

# 11/18/2024

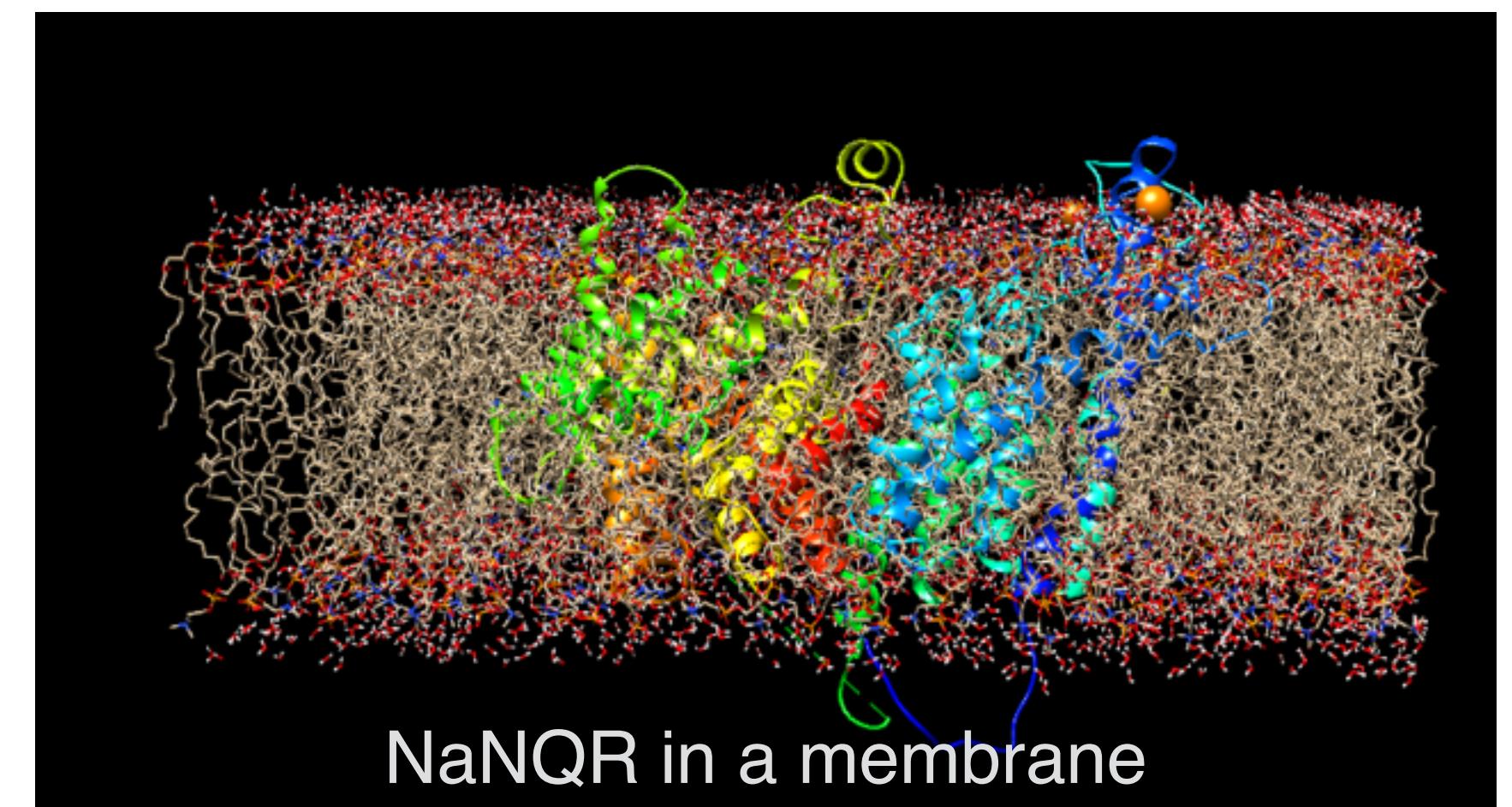
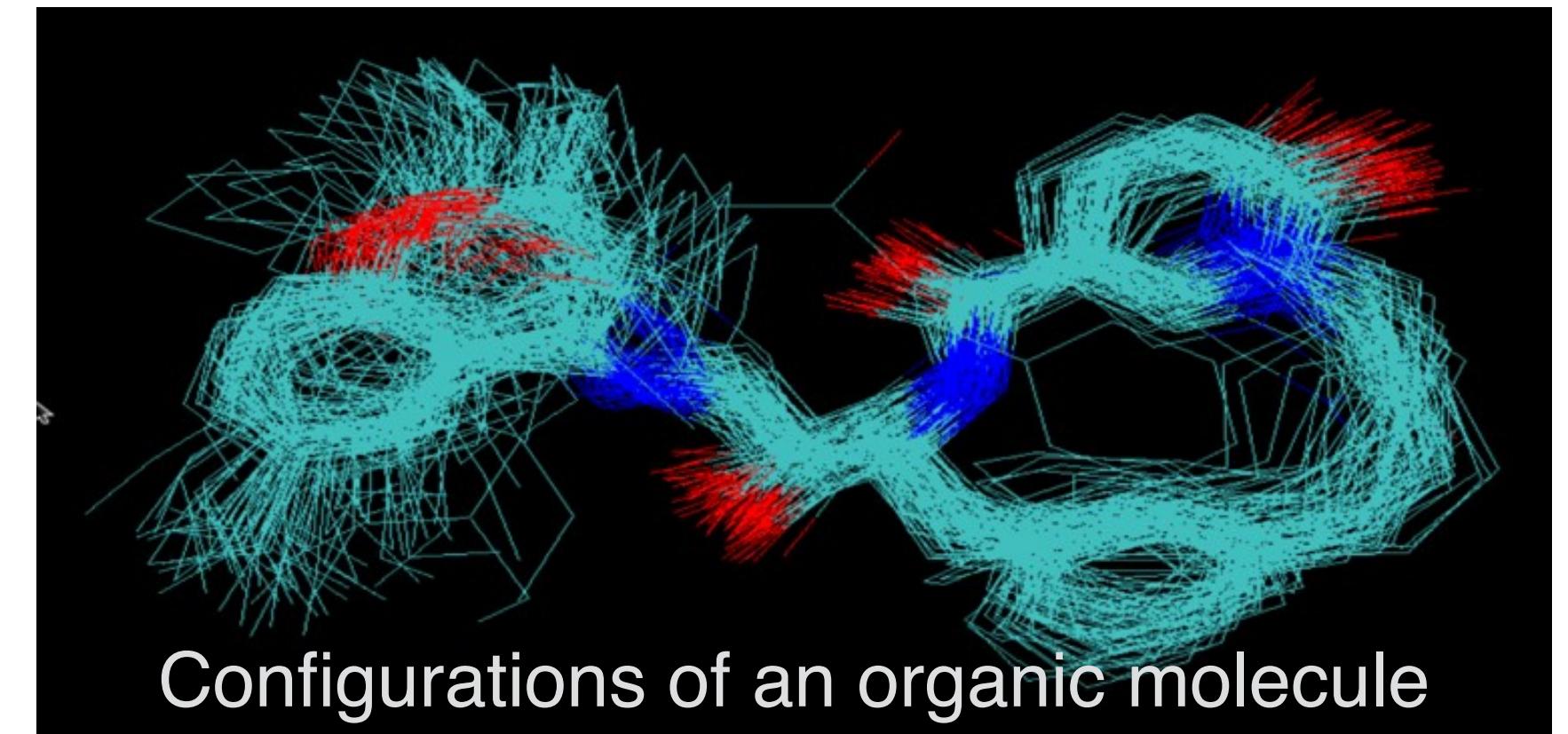
- Today's lecture is intended to help you achieve the following learning objective: Explain the concept of regions related to a QM/MM calculation. Compare and contrast QM/MM with molecular mechanics.
- Molecular Mechanics Force Fields
- Quantum Mechanics versus Molecular Mechanics
  - Differences between molecular mechanics and quantum mechanics?
- 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
- QM/MM exercise

# **Molecular Mechanics Force Fields**

# What are molecular mechanics force fields?

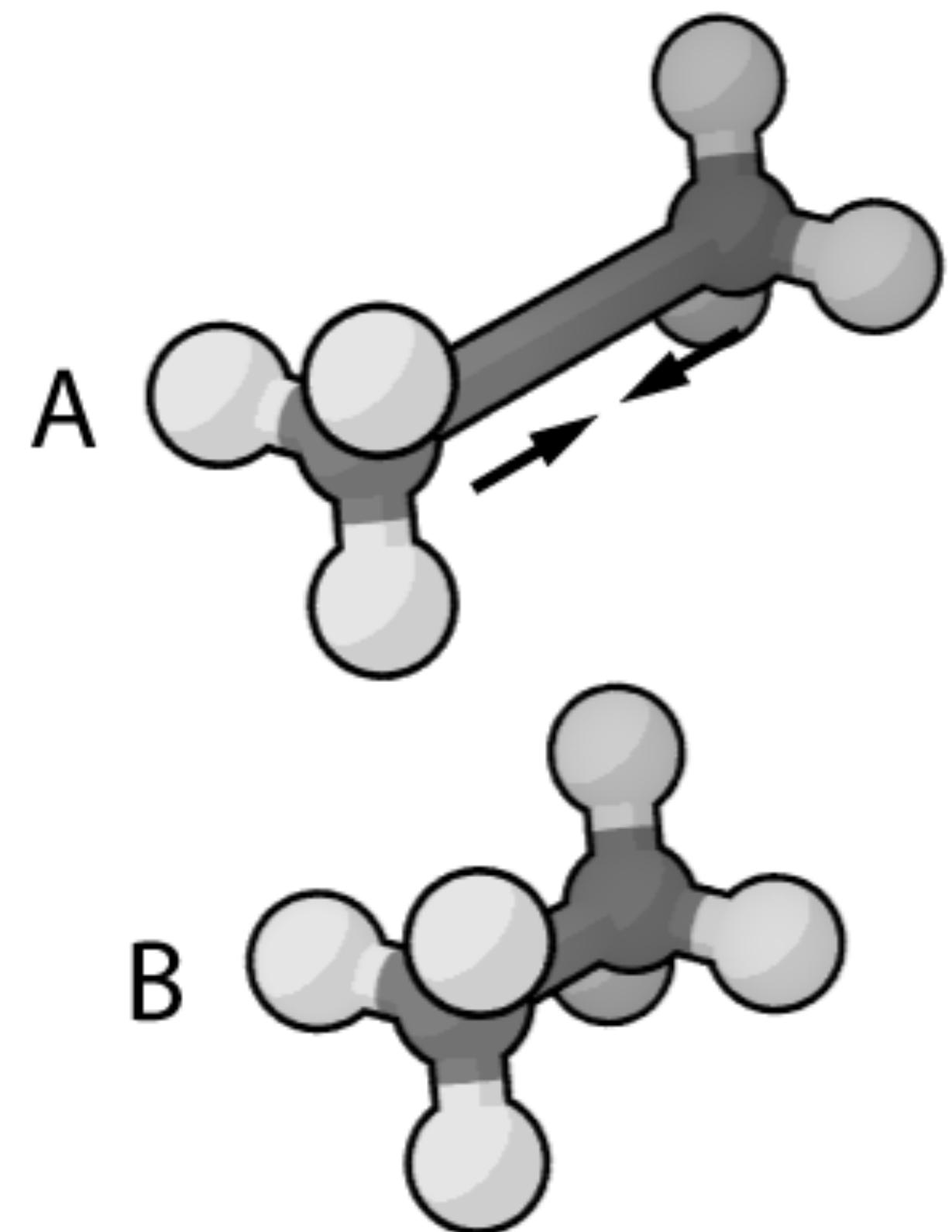
- **E(x)** - an equation describing the energy of a configuration of particles
- Input: positions of particles in a system
  - particles are usually atoms, but can be
    - collections of atoms (e.g. amino acid) in coarse-grained force fields
    - electrons pairs in a Drude oscillator model
- Output: potential energy

Some systems described by molecular mechanics

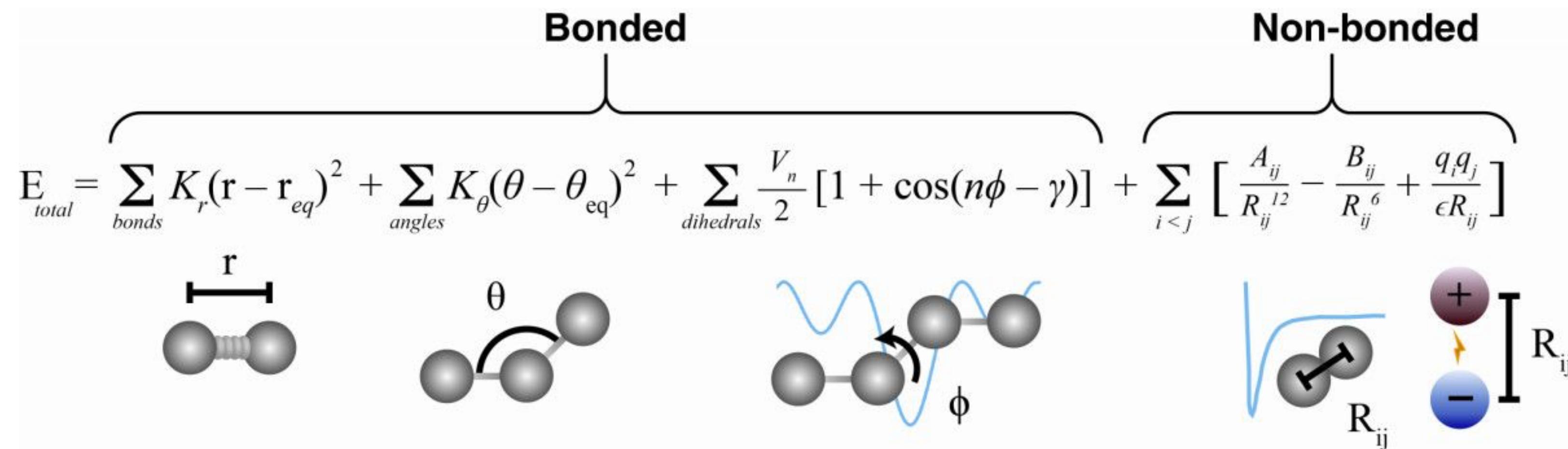


# How are they useful?

- Energy optimization provides reasonable structures
  - Helpful for building models that fit to experiment.
  - AMBER (Assisted Model Building with Energy Refinement) is a popular force field.
- Basis for many scoring functions in molecular docking.
- Gradients are helpful for optimization and to calculate forces in molecular dynamics simulations
- According to the Boltzmann distribution, energies specify probabilities,  $p(x) \propto e^{-\beta E(x)}$ .



# What are they made of?



From Figure 3 of  
Durant and McCammon, 2011

The potential energy of a system can be divided into those caused by interactions between atoms that are chemically bonded to one another and those caused by interactions between atoms that are not bonded. Chemical bonds and atomic angles are modeled using simple springs, and dihedral angles (that is, rotations about a bond) are modeled using a sinusoidal function that approximates the energy differences between eclipsed and staggered conformations. Non-bonded forces arise due to van der Waals interactions, modeled using the Lennard-Jones potential, and charged (electrostatic) interactions, modeled using Coulomb's law.

Taken from Figure 3 of Durrant & McCammon, 2011.

# Bonded Interactions

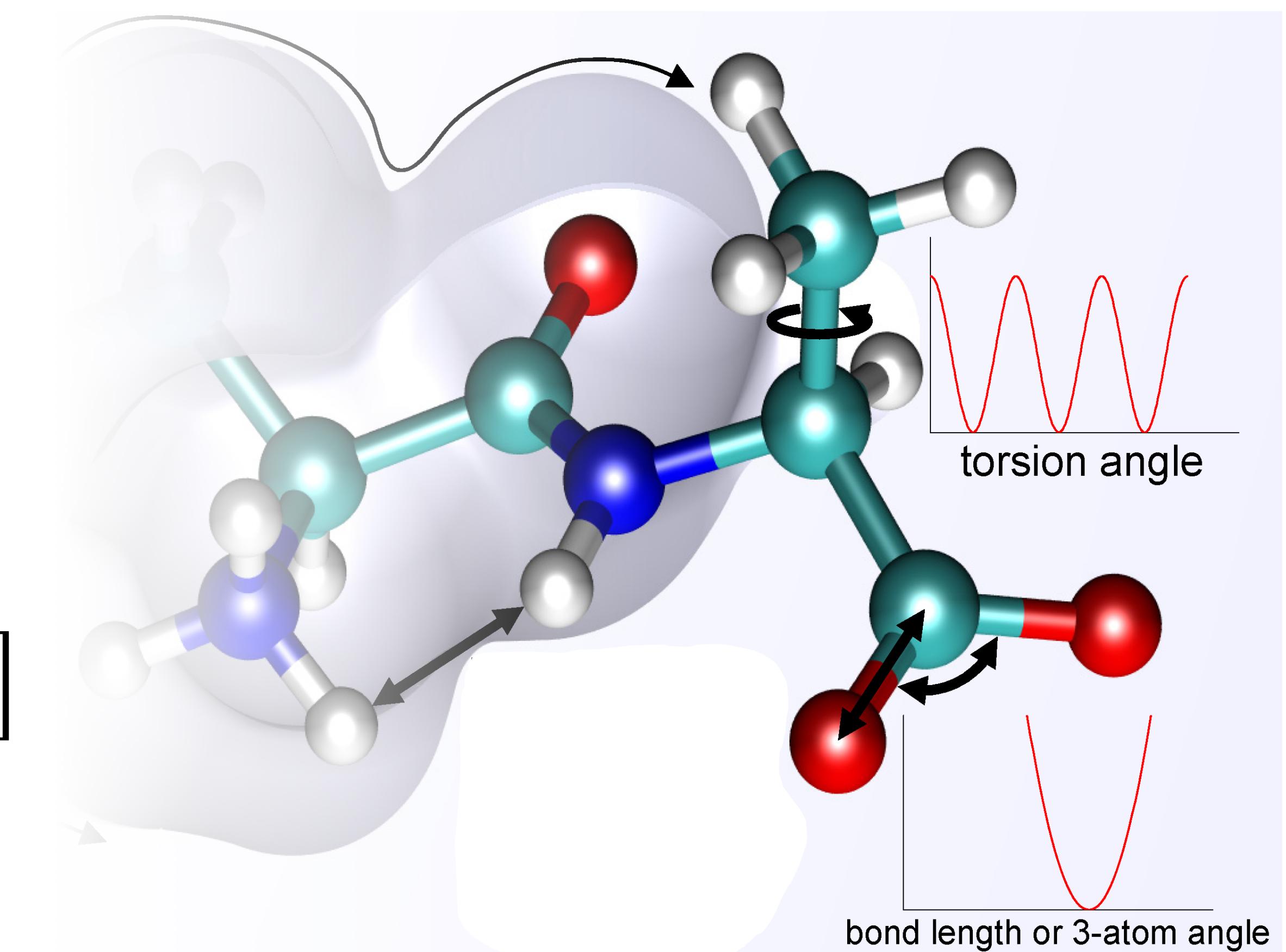
are between atoms that are covalently linked by three or fewer bonds

$$E_{bonds} = \sum_i^{Bonds} \frac{k_i}{2} (x_i - x_{i,o})^2$$

$$E_{angles} = \sum_i^{Angles} \frac{k_i}{2} (\omega_i - \omega_{i,o})^2$$

$$E_{torsions} = \sum_i^{Torsions} \frac{V_i}{2} [1 + \cos(n_i\phi_i - \gamma_i)]$$

$$E_{bonded} = E_{bonds} + E_{angles} + E_{torsions}$$



# Nonbonded Interactions

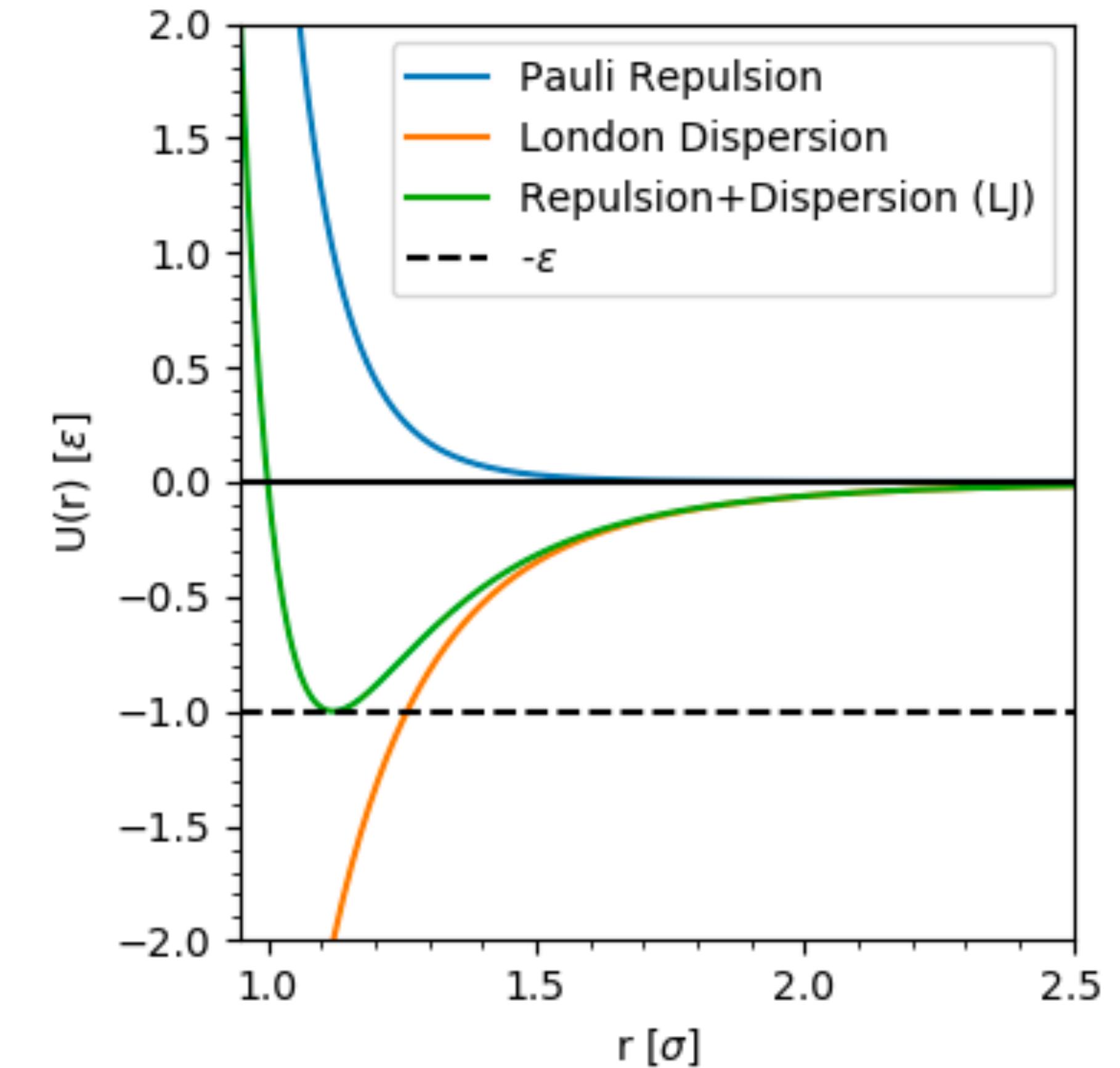
are between atoms that are not covalently linked or linked by more than three bonds

$$E_{Coloumbic} = \sum_{i,j}^{Atoms \ with \ i < j} \frac{q_i q_j}{\epsilon R_{i,j}}$$

$$E_{Lennard-Jones} = \sum_{i,j}^{Atoms \ with \ i < j} \frac{A_{i,j}}{R_{i,j}^{12}} - \frac{B_{i,j}}{R_{i,j}^6}$$

based on  $4\epsilon \left[ \left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 \right]$

$$E_{Non-Bonded} = E_{Coloumbic} + E_{Lennard-Jones}$$



# Where do parameters come from?

- QM + experiment
- AMBER (as discussed in Tian 2020)
  - “we also included in ff14SB a small empirical adjustment to ff99SB (using TIP3P water) to improve agreement with NMR data for short alanine peptides”
  - Quantum chemistry data in implicit solvent (opposed to gas)
- OpenFF 2.0.0 (<https://openforcefield.org/force-fields/force-fields/>)
  - A select set of the vdW parameters were trained against a set of experimental mass density and enthalpy of mixing measurements sourced from the NIST ThermoML archive.
  - A select set of the bond length, bond force constant, equilibrium angle, angle force constant and torsion barrier height parameters were trained against a set of QC computed optimized geometries and torsion profiles, whereby the output force field of the first step was used as the starting point.

# **Molecular Mechanics versus Quantum Mechanics**

# 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

# Property

MM	QM
	X
X	
X	
	X
	X
X	
	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.

<https://www.nobelprize.org/uploads/2018/06/popular-chemistryprize2013.pdf>

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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**Michael Levitt**

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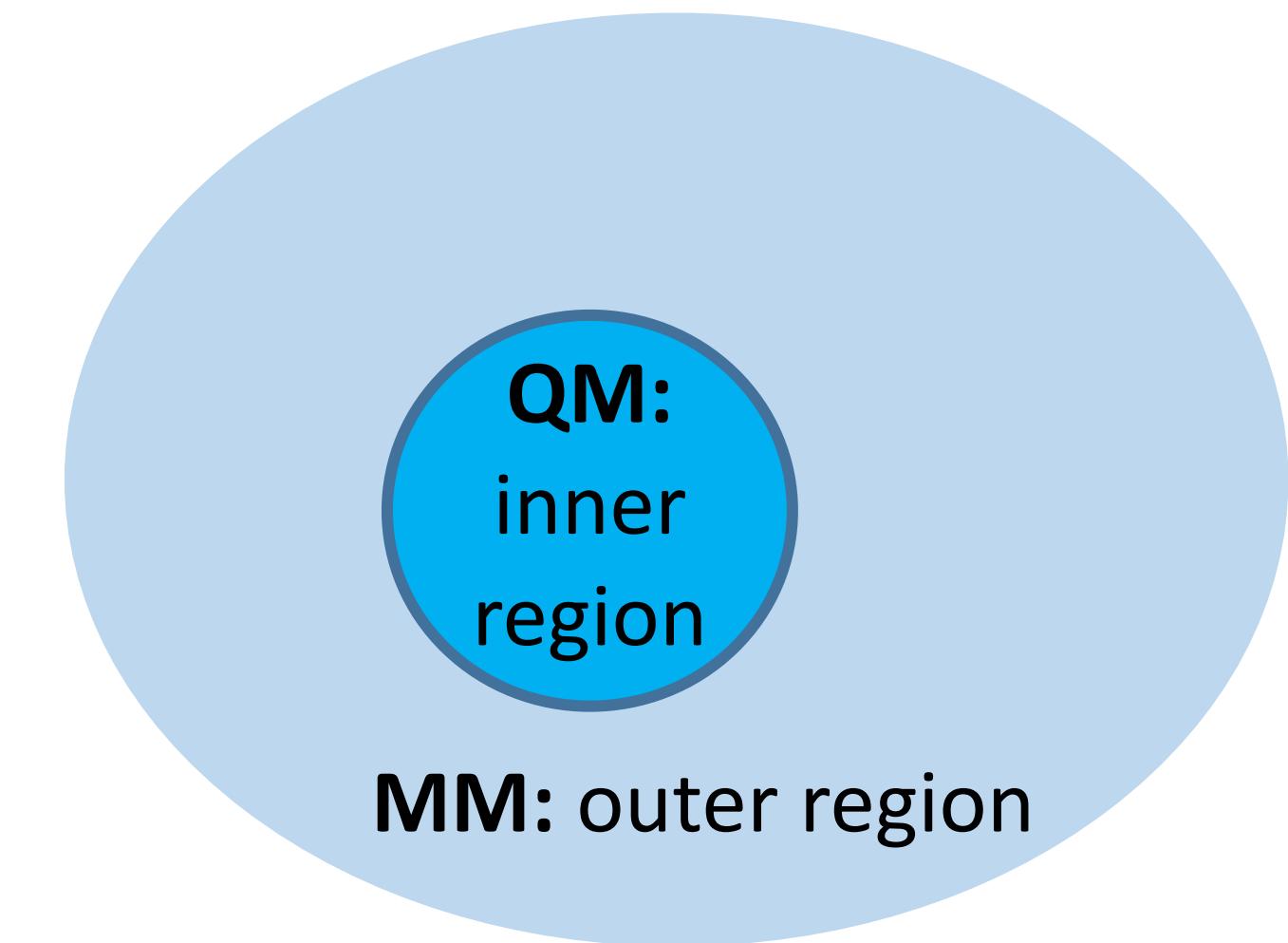
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**Arieh Warshel**

Prize share: 1/3

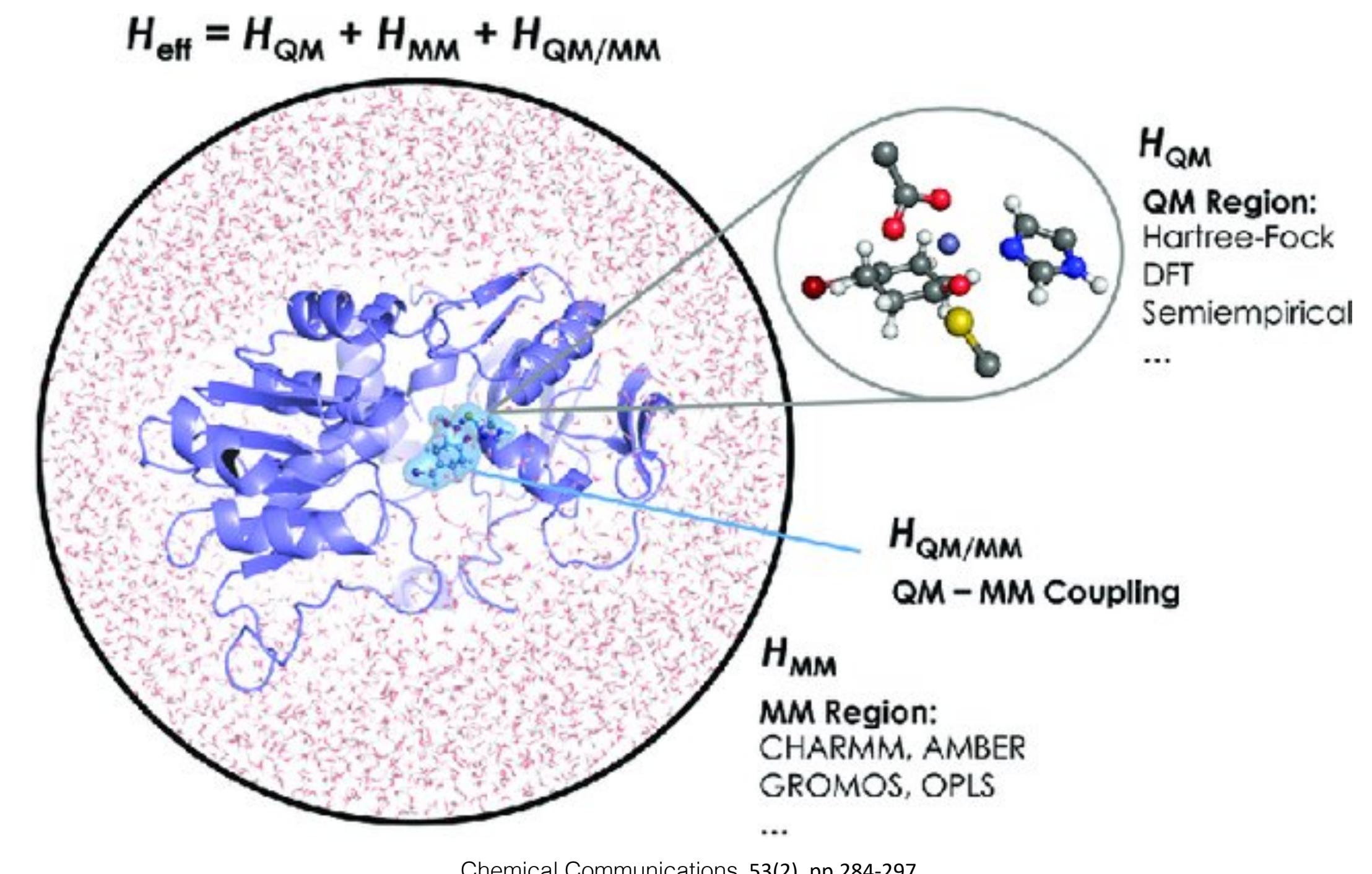
# Overcoming Limitations

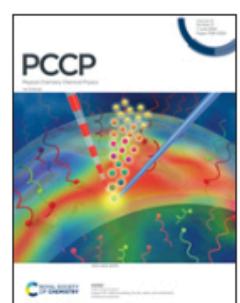
- QM is accurate but too slow for more than a few hundred atoms, even with modern supercomputers
- MM does not model
  - chemical reactions
  - electronic processes such as charge transfer / electronic excitation
- The QM/MM compromise
  - QM within a chemically active region
  - MM for the surroundings



# 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



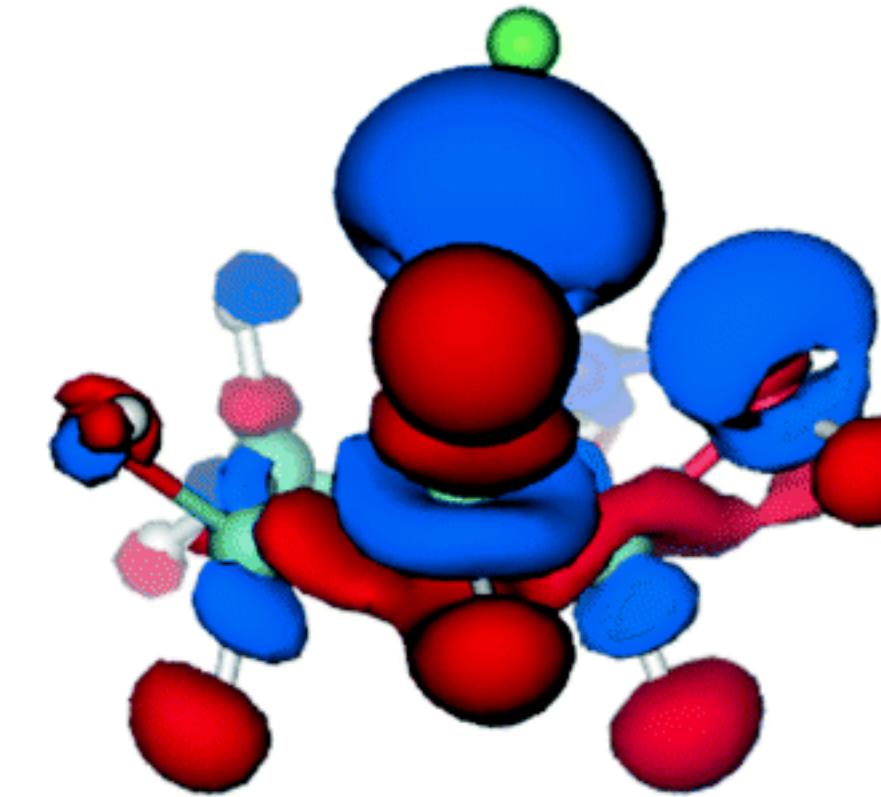


From the journal:

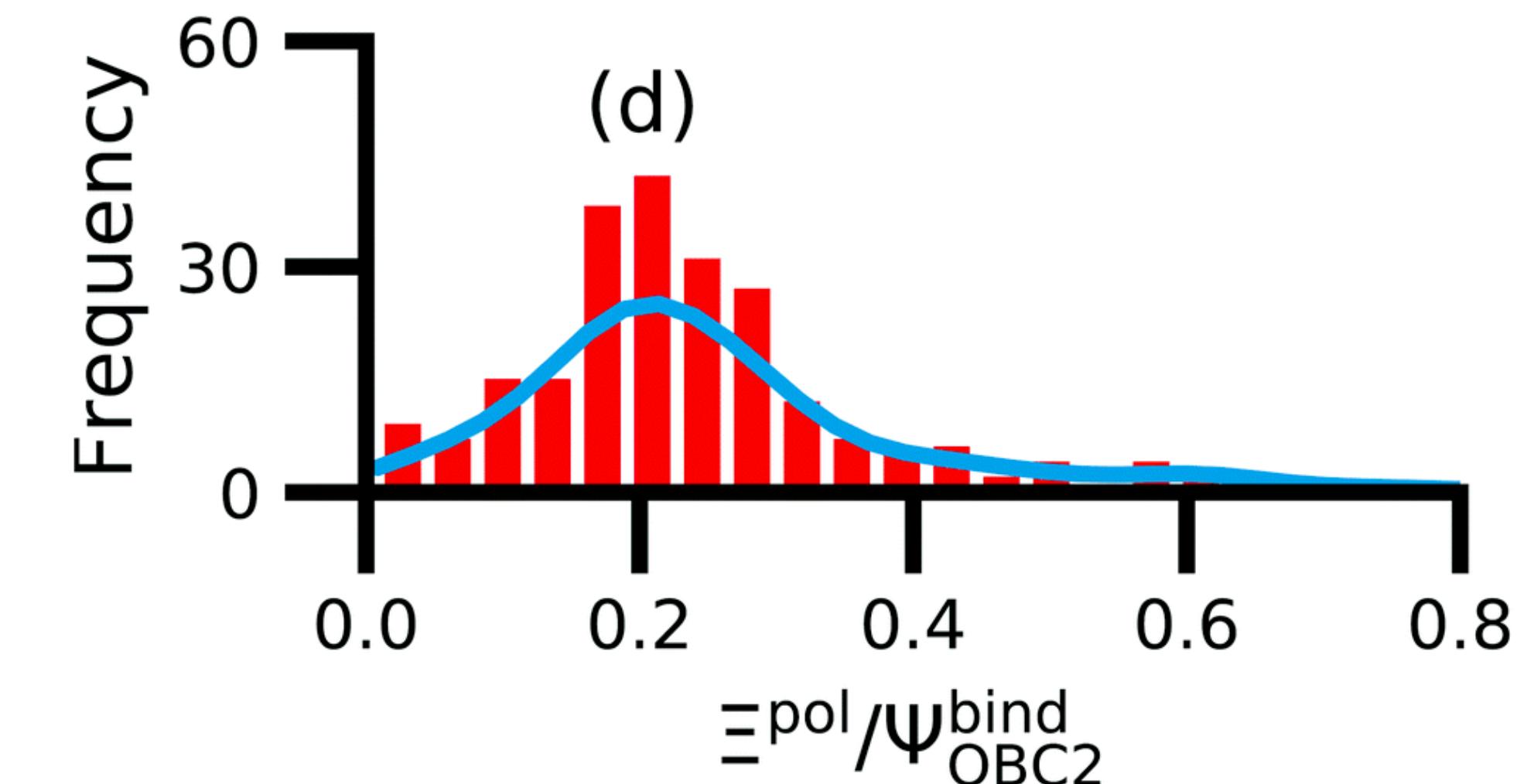
**Physical Chemistry Chemical Physics**

## 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>



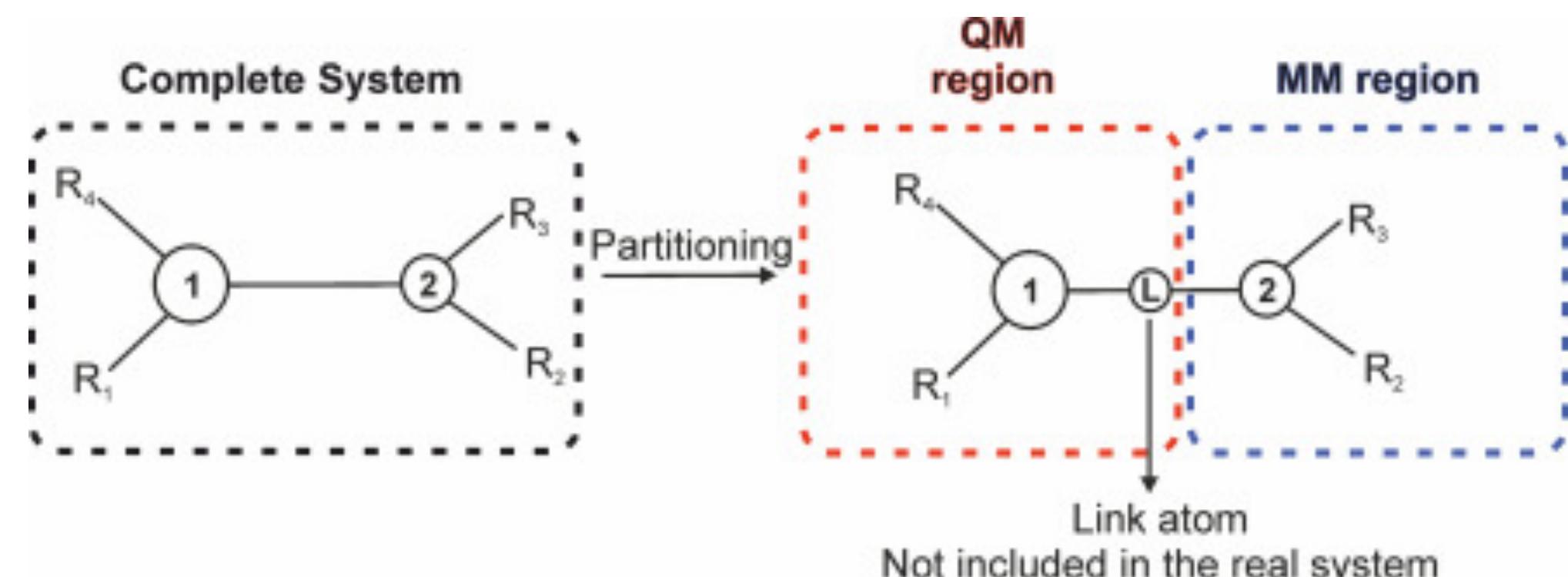
The difference in the electronic probability density is plotted. Blue and red contours illustrate the gain and loss of the electronic probability density due to the embedding field.



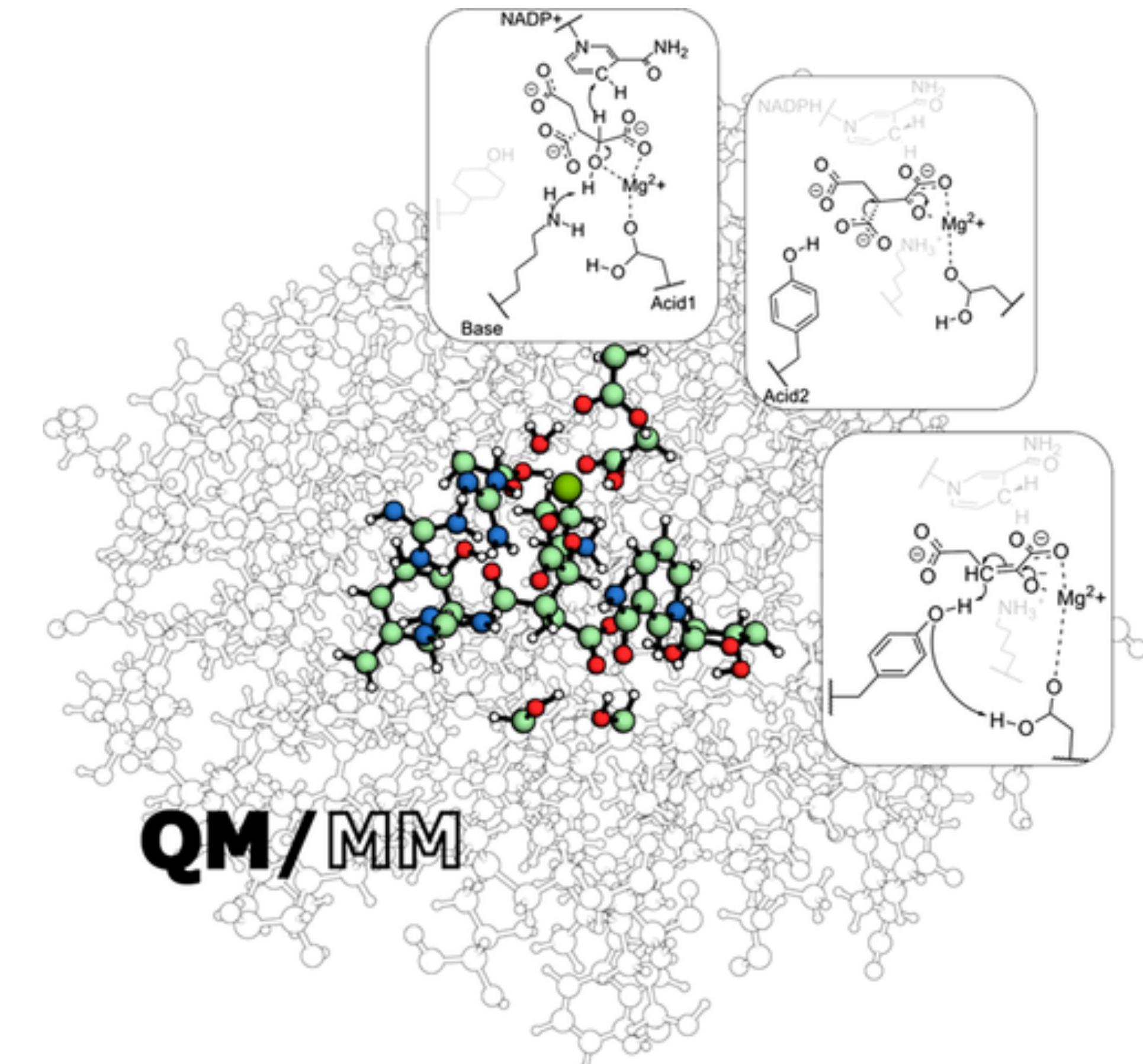
Polarization energy compared to binding energy for 286 complexes

# 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.



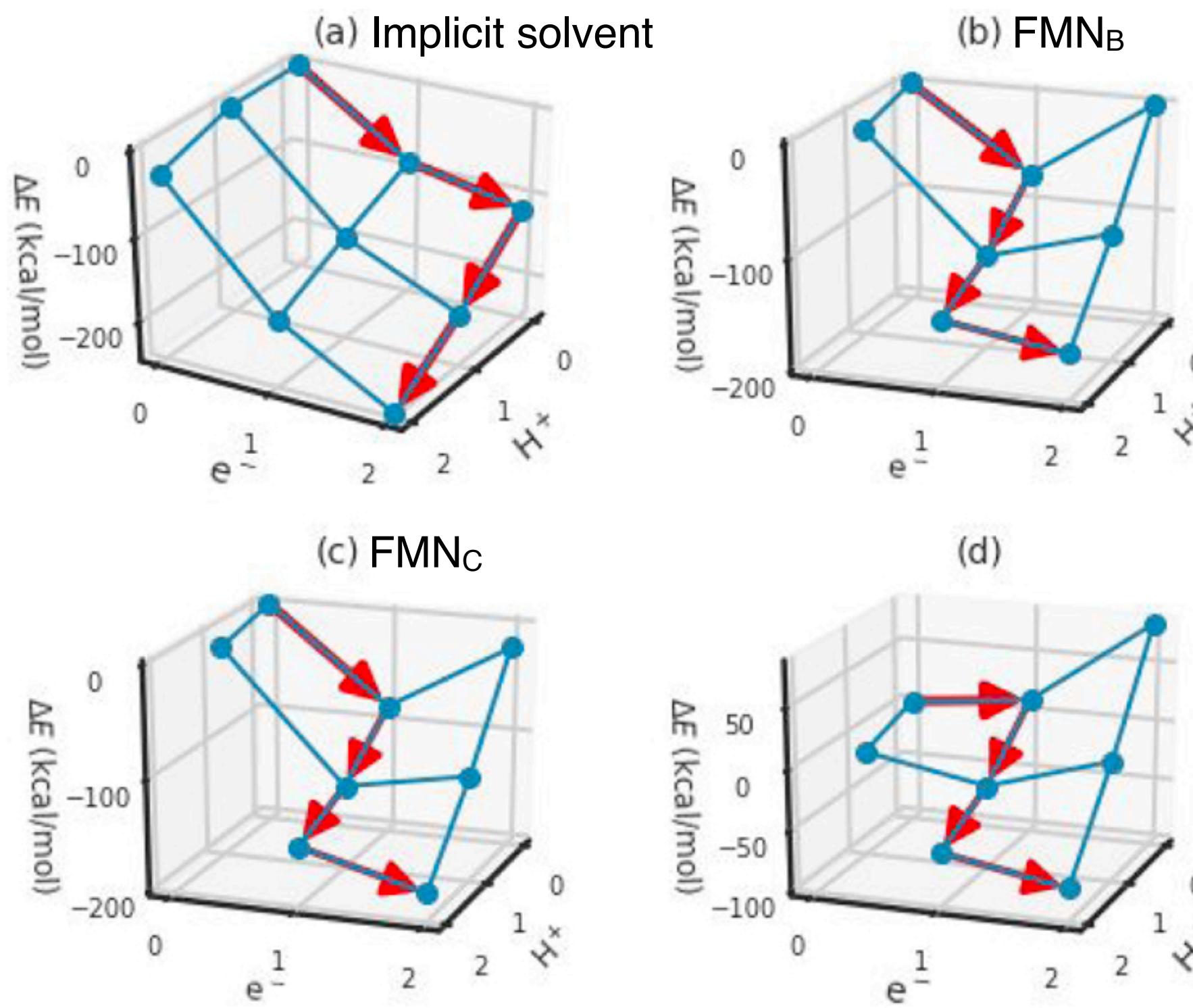
Sousa, S., Ribeiro, A., Neves, R., Brás, N., Cerqueira, N., Fernandes, P. and Ramos, M., 2016. Application of quantum mechanics/molecular mechanics methods in the study of enzymatic reaction mechanisms. *WIREs Computational Molecular Science*, 7(2).

RESEARCH ARTICLE

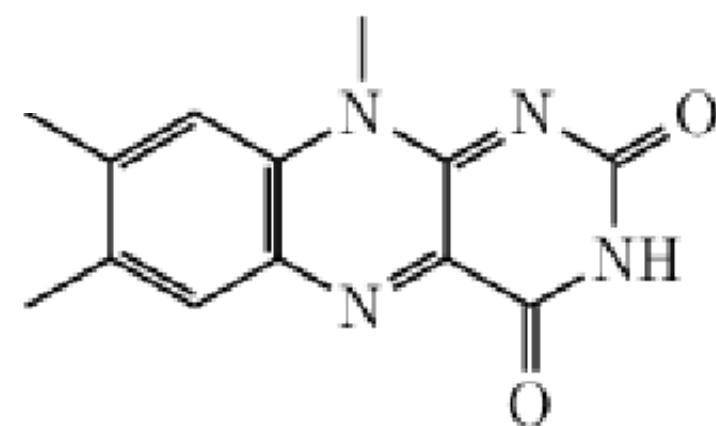
## Electrostatics and water occlusion regulate covalently-bound flavin mononucleotide cofactors of *Vibrio cholerae* respiratory complex NQR

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

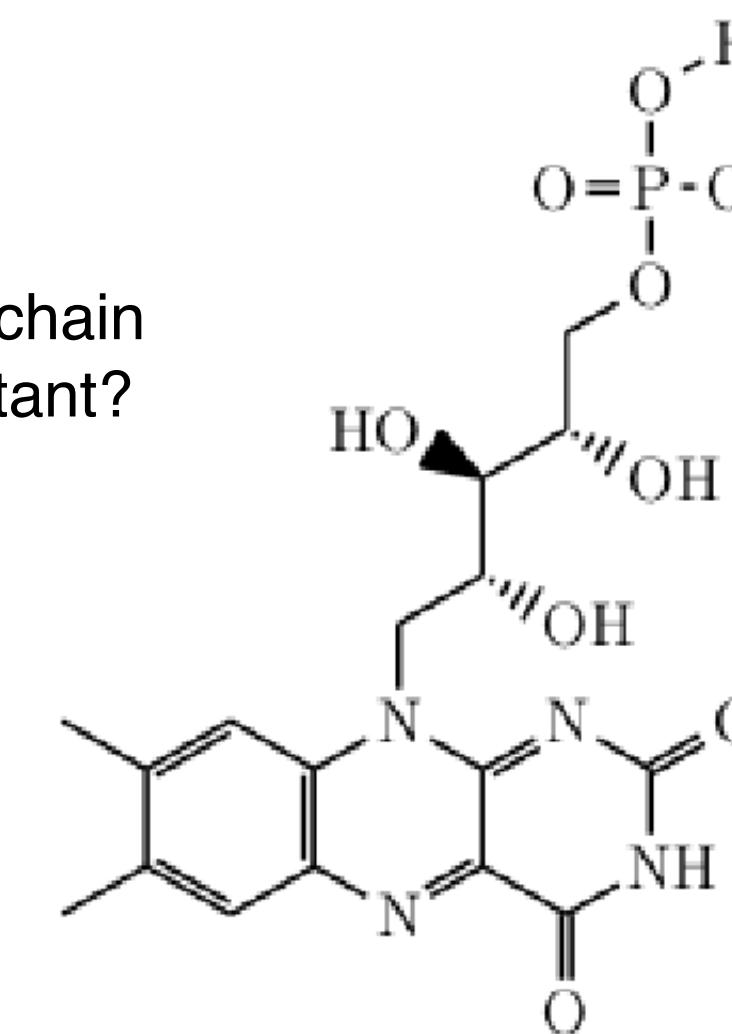
First published: 05 June 2021 | <https://doi.org/10.1002/prot.26158>



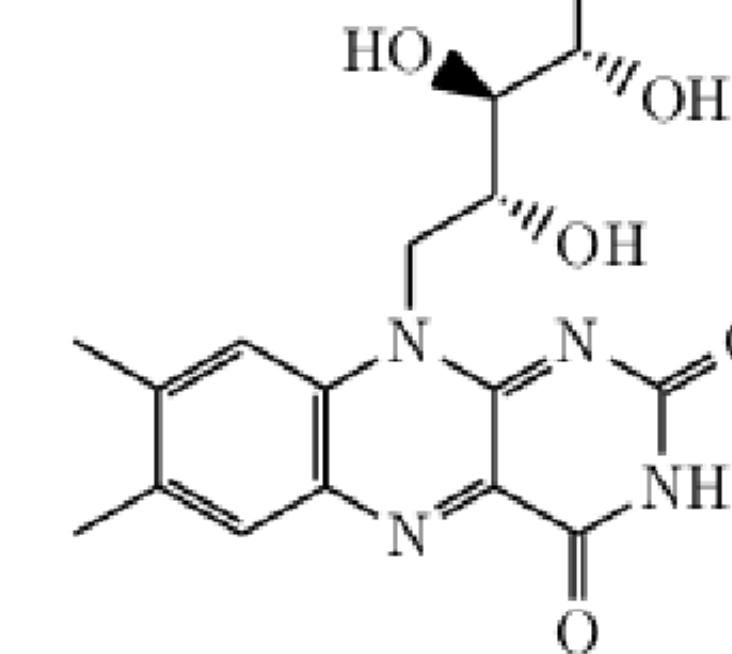
Is the chain important?



(a)

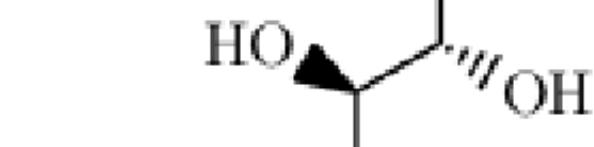
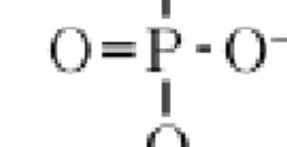
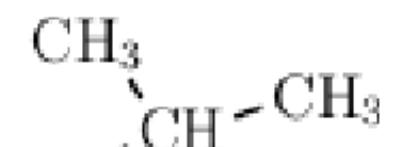


(b)



(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?