Conceptual DFT: the Linear response Function and Third Order Derivatives
Conceptual DFT: the Linear response Function and Third Order Derivatives

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1. Introduction: Chemical Concepts from DFT

2. The Linear response Function
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1. Introduction: Chemical Concepts from DFT

Fundamentals of DFT: the Electron Density Function as Carrier of Information


\( \rho(r) \) as basic variable

- \( \rho(r) \) determines \( N \) (normalization)
- "The external potential \( v(r) \) is determined, within a trivial additive constant, by the electron density \( \rho(r) \)"

\begin{center}
\begin{tikzpicture}

\node[anchor=south west,inner sep=0] (image) at (0,0) {
  \includegraphics[width=\textwidth]{example-image}\};

\node[anchor=north] at (image.south) {electrons};

\node[anchor=east] at (image.east) {\( \rho(r) \) for a given ground state};

\node[anchor=east] at (image.east) {compatible with a single \( v(r) \)};

\node[anchor=east] at (image.east) {- nuclei - position/charge};

\node[anchor=east] at (image.east) {\( v(r) \)};

\end{tikzpicture}
\end{center}
\[ \rho(r) \to H_{\text{op}} \to E = E[\rho] = \int \rho(r)v(r)dr + F_{\text{HK}}[\rho(r)] \]

- Variational Principle

\[ v(r) + \frac{\delta F_{\text{HK}}}{\delta \rho(r)} = \mu \]

\[ \int \rho(r)dr = N \]

- Practical implementation: Kohn Sham equations

Computational breakthrough

That branch of DFT aiming to give precision to often well known but rather vaguelly defined chemical concepts such as electronegativity, chemical hardness, softness, ..., to extend the existing descriptors and to use them either as such or within the context of principles such as the Electronegativity Equalization Principle, the HSAB principle, the Maximum Hardness Principle ...

Starting with Parr's landmark paper on the identification of $\mu$ as (the opposite of) the electronegativity.
Starting point for DFT perturbative approach to chemical reactivity

Consider \( E = E[N,v] \) Atomic, molecular system, perturbed in number of electrons and/or external potential

\[
dE = \left( \frac{\partial E}{\partial N} \right)_{v(\mathbf{r})} \, dN + \int \left( \frac{\delta E}{\delta v(\mathbf{r})} \right)_{N} \delta v(\mathbf{r}) \, d\mathbf{r}
\]

identification first order perturbation theory

\( \mu \)

identification \( \rho(\mathbf{r}) \)


\[
= - \chi \quad \text{(Iczkowski - Margrave electronegativity)}
\]
Identification of two first derivatives of E with respect to N and v in a DFT context → \textbf{response functions} in reactivity theory

\[
\begin{align*}
\frac{\partial E}{\partial N} &= \mu = -\chi \\
\frac{\partial^2 E}{\partial N^2} &= \eta \\
\frac{\delta E}{\delta v(r)} &= \rho(r) \\
\frac{\delta^2 E}{\delta v(r) \delta v(r')}/N &= \chi(r, r')
\end{align*}
\]

Chemical **hardness** = \( f(r) \)  

Chemical **Softness** = Fukui function

\[
S = \frac{1}{\eta}
\]
Combined descriptors


energy lowering at maximal uptake of electrons

\[
\Delta E = -\frac{\mu^2}{2\eta} = -\omega
\]

Reviews :

• P. Geerlings, F.De Proft, PCCP, 10, 3028 (2008)
Until now: focus on first and second order derivates

- $\mu = -\chi$ → Electronegativity Equalization Principle (EEM) (Sanderson, Mortier, ...)

- $\eta \rightarrow S = \frac{1}{\eta}$ → Chemical Hardness and Softness

  → HSAB Principle (Pearson, Parr)
  Maximum Hardness Principle (Pearson)

- $f(r)$

  $s(r) = Sf(r)$ → Fukui function and local Softness.
  → Local reactivity / selectivity (Parr, Yang)
What about the remaining second order derivative

\[ \chi(r, r') : \text{linear response function} \]

\[ = \left( \frac{\delta^2 E}{\delta v(r) \delta v(r')} \right) \]

- Computationally demanding
- Chemical Interpretation: six dimensional kernel
- Condensed Version

Fundamental Importance

1. Information about propagation of an (external potential) perturbation on position \( r' \) throughout the system

2. Berkowitz Parr relationship \((\text{JCP 88, 2554, 1988})\)

\[ \chi(r, r') = -s(r, r') + \frac{s(r)s(r')}{S} \]

\[ S \]

All information
What about third order derivatives in a pertubational approach?

- \( \left( \frac{\partial^3 E}{\partial N^3} \right)_v = \left( \frac{\partial \eta}{\partial N} \right)_v \): hyperhardness: known to be small

- \( \left( \frac{\delta^3 E}{\delta v(r) \delta v(r') \delta v(r'')} \right)_N = \left( \frac{\delta \chi(r,r',r'')}{\delta v(r'')} \right)_N \): awkward ...

? Importance of mixed “2+1” derivatives

- \( \left( \frac{\partial^3 E}{\partial^2 N \delta v(r)} \right)_N = \left( \frac{\delta \eta}{\delta v(r)} \right)_N = \left( \frac{\partial^2 \rho(r)}{\partial N^2} \right)_v = \left( \frac{\partial f(r)}{\partial N} \right)_v \) \quad \text{Dual descriptor}

Already a large number of applications: one shot representation of nucleophilic and electrophilic regions

- \( \left( \frac{\delta^3 E}{\partial N \delta v(r) \delta v(r')} \right)_v = \left( \frac{\delta \chi(r,r',r')}{\delta N} \right)_v = \left( \frac{\delta f(r)}{\delta v(r')} \right)_N \) \quad \text{Fukui kernel}

Polarization effects on Fukui function

unexplored

 Might play a role in describing change in polarizability upon ionization, electron attachment, ...
Today’s talk

• evaluation / interpretation of $\chi(r, r')$

• some examples of the computation / use of dual descriptor
2. The Linear Response function

- Some more formal discussions appeared in the literature some years ago (Parr, Senet, Cohen et al., Ayers)

- Liu and Ayers summarized the most important mathematical properties (*J.Chem Phys*, 131, 114406, 2009)

- How to come to numerical values and to use / interpret them
  - Early Hückel MO theory: mutual atom - atom polarizability \( \Pi_{rs} = \frac{\partial q_r}{\partial \alpha_s} \rightarrow \pi\)-electron system
  - Baekelandt, Wang: EEM
  - Cioslowski: approximate softness matrices

- NO direct, practical, generally applicable, nearly exact approach available
2.1 An Orbital based approach

- Single Slater determinant (say KS-DFT)
- Second order perturbation theory $V = \sum \delta v(r_i)$
- Closed shell, spin restricted calculations
- Frozen core
- $\Delta E_{i \rightarrow a} \sim \varepsilon_a - \varepsilon_i$

$$\chi(r, r') = 4 \sum_{i=1}^{N/2} \sum_{a=N/2+1}^{\infty} \frac{\varphi_i^*(r) \varphi_a(r) \varphi_a^*(r') \varphi_i(r')}{\varepsilon_i - \varepsilon_a}$$

$\varphi_i$: occupied orbitals
$\varphi_a$: unoccupied orbitals
$\varepsilon_i, \varepsilon_a$: orbital energies

Exact $(\delta \rho(r)/\delta v_{\text{KS}}(r'))_N \quad \text{Zeroth order approximation to the linear response kernel for the interacting system}$

$\rightarrow$ ? Visualisation /interpretation of this six dimensional kernel

• Condensation to an atom-condensed linear response matrix $\chi_{AB}$

• multi-center numerical integration scheme using Becke’s “fuzzy” Voronoi polyhedra

$$\chi_{AB} = \int \int_{V_A V_B} \chi(r,r') \, dr \, dr'$$

Ethanal (PBE-6-31+G*)

\[
\begin{array}{cccccccc}
  & C_1 & H_1 & O & C_2 & H_2 & H_3 & H_4 \\
 C_1 & -4.2080 & & & & & & \\
 H_1 & 0.6900 & -1.2365 & & & & & \\
 O & 2.7289 & 0.3338 & -3.7827 & & & & \\
 C_2 & 0.5067 & 0.1507 & 0.3522 & -3.3676 & & & \\
 H_2 & 0.0966 & 0.0024 & 0.1707 & 0.7813 & -1.1413 & & \\
 H_3 & 0.0966 & 0.0024 & 0.1707 & 0.7813 & 0.0372 & -1.1413 & \\
 H_4 & 0.0892 & 0.0572 & 0.0264 & 0.7950 & 0.0532 & 0.0532 & -1.0738 \\
\end{array}
\]

- diagonal elements: largest in absolute value;
  \( \chi_{c_1c_1} ; \chi_{oo} \): larger than in ethanol (-3.428, -2.187)
  \( \chi_{c_o} \) (0.873)

\[ \rightarrow \text{higher polarizability of } C=O \text{ vs } C-O \text{ bond} \]

- decrease in value of off-diagonal elements upon increasing interatomic distance
- correlation coefficient with ABEEM (C.S.Wang et al., CPL, 330, 132, 2000): 0.923

\[ \rightarrow \text{Confidence in use for exploration of (transmission) of inductive and mesomeric effects in organic chemistry:} \]
Transmission of a perturbation through a carbon chain

\[ \chi_{OX} \]  
(X = C_0, C_1, C_2 ...)

\[ \chi_{NX} \]

**Saturated systems**

- density response of C atoms on heteroatom perturbation decreases monotonously with distance

- exponential fit: \( r^2 = 0.982 \) (vide infra)

Characterizing and quantifying the inductive effect.
Unsaturated systems

- alternating values
  - $C_1, C_3, C_5$ of the chain: minima
  - $C_0, C_2, C_4, C_6$: maxima

**$R = OH, NH_2$: resonance structures**

$C_1, C_3, C_5$: mesomeric passive atoms
→ follow same trend as alkane structures (inductive effect)

$C_0, C_2, C_4, C_6$: mesomeric active atoms
→ effect remains consistently large even after 6 bonds (small decrease due to superposition of inductive and mesomeric effect)
**R = -CHO, -C≡N : resonance structures**

- Similar differences in trends between conjugated and nonconjugated systems highlighting fundamentally different character of inductive and mesomeric effect

- Higher values of $\chi_{OC_0}$ and $\chi_{NC_0}$ as compared to previous cases
  
  → polarizability of C=O and C≡N bonds

Cfr. also

- $\chi_{OO}$ R=OH -2.784 $\chi_{ON}$ R=CHO -4.312
- $\chi_{NN}$ R=NH$_2$ -3.592 $\chi_{NC}$ R=CN -6.040
A Comment on “the nearsightedness of electronic matter”

W. Kohn, PRL, 76, 3168, 1996
E. Prodan, W. Kohn, PNAS, 102, 11635, 2005

• For systems of many electrons and at constant \( \mu \)
  \( \Delta \rho(\mathbf{r}_0) \) induced by \( \Delta \mathbf{v}(\mathbf{r}') \) with \( \mathbf{r}' \) outside a radius \( R \) around
  \( \mathbf{r}_0 \) will always be smaller than a maximum magnitude \( \Delta \rho \)

\( \rightarrow \) maximum response of the electron density will decay monotonously as a function of \( R \).

\( \rightarrow \) Importance of softness kernel

\[
\left( \frac{\delta \rho(\mathbf{r})}{\delta \mathbf{v}(\mathbf{r}')} \right)_\mu
\]

• \( \mathbf{r}' \)

No numerical applications to atomic or molecular systems yet

\[ |\mathbf{r}'-\mathbf{r}_0| >> R \]
Softness kernel $s(r,r')$ (evaluated at constant $\mu$!): **nearsighted** (Ayers)

Linear response kernel $\chi(r,r')$ (evaluated at constant $N$): **not nearsighted**

Berkowitz - Parr relationship

$$\chi(r,r') = -s(r,r') + \frac{s(r)s(r')}{S}$$

farsighted contribution to $\chi(r,r')$

? Small electron transfer $\rightarrow$ neglect of this term

$\chi(r,r')$ behaves as $-s(r,r')$

declines exponentially as $r$ and $r'$ get further apart

(Prodan-Kohn)

(Cardenas...Ayers *JPCA, 113, 8660, 2009*)

Exponential decay as observed for the inductive effect in the systems above studied

*N. Sablon, F. De Proft, P. Geerlings, JPCLe., 1, 1228, 2010*
Some recent work: substituted benzenes vs cyclohexanes

- cyclohexane:  \( \chi \) decreases exponentially (inductive effect)
  - influence of OH small

- benzene:  maxima at C\(_2\), C\(_4\), C\(_6\): mesomerically active atoms (mesomeric effect)
  - minima at C\(_3\), C\(_5\): mesomerically inactive atoms
\[ \chi_{XC_i} \ (i = 1, 2, \ldots 6) \]

Importance of Inductive Effect

**Importance of Inductive Effect**

- Exponential decay: inductive effect
- Mesomeric active carbons 2, 4, 6
- Decreasing mesomeric activity
- Increasing electronegativity
• Similar behaviour for o,p and m directors

• Mesomerically active atoms: 2,4,6

• Hyperconjugation vs n-mesomeric effect

2.2 An alternative approach: direct evaluation of the second order functional derivative

\[
\left( \frac{\delta^2 E}{\delta v(r) \delta v(r')} \right)_N
\]

In line with earlier work concerning the transformation of \( \frac{\partial}{\partial N} \) to \( \frac{\delta}{\delta v(r)} \) expressions

- Fukui-functions
  \[
  f(r) = \left( \frac{\partial \rho(r)}{\partial N} \right)_v = \left( \frac{\delta \mu}{\delta v(r)} \right)_N
  \]
  Difficulties with \( \frac{\partial}{\partial N} \) derivative

- Dual descriptor
  \[
  f^{(2)}(r) = \left( \frac{\partial f(r)}{\partial N} \right)_v = \left( \frac{\delta \eta}{\delta v(r)} \right)_N
  \]

Methodology: earlier work (e.g. Fukui Function)\( \left( \frac{\delta Q}{\delta v} \right) \)

\[ Q[v+w_i] - Q[v] = \int \left( \frac{\delta Q[v]}{\delta v(r)} \right)_N w_i(r) \, dr + o \left( |w_i|^2 \right) \]

perturbation \( w_i(r) \) (i = 1, ..., P)

- Linear response regime
- Basis set expansion

\[ \left( \frac{\delta Q[v]}{\delta v(r)} \right)_N = \sum_{j=1}^{K} q_j \beta_j(r) \]

\[ \rightarrow Q[v+w_i] - Q[v] = \sum_{j=1}^{K} q_j \int w_i(r) \beta_j(r) \, dr \]

\[ d = Bq \]

Choose \( P > K \) → find \( q \) via least squares fitting

- Perturbations \( w_i(r) = \frac{-p_i}{|r-R_i|} \)

- Expansion functions • s on p type GTO centered on each center
  • exponents doubled as compared to primitive set
An example $\text{H}_2\text{CO}$  \hspace{1cm} Fukui function $f^+(r)$

![Graph of $f^+(r)$ for H$_2$CO]

Nucleophilic attack (including correct angle) at C

SCN$^-$  \hspace{1cm} Fukui function $f^-(r)$

![Graph of $f^-(r)$ for SCN$^-$]

Softer reaction site for an attacking electrophile: S

Turning to a second functional derivative

\[ \chi(r,r') = \left( \frac{\delta^2 E}{\delta v(r) \delta v(r')} \right)_N \]

\[ E[v+w_i] - 2E[v] + E[v-w_i] \approx \int \int \chi(r,r') w_i(r) w_i(r') \, dr \, dr' \]

\[ \chi(r,r') = \sum_{kl} q_{kl} \beta_k(r) \beta_l(r) \]

\[ E[v+w_i] - 2E[v] + E[v-w_i] = \sum_{kl} q_{kl} \int \beta_k(r) w_i(r) \, dr \int \beta_l(r') w_i(r') \, dr' \]

\[ q_{kl} \rightarrow \chi(r,r') \xrightarrow{\text{condensation}} \chi_{AB} \]

(in practice: direct evaluation in atom-condensed version)
An example $\text{H}_2\text{CO}$

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>C</th>
<th>O</th>
<th>H2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous method</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>H</td>
<td>-1.22</td>
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<tr>
<td>C</td>
<td>0.68</td>
<td>-4.35</td>
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<tr>
<td>O</td>
<td>0.34</td>
<td>2.99</td>
<td>-3.67</td>
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<td>H</td>
<td>0.19</td>
<td>0.68</td>
<td>0.34</td>
<td>-1.22</td>
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<tr>
<td>H</td>
<td>-1.21</td>
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<tr>
<td>C</td>
<td>1.19</td>
<td>-4.82</td>
<td></td>
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<tr>
<td>O</td>
<td>0.42</td>
<td>2.45</td>
<td>-3.28</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>-0.40</td>
<td>1.19</td>
<td>0.42</td>
<td>-1.21</td>
</tr>
</tbody>
</table>

Correlation coefficient between the matrix elements of the two methods:

$Y = 0.99x - 0.01$

$R^2 = 0.96$

Slope $\approx 1$
For other simple molecules (NH₃, CO, HCN, NNO) always a high correlation coefficient is obtained with a very small intercept; the slope varies between 1 and 2.

Intramolecular comparisons are similar between two approaches; for intermolecular sequencies the transition to s(r, r') might be advisable comparable with the switch from f(r) to s(r).

N. Sablon, P.W. Ayers, F. De Proft, P. Geerlings, submitted
2.3 Conclusions

- The **linear response function** comes within reach of a general, non-empirical computational strategy: the last method presented can serve as benchmark.

- It is the tool by excellence to investigate **how information on perturbations is propagated** through the system.

- **Atom condensation** is at stake, but can nowadays be done in a systematic way.

- The linear response function has been shown to account for the **difference in fall off behavior** of inductive and mesomeric affects and to connect them with the concept of nearsightedness.

- The way to the **softness kernel** \( s(r,r') \) has (almost) been paved.
3. Higher order derivatives

3.1 The dual descriptor

Consider

\[
\left( \frac{\delta^3 E}{\delta \nu(r) \partial N^2} \right) = \left( \frac{\partial^2 \rho(r)}{\partial N^2} \right) = \left( \frac{\partial f(r)}{\partial N} \right)_v = f^{(2)}(r) \rightarrow \text{Third order response function}
\]

- Introduced as a new descriptor, "dual descriptor"


\[f^{(2)}(r) = \left( \frac{\partial^2 \rho(r)}{\partial N^2} \right)_v \equiv \rho_{N+1}(r) - 2\rho_N(r) + \rho_{N-1}(r) \]

\[= (\rho_{N+1}(r) - \rho_N(r)) - (\rho_N(r) - \rho_{N-1}(r)) \]

\[\approx |\phi_{\text{LUMO}}(r)|^2 - |\phi_{\text{HOMO}}(r)|^2 \]

\[\rightarrow f^{(2)}(r) \begin{cases} > 0 & \text{electrophilic regions} \\ < 0 & \text{nucleophilic regions} \end{cases} \]

Large in electrophilic regions

Large in nucleophilic regions
→ a one shot picture of both electrophilic and nucleophilic regions in space

An example: Carbene (Singlet) (+/- 0.01 surface plot)

\[ f^{(2)} > 0 \]: electrophilic region (empty 2p orbital)

\[ f^{(2)} < 0 \]: Nucleophilic region (lone pair)

Favorable chemical reactions occur when regions that are **good electron acceptors** ($f^{(2)}(r) > 0$) are aligned with regions that are **good electron donors** ($f^{(2)}(r) < 0$)

Minimizing \[
\int \int \frac{f_A^{(2)}(r)f_B^{(2)}(r')}{|r-r'|} drdr'
\]

Confirmed by perturbation theoretical ansatz (P.W. Ayers)

A way to rationalize the celebrated Woodward Hoffmann rules is an orbital free, even wave function free context
One of our points of interest in recent years, coupled to another third order derivative:

\[ \left( \frac{\partial \eta}{\partial R} \right)_0 \text{ the initial hardness response} \]


Successful application to
- electrocyclisation
- cycloadditions
- sigmatropic reactions
- chelotropic reactions
The first case: Cycloadditions

Butadiene + ethene \[ \left[ \pi_4 \right] + \left[ \pi_2 \right] \]

| HOMO | LUMO | \( f^{(2)}(r) = |\phi_{LUMO}(r)|^2 - |\phi_{HOMO}(r)|^2 \) |
|------|------|---------------------------------|
| Ethene | ![Ethene HOMO](image) | ![Ethene LUMO](image) | ![Ethene Interaction](image) |
| Butadiene | ![Butadiene HOMO](image) | ![Butadiene LUMO](image) | ![Butadiene Interaction](image) |

Hückel | B3LYP/6-31G*
Molecules align so that favorable interactions (green lines) occur between their dual descriptors

\[ [\pi^4_s + \pi^2_s] \text{ "allowed"} \]
• The $[\pi_2s + \pi_2s]$ case: ethene + ethene

**supra/supra**: "repulsive"

↓

not allowed

**supra/antara**: can occur if the molecules rotate so that the double bonds become perpendicular

↓

allowed

(but steric demands too high to occur in practice)

Similar result by considering $\left(\frac{\partial \eta}{\partial R}\right)$ (initial hardness response)

→ WH rules for cycloadditions regained
The fourth case: Chelotropic Reactions

filled and vacant frontier orbitals for bonding to other atoms on the same atom (CO, singlet carbenes)

σ bonds broken or formed on the same atom, in casu S
The WH Rules on chelotropic reactions in an orbital context

4n case: linear chelotropic addition

- Disrotatory mode
- Non-linear case: mode is inverted
Linear Chelotropic Reaction: $4n$ system

Side view

Top view
The Initial Hardness Response

Energy and hardness profile $\frac{\partial \eta}{\partial \psi}$ Disrotatory mode in agreement with WH
Confirmed in the \((4n+2)\) case

\[
\begin{align*}
\text{SO}_2 & \rightarrow \text{C} \quad + \quad \text{SO}_2 \\
\text{Conrotatory} & \rightarrow \text{disrotatory} \\
\text{Disrotatory} & \rightarrow \text{conrotatory}
\end{align*}
\]

What about the non-linear case?
Nonlinear Chelotropic Reaction: $4n$ system

Side view

Top view
Energy and hardness \( (\partial \eta/\partial \phi) \) predict conrotatory mode \( (|Z|<0.5) \)
Confirmed in the 4n+2 case: disrotatory mode

\[ z = -0.3 \]
• The dual descriptor approach

**Linear Chelotropic Reaction: 4n System**

\[ f^{(2)}(\bar{r}) > 0 \text{ (red)} \]

\[ f^{(2)}(\bar{r}) < 0 \text{ (blue)} \]

Stabilizing interactions

Disrotatory
Nonlinear Chelotropic Reaction: 4n System

Destabilizing interactions

Conrotatory
3.2 Reconciling the dual descriptor and the initial hardness response

Dual descriptor

\[ f^{(2)}(\mathbf{r}) = \left( \frac{\partial f(\mathbf{r})}{\partial N} \right)_v = \left( \frac{\partial}{\partial N} \left( \frac{\delta \mu}{\delta v(\mathbf{r})} \right) \right)_v \]

\[ = \left( \frac{\delta}{\delta v(\mathbf{r})} \left( \frac{\partial \mu}{\partial N} \right)_v \right)_N = \left( \frac{\delta \eta}{\delta v(\mathbf{r})} \right)_N \]

Changes in \( v(\mathbf{r}) \) provoked by changes in nuclear configuration only

cf. \( \left( \frac{\partial \eta}{\partial R} \right)_N = \int \left( \frac{\delta \eta}{\delta v(\mathbf{r})} \right)_N \frac{\partial v(\mathbf{r})}{\partial R} d\mathbf{r} \)

\[ = \int f^{(2)}(\mathbf{r}) \frac{\partial v(\mathbf{r})}{\partial R} d\mathbf{r} \]

General Information refined via \( \frac{\partial v(\mathbf{r})}{\partial R} \) to initial Hardness Response.
WH rules regained in a conceptual DFT context for all four types of pericyclic reactions, thereby avoiding symmetry or phase based arguments

- initial hardness response
- dual descriptor "back of the envelope" approach
- two approaches internally consistent

Importance of third order derivatives
3.3 The chemical relevance of higher order \((n \geq 3)\) derivatives

Chemistry at **first order**: electronegativity (Pauling)

- Correction for hardness, softness, polarizability
- Incorporation of frontier MO Theory

**second order**: Fukui function, hardness, ...

→ linear response function, softness kernel

**third order**: • diagonal \((N\ or\ v)\): small or too hard to interpret

• non diagonal: fundamentally new information, eg. dual descriptor

**P.Geerlings, F.De Proft, PCCP, 10, 3028 (2008)**
4. Conclusions

• Conceptual DFT offers a broad spectrum of reactivity descriptors

• The “missing” second order derivative, the “linear response function”, comes within reach and is a tool to see how $\Delta v$ perturbations are propagated through a molecule.

• Selected third order derivatives may contain important chemical information
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