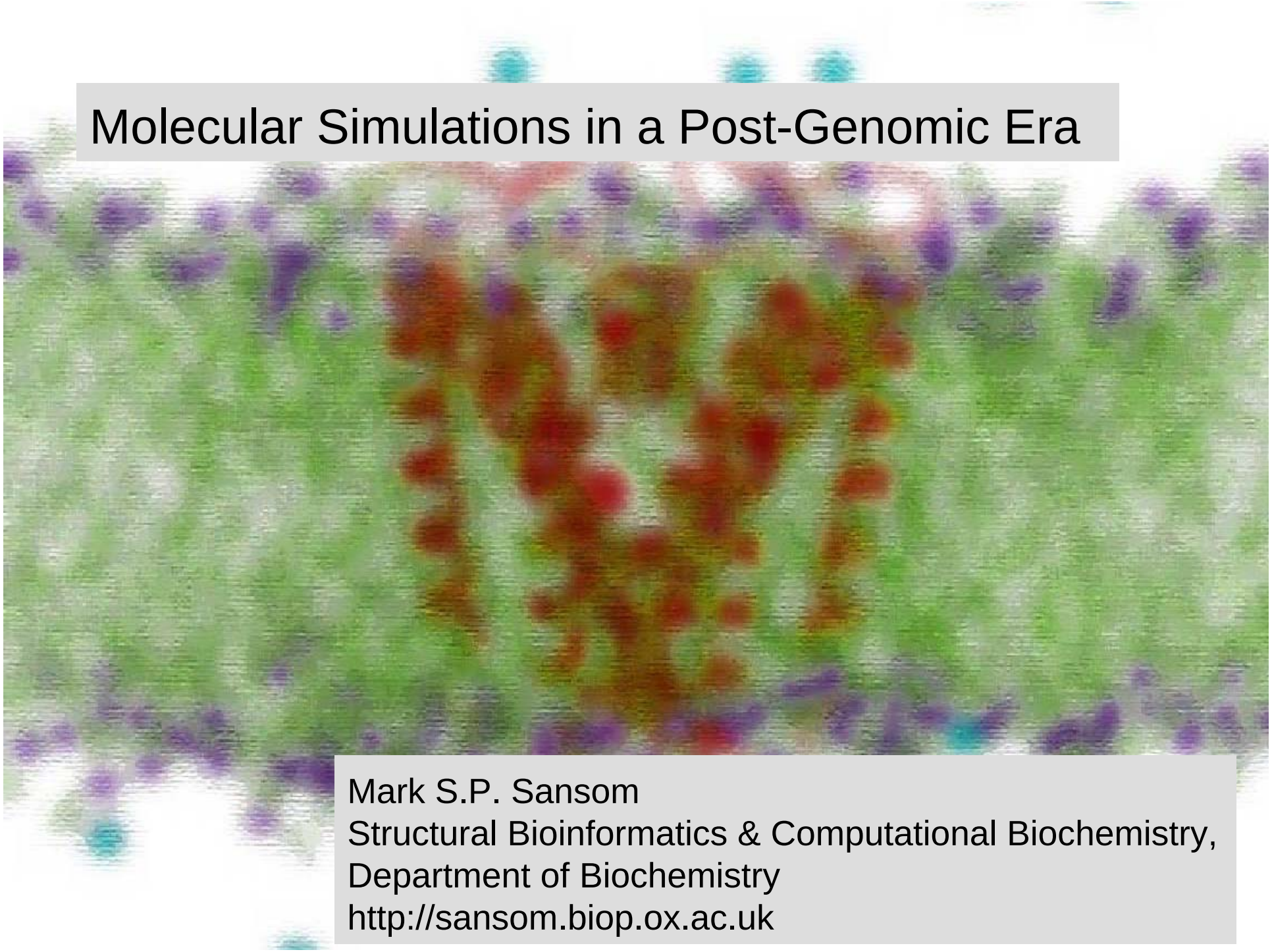
Molecular Simulations in a Post-Genomic Era



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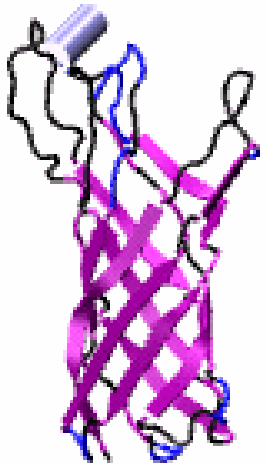
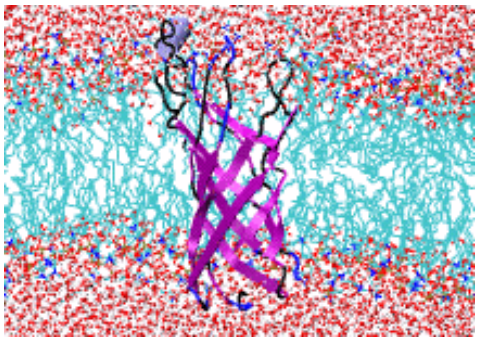
MD Simulations: from PDB to Dynamics

structure/model



simulation



analysis

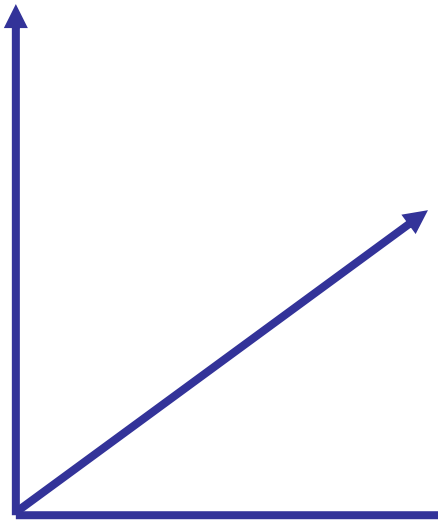
- Molecular simulations as a tool for protein structure analysis
- X-ray structure: average structure at 100 K in crystal
- MD simulations: dynamics at 300 K in ~cellular environment
- Challenge: to relate structural dynamics to biological function

Overview

- Challenges: from structural genomics & systems biology
- Advances in hardware: clusters, Grid computing & HPC
- Biology-driven simulations: structure-function relationships of proteins & more complex systems
- Simulation databases & pipelines
- BioSimGrid project (www.biosimgrid.org)
- IntBioSim: multi-level simulations
- National Grid Service (www.ngs.ac.uk) experiments

Three Key Directions

depth – improved models of interactions cf. physical chemistry

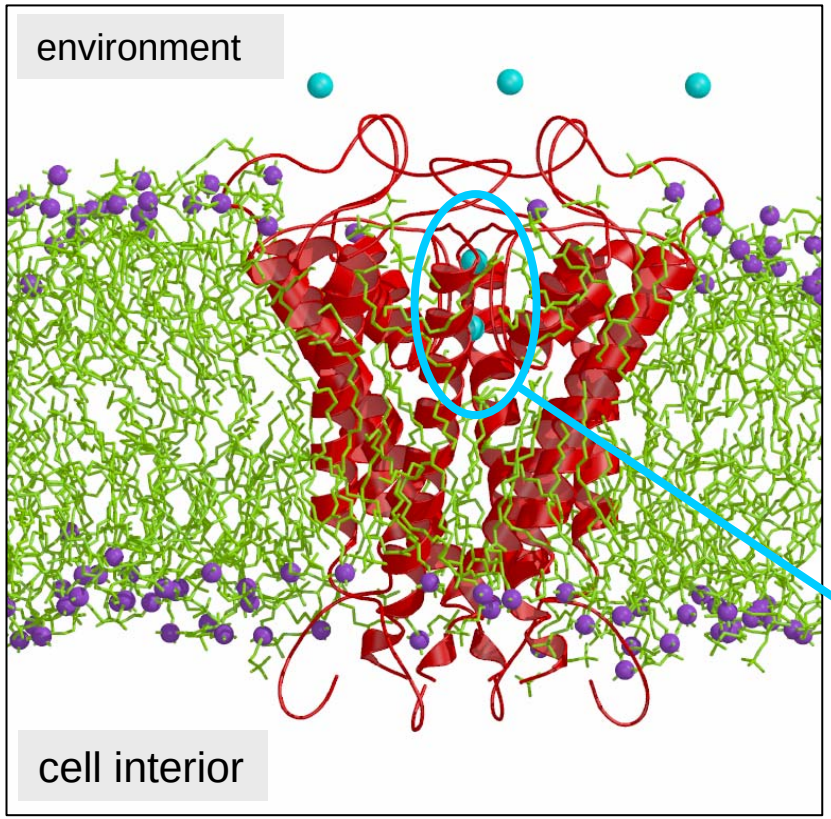


breadth – comparative simulations cf. structural genomics

complexity – multi-component systems cf. systems biology

- All three aspects – need HPC
- E-science issues – high-throughput & data integration

Complex Systems: MD Simulations of Biomolecules



water, ions

proteins & phospholipids

e.g. potassium channel

minimum system

50,000 to 100,000 atoms

biology

- Describe the forces on all atoms: $F = -dU(x)/dx$
- Integrate: $F = ma$ (a few million times…)
- Result: positions of all atoms for ~10 ns
- Experimental (static) structure → *in vivo* dynamics
- The challenge – to relate dynamics to function

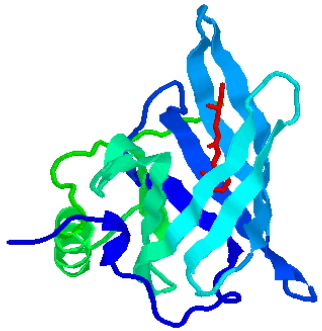
Molecular Dynamics Simulations of Biomolecules

- MD simulations of dynamics of biological molecules (proteins, DNA, membranes)
- Energy functions for MD
- Solvation & long range interactions
- Case studies:

  protein folding

  protein dynamics & large systems

X-ray (or NMR) experiments



static (average) structure

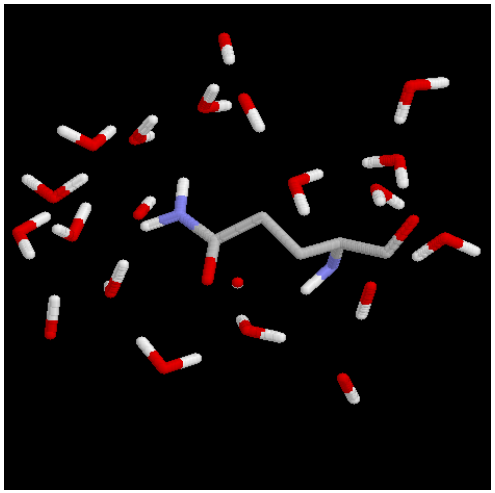
MD simulations

protein motions

Potential Energy Functions for MD

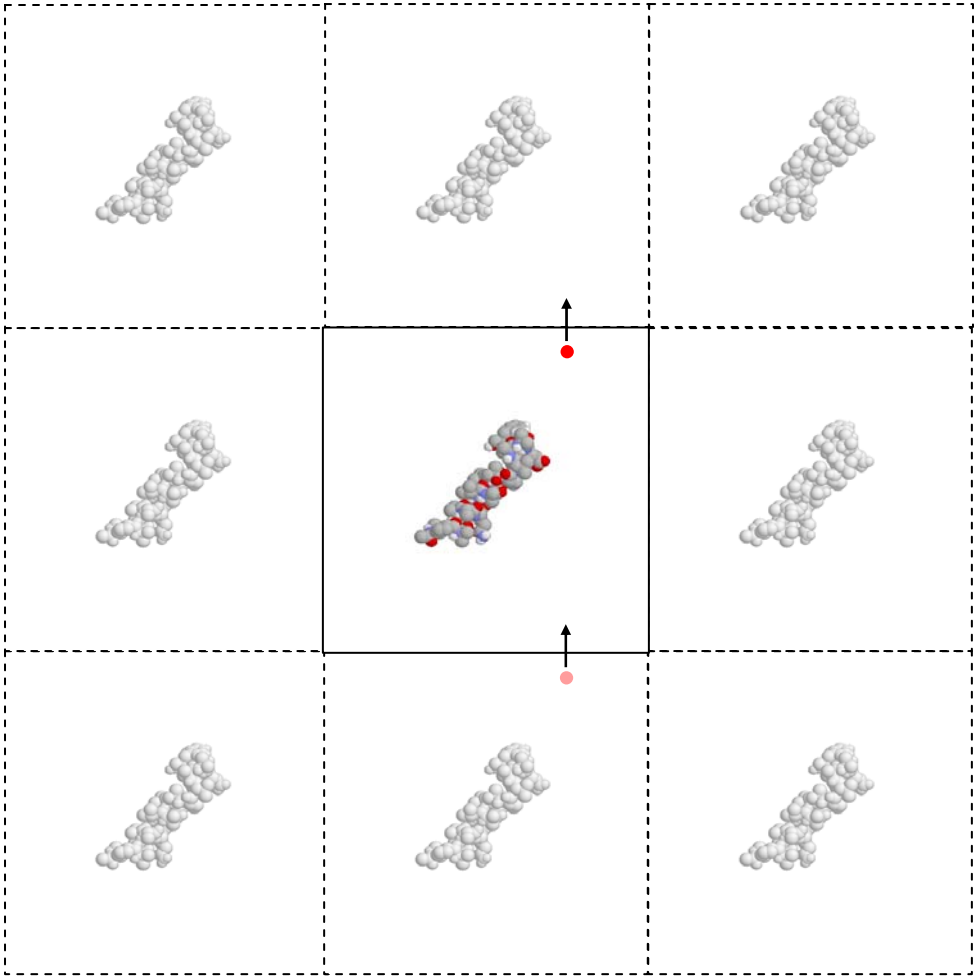
- Classical energy functions (no QM, i.e. “ball & springs” model)
- bonding interactions via simplified (harmonic) functions
- atoms treated as van der Waals spheres with single point charges
- Large systems – upto 10^6 atoms
- several packages - CHARMM, GROMACS, GROMOS, AMBER, NAMD

- $E = E_{BONDED} + E_{NON\text{-}BONDED}$
- $E_{BONDED} = E_{BONDS} + E_{ANGLES} + E_{TORSIONS}$
- $E_{NON\text{-}BONDED} = E_{VAN\ DER\ WAALS} + E_{ELECTROSTATICS}$
- Each term – simple function (e.g. quadratic)
- But … large number of pairwise interactions



Problems of a Finite System Size

- Restriction to relatively small systems e.g. 10x10x10 nm^3 = ca. $3x10^4$ atoms
- Finite system size introduces “boundary” problems
- Use of *periodic boundary* conditions to mimic an infinite system
- Long-range electrostatic effects are computationally expensive - use of either a cut-off or Ewald summation
- Need for solvation - large numbers of water molecules
- Timescales – 10 ns upwards (to ca. 1 μs)



Simulation & Analysis

Calculate forces on each atom

Update position of each atom after timestep δt e.g. δt = 1 fs (= 10^{-15}s)

Save atomic coordinates & energies every e.g. 1 ps (= 10^{-12} s) to give a *trajectory*

Off-line analysis

visualisation (movies)

sample structures (snapshots)

quantitative analyses
e.g. structural drift vs. time
e.g. fluctuations vs. residue

- New approaches – on line visualisation & interactive “steering” of simulations

Computational Resources

- Conventional supercomputers - research centres or universities
- e.g. HPCx (www.hpcx.ac.uk)
- Essential for very large scale simulations
- Fast communication between CPUs
- Code scaling issues

- PC (“beowulf”) clusters running Linux
- Individual research groups
- From small & hand-built (e.g. 16 nodes) to large & professional (e.g. 256 nodes)
- Communication between CPUs via conventional network technology

Parallelisation of Simulations

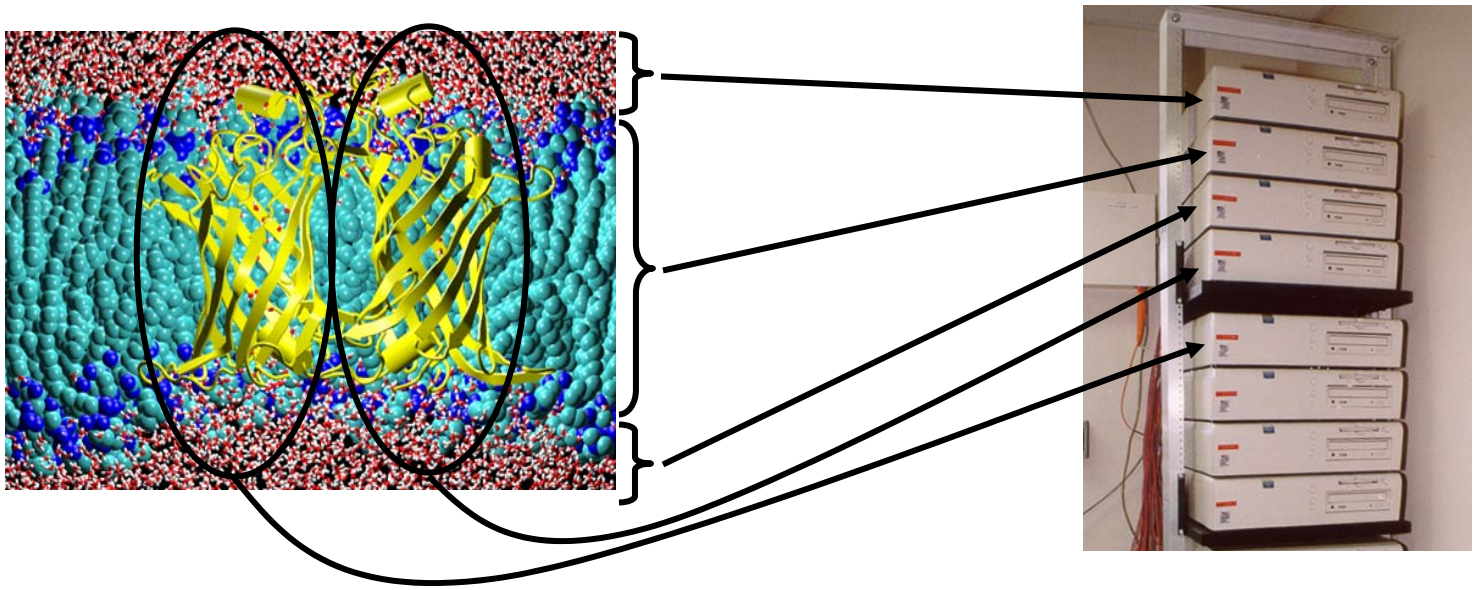
GRID
internet

Cluster
ethernet

HPC
shared memory

BlueGene
custom architecture

Inter-CPU communication speed



- Parallelization of codes – efficient partition of system onto CPUs
- Problem of long range interactions (FFT parallelization)

Reality Checks

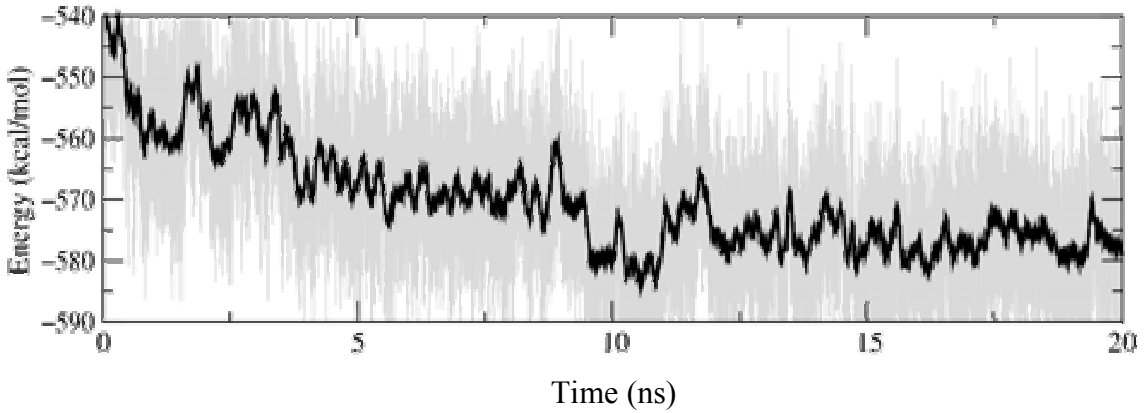
- How good are the forcefields?
- Sampling – need for longer simulation times
- Case studies:

  peptide folding – approaching NMR accuracy

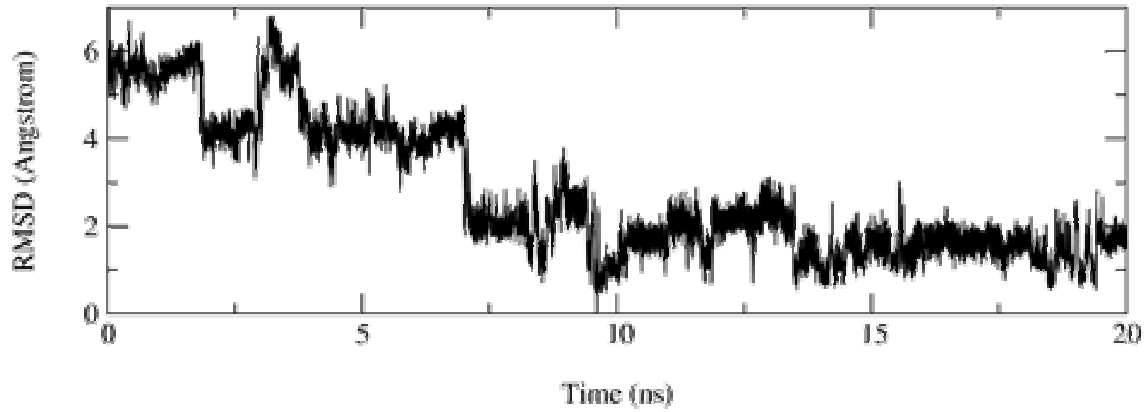
  K channels – improving on X-ray resolution

Trpcage Folding: A 20-mer Peptide

energy vs. time



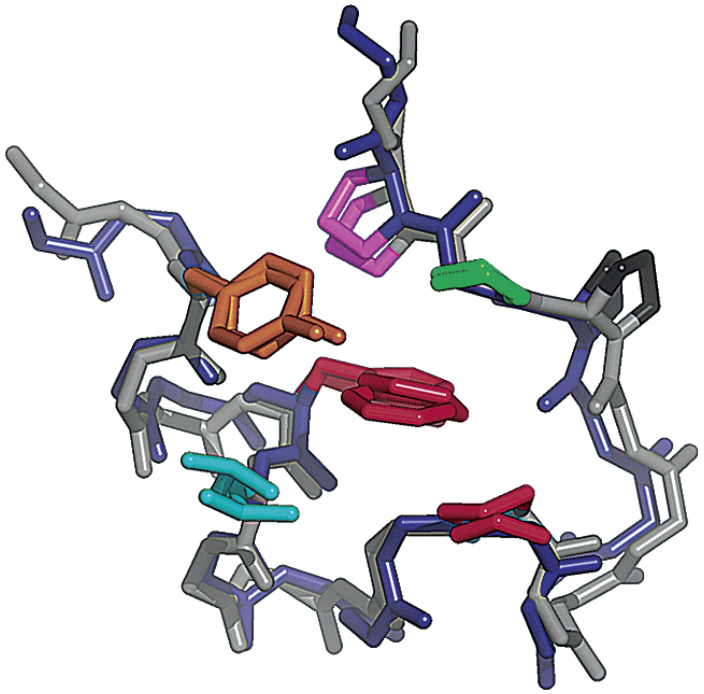
RMSD vs. time



B

All-Atom Structure Prediction and Folding Simulations of a Stable Protein
Simmerling et al. (2002) *JACS* 124:11258

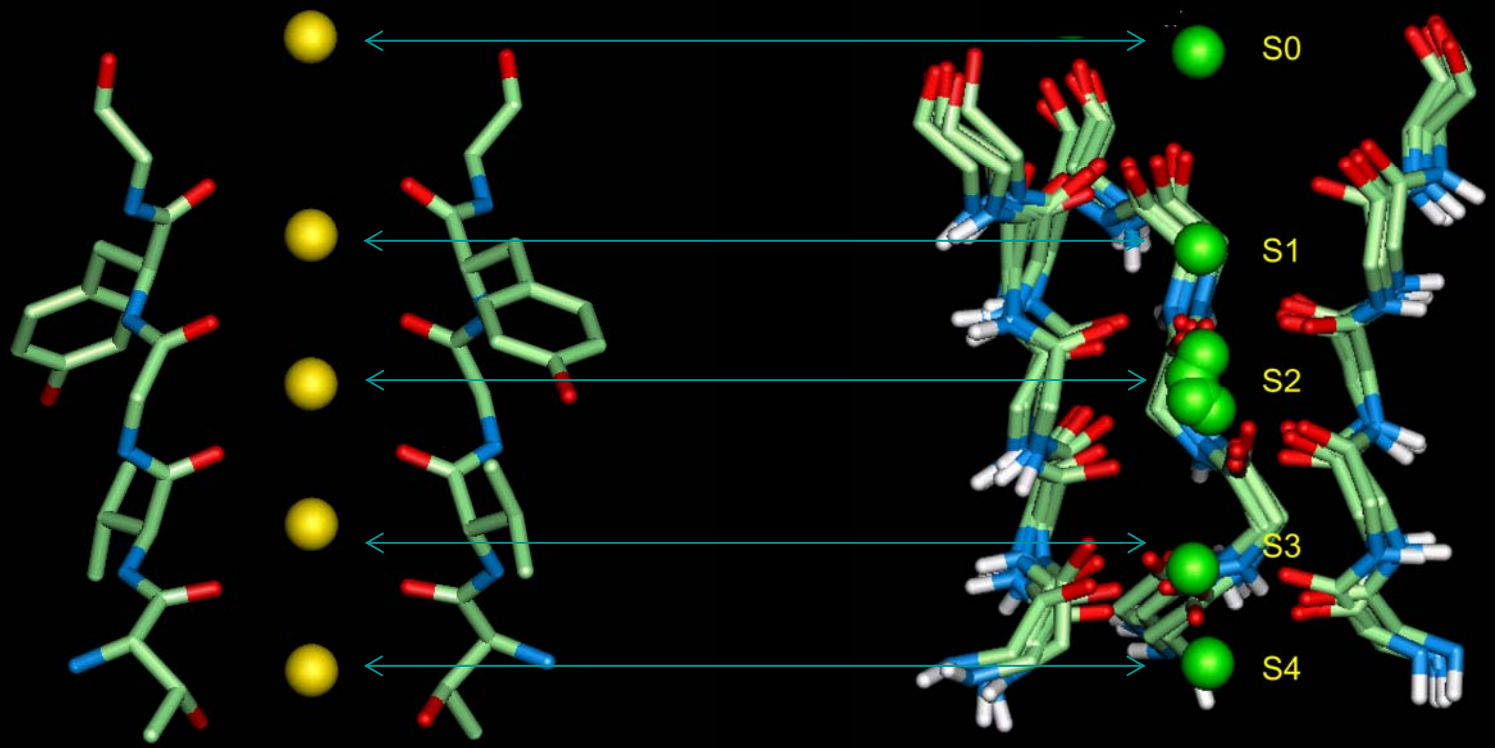
Trpcage: Experiment vs. Theory



- Simulated (blue) vs. experiment (grey)
- Good agreement (within experimental error)

- Only a very small “protein” – but successful
- Need to extend to larger & more complex systems

MD vs. X-Ray: A Reality Check

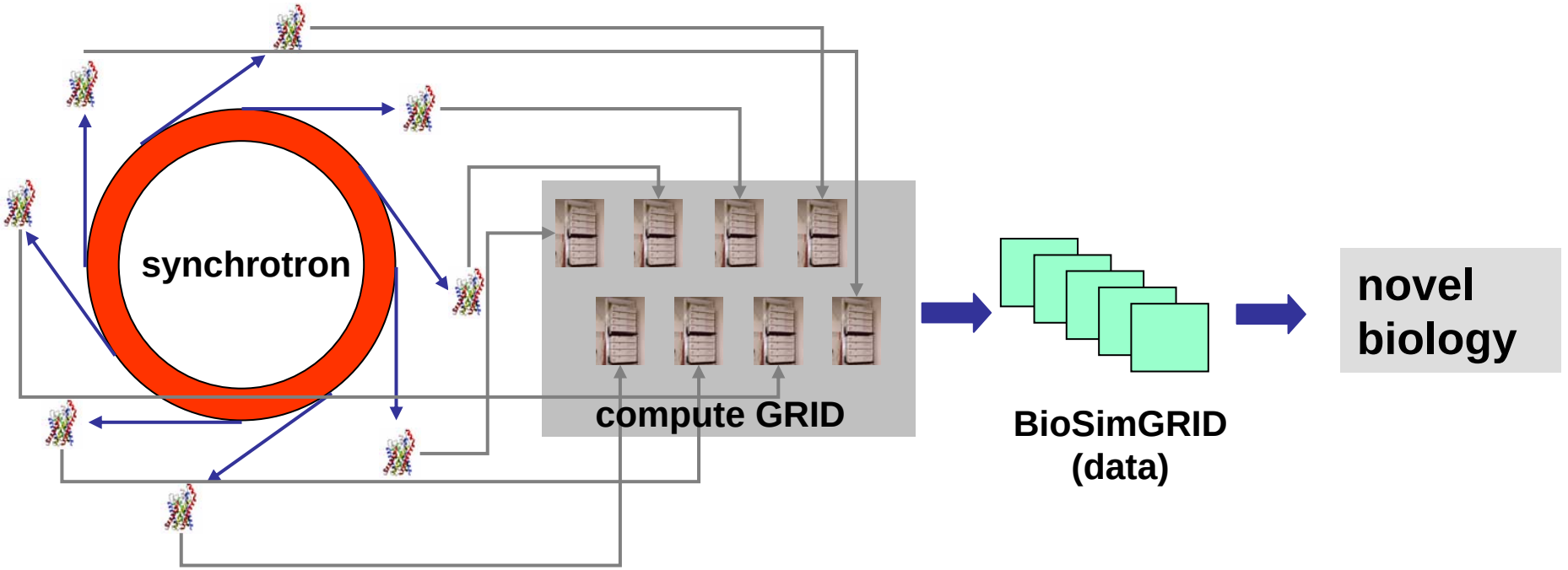


X-ray (2.0 Å)
MacKinnon et al. (2001)

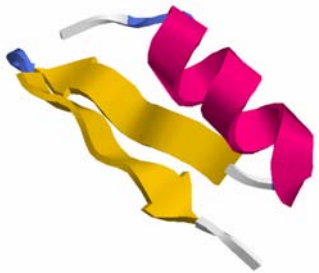
MD simulations
Shrivastava & Sansom (2000)

Towards HT MD

- Simulation pipeline
- QA tools & automated deposition

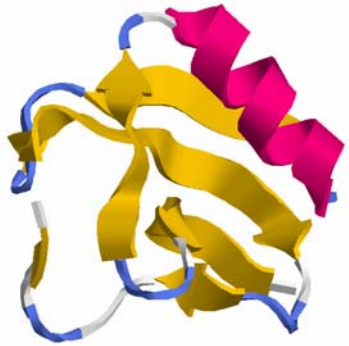


Comparative Simulations

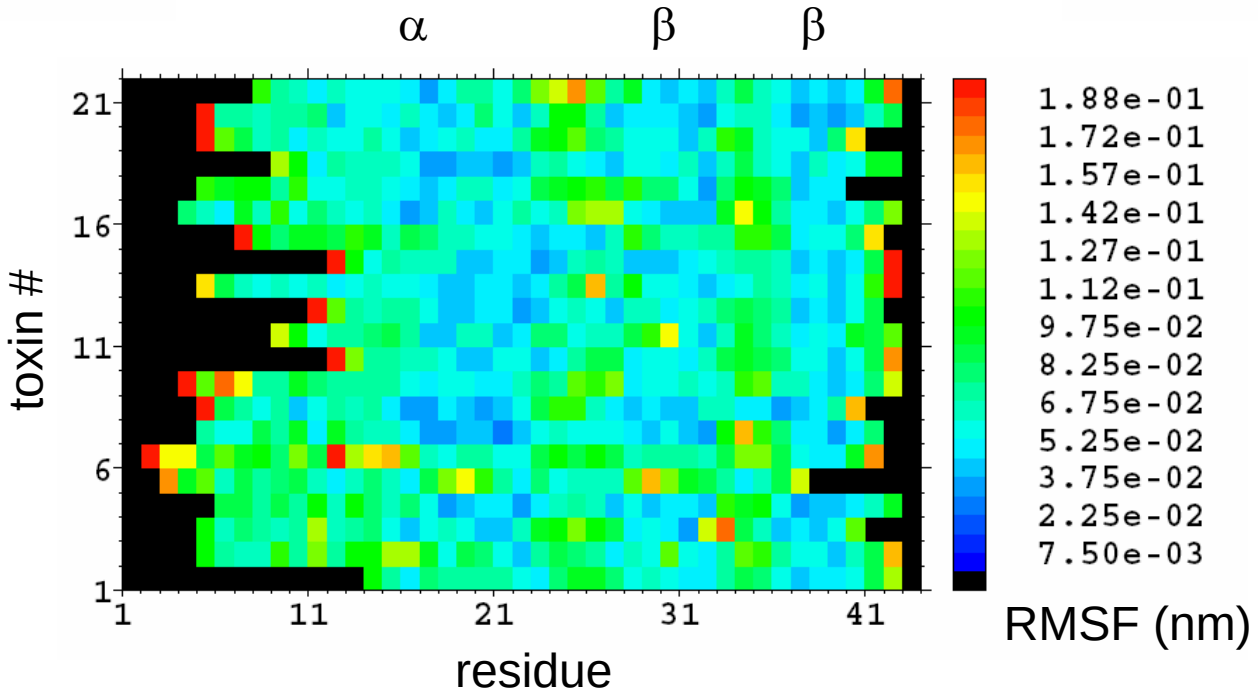


1acw

- 22 scorpion toxins (bind to K channels)
- Toxins have the same fold
- 10 ns MD run for each toxin
- Dynamic profile for a simple fold



1aho



Using the GRID

run simulation

(0.5 ns segments)

↓

check: energy, temperature & RMSD ‘on the fly’

↓

e-mail user re: simulation status

→

stop job if simulation unstable, or

if ok, resubmit for a further 0.5 ns

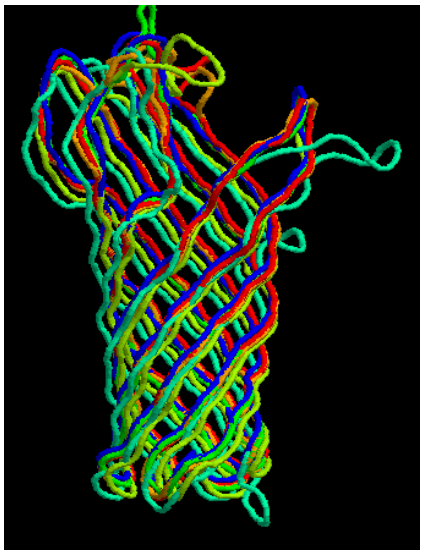
↑

iterate until simulation is complete

↑

integrate with biosimGRID for storage and analyses

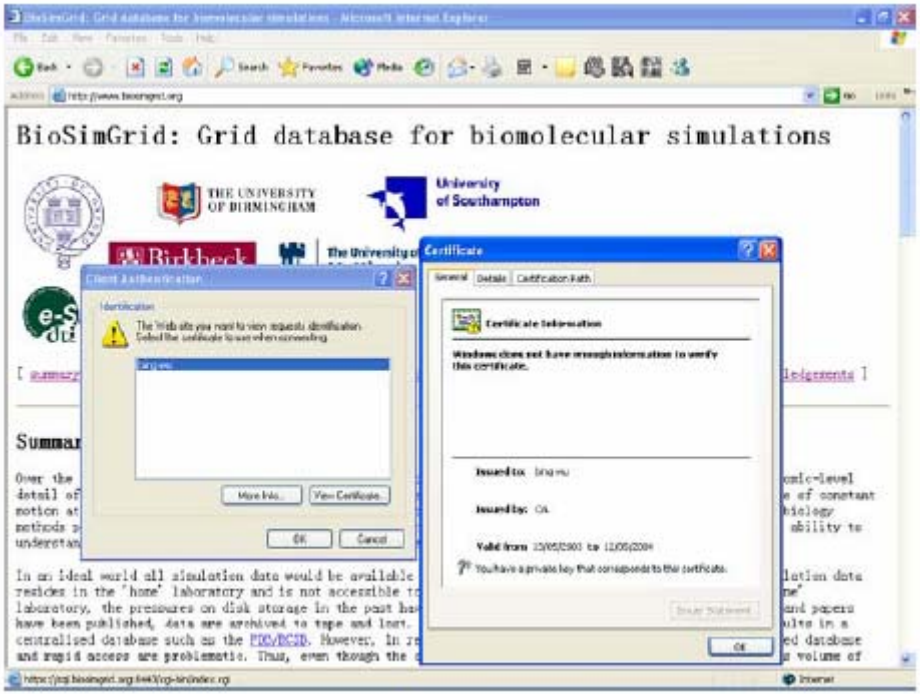
SHIDY- Shigella dysenteriae
SALTY- Salmonella typhimurium
ENTAE- Enterobacter aerogenes
SERMA- Serratia marcescens
HAEIN- Haemophilus influenzae



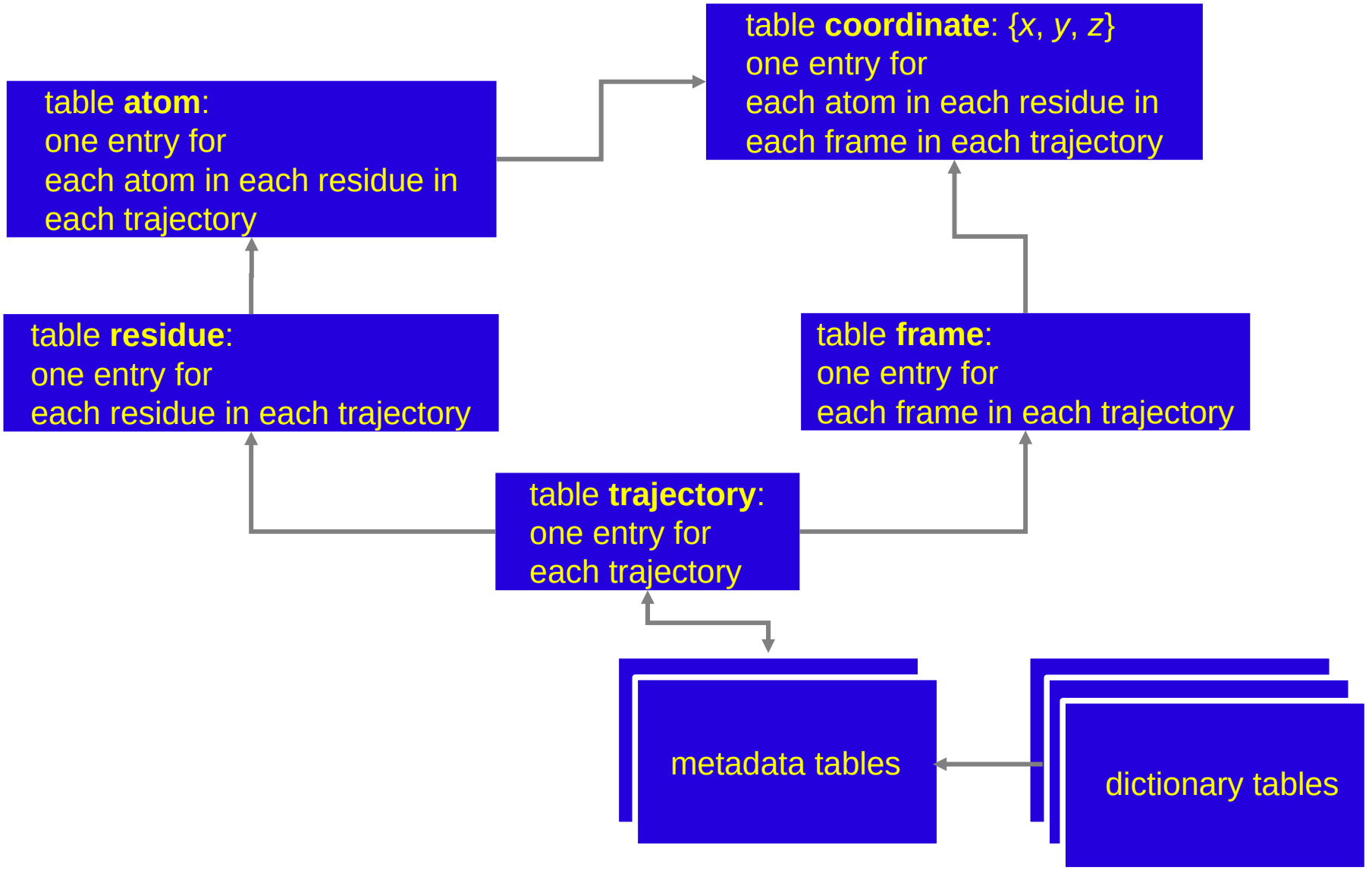
- Evaluation using the NGS (www.ngs.ac.uk)

Managing MD Data: BioSimGRID

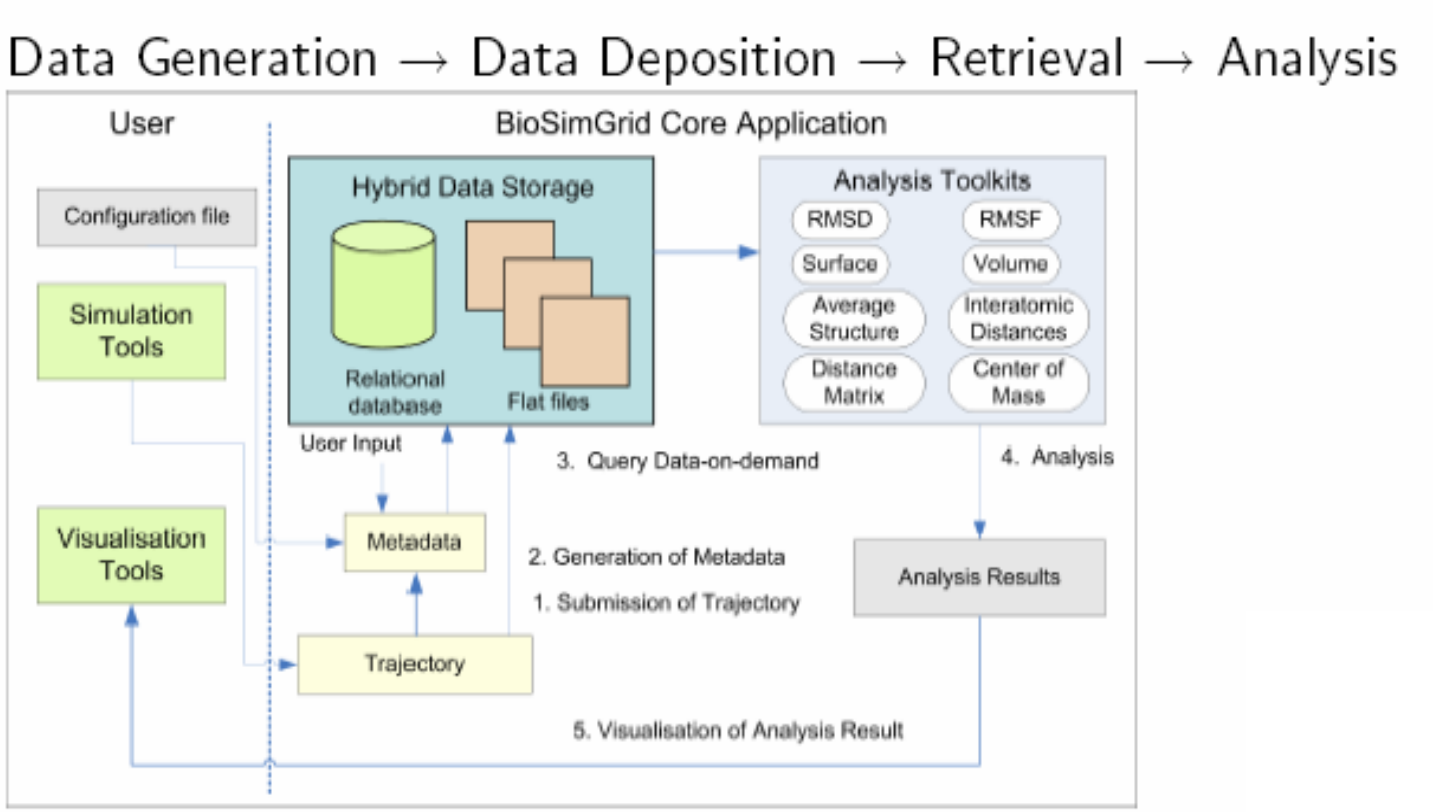
- www.biosimgrid.org
- Distributed database environment
- Software tools for interrogation and data-mining
- Generic analysis tools
- Annotation of simulation data
- Collaboration: Oxford, Southampton, Bristol, London, Nottingham, York

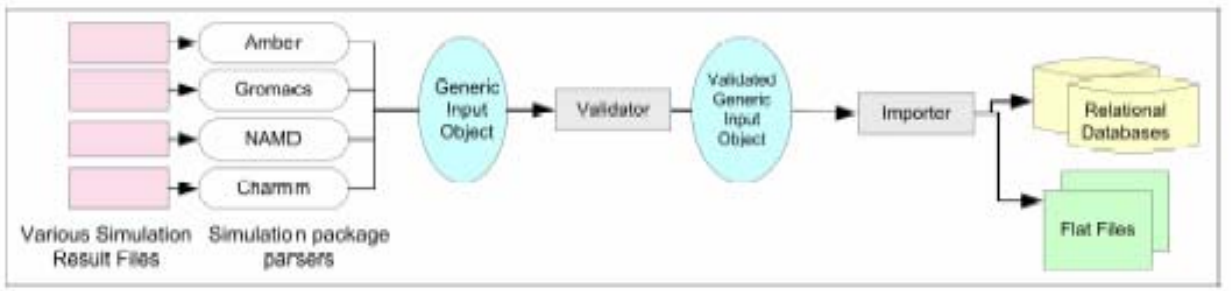


Database Design: Simplified

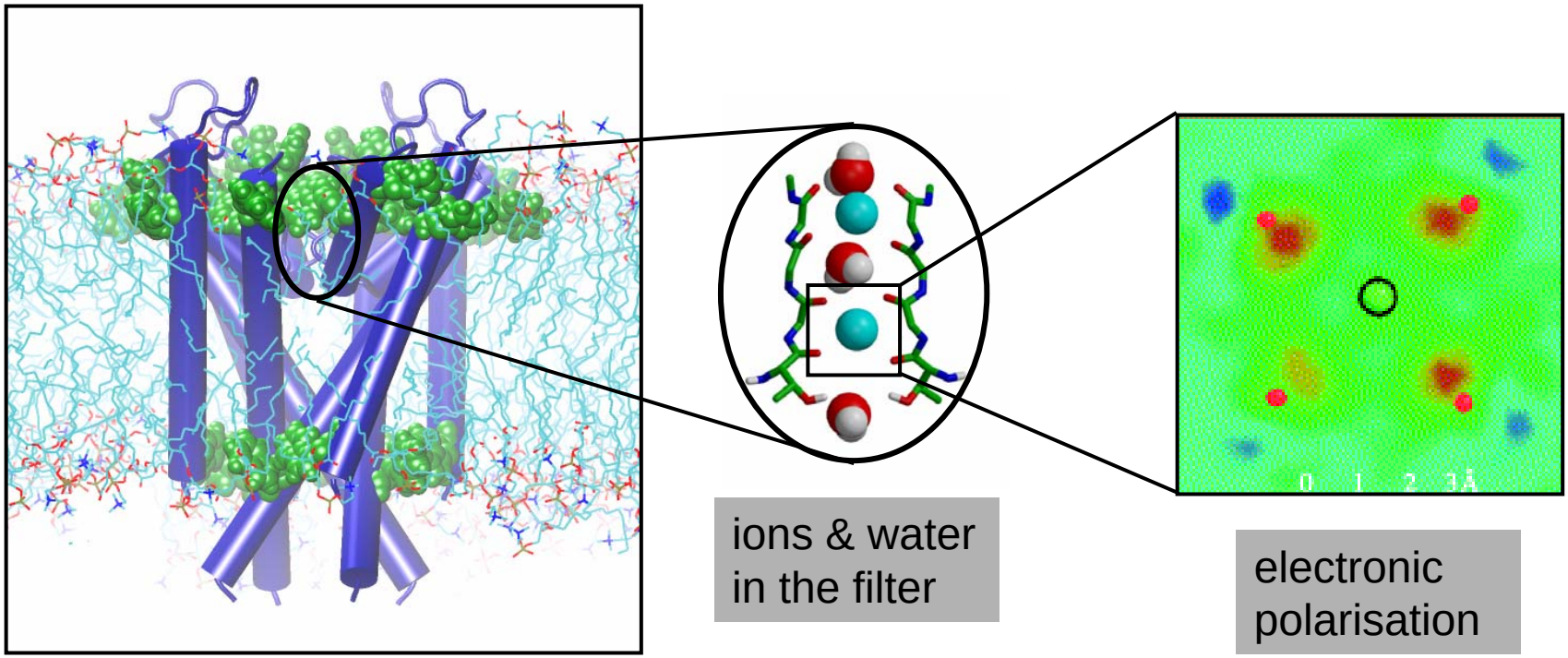


BioSimGrid Workflow





Back to Chemistry…



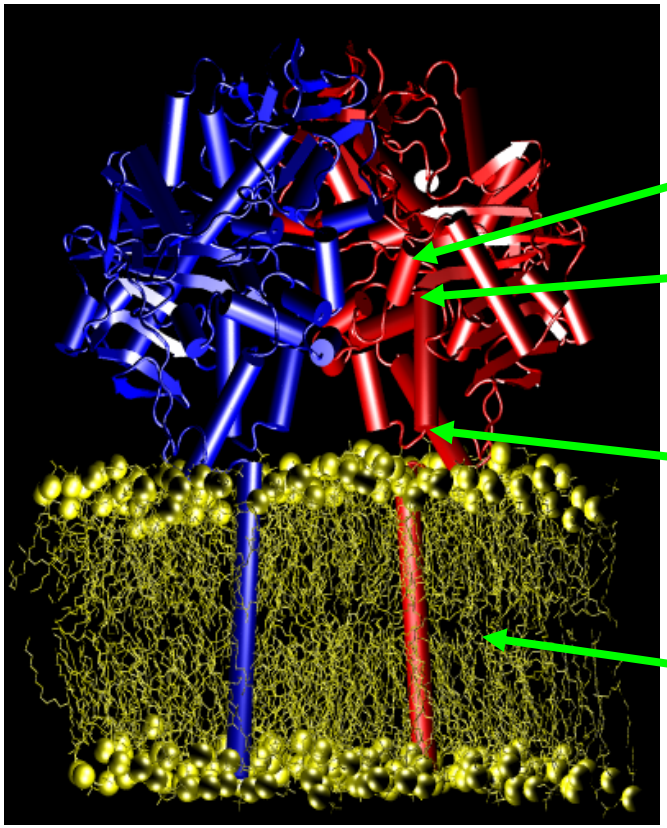
channel & membrane

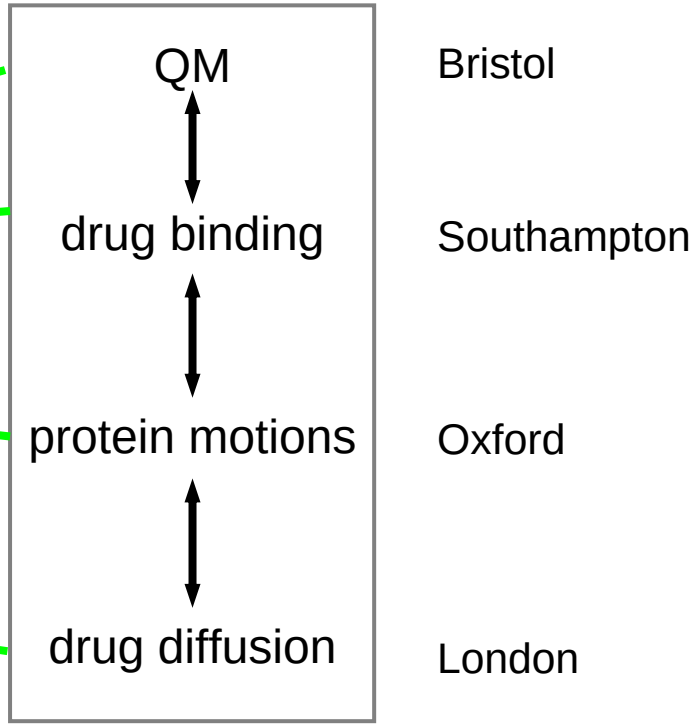
ions & water in the filter

electronic polarisation

- Ions and water in the channel – MD on >10 ns timescale reveals ion permeation Domene & Sansom (2003) *Biophys J* 85:2787
- *Ab initio* calculations for accurate energetics Guidoni & Carloni (2002) *BBA* 1563:1

Future Directions: Multiscale Biomolecular Simulations





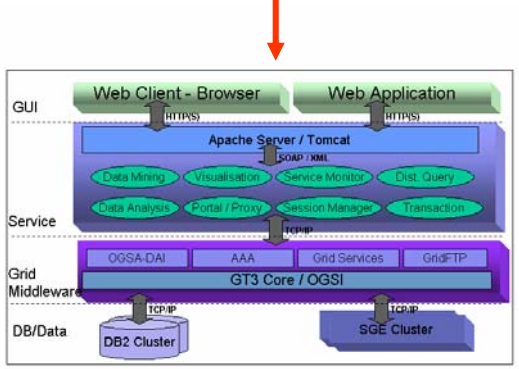
- Membrane bound enzymes – major drug targets (cf. ibruprofen, anti-depressants, endocannabinoids); gated access to active site coupled to membrane fluctuations
- Complex **multi-scale** problem: QM/MM; ligand binding; membrane/protein fluctuations; diffusive motion of substrates/drugs in multiple phases
- Need for integrated simulations on GRID-enabled HPC resources

Computational Challenges

HPCx

Linux cluster

IntBioSim

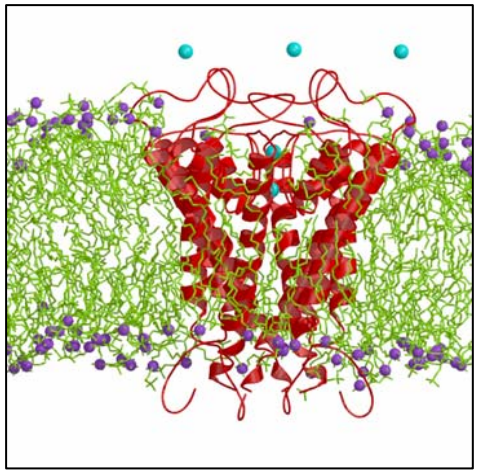


BioSimGRID database
www.biosimgrid.org

- Need to integrate HPC, cluster & database resources
- Collaboration: Oxford, Southampton, Bristol, London, Manchester

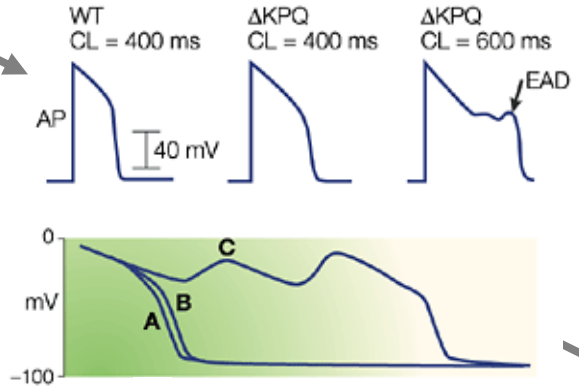
Towards Systems Biology

molecular

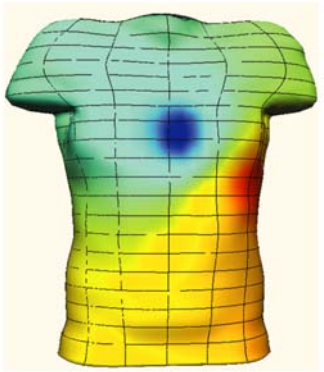


Noble (2002) *Nature Rev. Mol. Cell.Biol.* 3:460

cellular



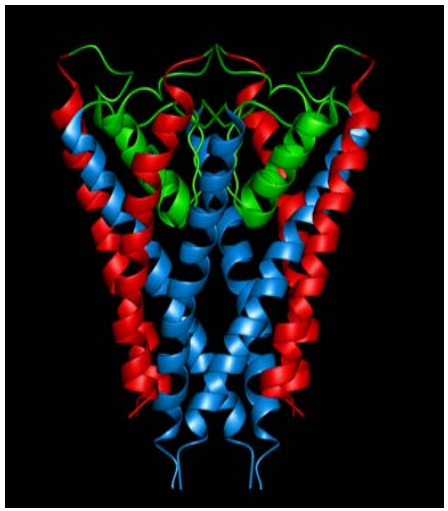
organism



- Aims: *in silico* knock outs and/or drug treatments
- Need to integrate *rigorously* if to deliver accurate & hence biomedically useful results
- Problem: how to link the different levels of description

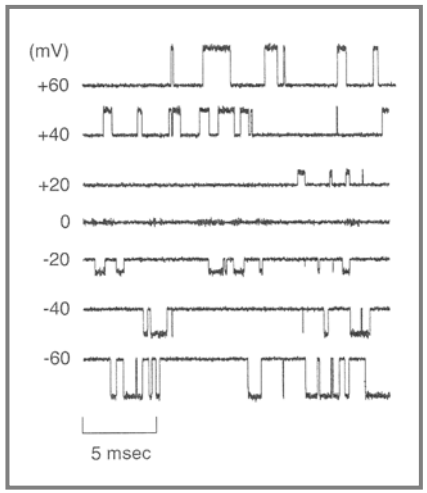
From Structure Towards Function

HT modelling & simulation
Channel & transporter model databases



Coarse-grained simulations

Physiological behaviour



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Collaborating Teams
BioSimGRID
IntBioSim
Integrative Biology
MPSI
Fran Ashcroft & OXION
Heart Physiome

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