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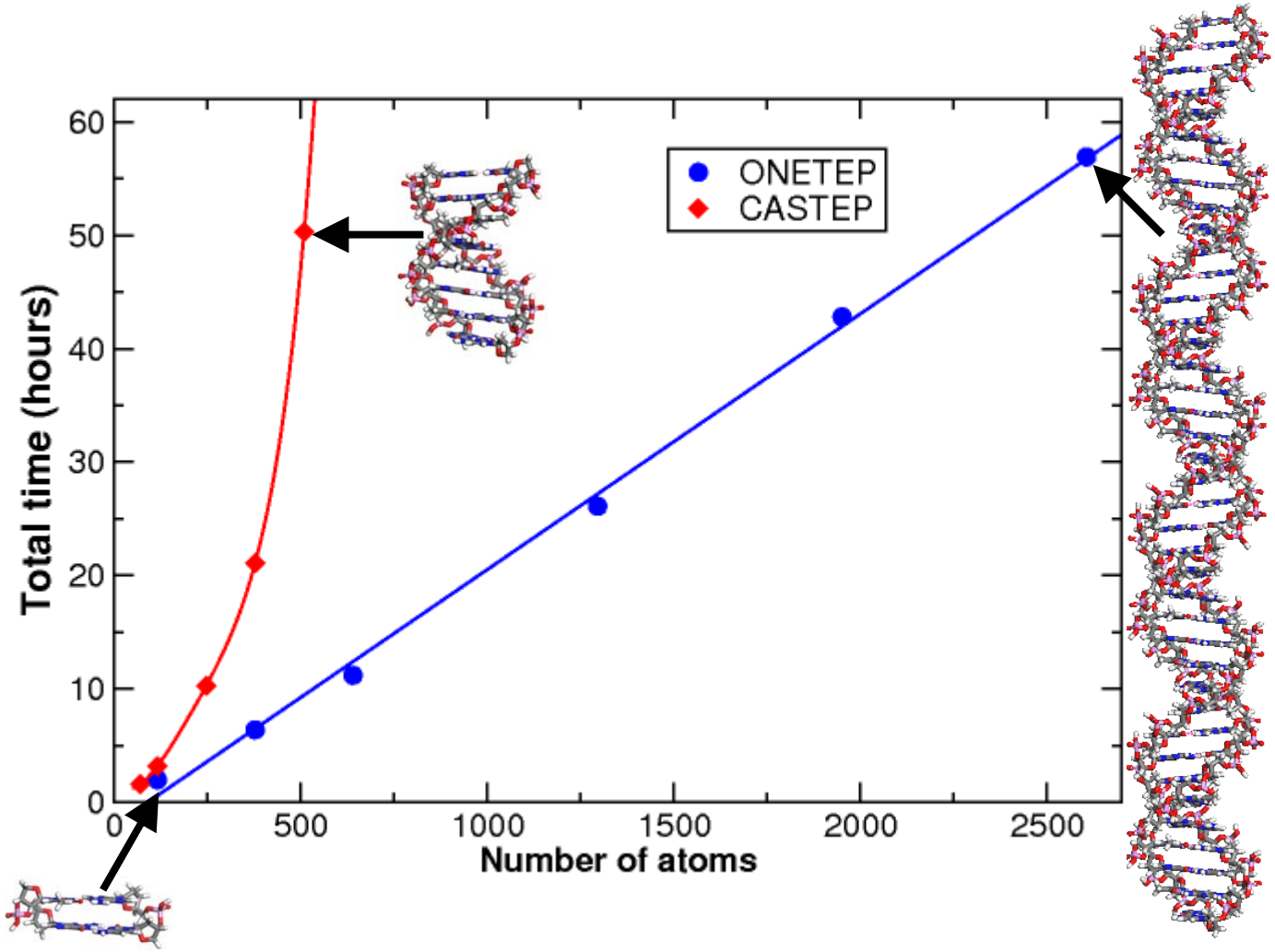
Biomolecular simulations with ONETEP

Chris-Kriton Skylaris

2004: First version of ONETEP

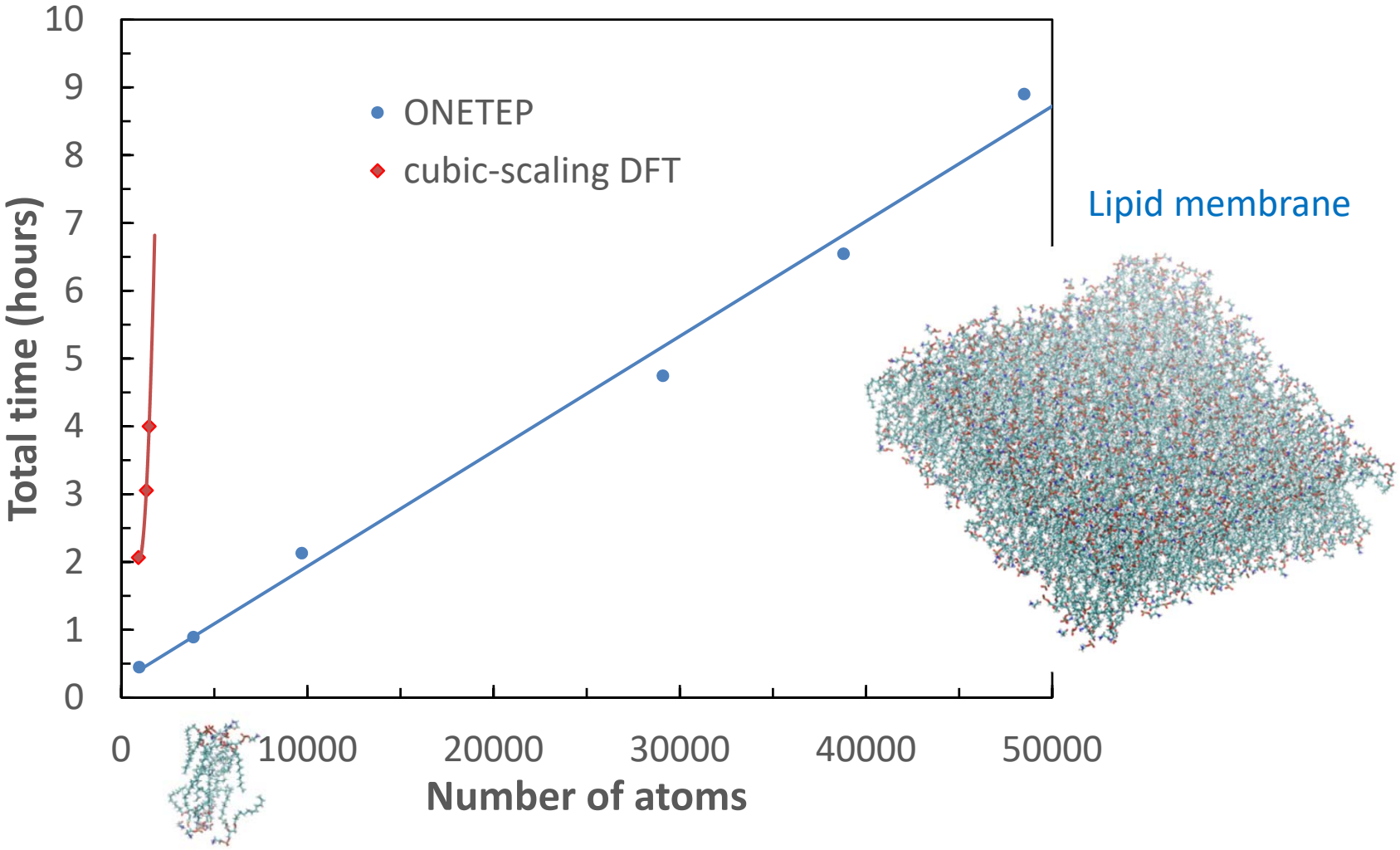
Calculations on 64 cores of “Franklin”, the 900-core SunFire 15K cluster of the CCHPCF



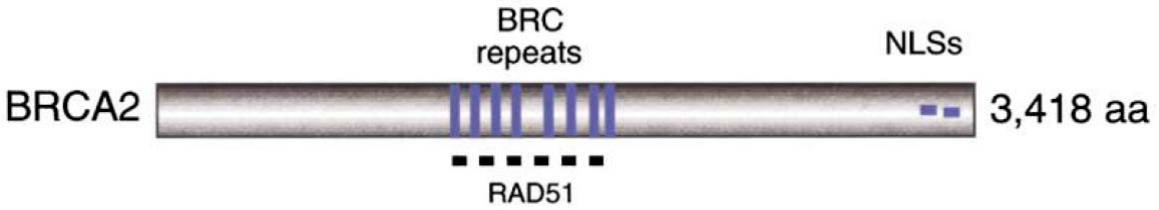
C.-K. Skylaris, P. D. Haynes, A. A. Mostofi and M. C. Payne, *J. Chem. Phys.* **122**, 084119 (2005).

2019: ONETEP v 5.2

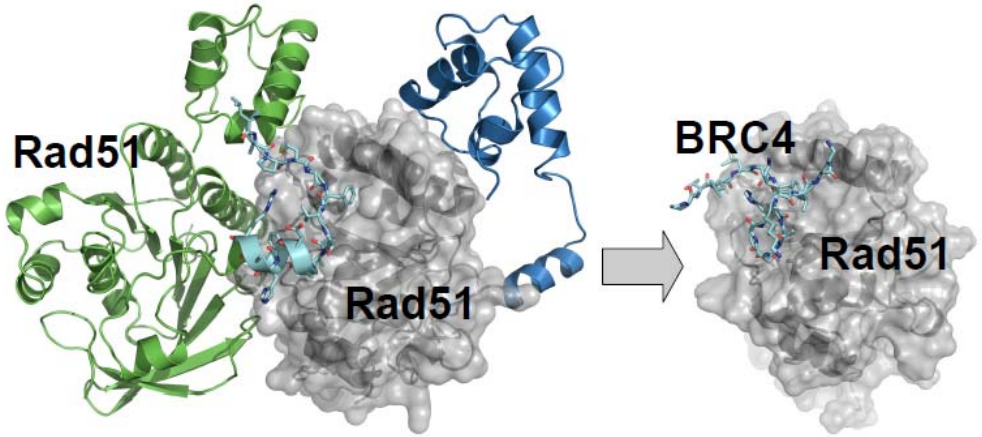
Calculations on1280 cores (MPI + OMP) Intel Skylake processors (Southampton)



Protein-protein interactions: Breast-cancer susceptibility protein (BRCA2)



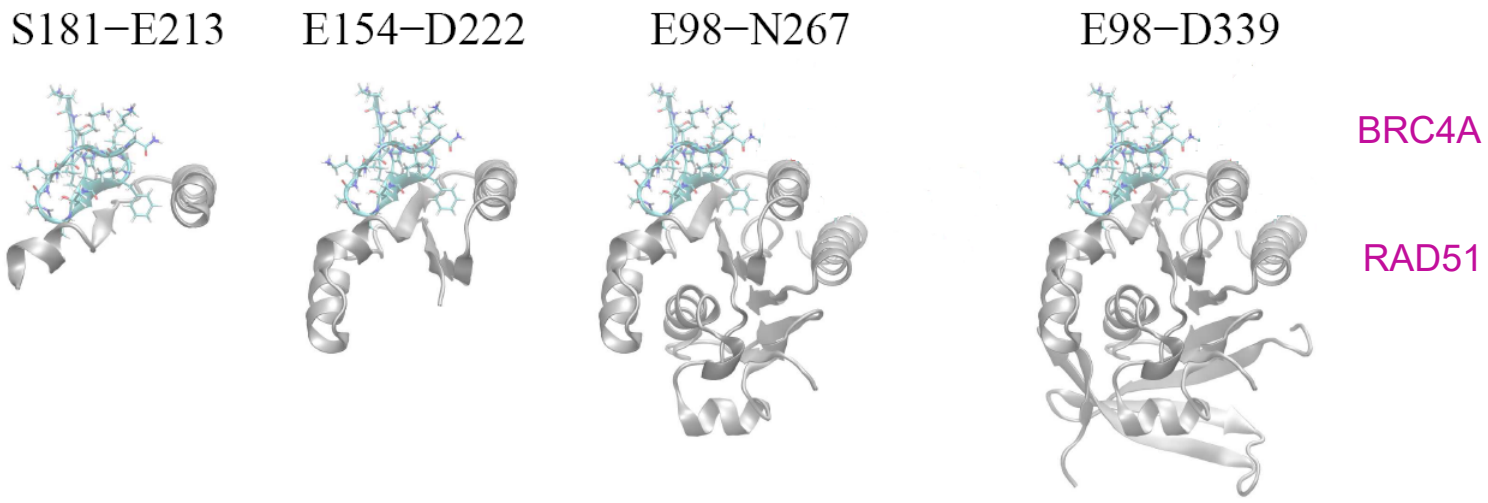
- Contains 8 BRC “repeats” of about 35-40 aa: BRC1, BRC2,...,BRC8
- Binds to the DNA recombination and repair protein Rad51 during DNA repair by Homologous Recombination (HR). The BRC repeats bind to RAD51 and compete for the Rad51-Rad51 self-oligomerisation interface:



- Despite significant sequence similarity, BRC repeats have varying affinities for Rad51 in experiments
- Want to compute the relative free energies of binding of each BRC repeat to Rad51 and compare to Rad51-Rad51 binding.

D. J. Cole, C.-K. Skylaris, E. Rajendra, A. R. Venkitaraman and M. C. Payne. *Europhysics Letters* **91** (2010) 3700.
D. J. Cole, E. Rajendra, M. Roberts-Thomson, B. Hardwick, G. J. McKenzie, M. C. Payne, A. R. Venkitaraman and C.-K. Skylaris. *PLoS Computational Biology* **7** (2011) e1002096

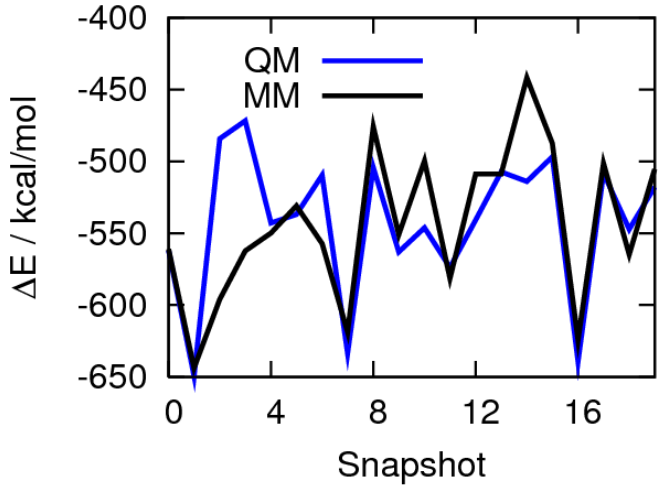
Convergence of binding free energies with RAD51 fragment size

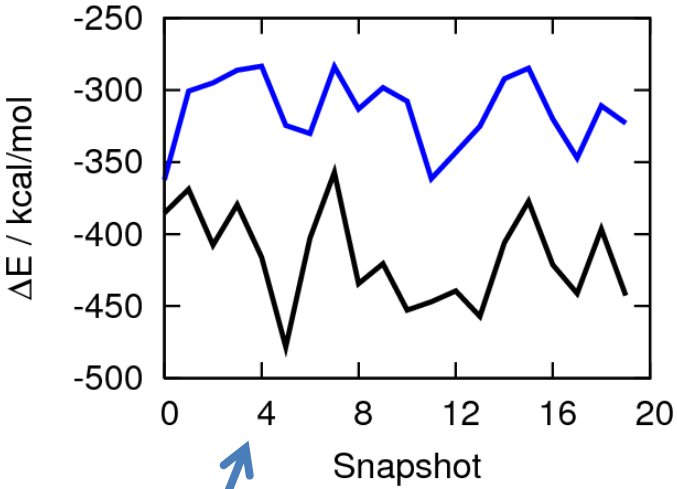


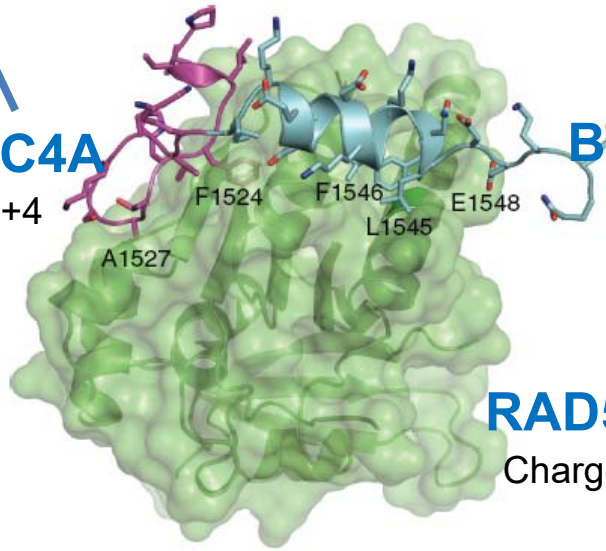
Residues	N_{Atoms}	ΔG_{MM}	ΔG_{QM}
S181-E213	737	-55.1	-63.1
E154-D222	1313	-57.7	-67.0
E98-N267	2780	-59.4	-65.6
E98-D339	3490	-59.5	-63.2

MM_PBSA and QM_PBSA calculations

Gas phase energies







BRC4A
Charge +4

BRC4B
Charge 0

RAD51
Charge -4

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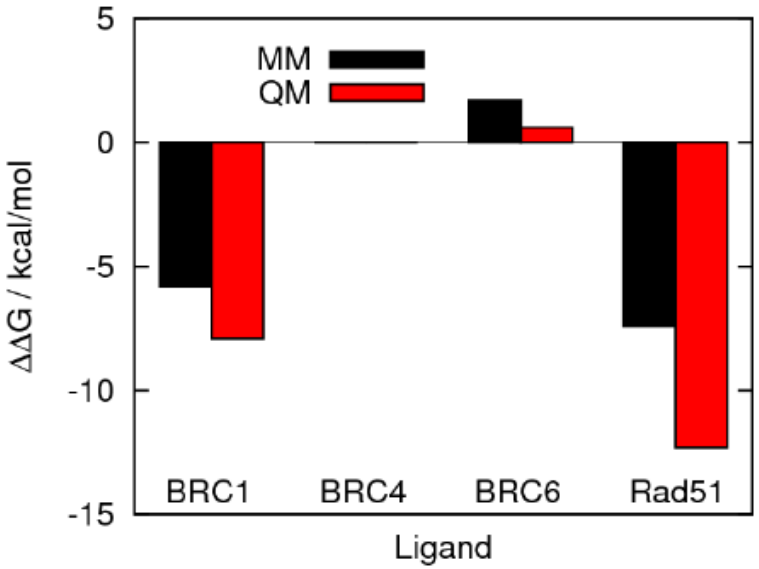
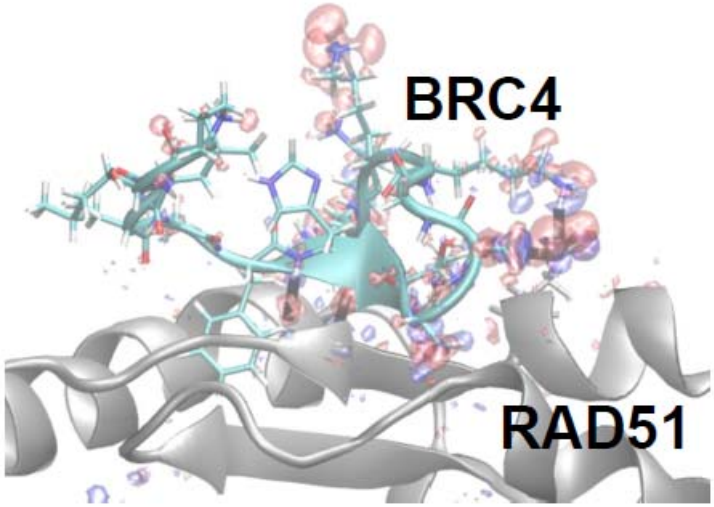
Relative free energies of binding





- Free energies of binding (relative to BRC4) in MM-PBSA and QM-PBSA are in good agreement and the order of binding affinity is unchanged.
- QM-PBSA still relies on the classical force field to sample the correct configurational space of the complex
- BUT, the solvent contribution has been taken into account in a very approximate way:

$$\Delta G_{PBSA}^{QM} = \Delta G_{PB} \times \left(\frac{\Delta E_{DFT}}{\Delta E_{EL}} \right)^{n_{PB}} + \Delta G_{SA}.$$

Implicit solvent model in ONETEP (2010 onwards)

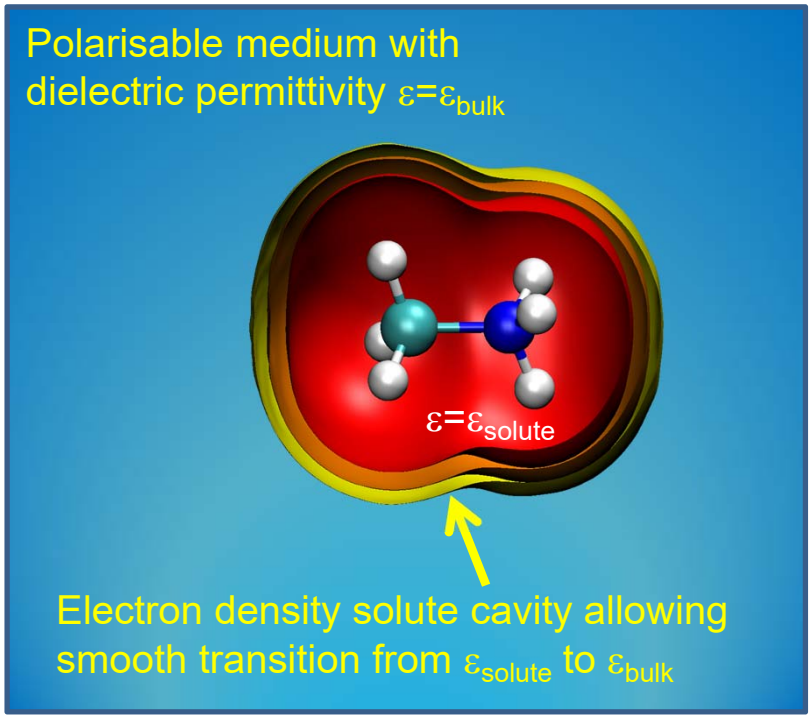
"Ab initio" or minimal parameter implicit solvent models

Fattebert and Gygi, *J. Comp. Chem.* **23**, 662 (2002)

- Solute cavity constructed from electron density of the solute
- Electrostatics by direct solution of the generalised Poisson equation
- Fully self-consistent: solute electrons polarised by solvent and vice versa

Our work [1]: accurate and highly parallel solvent model

- Reparametrized to provide accurate solvation free energies for neutral as well as for cationic and anionic species [1]
- Inclusion of dispersion-repulsion effects
- Parallel multigrid solver with high order defect correction – efficient use of supercomputing resources [2]
- Available within a robust linear-scaling DFT code (ONETEP) with near-complete basis set accuracy
- Can be part of multiscale simulation approaches, e.g. by combining with explicit solvent molecules

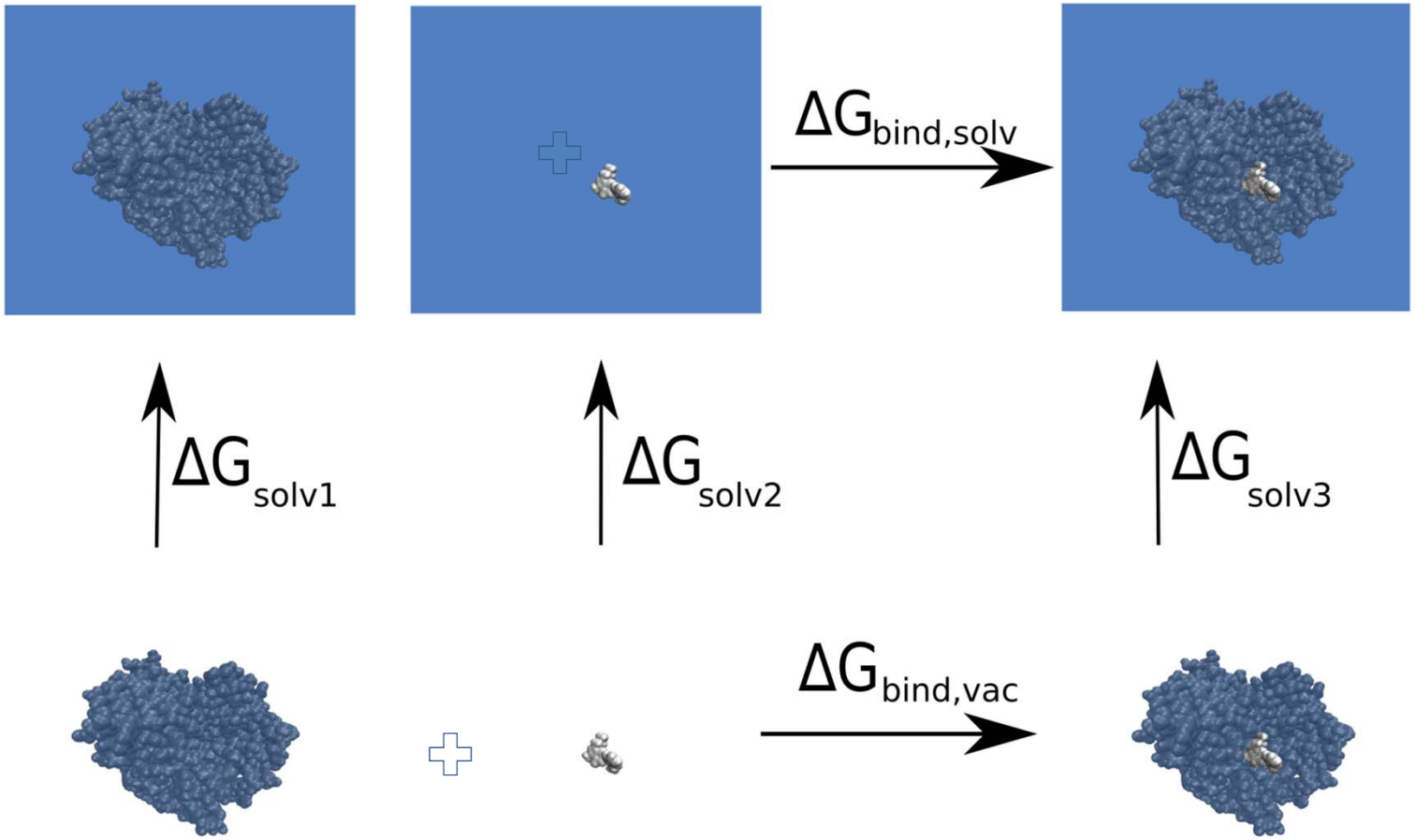


Approach	XC functional	rms error	max error	r
this work[a]	PBE	3.8	8.3	0.83
this work[b]	PBE	4.1	9.1	0.83
PCM	PBE	10.9	23.3	0.53
SMD	M05-2X	3.4	14.5	0.87
AMBER	(classical)	5.1	19.9	0.77

[1] Minimal parameter implicit solvent model for ab initio electronic structure calculations. J. Dziedzic, H. H. Helal, C.-K. Skylaris, A. A. Mostofi, and M. C. Payne. *Europhysics Letters* **95** (2011) 43001

[2] DL_MG: A Parallel Multigrid Poisson and Poisson-Boltzmann Solver for Electronic Structure Calculations in Vacuum and Solution. J. C. Womack, L. Anton, J. Dziedzic, P. Hasnip, M. Probert, and C.-K. Skylaris. *J. Chem. Theor. Comput*. **14** (2018) 1412

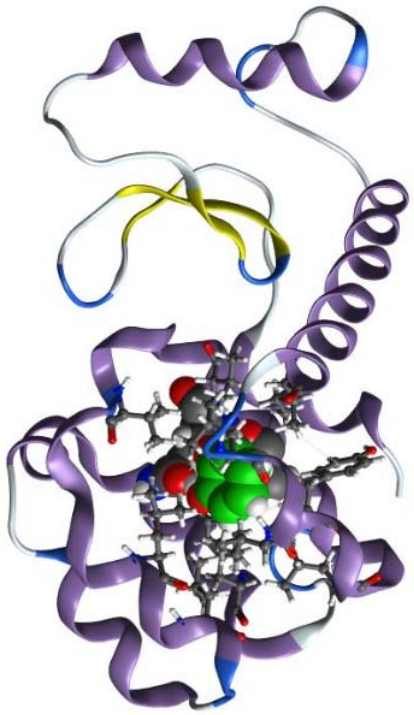
Protein – ligand free energies of binding



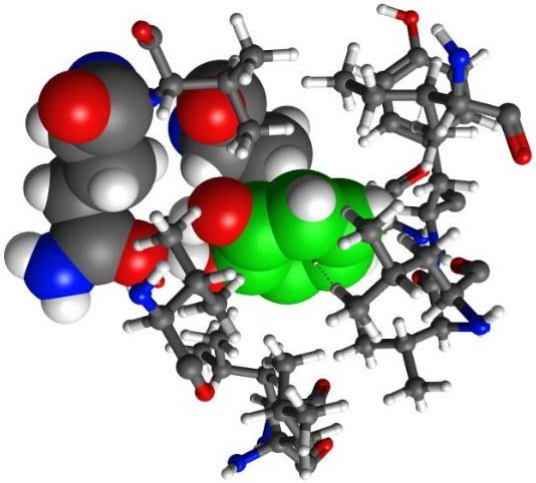
$$\Delta G_{bind,solv} = \Delta G_{bind,vac} + \Delta G_{solv3} - (\Delta G_{solv1} + \Delta G_{solv2})$$

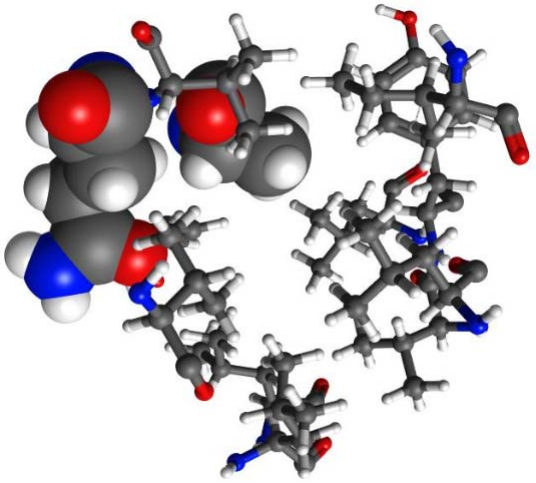
Applications to drug design: T4 Lysozyme L99A/M102Q protein

S. J. Fox, J. Dziedzic, T. Fox, C. S. Tautermann, and C.-K. Skylaris, *Proteins* **82** (2014) 3335-3346



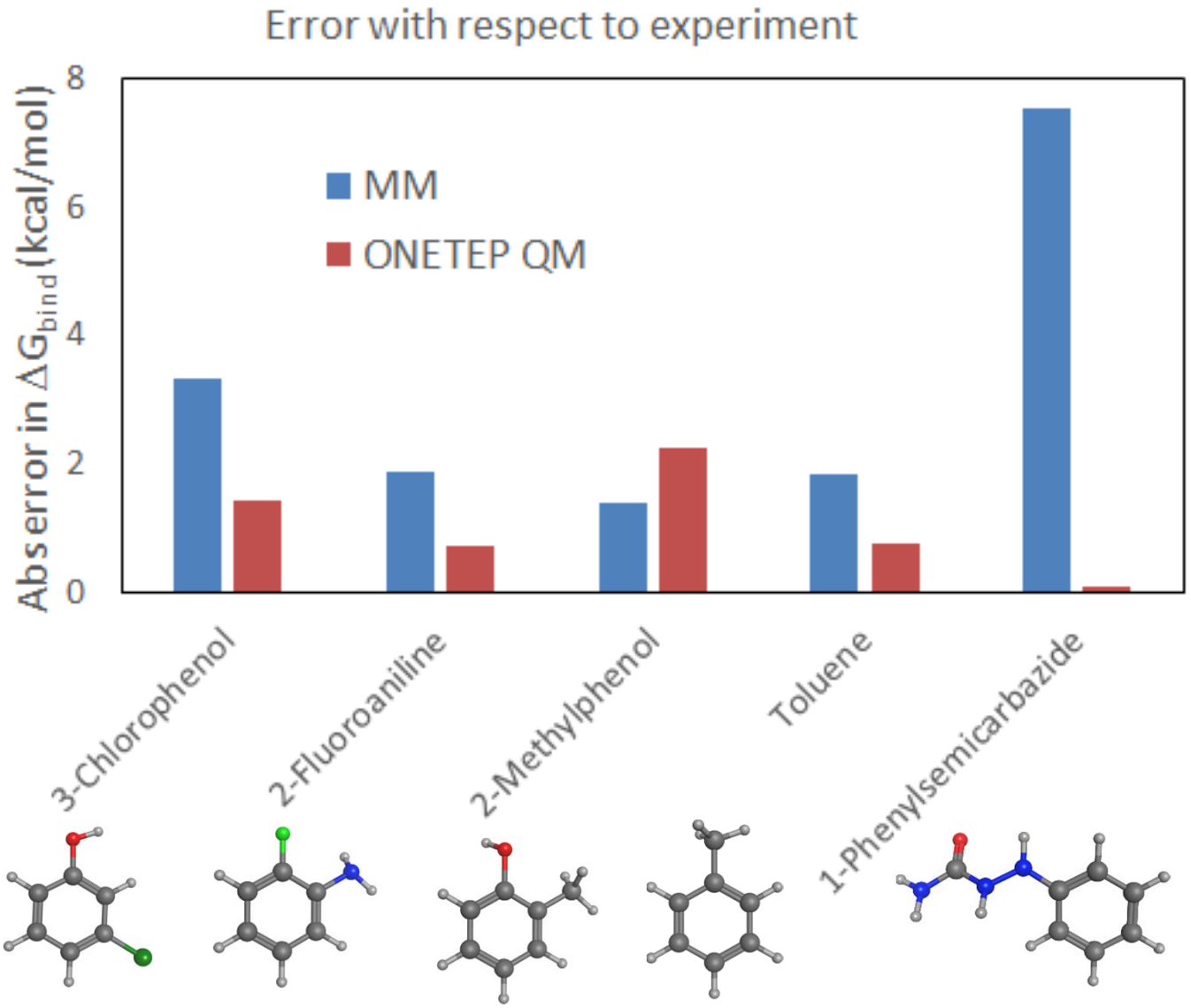
- 2616 atoms
- Polar binding site



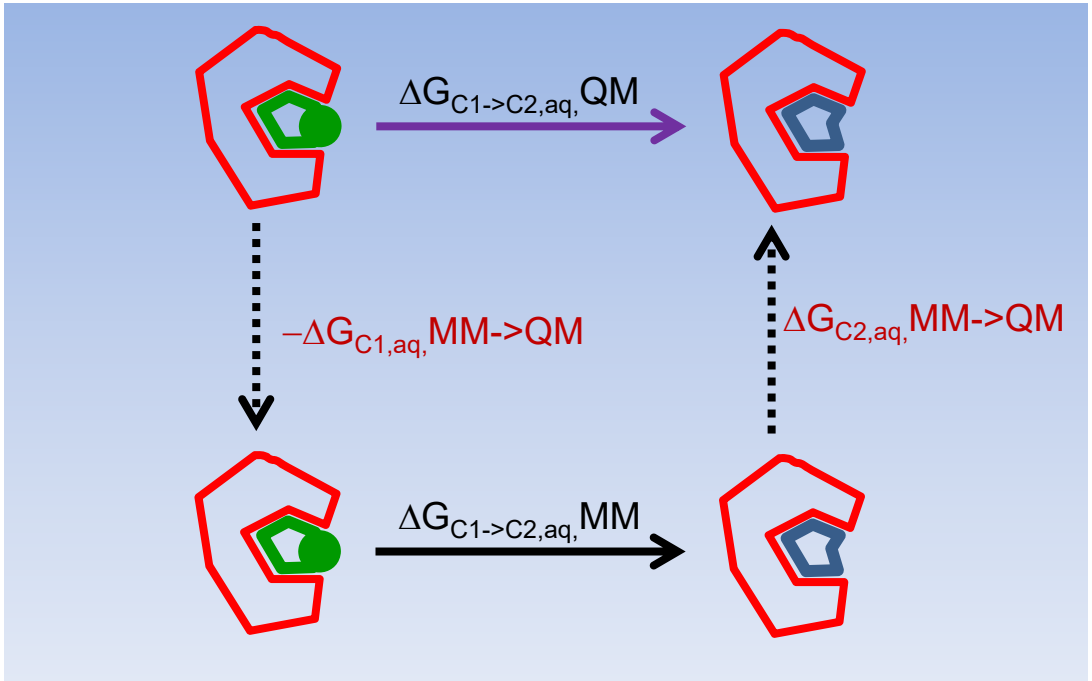


Complex of T4 Lysozyme L99A/M102Q and catechol

Free energies of binding: T4 Lysozyme L99A/M102Q



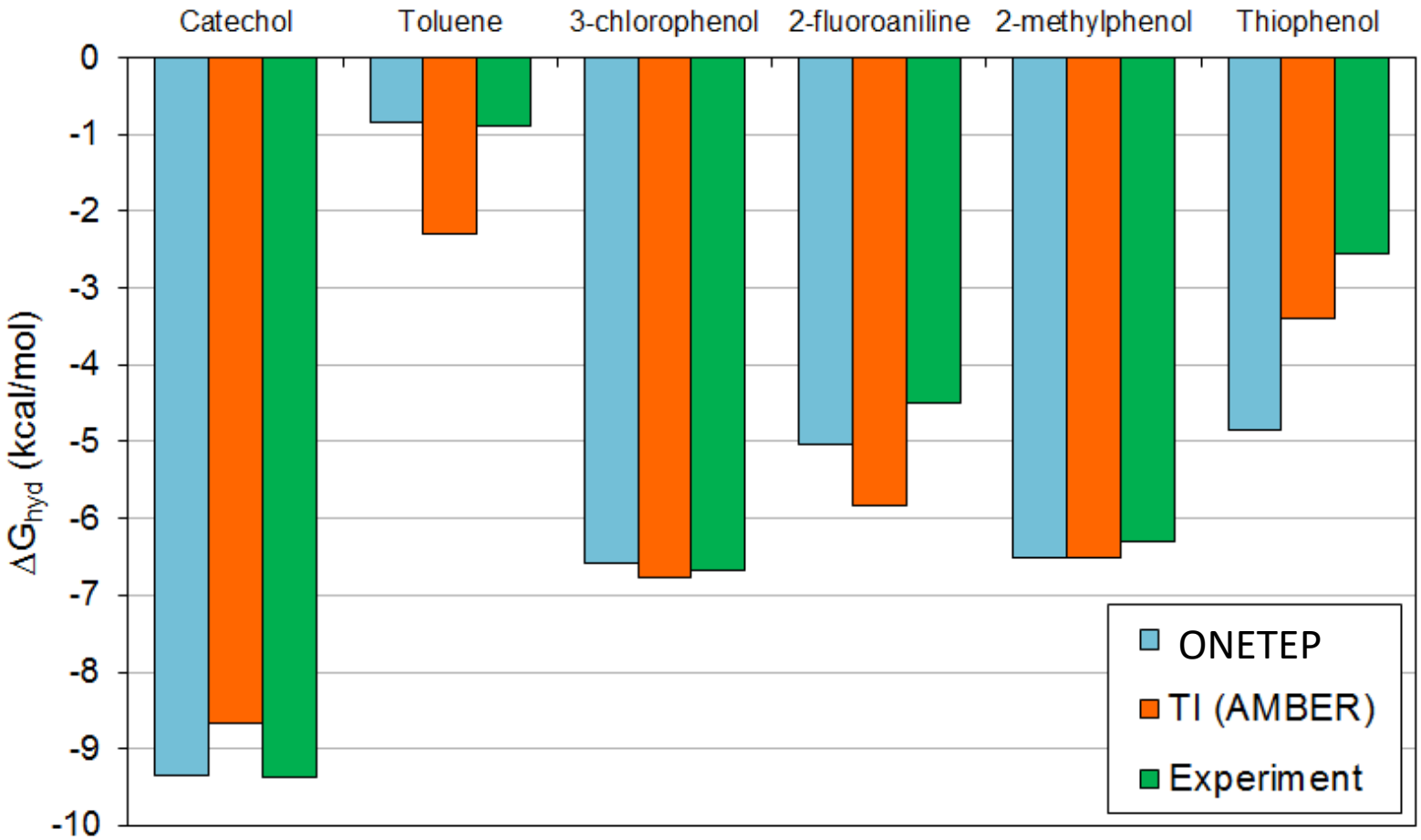
Rigorous methods for free energies in explicit water



How can we obtain $\Delta G_{C1,aq,}$MM->QM and $\Delta G_{C2,aq,}$MM->QM ?

Relative free energies of binding $\Delta\Delta G_{bind} = \Delta G_{bind2,aq} - \Delta G_{bind1,aq} = \Delta G_{C1->C1,aq} - \Delta G_{L1->L2,aq}$ TI, FEP

Free energies of hydration (300K)



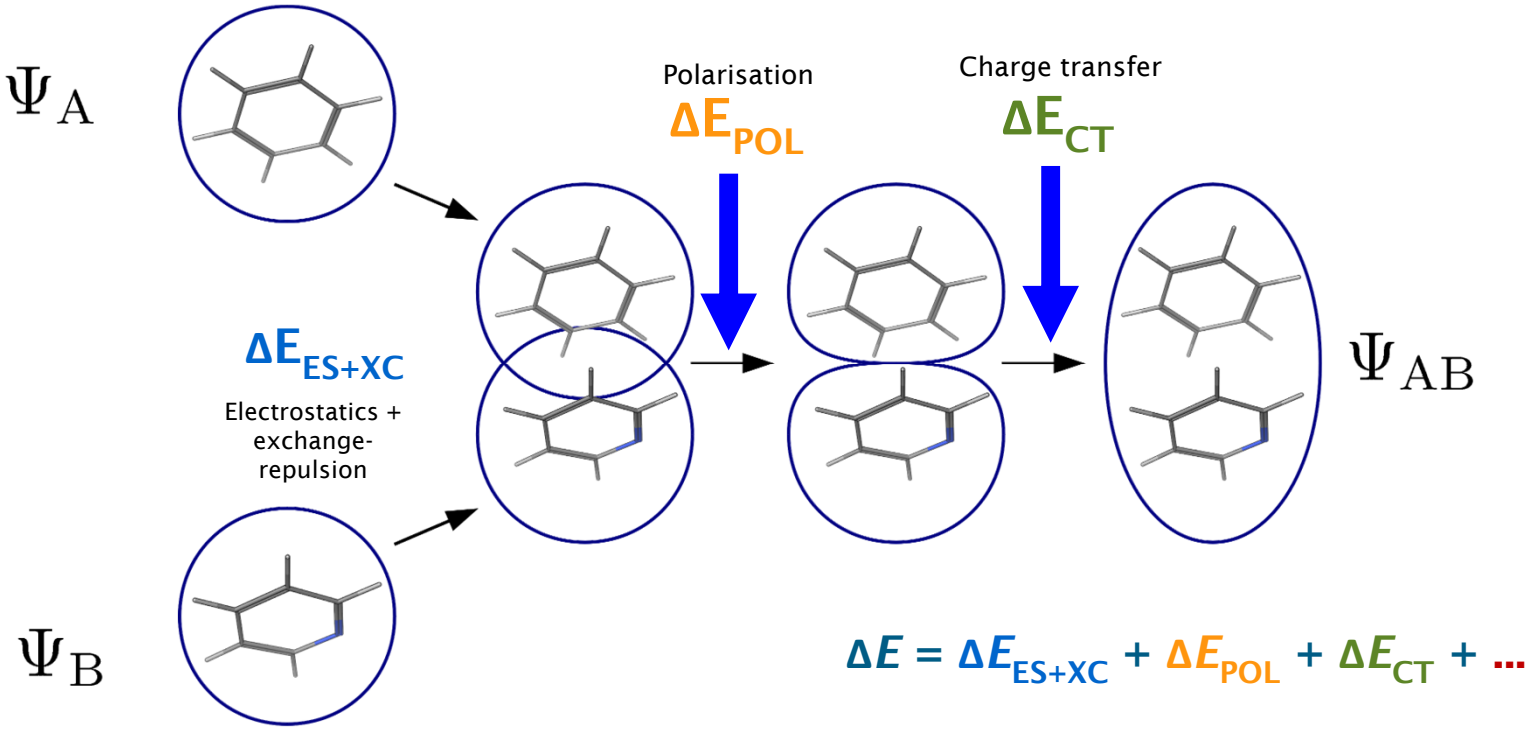
S. J. Fox, C. Pittock, C. S. Tautermann, T. Fox, C. Christ, N.O. J. Malcolm, J. W. Essex and C.-K Skylaris, *J. Phys. Chem. B* **117**, 9478 (2013)

Energy decomposition analysis (EDA)

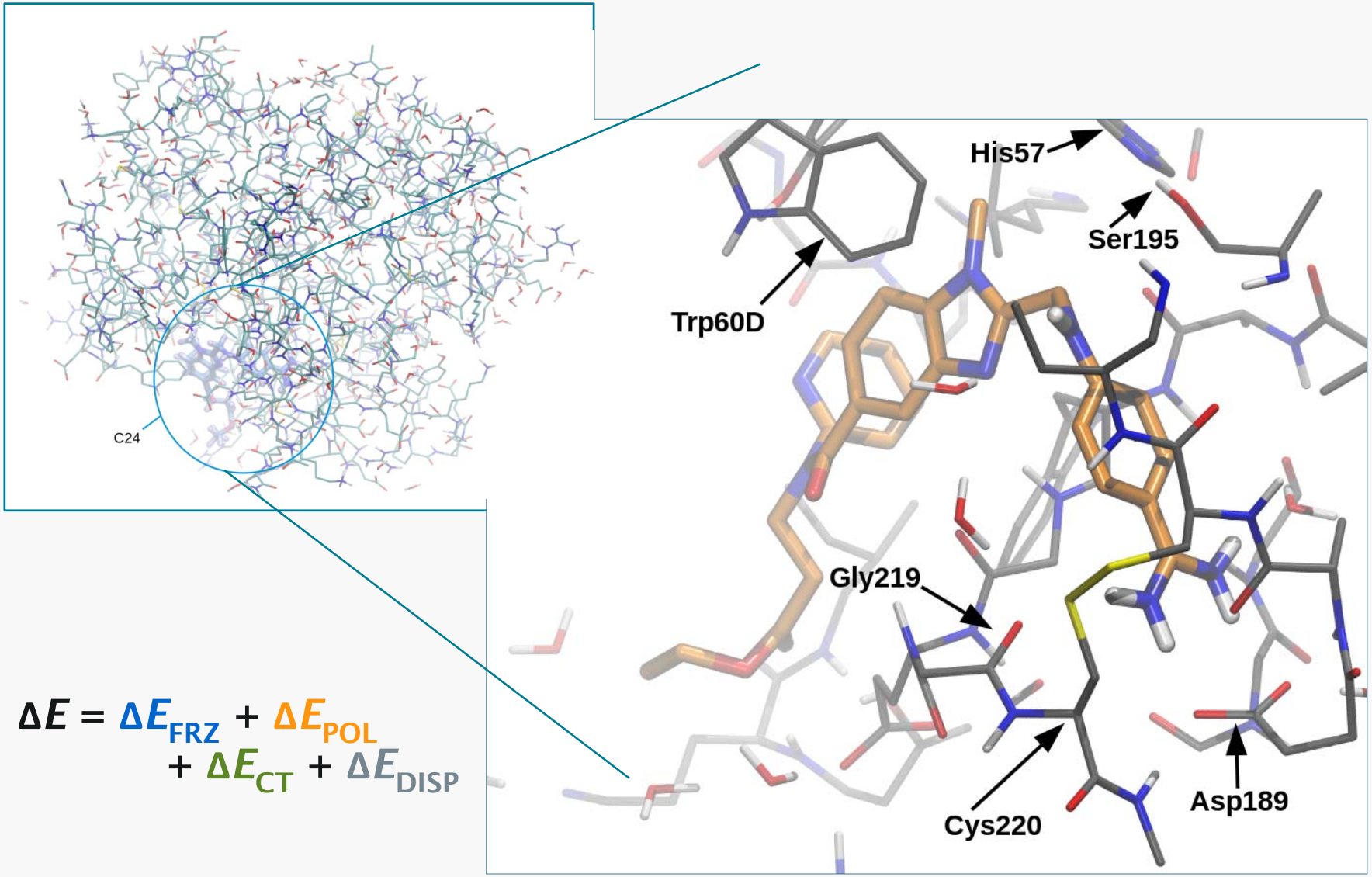
M. J. S. Phipps, T. Fox, C. S. Tautermann, C.-K. Skylaris, *Chem. Soc. Rev.* **44** (2015) 3177

M. J. S. Phipps, T. Fox, C. S. Tautermann, C.-K. Skylaris, *J. Chem.Theory Comput.*, **12** (2016) 3135

- Decompose any host-guest binding energy to chemically relevant components
- Inform the design of new host-guest ligands (e.g. in Pharma applications)
- Parameterise more approximate simulation methods (e.g. new MM approaches)



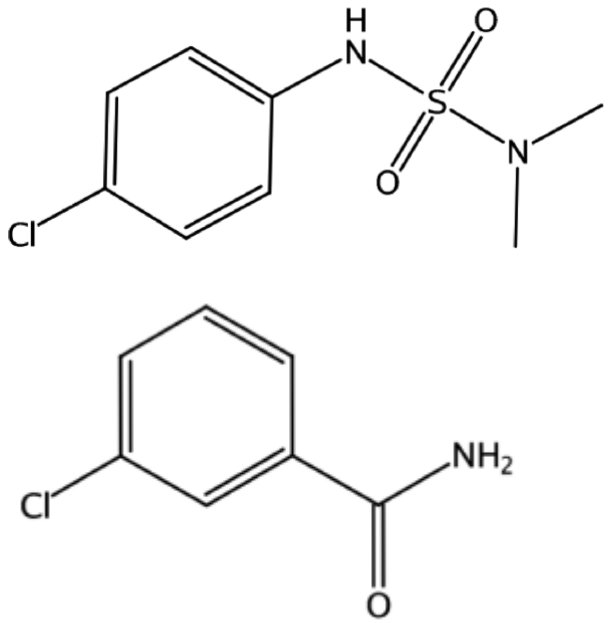
Thrombin protein-ligand complex (4975 atoms)



$$\Delta E = \Delta E_{FRZ} + \Delta E_{POL} + \Delta E_{CT} + \Delta E_{DISP}$$

Example: comparing L1 with L2

Energy Term (kcal/mol)	L1	L2
FRZ	2.1	2.8
ES	-35.2	-30.3
EX	-19.5	-16.5
REP	82.8	69.7
CORR	-26.0	-20.2
POL	-6.1	-5.3
CT	-11.4	-11.1
ΔE_{vac}(PBE/800eV)	-15.4	-13.6
SOLV	13.1	11.1
ΔE(PBE/800eV)	-2.3	-2.5



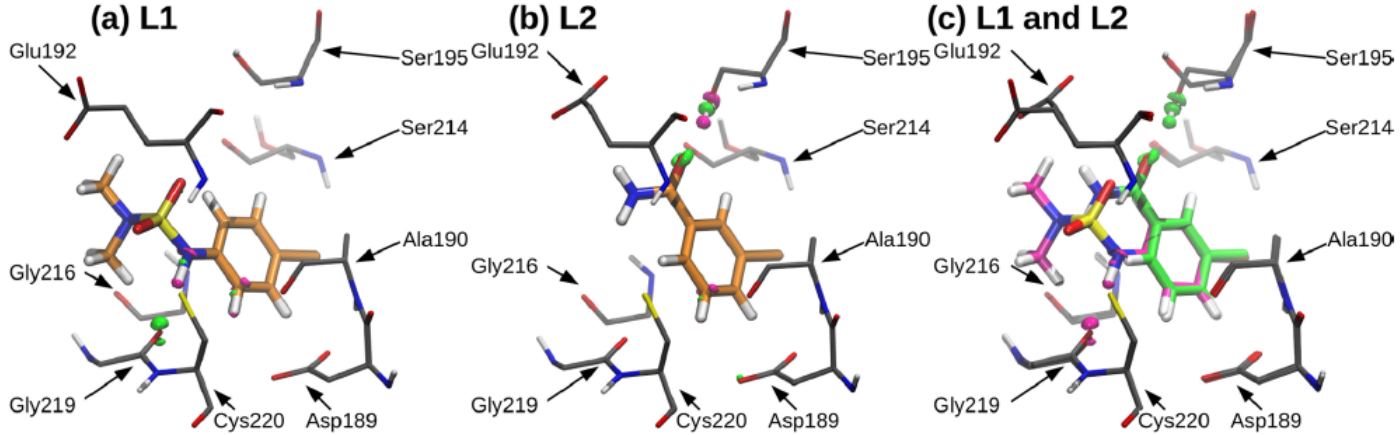
- Structurally comparable ligands with chlorobenzene group in common
- Essentially the same binding energies (-2.3 kcal/mol and -2.5 kcal/mol) but the actual EDA components are very different
- L1 has a Pauli (steric) repulsion which is 13.1 kcal/mol more unfavourable than L2. However this is counteracted by the other energy components which add up to eliminate this difference

Electron Density Difference (EDD)

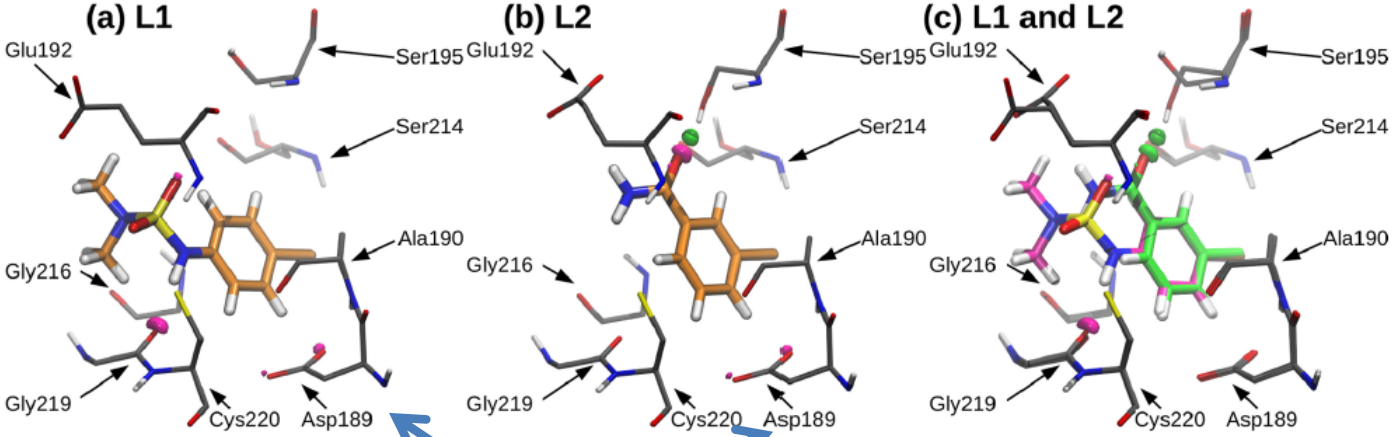
Visualising the interactions: L1 interacts with Gly219 L2 interacts with Ser195

ΔEDD

Polarisation EDD



Charge transfer EDD



Common interactions (with Asp189) cancel out in ΔEDD

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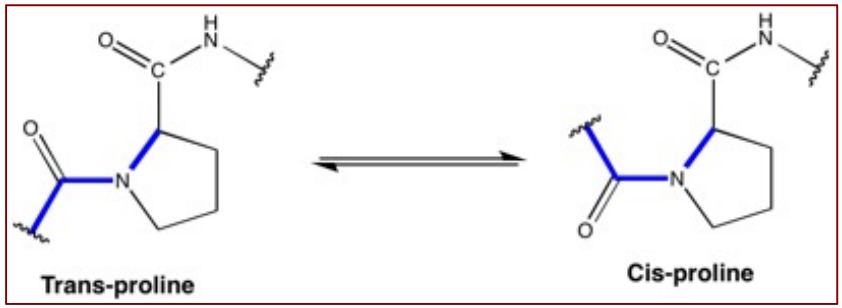
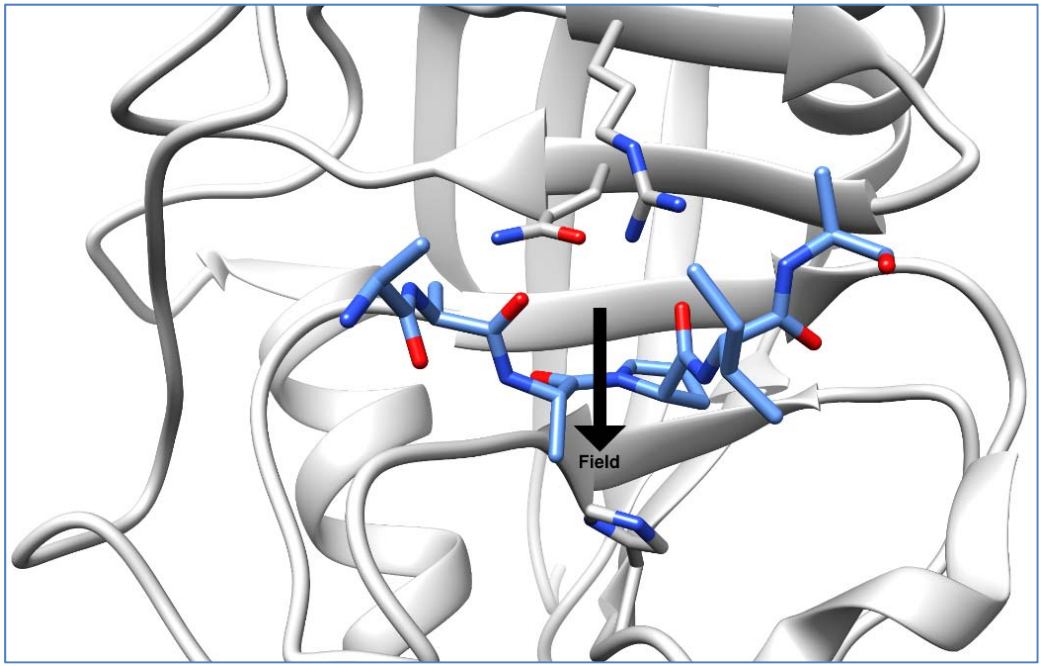
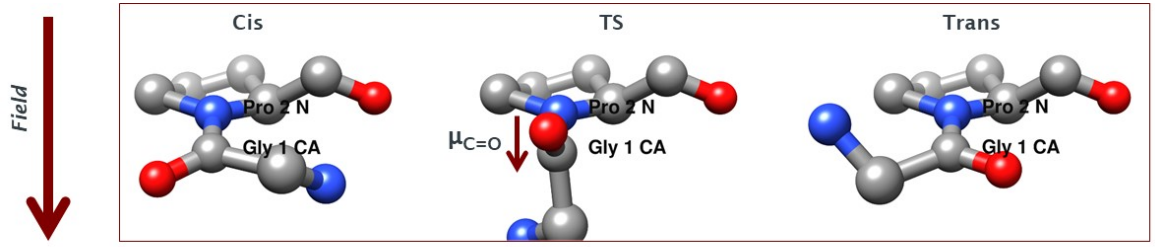
Using ONETEP to compute electric fields in enzymes: Cyclophilin A

Peptidylprolyl isomerase: Catalyses the cis/trans isomerisation of proline:



Proposed 'electrostatic handle'[1]





Environment field aligned with carbonyl dipole of preceding residue at transition state

1) Camilloni C. et al., PNAS, 2014, **28**, 10203-10208

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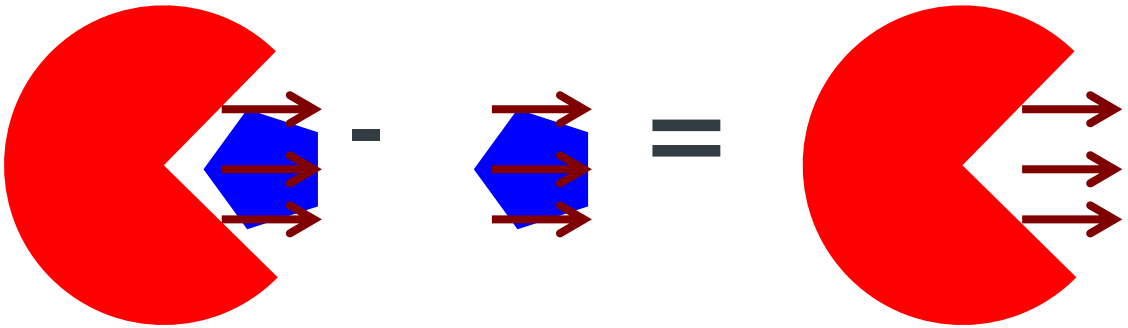
Calculation of electric fields in the enzyme active site with

- ONETEP
- A polarisable force field (AMOEBA)
- Fixed-charge force fields (AMBER, CHARMM)

$$U = U_{bond} + U_{angle} + U_{b\theta} + U_{oop} + U_{torsion} + U_{vdW} + U_{ele}^{perm} + U_{ele}^{ind}$$

Fundamentally, AMOEBA models polarisation *via* induced atomic dipoles:

'Environment field'



Calculate electric fields within the active site

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Comparison of calculated fields

- x,y,z field components at the carbonyl bond centre
- Combination of data from cis, trans, WT and R55A structures
- ONETEP calculations on 30 snapshots with ~20,000 atoms
- Fixed charge force fields slightly underestimate the magnitude of field components; weaker correlation; greater variability
- AMOEBA shows good correlation with DFT

Richard T. Bradshaw, Jacek Dziedzic, Chris-Kriton Skylaris, and Jonathan W. Essex, *In preparation*

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Thank you Mike!

Happy Birthday!