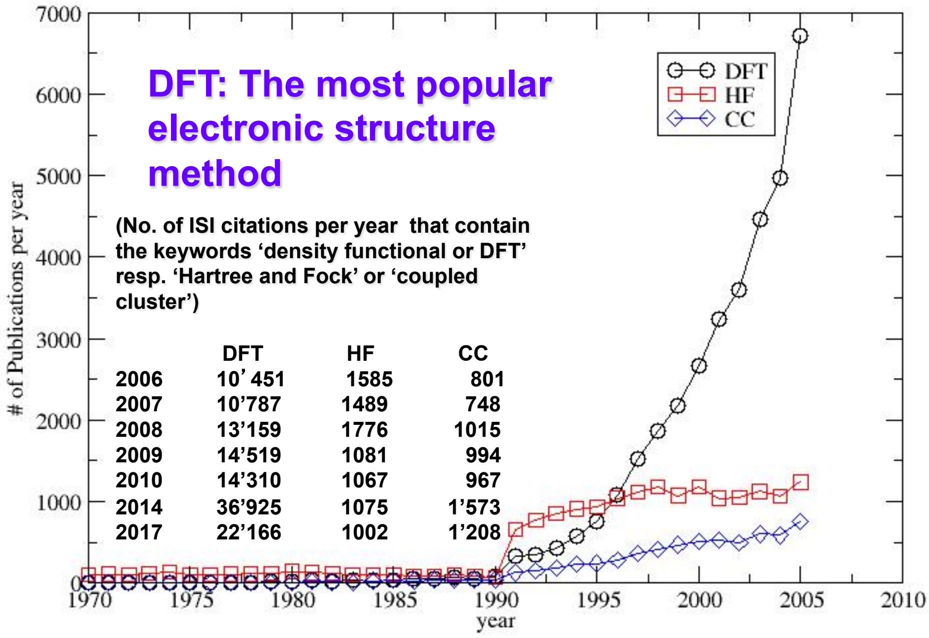
8. Density Functional Theory (DFT)

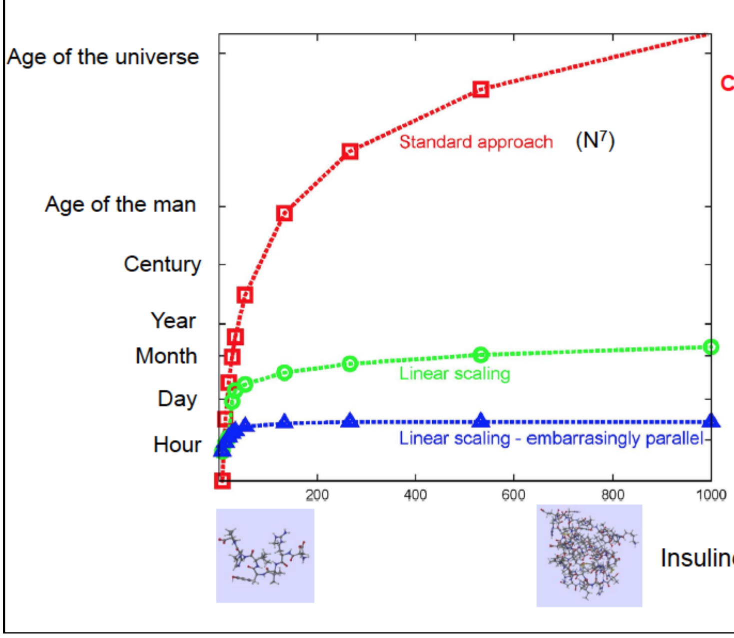
DFT: The most popular electronic structure method



(No. of ISI citations per year that contain the keywords ‘density functional or DFT’ resp. ‘Hartree and Fock’ or ‘coupled cluster’)

	DFT	HF	CC
2006	**10’ 451**	**1585**	**801**
2007	**10’787**	**1489**	**748**
2008	**13’159**	**1776**	**1015**
2009	**14’519**	**1081**	**994**
2010	**14’310**	**1067**	**967**
2014	**36’925**	**1075**	**1’573**
2017	**22’166**	**1002**	**1’208**

Scaling in Coupled Cluster theory CCSD(T)



Standard
Coupled Cluster
Canonical HF orbitals

DEC
Coupled Cluster
Local HF orbitals

Insuline

Taken from P. Jorgensen,
qLEAP Center, Aarhus

Walter Kohn and John Pople

1923-2016

Nobelprize in

Chemistry 1998

1925-2004

Kungliga
Svenska Vetenskapsakademien
har den 13 oktober 1998 beslutat
att med det
NOBELPRIS
som detta år tillerkännes den
som gjort den viktigaste kemiska
upptäckten eller förbättringen
med ena hälften belöna
Walter Kohn
för hans utveckling av täthets-
funktionalteorin

STOCKHOLM DEN 10 DECEMBER 1998

Jan S. Nilsson Erling Norrby

Schrödingers equations made easy with DFT !

Density Functional Theory (DFT)

An alternative possibility to find an approximate solution of the electronic Schrodinger equation

$$\boxed{H\Psi = E\Psi}$$

Let’s choose the electron density ρ(r) as central quantity:

$$\Psi\left(\vec{r}_1, \vec{r}_2, \vec{r}_3 \ldots \vec{r}_N\right) \rightarrow \rho\left(\vec{r}\right)$$

3N variables → 3 variables

Electron density:

$$\boxed{\rho = \frac{\#electrons}{V}} \quad \boxed{\rho\left(\vec{r}\right) = M \int \ldots \int \Psi^*\left(\vec{r}, \vec{r}_2, \vec{r}_3 .. \vec{r}_N\right) \Psi\left(\vec{r}, \vec{r}_2, \vec{r}_3 .. \vec{r}_N\right) d\vec{r}_2 .. d\vec{r}_N}$$

Ψ is normalized in such a way that

$$\boxed{\int \rho(\vec{r}) d\vec{r} = N}$$

Measure for the probability of finding an electron at a specific location.
The electron density is an observable (can be measured in e.g. an x-ray diffraction experiment).

Functionals and Functional Derivatives

Function: $\boxed{y = f(x)}$ **Maps a number (x) to another number (y)**

Functional: $F[\rho]$ **Maps a function f(x) to a number**

Example: $\Psi = \Psi[\rho](\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N)$

Derivatives: **dy/dx** **How does y vary for variations in x?:**

$$x \longrightarrow x + dx$$

$$f(x + dx) = f(x) + \frac{df}{dx} dx + \mathcal{O}(dx^2)$$

Functional Derivatives: **How does y vary for changes in f(x)?**

$$F[f(x) + \delta f(x)] = F[f(x)] + \int dx s(x) \delta f(x) \quad + O(\delta f^2) \, ,$$

$$s(x) = \frac{\delta F[f]}{\delta f(x)}$$

Functional derivative

Reasons for the Popularity of DFT Methods

Practical Reasons

To store the manyelectron wavefunction for an oxygen atom (8 electrons, 24 variables) with only 10 entries per coordinates and 1 byte per entry, we would need:

10^{24} bytes

5×10^{9} bytes per DVD → 2×10^{14} DVDs

10g per DVD → 2×10^{9}t DVDs

Whereas to store ρ(r), we only need 10^{3} bytes !

Physical Reasons

- **DFT is computationally very efficient: typicaly system sizes are 100 – 1000 atoms**
- **DFT is fairly accurate (bond lengths typically predicted within 1-2%, energies within few kcal/mol) even for systems with strong electron correlation effects, such as e.g. transition metals!**
- **many chemical concepts can be directly expressed in terms of ρ(r) (e.g. reactivity indices)**
- **can easily be combined with ab initio molecular dynamics**

What is Density Functional Theory?

Solution of the many-electron Schrödinger Equation that includes approximate exchange and correlation effects.

Electronic Schrödinger equation for fixed nuclear geometry:

$$\left[\boxed{-\frac{1}{2}\sum_i \nabla_i^2} \boxed{-\sum_{I,i}\frac{Z_I}{|\mathbf{R}_I-\mathbf{r}_i|}+\sum_{I>J}\frac{Z_IZ_J}{|\mathbf{R}_I-\mathbf{R}_J|}}+\boxed{\sum_{i>j}\frac{1}{|\mathbf{r}_i-\mathbf{r}_j|}}\right]\Psi(\mathbf{r},\mathbf{R})=E_{el}\Psi(\mathbf{r},\mathbf{R})$$

In a more compact form:

$$\left[\boxed{\hat{T}_e(\mathbf{r})}+\boxed{\hat{V}_{eN}(\mathbf{r},\mathbf{R})+\hat{V}_{NN}(\mathbf{R})}+\boxed{\hat{V}_{ee}(\mathbf{r})}\right]\Psi(\mathbf{r},\mathbf{R})=E_{el}\Psi(\mathbf{r},\mathbf{R})$$

kinetic energy operator

Electron-nuclei Coulomb potential

Nuclei-nuclei Interaction Potential (constant for fixed R)

Electron-electron repulsion potential

Convention:

$$v(\mathbf{r})=v(\mathbf{r},\mathbf{R}) \qquad \mathbf{R}_I\ \ (\mathbf{R}=(\mathbf{R}_1,\mathbf{R}_2,\ldots,\mathbf{R}_{Nu})$$

External potential

What is Density Functional Theory?

Conventional (wavefunction based) quantum chemical methods:

$$v(\mathbf{r},\mathbf{R}) \overset{SE}{\Longrightarrow} \Psi(\mathbf{r}_1,\mathbf{r}_2,\ldots,\mathbf{r}_n) \overset{\langle\Psi|\ldots|\Psi\rangle}{\Longrightarrow} \text{observable}$$

$\uparrow$

given external potential
(determined by geometry of the nuclei)

e.g. electron density $\rho(\mathbf{r})$

Density Functional theory:

$$\rho(\mathbf{r}) \Longrightarrow \Psi(\mathbf{r}_1,\mathbf{r}_2,\ldots,\mathbf{r}_n) \Longrightarrow v(\mathbf{r})$$

Unique relation between ρ(r) and v(r), all observables (including many electron wavefunction can be calculated from ρ(r)!!!!)

V(r) is the only system-dependent term,

$\hat{T}_e$ **and** $\hat{V}_{ee}(\mathbf{r})$ **are universal operators!!**

Literature on Density Functional Theory

1. R. M. Dreizler and E. K. U. Gross, *Density Functional Theory*, Springer, Berlin, 1990.
2. R. G. Parr and W. Yang, *Density-Functional Theory of Atoms and Molecules*, Oxford University Press, Oxford, 1989.
3. W. Koch and M. C. Holthausen, *A Chemist's Guide to Density Functional Theory*, John Wiley & Sons, New York, 2001.
4. R. O. Jones and O. Gunnarsson, *Rev. Mod. Phys.* 61, 689 (1989).
5. J. M. Seminario (Ed.), *Recent Developments and Applications of Modern DFT*, Elsevier, Amsterdam, 1996.

Theoretical foundations of DFT is based on Hohenberg-Kohn Theorems

The relation

$$\rho(\mathbf{r}) = M \int \dots \int \Psi(\mathbf{r}, \mathbf{r}_2, \dots, \mathbf{r}_N)\, \Psi^*(\mathbf{r}, \mathbf{r}_2, \dots, \mathbf{r}_N)\, d\mathbf{r}_2 \dots d\mathbf{r}_N$$

can be inverted, i.e. if the ground state density $\rho_0(\mathbf{r})$ is known, it is possible to calculate the ground state many-electron wavefunction $\Psi_0(\mathbf{r}_1, \mathbf{r}_2 \dots, \mathbf{r}_N)$.

Ψ_0 is a functional of $\rho_0(\mathbf{r})$: $\Psi = \Psi[\rho]$

→ any ground state observable is a functional of $\rho_0(\mathbf{r})$

The ground state wavefunction Ψ_0 is the one that minimizes the ground state energy and reproduces the ground state density $\rho_0(\mathbf{r})$

$$E_{v,0} = \min_{\Psi \to \rho_0} \langle \Psi | \hat{T} + \hat{V}_{ee} + \hat{V}_{eN} | \Psi \rangle$$

Theoretical foundations of DFT is based on Hohenberg-Kohn Theorems

For an arbitrary density ρ(r)

$$E_v[\rho] = \min_{\Psi \to \rho} \langle \Psi | \hat{T} + \hat{V}_{ee} + \hat{V}_{eN} | \Psi \rangle$$

If $\rho(r) \neq \rho_0(r)$ then $\Psi \neq \Psi_0$ and $E_v > E_0$. Variational principle for the ground state density!

One can write the total energy also as:

$$E_v[\rho] = \min_{\Psi \to \rho} \Psi | \hat{T} + \hat{V}_{ee} | \Psi \rangle + \int d^3r\, \rho(\mathbf{r}) v(\mathbf{r})$$
$$=: F[\rho] + V[\rho]$$

$$F[\rho] = \min_{\Psi \to \rho} \langle \Psi | \hat{T} + \hat{V}_{ee} | \Psi \rangle$$

Internal energy functional,
Independent of v(r), universal!!!

First Theorem: Hohenberg and Kohn (1964)

(Hohenberg&Kohn,Phys.Rev. 136, 864B, 1964)

- **The ground state energy of a system with N electrons in an external potential V_{ex} is a unique functional of the electron density**

$$\boxed{E = E\left[\rho\left(\vec{r}\right)\right]}$$

⍰ V_{ex} determines the exact $\rho\left(\vec{r}\right)$

[vice versa: V_{ex} is determined within an additive constant by $\rho\left(\vec{r}\right)$

[The ground state expectation value of any observable (i.e. of $\hat{H}$) is a unique functional of the ground state density $\rho\left(\vec{r}\right)$

Second Hohenberg and Kohn Theorem:

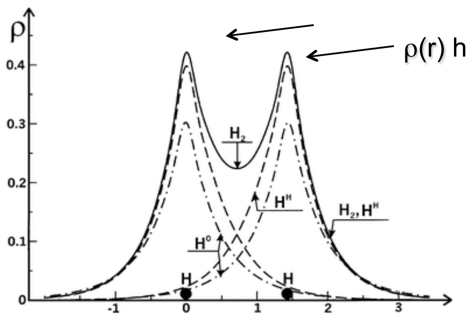
- **Variational principle:**

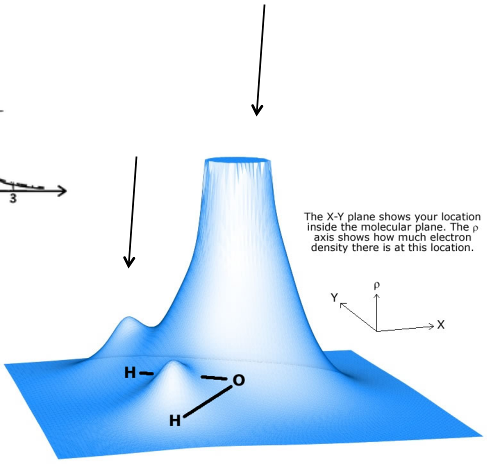
The total energy is minimal for the ground state density of the system $\rho_0\left(\vec{r}\right)$

$$\boxed{E\left[\rho\left(\vec{r}\right)\right]_{\min} = E_0 = E\left[\rho_0\left(\vec{r}\right)\right]}$$

Electron density distributions

ρ(r) has cusp at nuclear positions





The X-Y plane shows your location inside the molecular plane. The ρ axis shows how much electron density there is at this location.

Kato's cusp condition:

$$\boxed{Z_J = -\frac{a_0}{2\rho(\vec{r})}\frac{d\rho(\vec{r})}{d\vec{r}}\bigg|_{\vec{r}\to\vec{R}_J}}$$

Pictures taken from:
http://www.reed.edu/chemistry/roco/density/images/

Perdew's Jacobs Ladder

hybrid

hybrid meta

$\rho(r), \nabla\rho(r), \tau$ **meta**

$\rho(r), \nabla\rho(r)$ **GGA**

$\rho(r)$ **LDA**

The 'true' Density Functional Methods

The total energy of the system (and any other observable) is expressed as a functional of the density only:

$$\boxed{E_v[\rho] = T[\rho] + V_{ee}[\rho] + V_{eN}[\rho] = F[\rho] + V_{eN}[\rho]}$$

Some of these terms are easy to calculate, e.g. $V_{eN}[\rho]$:

$$v_{eN}(\mathbf{r}) = v_{ext}(\mathbf{r}) \qquad \hat{V}_{ext}(\mathbf{r}) = \sum_I \frac{Z_I}{|\mathbf{r} - \mathbf{R}_I|}$$

$$\boxed{V_{ext}[\rho] = \int d^3r\, \rho(\mathbf{r}) v_{ext}(\mathbf{r})}$$

Classical electrostatic energy of a charge distribution $\rho(r)$ in a potential $v_{ext}(r)$.

What is the form of the universal terms $T[\rho]$ and $V_{ee}[\rho]$?

The Thomas- Fermi Approximation

The electron-electron interaction is approximated by the classical Coulomb energy of a charge distribution $\rho(r)$ (as the Hartree term in the Hartree-Fock approximation).

$$\boxed{V_{ee} \approx V_{HF} = \frac{1}{2}\int d^3r \int d^3r' \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}}$$

It turns out that the most difficult term to express as a functional of the density, is the kinetic energy $T[\rho]$.

Thomas and Fermi suggested a first approximation for this term in the form of a local density approximation:

$$\boxed{T[\rho] \approx T^{LDA}[\rho] = \int t^{hom}(\rho(\mathbf{r}))d^3r}$$

Where $t^{hom}(\rho(r)$ is the kinetic energy density of a homogeneous electron gas with constant density $\rho(r)$.

Unfortunately, it turns out that this approximation is not very useful in chemistry: molecules are not bound !!!! ☹

Many, more sophisticated approximations have been suggested for T[ρ] but so far no sufficiently accurate *'pure'* density functional expression of T has been given!

How can we calculate the kinetic energy of an interacting many electron system?

This is very easy in a wavefunction formulation:

$$\boxed{T = -\frac{1}{2}\langle\Psi|\nabla^2|\Psi\rangle}$$

And in the case of noninteracting electrons, T is simply the sum of the kinetic energy of each electron:

$$\boxed{T = -\frac{1}{2}\sum_i\langle\phi_i|\nabla^2|\phi_i\rangle}$$

Kohn and Sham Formulation of DFT (1965)

(Kohn&Sham, Phys. Rev. 1140, 1133A, 1965)

The many-electron problem can be mapped exactly onto:

- **an auxiliary *noninteracting* reference system with the same density (i.e. the exact ground state density)**

- **where each electron moves in an effective 1-particle-potential due to all the other electrons**

$$\boxed{v_s(\mathbf{r}) = v_{ext}(\mathbf{r}) + v_H(\mathbf{r}) + v_{xc}(\mathbf{r})}$$

$$\boxed{T[\rho] = T_s[\rho] + T_c[\rho]}$$

$$\boxed{T_s[\rho] = -\frac{1}{2}\sum_i^N \int d^3r\, \phi_i^*(\mathbf{r})\nabla^2\phi_i(\mathbf{r})}$$

$$E[\{\phi_i\}] = -\sum_i \int \phi_i \nabla^2 \phi_i \vec{r} + \int V_{ion}(\vec{r})\rho(\vec{r})d\vec{r} + \frac{1}{2}\int \frac{\rho(\vec{r})\rho(\vec{r}\,')}{\vec{r}-\vec{r}\,'}d\vec{r}d\vec{r}\,' + E_{xc}[\rho(\vec{r})] + E_{ion}(\{\vec{R}_I\})$$

Kinetic energy of the non interacting system
External potential due to ionic cores
Hartree-term ~ classical Coulomb energy
exchange-correlation energy functional (includes also T_c)
core -core interaction

electron density
$$\rho(\vec{r}) = 2\sum_i |\phi_i(\vec{r})|^2$$

Kohn-Sham eqs (1 Schrödinger Equation for each effective particle):

$$\left[-\frac{1}{2}\nabla^2 + V_{ext}(\vec{r}) + V_H(\vec{r}) + V_{xc}(\vec{r})\right]\phi_i = \varepsilon_i\phi_i(\vec{r})$$

V_H: Hartree potential

$$V_H = \int \frac{\rho(\vec{r}\,')}{\vec{r}-\vec{r}\,'}d\vec{r}\,'$$

V_{XC}: exchange-correlation potential

$$V_{XC}(\vec{r}) = \int \frac{\delta E_{XC}[\rho(\vec{r})]}{\delta\rho(\vec{r})}$$

$$\varepsilon_{xc}(\rho(\vec{r})) = \rho(\vec{r})\frac{\delta\varepsilon_{xc}(\rho)}{\delta\rho}$$

exchange-correlation energy density

We have to find suitable approximations for ε_{xc}!

What about the local density approximation?

$$\varepsilon_{xc}\rho(\vec{r}) = \varepsilon_{xc}^{\mathrm{hom}}[\rho(\vec{r})]$$

$\varepsilon_{xc}^{\mathrm{hom}}$ ex-corr energy per particle of the uniform e-gas

Purely local density functional ! (i.e. only dependent on the local position)

⇒ local density approximation (LDA) $\varepsilon_{xc}^{\mathrm{hom}}\left[\rho(\vec{r})\right]$

Usually split into separate contributions from exchange and correlation

$$\boxed{\varepsilon_{xc}^{\mathrm{hom}}\left[\rho(\vec{r})\right]=\varepsilon_{x}^{\mathrm{hom}}\left[\rho(\vec{r})\right]+\varepsilon_{c}^{\mathrm{hom}}\left[\rho(\vec{r})\right]}$$

Exchange contribution $\varepsilon_{x}^{\mathrm{hom}}\left[\rho(\vec{r})\right]$ **:**

(P.A.M. Dirac, Proc. Cambridge Phil. Soc. 26, 376 (1930), E.P. Wigner, Trans. Fraraday Soc. 34, 678 (1987))

can be determined exactly !

$$\boxed{\varepsilon_{x}^{\mathrm{hom}}\left[\rho(\vec{r})\right]=-C_x\rho^{\frac{1}{3}}} \qquad \boxed{C_x=\frac{3}{4}\left(\frac{3}{\pi}\right)^{\frac{1}{3}}}$$

Correlation contribution $\varepsilon_{c}^{\mathrm{hom}}\left[\rho(\vec{r})\right]$ **:**

(D.M. Ceperly, B.J. Alder, Phys. Rev. Lett. 45, 566 (1980), G.Ortiz, P. Ballone, Phys. Rev. B 50, 1391 (1994))

Accurate (numerical) results available from Quantum Monte Carlo simulations

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→ Parameterized analytic forms that interpolate between different density regimes are available:

(e.g. J.P. Perdew, A. Zunger, Phys. Rev. B. 23, 5084 (1981))

In principle this is a very crude approximation! Molecules do not have a homogeneous electron density!!!

- E_{xc} of a non uniform system locally approximated by results of the uniform electron gas results

- should 'work' only for systems with almost constant or slowly varying density!

But: atoms and molecules are highly inhomogeneous systems

However LDA works remarkably well in practice:

Performance of LDA/LSDA:

☺ in general good structural properties:

- ⍰ bond lenghts up to 1-2%
- ⍰ bond angles ~ 1-2 degrees
- ⍰ torsional angles ~ a few degrees

☺ vibrational frequencies
~ 10% (phonon modes up to few %)

☺ cheap and good method for transition metals !

e.g. Cr_2, Mo_2 in good agreement with experiment (not bound in HF, UHF!)

☺ F_2 r_e within 3% (not bound in HF)

😐 atomization, dissociation energies over estimated (mainly due to errors for atoms), typically by 10-20%

☹ hydrogen-bonding overestimated

☹ van der Waals-complexes: strongly overestimated binding (e.g. noble gas dimers, Mg_2, Be_2: factor 2-4

Cr_2

	Re[Å]	De (eV)
HF	1.465	-19.4
CCSD	1.560	-2.9
CCSD(T)	1.621	0.5
DFT	1.59	1.5
exp	1.679	1.4

(Scuseria 1992)

Generalized Gradient Approximation (GGA)

$$\boxed{\begin{aligned} E_{xc}^{GGA} &= f_{xc}\left(\rho(\vec{r}),\left|\nabla\rho(\vec{r})\right|\right) \\ &= \int \varepsilon_{xc}\left(\rho(\vec{r})\right)\rho(\vec{r})d\vec{r} + E_{xc}^{GGA}\left(\rho(\vec{r}),\left|\nabla\rho(\vec{r})\right|\right) \end{aligned}}$$

f_{xc} : analytic function that contains a number of adjustable parameters

Determination of parameters:

- fully non empirical
- fit to exact Ex-Corr energies for atoms
- fit to experimental data (empirical)

⇒ many different forms (B88, P86, LYP, PW91, PBE, B3LYP etc..)

When the nuclei start to move:
Ab initio Molecular Dynamics

Classical dynamics of nuclei ($M_I >>> m_e$):

Newton's equations:

$$\boxed{M_I\ddot{R}_I = -\frac{\partial E}{\partial R_I}} \longleftarrow E^{KS}[\rho(r)]$$

1) Do DFT calculation for a given geometry {R}-> E^{KS}{R}
2) Calculate forces acting on every nuclei I as $\delta E^{KS}/\delta R_I$
3) Integrate equations of motion do get new positions of nuclei at time $t = t_o + \Delta t$
4) Go to 1)

When Newton meets Schrödinger...

Sir Isaac Newton
(1642 - 1727)

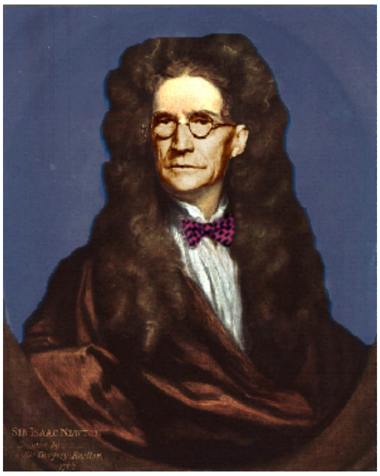
$$F = ma$$

Erwin Schrödinger
(1887 - 1961)

$$\hat{H}\Psi = \varepsilon\Psi$$

New-dinger

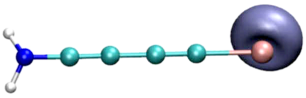
$$F = ma$$



$$\hat{H}\Psi = \varepsilon\Psi$$

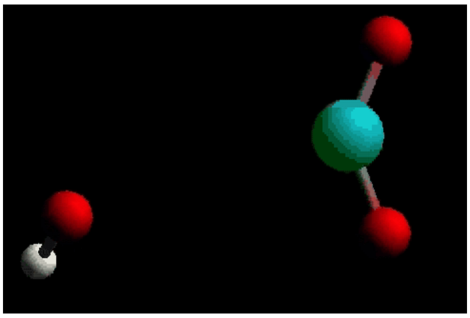
The ideal combination for
Ab Initio Molecular Dynamics

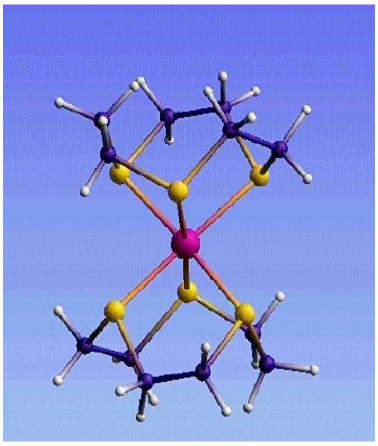
Electron Dynamics



Chemical Reactions:

NO_2• + OH• -> HNO_3



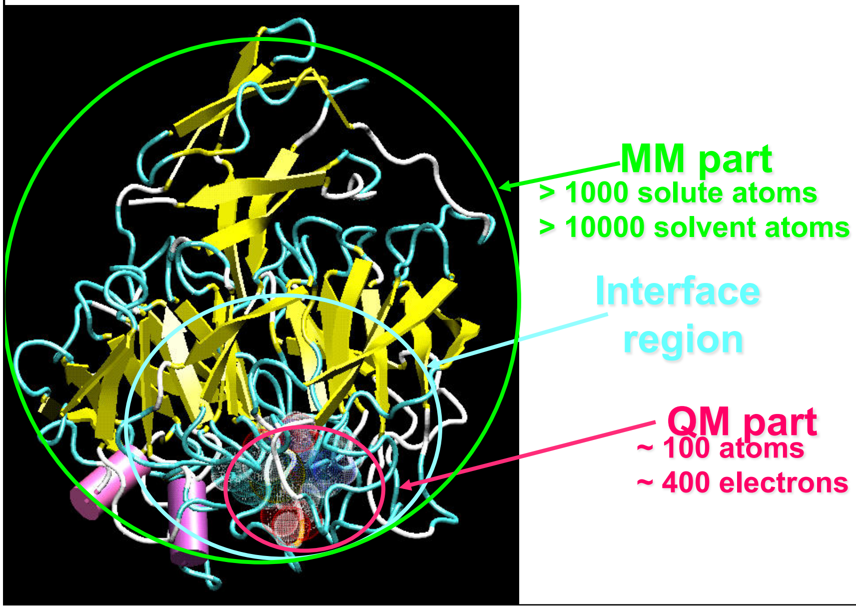


Nobelprize in Chemistry 2013

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

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

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



MM part

> 1000 solute atoms

> 10000 solvent atoms

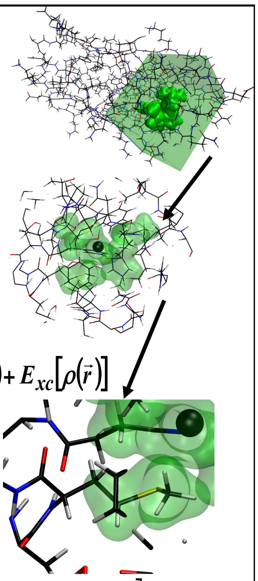
Interface region

QM part

~ 100 atoms

~ 400 electrons

QM/MM Car-Parrinello Simulations



QM/MM Lagrangian

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

E_{QM}: DFT

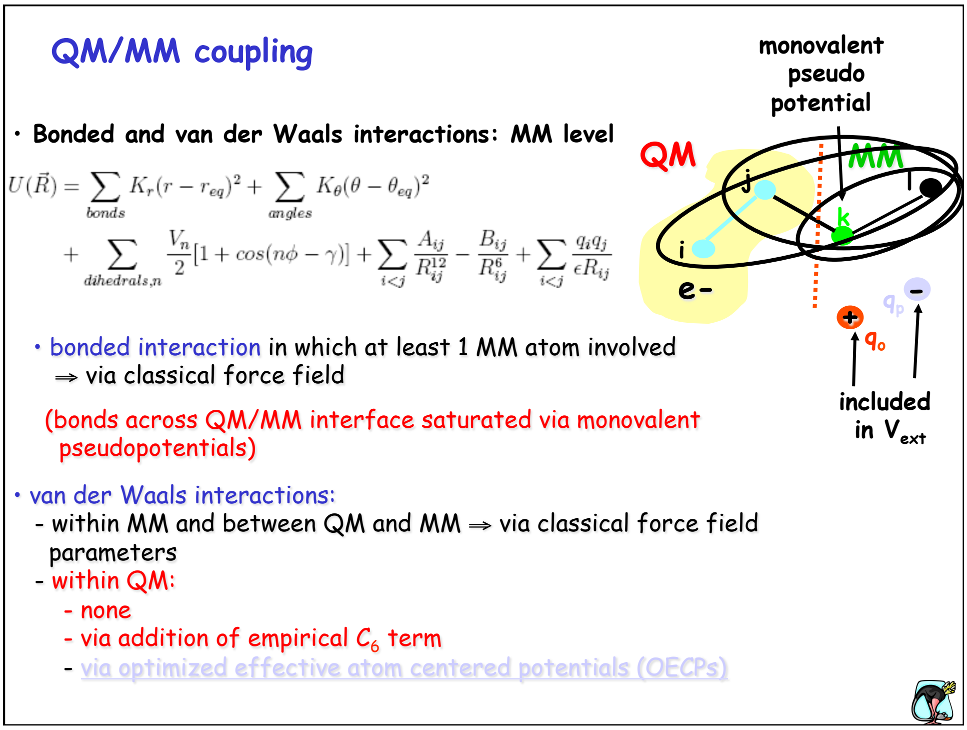
$$E_{KS}\left[\psi_i,\vec{R}_I\right] = -\frac{1}{2}\sum_i\int d\vec{r}\,\psi_i^*(\vec{r})\nabla\psi_i(\vec{r}) + \int d\vec{r}\,V_N(\vec{r})\rho(\vec{r}) + \frac{1}{2}\int d\vec{r}\,d\vec{r}'\,\rho(\vec{r})\frac{1}{|\vec{r}-\vec{r}'|}\rho(\vec{r}') + E_{xc}[\rho(\vec{r})]$$

E_{MM}: Standard biomolecular Force Field

$$E_{MM} = E_{MM}^{bonded} + E_{MM}^{non-bonded}$$

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

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



QM/MM coupling

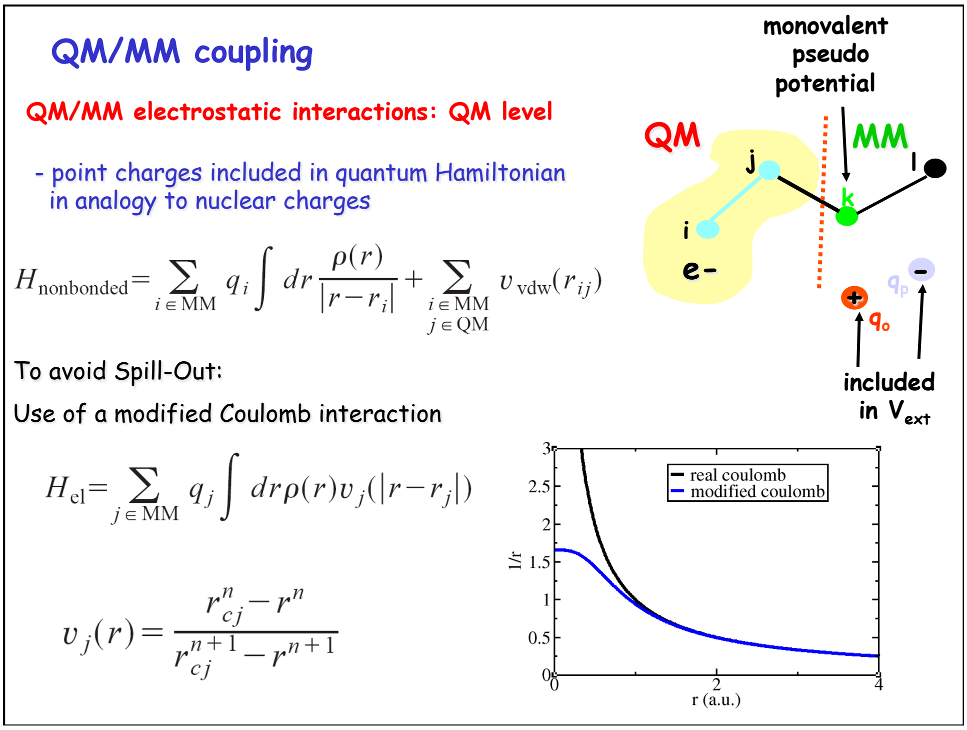
- **Bonded and van der Waals interactions: MM level**

$$U(\vec{R}) = \sum_{bonds} K_r(r-r_{eq})^2 + \sum_{angles} K_\theta(\theta-\theta_{eq})^2 + \sum_{dihedrals,n} \frac{V_n}{2}[1+cos(n\phi-\gamma)] + \sum_{i<j} \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \sum_{i<j} \frac{q_i q_j}{\epsilon R_{ij}}$$

- bonded interaction in which at least 1 MM atom involved
  ⇒ via classical force field

(bonds across QM/MM interface saturated via monovalent pseudopotentials)

- van der Waals interactions:
  - within MM and between QM and MM ⇒ via classical force field parameters
  - within QM:
    - none
    - via addition of empirical C_6 term
    - via optimized effective atom centered potentials (OECPs)



QM/MM coupling

QM/MM electrostatic interactions: QM level

- point charges included in quantum Hamiltonian in analogy to nuclear charges

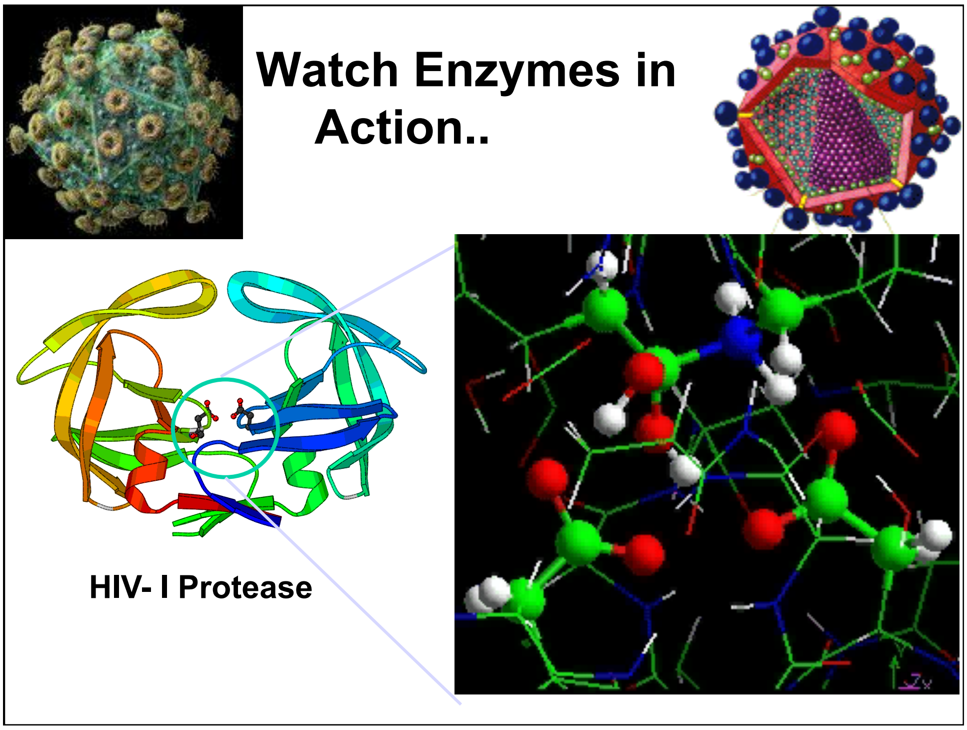
$$H_{\text{nonbonded}} = \sum_{i\in \text{MM}} q_i \int dr \frac{\rho(r)}{|r-r_i|} + \sum_{\substack{i\in \text{MM}\\ j\in \text{QM}}} v_{\text{vdw}}(r_{ij})$$

To avoid Spill-Out:

Use of a modified Coulomb interaction

$$H_{\text{el}} = \sum_{j\in \text{MM}} q_j \int dr \rho(r) v_j(|r-r_j|)$$

$$v_j(r) = \frac{r_{cj}^n - r^n}{r_{cj}^{n+1} - r^{n+1}}$$



Watch Enzymes in Action..

HIV- I Protease