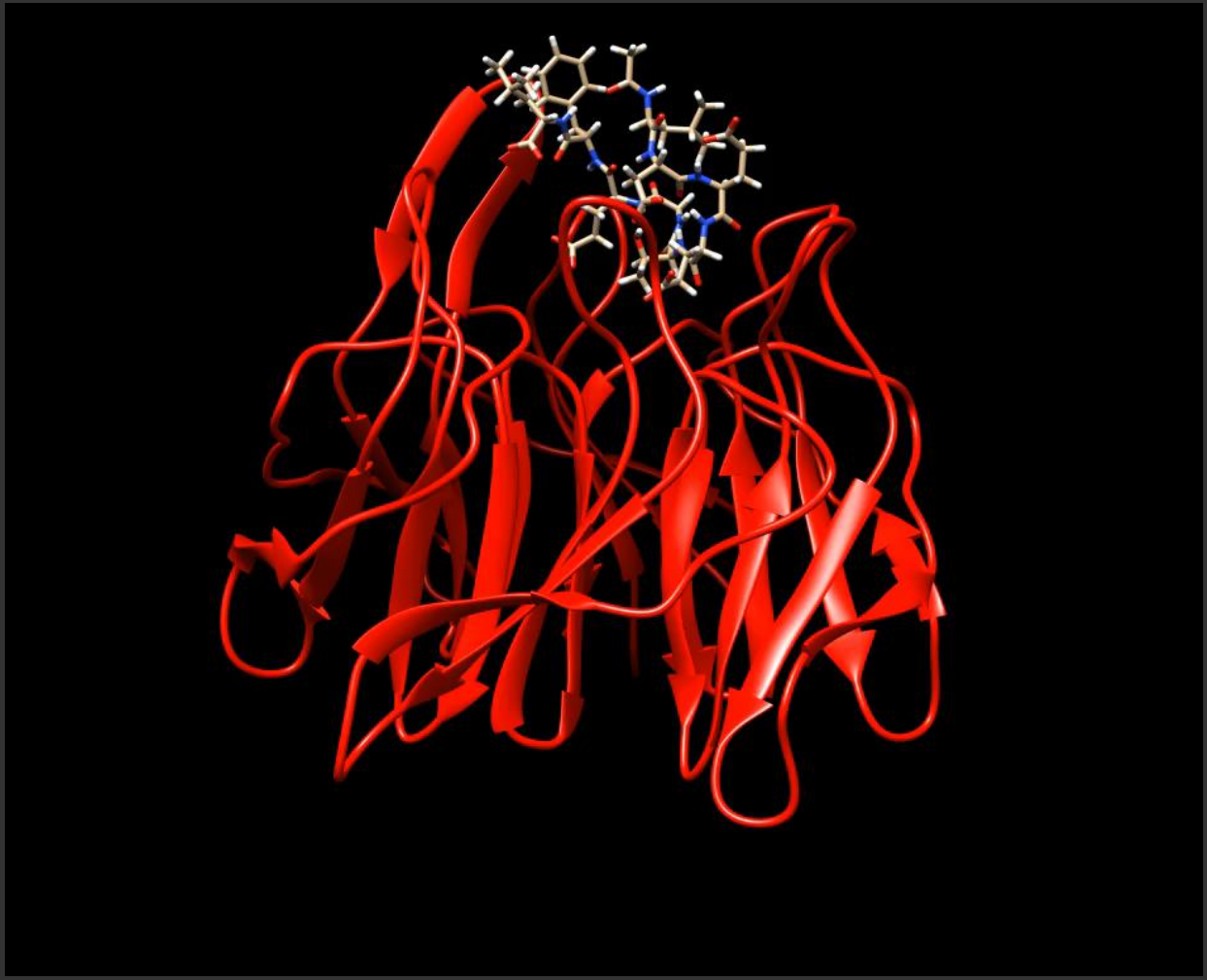
Nrf2 (red) is a transcription factor that increases the expression of a range of antioxidant, cytoprotective and anti-inflammatory genes



Concentrations are kept low by ubiquitination (facilitated by Keap1 (blue)), but this can be blocked with small molecules.

Therapeutic applications are in neurodegenerative conditions (*e.g.* Parkinson's & Alzheimer's diseases) and inflammatory conditions.

The bound form of Nrf2 Peptides

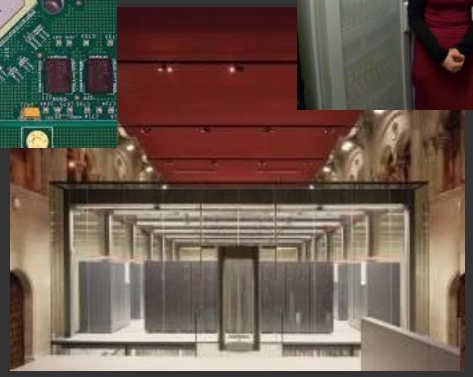


Limitations of MD for Molecular Recognition

Accuracy of empirical MD forcefields (MM improving – or use QM!!)

Dynamics and entropy (finite simulation timescales, ensemble averages)

Understanding the experimental data (e.g. environmental conditions, pH, salt etc)

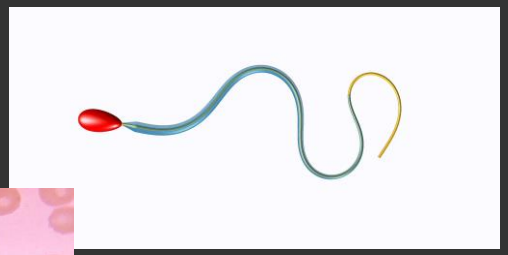


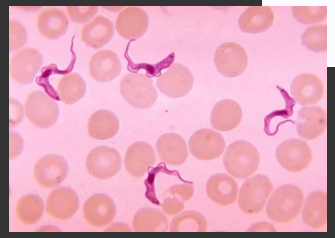
https://uk.pcmag.com/networking-communications-software/16824/what-is-cloud-computing

The Axoneme ~ A Macromolecular Machine

Hermes Gadelha, York

Sperm



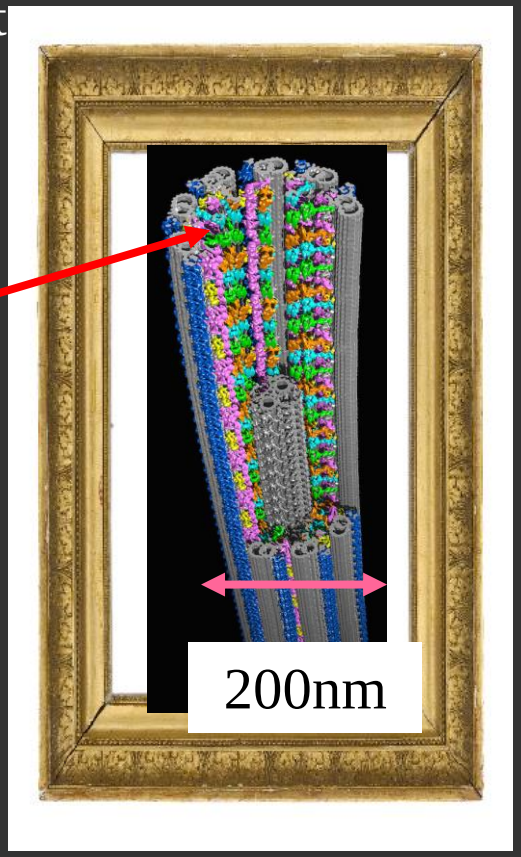


Trypanosomes

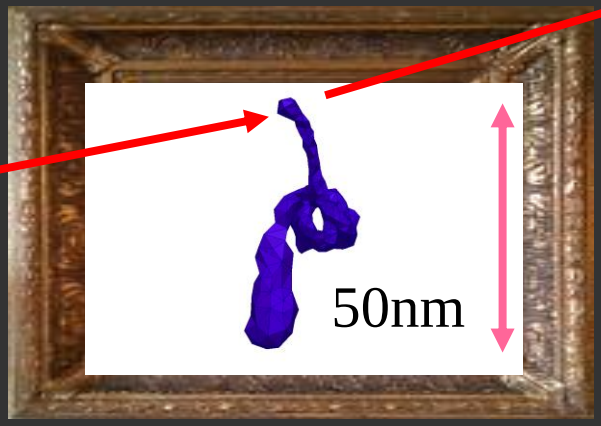
16 dyneins in 96nm repeat
9 MT doublets
50-100×96nm = 5-10µm

6×10^{8} atoms (non solvent)

Axoneme



Cryo-ET Nicastro lab



Dynein Motor

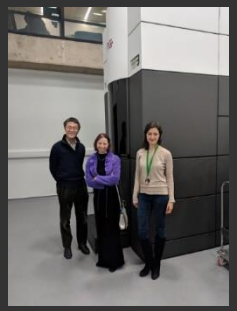
~1 million atoms in water (no tail)

10nm

Dynein MTBD

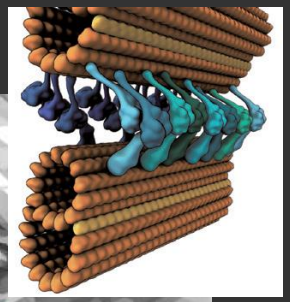
How do we identify the best protein-protein interactions to target to inhibit the action of the axoneme?

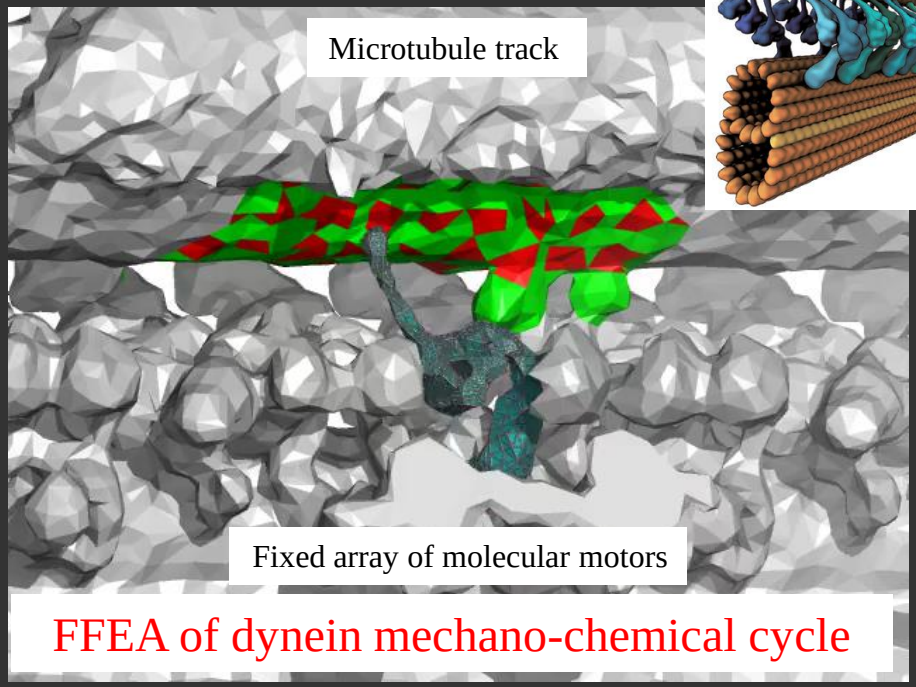
FFEA of Flagellar Dynein in Situ



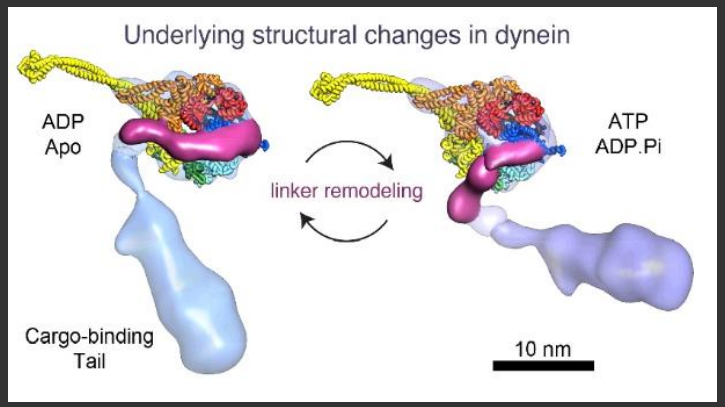
Dock 3D cryoEM of dynein into 3D tomogram of the axoneme

~1 µs FFEA shows dynamics *in situ*.





FFEA of dynein mechano-chemical cycle

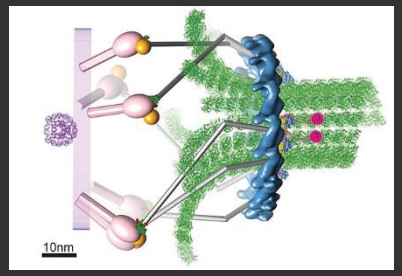


Red

Cryo-tomography: Bui et al, J Cell Biol 198, 913, 2012

Cyan

CryoEM: Burgess *et al Nature* (2003) 421, 715; Roberts *et al*, *Structure* (2012), 20 1670



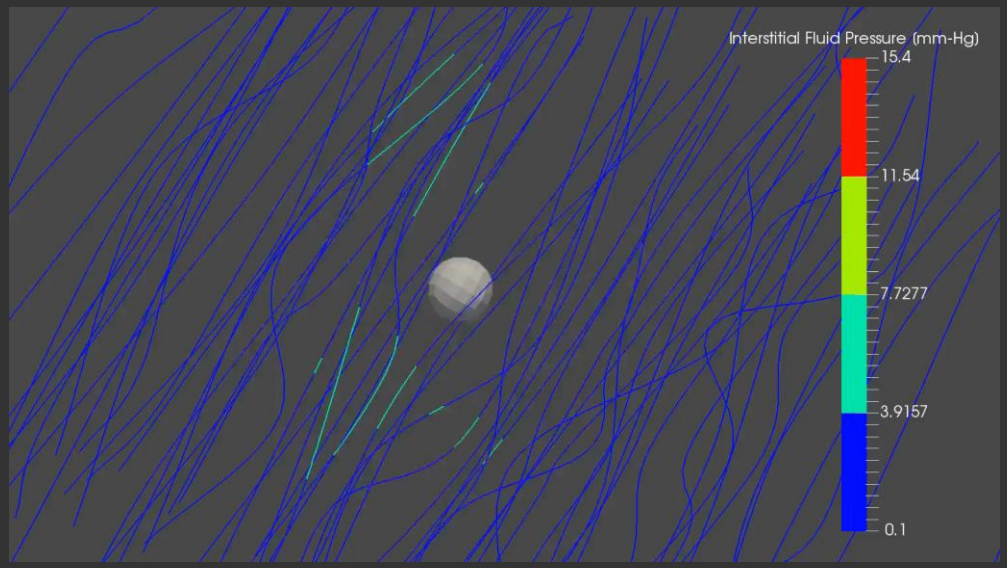
http://ffea.bitbucket.io/

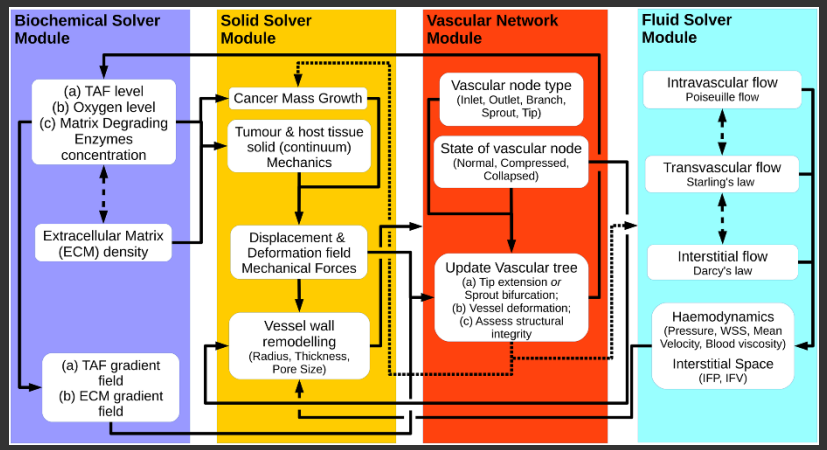
Solernou et al, PLoS Comp. Bio 2018

Tumour Angiogenesis

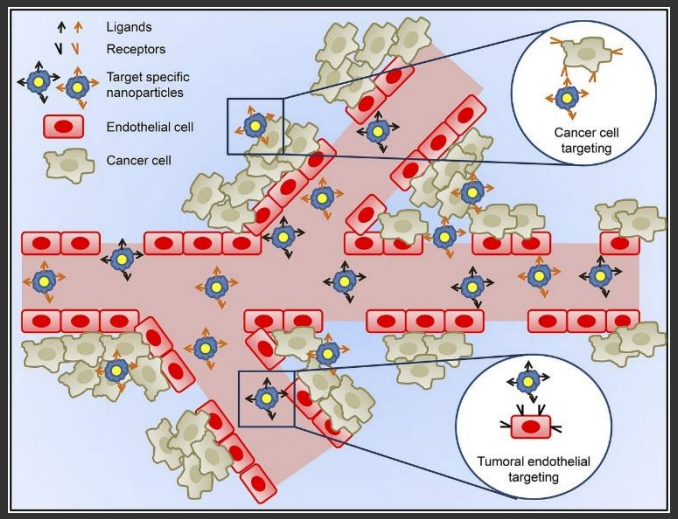
Vavourakis et al Plos Comp Bio 2017

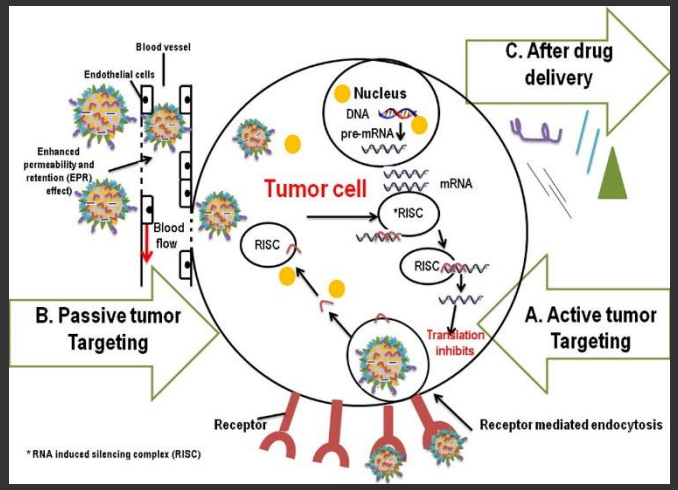
Finite Element models of solid tumours show the pattern of blood flow, and the difficulty of delivering chemotherapies *in situ*





Why do we need Multi-scale?





Many orders of magnitude difference in size between target/drug and patient

Active biological processes (e.g endocytosis) still poorly understood

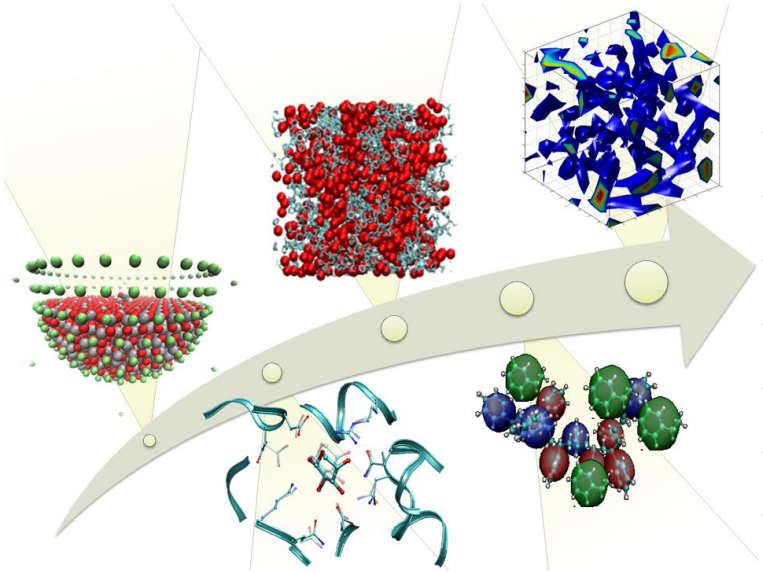
Coupling between different time and length-scales

Yingchoncharoen *et al* Pharm Rev 2016

Save The Date

4th CCPBioSim/CCP5 Manchester Multiscale Conference

Dates: 30 March – 1 April 2020
Venue: Manchester Conference Centre



Invited Speakers:

- Maria Fyta (Stuttgart, Germany)
- Frauke Gräter (Heidelberg, Germany)
- Syma Khalid (Southampton, UK)
- Horst Lillig (Greifswald, Germany)
- Céline Merlet (Toulouse, France)
- Irina Paci (Victoria, Canada)
- Lars Pastewka (Freiburg, Germany)
- Anđela Šarić (UCL, UK)

Registration will be announced on the CCPBioSim website, our mailing list and our twitter account (@ccpbiosim).

www.ccpbiosim.ac.uk/multiscale2020