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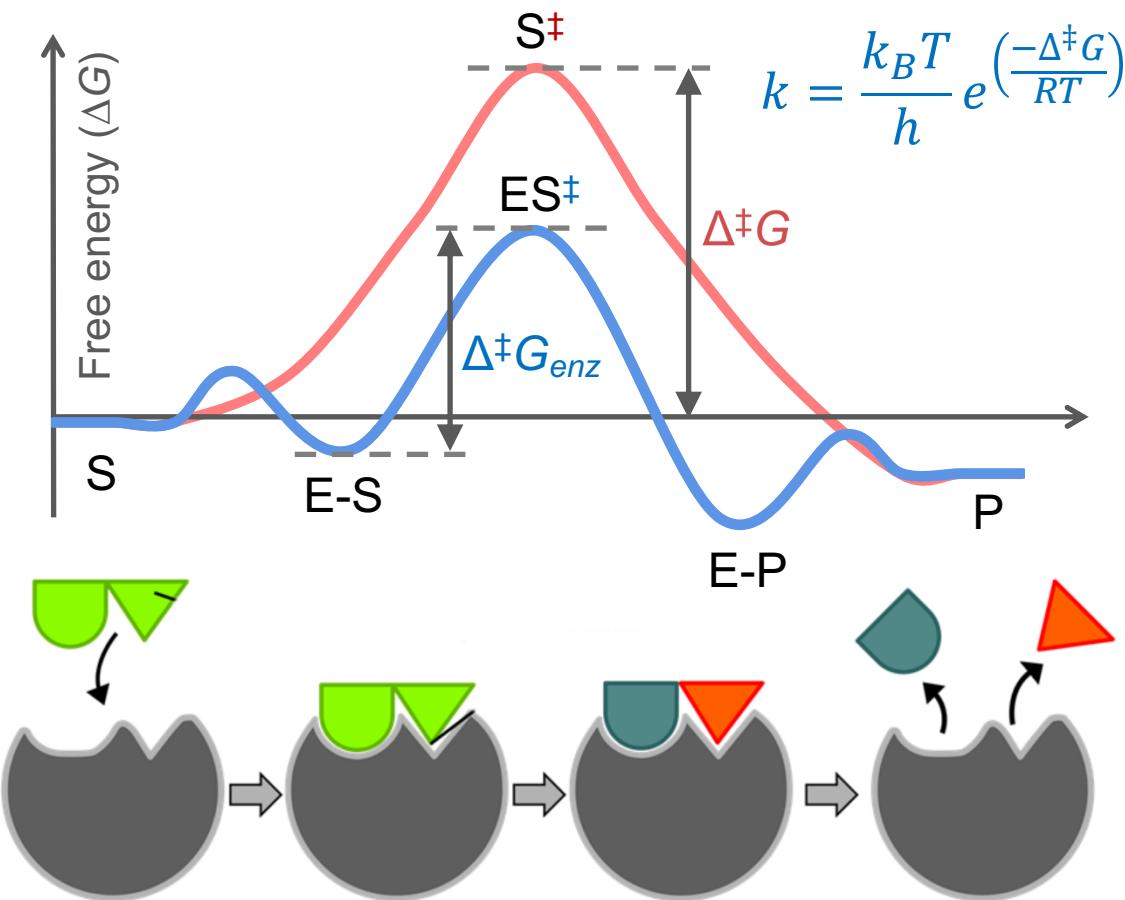


QM/MM modelling of enzyme reactions

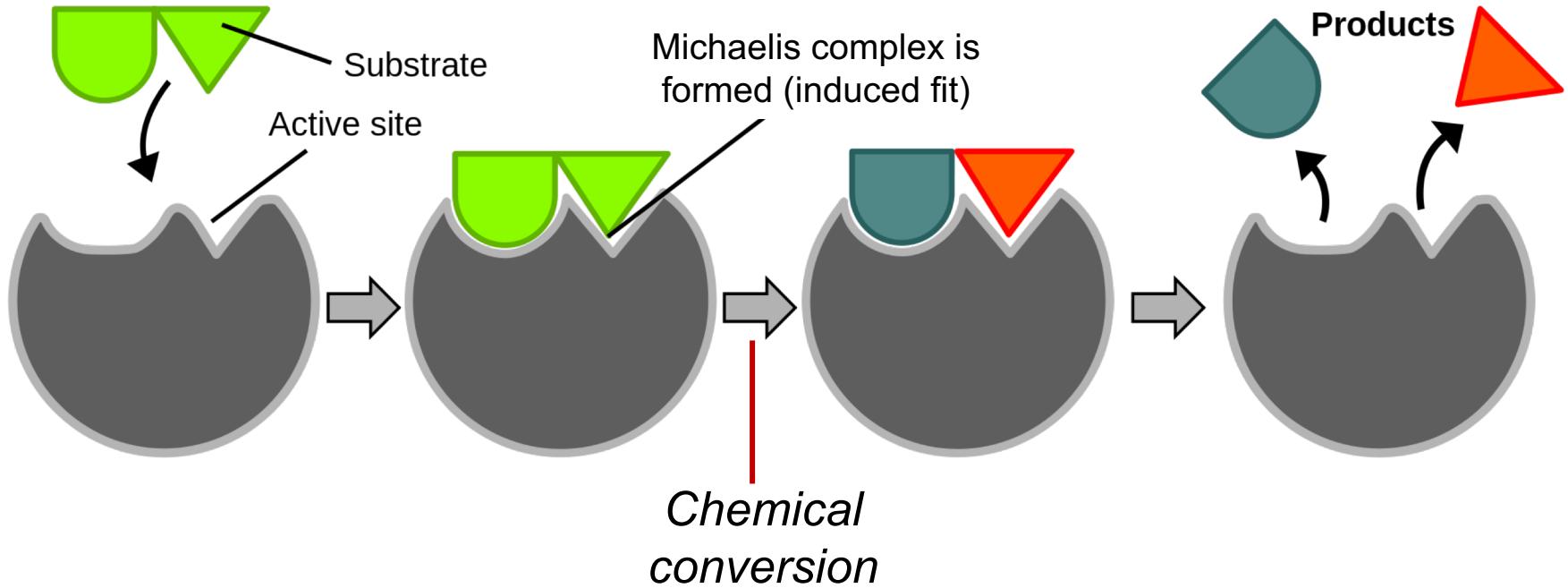
Marc W. van der Kamp

CCPBioSim tutorial workshop, Bristol, 24 May 2019

Enzymes are catalysts: they lower the activation energy for reaction



Enzyme catalytic cycles

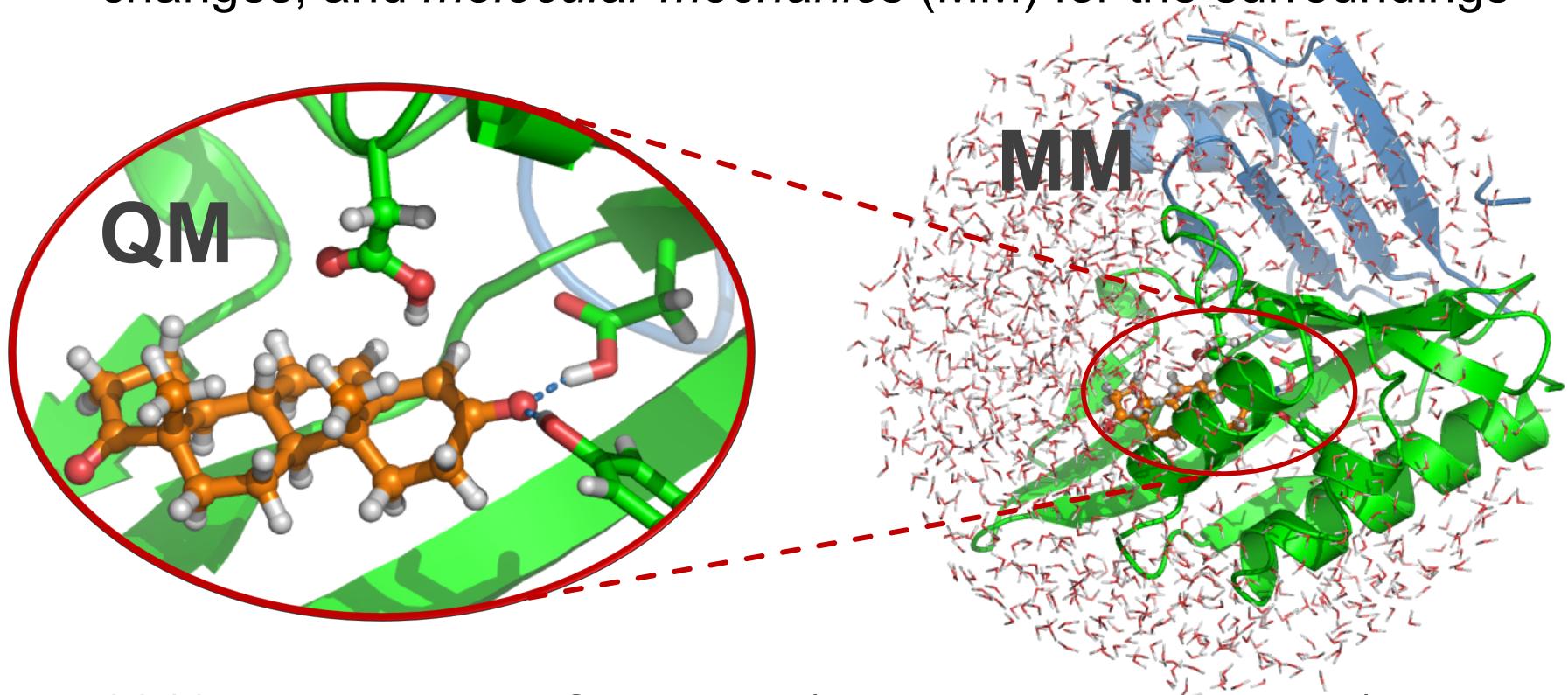


- Difficult to dissect experimentally: *use computer simulation*
- To simulate chemical change, we need to go beyond molecular mechanics



QM/MM enzyme reaction modelling

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

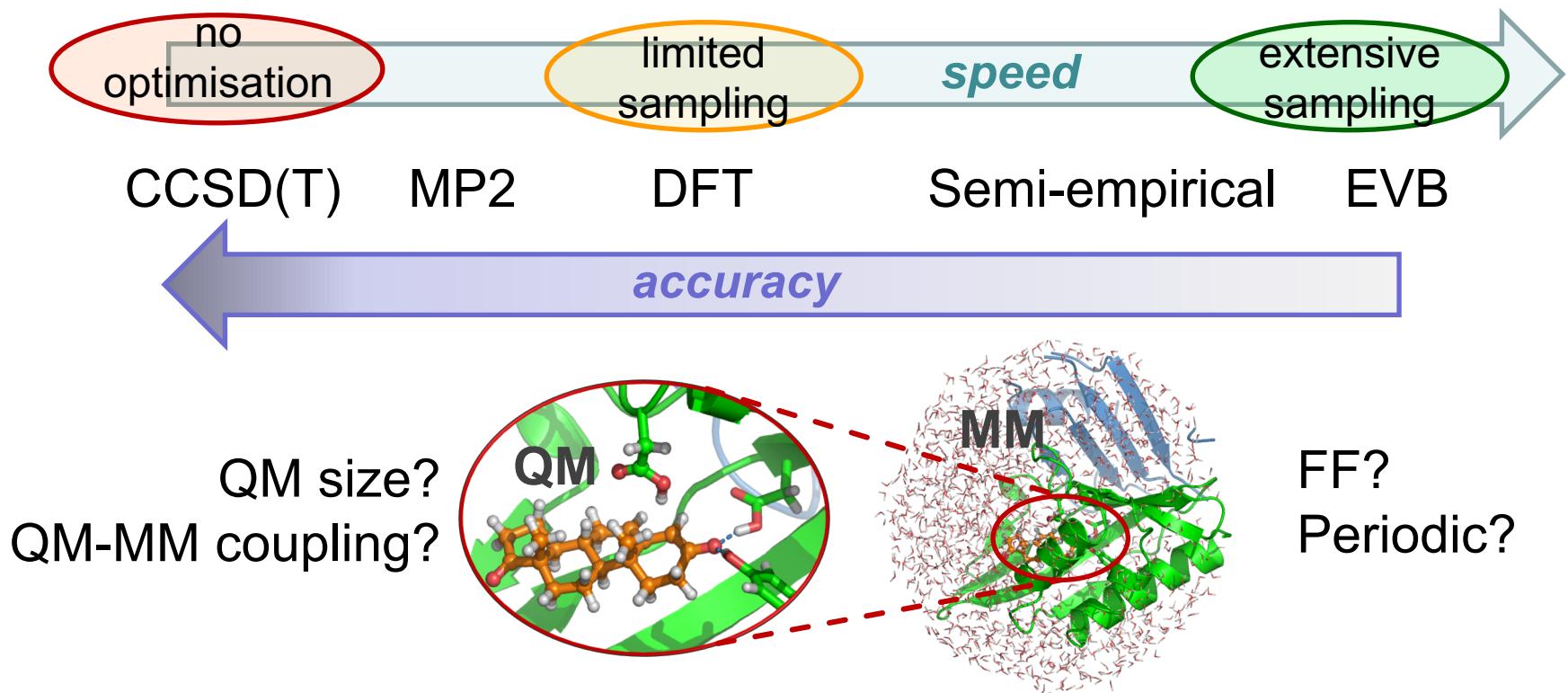


- 2013 Nobel prize in Chemistry (Karplus, Levitt, Warshel)
- QM/MM for enzymes: Van der Kamp, Mulholland (2013) *Biochem* 52: 2708



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QM/MM simulation: accuracy vs. speed



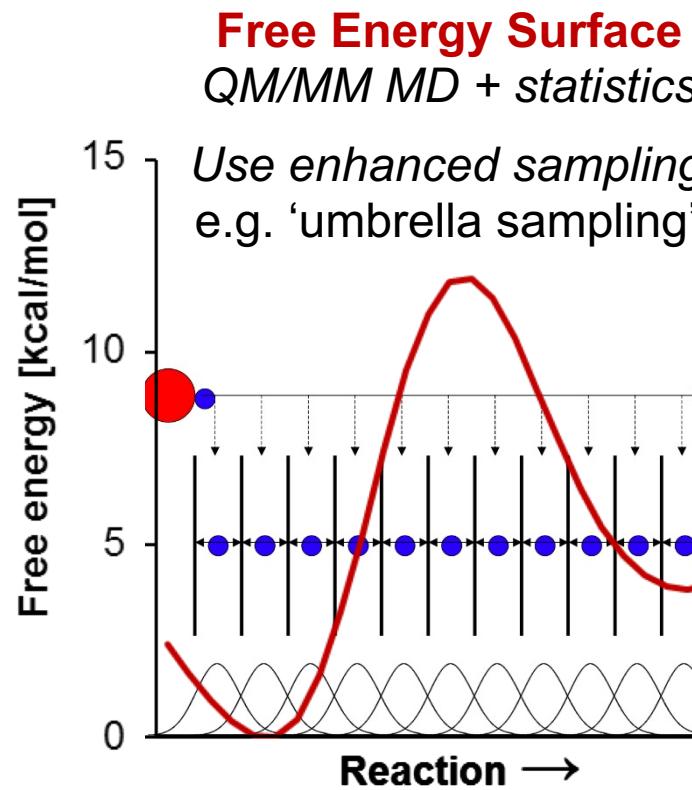
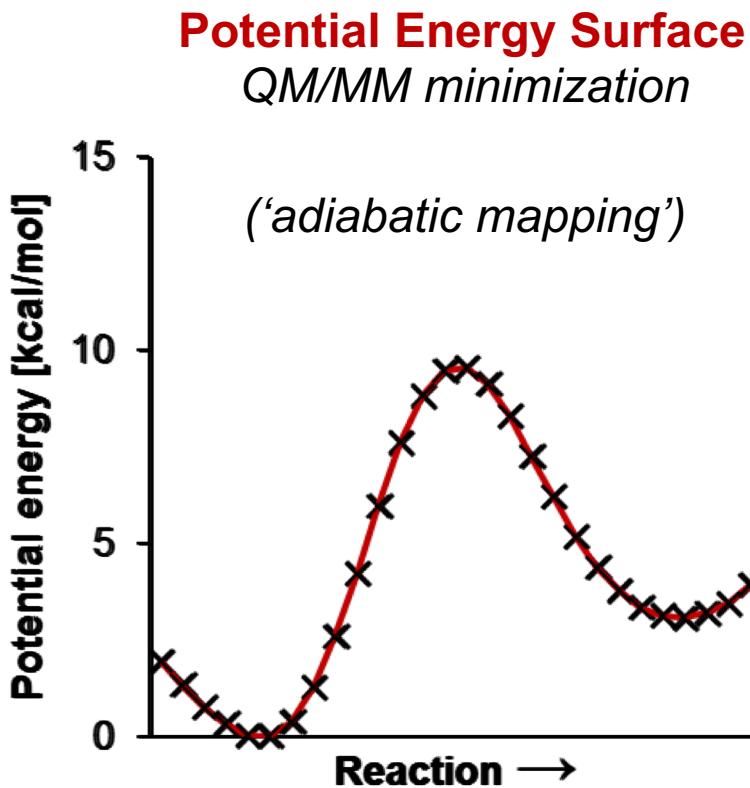
- Ease of use? Transferability? Computer resources? etc.
- ***Human time??*** (model setup, parameterisation)



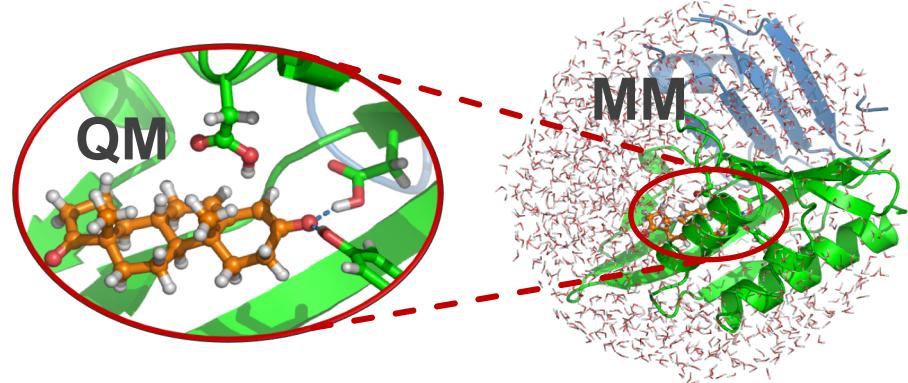
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QM/MM reaction modelling

- To overcome activation energy, need to ‘force’ a reaction happening: apply ‘bias’ along a ‘reaction coordinate’



QM/MM modelling



- Additive approach (used by most, incl. in CHARMM, AMBER):

$$E_{\text{total}} = E_{\text{QM(QM)}} + E_{\text{MM(MM)}} + E_{\text{QM-MM interaction}}$$

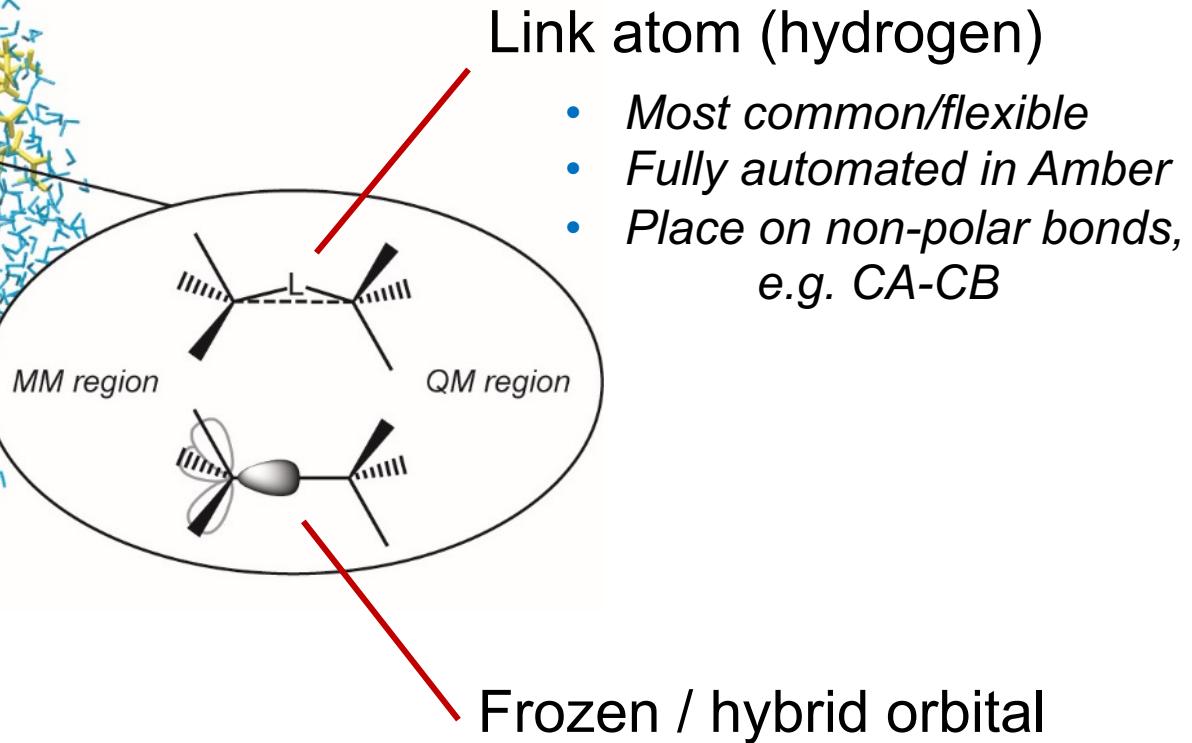
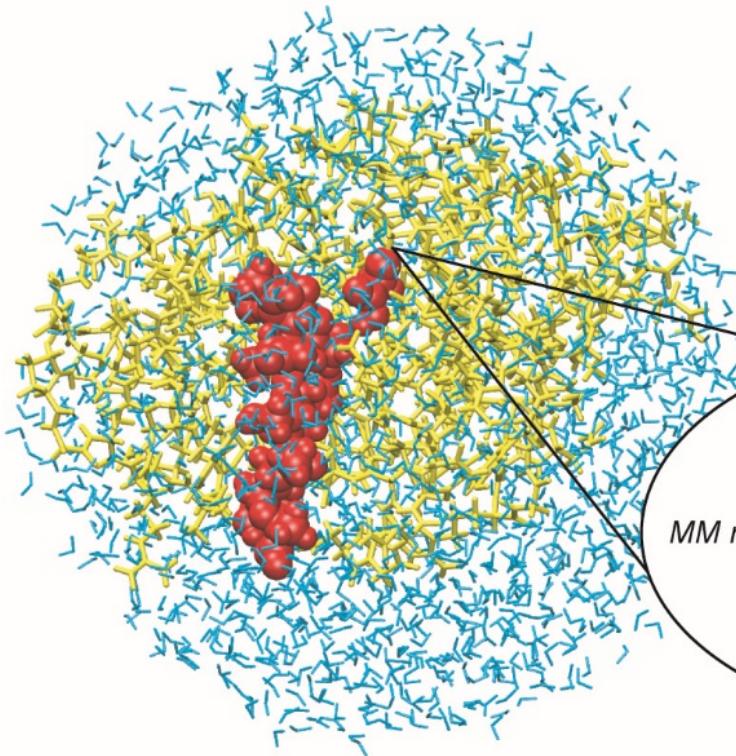
$$\hat{H}_{\text{QM/MM}} = - \sum_i^{\text{electrons}} \sum_j^{\text{MM atoms}} \frac{Q_j}{r_{ij}} + \sum_i^{\text{nuclei}} \sum_j^{\text{MM atoms}} \frac{Z_i Q_j}{R_{ij}} + \sum_i^{\text{nuclei}} \sum_j^{\text{MM atoms}} \left\{ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} \right\}$$

- Subtractive approach (ONIOM method in Gaussian):

$$E_{\text{total}} = E_{\text{MM,total}} + E_{\text{QM(QM)}} - E_{\text{MM(QM)}}$$

- Must account for polarization of QM region by MM charges ('electrostatic embedding')

QM/MM modelling across bonds



(Required for Additive approach)



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QS Quantum Mechanical (QM) modelling

- Solve (approximate) Schrödinger equation: $E\Psi = \hat{H}\Psi$
 - Electrons are modelled explicitly (requires no/few parameters)
 - Polarisation, charge transfer and *bond making/breaking*

'Flavours' of QM

- **Semi-empirical:** AM1, PM3, PM6, DFTB
 - *Fast* calculation by using empirical parameters, **but** can be inaccurate
- **Ab initio:** HF (Hartree-Fock), MP2, CCSD(T)
 - Can get 'exact' solutions, but approaching full Schrödinger equation gets *very slow*. Need *basis set*, e.g. 6-31+G(d), cc-pVDZ.
- **Density Functional Theory (DFT):** BLYP, B3LYP, M06-2X
 - Work out the electron density with *functionals*. Faster than accurate *ab initio*, similar accuracy (but not always!).



Analysing enzyme-catalysed reactions

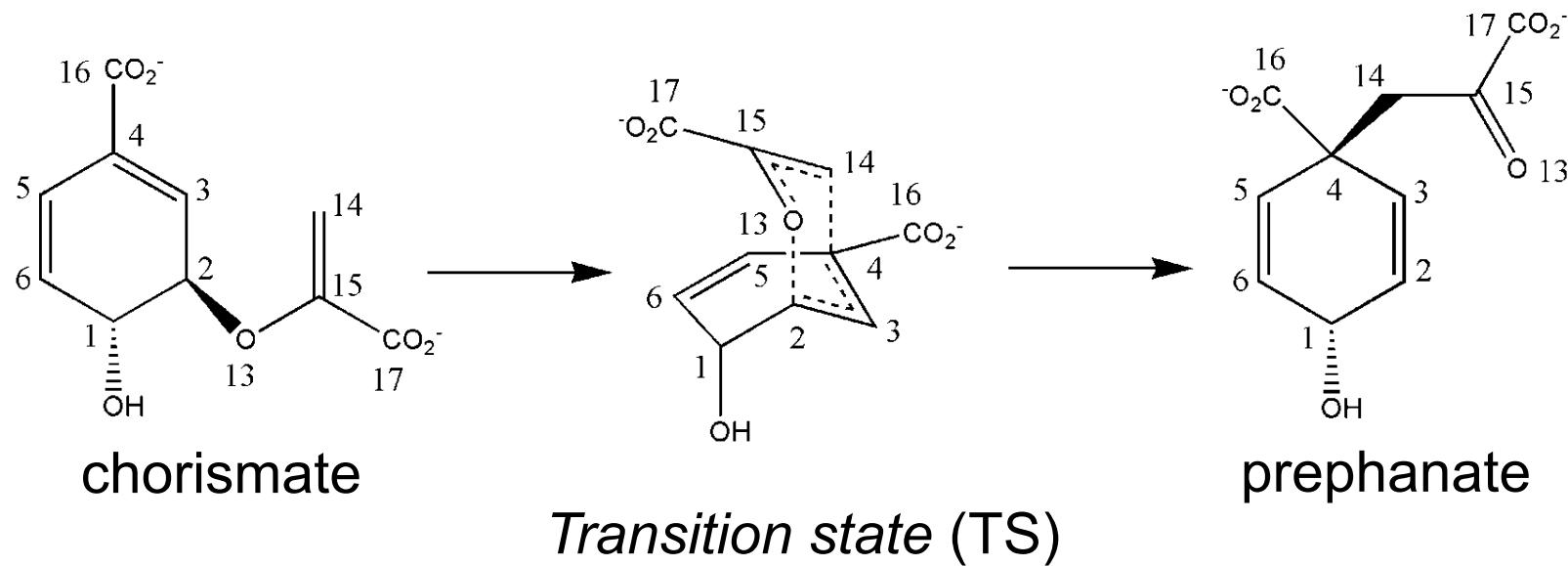
With QM/MM reaction modelling we can:

- Determine mechanism of reaction
- Identify intermediates, catalytic residues, transition states
- Analyse contributions to catalysis, e.g. hydrogen bonds, electrostatic effects
- Explore conformational effects and dynamics
- Atomic level description of reaction ('movie')
- Relate enzyme structure to activity



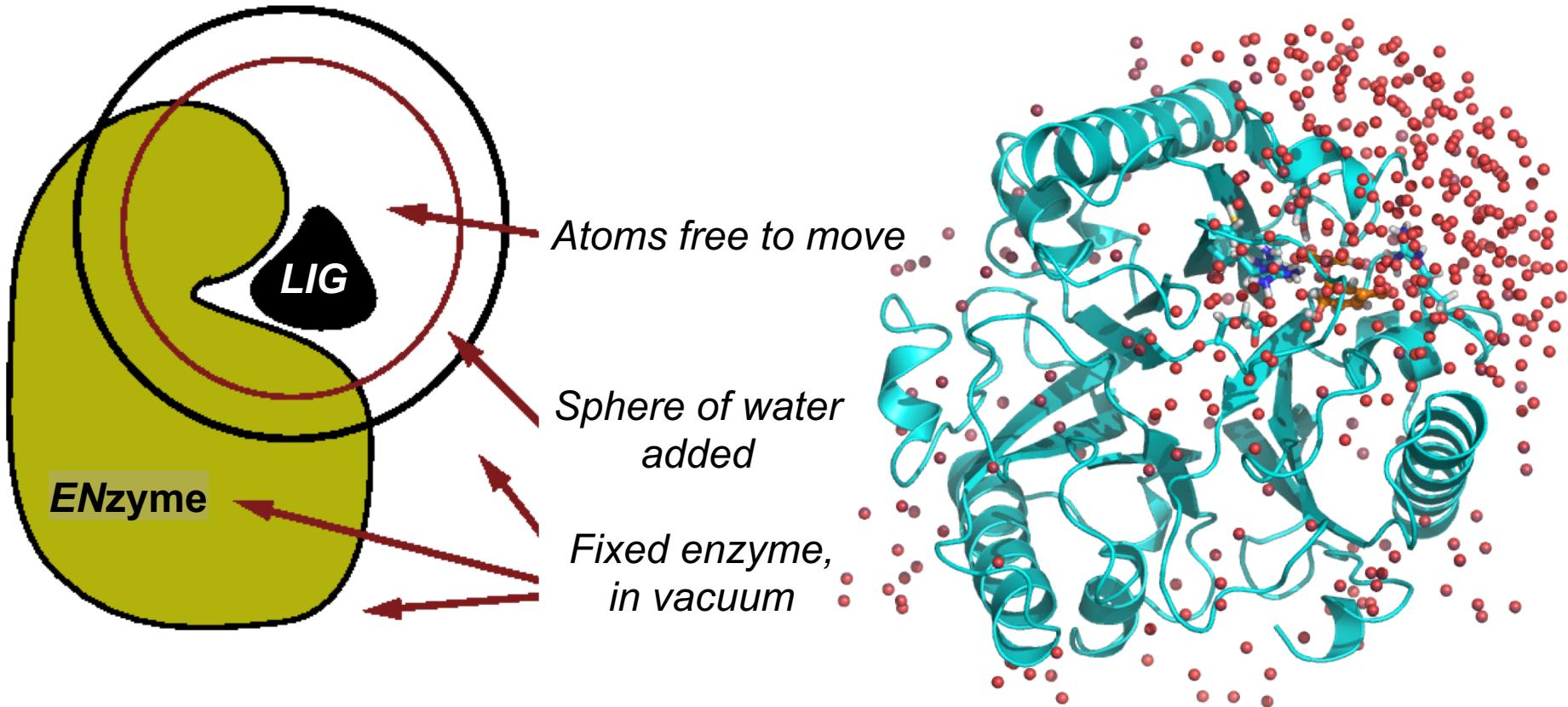
Flame Chorismate mutase (CM)

- Shikimate pathway (aromatic amino acid synthesis)
- Claisen rearrangement reaction
- Same mechanism in enzyme, solution and catalytic antibody: no covalent catalysis
- Debates: Why is the reaction so much faster in the enzyme?



Enlighten + QM/MM: chorismate mutase

- Protocols and PyMOL plugin for enzyme-substrate modelling



- Can be used to prepare for QM/MM
(e.g. used in: Byrne MJ et al. 2016, JACS 19: 6095)

Enlighten automated protocols

Generic protocols, designed to be run on desktop PCs:

PREP for all steps necessary prior to MM simulation (using **AmberTools**):

- Ligand parameterization (General Amber Force Field, GAFF)
- Add hydrogens, residue flips, histidine tautomers, disulfide bonds
- Check protonation states (in presence of ligand; **PropKa 3.1**)
- Add solvation sphere (water)
- Create simulation input files

STRUCT for structural effects (brief simulated annealing MD & minimization)

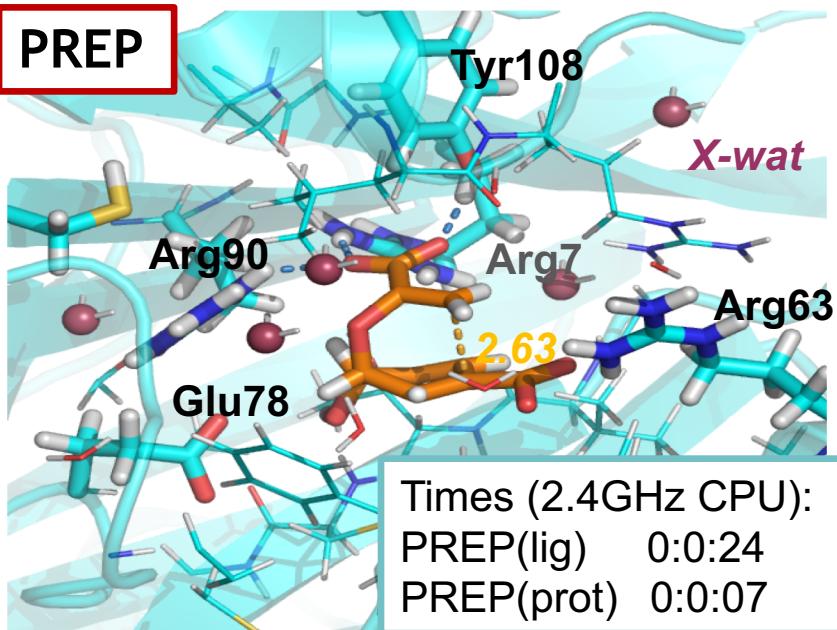
DYNAM for ligand behavior in active site (further molecular dynamics)

QM for electronic structure of ligand in enzyme

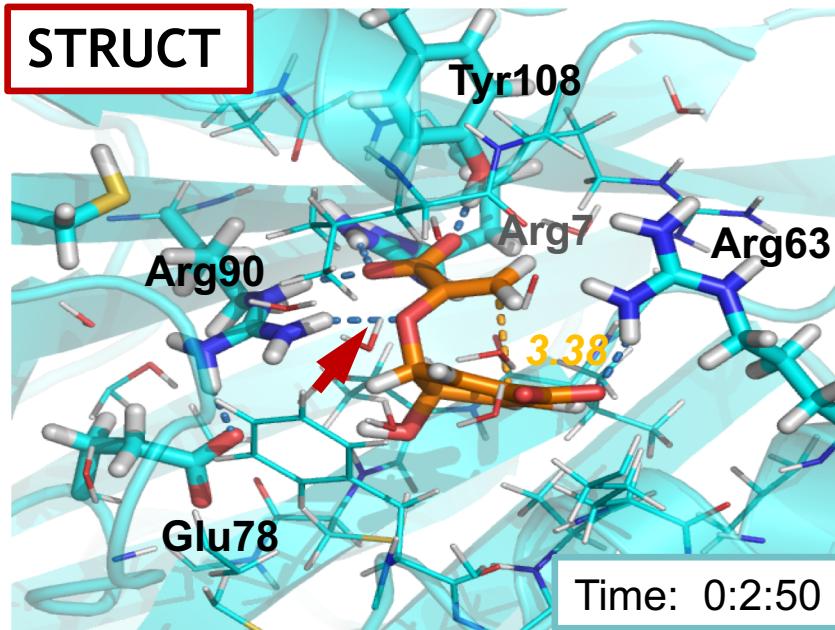
PyMOL plugin for: **PREP, STRUCT, DYNAM**

2CHT.pdb : select 1st trimer, keep only one TSA & change to chorismate

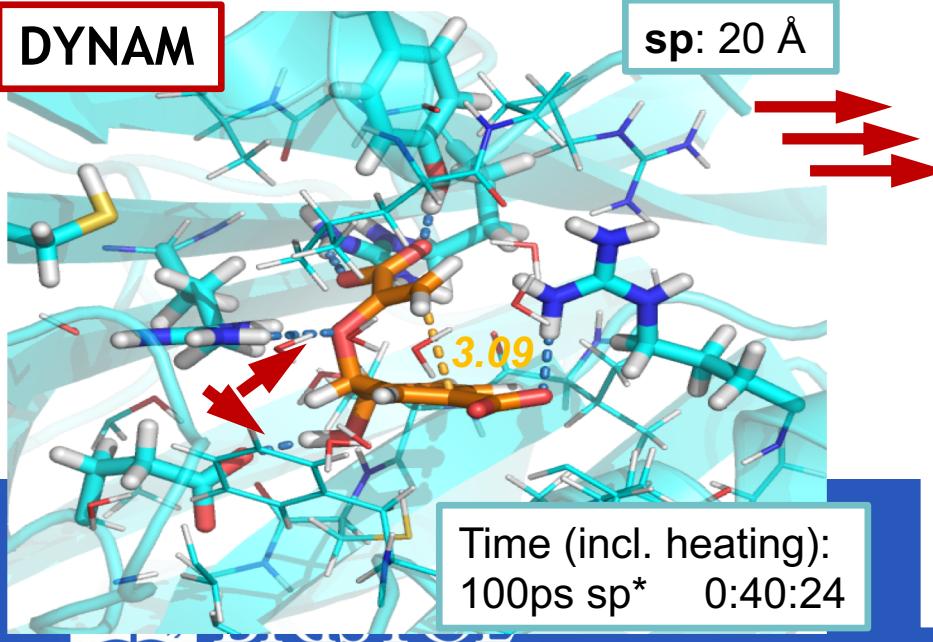
PREP



STRUCT

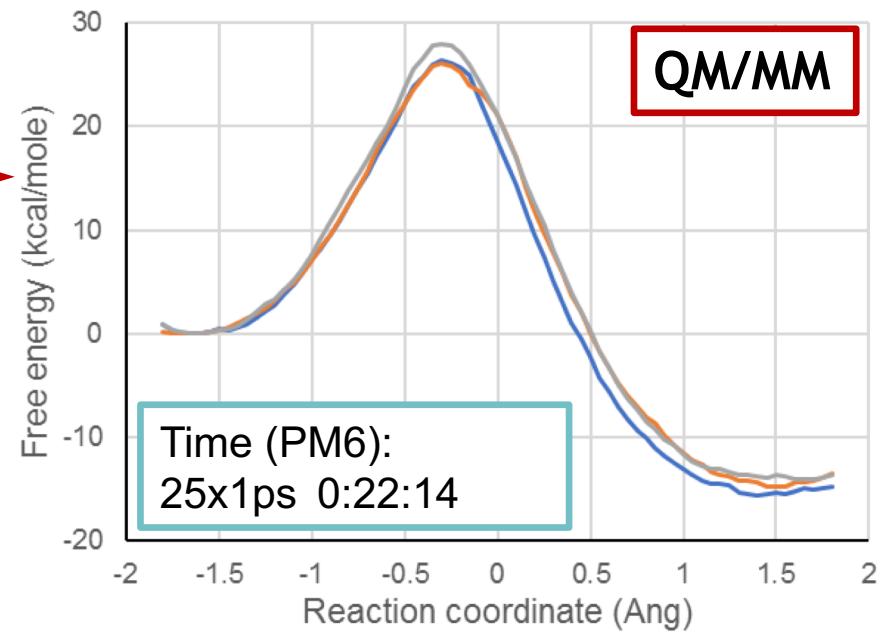


DYNAM



Time (incl. heating):
100ps sp* 0:40:24

QM/MM



https://ccpbiosim.github.io/qmmm_workshop

