# Simulations of chemical reaction in biomolecules
(Hybrid QM/MM molecular dynamics)

QM/MM Modeling Approach

- Couple quantum mechanics and molecular mechanics approaches
- QM treatment of the active site
  - reacting centre
  - excited state processes (e.g. spectroscopy)
  - problem structures (e.g. complex transition metal centre)
- Classical MM treatment of environment
  - enzyme structure
  - zeolite framework
  - explicit solvent molecules
 - bulky organometallic ligands
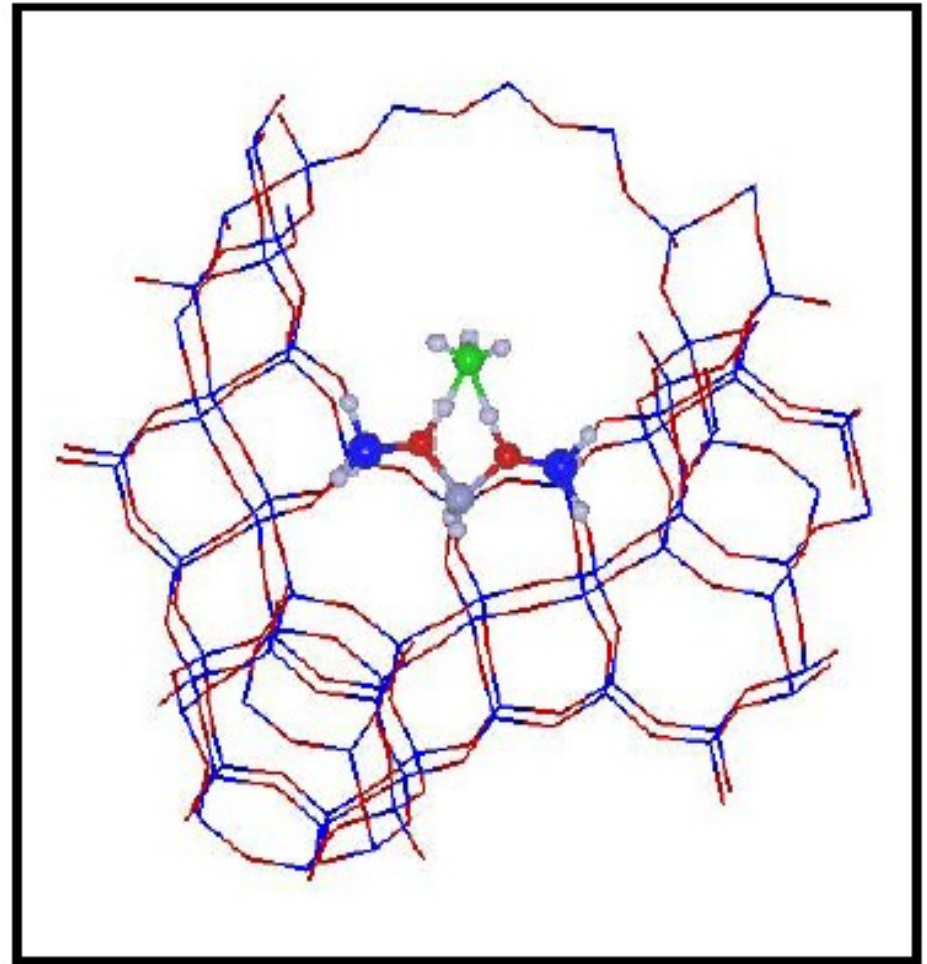
Historical Overview

- **1976**   Warshel, Levitt   MM+Semi-empirical
  - study of Lysozyme
- **1986**   Kollmann, Singh   QUEST
  - ab-initio (Gaussian-80/UCSF) + AMBER
- **1990**   Field, Bash, Karplus   CHARMM/AM1
  - full semi-empirical dynamics implementation
- **1992**   Bernardi, Olivucci, Robb   MMVB
  - simulation on MC-SCF results using VB
- **1995**   van Duijnen, de Vries   HONDO/DRF
  - direct reaction field model of polarisation

Historical Overview

- 1995   Morokuma   IMOMM
  - mechanical embedding with "hidden variable" optimisation
- 1996   Bakowies and Thiel   MNDO/MM
  - mechanical, electrostatic and polarised semi-empirical models
- 1997   Eichler, Kölmel, and Sauer QM/Pot
  - subtractive coupling of GULP/TURBOMOLE

Hybrid computational schemes
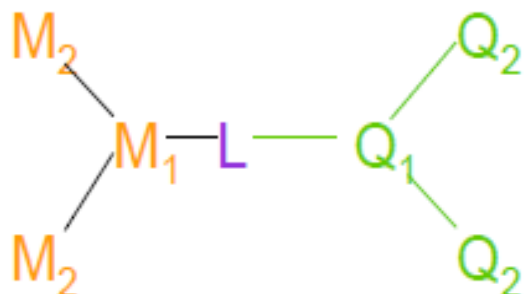
QM/MM Couplings

Unpolarised

QM polarisation

   choice of charges?

MM polarisation

  ¤ shell model

  ¤ dipole polarisabilities

Termination Atoms

Chemical type

hydrogen atoms, pseudopotentials
adjusted connection atoms, localised orbitals

Charge perturbations

none, charge deletion, charge shift,
selection of 1e integrals, double link atoms

Total Energy Expression

Uncorrected

   $E(M,MM) + E(QL,QM)$

Boundary corrected

   $E(M,MM) + E(QL,QM) - E(L,MM)$

Subtractive

   $E(MQ,MM) + E(QL,QM) - E(QL,MM)$

Termination of QM region

- **Boundary region approaches**
  - Boundary atoms are present in both QM and MM calculations
  - Range of representations within QM code
    - Modified *ab-initio* atom with model potential
    - Semi-empirical parameterisation
    - Frozen orbitals
  - Re-parameterised MM potentials

- **Link atom schemes**
  - Terminating (link) atoms are invisible to MM calculations
    - Hydrogen, pseudo-halogen, etc.
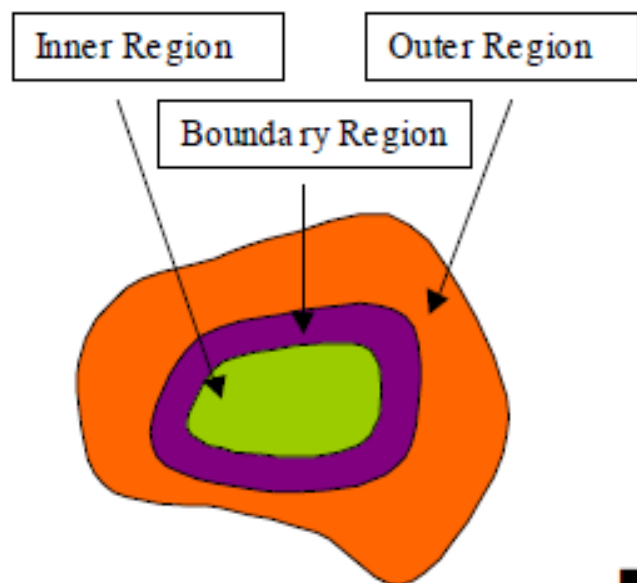
Choice of QM model

- **Applicability**
  - Most QM methods are suitable
    - Semi-empirical
    - Empirical valence bond (Warshel, MOLARIS)
    - MM-VB (Robb, fitted to CASSCF)
    - *ab-initio*
    - DFT
      - **Gaussian basis**
      - **Plane wave (CP) - Zeigler, Parrinello, Rothlisburger**
- **Requirements for QM methods**
  - For electrostatic embedding need to insert extra nuclei in Hamiltonian
    - Cost implications, e.g. derivatives, Hessians

Choice of MM model

Choice of parameterisation model will be based on nature of the chemical system

- Valence forcefields
    - ❖ Macromolecular force fields
        - CHARMM, Quest (AMBER)
    - ❖ MM2/MM3
        - MNDO/MM, IMOMM
    - ❖ Commercial generation eg CFF (Discover)
        - Electronegativity equalisation
- Ionic forcefields
    - ❖ Shell Model

Valence force fields

- Used for covalently bound molecules and networks

- Terms associated with bonded groups
  - bonds
    - e.g. harmonic, quartic
  - angles
    - e.g. harmonic, quartic
  - dihedral (torsion) angles
    - sin,cos (rotational barriers)
    - harmonic (e..g planarity constraints)
  - sometimes other cross-terms
    - bond-bond coupling
    - bond-angle coupling
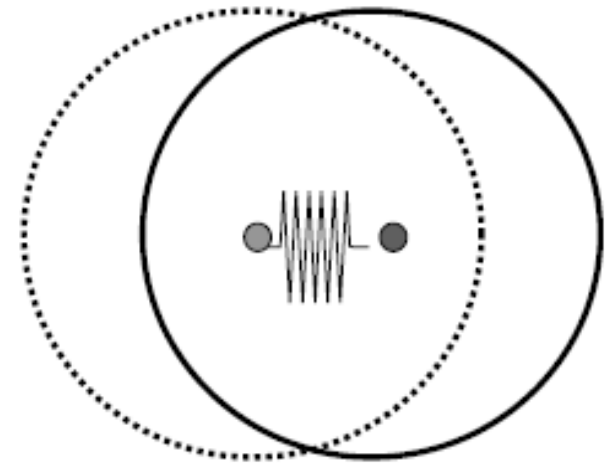
Valence force fields

- **Non-bonded terms**
  - Summed over all non-covalently-bound pairs
    - always exclude bonded pairs
    - exclude 1,3 interactions for angles
    - sometimes scale 1,4 interactions for dihedrals
  - van der Waals
    - Buckingham, Lennard-Jones
  - electrostatics
    - simple coulomb ($q_i q_j / r$)
      - Need to decide the atomic charges …
    - distance-dependent dielectric
      - Approximate correction for solvation
- **Examples**
  - MM2, AMBER, CHARMM, UFF, CFF, CVFF

Shell model force fields

- **Typically used for ionic solids**
- **Leading terms are non-bonded**
  - Electrostatics
    - often based on formal charges
    - polarisability of ions included by splitting total ion charge in
      - **Core (often +ve) and Shell (-ve), modelling the valence electrons**
      - **Shell can shift in response to electrostatic forces, restoring forces from harmonic "spring"**
  - van der Waals
    - sometimes compute using shell position
- **Can also incorporate 3-body terms**
    - some bond angles are preferred over others, introducing covalent character

Core position

Shell position

Choice of MM model

- **Practical considerations**
  - We must be able to remove selected forcefield terms from topology to avoid double counting in both QM and MM
    - handling of link atoms is easier for valence forcefields than for ionic ones
  - Need vdW parameters for interaction with QM
    - always
  - QM charges
    - need for some embedding schemes
  - numerical noise (e.g. MM cutoffs) important for transition states *etc.*
- **Future prospects**
  - DMA (distributed multipole analysis)
  - Other models for polarisation
    - can be difficult to obtain the correct polarisation at the boundary

Conventional QM/MM Scheme

- **Termination**
  - hydrogen, adjusted connection atom, pseudo-halogen
- **Coupling**
  - Unpolarised
  - QM polarisation
  - MM Polarisation (Direct Reaction Field)
- **Energy Expression**
  - No correction (Q2-Q1-L force constant mimics Q2-Q1-M1)

- **MM Charge Adjustments**
  - Deletion (first charge group)
  - Shift (M1->M2)
  - Integral selection (semi-empirical)
- **Advantages**
  - Robust
- **Disadvantages**
  - charge perturbation at boundary
- **Applications**
  - zeolites
  - enzymes

QM/MM Coupling

- **Energy Expression**

  $E(MQ,MM) + E(QL,QM) - E(QL,MM)$

  - includes boundary correction
  - can treat polarisation of both the MM and QM regions at the force-field level

- **Termination**

  - Any (provided a force field model for QL is available)

- **Advantages**

  - Potentially highly accurate (free from artefacts)
  - Can also be used for QM/QM schemes (*e.g.* IMOMO, Morokuma *et al*)

- **Disadvantages**

  - Need for accurate forcefields
  - Possible catastrophies on potential energy surface
  - No electrostatic influence on QM wavefunction

- **Applications**

  - Zeolites (Sauer *et al*)

QM/MM non-bonded interactions

- **Short-range forces (van der Waals)**
  - Typically will follow MM conventions (pair potentials etc), sometimes reparameterisation is performed to reflect replacement of point charges interactions with QM/MM electrostatic terms.

- **Electrostatic interactions:**
  - Mechanical Embedding
    - in vacuo QM calculation coupled classically to MM via point charges at QM nuclear sites
  - Electrostatic Embedding
    - MM atoms appear as centres generating electrostatic contribution to QM Hamiltonian
  - Polarised Embedding
    - MM polarisability is coupled to QM charge density

Mechanical embedding

- **Advantages**
  - MM and QM energies are separable
    - separate MM relaxation, annealing etc possible
  - QM/MM terms can be integrated directly into the forcefield
  - No interactions between link atoms and MM centres
  - QM energies, gradient, Hessian are the same cost as gas phase
- **Drawbacks**
  - No model for polarisation of QM region
  - Electrostatic coupling requires atomic charges for QM atoms
   - generally these will be dependent on reaction coordinate
- **Examples**
    - IMOMM (Morokuma)
    - MNDO/MM (Bakowies and Thiel)

Electrostatic embedding

- **(i) Assign MM Charges for pure MM system**
  - Derived from empirical schemes (e.g. as part of forcefield)
  - Fitted to electrostatic potentials
  - Formal charges (e.g. shell model potentials)
  - Electronegativity equalisation (e.g. QEq)
- **(ii) Delete MM charges on atoms in inner region**
  - Attempt to ensure that MM "defect" + terminated QM region has
    - correct total charge
    - approximately correct dipole moment
- **(iii) Insert charges on MM centres into QM Hamiltonian**
  - Explicit point charges
  - Smeared point charges
  - Semi-empirical core interaction terms
  - Make adjustments to closest charges (deletion, shift etc)
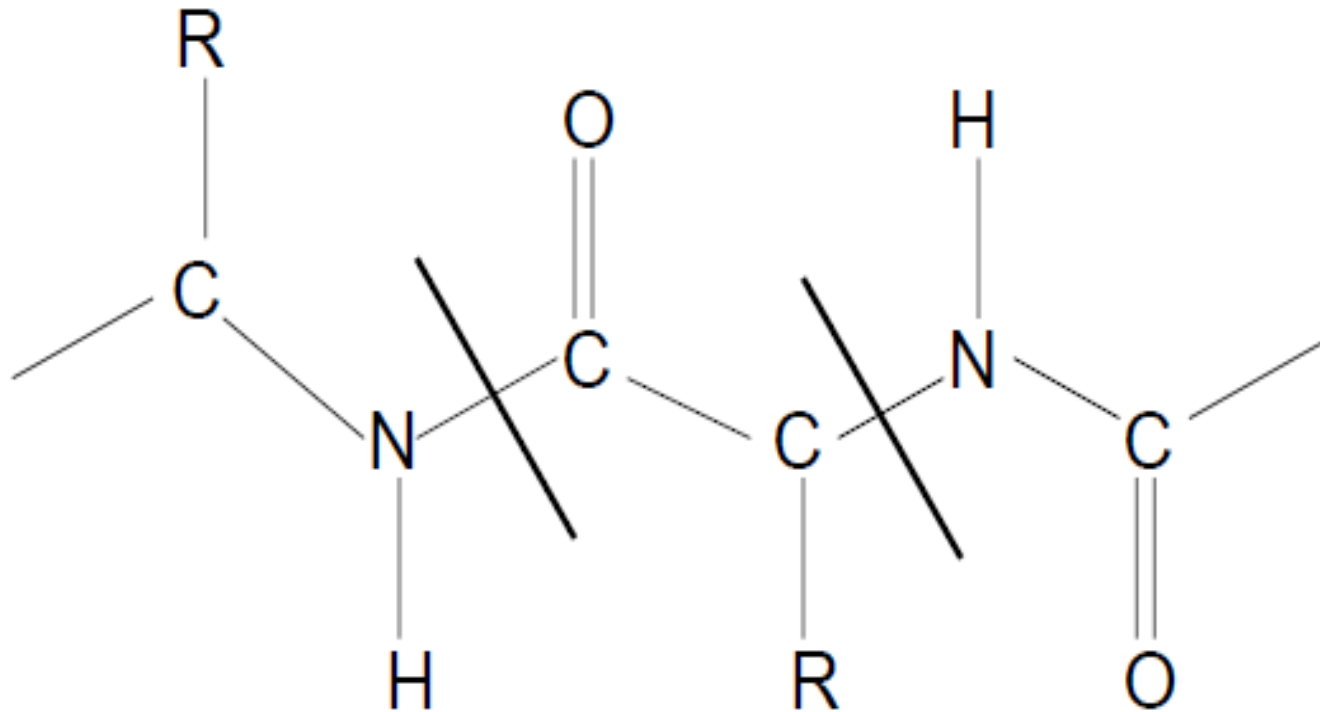
Neutral charge embedding
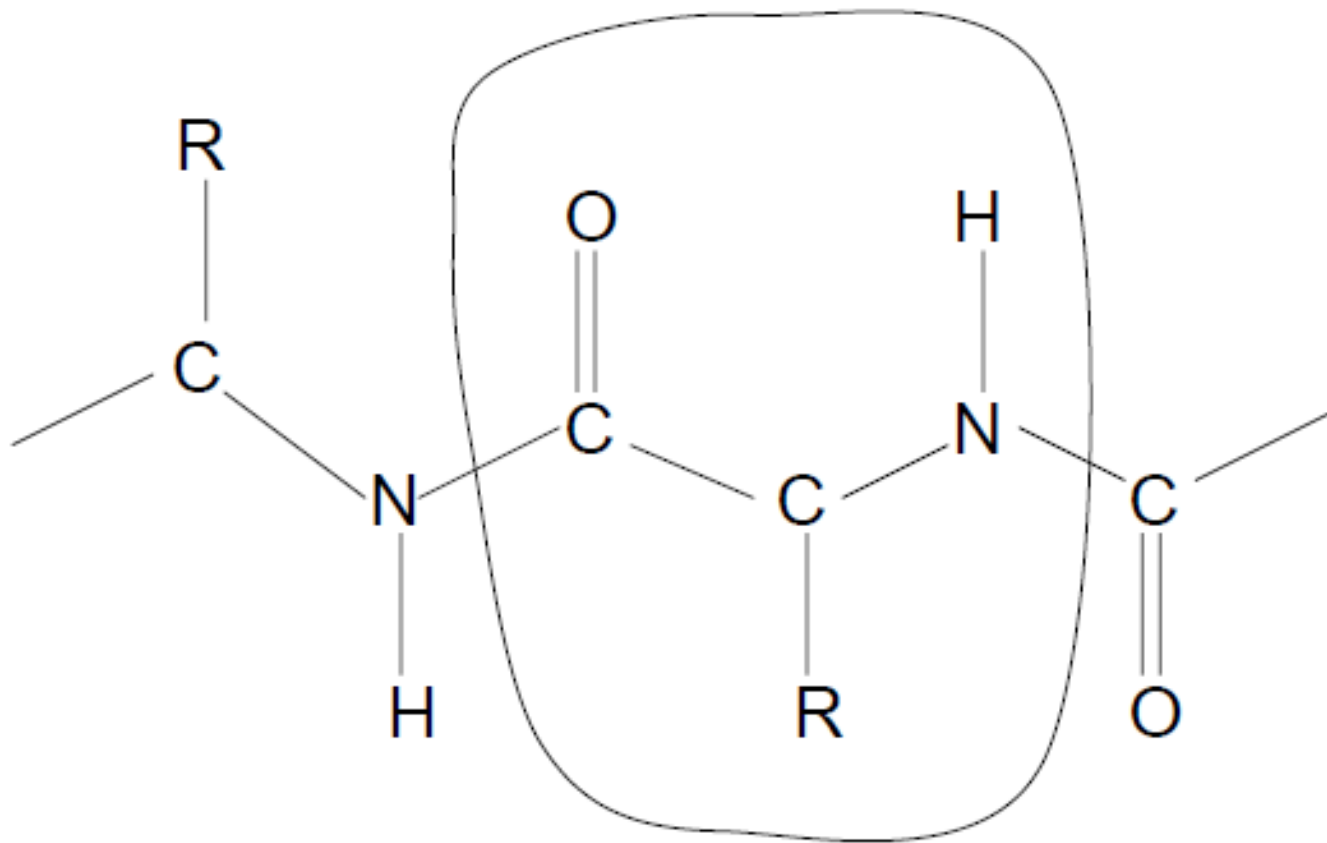
- Deletion according to force-field neutral charge-group definitions
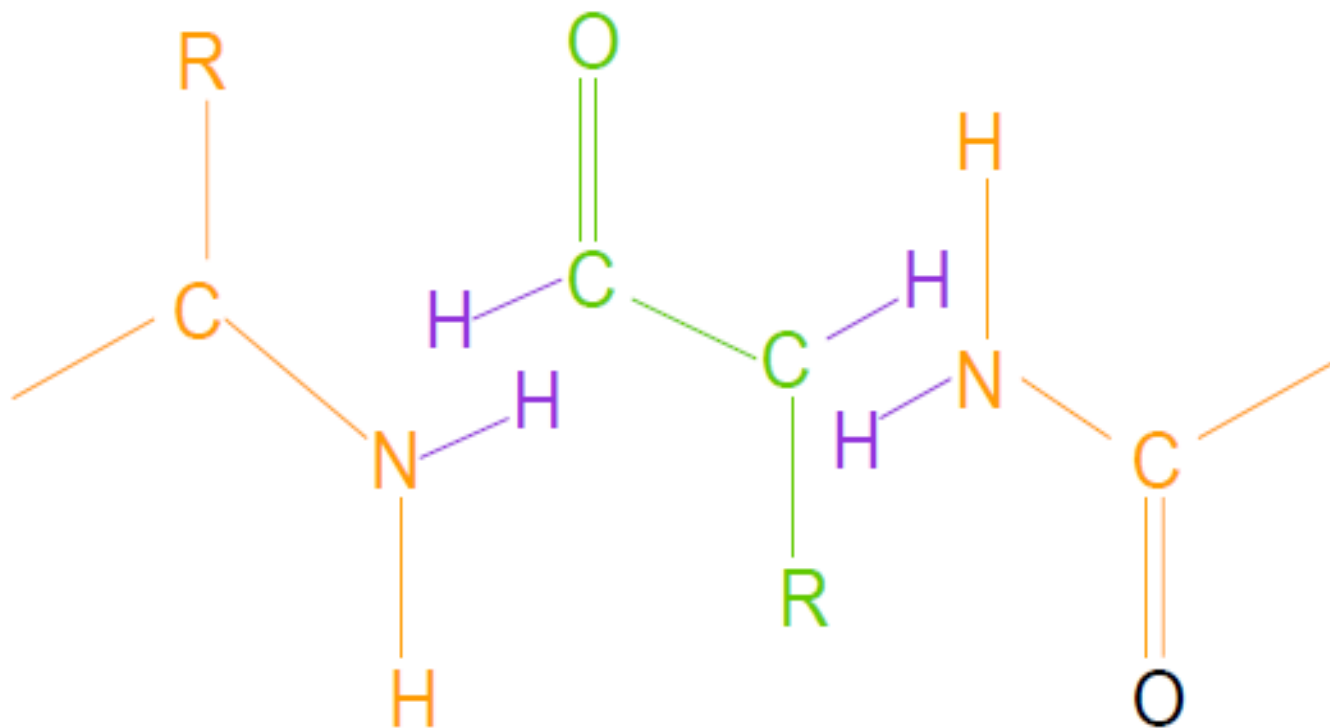
Neutral charge embedding
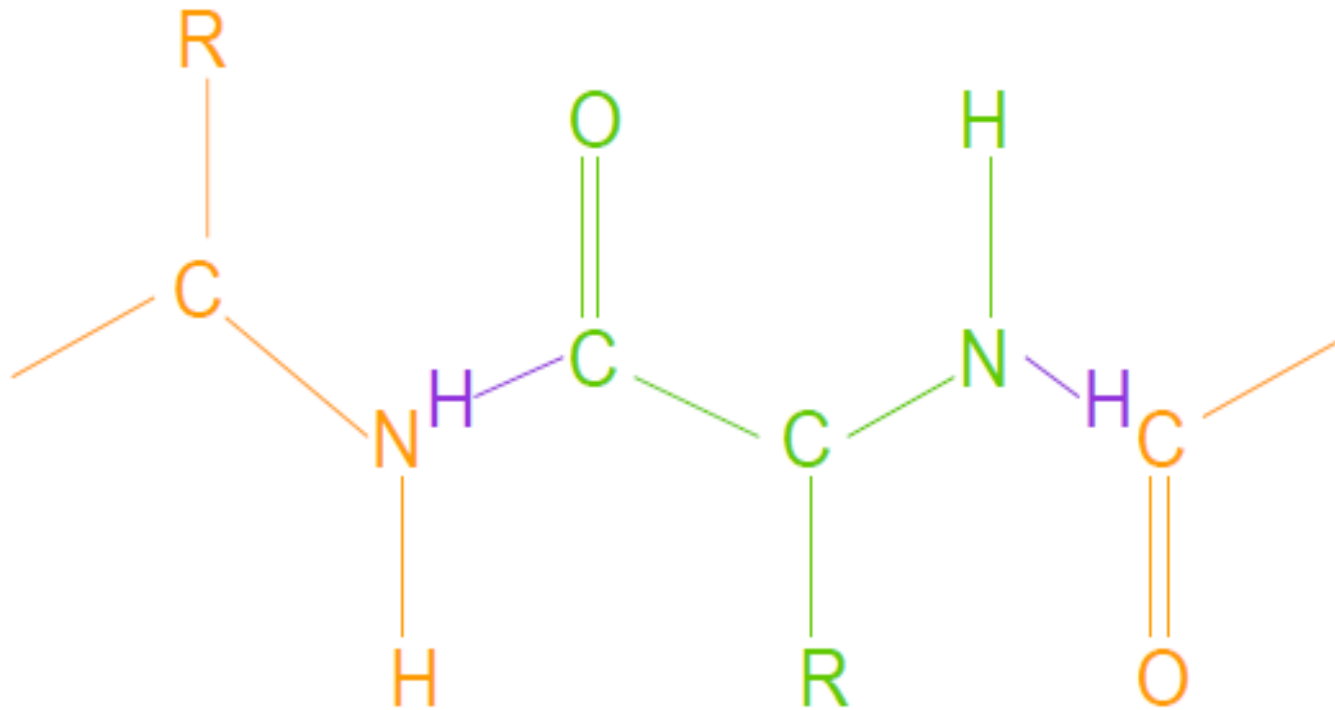
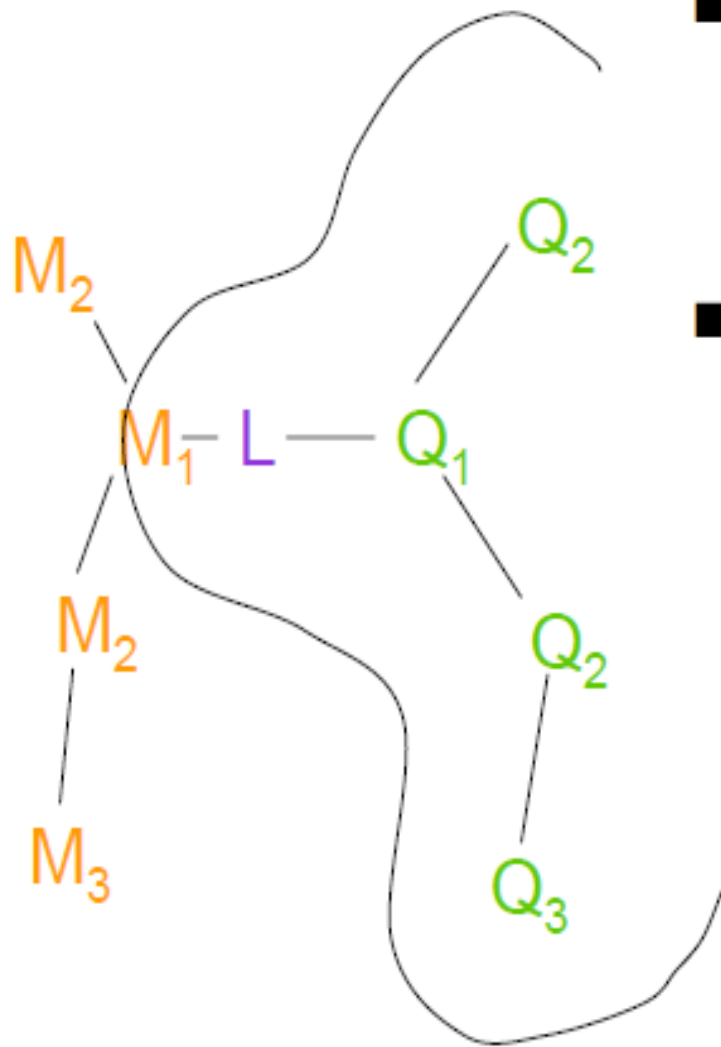- Total charge conserved, poor dipole moments

Neutral charge embedding

- Suggestion from Brooks (NIH) for general deletion (not on a force-field neutral charge-group boundary)

Neutral charge embedding

- All fragments are common chemical entities, automatic charge assignment is possible.

Boundary adjustments

- Some of the classical centres will lie close to link atom (L)

- Artefacts can result if charge at the M_1 centre is included in Hamiltonian, many adjustment schemes have been suggested
  - Adjustments to polarising field can be made independently from specification of MM…MM interactions
  - Similar adjustments may are needed if M_1 is classified as a boundary atom, depending on M_1 treatment.

Software implementation

- Specialised for a classical modelling approach, by integrating QM code into MM package
  - CHARMM + GAMESS(US,UK), MNDO (Harvard & NIH)
  - AMBER + Gaussian (UCSF, Manchester)
  - QM/Pot, GULP + TURBOMOLE (Berlin)

- Advantages
  - Good MD capabilities, model building etc

- Disadvantages
  - Restricted to certain classes of systems by forcefield choice