# Advances in Hybrid Potential Simulations of Condensed Phase Systems

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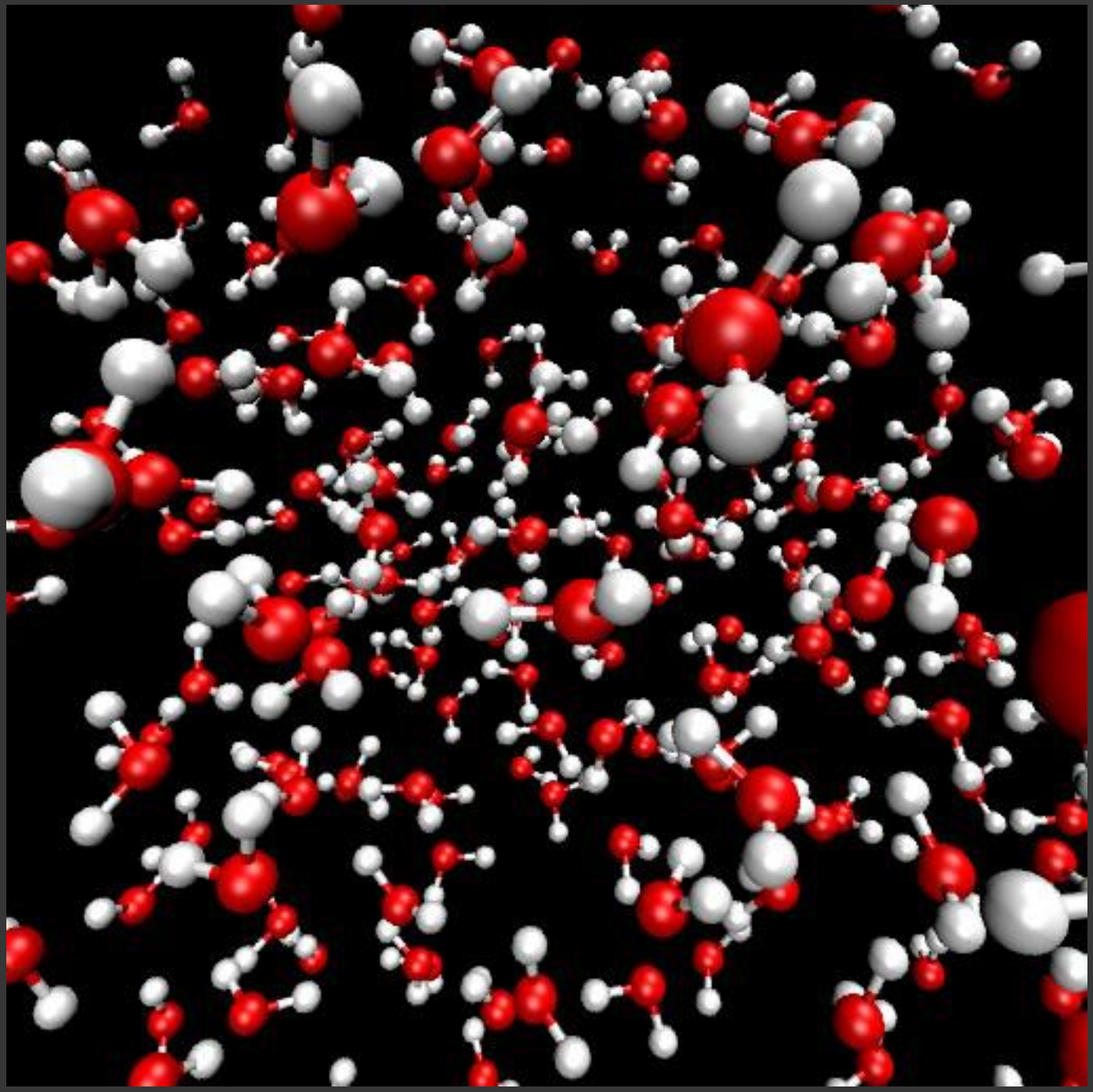
# Outline

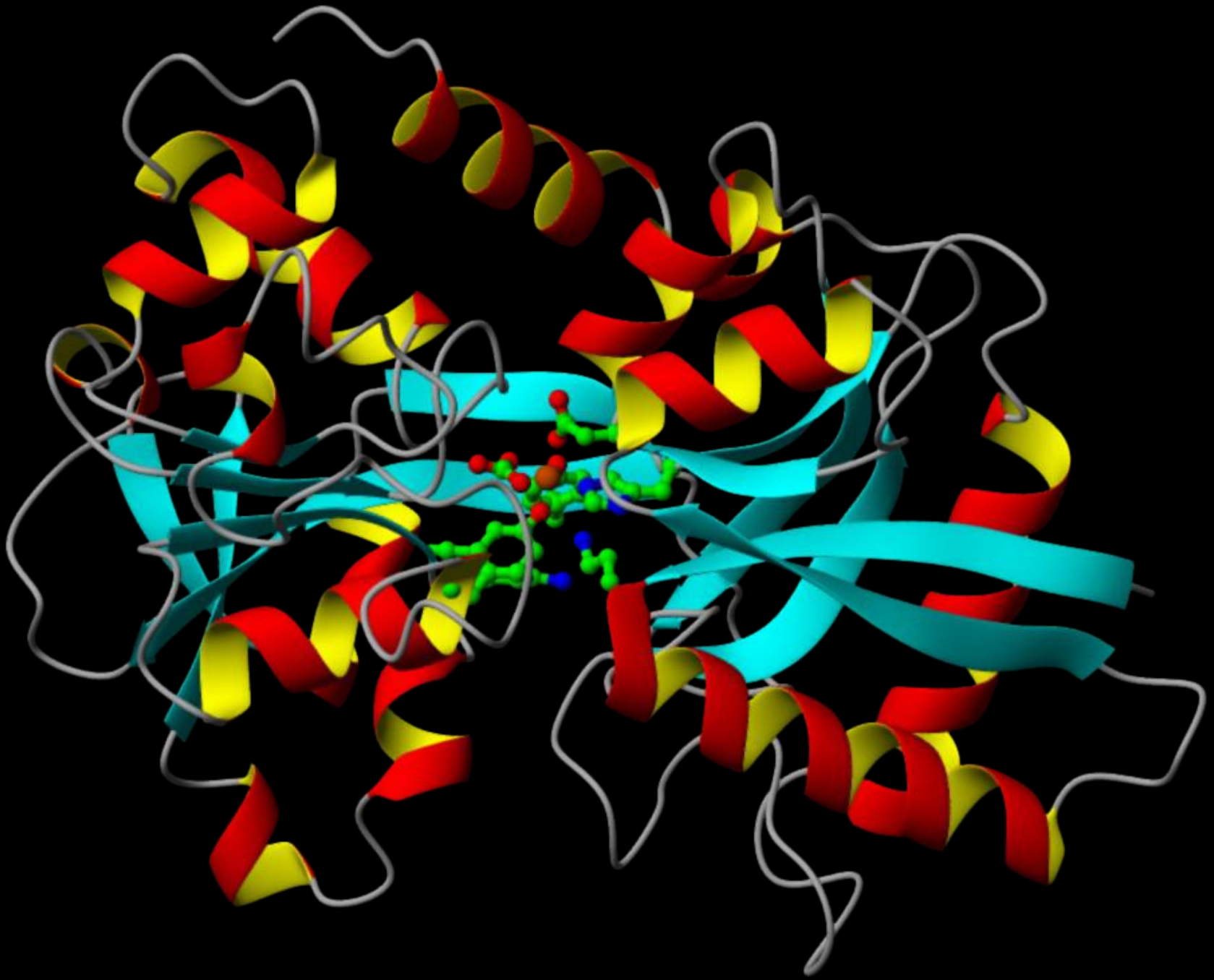
- Introduction
- Hybrid Potentials & Dynamo
- Examples
- Adaptive Algorithms

# Acknowledgements

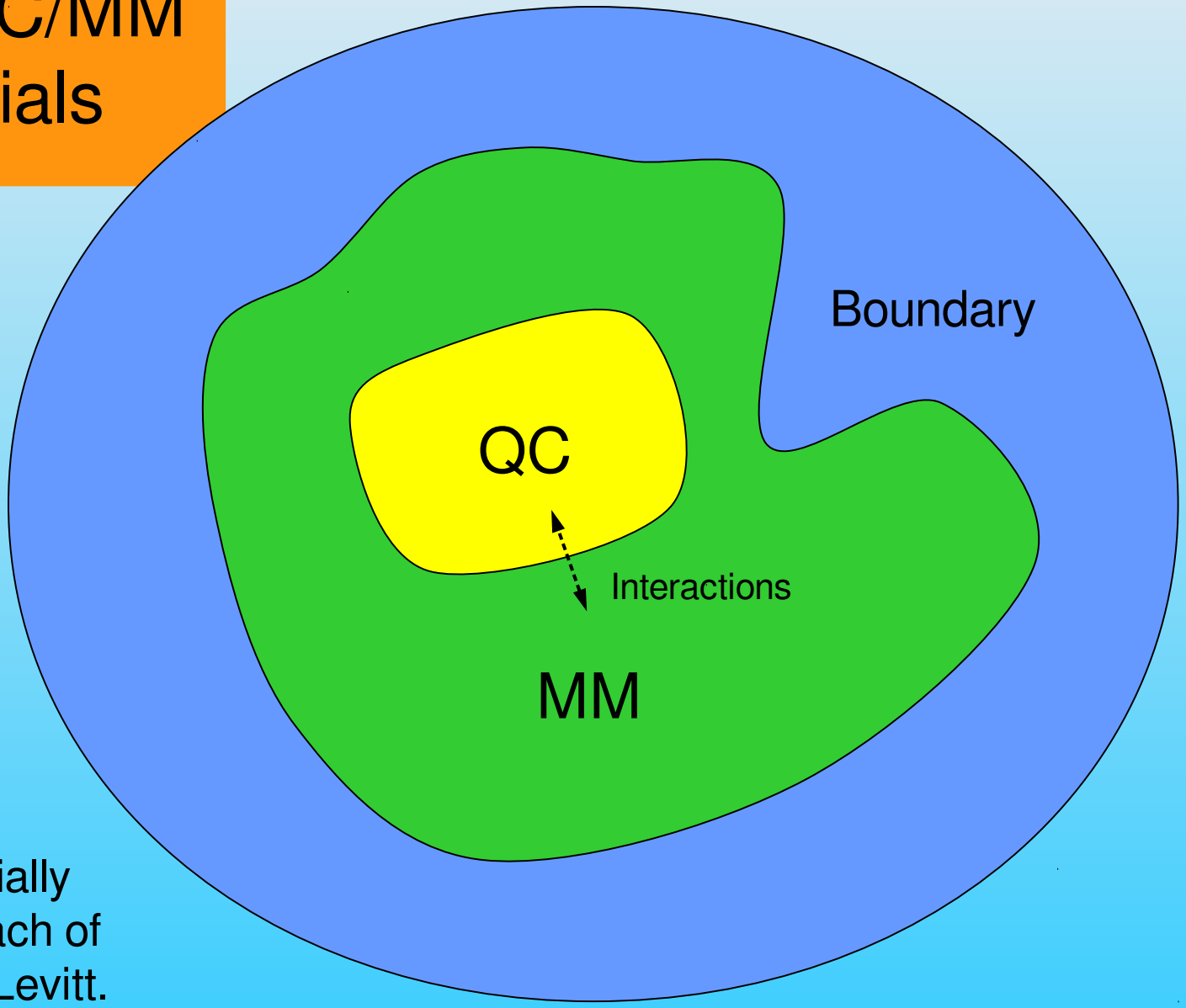
- The Dynamo team and community

- CBM/BIG – CEA
- Theory Group – ILL





# Hybrid QC/MM Potentials




Inspired initially by the approach of Warshel and Levitt.

# QC/MM Methods I

*QC Potentials:*

$$\hat{H}\Psi = E\Psi$$

- *Ab initio* DFT and HF — Gaussian basis functions.
- Various semi-empirical methods.

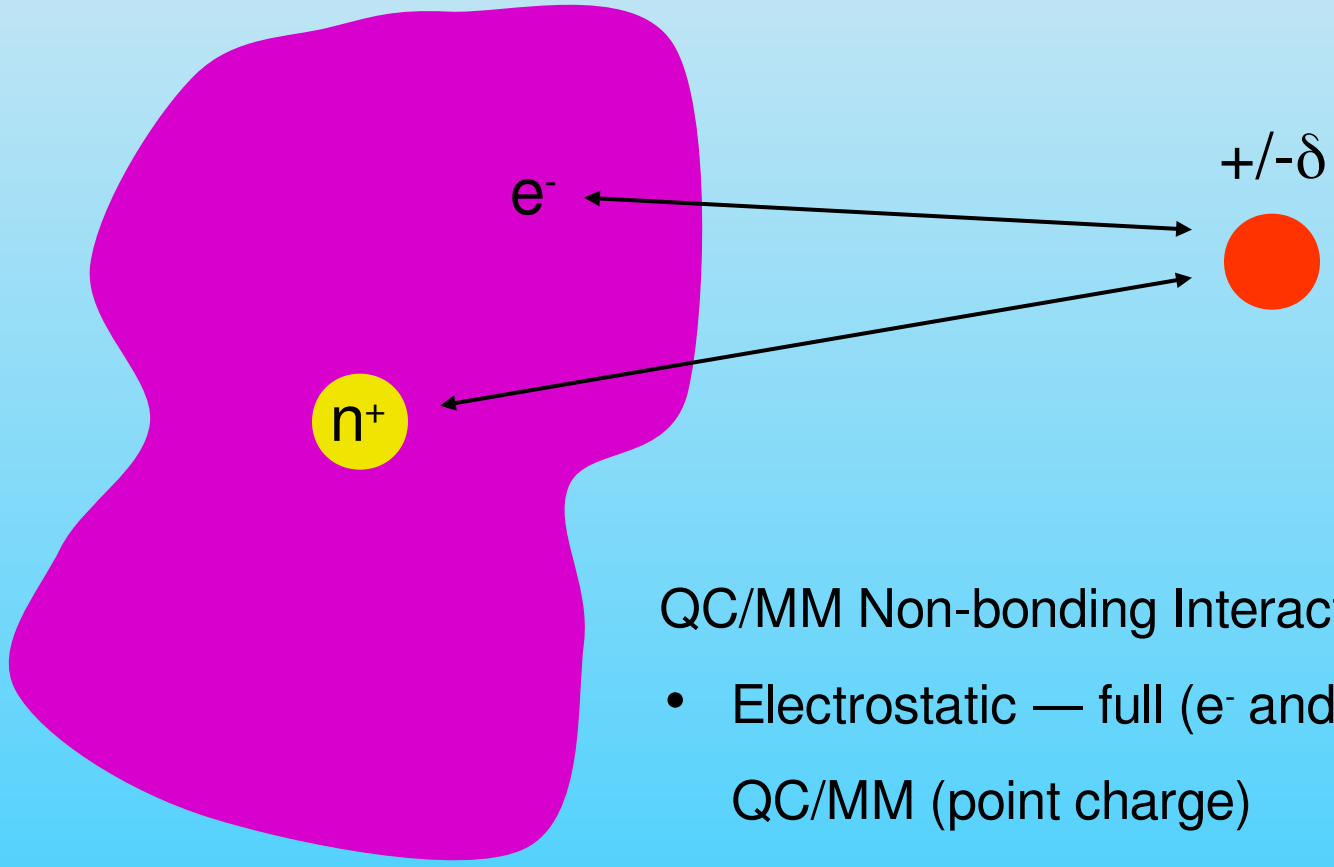
*MM Potentials:*

- AMBER, CHARMM, OPLS-AA, UFF force fields.

*Boundary Methods:*

- Periodic boundary conditions.
- Truncated systems.

# QC/MM Methods II

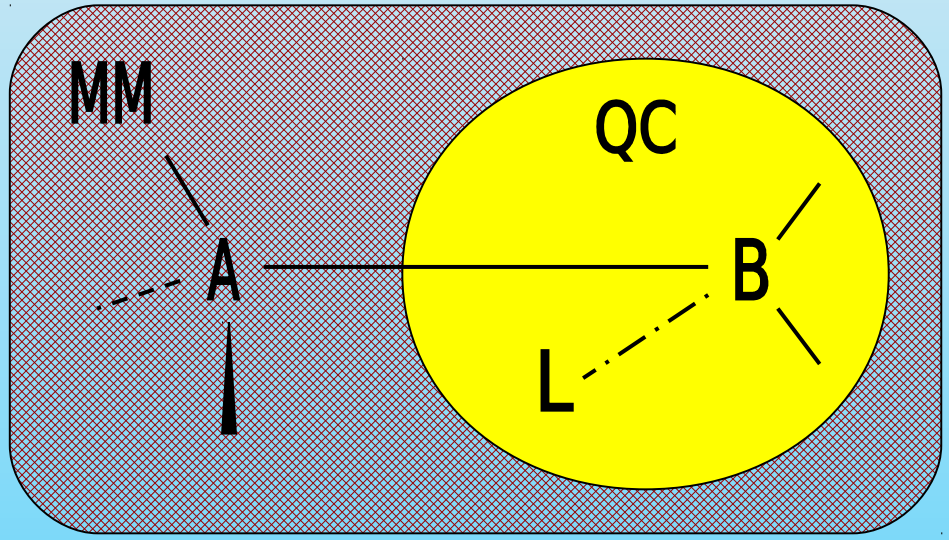


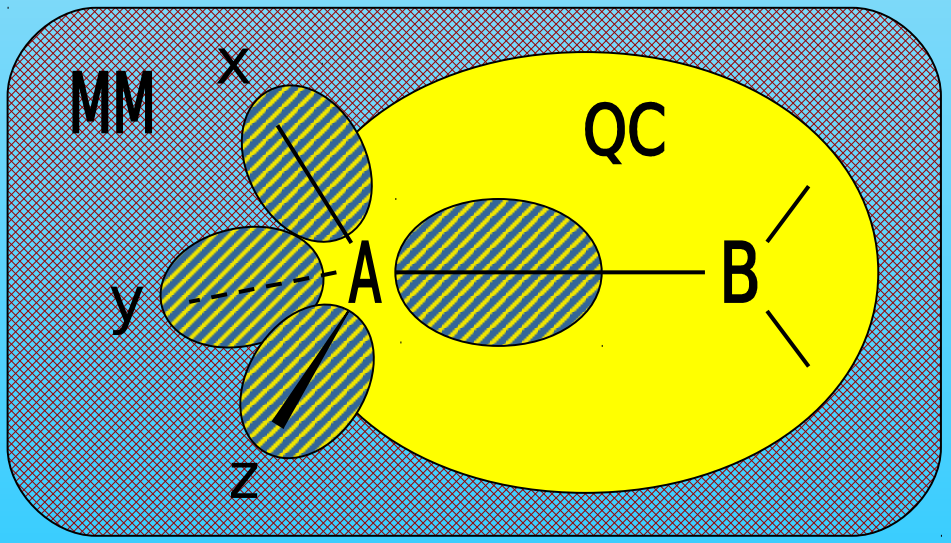

QC/MM Non-bonding Interactions:

- Electrostatic — full ($e^-$ and $n^+$) or multipole QC/MM (point charge)
- Lennard-Jones
- Polarization

# QC/MM Methods III

Link Atom Method




Hybrid Orbital Methods

# QC/MM Methods IV

Putting the separate terms together gives, for MO and DFT methods, respectively:

$$\hat{H}_{\text{Eff}}\,\Psi = E\,\Psi \quad \text{where} \quad \hat{H}_{\text{Eff}} = \hat{H}_{\text{QC}} + \hat{H}_{\text{MM}} + \hat{H}_{\text{QC/MM}}$$

$$E[\rho] = E_{\text{QC}}[\rho] + E_{\text{MM}} + E_{\text{QC/MM}}[\rho]$$

Solving the HF or DFT/KS equations gives the potential energy of the system as well as the wavefunction or electron density. The forces on the particles can be determined from the energy as:

$$F = -\partial E / \partial R$$

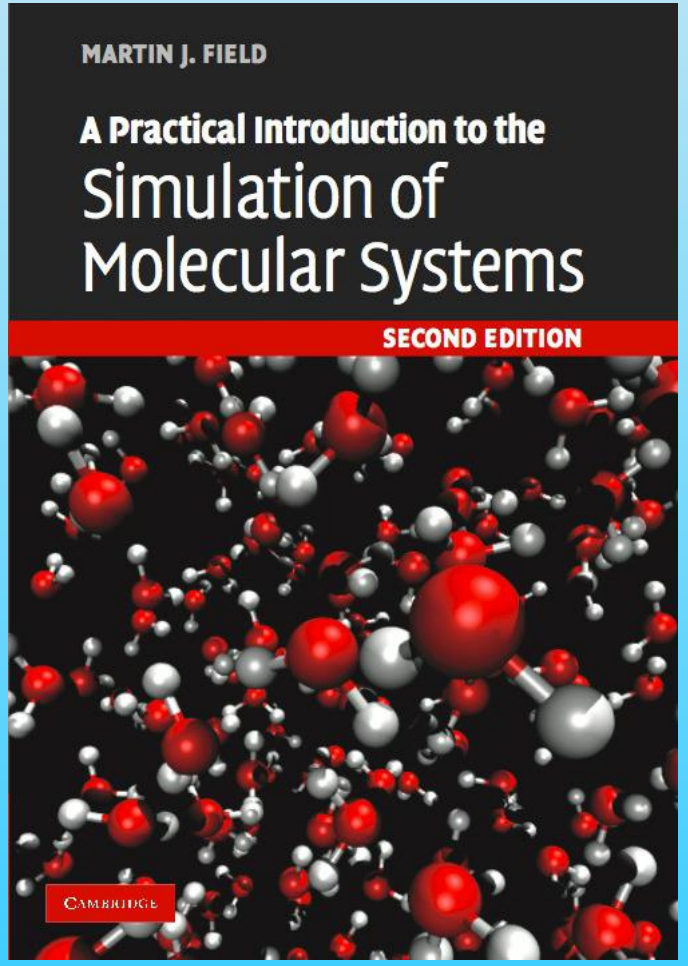
and then used in the appropriate simulation algorithm.

# pDynamo I

- M. J. Field. *A Practical Introduction to the Simulation of Molecular Systems*. Cambridge University Press, Cambridge, 2007 (2nd edition).
- M. J. Field. *The pDynamo Library for Molecular Simulations using Hybrid Quantum Mechanical and Molecular Mechanical Potentials*. J. Chem. Theo. Comput. 4, 1151-1161 (2008).

The library is available at:

http://www.pdynamo.org



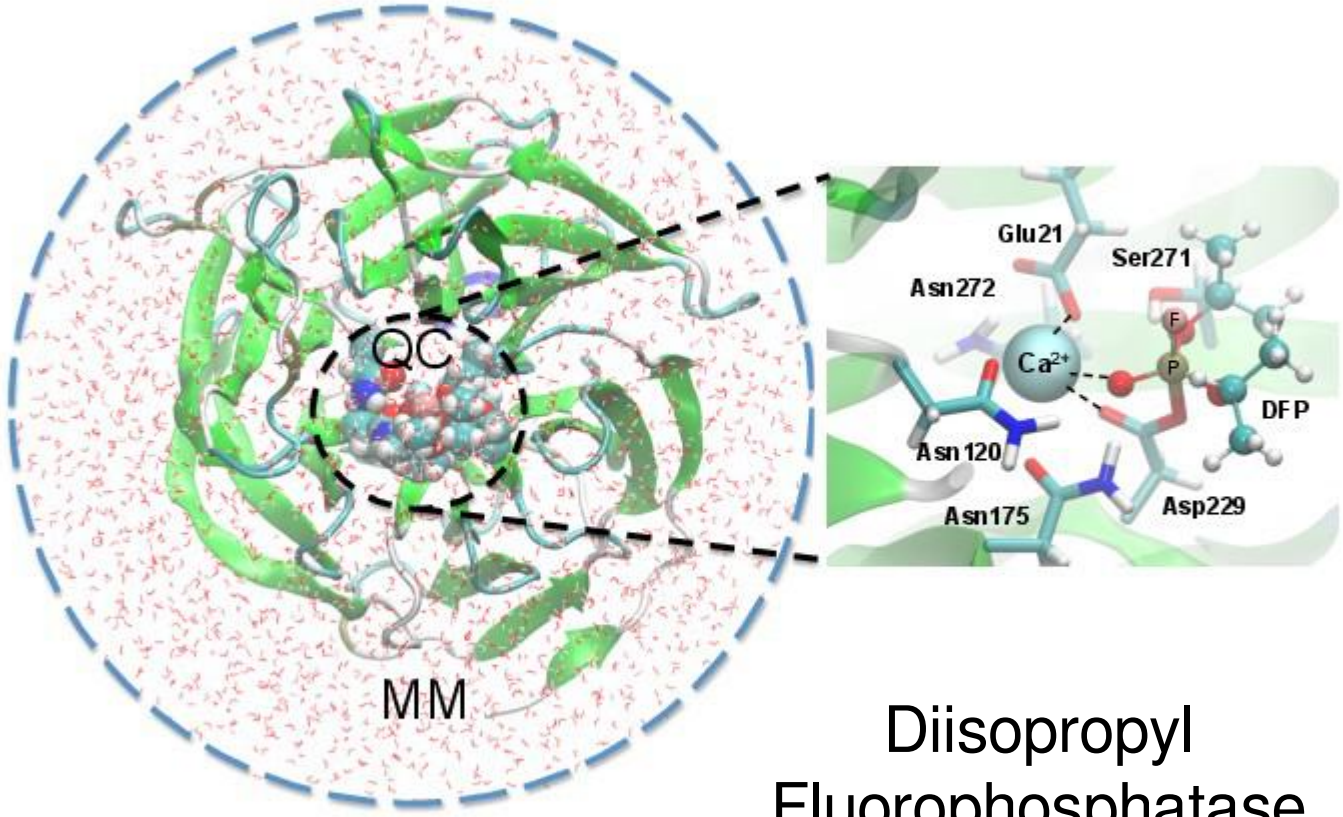
# pDynamo II

A platform for the development and testing of simulation algorithms that is *clear, extensible, simple and reasonably efficient*.

- Python/C:
  - Python for the majority of operations .
  - C for speed.
- A series of Python packages.
- Object-oriented structure.
- Provides a framework to build complex algorithms:

  ONIOM, path integrals, replica exchange, ...

# Enzymes I

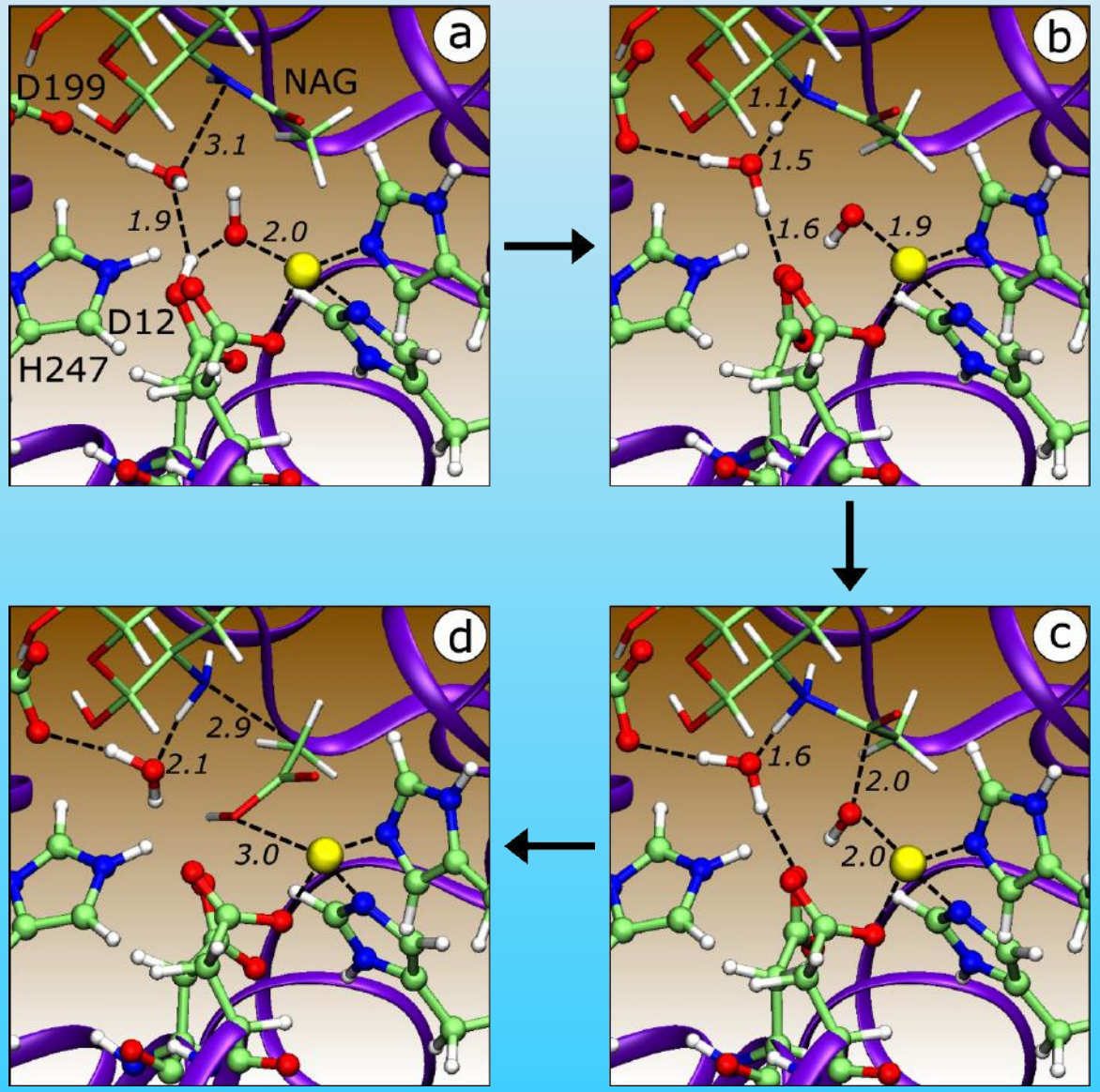



Diisopropyl Fluorophosphatase

*JPC B 2014*

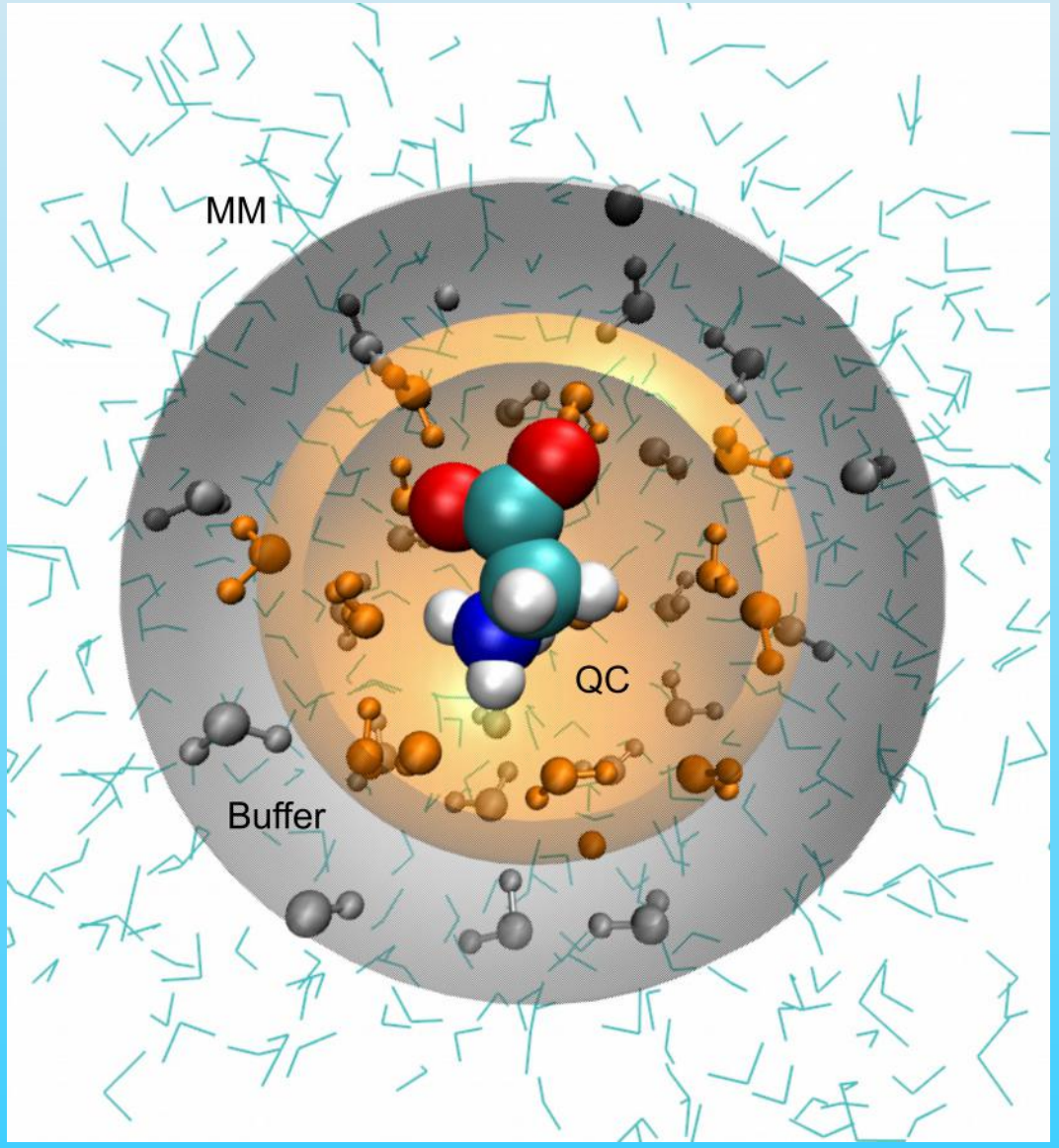
# Enzymes II

Peptidoglycan
Deacetylase
*JCP B 2017*



# Adaptive QC/MM Methods I

A buffer zone in which there is a smooth transition between QC and MM representations.



# Adaptive QC/MM Methods II

Existing algorithms include:

- Hot-spot methods of Hofer, Rode *et al.* (single or double QC calculation with smoothing of forces only).
- Permuted adaptive partitioning method and its derivatives from Heyden, Lin and Truhlar, along with developments by others (Bulo *et al*, …).

All methods are either (i) very costly or (ii) numerically inconsistent.

# Adaptive QC/MM Methods III

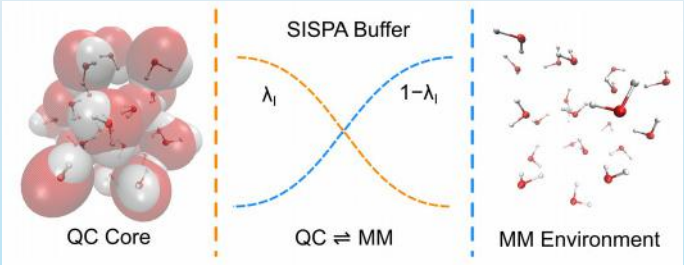
The PAP method considers all $2^N$ possible QC/MM partitionings that arise from the N transformable fragments within the buffer zone. Each fragment is given a weight, $\lambda_I$, that determines its QC ($\lambda_I$) or MM ($1-\lambda_I$) character. This gives the energy:

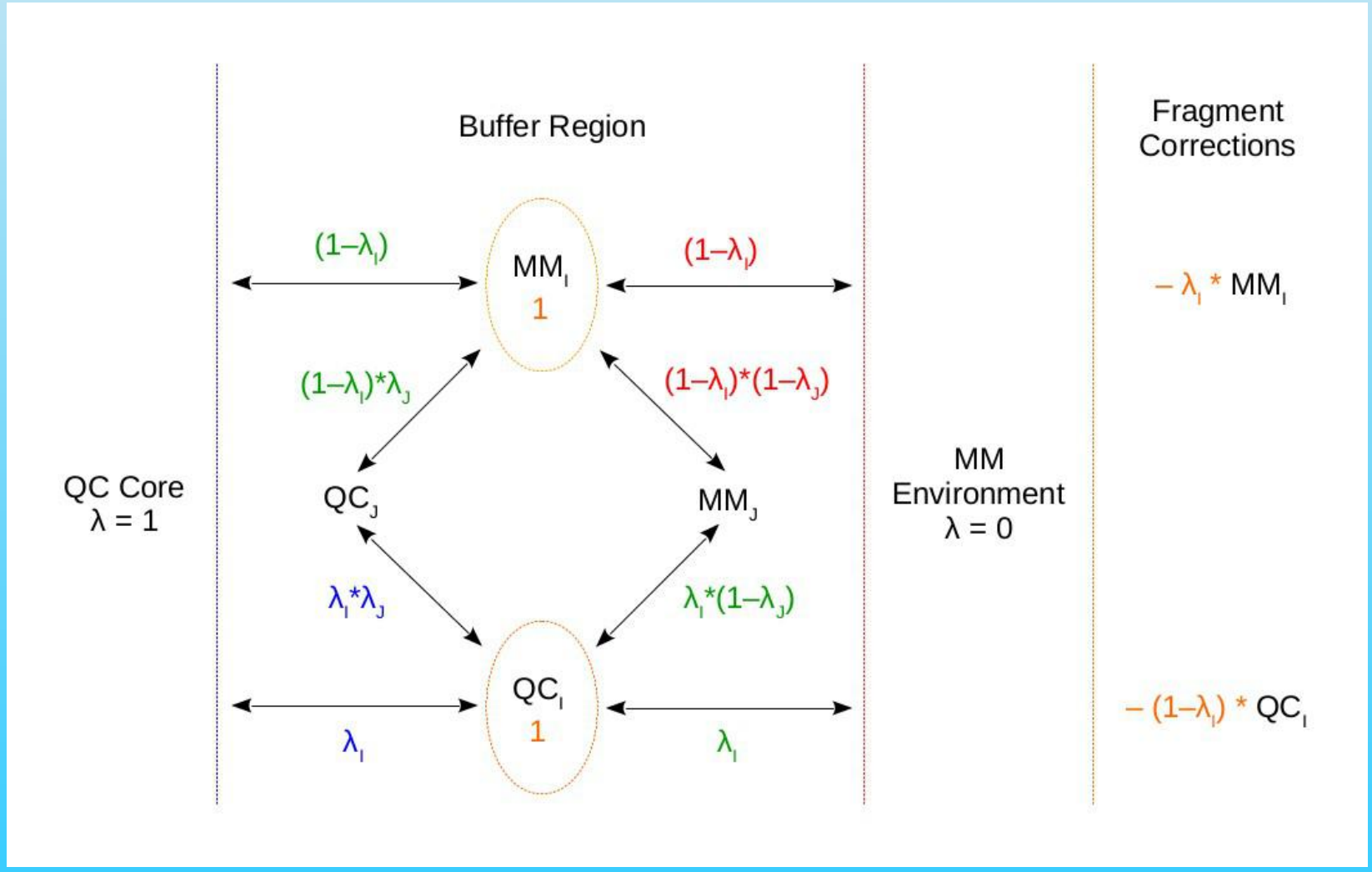
$$E_{PAP} = \sum_{P=1}^{2^N} w_P E_P$$

$$w_P = \prod_{I \in QC} \lambda_I \prod_{J \in MM} (1 - \lambda_J)$$

Can we use this scaling idea in a more efficient fashion?

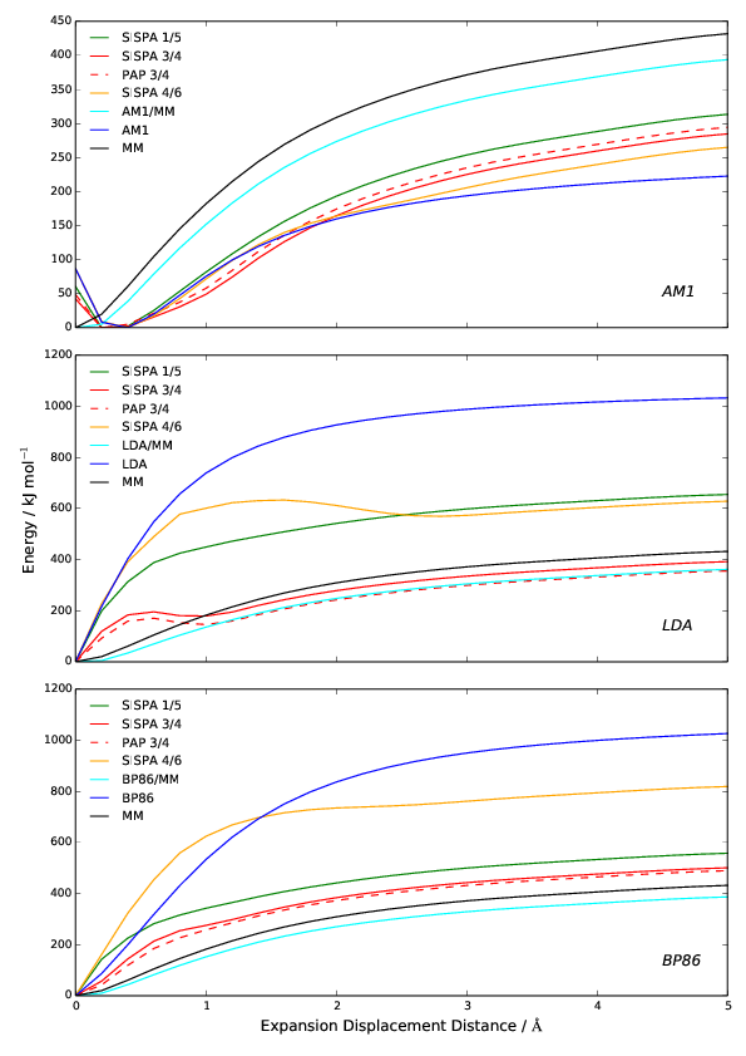
# SISPA Algorithm I

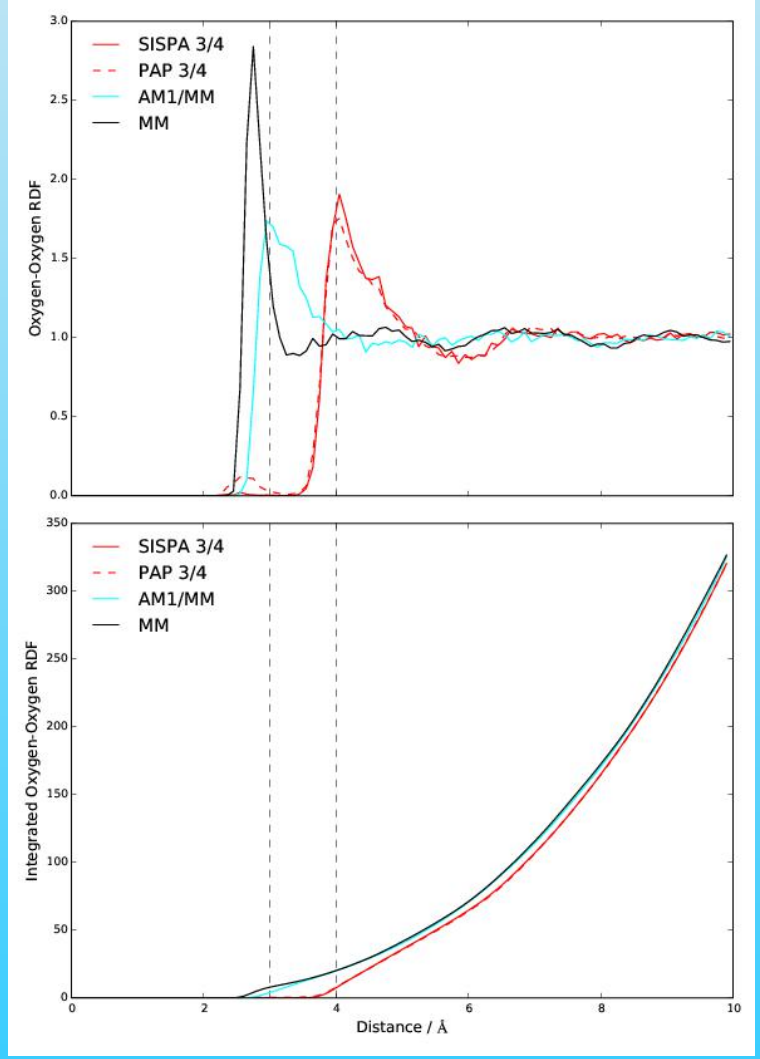


# SISPA Algorithm II

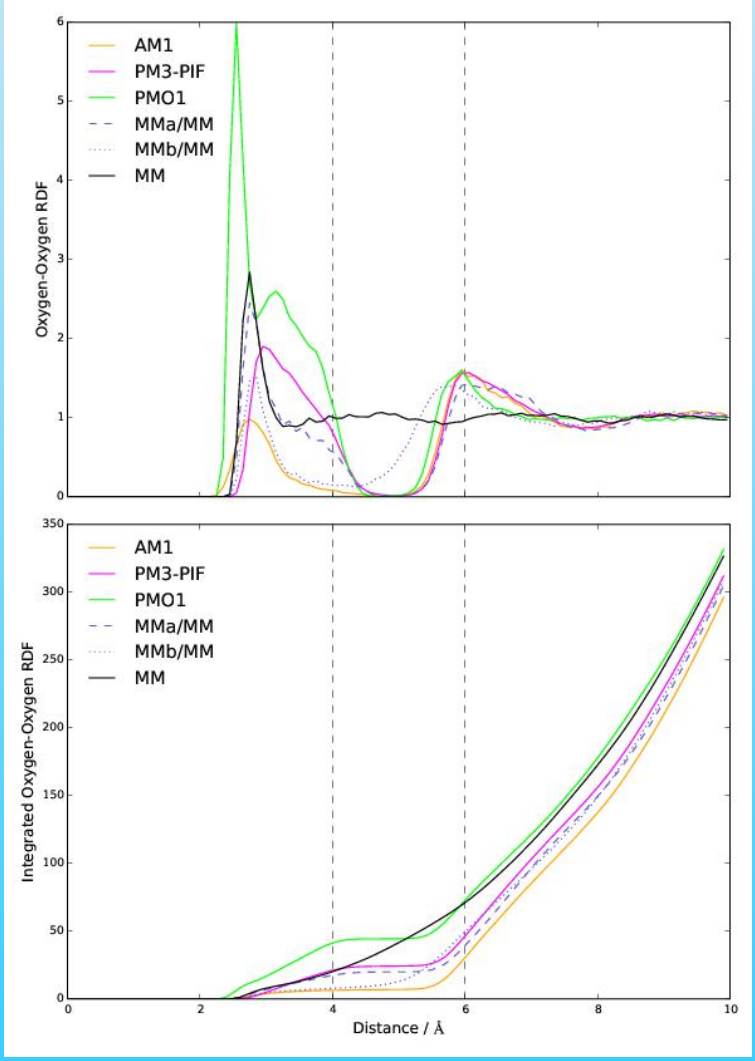
Single QC calculation with continuous energy and forces.

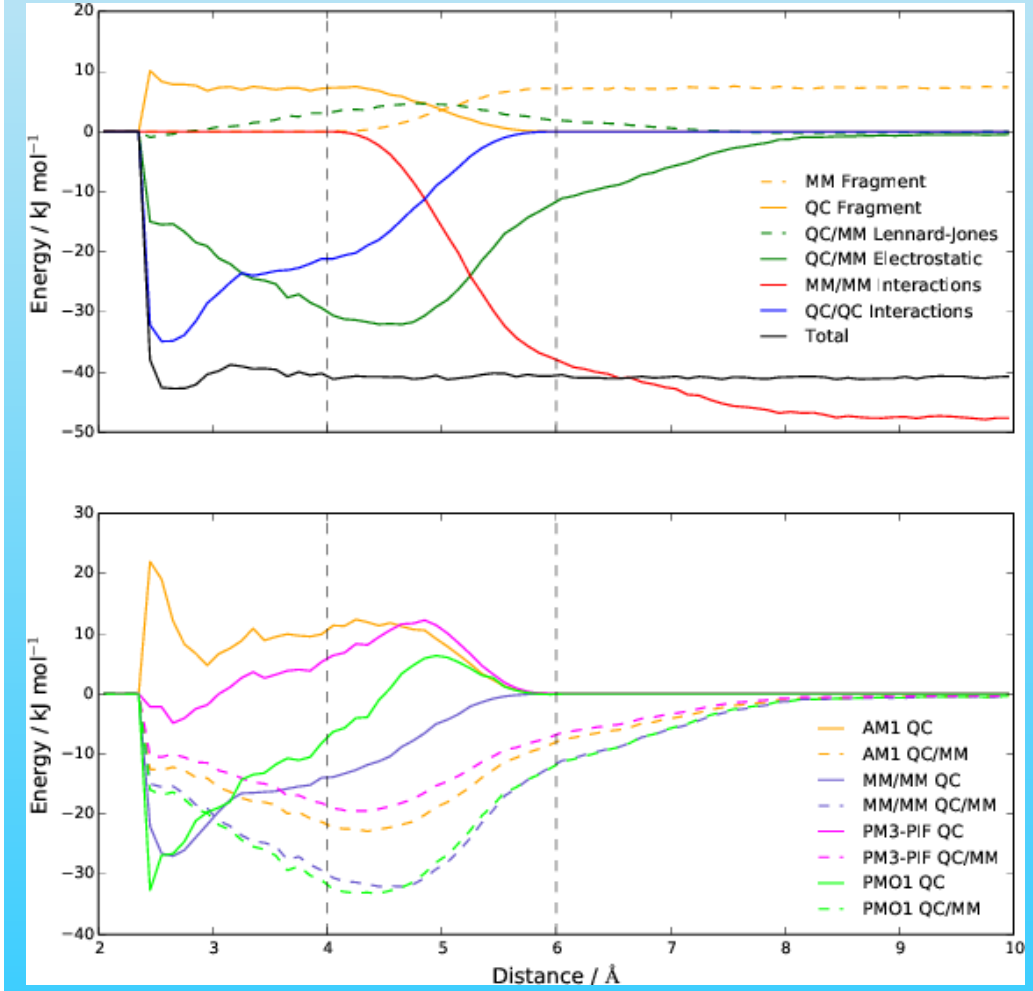


# SISPA Algorithm III

Results very sensitive to the balance between the QC and MM potentials.



# SISPA Algorithm IV

- An adaptive QC/MM algorithm that has approximately the same cost as a fixed partitioning QC/MM method and is numerically consistent.
- Non-trivial to implement.
- Adaptive algorithms, including SISPA, place extra demands on the compatibility of the individual potentials and their coupling.

Field MJ. *An Algorithm for Adaptive QC/MM Simulations*.
J Chem Theor Comp 9 (2017) 2342–2351.
DOI: 10.1021/acs.jctc.7b00099

Thank you for your attention!