Quantum Mechanics in Biology

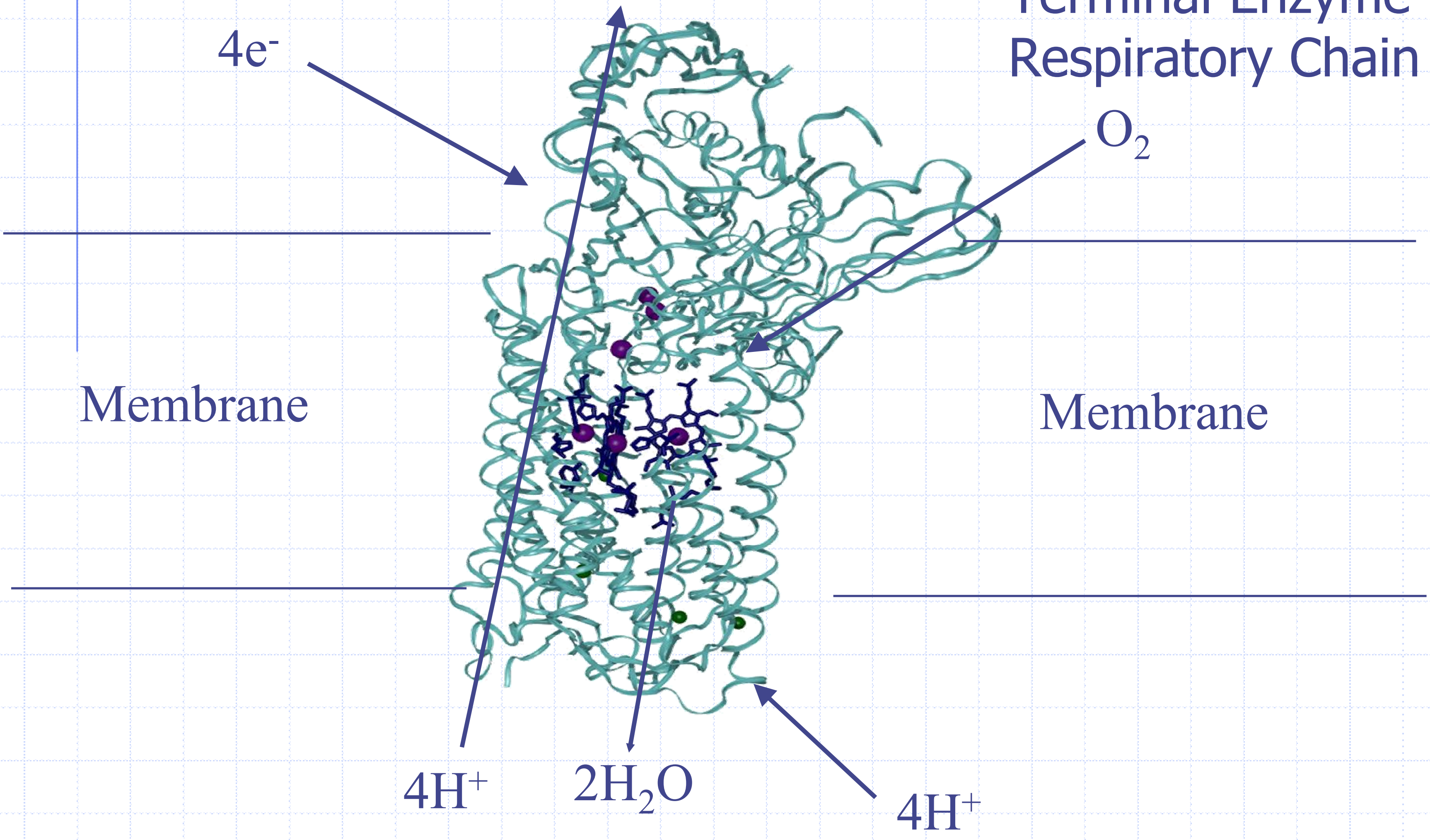
Todd J. Martinez

Quantum Biology

- Is quantum mechanics necessary for biology?
  - Yes, but mostly for “light” particles…
- Electrons
  - Force Fields
  - Bond-Rearrangement
  - Electron Transfer
- Nuclei
  - Tunneling – Proton Transfer
  - Multiple electronic states – Photobiology

Cytochrome *c* Oxidase – ET/PT/Bond Rearrangement

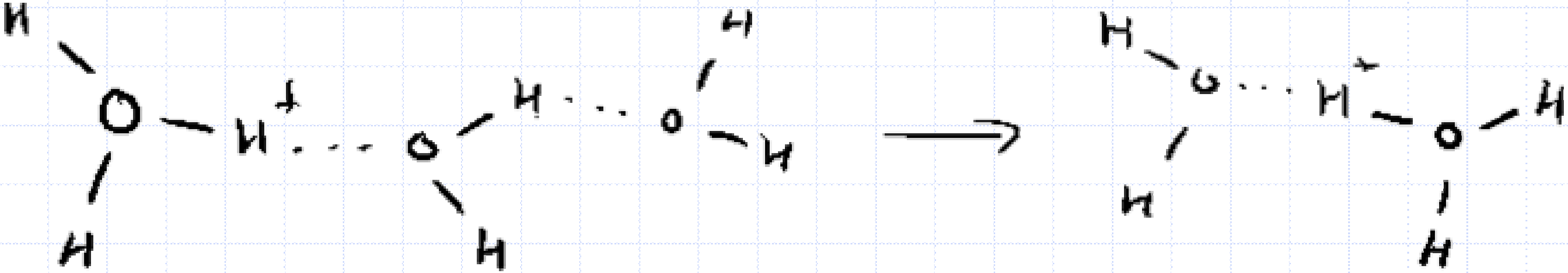
Terminal Enzyme in Respiratory Chain



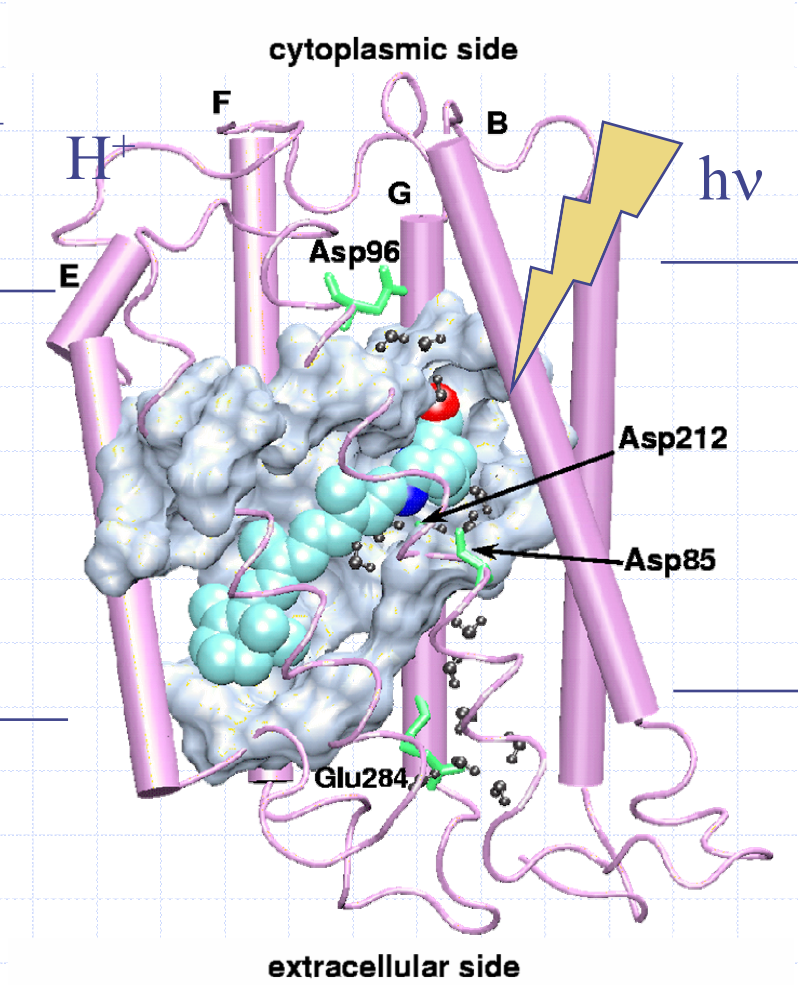
Proton Transfer

very heavy particle

light particle; can tunnel through barrier



Bacteriorhodopsin – Light-Induced Proton Pump



H^+ H^+

hν

Membrane

Membrane

H^+

Need QM to describe excited state

And bond-rearrangement associated with H^+ pump

Force Fields – The Building Block of Biomolecular Simulations

$$V(\vec{R}) = \sum_{i \in bonds} k_{i,bond}\left(r_{i,bond} - r_{i,bond}^{eq}\right) + \sum_{i \in angles} k_{i,angle}\left(\theta_{i,angle} - \theta_{i,angle}^{eq}\right) + \cdots$$

$$+\tfrac{1}{2}\sum_{\substack{i \neq j \\ i,j \in atoms}} \frac{q_i q_j}{\left|r_i - r_j\right|} + \tfrac{1}{2}\sum_{\substack{i \neq j \\ i,j \in atoms}} V_{LJ}^{ij}\left(\left|r_i - r_j\right|\right)$$

But where does this come from? In reality,

$$\widehat{H}_{electronic}(\vec{R})\psi_{i,electronic}(\vec{r}_{electronic};\vec{R}) = E_{i,electronic}(\vec{R})\psi_{i,electronic}(\vec{r}_{electronic};\vec{R})$$

Electronic Schrodinger Equation

Electronic Hamiltonian

$$\hat{H}_{electronic} = \sum_{i} \hat{T}(i) - \sum_{iA} \frac{Z_A}{r_{iA}} + \sum_{i,j} \frac{1}{r_{ij}} + \sum_{A,B} \frac{Z_A Z_B}{R_{AB}}$$

Kinetic Energy of electrons

Electron-nucleus attraction

Electron-electron repulsion

Nuclear-nuclear repulsion

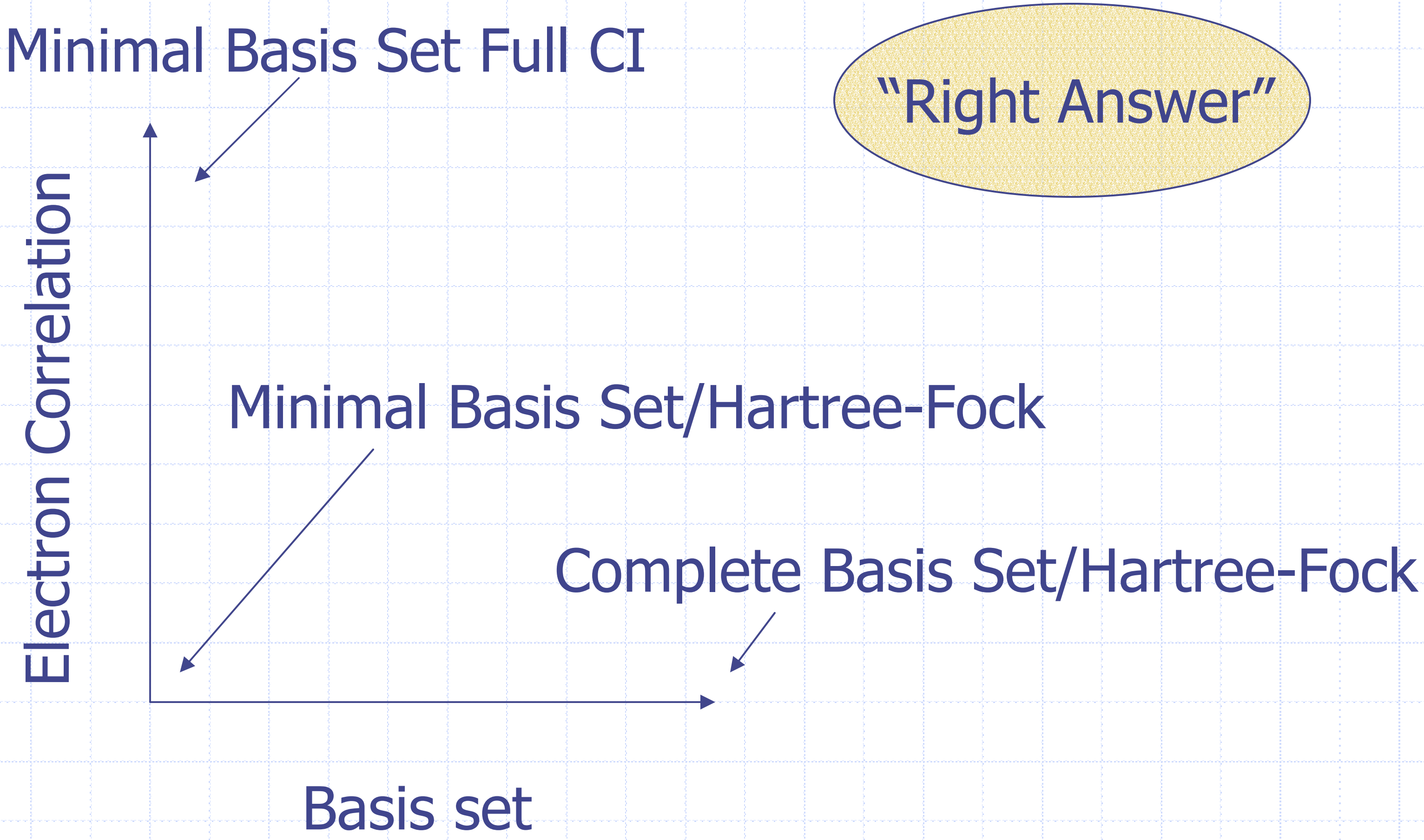
Ab Initio Quantum Chemistry

- The Good…
  - Well-defined hierarchy – in principle always know route to improve results
  - Prescriptions for thermochemistry with kcal/mol accuracy exist (but may not always be practical)
  - Excited electronic states without special treatment

- The Bad…
  - Periodic boundary conditions are difficult
  - Can be computationally costly; even "showcase" calculations on > 200 atoms are rare

Quantum Chemical “Canon”

- Two-pronged Hierarchy



Minimal Basis Set Full CI

“Right Answer”

Minimal Basis Set/Hartree-Fock

Complete Basis Set/Hartree-Fock

Electron Correlation

Basis set

The Never-Ending Contraction

$$\chi_k^{AO,CBF} = \sum_{p=1}^{N_k} c_{pk}^{\mathrm{Pr}\,im->CBF}\, \tilde{\chi}_p^{AO,primitive}(r,R)$$

Every atomic orbital is a fixed contraction of Gaussians

One-particle basis set

$$\phi_i^{MO} = \sum_{k=1}^{N_{CBF}} c_{ik}^{MO}(R)\, \chi_k^{AO,CBF}(r,R)$$

Molecular orbitals are orthogonal contractions of AOs

$$\psi_\mu(r,R) = A\left[\prod_i \phi_i^{MO}(r,R)\right]$$

Antisymmetrized products of MOs

Many-particle Basis set

$$\Psi_{elec}(r,R) = \sum_{\mu=1}^{N_{AP}} c_\mu^{CI}(R)\, \psi_\mu(r,R)$$

Total electronic wfn is contraction of APs

Basis Sets (One-Particle)

- Centered on atoms – this means we need fewer functions because geometry of molecule is embedded in basis set
- Ideally, exponentially-decaying. This is the form of H atom solutions and is also the correct decay behavior for the density of a molecule. But then integrals are intractable…
- This is the reason for the fixed contractions of Gaussians – try to mimic exponential decay and cusp with l.c. of Gaussians

Adding Basis Functions:	Reeves and Harrison, JCP **39** 11 (1963)
	Bardo and Ruedenberg, JCP **59** 5956 (1973)
	Schmidt and Ruedenberg, JCP **71** 3951 (1979)

Gaussians vs. Plane Waves

Atom-centered

- Places basis functions in the important regions
- Gradient of energy with respect to atom coordinates will be complicated (need derivatives of basis functions)
- Linear dependence could be a problem
- Localized – Good for reducing scaling…

Plane Waves

- Force periodic description (could be good)
- Gradients are trivial
- Need *many* more basis functions…
- Required integrals are easier

Basis Set Classification

Minimal Basis Set (MBS)

One CBF per occupied orbital on an atom

E.g., H has one *s* function, C has 2*s* and 1*p*

***n*-zeta**

n CBF per occupied orbital on an atom

Valence *n*-zeta

MBS for core (1*s* of C), *n*-zeta for valence

Polarized

Add higher angular momentum functions than MBS – e.g., *d* functions on C

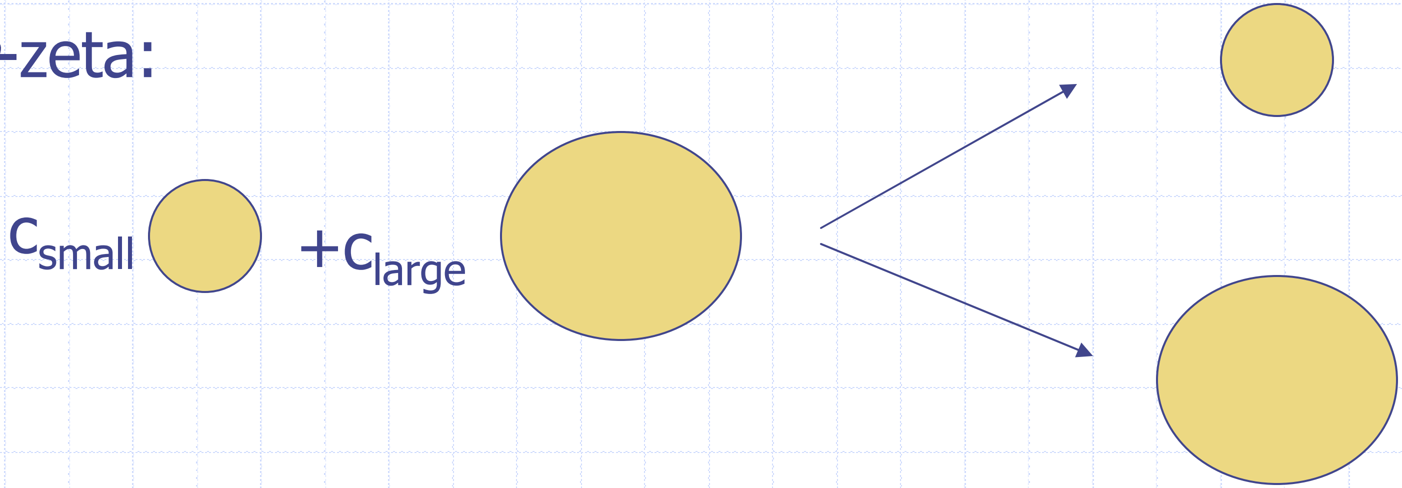
Diffuse or augmented

Add much wider functions to describe weakly bound electrons and/or Rydberg states

Physical Interpretation

- Could just say more functions = more complete, but this gives no insight…

n-zeta:

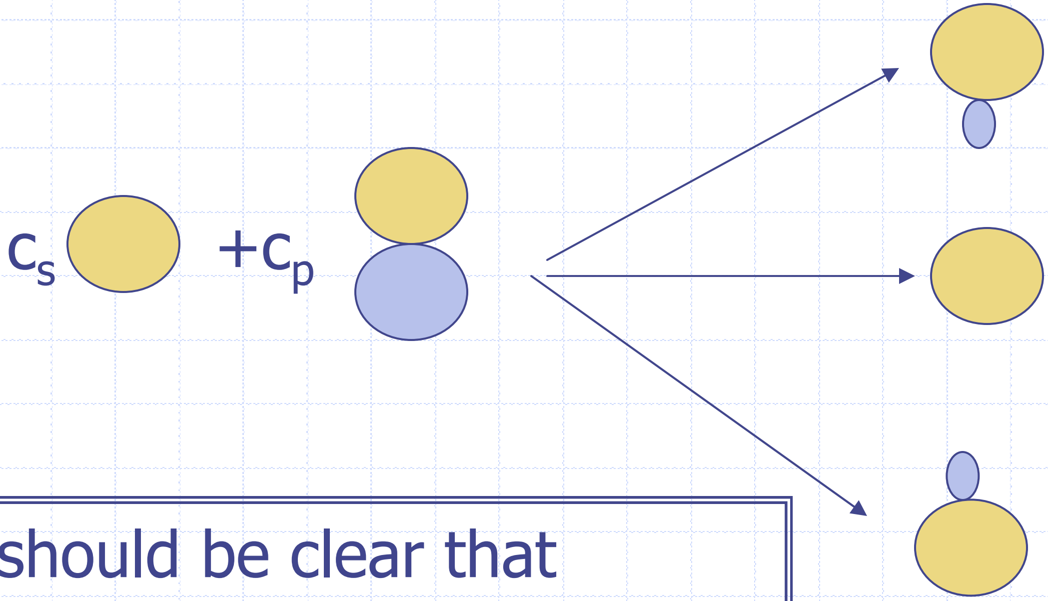


c_{small} $+c_{large}$

Allows orbitals to “breathe,”
i.e. to change their radial extent

Physical Interpretation II

Polarization functions:



It should be clear that extra valence and polarization functions will be most important when bonds are stretched or atoms are overcoordinated

Example for H atom; generally polarization functions allow orbitals to “bend”

Alphabet Soup of Basis Sets

After > 30 years, only a handful of basis sets still used:

- STO-3G – The last MBS standing…
- "Pople-style" – m-$n_1 \ldots n_X$G *X*-zeta
  - m =# prim in core n_i =# prim in ith valence AO
  - 3-21G – Pathologically good geometries for closed-shell molecules w/HF (cancellation of errors)
  - 6-31G, 6-31G*, 6-31G**, 6-31G+, 6-31G++
  - * = polarization on non-H ** = polarization on all
  - \+ = diffuse on non-H ++ = diffuse on all
- cc-pvXz, aug-cc-pvXz – *X*-zeta - "correlation-consistent" best, but tend to be larger than Pople sets

Hartree-Fock

- Truncating the many-particle basis set at one term gives Hartree-Fock

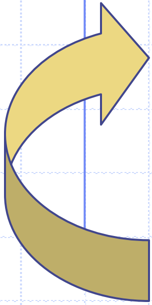
$$\Psi_{HF} = A\left[\prod_i \left\{\sum_{k=1}^{N_{CBF}} c_{ki}^{MO}\left(R\right)\chi_k^{AO,CBF}\left(r,R\right)\right\}\right]$$

- Can be shown that this implies a nonlinear effective one-particle problem

$$\hat{F}\left(c^{MO}\right) = \sum_i \hat{h}(i) + \left(\sum_{j\in occ} 2\hat{J}_j\left(c^{MO}\right) - \hat{K}_j\left(c^{MO}\right)\right)$$

$$\hat{H}\left(\vec{R}\right)\psi\left(\vec{R}\right) = E\psi\left(\vec{R}\right) \to \hat{F}\left(\left\{\varphi(r)\right\}\right)\varphi_i\left(r\right) = \varepsilon_i\varphi_i\left(r\right)$$

Self-Consistent Field



- Guess solution (c^{MO})
- Build Fock Matrix
- Solve eigenvalue equation Fc=Ec
- If coefficients are stil changing

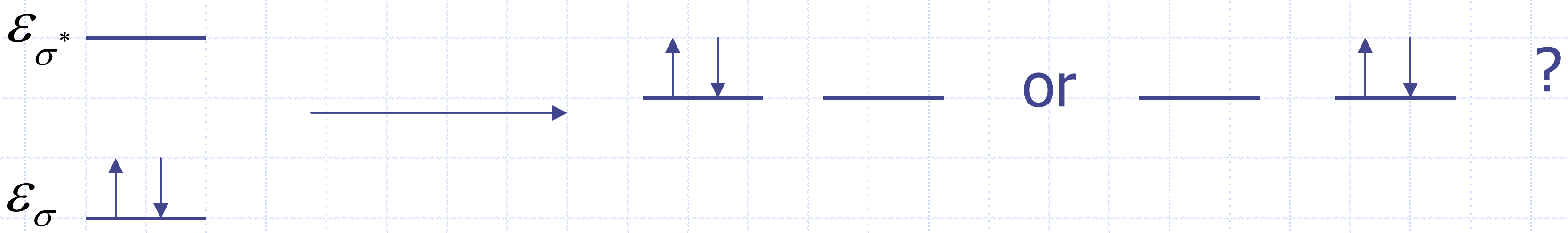
“Static” Correlation

Consider HF wavefunction at dissociation for H_2:

MOs:
$$\phi_\sigma = \chi_{left} + \chi_{right}$$
$$\phi_{\sigma^*} = \chi_{left} - \chi_{right}$$

$$\psi_{HF} = A\left(\phi_\sigma \phi_\sigma \left(\alpha\beta - \beta\alpha\right)\right)$$

Infinite separation



Finite $R_{H\text{-}H}$

Expand in AOs: $\psi_{HF} = \chi_l\chi_l + \chi_r\chi_r + \chi_l\chi_r + \chi_r\chi_l$

Need more than one determinant!

Restricted vs. Unrestricted

Can solve the previous problem by allowing orbitals to be singly occupied (unrestricted HF)

$$\psi_{UHF} = A\left(\phi_\sigma \phi'_\sigma \left(\alpha\beta - \beta\alpha\right)\right)$$

Problem: This is *not* a spin eigenfunction

$$\hat{S}^2 \psi_{UHF} \neq S(S+1)\psi_{UHF}$$

Why didn't we write:

$$\tilde{\psi}_{UHF} = A\left(\phi'_\sigma \phi_\sigma \left(\alpha\beta - \beta\alpha\right)\right) \quad ?$$

In fact, pure spin state is l.c. of the two…

$$\psi_{\text{singlet}} \propto \psi_{UHF} + \tilde{\psi}_{UHF} \qquad \psi_{\text{triplet}} \propto \psi_{UHF} - \tilde{\psi}_{UHF}$$

Describing Correlation

- Easiest Way: Moller-Plesset Perturbation Theory (MPn)

$$\hat{H}_0 = \hat{H} - \sum_{i=1}^{N_{el}} \hat{F}(i)$$

Series diverges for stretched bonds!?!
Only first correction (MP2) is worthwhile

- More stable: configuration interaction (CI)
  - Solve for CI coefficients variationally

creation/annihilation operators

$$\psi_{CI} = \left(c_0^{CI} + \sum_{i,a} a_a^\dagger a_i c_{ia}^{CI} + \sum_{ijab} a_a^\dagger a_b^\dagger a_i a_j c_{ijab}^{CI} + \cdots \right) \psi_{SCF}$$

truncated at some excitation level (FCI=no truncation)

may be HF or multi-determinant

Multi-Determinant HF (MCSCF)

- HF solves only for c^{MO} – Add c^{CI} and solve for both
- "Active Space" – the set of orbitals where electronic occupation varies

  e.g. for H_2:

$$\phi_\sigma \phi_\sigma ; \phi_\sigma \phi_{\sigma^*} ; \phi_{\sigma^*} \phi_{\sigma^*}$$

- CASSCF – "Complete" active space – all rearrangements of electrons allowed within active space

Size Consistency

E(A_N) for A infinitely separated should be NE(A)…
This simple requirement is not met by truncated CI.

- E should be additive for noninteracting systems
- ψ should be a product

Exponential maps products to sums…
Alternative (Coupled Cluster):

$$\psi_{CC} = e^{\left(\sum_{i,a} a_a^{\dagger} a_i c_{ia}^{CC} + \sum_{ijab} a_a^{\dagger} a_b^{\dagger} a_i a_j c_{ijab}^{CC} + \cdots\right)} \psi_0$$

When exponential ansatz is expanded, find contributions from excitations up to all orders…

1 kcal/mol accuracy possible, but can fail for bond-breaking because there are no good multi-reference versions…

Density Functional Theory

- Is there another way?
- DFT replaces the wavefunction with charge density as the fundamental unknown

$$\rho\left(r_1\right)=\int dr_2\cdots dr_n\psi^*\left(r_1\cdots r_n\right)\psi\left(r_1\cdots r_n\right)$$

Wavefunction – 3n coordinates

Charge Density – 3 coordinates

DFT can be better than HF. How can this be?

DFT – Functionals

- DFT expression for the energy:

$$E[\rho] = T[\rho] + \int \rho V_{nuclei} + \int \frac{\rho(r)\rho(r')}{|r-r'|} dr dr' + K_{XC}[\rho]$$

e- e- repulsion

Kinetic energy

e-/nuclei attraction   Exchange / Correlation

[] denotes functional – take function and return a number
For example, a definite integral is a type of functional…

$$I[f] = \int_a^b f(r) dr$$

So How Can This Work?

- K_{XC} is UNKNOWN!! (And is unlikely to ever be known in a form which is simpler than solving the electronic Schrodinger equation)
- T is also unknown, but can be approximated if the density is associated with a wavefunction.
- Kohn-Sham procedure:

$$\psi_{KS} = \hat{A}\prod \phi_i$$

$$\rho = \sum_i \left(\phi_i\right)^2$$

$$T[\rho] \approx \left\langle \psi_{KS} \,|\, \hat{T} \,|\, \psi_{KS} \right\rangle$$

DFT and HF

- Need to define K_{XC}
- Exactly the same ansatz is used as HF – the only difference is in the Fockian operator

$$\hat{F}_{HF}\left(c^{MO}\right)=\sum_i \hat{h}(i)+\left(\sum_{j\in occ} 2\hat{J}_j\left(c^{MO}\right)-\hat{K}_j\left(c^{MO}\right)\right)$$

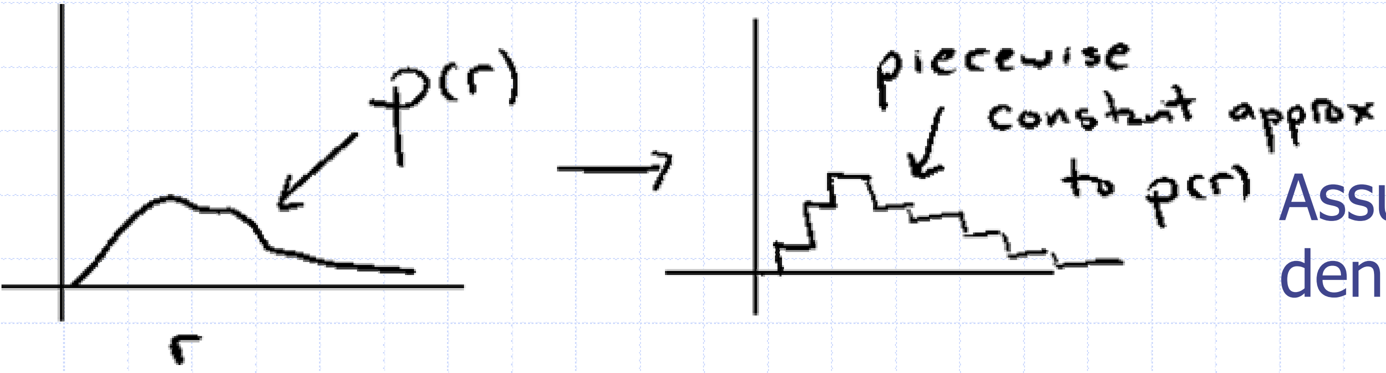
$$\hat{F}_{KS}\left(c^{MO}\right)=\sum_i \hat{h}(i)+\left(\sum_{j\in occ} 2\hat{J}_j\left(c^{MO}\right)-a_K\hat{K}_j\left(c^{MO}\right)\right)+\hat{K}_{xc}\left[\rho,\nabla\rho\right]$$

Same SCF procedure as in HF since the equation is nonlinear…

Local Density Approximation (LDA)

- K_{XC} *is* known numerically for homogeneous gas of electrons
- Assume density is slowly varying:

$$K_{XC}[\rho] = \frac{\int K_{XC}^{\mathrm{hom}ogenous,exact}[\rho]dr}{\int dr}$$

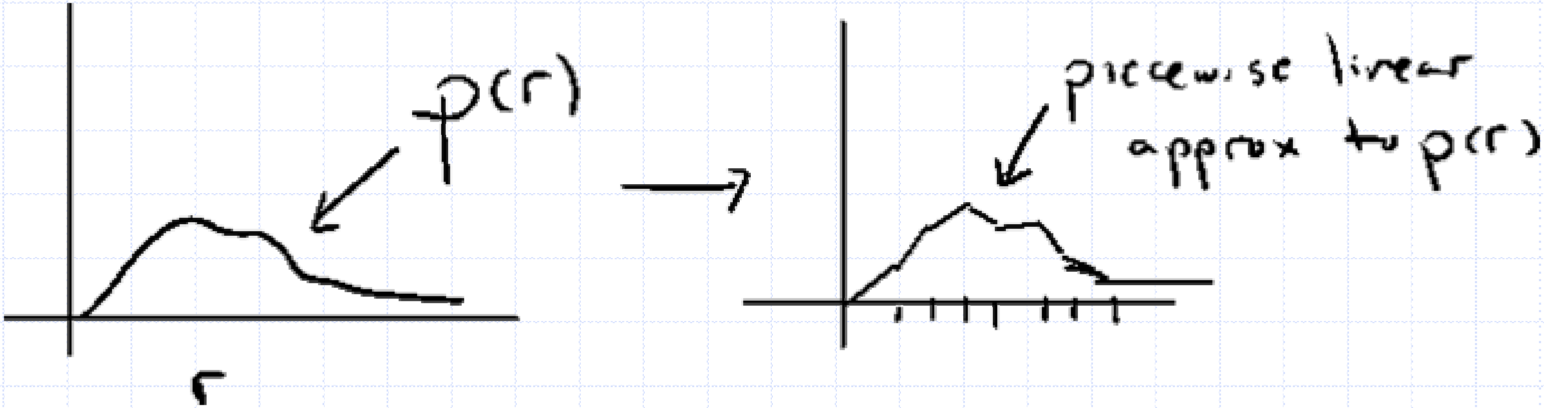


Assume constant density in each region

Problem: Errors are large (up to 30kcal/mol)

Gradient Corrections

- Piecewise-linear approximation to density
- Exact results not known; hence there are several "gradient-corrected" functionals
- $K_{XC} \rightarrow K_{XC}[\rho, \nabla\rho]$



Examples: BLYP, PW91

Much improved approximation, but errors can still be as large as 10 kcal/mol

Hybrid Functionals

- The Coulomb interaction we wrote counts the interaction of electrons with themselves
- In Hartree-Fock, this is exactly canceled by exchange integrals
- Try adding in some Hartree-Fock exchange
- B3LYP is most popular functional of this type
- Errors go down to 3-5 kcal/mol in most cases
- Cost still roughly same as HF

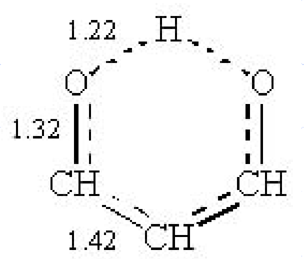
Behavior of HF and DFT

- By definition, HF has no electron correlation
  As we saw earlier, this implies more serious errors for stretched/distorted bonds, i.e. disfavors overcoordination
- Pure DFT overestimates correlation
  Preference for overcoordination
- Hence success of hybrid functionals which add exchange to DFT, e.g. B3LYP

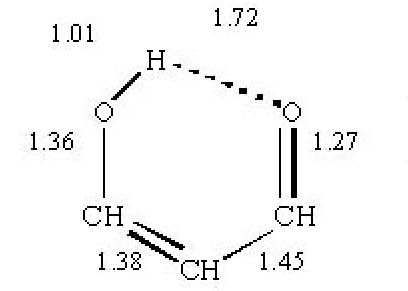
- Hartree-Fock alone is *not* very useful – barriers are usually overestimated by more than DFT underestimates

Problems with DFT

- Is DFT a panacea? No!
  - Even the best DFT often yield errors of 5 kcal/mol
  - No hierarchy for improvement
    - Different functionals = Different answers
  - Poor for proton transfer and bond rearrangment
    - Tendency to overcoordinate…
    - Extreme example: LDA predicts no proton transfer barrier in malonaldehyde



instead of



- No satisfactory route to excited electronic states

Semiempirical Methods

- Basic approximation:

$$\int \frac{\phi_{\mu 1}\left(r_1\right)\phi_{\nu 2}\left(r_1\right)\phi_{\eta 3}\left(r_2\right)\phi_{\tau 4}\left(r_2\right)}{\left|r_1 - r_2\right|} = \delta_{\mu\nu}\delta_{\eta\tau}$$

Atomic indices for basis functions

- Hartree-Fock type of SCF using this (and related) integral approximations
- Problem: Need to parameterize remaining integrals to model correlation
- Many variants (MNDO, AM1, PM3)

Semiempirical Methods

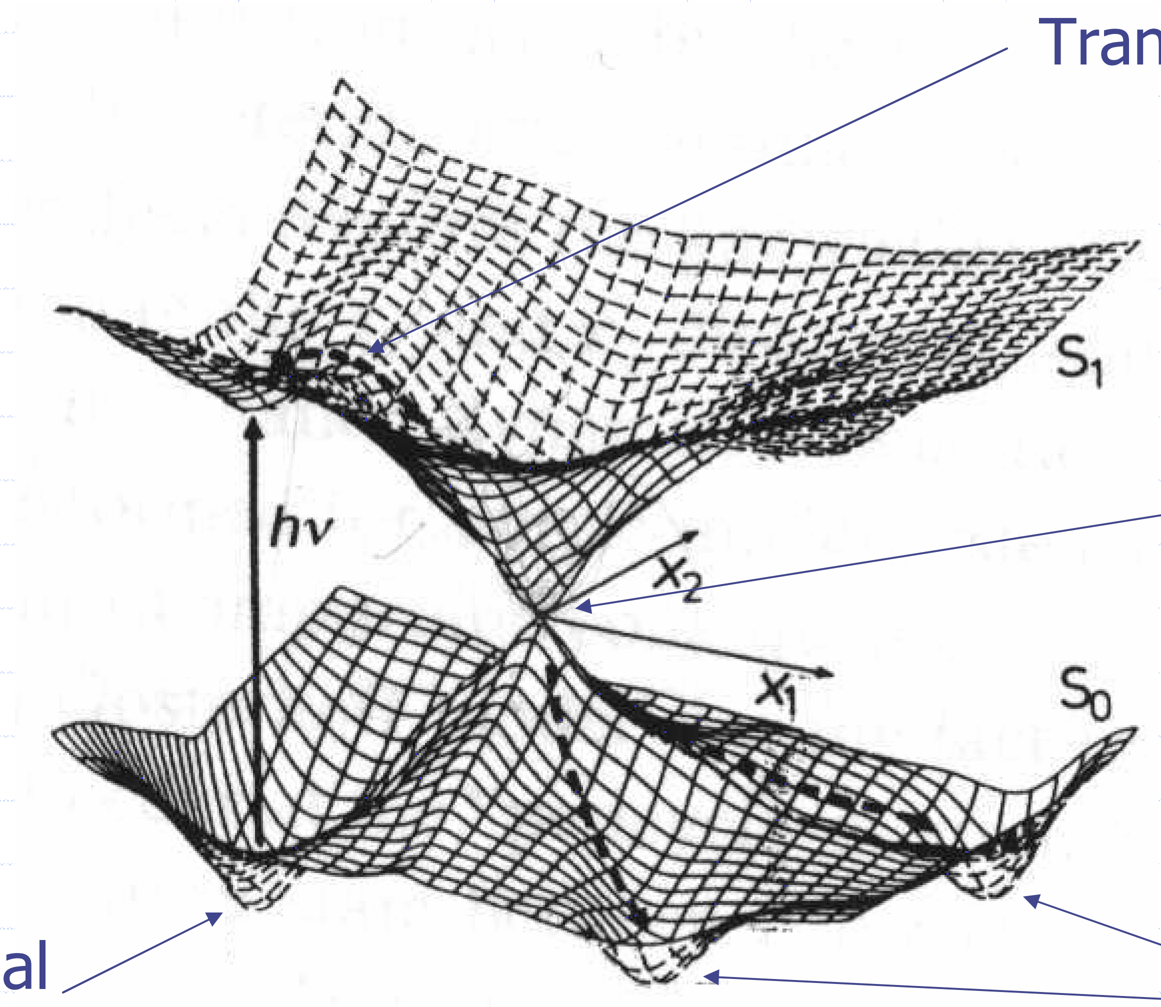
- Advantages
  - Cheaper than DFT
  - Only truly viable QM-like methods for entire proteins, but even small proteins are barely within reach
  - Can be reparameterized for each system/process
- Disadvantages
  - H-bond strengths often wrong by several kcal/mol
  - Still expensive

Summary of Methods

	Var?	Multi Ref?	Size Consistent?	Approx Error in 10 kcal/mol barrier height
RHF	Y	N	N	5-15
UHF	Y	N	Y	5-15
CASSCF	Y	Y	Nearly	3-7
CI	Y	Y	Only Full-CI	1-5
CC	N	N	Y	0.1-3
MP2	N	N	Y	4-10
DFT	N	N	Y/N	1-5

N.B. There are multi-reference perturbation and CC theories, esp. CASPT2 has been successful but sometimes has technical problems

PES Topography



Transition State

Conical Intersection

Global Minimum

Local Minima

Important Points

- Normally, only look for stationary points

$$\left.\frac{\partial E(\vec{R})}{\partial \vec{R}}\right|_{\vec{R}_{stationary}} = 0$$

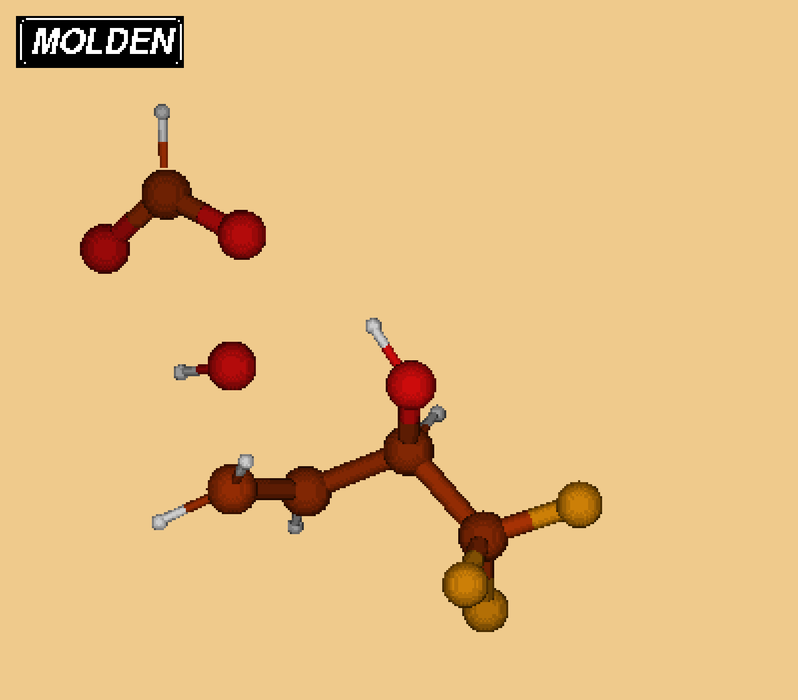
- These geometries may be local minima, global minima, transition states or higher order saddle points
- How to check?
  - Build and diagonalize the "Hessian" matrix

$$\begin{pmatrix} \frac{\partial^2 E}{\partial R_1^2} & & \frac{\partial^2 E}{\partial R_1 \partial R_N} \\ & \ddots & \\ \frac{\partial^2 E}{\partial R_N \partial R_1} & & \frac{\partial^2 E}{\partial R_N^2} \end{pmatrix}$$

- Count negative eigenvalues
  - 0 → local minimum
  - 1 → saddle point
  - >1 → useless

Hessian Matrix

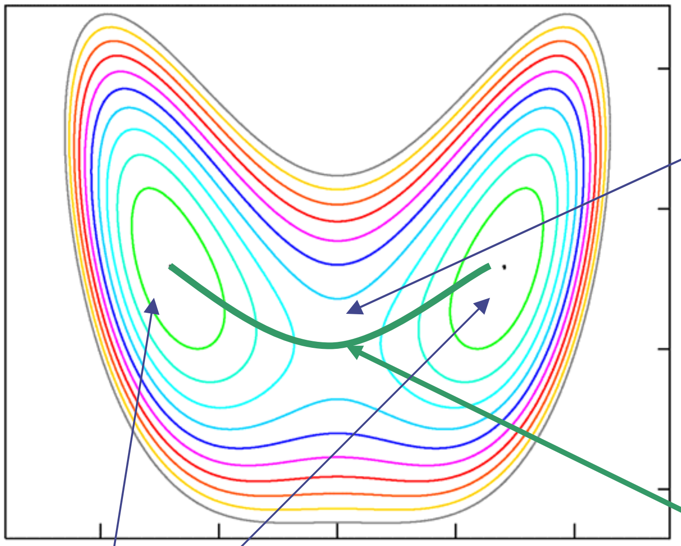
- Generally built in Cartesian coordinates
  - Will have 6 zero eigenvalues corresponding to rotation and translation
  - These must be identified and ignored in the analysis
  - How to identify? Animate normal modes, e.g. with MolDen
- Disadvantage – Expensive (10x Energy Calculation)



Special Warning!

- When a molecule has symmetry beware of optimizing to saddle points!
- If you enforce symmetry, obviously will maintain symmetry
- But, just starting from a high symmetry geometry is enough, because symmetry requires that gradient is nonzero *only* with respect to totally-symmetric modes
- Example: Try optimizing the geometry of water starting with perfectly linear molecule for initial guess…
- Conclusions:
  - Avoid high symmetry starting points
  - Always verify that stationary points are minima, at least by perturbing geometry (but Hessian is best)

Intrinsic Reaction Path (IRC)



Transition State

IRC is relevant *only* if all kinetic energy is drained instantaneously from the molecule, i.e. NEVER.

Local minima

Minimum energy path (MEP) or IRC