Molecular mechanics and its integration to Quantum mechanics (QM/MM)

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The need for molecular mechanics

- **For very large systems**, as in biochemical applications, it is **not computationally practicable to use solely quantum mechanical approaches** as such systems would contain enormous basis sets and would consume large chunks of computer time and memory.
• When huge biological systems like nucleic acids and the reactions they undergo are analyzed, often a mixture of quantum mechanics and molecular mechanics is employed.

• Molecular mechanics uses potential functions from classical mechanics to compute the potential energy for a specified arrangement of atoms.
What is molecular mechanics?

- In molecular mechanics (MM), the electrons in the system under study are not considered explicitly but rather each atom (the atomic nucleus and the associated electrons of the atom) is treated as a single particle.
- Therefore MM is not very useful for analyzing chemical problems where electronic effects are critical.
• **MM method** uses a model of a molecule as composed of atoms held together by bonds.

• Using **parameters like bond-stretching and bond-bending force constants**, and allowing for interactions between **non-bonded atoms**, the method constructs **a potential-energy expression** that is a function of the atomic positions.
A typical molecular mechanics potential energy expression looks like below.

\[ E = E_{str} + E_{bend} + E_{tor} + E_{nb} \]

\[ E = \text{Total potential energy} \]

\[ E_{str} = \text{Potential due to bond stretching} \]

\[ E_{bend} = \text{Potential due to bond bending} \]

\[ E_{tor} = \text{Potential due to bond twisting (torsion)} \]

\[ E_{nb} = \text{Potential due to interaction between non-bonded atoms} \]
Typical expressions for the potential energy terms are:

\[ E_{\text{str}} = \sum \frac{1}{2} k_b (r - r_0)^2 \]

\[ E_{\text{bend}} = \sum \frac{1}{2} k_\theta (\theta - \theta_0)^2 \]

\[ E_{\text{tor}} = \sum A \{1 + \cos(n\tau - \phi)\} \]

\[ E_{\text{nb}} = \sum_{i>j} \left\{ -\frac{C_{ij}}{r_{ij}^6} + \frac{D_{ij}}{r_{ij}^{12}} + \frac{q_i q_j \phi_0}{\varepsilon r_{ij}} \right\} \]

\[ k_b = \text{empirical force constant} \]
\[ r_0 = \text{equilibrium bond length} \]
\[ k_\theta = \text{force constant for the angular spring} \]
\[ \theta_0 = \text{equilibrium angle} \]
The force on an atom due to the interaction potential ($E_{nb}$) is found by taking the first derivative of $E_{nb}$.

If the interaction potential is Lennard-Jones potential

$$E_{nb} = 4\varepsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right]$$

The force is given by

$$F_{LJ} = \frac{\partial E_{nb}(r)}{\partial r} = -24\varepsilon \left[ 2 \left( \frac{\sigma^{12}}{r^{13}} \right) + \left( \frac{\sigma^6}{r^7} \right) \right]$$

Accelerations and related velocities are calculated using Newton’s laws of motion.
By minimizing the potential energy expression for various atomic arrangements, the MM method predicts equilibrium geometries and relative energies.

The specific set equations and the related parameters that describe the potential energy of the system are collectively known as a force field.

Some common force fields for studies of proteins and nucleic acids are AMBER and CHARMM.
• Calculations using MM take significantly less computer time than QM methods.

• However MM methods alone do not provide descriptions in terms of electrons or orbitals.

• **Why not treat certain parts of the system accurately** (that is, quantum mechanically) while **treating other parts of the system with much faster methods of lower accuracy**? That is where **QM/MM** comes in.
• The QM/MM procedure is applicable when the system can be partitioned into two regions.

• One region (the ‘active site’) requires an accurate QM calculation of its potential.

• The second region (the rest of the system) acts as a perturbation on the active site and can be treated with an approximate and fast MM calculation of its potential.
By using a quantum mechanical calculation, bond-breaking and bond-forming can be treated at the active site yet still take into account the role of the surrounding atoms using MM.
General mechanism of QM/MM

- Conformation of the atoms in the active site (QM subsystem) is fixed and the MM calculation is performed on the MM subsystem.
- In this MM calculation, the effects of the QM subsystem on the MM subsystem potential are taken into account by treating the QM atoms as fixed MM atoms.
- Then the QM method is applied to the active site (e.g., an SCF calculation) which takes into account the potential energy of the MM subsystem as well.
- From the QM calculation, a preferred (lower energy) geometry of the QM subsystem is located.
- With this new active site conformation, the entire process is repeated until the geometry of all the atoms in the system is converged.
Total energy of a QM/MM system

- The total energy $E_{TOT}$ for the QM/MM system can be written:

$$E_{TOT} = E_{QM} + E_{MM} + E_{QM/MM}$$

- **EQM**: Energy of those parts of the system treated exclusively with QM
- **EMM**: Energy of the purely molecular mechanical parts of the system
- **EQM/MM**: Energy of interaction between the QM and MM parts of the system.
The Hamiltonian of a QM/MM system

\[ H_{QM/MM} = -\sum_i \sum_M \frac{q_M}{r_{i,M}} + \sum_\alpha \sum_M \frac{Z_\alpha q_M}{R_{\alpha,M}} + \sum_\alpha \sum_M \left( \frac{A_{\alpha,M}}{R_{\alpha,M}^{12}} - \frac{C_{\alpha,M}}{R_{\alpha,M}^6} \right) \]

1. Electrostatic interactions between the electrons of the QM region and the MM nuclei
2. Electrostatic interactions between QM and MM nuclei
3. Van der Walls interactions between QM and MM atoms

\( i = \text{QM electron} \quad \alpha = \text{QM nucleus} \quad M = \text{MM nucleus} \quad q_M = \text{partial atomic charge of } M \)
**Ways of integrating QM and MM**

- **IMOMM (integrated molecular orbital plus molecular mechanics) method**

\[
E_{\text{IMOMM}} = E_{\text{real, low}} + \left[ E_{\text{model, high}} - E_{\text{model, low}} \right]
\]

- **\(E_{\text{real, low}}\)** - Energy of the real system calculated using low-level MM calculations
- **\(E_{\text{model, high}}\)** - Energy of the smaller model system calculated using high-level QM calculations
- **\(E_{\text{model, low}}\)** - Energy of the smaller model system calculated using low-level MM calculations.
\[ E_{IMOMM} = E_{(real,low)} + \left[ E_{(model,high)} - E_{(model,low)} \right] \]

The quantity in the brackets gives an estimate of \( E_{(real,high)} - E_{(real,low)} \) so that \( E_{IMOMO} \) is an approximation to \( E_{(real,high)} \).

The high level might be MP2, MP4, CCSD(T), CASSCF, and so on.
ONIOM (our Own N-layered Integrated molecular Orbital + molecular Mechanics)

- The ONIOM method is an extension of IMOMM that performs calculations on \( n \) different systems using \( n \) levels of calculation.

- Each system and calculation constitute a layer.

- The IMOMM method is a version of ONIOM with \( n=2 \)
- **ONIOM** uses the same concept as IMOMM.
- The advantage of ONIOM is that it can be easily extended to three or multiple layers.

**ONIOM3**

(A)

Real System (R)

- **Intermediate System (IM)**
  - First Layer
  - Bond-formation/breaking takes place.
  - Use the “High level” (H) method.

- **Small Model System (SM)**
  - Second Layer
  - Electronic effect on the first layer.
  - Use the “Medium level” (M) method.

- **Third Layer**
  - Environmental effects on the first layer.
  - Use the “Low level” (L) method.
• The most important questions when using ONIOM scheme are
  - how to select the methods that will be combined.
  - how to partition the system into high and low level layers.

○ If one knows by intuition who the major players and minor players are, the major players should be included in the model system to be treated at a high level, while the minor players can only be treated at a low level.
For example in chemical reactions in solvated cluster (the real system) the reactants (and possibly a few solvent molecules directly involved in the reaction) will constitute the model system.

The rest of the system will only be treated at the low-level.
There are cases where the ONIOM method does not work.

In such cases one cannot identify major players or minor players.
References

Thank You!