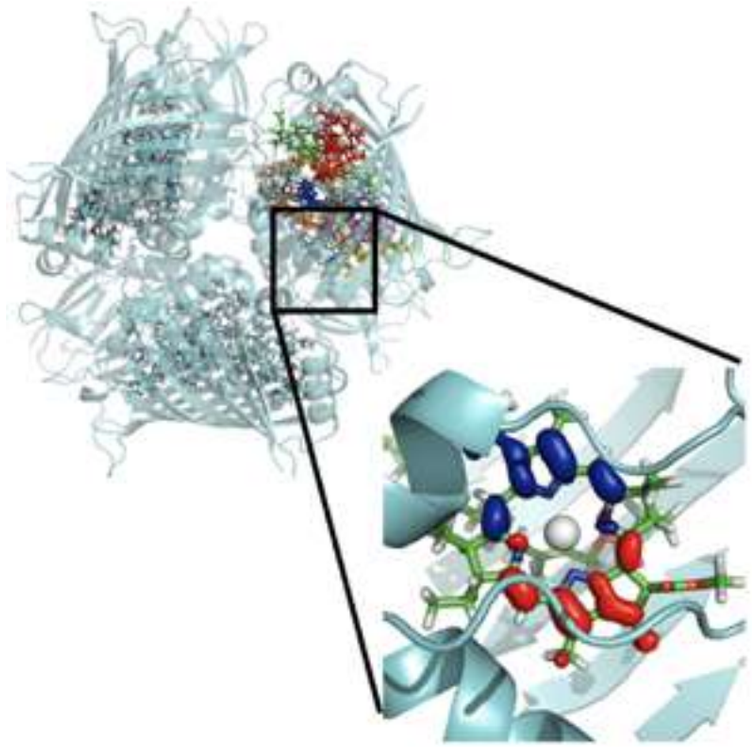
What can quantum mechanical simulations of biological molecules teach us about nanoscale design?



Daniel Cole

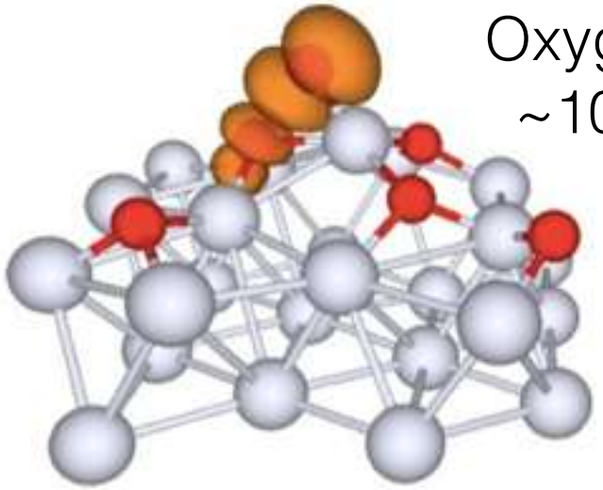
School of Chemistry, Newcastle University

Newcastle University

First Principles Quantum Mechanics

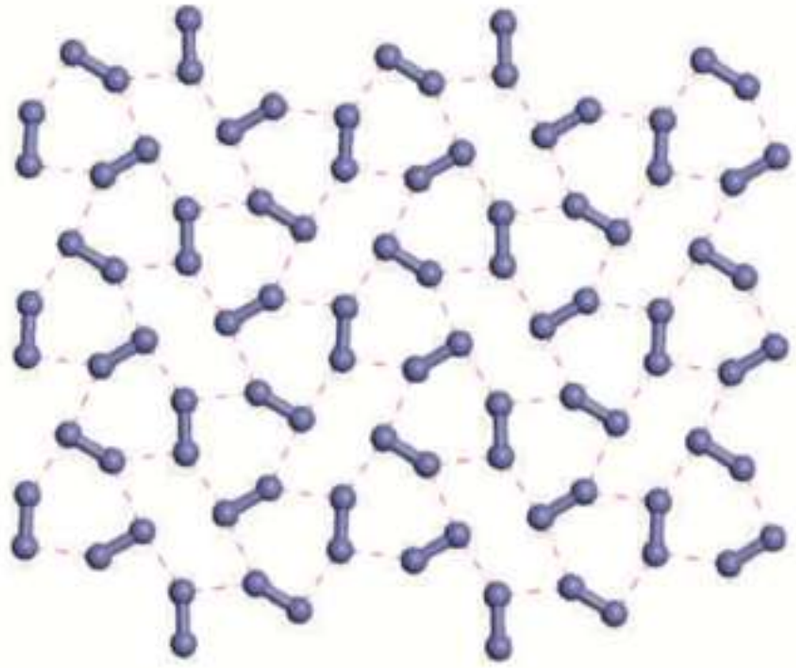
$$\hat{H}\psi = \varepsilon\psi$$

Density functional theory (DFT) has been very successful in e.g. the electronics industry for predicting properties of materials and functional mechanisms.



Oxygen absorption on silicon
~100 atoms, 10^{-12} seconds

L. Colombi Ciacchi and M. Payne, Phys. Rev. Lett. 95, 196101 (2005)



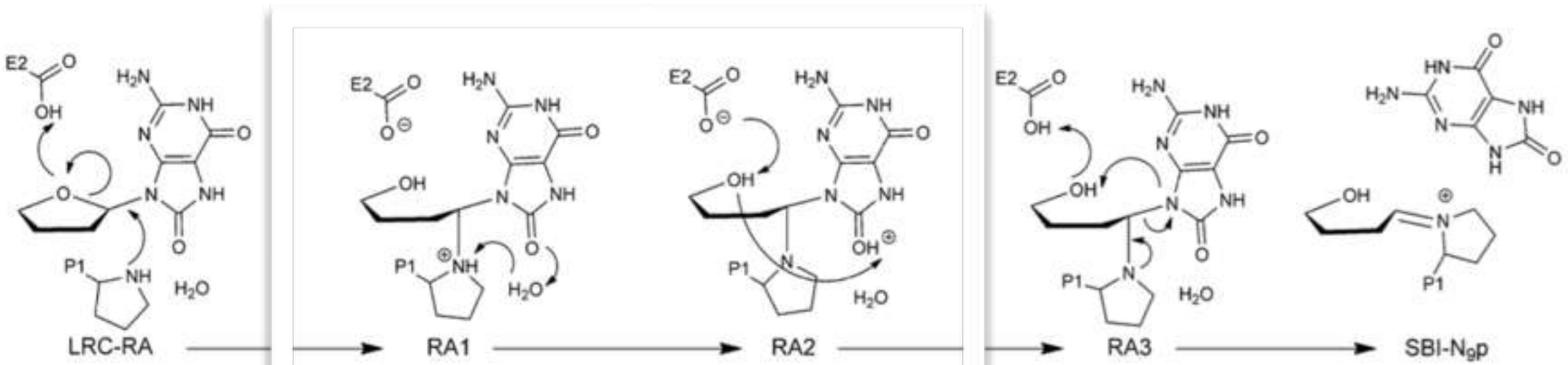
Proposed structure of solid hydrogen at 300 GPa

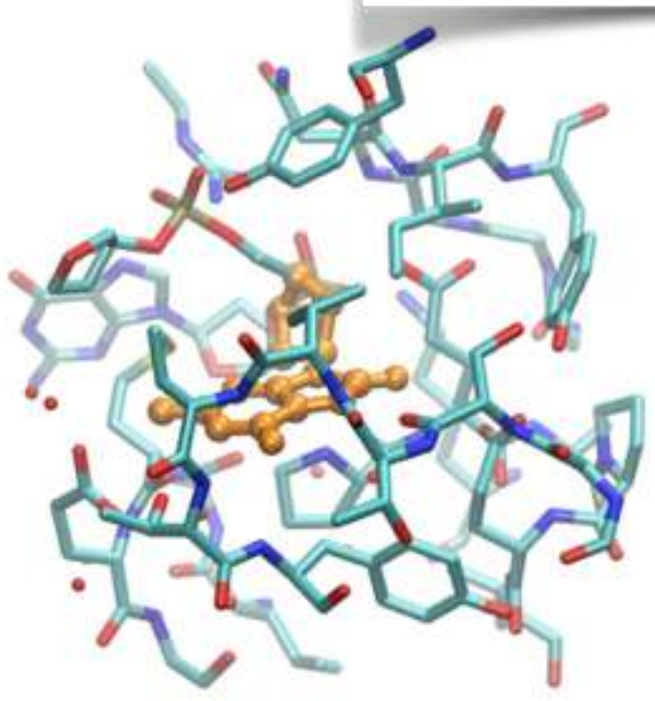
C. J. Pickard & R. J. Needs Nat. Phys. 3, 473 (2007)

Can the same methods be used in biology for the prediction of structure/ function relationships?
And can we improve biological ‘machines’ or fix them when they go wrong?
What can we learn from nature about nanoscale design?

The Length Scale Problem

Deprotonation of proline in the second stage of repair of oxidised guanine by the bacterial glycosylase, MutM





QM atoms	Barrier (kcal/mol)
143	28
278	6
493	14
606	14

Sadeghian et al., Angew. Chem. Int. Ed. 53, 10044 (2014)

Linear-Scaling DFT

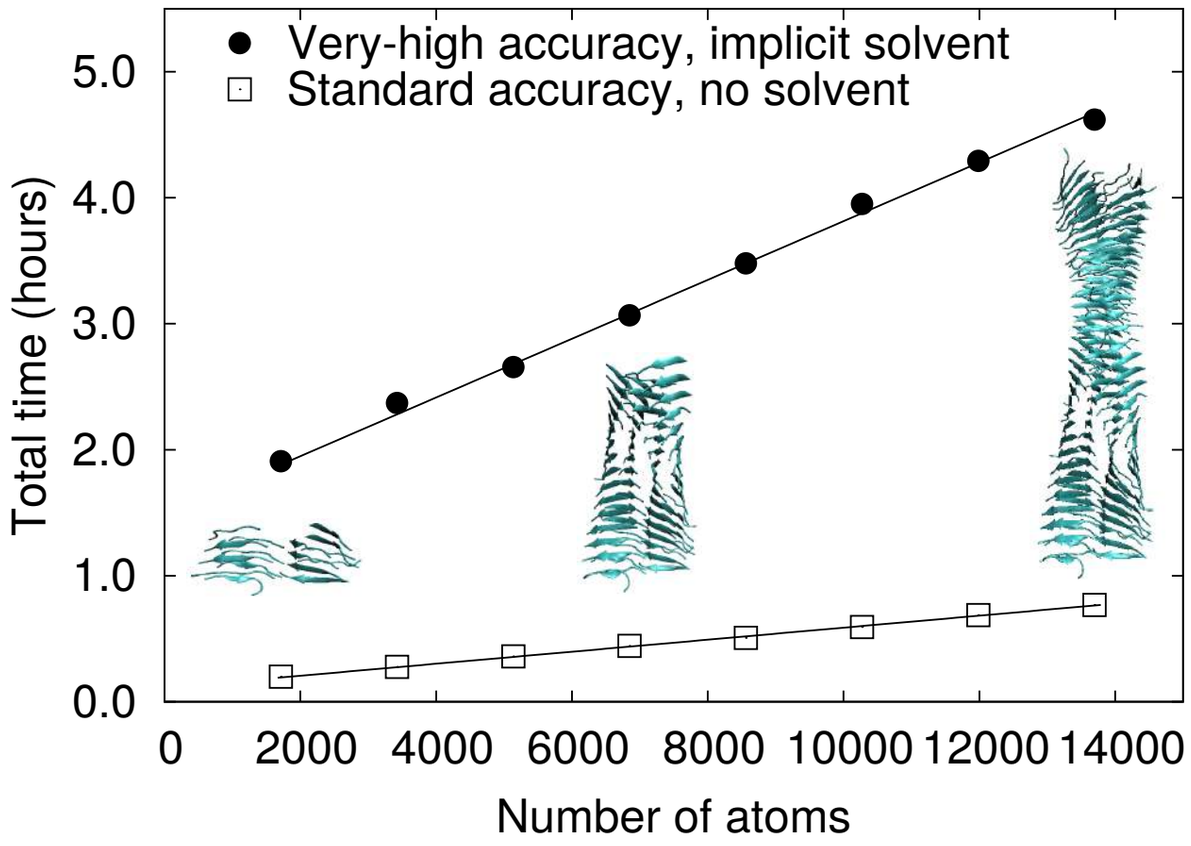
The ONETEP linear-scaling DFT approach combines near-complete basis set **accuracy** with a computational cost that scales **linearly** with system size.

DFT simulations can now be employed in much larger systems, *including entire proteins*.

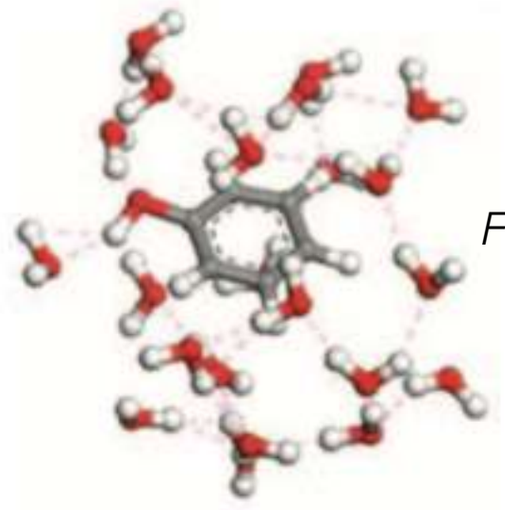
www.onetep.org/

C. K. Skylaris, P. D. Haynes, A. Mostofi, M. C. Payne
J. Chem. Phys. **2005**, *122*, 084119

3840 cores on ARCHER supercomputer

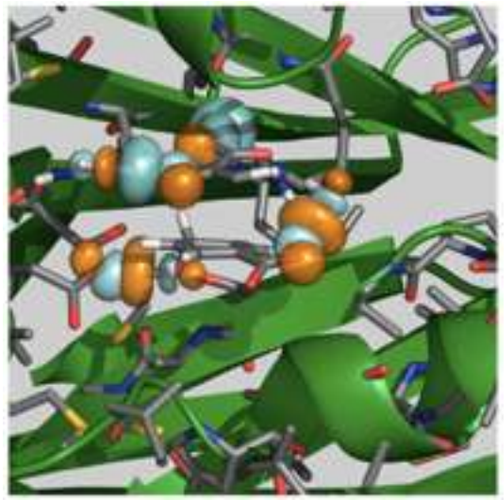


	No. functions	ΔE / kcal/mol
ONETEP	166	-7.04
Gaussian (cc-PVQZ)	3780	-7.22

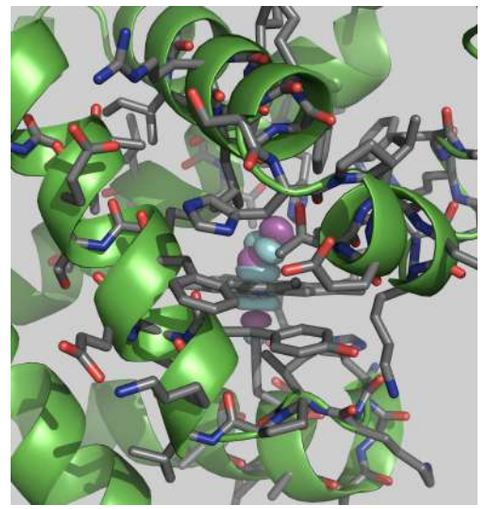


Fox et al., J. Chem. Phys. 135, 224107 (2011)

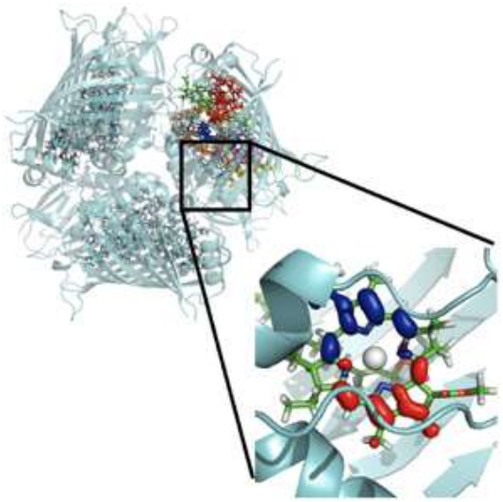
ONETEP Biological Applications



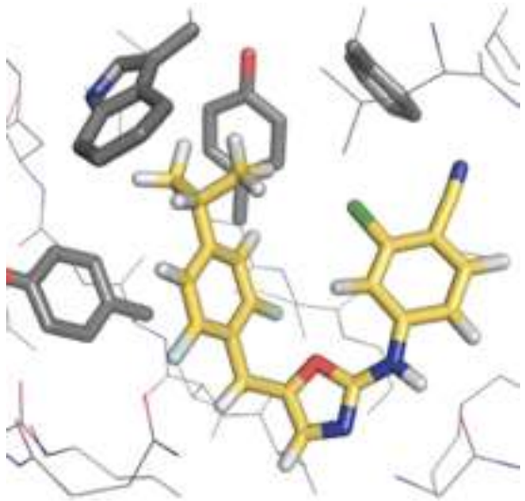
Transition state searching in enzymes



Protein-ligand binding in metalloproteins



Optical spectroscopy in a light-harvesting protein

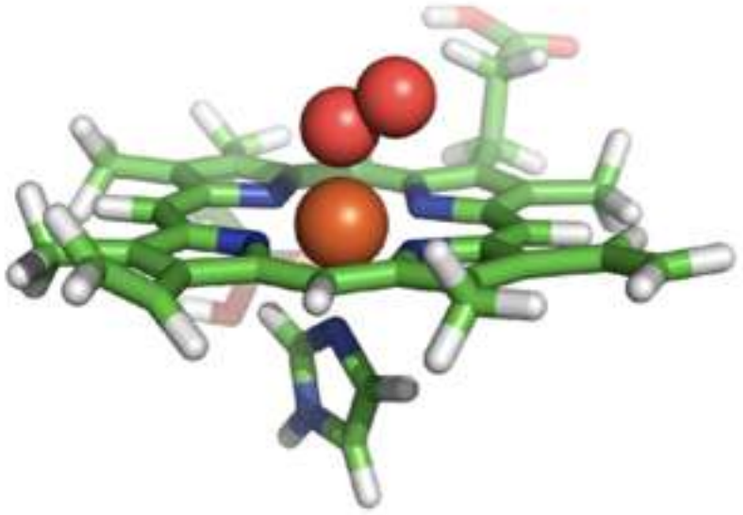


Classical force field parameterisation for drug discovery

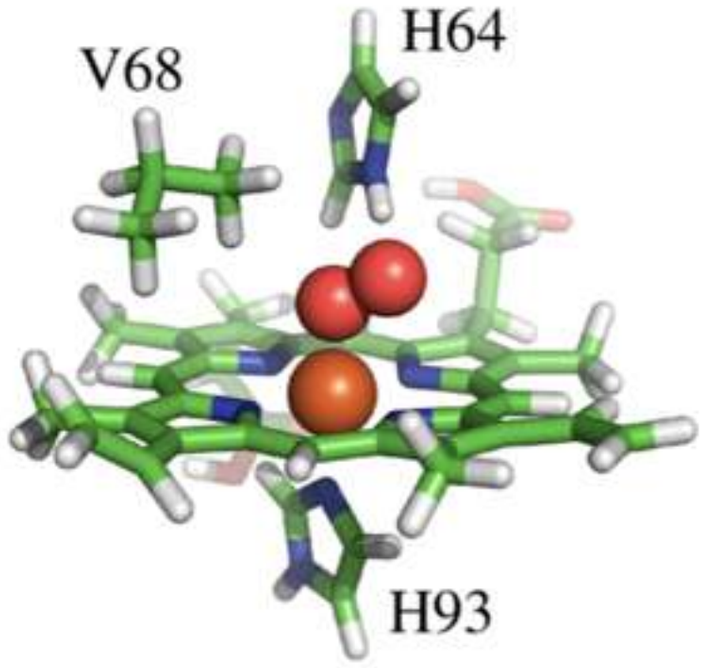
"Applications of Large-Scale DFT in Biology", D. J. Cole & N. D. M. Hine
Journal of Physics: Condensed Matter, 28, 393001 (2016)

Metalloproteins

$K_{CO}:K_{O_2}$ ~ 20,000
ΔΔE = 5.9 kcal/mol

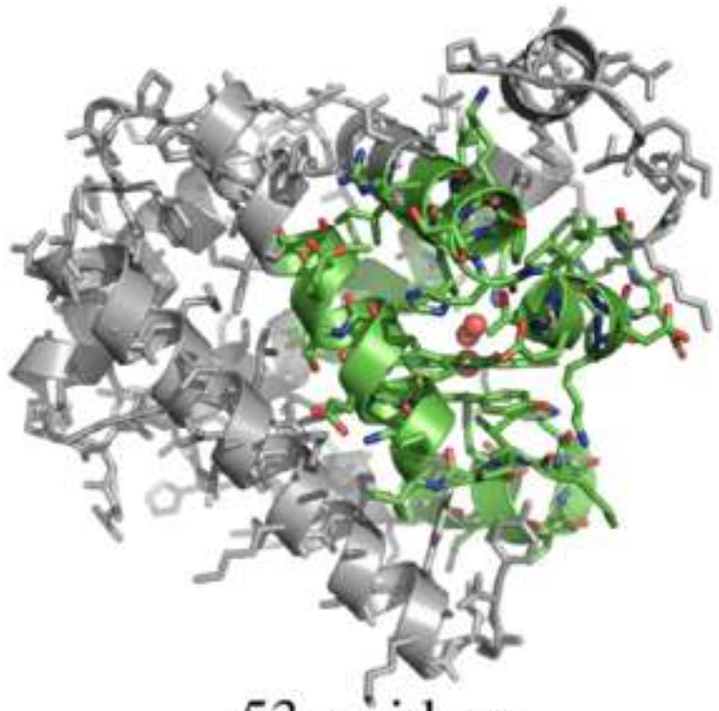


1 residue



3 residues

$K_{CO}:K_{O_2}$ ~ 20
ΔΔE = 1.9 kcal/mol

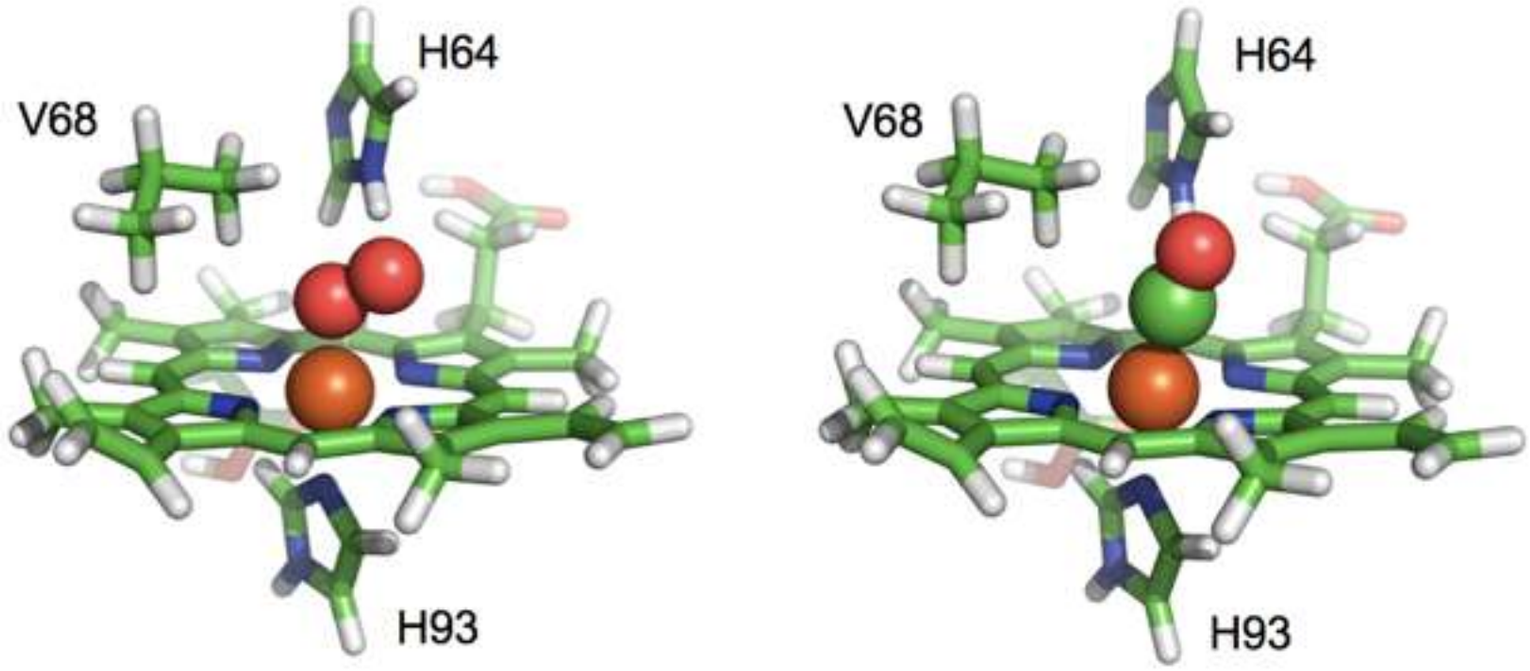


53 residues

Myoglobin is small protein responsible for storing O_2 in muscle tissue.
Function hindered by CO.

Olson, *J. Biol. Inorg. Chem.* **2**, 544 (1997)

Discrimination Mechanism



Charge transfer higher to O_2 than CO
Stronger H-bond between O_2 and residue H64
- protein-ligand interactions favour O_2 by **3.6 kcal/mol**

Steric effect on CO shown to be small
- strain energy stored in protein **~0 kcal/mol**

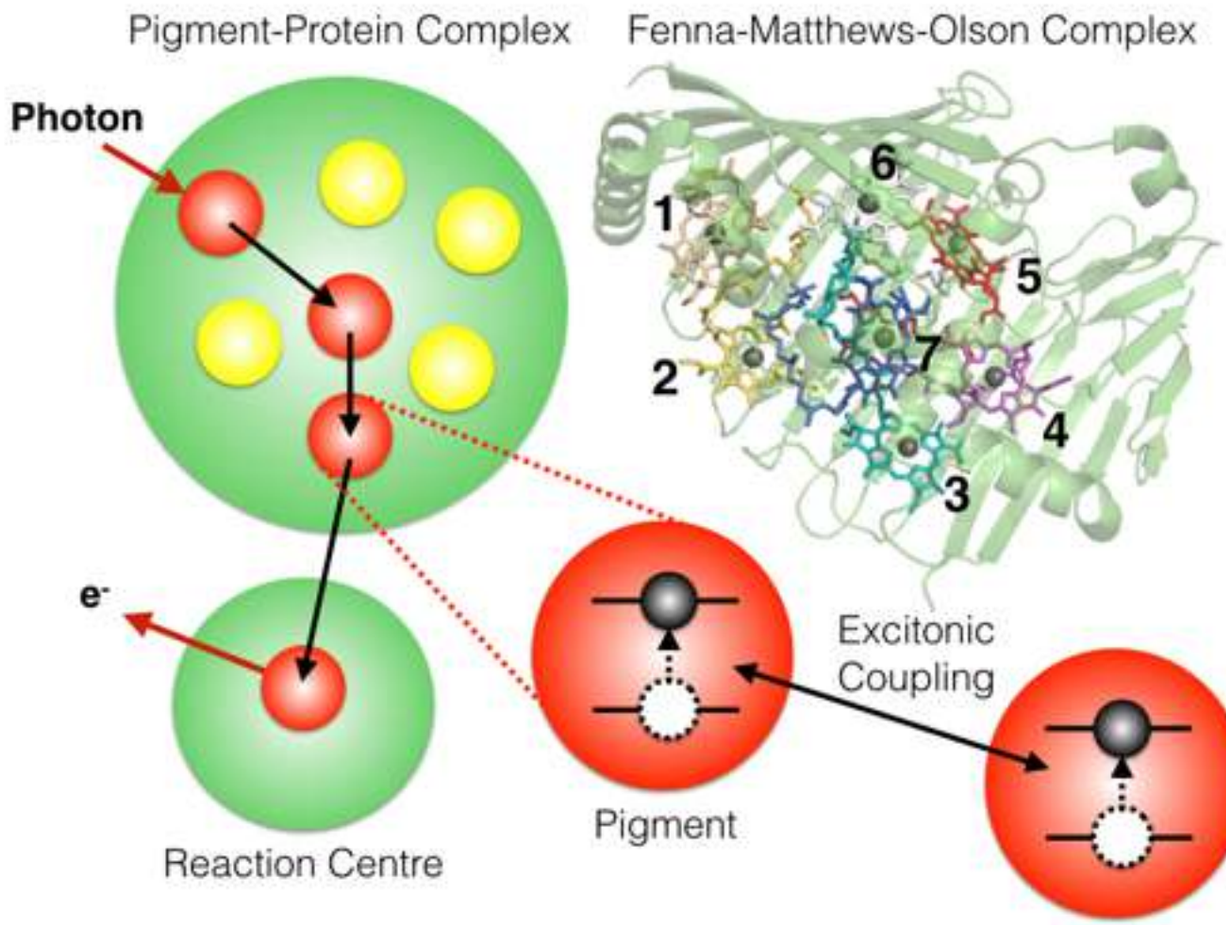
Computational studies require accurate treatment of Fe chemistry and long-ranged electrostatic interactions between O_2 and protein

D. Cole, D. O'Regan, M. Payne, *J. Phys. Chem. Lett.* **3**, 1448 (2012)
C. Weber, D. Cole, D. O'Regan, M. Payne, *Proc. Natl. Acad. Sci. USA* **111**, 5790 (2014)

FMO Complex

Fenna-Matthews-Olson (FMO) complex: funnels electronic excitations (excitons) to reaction centre where they are used to release electrons for photosynthesis.

X-ray diffraction reveals a trimeric structure. Each monomer contains 7 bacterio-chlorophyll pigments.



Exciton transfer through FMO modelled by pigment-protein complex (PPC) Hamiltonian:

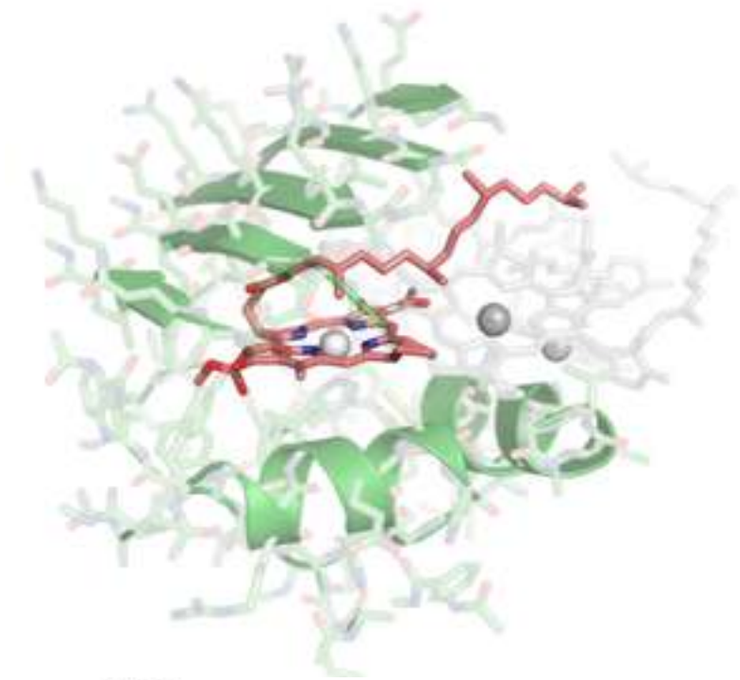
$$H = \sum_i \varepsilon_i |i\rangle\langle i| + \sum_{i \neq j} J_{ij} |i\rangle\langle j|$$

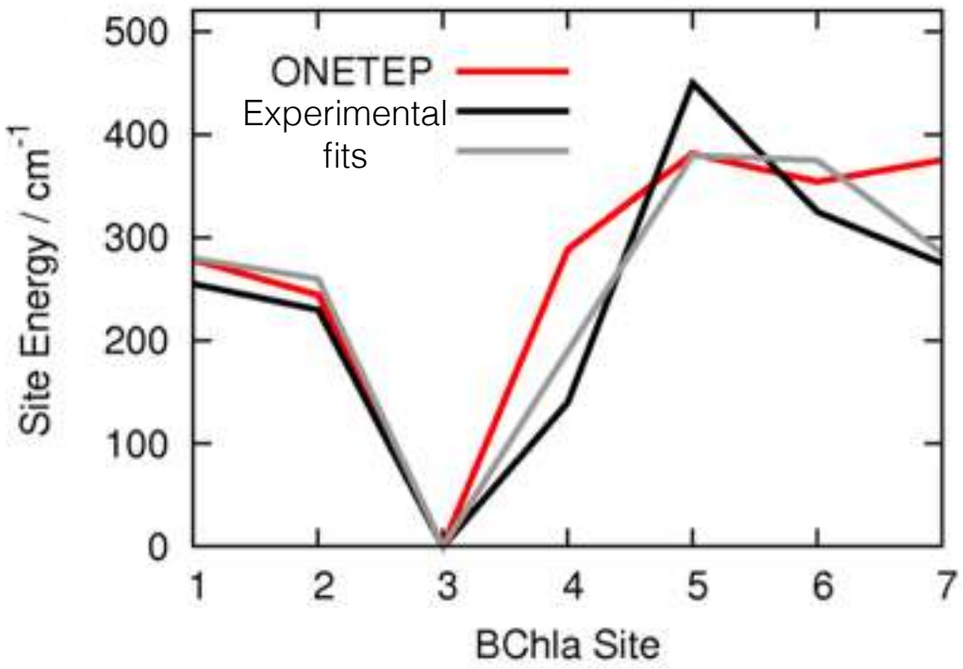
site energies — coupling between optical transitions

A. W. Chin et al., *Nature Phys.*, **2013**, *9*, 113-118

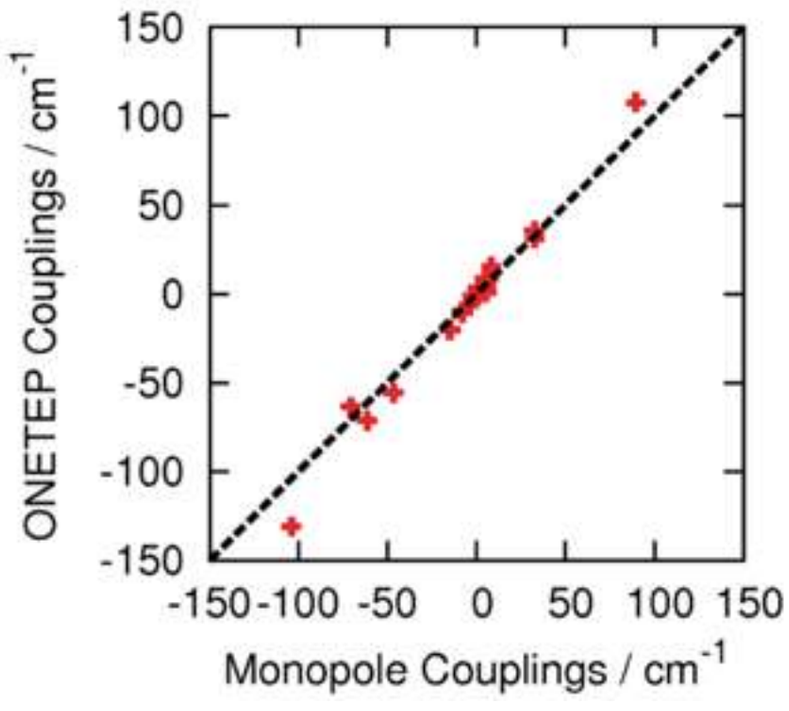
DFT results

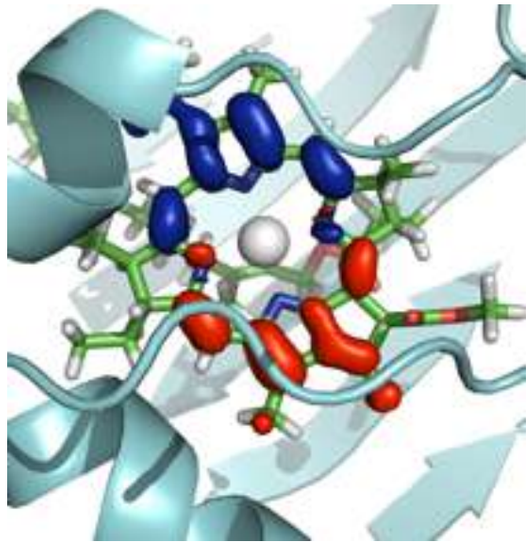
ε_i:





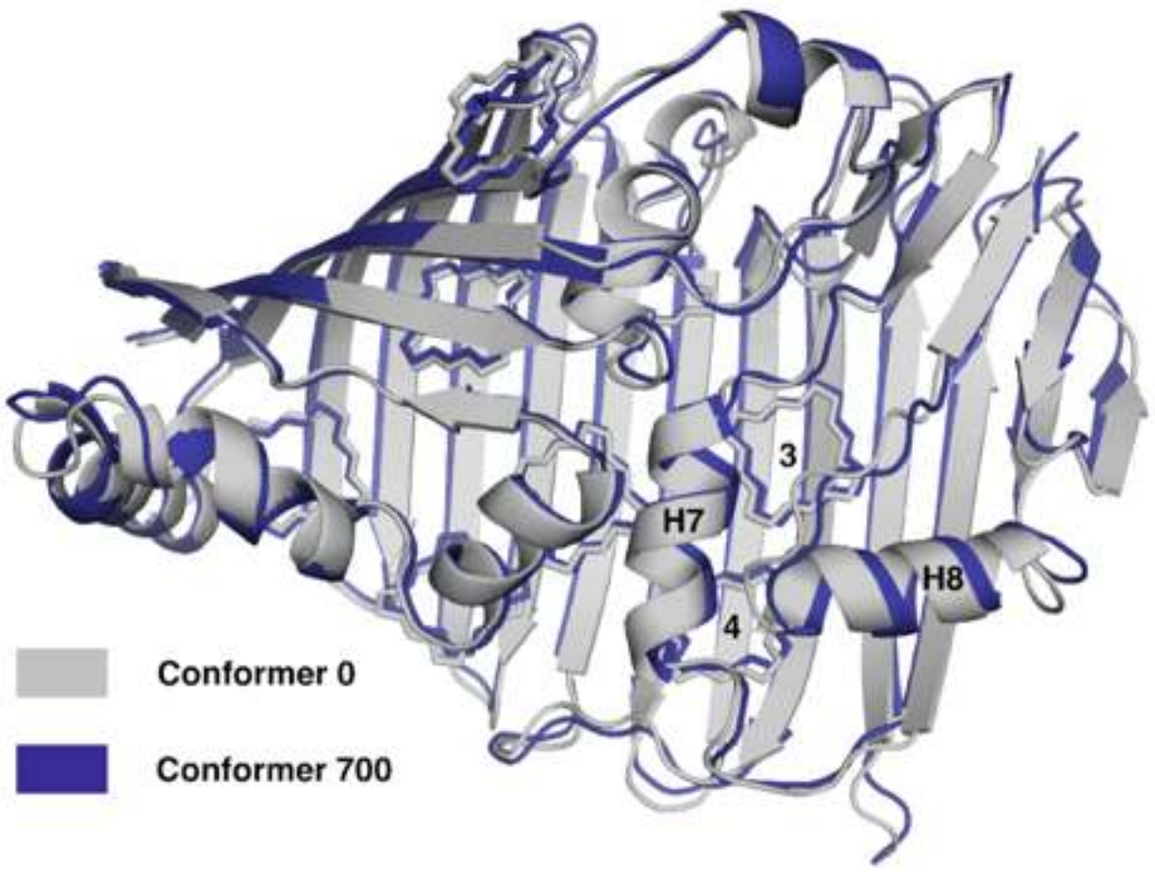
J_{ij}:

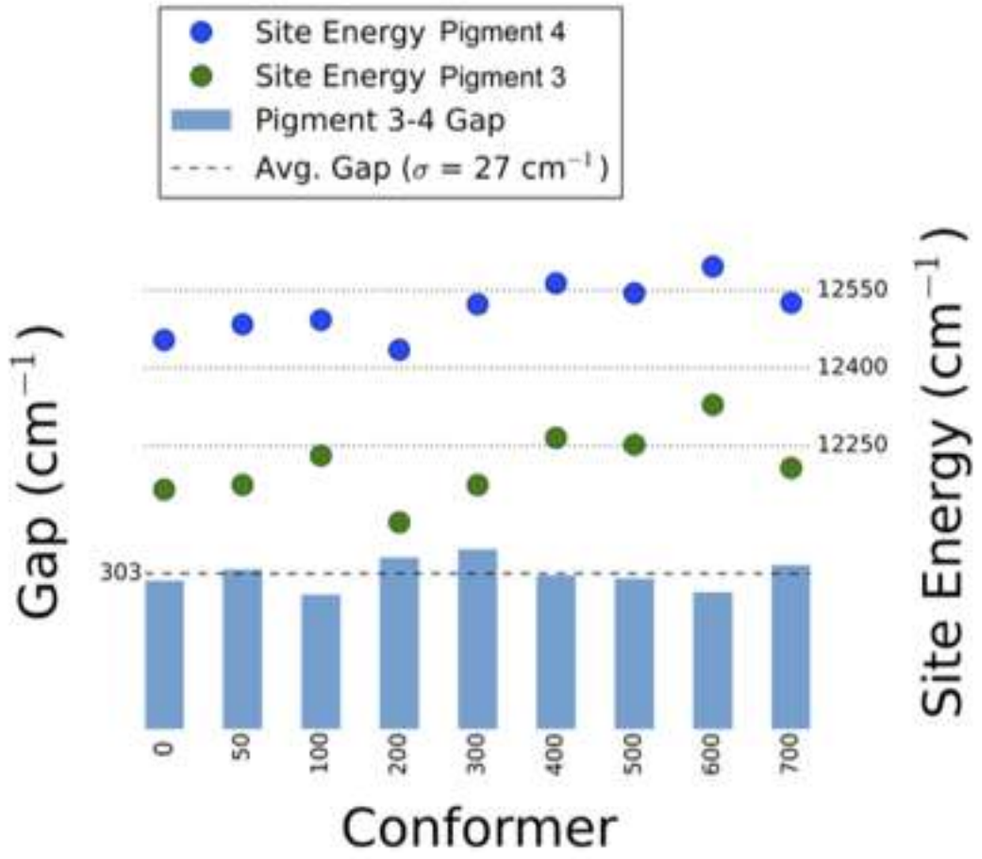




D. Cole, A. Chin, N. Hine, P. Haynes, M. Payne, J. Phys. Chem. Lett., ***4****, 4206 (2013)*

Pigment-Protein Dynamics



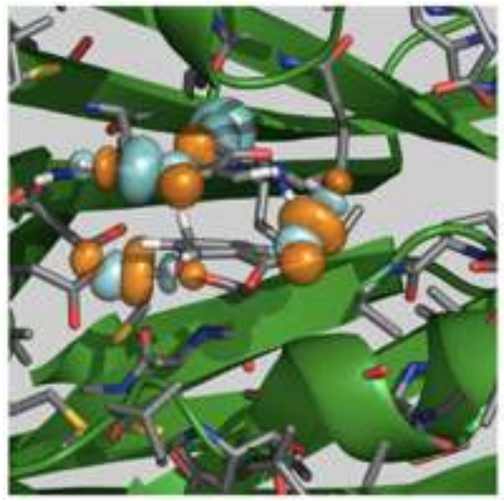


Pigment-protein dynamics simulated using the FRODA constrained geometric dynamics software.

Snapshots post-processed to investigate effects of thermal disorder on excitonic energy landscape.

A. Fokas, D. Cole, N. Hine, S. Wells, M. Payne, A. Chin, in preparation (2017)
*A. Fokas, D. Cole, A. Chin, Photosynth. Res., **122**, 275 (2014)*

ONETEP Biological Applications



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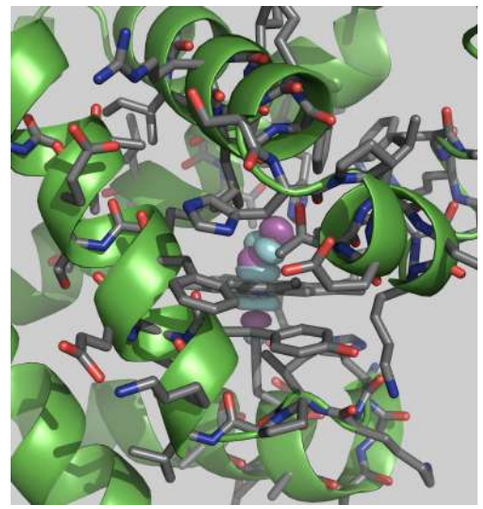
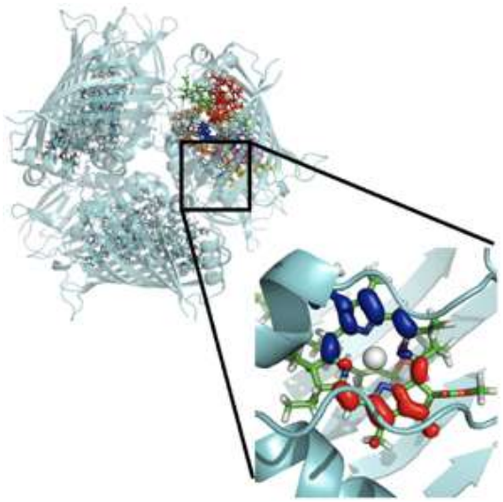
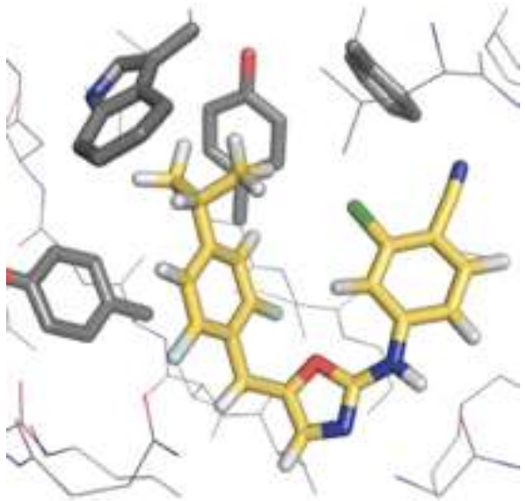


Protein-ligand binding in metalloproteins



Optical spectroscopy in a light-harvesting protein



Classical force field parameterisation for drug discovery

"Applications of Large-Scale DFT in Biology", D. J. Cole & N. D. M. Hine
Journal of Physics: Condensed Matter, 28, 393001 (2016)

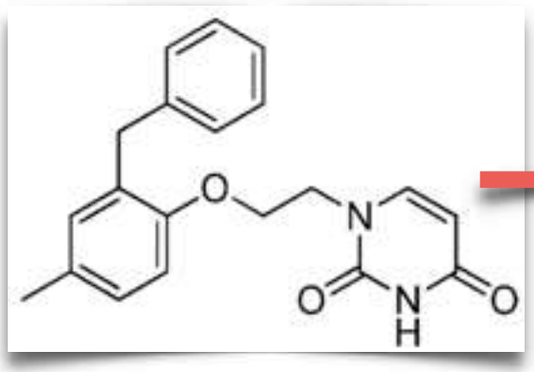
Free Energy Perturbation

Computational drug design used in conjunction with synthesis, binding assays and x-ray crystallography.

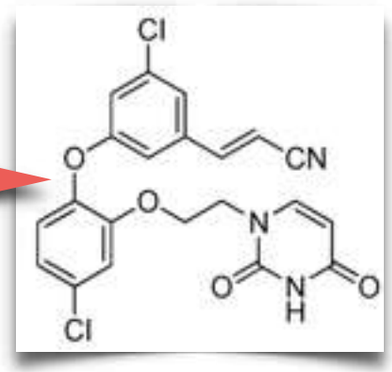
Computational approach uses free energy perturbation (FEP) for lead optimisation.

Notable successes include computationally-guided design of non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs).

5μM docking hit



55pM inhibitor



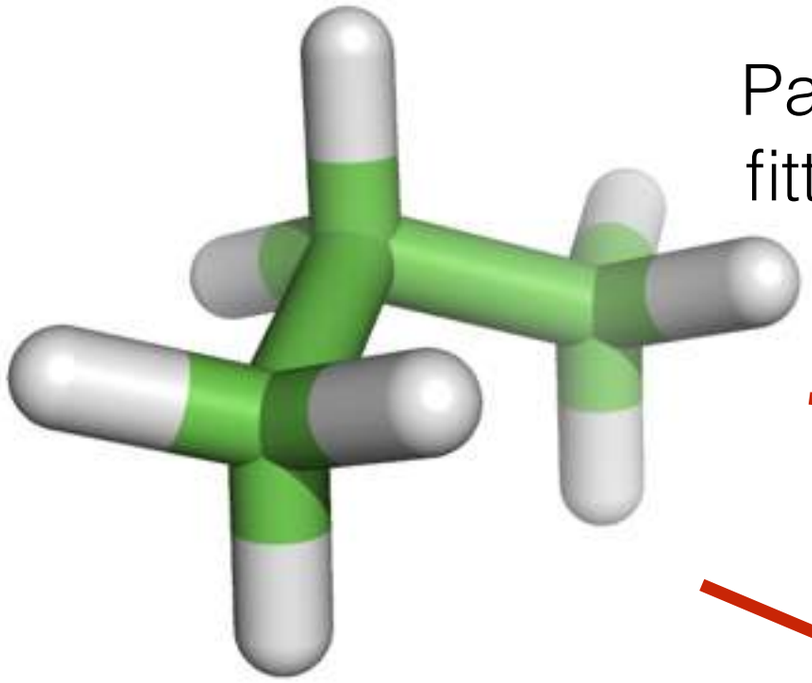
M. Bollini *et al.*, *J. Med. Chem.* **2011**, *54*, 8582
W. G. Lee *et al.*, *J. Am. Chem. Soc.* **2013**, *135*, 16705

But predictive power of FEP is limited by the accuracy of the underlying classical molecular mechanics force field, whose parameters are highly empirical:

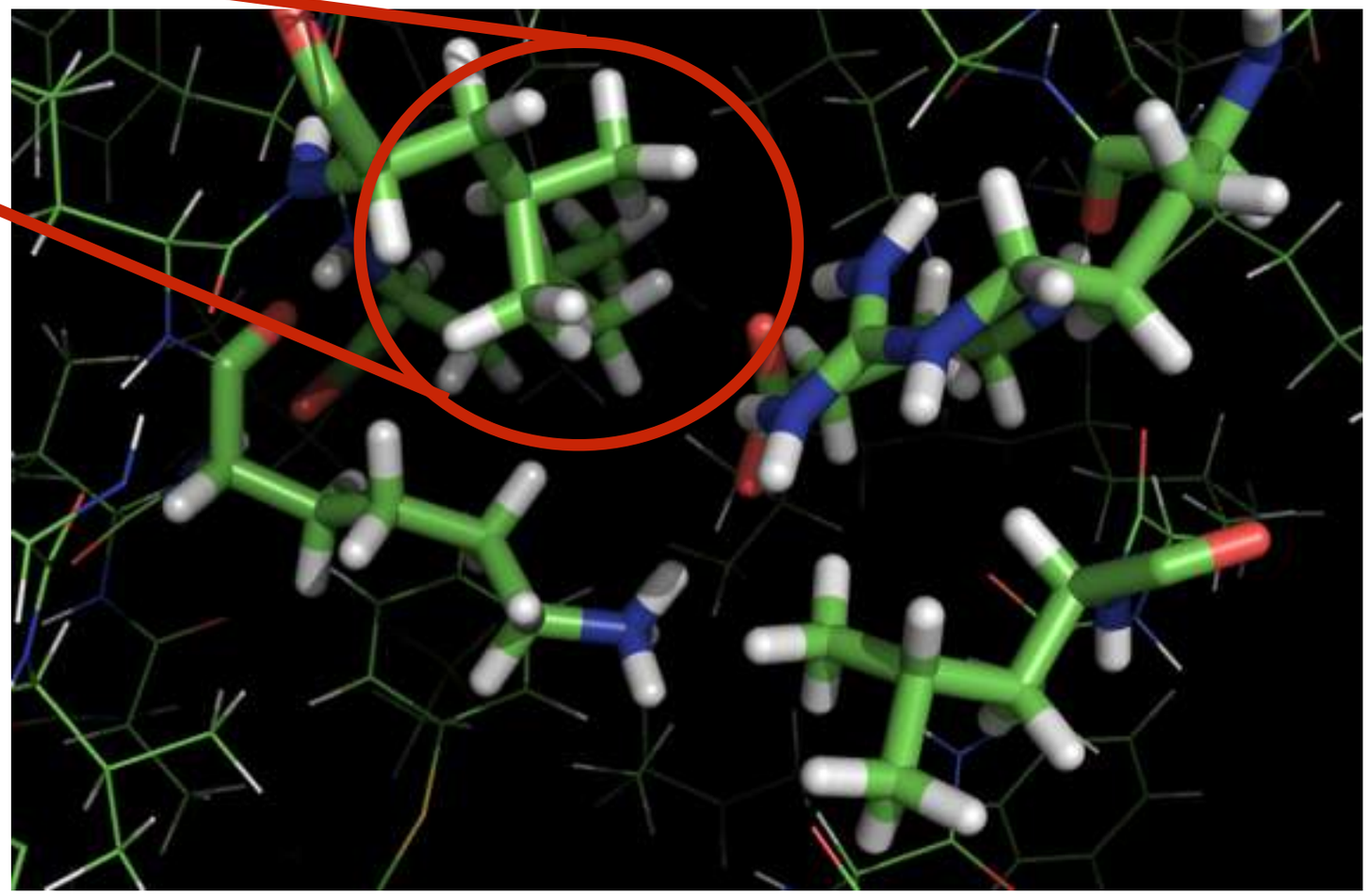
$$U(\mathbf{R}) = \sum_{\text{bonds b}} K_{\mathrm{b}}(r_{\mathrm{b}} - r0)^2 + \sum_{\text{angles a}} K_{\theta}(\theta_{\mathrm{a}} - \theta_0)^2 + \sum_{\text{dihedrals d}} K_{\chi}\left(1 + cos(n\chi_{\mathrm{d}} - \sigma)\right)$$

$$+ \sum_{\text{impropers } \eta} K_{\eta}(\phi_{\eta} - \phi_0)^2 + \sum_{\text{nonbonded pairs ij}} \left(\left[\frac{C_{ij}^{(12)}}{r_{ij}^{12}} - \frac{C_{ij}^{(6)}}{r_{ij}^{6}} \right] \right) + \sum_{i<j} \frac{q_i q_j}{r_{ij}}$$

Force Field Parameterisation



Parameters for e.g. propane obtained by fitting to empirical properties of liquid, or QM binding energy data etc.



Assumed that parameters for valine are the same as propane in all environments.

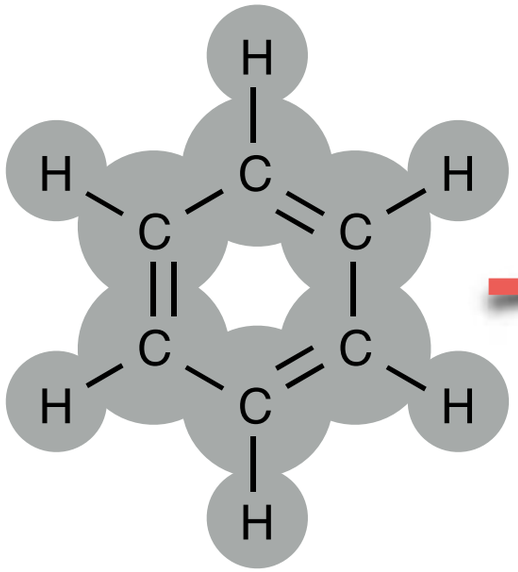
Our belief is that it would be preferable to compute parameters that are specific to their environment.

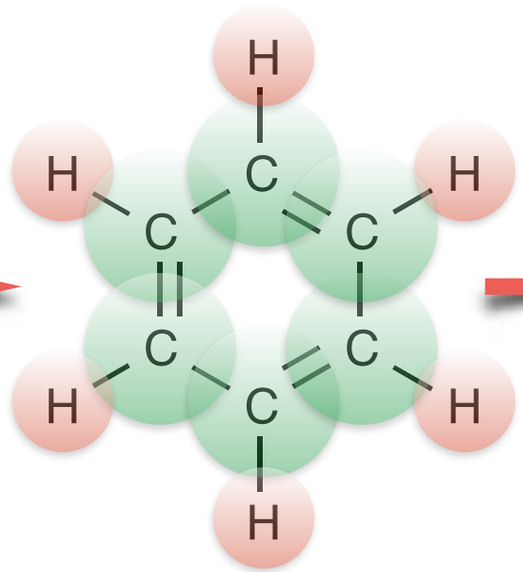
Project Objectives

DFT Calculation computes total electron density

Electrons partitioned amongst the atoms in the system

Atomistic force field parameters computed directly from partitioned electron density





Atomic Charges

Dispersion

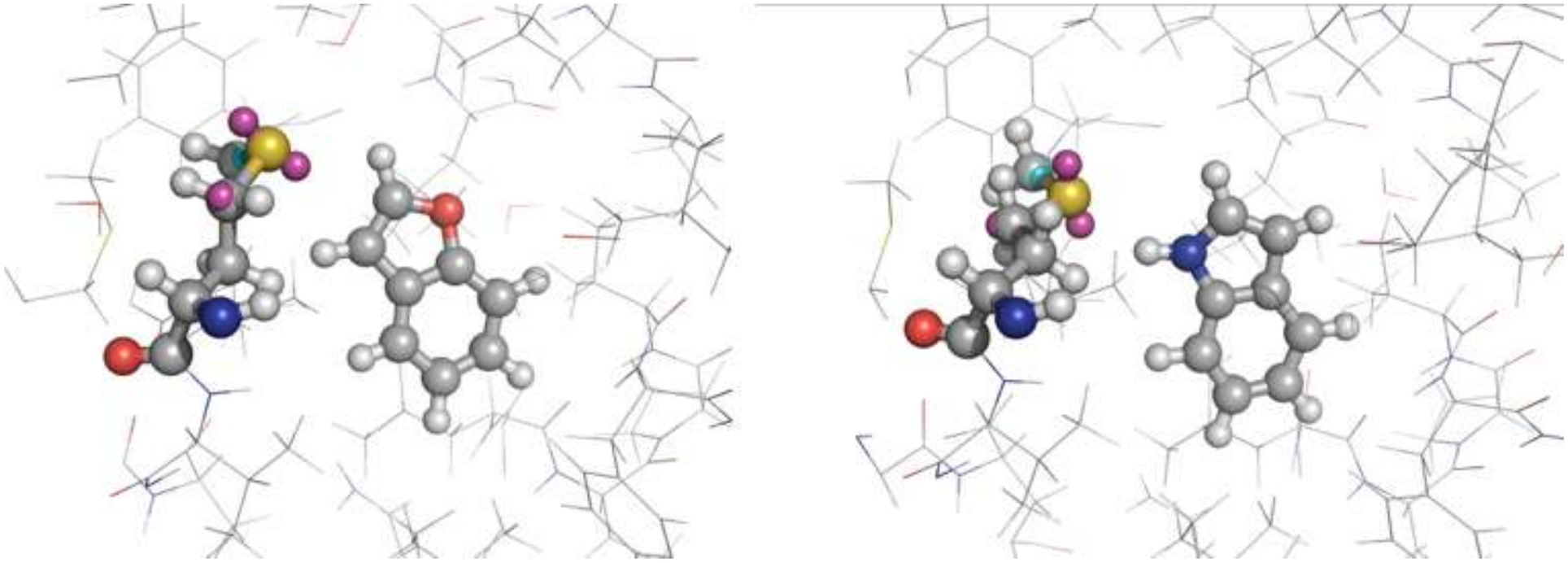
Exchange repulsion

$$U(\mathbf{R}) = \sum_{\text{bonds b}} K_{\mathrm{b}}(r_{\mathrm{b}} - r0)^2 + \sum_{\text{angles a}} K_{\theta}(\theta_{\mathrm{a}} - \theta_0)^2 + \sum_{\text{dihedrals d}} K_{\chi}\left(1 + cos(n\chi_{\mathrm{d}} - \sigma)\right)$$

$$+ \sum_{\text{impropers } \eta} K_{\eta}(\phi_{\eta} - \phi_0)^2 + \sum_{\text{nonbonded pairs ij}} \left(\left[\frac{C_{ij}^{(12)}}{r_{ij}^{12}} - \frac{C_{ij}^{(6)}}{r_{ij}^{6}} \right] \right) + \sum_{i<j} \frac{q_i q_j}{r_{ij}}$$

Example Application

Relative free energy of binding of indole and benzofuran to the L99A mutant of T4 lysozyme:



	$\Delta\Delta G_{bind}$ / kcal/mol
OPLS	-2.4
This Work	-0.4
Experiment	-0.6

D. Cole, J. Vilseck, J. Tirado-Rives, M. Payne, W. Jorgensen, *JCTC,* **2016**, *12,* 2312

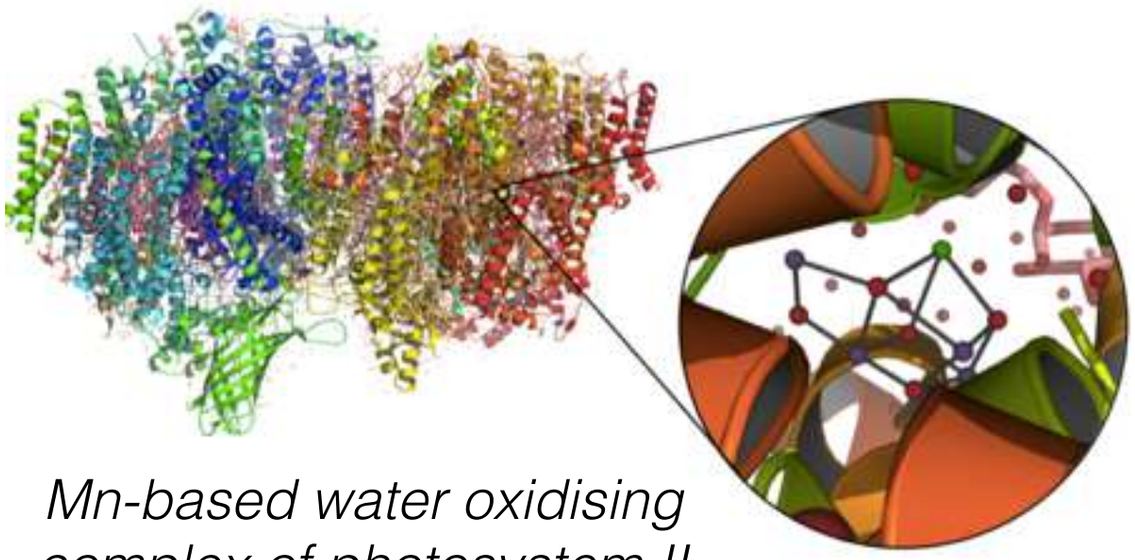
Summary

Shown that it is feasible to use QM in biology to examine structure/function relationships.

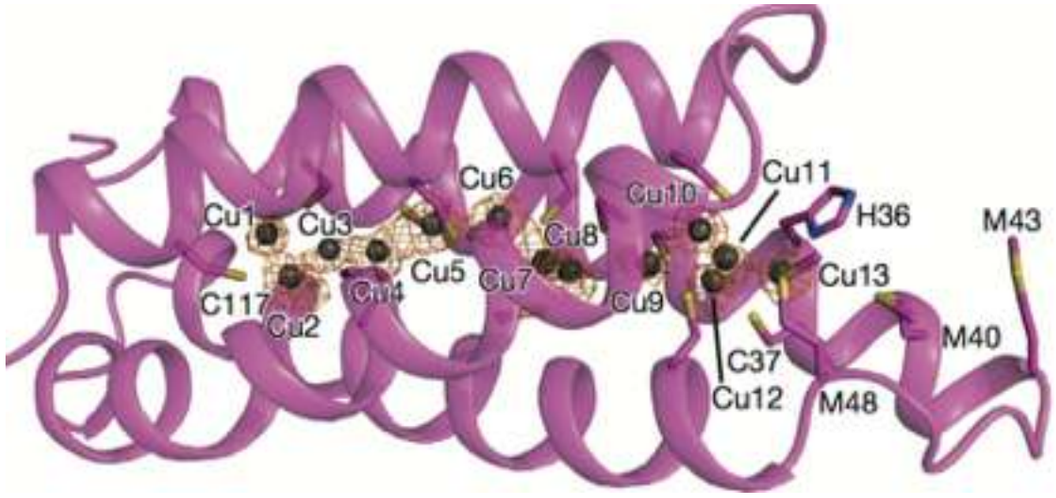
Sampling conformational space will be important for future studies (particularly for computer-aided drug design).

What can we learn from nature about nanoscale design?

Aim to move away from ‘toy models’ towards predictive modelling.



Mn-based water oxidising complex of photosystem II



Cu storing protein in methane-oxidising bacteria (group of C. Dennison (ICaMB))

Vita et al., Nature, 525, 140 (2015)