

# 10/21/2024

- Today's lecture is intended to help you achieve the following learning objective: Explain the concept of regions related to a QM/MM calculation. Compare and contrast QM/MM with molecular mechanics.
- Quantum Mechanics in Chemistry
  - What are the differences between molecular mechanics and quantum mechanics?
  - The Schrodinger Equation
  - Basis Sets
  - Overview of QM methods
- Quantum Mechanics/Molecular Mechanics calculations
  - The 2013 Nobel Prize in Chemistry
  - How do hybrid calculations overcome the limitations of QM and MM?
  - The QM/MM Hamiltonian
  - Factors in selecting the QM region

# **Quantum Mechanics in Chemistry: An Overview**

Learn more in Chem 454/550, offered Spring 2023!

# Molecular mechanics vs Quantum mechanics

- inputs
  - coordinates
  - force field functions
  - force field parameters, including partial charge
- outputs
  - energy
  - electron density (from coordinates and partial charge)
- fast approximation to QM
- energy is differentiable

- inputs
  - coordinates
  - net charge
  - total spin
  - basis set
- outputs
  - energy
  - wave function, which yields electron density and other properties
- highly accurate in gas phase
- philosophically confusing

# The Schrödinger Equation

- The time-independent Schrödinger equation is  $\hat{H}\Psi = E\Psi$ 
  - $\hat{H}$  is the Hamiltonian operator
  - $\Psi$  is the wavefunction, where  $|\Psi|^2$  is the electron density
  - $E$  is the energy
- Born-Oppenheimer Approximation
  - mass of the nucleus  $\gg$  mass of electron
  - velocity of electrons is much faster
  - electronic properties can be determined for fixed nuclei

- Based on BO approximation, the electronic Hamiltonian is

$$\hat{H}_{\text{elec}} = - \sum_{i=1}^N \frac{1}{2} \nabla_i^2 - \sum_{i=1}^N \sum_{A=1}^M \frac{Z_A}{|\mathbf{r}_i - \mathbf{R}_A|} + \sum_{i=1}^N \sum_{j>i}^N \frac{1}{|\mathbf{r}_i - \mathbf{r}_j|}$$

$$E_{\text{elec}} = \langle \Psi_{\text{elec}} | \hat{H}_{\text{elec}} | \Psi_{\text{elec}} \rangle$$

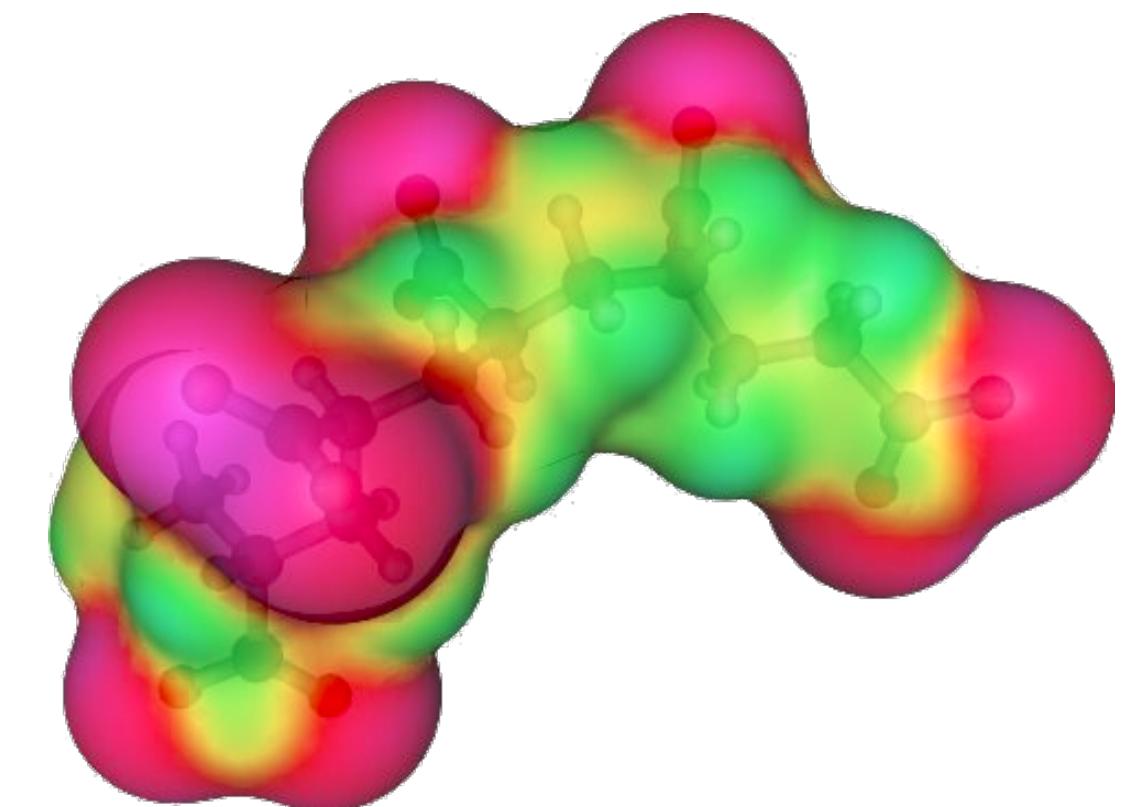
$$E_{\text{QM}} = E_{\text{elec}} + \sum_{A=1}^M \sum_{B>A}^M \frac{1}{|\mathbf{R}_A - \mathbf{R}_B|}$$

- Includes kinetic energy, electron-nuclear attraction, and electron-electron repulsion

# Solvation

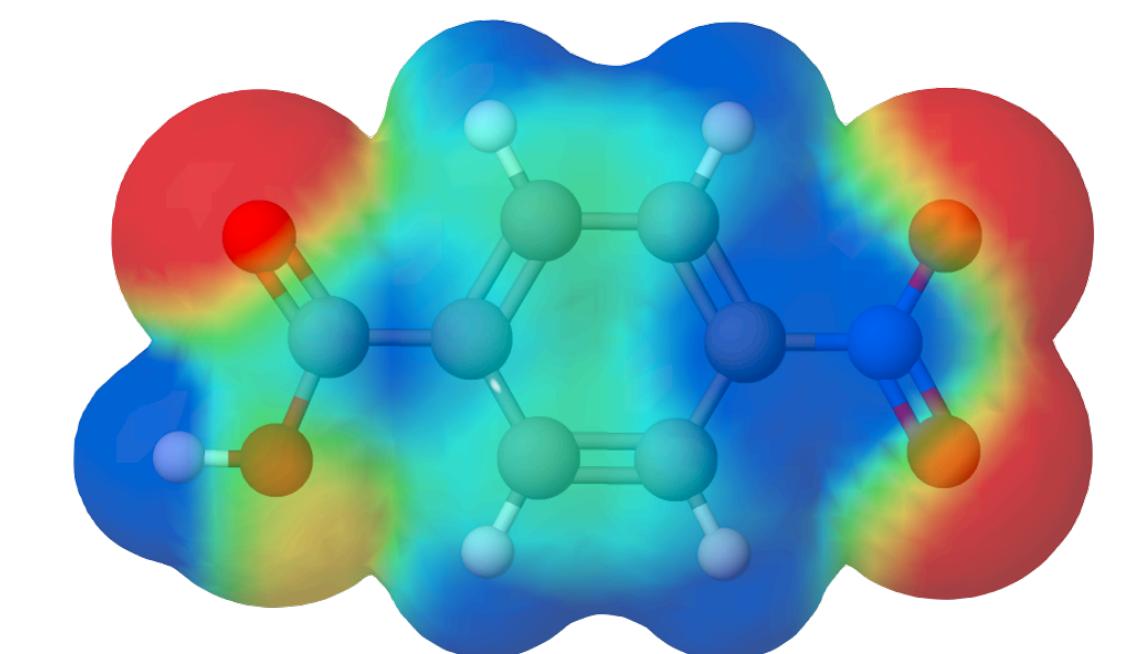
- As in MM, continuum solvation methods used to model solvent in QM
  - Polarizable continuum model (PCM)
  - COnductor-like Screening MOdel (COSMO) - solvent is treated as a set of apparent charges on the surface of the solute cavity. These charges interact with the system according to Coulomb's law,

$$\hat{H}_{[I/\text{sol}]} = \frac{f(\varepsilon)}{2} \left[ - \sum_{i \in I} \sum_{s \in \Gamma} \frac{q_s}{|\mathbf{r}_i - \mathbf{R}_s|} + \sum_{A \in I} \sum_{s \in \Gamma} \frac{Z_A q_s}{|\mathbf{R}_A - \mathbf{R}_s|} \right],$$



COSMO surface of a pentaacrylate molecule (red = negative, green = positive equilibrium layer).

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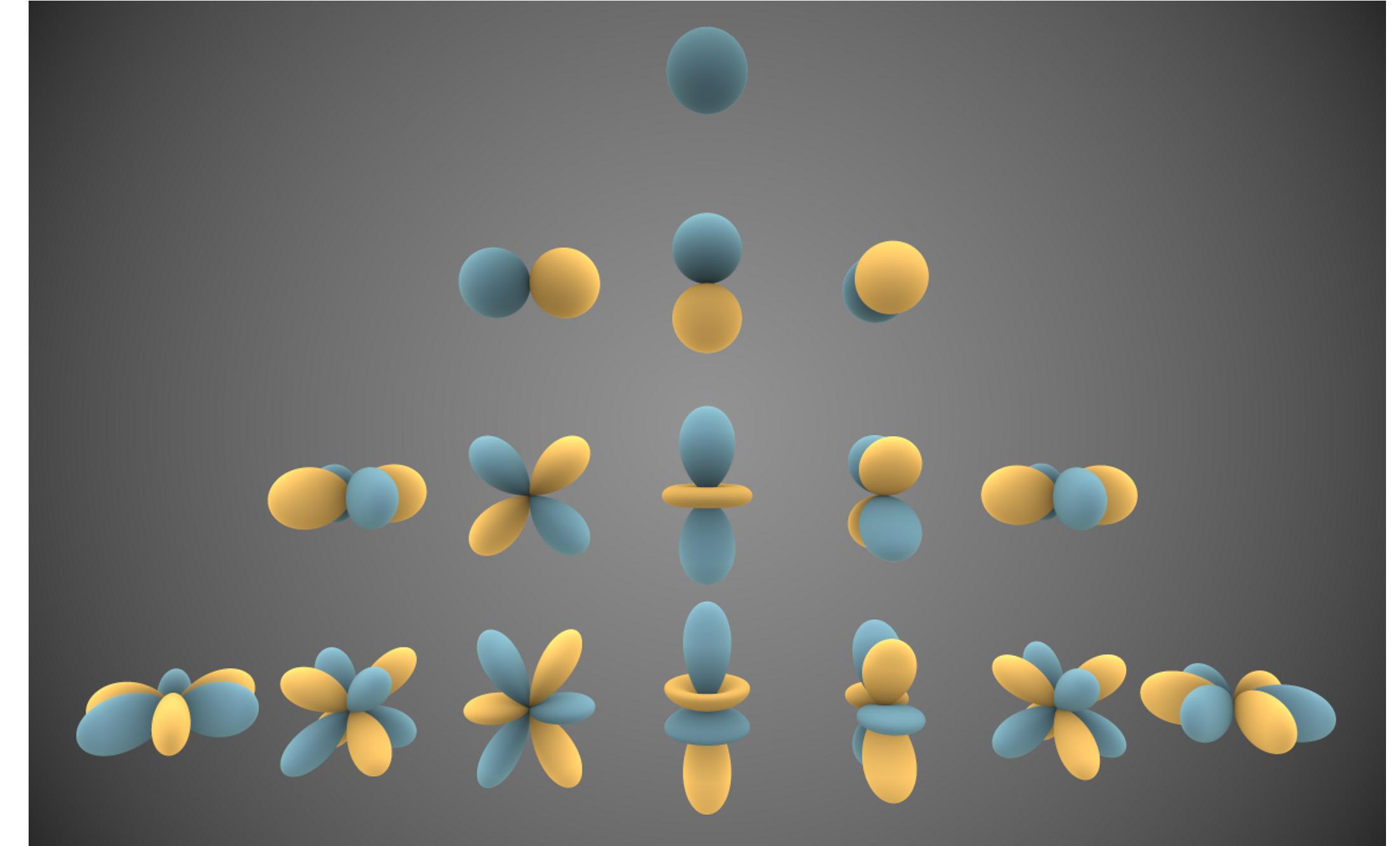


Charge density surface of 4-nitro-benzoic acid

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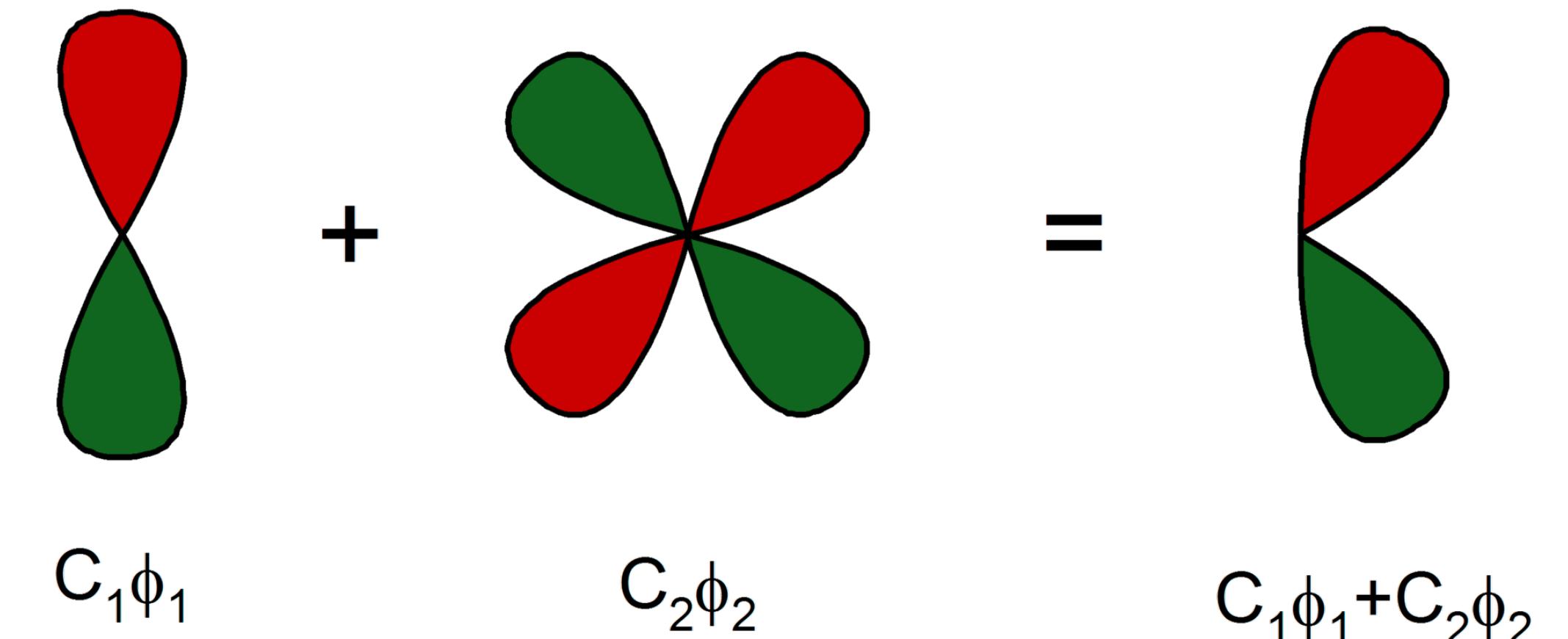
# Basis sets

- Generically, a collection of functions that are combined into a more complex function
- For QM, a set of one-particle functions used to build molecular orbitals
- Variation theorem - no approximate wave function can have lower energy than the exact ground state energy of the system
- Larger basis set enables greater accuracy but higher cost of parameter optimization



Spherical harmonics, which describe atomic orbitals

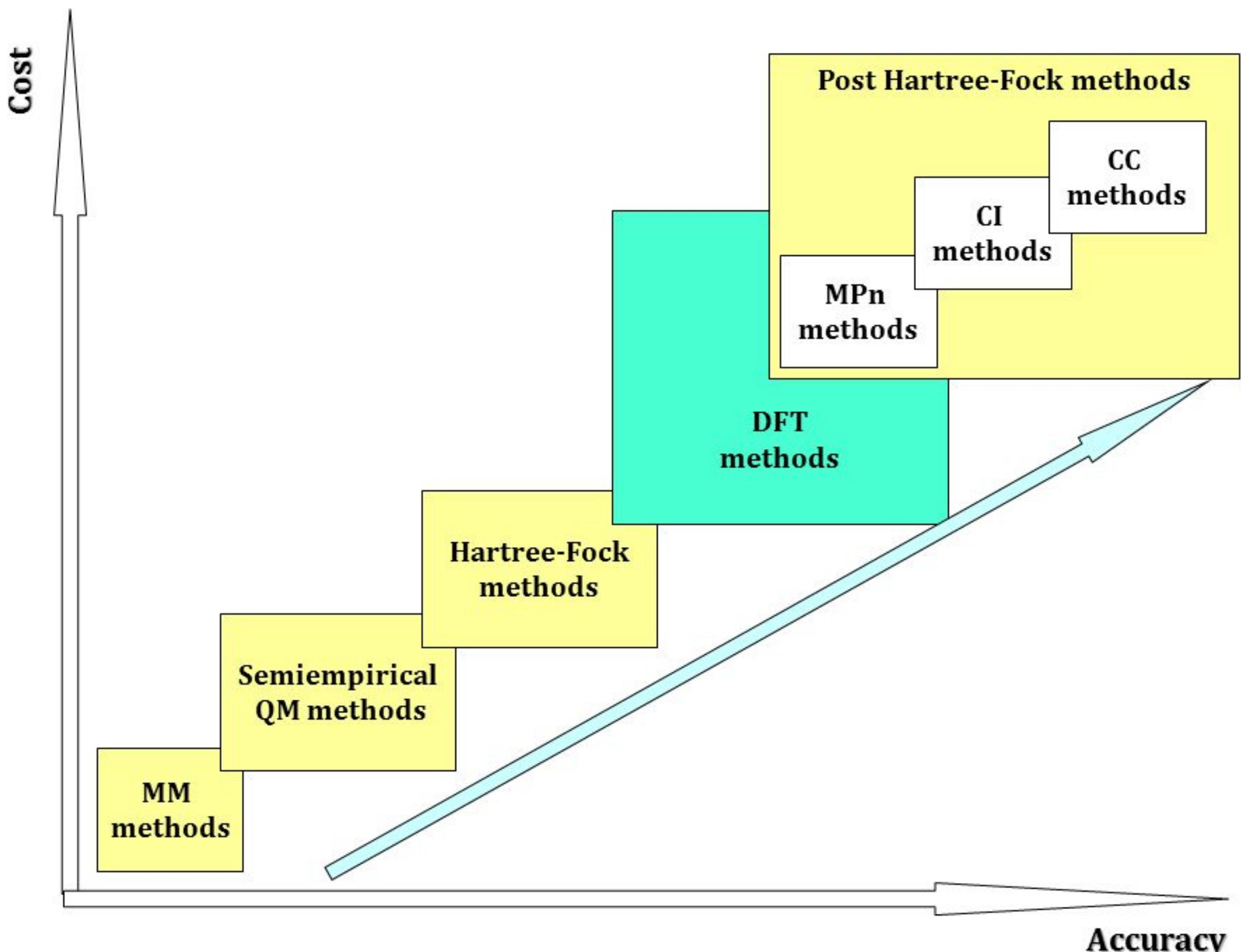
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Linear combinations of functions are more complex functions

A d-polarization function added to a p orbital. (CC-BY-SA-3.0; Rifleman 82)

# Accuracy and Cost of Methods



- Semiempirical - some basis function parameters fixed
- Hartree-Fock - electrons experience mean field of other electrons
- DFT, Density Functional Theory - currently most popular, based on electron density opposed to wave function
- MPn, Møller–Plesset perturbation theory - approximation method
- CI, Configuration Interaction
- CC, Coupled Cluster - maximizes accuracy with full electron correlations



Let's Check!

<b>Property</b>	<b>MM</b>	<b>QM</b>
Separate models of nuclei and electrons		X
Energy depends on nuclei not electron positions	X	
Faster	X	
Electrons may be delocalized		X
Explicit electron – electron interactions		X
Differentiable energy function facilitates optimization and molecular mechanics	X	
More complex function guarantees more accuracy		X

# Quantum Mechanics / Molecular Mechanics



**Figure 2.** Newton and Schrödinger's cat. Previously, classical physics and quantum chemistry belonged to rivalling worlds. The Nobel Laureates in Chemistry 2013 have opened a gate between those worlds and have brought about a flourishing collaboration.

Martin Karplus  
Michael Levitt  
Arieh Warshel

# The Nobel Prize in Chemistry 2013

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**Martin Karplus**

Prize share: 1/3



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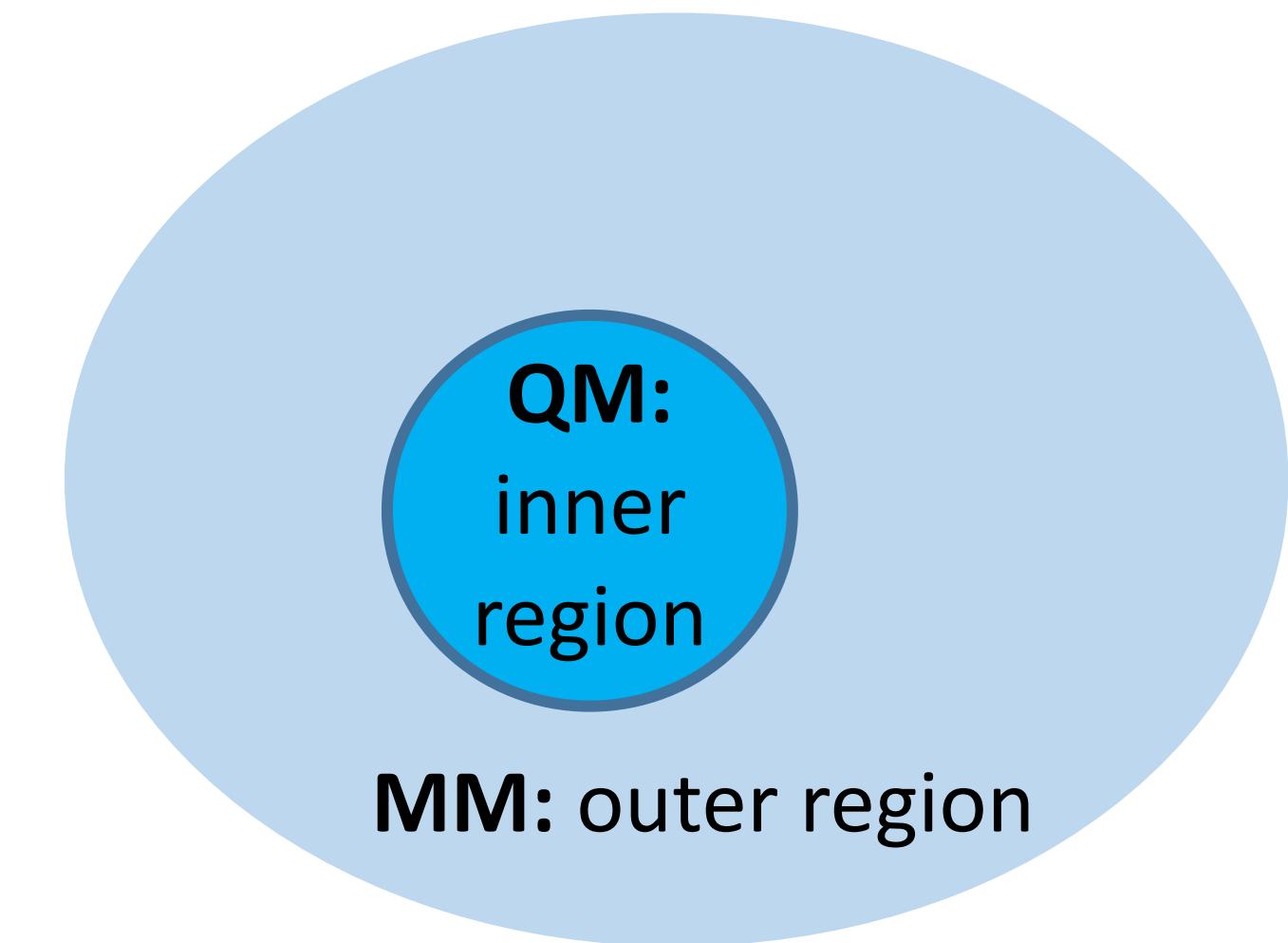
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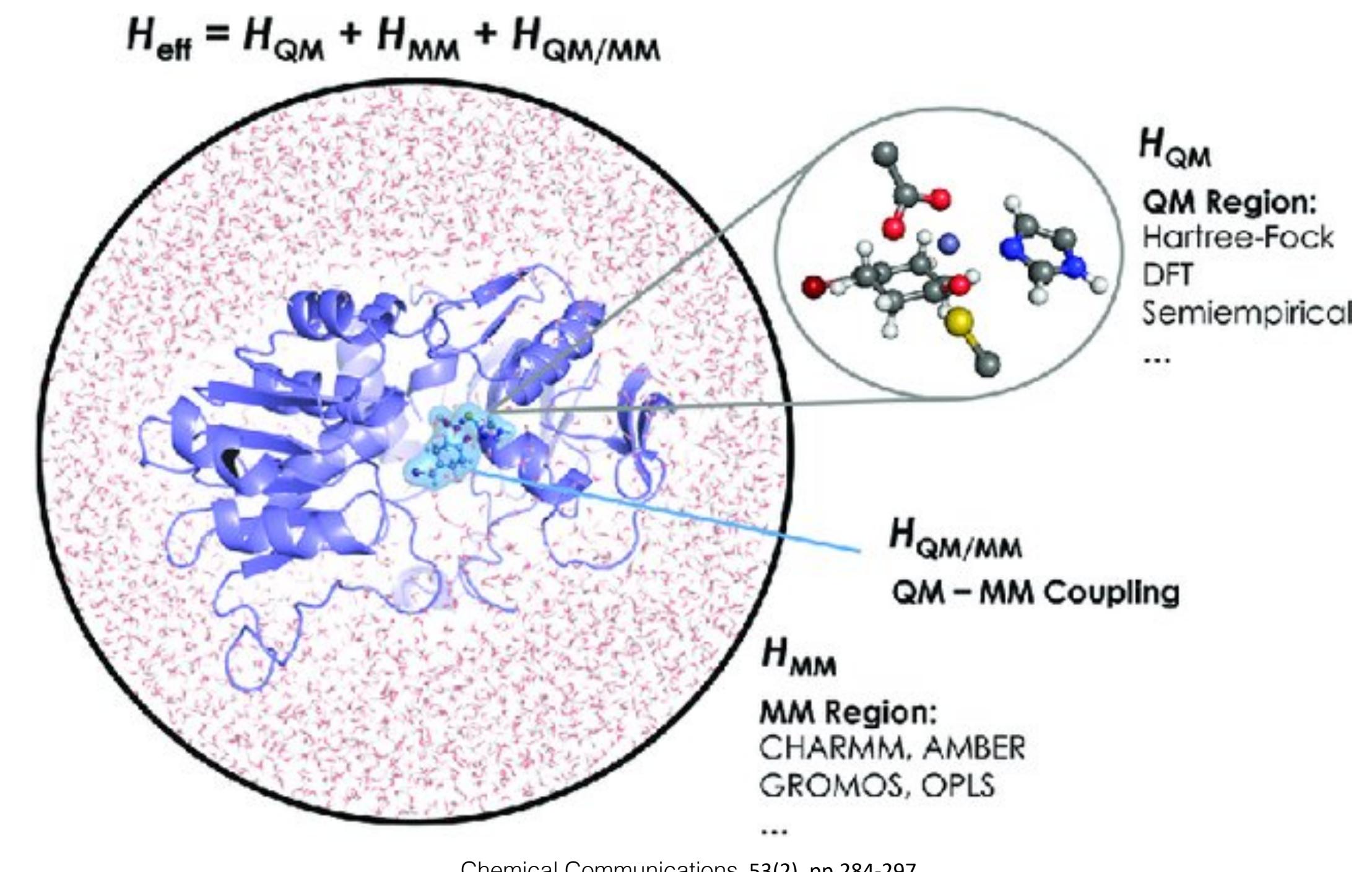
# Overcoming Limitations

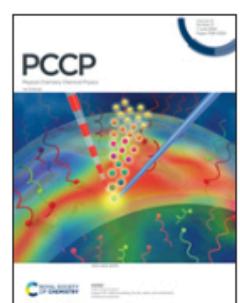
- QM is accurate but too slow for more than a few hundred atoms, even with modern supercomputers
- MM does not model
  - chemical reactions
  - electronic processes such as charge transfer / electronic excitation
- The QM/MM compromise
  - QM within a chemically active region
  - MM for the surroundings



# The QM/MM Hamiltonian

- QM region
- MM region
- Coupling
  - bonded and vdW (Lennard-Jones)
  - electrostatic between point charges in MM region and
    - point charges assigned to atoms in the QM region or
    - expectation value of electrostatic potential energy



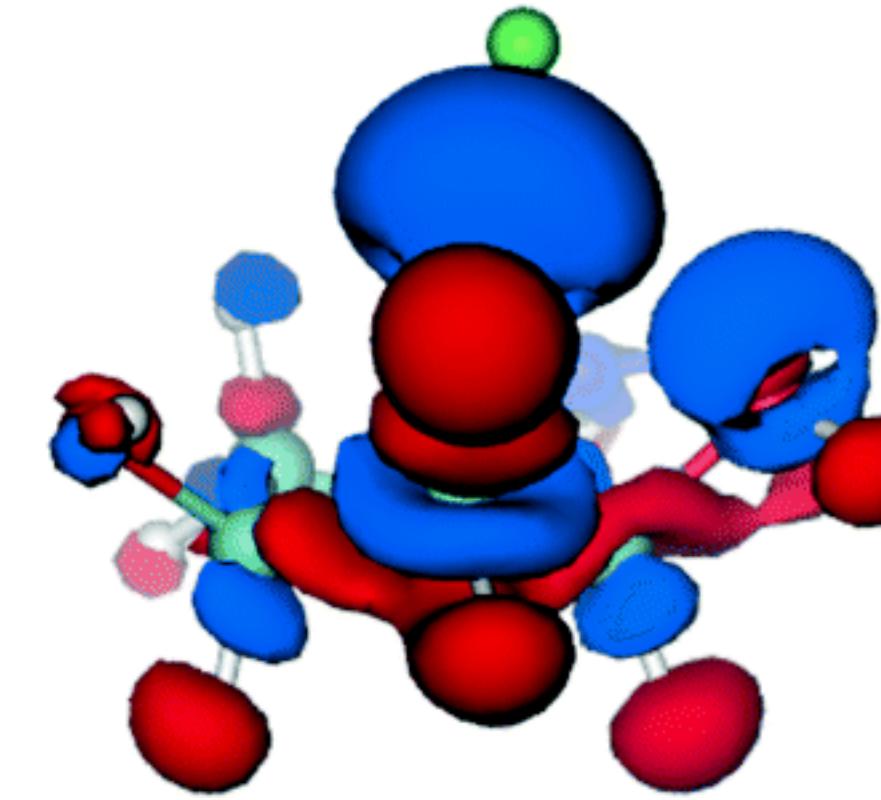


From the journal:

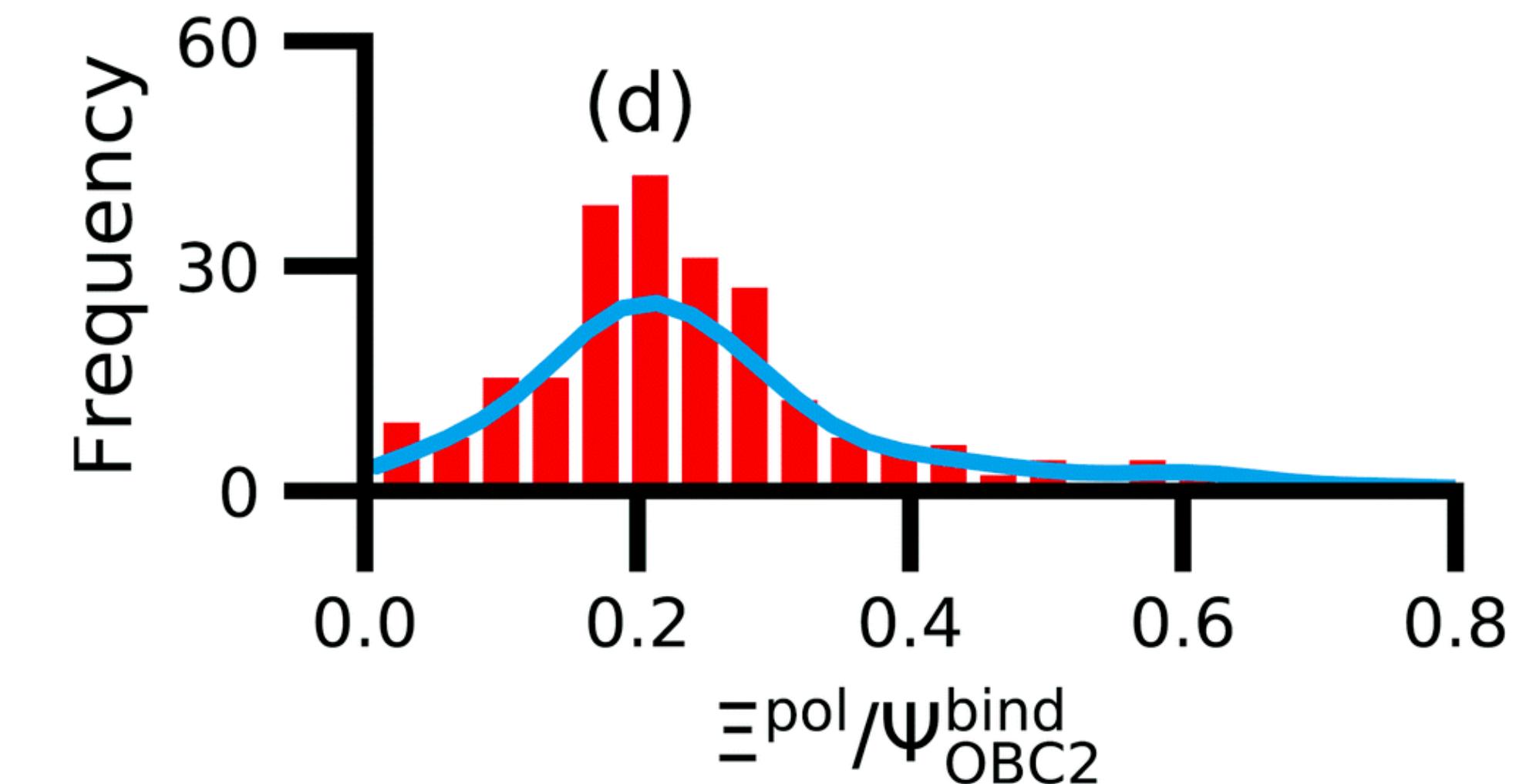
**Physical Chemistry Chemical Physics**

## On the polarization of ligands by proteins†

Soohaeng Yoo Willow,<sup>a</sup> Bing Xie,<sup>a</sup> Jason Lawrence,<sup>b</sup> Robert S. Eisenberg <sup>c</sup> and David D. L. Minh \*<sup>a</sup>



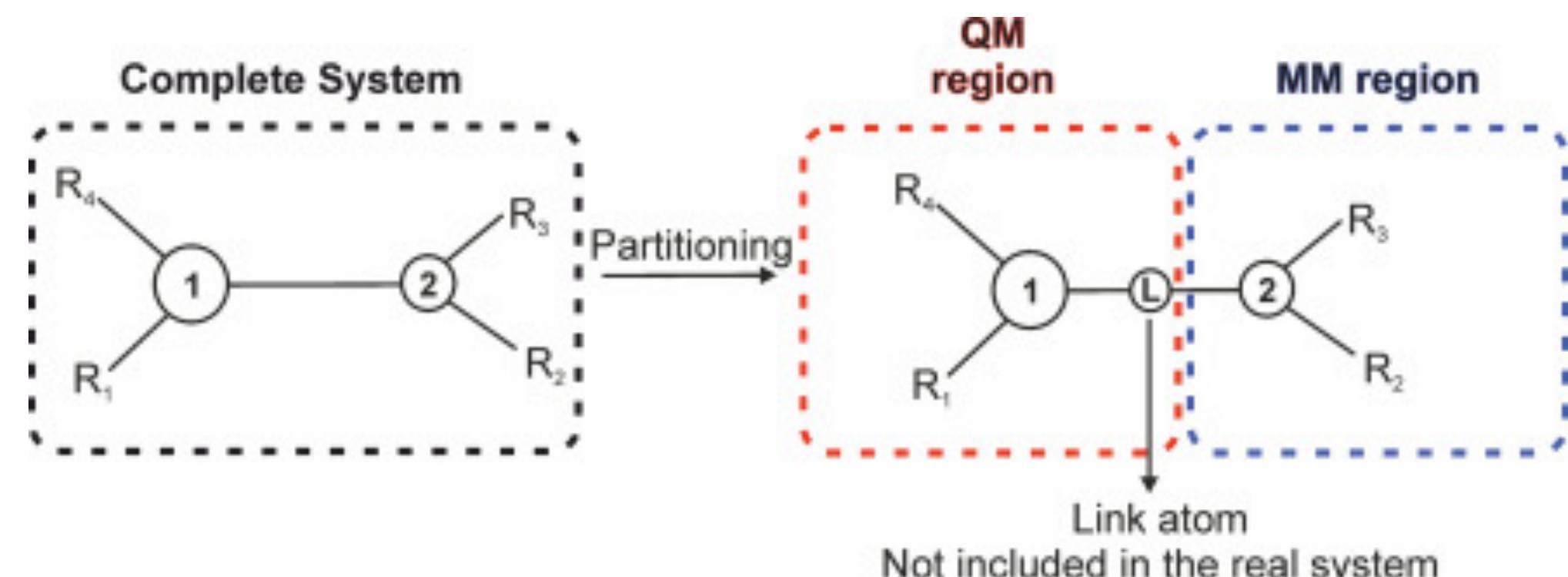
The difference in the electronic probability density is plotted. Blue and red contours illustrate the gain and loss of the electronic probability density due to the embedding field.



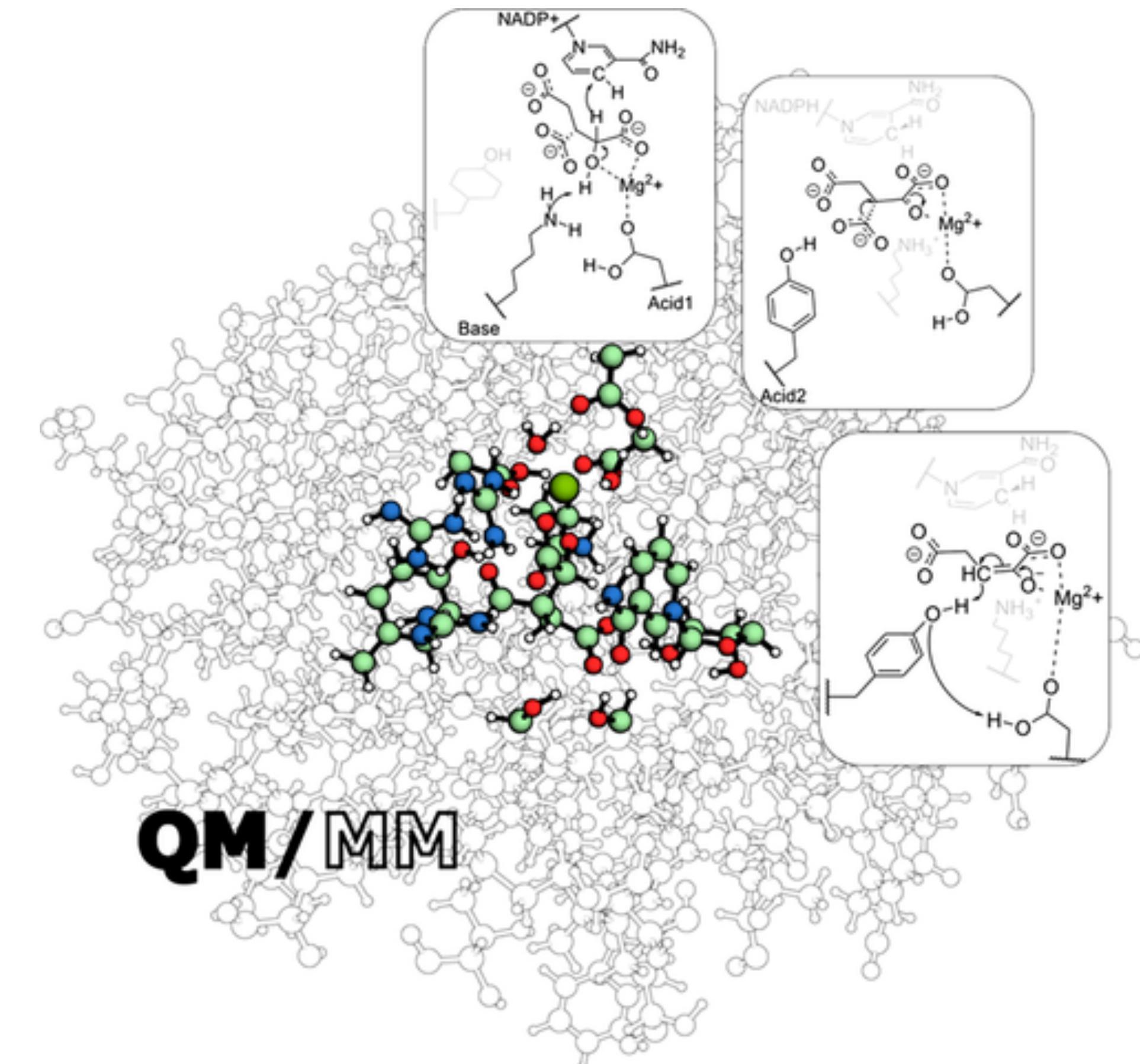
Polarization energy compared to binding energy for 286 complexes

# The Boundary

- The boundary between QM and MM regions should be
  - far away from the reactive center
  - not involve bond formation and bond breaking
- Bonds across regions can be capped (CA-CB -> CB-H), but complete molecules preferable



Navizet, I., 2020. QM/MM Study of Bioluminescent Systems. *Challenges and Advances in Computational Chemistry and Physics*, pp.227-270.



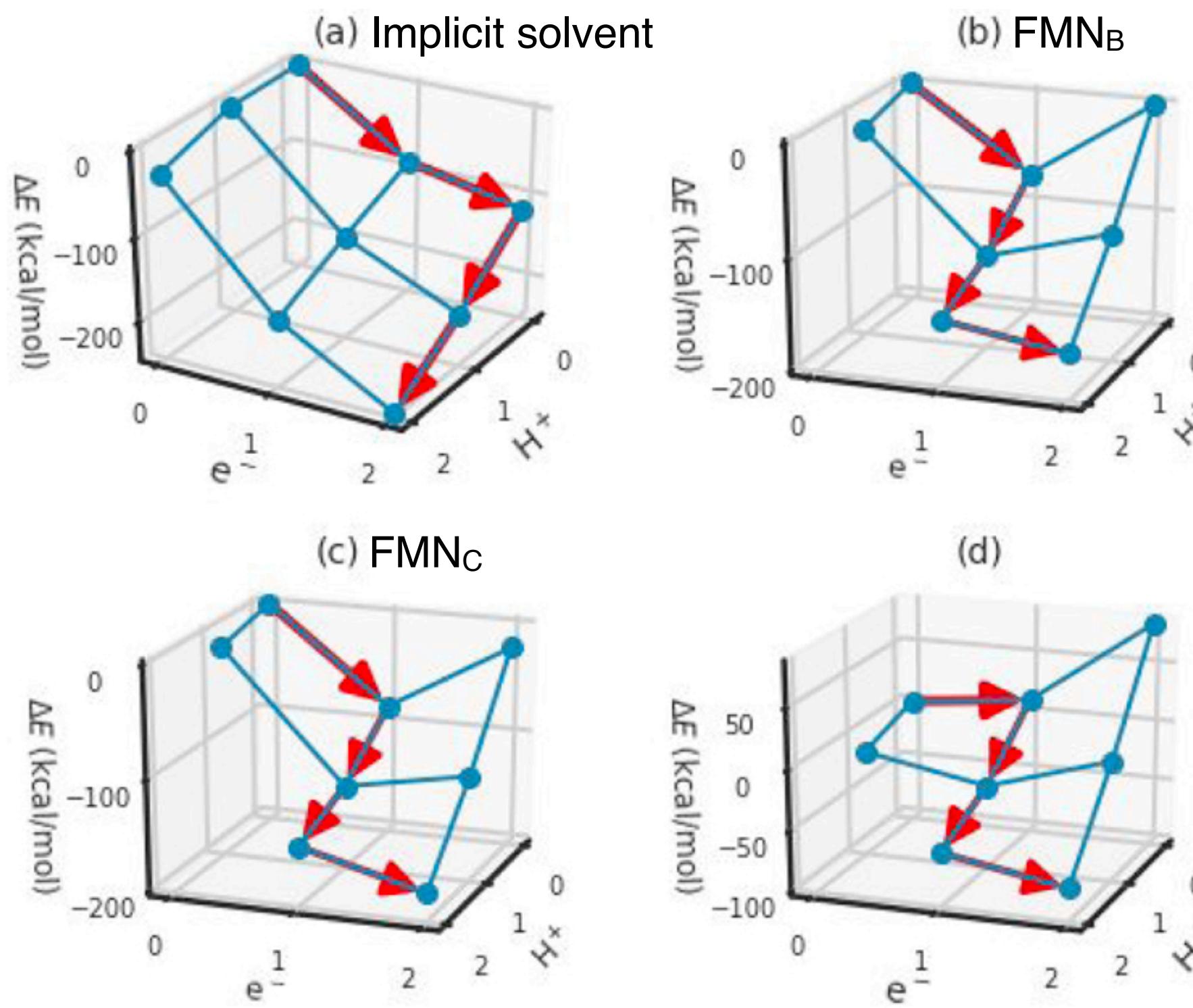
Sousa, S., Ribeiro, A., Neves, R., Brás, N., Cerqueira, N., Fernandes, P. and Ramos, M., 2016. Application of quantum mechanics/molecular mechanics methods in the study of enzymatic reaction mechanisms. *WIREs Computational Molecular Science*, 7(2).

RESEARCH ARTICLE

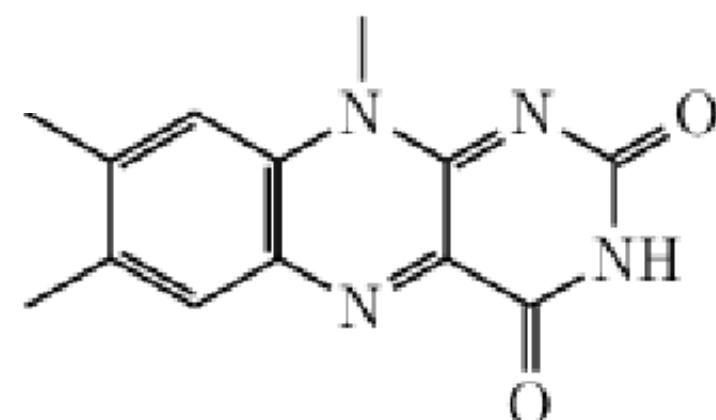
## Electrostatics and water occlusion regulate covalently-bound flavin mononucleotide cofactors of *Vibrio cholerae* respiratory complex NQR

Soohaeng Yoo Willow, Ming Yuan, Oscar Juárez ✉, David D. L. Minh ✉

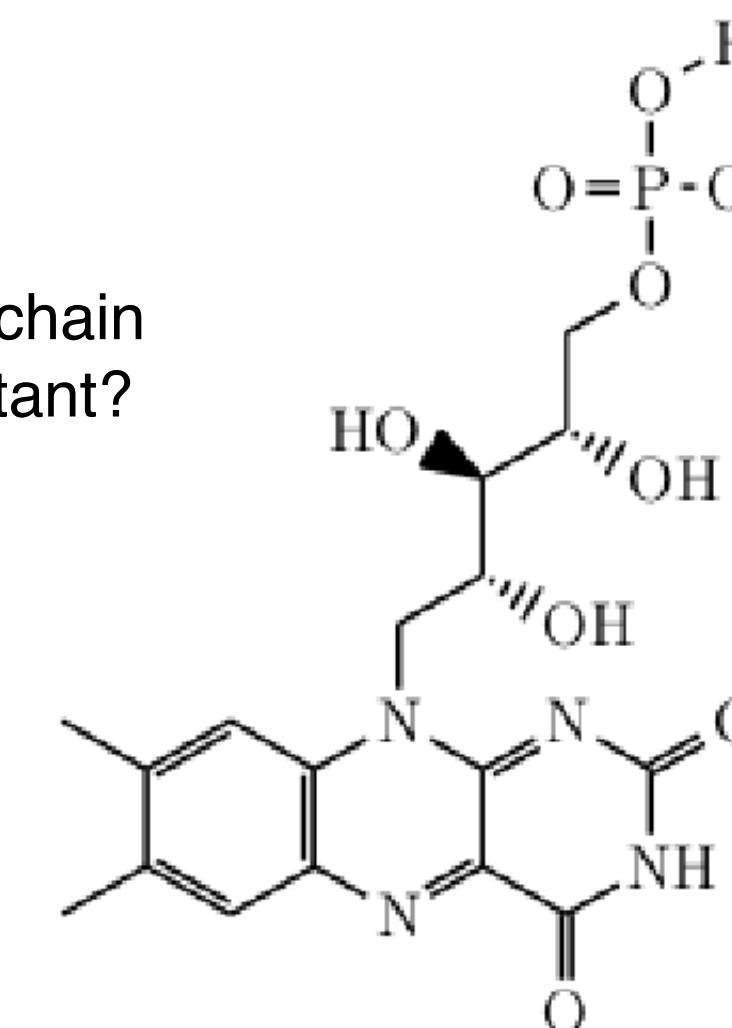
First published: 05 June 2021 | <https://doi.org/10.1002/prot.26158>



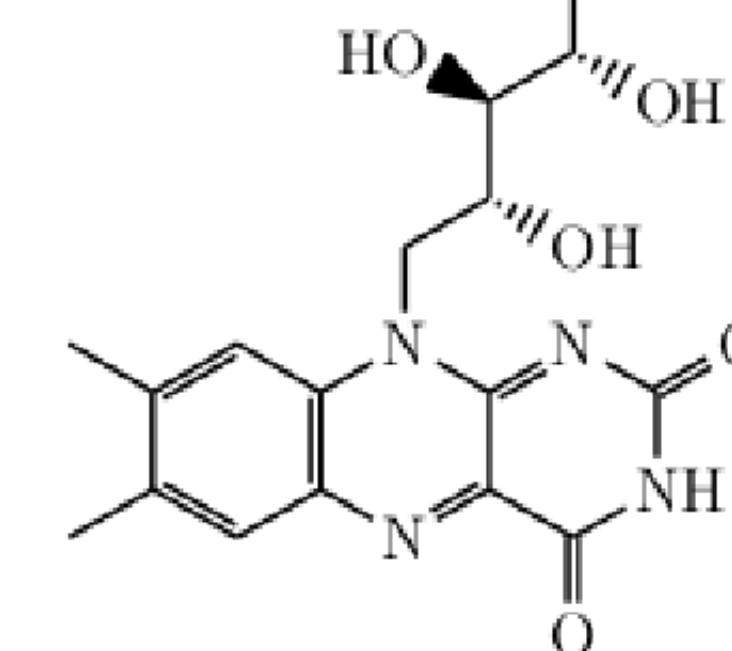
Is the chain important?



(a)

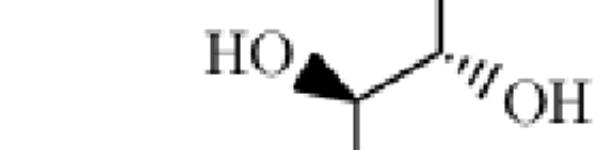
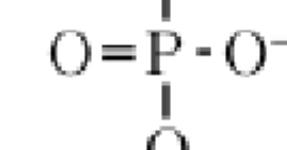
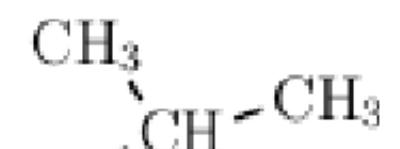


(b)



(c)

Is the covalent bond important?



**Figure S2. Flavin mononucleotide (FMN) structures used in the simulations.** a) truncated, b) native, and c) long chain FMN were used for the estimation of the effect of the chain length on the change in the potential energy as a function of the number of hydrogen atoms.

**Table S1. The potential energies of the  $\text{FMNH}_n$  molecules for two different environments. The energy values are provided in the Hartree atomic unit ( $E_h$ ). Molecular structures for truncated, native, and long chain FMN are provided in Figure S2.**

Environment	Gas			Embedded		
	Chain Length	Truncated	Native	Long	Truncated	Native
$E(n=0)$	-866.9991	-1888.0764	-2005.1989	-867.0538	-1888.1718	-2005.2906
$E(n=1) - E(n=0)$	-0.5934	-0.5913	-0.5913	-0.6284	-0.5738	-0.5738
$E(n=2)-E(n=0)$	-1.15821	-1.1698	-1.1696	-1.1831	-1.1561	-1.1557

# Review questions

- What is the difference between a QM calculation in gas versus in a region within a protein?
- Describe a way to handle a covalent bond between the QM and MM region of a QM/MM calculation.
- In a QM/MM calculation, how can we tell whether the QM region is large enough?