Chapter 5:

Molecular Dynamics Simulations (2)

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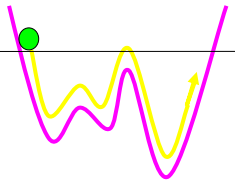
Determination of V(R)



First-Principles Surfaces:

- Pointwise QM determination of the full 3N dim PES
  $\Rightarrow$ only practicable for very small molecules

- PES determined on the fly where it is needed: Car-Parrinello MD
  $\Rightarrow$ <1000 atoms

Empirical Interaction Potentials:

- Choice of functional form:

$$V(\{R_I\}) \cong \sum_I V_1(R_I) + \sum_I \sum_{J>I} V_2(R_I, R_J) + \sum_I \sum_{J>I} \sum_{K>J} V_3(R_I, R_J, R_K) + \ldots$$

- most of the time truncated after pair-potential term
- few many-body force fields (3-body: Axilrod-Teller, n-body: Tersoff, glue potential, embedded atom method (EAM) => especially for metals)

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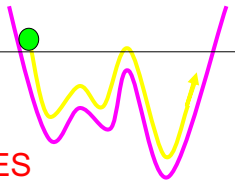
Determination of V(R)



First-Principles Surfaces:

- Pointwise QM determination of the full 3N dim PES
  ⇒ only practicable for very small molecules
- PES determined on the fly where it is needed: Car-Parrinello MD
  ⇒ <1000 atoms

Empirical Interaction Potentials:

- Choice of functional form
  (2-body? Many-body? Nonpolarizable/Polarizable ? All atom/united atom?)
- Parameterized with experimental or QC data on small gas phase molecules (plus adaption to condensed phase environment)

Exp. Dipole moment H_2O 1.85D (gas phase)
~3 D (water)

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Materials: Interatomic potentials

https://www.ctcms.nist.gov/potentials

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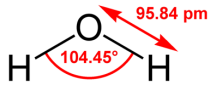
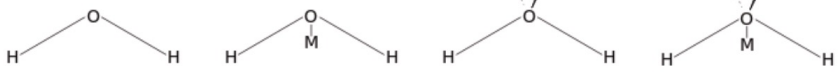
Force Fields for Water



Dipole moment:
gas phase 1.85D
liquid ca. 3D

Most common:

- Rigid water molecules
- Fix point charges on O, H and possibly on other sites
- Van Der Waals interactions on oxygens only



3-site SPC, SPCE, TIP3P | 4-site TIP4P | 5-site TIP5P | 6-site TIP6P

	TIPS[4]	SPC[5]	TIP3P[6]	SPC/E[7]
r(OH), Å	0.9572	1.0	0.9572	1.0
HOH, deg	104.52	109.47	104.52	109.47
A × 10^{-3}, kcal Å^{12}/mol	580.0	629.4	582.0	629.4
B, kcal Å^{6}/mol	525.0	625.5	595.0	625.5
q(O)	–0.80	–0.82	–0.834	–0.8476
q(H)	+0.40	+0.41	+0.417	+0.4238

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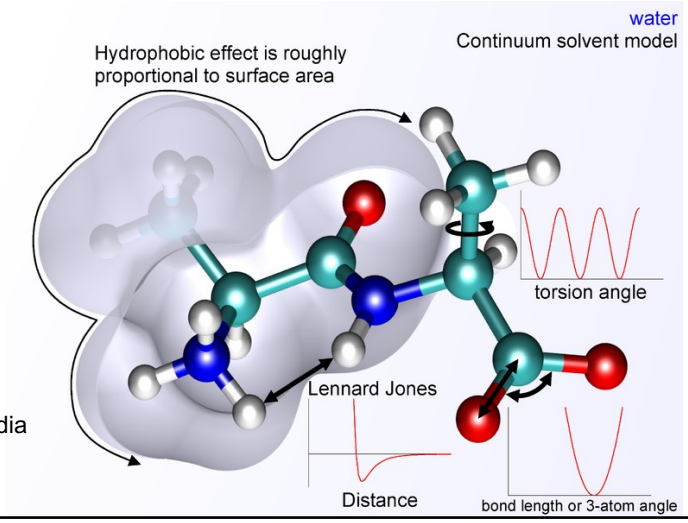
(Bio)Molecular Force Fields

- molecules modeled as classical mechanical objects with electrostatic charge interactions
- no explicit electrons only set of classical particles or interaction sites
- no quantum effects



© Picture from wikipedia

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Standard (Bio)molecular Force Field

$$H_{MM} = \sum_b \frac{1}{2} k_b (r_{ij} - b_0)^2 + \sum_\theta \frac{1}{2} k_\theta (\theta_{ijk} - \theta_0)^2$$

Bond term angle term

$$+ \sum_\varphi \sum_n k_n \left[1 + \cos(n\varphi_{ijkh} - \varphi_0)\right]$$

Torsional term

$$+ \sum_{lm} \frac{q_l q_m}{4\pi\varepsilon_0 r_{lm}} + \sum_{op} 4\varepsilon \left(\left(\frac{\sigma}{r_{op}} \right)^{12} - \left(\frac{\sigma}{r_{op}} \right)^{6} \right)$$

electrostatics Lennard-Jones 12-6

- GROMOS, AMBER, CHARMM, OPLS-AA, MM3, SYBIL, UFF, SPC, SPC/E, TIP3P, TIP4P, TIP5P etc..

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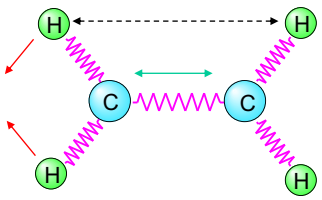
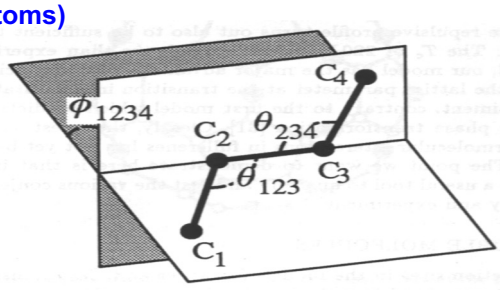
chemical bonds (2 adjacent atoms):
-> described by mechanical springs: bond potential (harmonic, anharmonic, Morse etc..)
force constants e.g. from stretching modes
bond angles (3 adjacent atoms): ditto (harmonic, anharmonic etc..),
→ force constants e.g. from bending modes
Torsional Potentials (4 adjacent atoms)





- **electrostatic interactions:** Coulomb interaction between effective (atom centered or off-site) point charges

- **van der Waals interactions (Pauli repulsion & dispersion):** Lennard-Jones 12-6, n-m, Williams exponential

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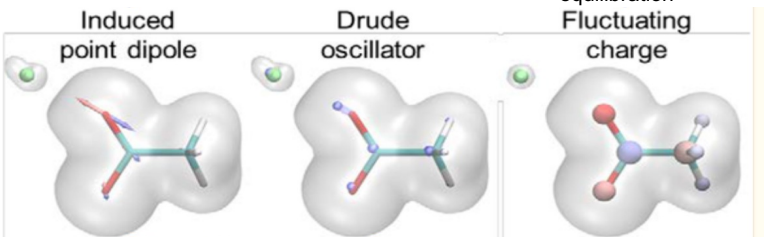
Polarizable Force Field Models



$\mu^{ind} = \alpha E$

μ^{ind}: induced atomic dipole
α: atomic polarizability
E: electric field

$\alpha = q_D^2 / k_D$

q_D: charge of Drude particle
k_D: harmonic spring constant

atomic charges redistributed to equalize electronegativity at each site

$$\chi_\alpha = \left(\frac{\partial E_\alpha}{\partial q_\alpha}\right) = \chi_\alpha^* + 2\eta_\alpha^* q_\alpha + k \sum_{\beta \neq \alpha} \frac{q_\beta}{R_{\alpha\beta}}$$

X: electronegativity; η: chemical harness

Energy needed for charge redistribution E_{self}

$$E_{self}^{Ind} = \sum_i \frac{1}{2} \alpha_i^{-1} \boldsymbol{\mu}_i^2 \qquad E_{self}^{Drude} = \sum_i \frac{1}{2} k_{D,i} \mathbf{d}_i^2 \qquad E_{self}^{FQ} = \sum_i \left(\chi_i q_i + \eta_i q_i^2\right)$$

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AMOEBA (atomic multipole optimized energetics for biomolecular applications)

Ponder et al. J. Comp. Chem. 23, 1497 (2002)

Induced dipole model

$$U = U_{bond} + U_{angle} + U_{b\theta} + U_{oop} + U_{torsion} + U_{vdW} + U_{ele}^{perm} + U_{ele}^{ind}$$

Bond and angle potentials include anharmonicity effects through higher order terms:

$$U_{bond} = K_b (b - b_0)^2 [1 - 2.55(b - b_0) + (7/12)2.55(b - b_0)^2]$$

$$U_{angle} = K_\theta (\theta - \theta_0)^2 [1 - 0.014(\theta - \theta_0) + 5.6 \times 10^{-5} (\theta - \theta_0)^2 - 7.0 \times 10^{-7} (\theta - \theta_0)^3 + 2.2 \times 10^{-8} (\theta - \theta_0)^4]$$

Additional bond-angle coupling terms and

$$U_{b\theta} = K_{b\theta} [(b - b_0) + (b' - b_0')](\theta - \theta_0)$$

$$U_{oop} = K_\chi \chi^2$$

potentials to keep sp^2 carbons planar

standard torsion potential

$$U_{torsion} = \sum_n K_{n\phi} [1 + \cos(n\phi \pm \delta)]$$

Van der Waals interactions: buffered 14-7:

$$U_{vdw}(ij) = \varepsilon_{ij} \left(\frac{1.07}{\rho_{ij} + 0.07}\right)^7 \left(\frac{1.12}{\rho_{ij}^7 + 0.12} - 2\right)$$

$\rho_{ij} = R_{ij} / R_{ij}^0$

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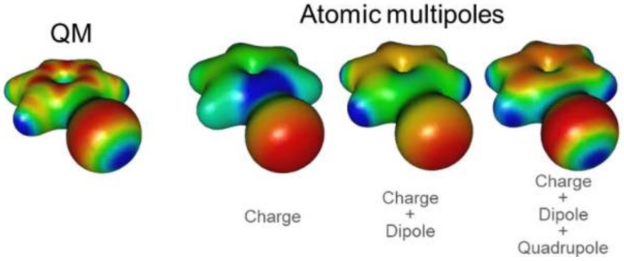
AMOEBA Electrostatic Interactions

$$U_{\text{ele}}^{\text{perm}} = U_{\text{ele}}^{\text{perm}} + U_{\text{ele}}^{\text{ind}}$$

q: atomic charge
μ: atomic dipole moment
Q: atomic quadrupole moment

$U_{\text{ele}}^{\text{perm}}$ via atomic multipole expansion $\mathbf{M} = [q, \mu_x, \mu_y, \mu_z, Q_{xx}, Q_{xy}, Q_{xz}, ..., Q_{zz}]^{\text{T}}$

Atomic multipoles



Coulomb interactions of permanent multipole moments: charge-charge, charge-dipole etc..

Induced dipoles

$U_{\text{ele}}^{\text{ind}}$

$\mu^{\text{ind}} = \alpha E$

E: total electric field generated by all other permanent atomic multipoles and induced dipoles

$$U_{\text{ele}}^{\text{ind}} = -\frac{1}{2}\sum_i (\mu_i^{\text{ind}})^T E_i$$

=> has to be solved self-consistently

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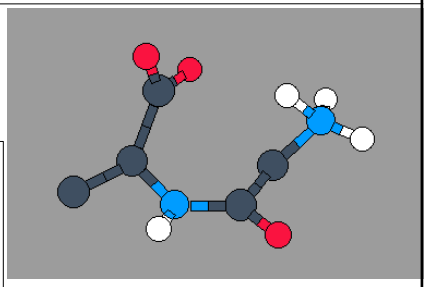
Are Polarization Effects Important?

Standard Deviation of the Electrostatic Potential

$$SD(t) = \frac{1}{T}\int_0^T dt' \sqrt{\frac{\sum_{j\in MM}\left(\sum_{i\in QM}\frac{q_i^{ESP}(t)}{r_{ij}(t')} - V_j(t')\right)^2}{\sum_{j\in MM} V_j(t')^2}}$$



Gly-Ala in Water (SPC), QM Based MD 10ps, 300K

Potential:		Dipole Moment:	
AMBER95:	6-13 %	AMBER95:	6 %
GROMOS96:	9-16 %	GROMOS96:	7 %
D-RESP:	6-8 %	D-RESP:	3 %
D-RESP(pol):	5 %	D-RESP(pol):	2 %

H. Hugosson et al., J.Comp. Chem. 27, 672 (2006); P. Maurer, et al. JCTC (2007)

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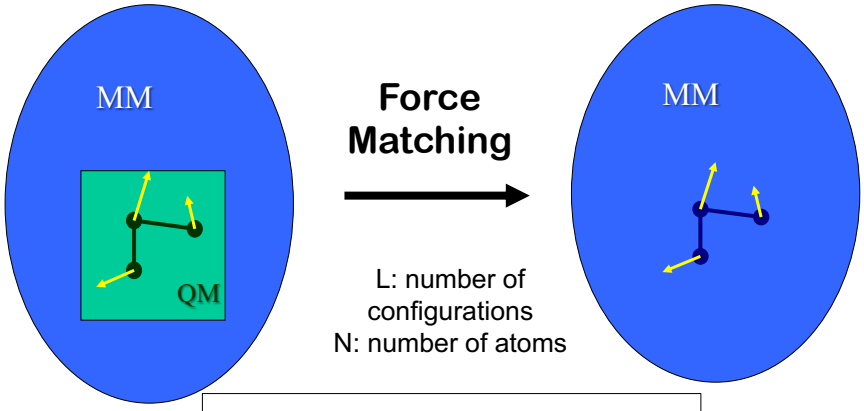
Automatized Generation of Force Fields

Force field parameters σ_i fitted to minimize difference between reference and force field forces on each atom



L: number of configurations
N: number of atoms

$$\{\sigma_i\} = \arg\min \Lambda(\{\sigma_i\})$$
$$= \frac{1}{L \cdot N} \sum_{l=1}^{L} \sum_{\alpha=1}^{N} |F_{l\alpha}^{\mathrm{MM}}(\{\sigma_i\}) - F_{l\alpha}^{\mathrm{QM/MM}}|^2$$

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Machine Learning Potentials

Recent review: Unke et al. Chem. Rev. 121, 16, 10142 (2021)

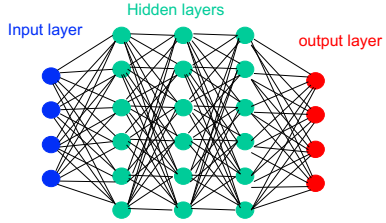
Kernel Methods:

$$E_A = \sum_{I \in A} \epsilon_{\mathrm{local}}(\boldsymbol{M}_I) = \sum_I \sum_J \alpha_J k(\boldsymbol{M}_J, \boldsymbol{M}_I) = \sum_I \boldsymbol{k}_I \boldsymbol{\alpha}$$

$$\boldsymbol{F}_L = -\frac{\partial}{\partial \boldsymbol{R}_L}[E_A] = -\frac{\partial}{\partial \boldsymbol{R}_L}[E_A] = -\sum_I \frac{\partial}{\partial \boldsymbol{R}_L}[\boldsymbol{k}_I]\,\boldsymbol{\alpha}$$
$$= -\sum_I \sum_J \alpha_J \frac{\partial}{\partial \boldsymbol{M}_I} k(\boldsymbol{M}_J, \boldsymbol{M}_I) \frac{\partial \boldsymbol{M}_I}{\partial \boldsymbol{R}_L}$$

M: descriptor of chemical environment of atom I

Neural Networks:



- Descriptor Based NNs
- End-to-end (input atomic charges and coordinates)

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Machine Learning Potentials

Important to impose physical constraints:

- Energy conservation (consistency of energy and forces)
- Translational invariance
- Rotational invariance
- Permutational invariance

Advantages:

- Do not need to know anything about interactions/form of the potential
- Automatized: no tedious FF development
- Can also be used for chemical reactions & charge transfer phenomena

Disadvantages:

- Have to generate enough training data
- 1-3 orders of magnitude slower than FF based MD
- Can become unreliable when getting into regions far from training set
- Makes no use of physical knowledge even when it would be available

Software packages for ML-FFs:

AMP (⇔ ASE)
Aenet
DeePMD(⇔LAMMPS)
PhysNet
TensorMol

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MOLECULAR DYNAMICS PACKAGES

OpenMM	http://openmm.org
AMBER	http://ambermd.org
CHARMM	https://www.charmm.org/charmm/
GROMOS	http://www.gromos.net
GROMACS	http://www.gromacs.org free (incl. source)
NAMD	http://www.ks.uiuc.edu/Research/namd/ free (incl. source)
TINKER	https://dasher.wustl.edu/tinker free (incl. source)
X-PLOR	ahttp://www.csb.yale.edu/userguides/datamanip/xplor
DL-POLY	https://www.scd.stfc.ac.uk/Pages/DL_POLY.aspx
LAMMPS	https://lammps.sandia.gov

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Limitations of Empirical Force Fields

⇒ **Transferability Problem**
empirical force fields are only parameterized for a given electronic environment, cannot adjust to large changes in the electron distribution
(e.g. different types of chemical bonding)

⇒ **cannot treat breaking and forming of chemical bonds**
⇒ **no chemical reactions!**

⇒ **many-body effects (polarization)!**

⇒ **transition metals difficult to treat!**

⇒ **parameter-free first-principles MD**

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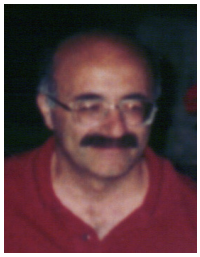
Car - Parrinello Molecular Dynamics

$$L = \sum_I 1/2 M_I \dot{R}_I^2 + \sum_i \mu \langle \dot{\phi}_i | \dot{\phi}_i \rangle - E[\{\phi_i\},\{R_I\}] + \sum_{ij} \Lambda_{ij} \left[\{ \int \phi_i(r) \phi_j(r) dr \} - \delta_{ij} \right]$$

Roberto Car

Michele Parrinello



$$M_I \ddot{R}_I = -\frac{\delta E}{\delta R_I}$$

$$\mu \ddot{\phi}_i = -H\phi_i + \sum_j \Lambda_{ij} \phi_j$$

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Does this fictitious dynamics have anything to do with the real physical dynamics???

• if $$\mu << M_I's \rightarrow K_e \approx 0$$

the total energy of the system is ≈ the real physical total energy:

$$K_e + K_I + E_{pot} \approx K_I + E_{pot}$$

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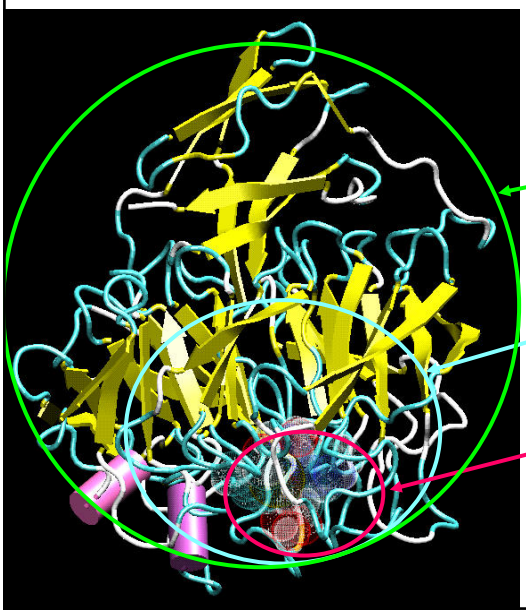
Mixed Quantum Mechanical / Molecular (QM/MM) Mechanical Methods



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Nobelprize in Chemistry 2013

Martin Karplus **Michael Levitt** **Arieh Warshel**

***"for the development of multiscale models for complex chemical systems"*: mixed quantum mechanical/molecular mechancial (QM/MM) simulations**

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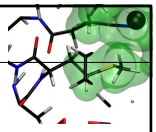
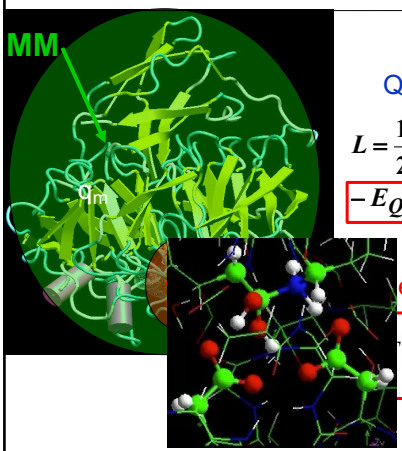
Mixed QM/MM Car-Parrinello Simulations





CPMD (www.cpmd.org)

QM/MM Extended CP Lagrangian:

$$L = \frac{1}{2}\mu\sum_i\int d\vec{r}\,\dot{\psi}_i^*(\vec{r})\dot{\psi}_i(\vec{r}) + \frac{1}{2}\sum_I M_I\dot{\vec{R}}_I^2 - E_{MM} - E_{QM/MM} - E_{QM} + \sum_{i,j}\Lambda_{i,j}\left(\int d\vec{r}\,\psi_i^*(\vec{r})\psi_j(\vec{r}) - \delta_{i,j}\right)$$

ectronic ground state $E_{QM} = E^{DFT}$ (ps, pw, GGA)

$$\left[\rho\right] + \int_\Omega V^{ex}(\vec{r})\rho(\vec{r})dr + \frac{1}{2}\iint\frac{\rho(\vec{r}_1)\rho(\vec{r}_2)}{r_{12}}d\vec{r}_1 d\vec{r}_2 + E_{xc}\left[\rho\right] + \frac{1}{2}\sum_I\sum_J\frac{Z_I Z_J}{R_{IJ}}$$

$$E_{MM}^{bonded} = \sum_b\frac{1}{2}k_b(r_{ij}-b_0)^2 + \sum_\theta\frac{1}{2}k_\theta(\theta_{ijk}-\theta_0)^2 + \sum_\varphi\sum_n k_n\left[1+\cos(n\varphi_{ijkl}-\varphi_0)\right]$$

$$E_{MM}^{non-bonded} = \sum_{lm}\frac{q_l q_m}{4\pi\varepsilon_0 r_{lm}} + \sum_{op}4\varepsilon_{op}\left(\left(\frac{\sigma_{op}}{r_{op}}\right)^{12} - \left(\frac{\sigma_{op}}{r_{op}}\right)^{6}\right)$$

E_{MM}: AMBER or GROMOS
Non-polarizable

JCP 116, 6941 (2002); JPCB 106, 7300 (2002); JPCB 108,7963 (2004); reviews in: CHIMIA 56, 11 (2002); CHIMIA 59, 493 (2005); CHIMIA ***9****, 667-671 (2011); CHIMIA 65, 330-333 (2011)*

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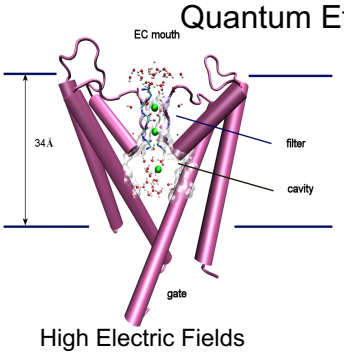
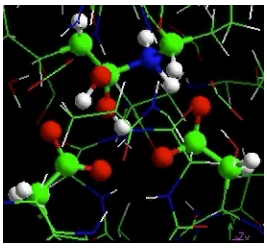
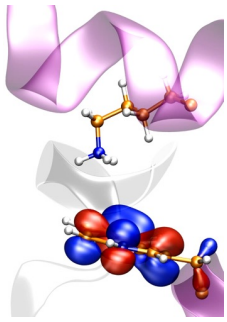
Quantum Effects in Biological Systems



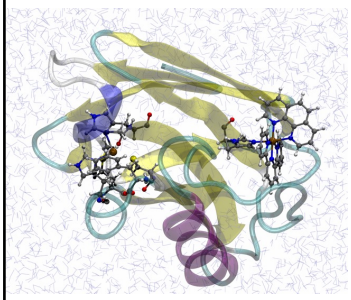
High Electric Fields



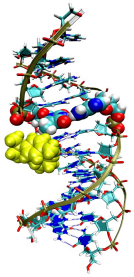
Enzymatic Reactions



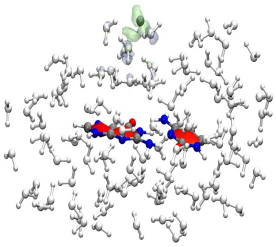
Photoreactions



Electron Transfer



Transition Metals



Radiation Damage

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