Theor Chem Acc (2017) 136:19
DOI 10.1007/s00214-016-2036-0

REGULAR ARTICLE

The local response of global descriptors

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Received: 12 July 2016 / Accepted: 30 November 2016 / Published online: 29 December 2016

Abstract We consider the problem of defining an appropriate local descriptor corresponding to an arbitrary global descriptor. Although it does not seem easy to rigorously and uniquely define local analogues of derived global descriptors (e.g., the electrophilicity) or the fundamental global descriptors associated with the canonical ensemble (e.g., the hardness), the local response of these global descriptors can be defined unambiguously. We look at the local response of the global electrophilicity and compare it to the conventional, ad hoc, definition of the local electrophilicity. The local response of global nucleofugality and electrofugality is also discussed.

Keywords Conceptual density functional theory · Electrophilicity · Local reactivity descriptor · Response function · Chemical reactivity indicator

1 Motivation and background

In the density functional theory (DFT) approach to chemical reactivity, often called conceptual DFT [1–5], the key reactivity indicators are the responses of the system to changes in the global parameters (usually the number of electrons, N, or the electronic chemical potential, μ) and a local function (usually the external potential, $v(\mathbf{r})$) that define the system. In addition to these *fundamental* reactivity indicators, there are additional derived indicators, which combine the fundamental response function-based indicators in expressions that have been found to be empirically useful or, occasionally, mathematically interesting. These composite indicators include the electrophilicity [6–9], nucleofugality [2, 10], the electron-donating and electron-accepting powers, etc. [11, 12].

The fundamental global reactivity indicators are built from derivatives of the energy with respect to the number of electrons, $\left(\partial^k E/\partial N^k\right)_{v(\mathbf{r})}$, and the derivatives of the grand potential, $\Omega = E - \mu N$, with respect to the chemical potential, $\left(\partial^k \Omega/\partial \mu^k\right)_{v(\mathbf{r})}$ [13]. The functional derivative of a global indicator with respect to $v(\mathbf{r})$ is a local reactivity indicator. In addition to these “fundamental” local indicators, there are also the “derived” local analogues to global indicators. All these local quantities, like the local softness and the local electrophilicity, are defined so that the integral over all space of the local descriptor property $p_{\text{Local}}(\mathbf{r})$ is equal to the global descriptor P_{Global}, i.e. [9, 14, 15],

$$P_{\text{Global}} = \int p_{\text{Local}}(\mathbf{r})\mathrm{d}\mathbf{r} \qquad (1)$$

This allows one to not only determine the overall reactivity of a molecule, but to determine which portions of the molecule make the greatest contribution to its overall reactivity [16, 17], and therefore determine the molecule’s

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Published as part of the special collection of articles “Festschrift in honour of A. Vela”.

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$$\begin{tikzcd}
 & & & & \Omega[\mu, v(\mathbf{r})] \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r})"] & & & & \\
 & & & -N \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r})"] & & \rho(\mathbf{r}) \arrow[ll, dashed, "-\int d\mathbf{r}"'] \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r}')"] & & & \\
 & & -S \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r})"] & & s(\mathbf{r}) \arrow[ll, dashed, "-\int d\mathbf{r}"'] \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r}')"] & & -s(\mathbf{r}, \mathbf{r}') \arrow[ll, dashed, "-\int d\mathbf{r}'"'] \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r}'')"] & & \\
 & -S^{(2)} \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r})"] & & s^{(2)}(\mathbf{r}) \arrow[ll, dashed, "-\int d\mathbf{r}"'] \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r}')"] & & -s^{(2)}(\mathbf{r}, \mathbf{r}') \arrow[ll, dashed, "-\int d\mathbf{r}'"'] \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r}'')"] & & s^{(2)}(\mathbf{r}, \mathbf{r}', \mathbf{r}'') \arrow[ll, dashed, "-\int d\mathbf{r}''"'] \arrow[dl, "\partial\mu"'] \arrow[dr, "\delta v(\mathbf{r}''')"] & \\
\cdots & & \cdots & & \cdots & & \cdots & & \cdots
\end{tikzcd}$$

Fig. 1 Fundamental global, local and nonlocal reactivity indicators of the grand potential, Ω, obtained by taking its derivatives with respect to chemical potential μ and its functional derivatives with respect to external potential $v(\mathbf{r})$. Notice that by integration with respect to spatial coordinate(s), one can reduce the nonlocal indicators to local indicators, and local indicators to global indicators

regioselectivity. It is common to *define* the local analogue of a global descriptor by multiplying the global descriptor by the Fukui function,

$$p_{\text{Local}}(\mathbf{r}) = P_{\text{Global}} \cdot f(\mathbf{r}) \tag{2}$$

where the Fukui function is defined as [18–20]

$$f(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_{v(\mathbf{r})} = \left(\frac{\delta \mu}{\delta v(\mathbf{r})}\right)_N \tag{3}$$

This is the approach that is used, for example, to generate "derived" local descriptors like the local electrophilicity [9]. However, this approach is ad hoc, as Eq. (1) will be satisfied for any formula of the form

$$\begin{aligned} p_{\text{Local}}(\mathbf{r}) &= P_{\text{Global}} \cdot g(\mathbf{r}) \\ 1 &= \int g(\mathbf{r})d\mathbf{r} \end{aligned} \tag{4}$$

The motivation for Eq. (1) is the structure of the derivatives of the grand potential, as represented in Fig. 1. In this case, the global reactivity indicators, defined as [15, 21–23]

$$S^{(k-1)} = -\left(\frac{\partial^k \Omega}{\partial \mu^k}\right)_{v(\mathbf{r})} \qquad k = 0, 1, \ldots \tag{5}$$

are integrals of the local indicators in the second column of Fig. 1,

$$s^{(k-1)}(\mathbf{r}) = \left(\frac{\delta}{\delta v(\mathbf{r})}\left(\frac{\partial^{k-1}\Omega}{\partial \mu^{k-1}}\right)_{v(\mathbf{r})}\right)_\mu \qquad k = 1, 2, \ldots \tag{6}$$

$$\int s^{(k-1)}(\mathbf{r})d\mathbf{r} = S^{(k-1)} \tag{7}$$

which are, in turn, integrals of the nonlocal indicators in the third column of Fig. 1,

$$s^{(k-1)}(\mathbf{r}, \mathbf{r}') = -\left(\frac{\delta^2}{\delta v(\mathbf{r})\delta v(\mathbf{r}')}\left(\frac{\partial^{k-2}\Omega}{\partial \mu^{k-2}}\right)_{v(\mathbf{r})}\right)_\mu \qquad k = 2, 3, \ldots \tag{8}$$

$$\int s^{(k-1)}(\mathbf{r}, \mathbf{r}')d\mathbf{r}' = s^{(k-1)}(\mathbf{r}) \quad k = 2, 3, \ldots \tag{9}$$

and so on [15]. These relations are all "inherited" by differentiating the fundamental $k = 1$ equation repeatedly with respect to μ (obtaining Eq. 7) and $v(\mathbf{r})$ (obtaining Eq. 9),

$$S^{(0)} = -\left(\frac{\partial \Omega}{\partial \mu}\right) = N = \int \rho(\mathbf{r})d\mathbf{r} = \int \left(\frac{\delta \Omega}{\delta v(\mathbf{r})}\right)_\mu d\mathbf{r} = \int s^{(0)}(\mathbf{r})d\mathbf{r} \tag{10}$$

In the defining equations for the grand canonical ensemble, we have chosen to overload the notation for the global (hyper)softness, local (hyper)softness and (hyper)softness kernel by defining the zeroth derivative as the identity operator. Therefore, $S^{(-1)}$ is minus one times the grand potential itself, $S^{(-1)} = -\Omega$, and $S^{(0)} = N$. Similarly, $s^{(0)}(\mathbf{r})$ is simply the ground-state electron density. This extension of the usual definition is convenient since it allows us to write the initial condition for the normalization conditions, Eq. (10), in a compact way.

Notice that in Eq. (10) the shape function, $\sigma(\mathbf{r}) = \rho(\mathbf{r})/N$, not the Fukui function, plays the role of function $g(\mathbf{r})$ in Eq. (4) [24–26]. For $k = 2$, we have

$$\begin{aligned} S^{(1)} &= -\left(\frac{\partial^2 \Omega}{\partial \mu^2}\right) = S = \int s(\mathbf{r})d\mathbf{r} \\ &= \int \left(\frac{\delta}{\delta v(\mathbf{r})}\left(\frac{\partial \Omega}{\partial \mu}\right)_{v(\mathbf{r})}\right)_\mu d\mathbf{r} = \int s^{(1)}(\mathbf{r})d\mathbf{r} \end{aligned} \tag{11}$$

In this case, the function $g(\mathbf{r})$ in Eq. (4) is the Fukui function, $s(\mathbf{r}) = S \cdot f(\mathbf{r})$ [14]. Finally, for $k = 3$, we have

$$S^{(2)} = -\left(\frac{\partial^3 \Omega}{\partial \mu^3}\right) = \int s^{(2)}(\mathbf{r})\mathrm{d}\mathbf{r} = \int \left(\frac{\delta}{\delta v(\mathbf{r})}\left(\frac{\partial^2 \Omega}{\partial \mu^2}\right)_{v(\mathbf{r})}\right)_{\mu} \mathrm{d}\mathbf{r} \tag{12}$$

and the function $g(\mathbf{r})$ in Eq. (4) is again not the Fukui function, but instead [27, 28]

$$s^{(2)}(\mathbf{r}) = S^{(2)}\left(f(\mathbf{r}) - \frac{S^2}{S^{(2)}} f^{(2)}(\mathbf{r})\right) \tag{13}$$

where $f^{(2)}(\mathbf{r}) = \left(\partial^2 \rho(\mathbf{r}) / \partial N^2\right)_{v(\mathbf{r})}$ is the dual descriptor [27, 29–31].

Because the most appropriate choice of $g(\mathbf{r})$ in Eq. (4) clearly depends on which global reactivity indicator one is interested in, we concur with Cedillo, Contreras, Morell, Gazquez, Vela, Guegan, and Chermette that it is undesirable to automatically define local versions of global descriptors to be the product of the global descriptor and the Fukui function [12, 32]. The Fukui function approach, for example, leads to incorrect results for derivatives of the grand potential, which is arguably the only case where local descriptors can be unambiguously defined within the conventional mathematical framework of conceptual DFT. Motivated by the structure of the grand canonical ensemble indicators, however, it seems sensible to define the local representation of a global descriptor as the functional derivative with respect to $v(\mathbf{r})$ of the antiderivative of the global descriptor with respect to μ. (i.e, in analogy to the grand canonical ensemble descriptors, a local descriptor could be defined by replacing a derivative with respect to μ with a derivative with respect to $v(\mathbf{r})$). For global reactivity indicators that have zero value when the chemical potential is zero, this motivates the definition

$$p_{\text{local}}(\mathbf{r}) = \left(\frac{\delta}{\delta v(\mathbf{r})}\left[\int_0^{\mu} P_{\text{Global}}(m)\mathrm{d}m\right]\right)_{\mu} \tag{14}$$

This definition recovers the traditional local versions of the fundamental global descriptors defined as derivatives of the grand potential, but except for those descriptors and others closely related to them, the integral of this local descriptor is not equal to the corresponding global descriptor. To see this, consider applying the same recipe to define local chemical potential

$$\mu(\mathbf{r}) = \left(\frac{\delta}{\delta v(\mathbf{r})}\int_0^{\mu} m\mathrm{d}m\right)_{\mu} = \left(\frac{\delta\left(\frac{1}{2}\mu^2\right)}{\delta v(\mathbf{r})}\right)_{\mu} = 0 \tag{15}$$

which does not integrate to the global chemical potential. Similarly, using this approach to define the local electrophilicity gives

$$\begin{aligned}\omega(\mathbf{r}) &= \left(\frac{\delta}{\delta v(\mathbf{r})}\int_0^{\mu}\left(\frac{m^2}{2}\left(\frac{\partial N}{\partial m}\right)_{v(\mathbf{r})}\right)\mathrm{d}m\right)_{\mu} \\ &= -\mu^2 s(\mathbf{r}) + 2\mu\rho[\mu;\mathbf{r}] - 2\int_0^{\mu}\rho[m;\mathbf{r}]\mathrm{d}m\end{aligned} \tag{16}$$

where $\rho[\mu;\mathbf{r}]$ denotes the ground-state electron density of the system with chemical potential μ and $s(\mathbf{r})$ is the local softness of that system. The obvious approach of using the antiderivative to link local and global descriptors, therefore, seems unpromising.

2 The local response of global descriptors

How then should one define the local analogue of a global reactivity indicator? Multiplying by the Fukui function is arbitrary and inconsistent with established definitions for derivatives of the grand potential, while the strategy in Eq. (14) is inconsistent with the requirement that the integral of the local descriptor recovers the global descriptor as in Eq. (1). We have deliberated on this dilemma at some length and decided that it was sensible to avoid the issue by defining, instead, the local response of a global reactivity indicator in the straightforward way, by differentiation with respect to the external potential (at either constant N or constant μ). That is, we define,

$$\ell_{P_{\text{Global}};\mu}(\mathbf{r}) = \left(\frac{\delta P_{\text{Global}}}{\delta v(\mathbf{r})}\right)_{\mu} \tag{17}$$

$$\ell_{P_{\text{Global}};N}(\mathbf{r}) = \left(\frac{\delta P_{\text{Global}}}{\delta v(\mathbf{r})}\right)_{N} \tag{18}$$

as the local response of the global descriptors. In contrast to p_{local}, these local responses do not give back P_{Global} when integrated over all space. In the same manner, higher-order derivatives with respect to $v(\mathbf{r})$ would define the nonlocal responses of the global descriptors, which is a topic we defer for future research. Considering this definition, the local response of fundamental global indicators, like chemical potential and chemical hardness, are already known local indicators, like Fukui function and dual descriptor. However, this is not the case for derived global indicators.

To exemplify the definition in Eq. (18) for derived global indicators, the local response of nucleofugality and electrofugality is derived [2, 10],

$$\begin{aligned}\ell_{\text{Nucleofugality};N}(\mathbf{r}) &= \left(\frac{\delta[E(N_0+1)-E(N_{\max})]}{\delta v(\mathbf{r})}\right)_N = \rho_{N_0+1}(\mathbf{r}) - \rho_{N_{\max}}(\mathbf{r}) \\ \ell_{\text{Electrofugality};N}(\mathbf{r}) &= \left(\frac{\delta[E(N_0-1)-E(N_{\max})]}{\delta v(\mathbf{r})}\right)_N = \rho_{N_0-1}(\mathbf{r}) - \rho_{N_{\max}}(\mathbf{r})\end{aligned} \tag{19}$$

where N_0 and $N_{\max}$ are the reference number of electrons and the maximum number of bound electrons, respectively, and $N_{\max} = -\frac{\mu}{\eta}$ for the quadratic energy model. When integrated over all space, the local responses in Eq. (19) result in $N_0 + 1 - N_{\max} = 1 - \Delta N_{\max}$ and $N_{\max} - N_0 + 1 = 1 + \Delta N_{\max}$, respectively. As these derived global indicators were specifically defined for the quadratic $E(N)$ model [33–36], Eq. (19) should be evaluated using the quadratic model for the electron density of N-electron system [37],

$$\begin{aligned}\rho_N(\mathbf{r}) &= \rho_{N_0}(\mathbf{r}) + (N-N_0)\underbrace{\left(\frac{\rho_{N_0+1}(\mathbf{r}) - \rho_{N_0-1}(\mathbf{r})}{2}\right)}_{f(\mathbf{r})} \\ &\quad + \frac{(N-N_0)^2}{2}\underbrace{\left(\rho_{N_0+1}(\mathbf{r}) - 2\rho_{N_0}(\mathbf{r}) + \rho_{N_0-1}(\mathbf{r})\right)}_{f^{(2)}(\mathbf{r})}\end{aligned} \tag{20}$$

The associated quadratic local responses of nucleofugality and electrofugality are:

$$\begin{aligned}\ell_{\text{Nucleofugality};N}(\mathbf{r}) &= \left(\frac{\mu+\eta}{\eta}\right)f(\mathbf{r}) + \left(\frac{\eta^2-\mu^2}{2\eta^2}\right)f^{(2)}(\mathbf{r}) \\ \ell_{\text{Electrofugality};N}(\mathbf{r}) &= \left(\frac{\mu-\eta}{\eta}\right)f(\mathbf{r}) + \left(\frac{\eta^2-\mu^2}{2\eta^2}\right)f^{(2)}(\mathbf{r})\end{aligned} \tag{21}$$

A more controversial example is the local response of electrophilicity ω defined as,

$$\begin{aligned}\ell_{\omega;N}(\mathbf{r}) &= \left(\frac{\delta\omega}{\delta v(\mathbf{r})}\right)_N = \left(\frac{\delta[E(N_{\max}) - E(N_0)]}{\delta v(\mathbf{r})}\right)_N \\ &= \rho_{N_{\max}}(\mathbf{r}) - \rho_{N_0}(\mathbf{r})\end{aligned} \tag{22}$$

This results in $N_{\max} - N_0 = \Delta N_{\max}$ when integrated over all space. As $\Delta N_{\max}$ and ω are defined for the quadratic energy model, we use the corresponding Fukui function and dual descriptor expressions in Eq. (20) to simplify the local responses

$$\begin{aligned}\ell_{\omega;N}(\mathbf{r}) &= -\left(\frac{\mu}{\eta}\right)f(\mathbf{r}) + \frac{1}{2}\left(\frac{\mu}{\eta}\right)^2 f^{(2)}(\mathbf{r}) \\ &= -\left(\frac{\mu}{\eta}\right)\left(\frac{\rho_{N_0+1}(\mathbf{r}) - \rho_{N_0-1}(\mathbf{r})}{2}\right) \\ &\quad + \left(\frac{\mu}{\eta}\right)^2\left(\frac{\rho_{N_0+1}(\mathbf{r}) - 2\rho_{N_0}(\mathbf{r}) + \rho_{N_0-1}(\mathbf{r})}{2}\right)\end{aligned} \tag{23}$$

This can also be derived directly by taking the functional derivative of electrophilicity defined within the quadratic energy model:

$$\begin{aligned}\ell_{\omega;N}(\mathbf{r}) &= \left(\frac{\delta\omega}{\delta v(\mathbf{r})}\right)_N = \left(\frac{\delta\left(\frac{-\mu^2}{2\eta}\right)}{\delta v(\mathbf{r})}\right)_N \\ &= -\left(\frac{\mu}{\eta}\right)f(\mathbf{r}) + \frac{1}{2}\left(\frac{\mu}{\eta}\right)^2 f^{(2)}(\mathbf{r}) \\ &= \omega\left(-\frac{2}{\mu}f(\mathbf{r}) + \frac{1}{\eta}f^{(2)}(\mathbf{r})\right)\end{aligned} \tag{24}$$

and

$$\begin{aligned}\ell_{\omega;\mu}(\mathbf{r}) &= \left(\frac{\delta\omega}{\delta v(\mathbf{r})}\right)_\mu = \left(\frac{\delta\left(\frac{1}{2}\mu^2 S\right)}{\delta v(\mathbf{r})}\right)_\mu = -\tfrac{1}{2}\mu^2 s^{(2)}(\mathbf{r}) \\ &= -\tfrac{1}{2}\mu^2\left(S^{(2)}f(\mathbf{r}) - S^2 f^{(2)}(\mathbf{r})\right) \\ &= \omega\left(S\cdot f^{(2)}(\mathbf{r}) - \frac{S^{(2)}}{S}f(\mathbf{r})\right)\end{aligned} \tag{25}$$

The final expression for the local response of the electrophilicity in Eq. (24) is almost the same as the local electrophilicity measure Morell et al. derived by computing the change in electron density when the system gains $\Delta N_{\max} = \frac{-\mu}{\eta}$ electrons. They derived it by truncating the electron density Taylor series at second order, thereby assuming a quick convergence of the series when $\left|\frac{\mu}{\eta}\right| < 1$. However, Morell et al. insert the chemical potential and Fukui function derived from the piece-wise linear energy model into Eq. (24), i.e.

$$\begin{aligned}\Delta\rho_\omega(\mathbf{r}) &= -\left(\frac{\mu^+}{\eta}\right)f^+(\mathbf{r}) + \frac{1}{2}\left(\frac{\mu^+}{\eta}\right)^2 f^{(2)}(\mathbf{r}) \\ &= -\left(\frac{-A}{I-A}\right)\left(\rho_{N_0+1}(\mathbf{r}) - \rho_{N_0}(\mathbf{r})\right) + \left(\frac{-A}{I-A}\right)^2 \\ &\quad \times\left(\frac{\rho_{N_0+1}(\mathbf{r}) - 2\rho_{N_0}(\mathbf{r}) + \rho_{N_0-1}(\mathbf{r})}{2}\right)\end{aligned} \tag{26}$$

where I and A are the ionization potential and electron affinity of the N_0-electron system, respectively. It is important to note that $\Delta\rho_\omega(\mathbf{r})$ corresponds to the change in electron density when the system obtains $-\left(\frac{\mu^+}{\eta}\right) = \frac{A}{I-A}$ electrons, which is smaller than $\Delta N_{\max} = \frac{-\mu}{\eta} = \frac{I+A}{2(I-A)}$ whenever $I > A$ (as is believed to be universally true for isolated molecules). In addition, when the electron affinity of the system is negative, $E(N_0) < E(N_0+1)$, $-\left(\frac{\mu^+}{\eta}\right) < 0$. In the not uncommon case of zero electron affinity, $\Delta\rho_\omega(\mathbf{r}) = 0$ at every point in space. Also, because electron affinity is usually small, $\Delta\rho_\omega(\mathbf{r})$ usually gives very small values when condensed to atoms, regardless of the specific partitioning scheme one chooses.

Table 1 Quadratic global reactivity descriptors of carbonyl compounds computed (in a.u.) using the frontier molecular orbital (FMO) and finite-difference (FD) approximations

Molecule	$\log K_{eq}$	Frontier molecular orbital (FMO)					Finite difference (FD)				
		$-\mu$	η	$\Delta N_{\max}$	ω	A/η	$-\mu$	η	$\Delta N_{\max}$	ω	A/η
Formaldehyde	3.35	0.173	0.218	0.795	0.069	0.295	0.188	0.426	0.443	0.042	−0.057
Chloroacetaldehyde	1.57	0.173	0.232	0.746	0.065	0.246	0.185	0.400	0.461	0.043	−0.039
Acetaldehyde	−0.08	0.155	0.229	0.678	0.053	0.178	0.176	0.399	0.442	0.039	−0.058
Propionaldehyde	−0.15	0.152	0.230	0.662	0.050	0.162	0.173	0.388	0.447	0.039	−0.053
Benzaldehyde	−2.08	0.175	0.190	0.921	0.081	0.421	0.179	0.339	0.528	0.047	0.028
Acetone	−2.86	0.144	0.231	0.625	0.045	0.125	0.169	0.374	0.452	0.038	−0.048

From left to right, the columns represent: equilibrium constant for the addition reaction of H_2O to the aldehyde, $R_2C=O$, forming the diol, $R_2C(OH)_2$, in solution at 298 K, negative chemical potential, chemical hardness, change in the number of electrons when the system obtains $N_{\max}$ electrons, electrophilicity, and change in the number of electrons according to Morell's electrophilicity

3 Numerical tests and results

To validate the plausible utility of our approach using the local responses of global indicators, we will focus on the electrophilicity and examine the usefulness of its local counterparts for revealing chemical trends. Specifically, we consider the small set of carbonyl compounds proposed by Cedillo and Contreras containing, from highest to lowest electrophilic character, formaldehyde, chloroacetaldehyde, acetaldehyde, propionaldehyde, benzaldehyde, and acetone [32]. The carbon in the carbonyl functional group is susceptible to nucleophilic attack by a water molecule to form a diol, so local electrophilicity indicators should (1) identify this carbon as the most electrophilic site and (2) sort the above compounds in the appropriate relative reactivity order. To test these chemical selectivity and reactivity principles, we condensed to atoms [38–41] the local response of the electrophilicity $\ell_{\omega;N}(\mathbf{r})$ (Eq. (23)), the local electrophilicity measure proposed by Morell et al. $\Delta\rho_\omega(\mathbf{r})$ (Eq. 26), the traditional local electrophilicity $\omega(\mathbf{r}) = \omega \cdot f^+(\mathbf{r})$ [using the multiply-by-the-Fukui-function strategy in Eq. (2)], the quadratic Fukui function $f(\mathbf{r}) = 0.5\big(\rho_{N_0+1}(\mathbf{r}) - \rho_{N_0-1}(\mathbf{r})\big)$, and the linear Fukui function $f^+(\mathbf{r}) = \rho_{N_0+1}(\mathbf{r}) - \rho_{N_0}(\mathbf{r})$.

Besides the choice of partitioning scheme, there are several approaches to compute each of these quantities. It is possible to compute the densities and energies of the cation and anion corresponding to each compound (1) using energies and the densities of the frontier molecular orbitals (FMO) [18, 19] or (2) using a finite-difference (FD) approach where single-point calculations are performed for the anion and cation at the geometry of the neutral molecule [42, 43]. In addition, when condensing a local indicator, it is possible to employ the popular "response of molecular fragment (RMF)" approach or the less commonly used "fragment of molecular response (FMR)" approach [44].

In our study, we have considered Hirshfeld [45], Iterative Hirshfeld [46], and Becke partitioning schemes [47] and computed each of the above-mentioned quantities using the FMO and FD approaches, which are then condensed by RMF and FMR methods. All quantum chemistry calculations are performed with Gaussian09 (version C.01) [48] using UB3LYP/6-311++G** level of theory, ultrafine integration grids, and stable = opt keyword to ensure that the self-consistent field iterations converge to a true minimum. Post-processing of the electron density is carried out with HORTON 2.0.0 [49], and reactivity indicators are computed using the ChemTools [50] packages.

Table 1 provides a coarse-grained description of carbonyl compounds by tabulating various global indicators within the framework of quadratic energy model. Among these, the global electrophilicity indicator is the crudest descriptor of the molecules' relative reactivity. As expected, the global electrophilicity decreases in each column for both FMO and FD approaches, except for benzaldehyde. This may be attributed to the fact benzaldehyde is much bigger than the other molecules, and it is difficult to compare the overall reactivity of molecules with very different sizes, as larger molecules have additional reactive sites.

The atom-condensed local descriptors for carbon and oxygen of the carbonyl functional group as well as the alpha carbon attached to the carbonyl group are presented in Tables 2, 3 and 4 for various approaches. The FMR and RMF results are the same for Hirshfeld and Becke schemes [45, 47], so we only consider FMO and FD approaches for those partitioning methods (Tables 2, 3). Only the FMO approach is considered for partitioning based on Iterative Hirshfeld (Table 4), because the Iterative Hirshfeld method commonly results in unrealistic charges for the anion density $\rho_{N_0+1}(\mathbf{r})$, so that the FD approach becomes unreliable. (This could be remedied by suitably defining the density of unbound proatoms, but we do not pursue that refinement here [51–55].)

Table 2 Atom condensed local reactivity descriptors of carbonyl compounds using the Hirshfeld partitioning scheme

Molecules	Frontier molecular orbital (FMO)				Finite difference (FD)			
	$\ell_{\omega;N}(\mathbf{r})$	$\Delta\rho_w(\mathbf{r})$	$f^+(\mathbf{r})$	$f(\mathbf{r})$	$\ell_{\omega;N}(\mathbf{r})$	$\Delta\rho_w(\mathbf{r})$	$f^+(\mathbf{r})$	$f(\mathbf{r})$
Formaldehyde								
O	0.296	0.088	0.342	0.489	0.102	−0.009	0.150	0.295
C	0.370	0.163	0.501	0.328	0.131	−0.018	0.321	0.277
Chloroacetaldehyde								
O	0.276	0.077	0.341	0.455	0.066	−0.004	0.089	0.192
C	0.305	0.120	0.449	0.291	0.064	−0.005	0.140	0.136
C_α	0.056	0.016	0.070	0.087	0.048	−0.005	0.117	0.093
Acetaldehyde								
O	0.258	0.055	0.333	0.481	0.068	−0.004	0.057	0.229
C	0.273	0.086	0.453	0.294	0.053	−0.006	0.102	0.132
C_α	0.051	0.012	0.070	0.086	0.064	−0.009	0.165	0.130
Propionaldehyde								
O	0.249	0.050	0.329	0.467	0.061	−0.003	0.047	0.209
C	0.262	0.077	0.448	0.293	0.046	−0.005	0.085	0.118
C_α	0.050	0.011	0.069	0.087	0.039	−0.005	0.091	0.083
Benzaldehyde								
O	0.192	0.042	0.191	0.411	0.091	0.004	0.158	0.187
C	0.205	0.104	0.226	0.178	0.070	0.004	0.148	0.114
C_α	0.098	0.047	0.107	0.097	0.029	0.001	0.052	0.056
Acetone								
O	0.227	0.035	0.303	0.465	0.062	−0.003	0.046	0.211
C	0.211	0.051	0.390	0.252	0.030	−0.002	0.047	0.082
C_α	0.044	0.008	0.063	0.081	0.044	−0.005	0.104	0.093

These are computed for both frontier molecular orbital (FMO) and finite-difference (FD) approximations, but only the values for oxygen and carbon of the carbonyl group as well as the carbon attached to it, C_α, are reported. The same level of theory was used to compute the proatom densities used in the Hirshfeld partitioning

Condensed values of the local response of the electrophilicity, $\ell_{\omega;N}(\mathbf{r})$, computed with the FMO approach, largely succeed at both predicting the electrophilic atom and sorting carbonyl compounds based on their relative electrophilicity expect for benzaldehyde. (Benzaldehyde is misplaced between chloroacetaldehyde and acetaldehyde by the Hirshfeld and Becke schemes, but is recognized as the least electrophilic compound by Iterative Hirshfeld partitioning in the RMF approach.) The fragment of molecular response condensation approach combined with Iterative Hirshfeld partitioning does not perform as well in this case (Table 4). Surprisingly, and in contrast to some previous mathematical and computational studies [56, 57], when the FMO approximation is replaced by the more mathematically rigorous FD method for computing reactivity indicators, the values of condensed $\ell_{\omega;N}(\mathbf{r})$ often erroneously identifies oxygen as the electrophilic center; we speculate that this is because the energy and electron density of the anion are unreliable for unbound anions. Condensed values of the $\Delta\rho_\omega(\mathbf{r})$ local electrophilicity computed using the FMO approximation correctly specify the carbon of the carbonyl group as the most electrophilic atom, and sensibly sort compounds based on their electrophilic nature regardless of the partitioning/condensing scheme used (except that benzaldehyde is placed in between chloroacetaldehyde and acetaldehyde). When the FD method is used to compute the reactivity indicators, however, the extremely small values of the electron affinity, A, lead to near-zero condensed reactivity values which cannot reveal the electrophilic region of the compounds.

Condensed values of traditional electrophilicity $\omega(\mathbf{r}) = \omega \cdot f^+(\mathbf{r})$ are not included in the tables. These can be simply obtained by multiplying the global electrophilicity ω in Table 1 by the condensed Fukui function

Table 3 Atom condensed local reactivity descriptors of carbonyl compounds using the Becke partitioning scheme

Molecule	Frontier molecular orbital (FMO)				Finite difference (FD)			
	$\ell_{\omega;N}(\mathbf{r})$	$\Delta\rho_w(\mathbf{r})$	$f^+(\mathbf{r})$	$f(\mathbf{r})$	$\ell_{\omega;N}(\mathbf{r})$	$\Delta\rho_w(\mathbf{r})$	$f^+(\mathbf{r})$	$f(\mathbf{r})$
Formaldehyde								
O	0.294	0.086	0.338	0.495	0.119	−0.011	0.192	0.328
C	0.402	0.182	0.550	0.333	0.093	−0.013	0.222	0.200
Chloroacetaldehyde								
O	0.271	0.074	0.332	0.454	0.073	−0.004	0.105	0.203
C	0.337	0.135	0.503	0.304	0.047	−0.004	0.101	0.102
C_α	0.041	0.010	0.047	0.078	0.013	−0.001	0.023	0.034
Acetaldehyde								
O	0.257	0.053	0.327	0.487	0.081	−0.006	0.090	0.258
C	0.301	0.097	0.508	0.309	0.038	−0.004	0.066	0.100
C_α	0.038	0.007	0.047	0.077	0.023	−0.003	0.046	0.056
Propionaldehyde								
O	0.247	0.048	0.323	0.473	0.073	−0.004	0.075	0.235
C	0.291	0.087	0.505	0.309	0.033	−0.003	0.056	0.090
C_α	0.039	0.007	0.048	0.079	0.014	−0.001	0.023	0.040
Benzaldehyde								
O	0.192	0.039	0.190	0.420	0.099	0.005	0.173	0.203
C	0.220	0.115	0.245	0.175	0.066	0.004	0.145	0.103
C_α	0.097	0.046	0.106	0.099	0.027	0.001	0.048	0.054
Acetone								
O	0.226	0.034	0.296	0.472	0.076	−0.004	0.079	0.242
C	0.234	0.057	0.437	0.270	0.028	−0.002	0.043	0.075
C_α	0.032	0.004	0.040	0.071	0.017	−0.001	0.030	0.044

These are computed for both frontier molecular orbital (FMO) and finite-difference (FD) approximations, but only the values for oxygen and carbon of the carbonyl group as well as the carbon attached to it, C_α, are reported

values in Tables 2, 3 and 4. The global electrophilicity is usually small, $\omega < 0.1$ a.u., so the condensed local electrophilicity values are smaller than the values of the condensed Fukui functions. However, because of the existing trend in global electrophilicity ω values and condensed Fukui function values, the condensed local electrophilicity defined by $\omega(\mathbf{r}) = \omega \cdot f^+(\mathbf{r})$ follows the same trend as the condensed $f^+(\mathbf{r})$ tabulated in Tables 2, 3 and 4. Condensed values of the Fukui function from above, $f^+(\mathbf{r}) = \rho_{N_0+1}(\mathbf{r}) - \rho_{N_0}(\mathbf{r})$, calculated by FMO approach in Tables 2, 3 and 4 unanimously select the carbonyl carbon as the most electrophilic atom; however, $f^+(\mathbf{r})$ incorrectly identifies benzaldehyde as the least electrophilic compound and occasionally considers acetaldehyde to be more electrophilic than chloroacetaldehyde. Using FD to calculate the condensed Fukui function from above results in a scattered picture that does not correlate with chemical trends. Condensed values of the Fukui function from the quadratic model, $f(\mathbf{r}) = 0.5\left(\rho_{N_0+1}(\mathbf{r}) - \rho_{N_0-1}(\mathbf{r})\right)$, in Tables 2, 3 and 4 do not comply with chemical intuition as they identify oxygen as the electrophilic center.

4 Summary

The local response of a global property, as defined in Eqs. (17) and (18), has useful chemical properties and, importantly, allows us to unambiguously define a relevant local counterpart to *any* global reactivity indicator. These local response descriptors measure the change in a global property (e.g., the electrophilicity) with respect to a probe of the external potential and should therefore represent how that global property at different positions in space changes when a reagent approaches. In this sense, the local responses of global descriptors, $\ell_{P_{\text{Global}},\mu\text{or}N}$, may be useful measures of the regioselectivity of a system whose reactivity is governed by the corresponding global descriptor, P_{Global}.

To assess the utility of this definition, we performed a preliminary numerical study of the electrophilicity of carbonyl compounds. Because the set of compounds we consider is small and its chemical diversity is low, we do not feel it is appropriate to make definitive pronouncements about the relative quality of different reactivity measures

Table 4 Atom condensed local reactivity descriptors of carbonyl compounds using the Iterative Hirshfeld partitioning scheme using frontier molecular orbital (FMO) approach

Molecule	Response of molecular fragment				Fragment of molecular response			
	$\ell_{\omega;N}(\mathbf{r})$	$\Delta\rho_w(\mathbf{r})$	$f^+(\mathbf{r})$	$f(\mathbf{r})$	$\ell_{\omega;N}(\mathbf{r})$	$\Delta\rho_w(\mathbf{r})$	$f^+(\mathbf{r})$	$f(\mathbf{r})$
Formaldeh								
O	0.262	0.050	0.264	0.582	0.315	0.096	0.367	0.508
C	0.560	0.288	0.815	0.272	0.347	0.153	0.470	0.305
Chloroacetaldehyde								
O	0.258	0.053	0.279	0.541	0.289	0.082	0.360	0.470
C	0.508	0.230	0.810	0.304	0.280	0.110	0.413	0.264
C_α	−0.066	−0.047	−0.142	0.066	0.071	0.022	0.093	0.103
Acetaldehyde								
O	0.248	0.038	0.268	0.572	0.271	0.058	0.353	0.497
C	0.426	0.157	0.790	0.289	0.245	0.078	0.408	0.261
C_α	−0.036	−0.024	−0.106	0.057	0.073	0.019	0.105	0.110
Propionaldehyde								
O	0.242	0.036	0.267	0.559	0.261	0.053	0.349	0.482
C	0.421	0.144	0.806	0.301	0.238	0.070	0.409	0.263
C_α	−0.040	−0.026	−0.128	0.073	0.063	0.015	0.091	0.101
Benzaldehyde								
O	0.182	0.006	0.168	0.534	0.202	0.046	0.201	0.423
C	0.298	0.197	0.346	0.055	0.189	0.096	0.209	0.161
C_α	0.046	0.001	0.042	0.137	0.103	0.050	0.113	0.101
Acetone								
O	0.232	0.027	0.256	0.562	0.236	0.037	0.318	0.479
C	0.339	0.094	0.704	0.275	0.188	0.046	0.349	0.220
C_α	−0.030	−0.015	−0.102	0.043	0.062	0.012	0.097	0.102

These are computed for both response-of-molecular-fragment and fragment-of-molecular-response approaches, but only the values for oxygen and carbon of the carbonyl group as well as the carbon attached to it, C_α, are reported. The same level of theory was used to compute the proatom densities used in the Iterative Hirshfeld partitioning

from this study. Our aim was only to see whether or not the approach we are proposing is sensible, deferring a thorough study with a large and diverse set of electrophiles to future work. Based on this set, however, we can say that the local response of the global electrophilicity, $\ell_{\omega;N}(\mathbf{r})$, seems to work about as well as Morell's local response $\Delta\rho_\omega(\mathbf{r})$ and the traditional $\omega(\mathbf{r})$, but it has the conceptual advantage of being mathematically motivated (unlike $\omega(\mathbf{r})$) and derived in an intrinsically consistent way, without mixing and matching different models for the energy/density as a function of the number of electrons (unlike $\Delta\rho_\omega(\mathbf{r})$). We observed that the results are basically insensitive to the atomic partitioning method we used. However, the finite-difference approach should be used with caution, because in most cases the computed anion has a slightly higher energy than the neutral molecule, $E(N_0) < E(N_0 + 1)$ at the same geometry, and the extra electron is only basis-set bound, so the electron density of the anion is unphysical. This is why in most cases considered, the finite-difference approach had a poor performance and in most cases failed to detect the electrophilic atom. It was also noticed that the linear Fukui function $f^+(\mathbf{r})$ reveals the same trends as local electrophilicity indicators. This questions the added value of numerous attempts to define a local counterpart to the global electrophilicity.

Acknowledgements PWA and FHZ wish to thank NSERC of Canada and Compute Canada for monetary and computing support. FHZ, SF, and TV thank the FWO of Belgium. TV thanks the Research Board of Ghent University (BOF). EVM thanks Nucleus Millennium CPC #120082 and Fondecyt #1160197.

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