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# The Linear Response Function as a Descriptor of Non-Covalent Interactions: Hydrogen and Halogen bonds

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**Abstract**

An extension of the use of the Linear Response Function to interpret non-covalent interactions is put forward. Due to its computational intricacies, most applications until now have been done on isolated atoms or molecules using coupled perturbed Hartree Fock or Kohn Sham theory thereby adopting the simplest level for the LRF evaluation, the Independent Particle Approximation . The previously presented possibilities for extension (the Random Phase and the "full" expression) are scrutinised, thereby highlighting the intricacies in the evaluation of the exchange correlation term in the case of meta GGAs and Hybrid functionals, and implemented. A set of 25 hydrogen bonded and 11 Halogen bonded systems, selected from Hobzas S66 and X 40 compilations, were used to investigate the correlation between the stabilization energy due to these non- covalent interactions and the relevant atom-atom condensed LRF matrix element. The lack of a relevant correlation in the case of hydrogen bonding is contrasted with the excellent result for the halogen bonds.

The correlation between the full option and the IPA is high providing support for our previous work using the IPA approximation as is also the case for the previously used Iterative Hirshfeld condensation and the more advanced FOHI method making use of fractional occupation numbers. The fundamental difference between hydrogen and halogen bond behaviour and the retrieval of the stability sequence within the halogen bonds series are traced back to the nature of the LRF as a response function for perturbations in the external potential putting polarisation effects and the polarisability of the atoms of the donor- acceptor couple at the forefront . The extension to the use of the softness kernel is advocated and already invoked to rectify the behavior of two deviating complexes involving S as second row halogen bond acceptor atom.

**Keywords:** Conceptual DFT, Linear Response Function, Coupled Perturbed Kohn Sham Theory, Hydrogen Bonds, Halogen Bonds , Polarization, Polarizability, Softness Kernel

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# 1 Introduction

Considered nowadays as a full-fledged part of Density Functional Theory[1, 2] Conceptual DFT (CDFT) has gained widespread interest over recent decades in its endeavour to provide sharp definitions for sometimes long standing but rather vaguely defined chemical concepts, enabling, as a consequence and in principle, their numerical evaluation. [3–12] Central in this ansatz, launched by Parr in the late eighties [2, 3], is the response function concept [13] in the context of the energy $E = E[N, v]$ functional, describing chemical reactivity in terms of the response of an atom, molecule to perturbations/changes in its number of electrons, $N$, and/or the external potential $v$ (the potential felt by the electrons due to the nuclei in the case of an isolated system), typical for a chemical reaction. These response functions arise in a natural way by a functional Taylor series expansion of $E = E[N, v]$ functional. They consist of partial, functional or mixed derivatives of the type $\frac{\partial^n E[N,v]}{\partial^m N \delta v(\mathbf{r}_1)\delta v(\mathbf{r}_2)...\delta v(\mathbf{r}_{m'})}$

(with $n = m + m'$) indicating the *sensitivity* of a system towards perturbations in $N$ and/or $v$, the final answer to the perturbation being the product of these response functions and the magnitude of the perturbation, written - when considered to be finite - as $\Delta N$ or $\Delta v(\mathbf{r})$ to the appropriate power. This stresses the fact that that response functions are intrinsic properties of the system, i.e. only function of the nature of the system, not a function of the (magnitude) of the perturbation and that they can be expected to bear information about the intrinsic reactivity of the system.

The study of the response functions $\frac{\partial^n E[N,v]}{\partial^m N \delta v(\mathbf{r}_1)\delta v(\mathbf{r}_2)...\delta v(\mathbf{r}_{m'})}$, and their use, either as such or in the context of a number of principles, such as Sanderson's Electronegativity Equalization Principle [14] (and its associated Electronegativity Equalization Method (EEM) [15]), Pearson's Hard and Soft Acids and Bases (HSAB) [16–18] and his Maximum Hardness Principles (MHP) [18, 19], is in fact the "fil rouge" in the history and development of Conceptual DFT. [20] From the nineties on, a practical way to classify and interconnect the variety of response functions is the "Response Function Tree" [2, 4, 5, 21]. It displays how, adopting the usual sequence, 'pure' $N$ derivatives are at the extreme left, 'pure' $v$ derivatives at the extreme right at a given order of perturbation $n$, and that when going from left to right one passes, through mixed derivatives, from global (i.e. $\mathbf{r}$-independent), to local (i.e. $\mathbf{r}$-dependent) to non-local (depending on $\mathbf{r}$, $\mathbf{r}'$, $\mathbf{r}''$, $\ldots$) descriptors (Figure 1) The $n = 1$ derivatives (the electronic chemical potential [22] and the electron density itself $\rho(\mathbf{r})$, being global and local in nature, respectively) and two of the three $n = 2$ derivatives (the chemical hardness [16] and the electronic Fukui function $f(\mathbf{r})$ [2, 23], again being global and local in nature respectively) have received widespread attention in the past decades and have been extensively commented on in various review papers. On the contrary, the utmost right $n = 2$ derivative, non-local in nature, received much less attention until some years ago. This second functional derivative of $E$ with respect to the external potential at constant number of electrons, $\left(\frac{\delta^2 E}{\delta v(\mathbf{r}_1)\delta v(\mathbf{r}_2)}\right)_N$, usually written as $\chi(\mathbf{r}, \mathbf{r}')$, is a kernel and is commonly referred to as the Linear Response Function (LRF). [2, 4, 5, 24–26] The reasons why its importance in CDFT was limited in the early years of CDFT are clear: this descriptor is (much) more complicated than its $n = 1$ or $n = 2$ congeners, being a function of six variables, turns out hard to evaluate and, even after evaluation, its representation and interpretation is much more demanding than for the other response functions, being at most functions of three variables like the density and the Fukui function. Remarkably the frequency dependent form of the LRF, $\chi(\mathbf{r}, \mathbf{r}', \omega)$, has a long standing tradition in Time Dependent DFT.[27] where thanks to pioneering work by Gross [28, 29] and the elegant matrix formulation by Casida [30, 31], it offers a routinely available road to compute the electronic transition energies/frequencies as its poles and on the fly its intensities and assignments. This remarkable computational evolution however was not accompanied by parallel investigations on different ways of evaluating, representing and especially chemically interpreting its frequency independent, or static, congener, $\chi(\mathbf{r}, \mathbf{r}')$. However , in work mainly published by the group of two of the present authors, published in the past 10 to 15 years, it was shown how to calculate this response function at different levels of approximation, how to come to adequate 1, 2 and 3D representations, and above all, how to extract important chemical information from this linear response function . We thereby concentrated on a variety of atomic and molecular properties such as atomic shell structure, [32–34] inductive and mesomeric effects in organic molecules, [35] electron delocalization, [36] aromaticity and anti-aromaticity in organic and inorganic ring systems, [37–39] and the link with electrical conductance [40], based on analogies with Coulsons atom-atom polarizability in $\pi$-electron systems.[41] At a more fundamental level the LRF was exploited in scrutinizing Kohn's Nearsightedness of Electronic Matter (NEM) concept, [42, 43] invoking also the the softness kernel $s(\mathbf{r}, \mathbf{r}')$, [44] the grand canonical analogue of the LRF with the grand potential $\Omega[\mu, v]$ replacing the energy functional as key quantity. Numerical evidence was thereby presented [45] for the link between Kohn's Nearsightedness principle and the chemical transferability of functional groups, [46] a cornerstone in rationalizing organic chemistry. [47]

This short status-report of the chemistry hidden in this at first awkward kernel shows that until now essentially intramolecular phenomena were addressed, exploiting the properties of covalent bonds and that the LRF was rarely used in discussing intermolecular interactions, as could be expected in the context of chemical reactivity . An exception is the study of Diels-Alder reactions and the trimerization of acetylene [39] where it was shown that the evolution of the para (1,4) linear response function upon six-ring formation shows a maximum at the transition state , the $\sigma$-$\pi$ decomposition in the latter case being in agreement with ring- current maps and Nucleus Independent Shift analysis.

Moreover, to the best of our knowledge the possible role of the LRF in discussing /interpreting non-covalent interactions has until now not been undertaken yet. In the present paper a first attempt in this direction is reported: starting with a long standing and key member of the non-covalent interaction family, the hydrogen bond [48], but with an extension to its congener, the halogen bond. Although known for more than a century, it only received widespread interest both from theoretical and experimental side in recent years. [49–51] The sigma-hole concept, as scrutinized by Politzer and coworkers, [52, 53] thereby played a fundamental role when rationalising and classifying this kind of interaction in different constellations (e.g. when passing, as halogen, from fluorine, to chlorine, bromine and iodine but also when passing from halogen to chalcogen [54], pnictogen [55] and tetrel [56] bonds, replacing the halogen by a group 16, 15, and 14 atom). Its literature is vast, but it looked tempting for us to see in this proof-of-concept paper, and in view of our recent interest in halogen, chalcogen, pnictogen and tetrel bonds [57–59] if a concept like the LRF, originating in a totally different context , might also be invoked to get (maybe alternative) insights into this series of non-covalent interactions.

The test-bank for our exploration consists of Hobza's well-known S66 and X40 H-bond and halogen bonded (X-bond) data set [60, 61] in which all systems have been calculated at the same uniform, high quality level for both equilibrium geometries and interaction energies, affording in the latter case a uniform level comparison between the strength of a H or X-bond and LRF data. On the fly we will also present the first report on the influence of the various levels of theory which can be used for the calculation of the LRF in a Coupled Perturbed Kohn Sham ansatz [62, 63], the only ansatz, with one exception [64] used to evaluate the LRF until now . Again with only one exception[45] , the simplest level of theory, the Independent Particle Approximation, was used hitherto in this context whereas Coupled Perturbed Kohn Sham theory displays various levels of approximation from which the IPA approach is only the most approximate one . Our aim was to investigate the passage to less approximate schemes , such as the Random Phase Approximation and the "full" CPKS ansatz showing also the intricacies of its implementation when DFT exchange correlation potentials of fundamentally different nature are used (

LDA, GGA , Hybrids). Finally the sensitivity of the results to the condensation technique , used upon integration of the six dimensional kernel into an atom by atom matrix, is tested.

<<< **INSERT FIGURE 1 HERE** >>>

The structure of this paper is as follows. In Section 2 (Theory and Computational Aspects), the basic theory of the LRF is summarised, paying particular attention to the different levels of approximation of the CPKS ansatz, their implementation with different types of DFT functionals and the two condensation techniques that will be compared. Finally, the selection of systems from the complete S66 and X40 basis is justified and information is given on the codes at use in this study. In section 3 (Results and Discussion) at first an overview will be given on the overall results, comparing Hobza's interaction energies with the relevant LRF characteristics. Narrowing the picture to X-bonds in a second stage for reasons that will be explained, these results will be used to investigate the methodological issues mentioned before. Finally a detailed explanation for the failures and successes in the field of H and X bonds respectively will be given. In Section 3 (Conclusions) the intermediate conclusions are gathered in an overall take home message and an outlook for future investigations .

# 2 Theory and Computational Aspects

## 2.1 Basic Theory

Details about the basic theory highlighted in the section can be found in references [24, 26]; the at first awkward expression for $\chi$,

$$\chi(\mathbf{r},\mathbf{r}') = \left(\frac{\delta^2 E}{\delta v(\mathbf{r})\delta v(\mathbf{r}')}\right)_N \tag{1}$$

becomes more transparent when realizing that

$$\left(\frac{\delta E}{\delta v(\mathbf{r})}\right)_N = \rho(\mathbf{r}) \tag{2}$$

turning Eq. (1) into

$$\chi(\mathbf{r},\mathbf{r}') = \left(\frac{\delta \rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right)_N = \left(\frac{\delta \rho(\mathbf{r}')}{\delta v(\mathbf{r})}\right)_N = \chi(\mathbf{r}',\mathbf{r}) \tag{3}$$

This expression yields a simple physical interpretation of the Linear Response Function and reveals the interest in scrutinising its chemical relevance: $\chi(\mathbf{r},\mathbf{r}')$ indeed represents the sensitivity of the density at position $\mathbf{r}$ to a change in the external potential at position $\mathbf{r}'$ or vice versa, which is clearly important to be considered at the onset of a chemical reaction, the playground of conceptual DFT. The first order change in the density $\Delta\rho(\mathbf{r})$ upon a perturbation $\Delta v(\mathbf{r}')$

$$\Delta\rho(\mathbf{r}) = \int \left(\frac{\delta \rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right)_N \Delta v(\mathbf{r}')d\mathbf{r}' = \int \chi(\mathbf{r},\mathbf{r}')\Delta v(\mathbf{r}')d\mathbf{r}' \tag{4}$$

then reveals the terminology: $\chi(\mathbf{r},\mathbf{r}')$ characterizes the linear response of the density at position $\mathbf{r}$ upon (perturbation) of the potential at position $\mathbf{r}'$. This simple relationship between both quantities only holds when the strength of the perturbation is small and higher order terms can be neglected. Note that the term ‘linear’ is at first sight contradictory with the position of the linear response function in the CDFT tree, the reason being that the tree is based on the energy functional, for which $\chi(\mathbf{r},\mathbf{r}')$ characterises the quadratic response. The most general expression for the linear response function can be obtained from standard, first order perturbation theory [2] starting from the density expression for a $N$ electron system described by a wave function $\Psi$ (considered to be real and time independent)

$$\Psi = \Psi(\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_N) \tag{5}$$

where $\mathbf{x}_i$ is a four-vector containing three spatial coordinates gathered in $\mathbf{r}_i$ and a spin variable $s_i$.The density at position $\mathbf{r}$, $\rho(\mathbf{r})$, is then given by

$$\rho(\mathbf{r}) = N \int \ldots \int \Psi^*(\mathbf{x}, \mathbf{x}_2, \ldots, \mathbf{x}_N)\Psi(\mathbf{x}, \mathbf{x}_2, \ldots, \mathbf{x}_N) ds d\mathbf{x}_2 d\mathbf{x}_3 \ldots d\mathbf{x}_N \tag{6}$$

Considering now a one-electron perturbation in the potential

$$\Delta V = \sum_i \Delta v(\mathbf{r}_i) \tag{7}$$

first order perturbation theory yields

$$\begin{aligned}\Delta\rho(\mathbf{r}_1) =& N \int \ldots \int \left(\Psi^*\Psi - \Psi_0^{*(0)}\Psi_0^{(0)}\right) ds_1 d\mathbf{x}_2 d\mathbf{x}_3 \ldots d\mathbf{x}_N \\ =& 2N \sum_{j>0} \left(E_0^{(0)} - E_j^{(0)}\right)^{-1} \langle \Psi_j^{(0)} | \Delta V | \Psi_0^{(0)} \rangle \\ & \times \int \ldots \int \Psi_0^{*(0)} \Psi_j^{(0)} ds_1 d\mathbf{x}_2 d\mathbf{x}_3 \ldots d\mathbf{x}_N\end{aligned} \tag{8}$$

where the summation over $j$ runs over all excited states $\Psi_j$, $\Psi_0$ denoting the ground state, with associated energy levels $E_j$ and $E_0$ and the superscript (0) denotes the unperturbed system. Evaluating the $\Delta V$ matrix elements and comparing (8) with (4) then yields

$$\begin{aligned}\chi(\mathbf{r}_1, \mathbf{r}_2) =& 2N^2 \sum_{j>0} \left(E_0^{(0)} - E_j^{(0)}\right)^{-1} \int \ldots \int \Psi_j^{*(0)} \Psi_0^{(0)} ds_2 d\mathbf{x}_1 d\mathbf{x}_3 \ldots d\mathbf{x}_N \\ & \times \int \ldots \int \Psi_0^{*(0)} \Psi_1^{(0)} ds_1 d\mathbf{x}_2 d\mathbf{x}_3 \ldots d\mathbf{x}_N\end{aligned} \tag{9}$$

or introducing the density operator $\rho_{\mathrm{op}}(\mathbf{r})$

$$\chi(\mathbf{r},\mathbf{r}') = 2\sum_{j>0}\left(E_0^{(0)} - E_j^{(0)}\right)^{-1} \langle j|\rho_{\mathrm{op}}(\mathbf{r})|0\rangle\langle 0|\rho_{\mathrm{op}}(\mathbf{r}')|j\rangle \tag{10}$$

The frequency dependent counterpart $\chi(\mathbf{r},\mathbf{r}';\ \omega)$ of the LRF as used in Time Dependent DFT[27] boils down to this expression for zero frequency and in the case of real orbitals .

## 2.2 The Coupled Perturbed Kohn Sham approach and its implementation

As stated above, confronted with the summation over all excited states, work in this field has nearly always been done using a Coupled Perturbed Hartree Fock (HF) or Kohn Sham (KS) ansatz. In the Coupled Perturbed approaches [24, 26, 63] one starts from a single Slater determinant for the unperturbed system involving orbitals $\phi_i$, solutions of the unperturbed HF or KS equations, whose change under perturbation is evaluated at different orders. In the case of a closed shell system and considering again real orbitals the first order equations then yield (for a complete derivation see [24, 26]

$$\chi(\mathbf{r},\mathbf{r}') = \left(\frac{\delta\rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right)_N = -4\sum_{ia}\sum_{jb}\left(\mathbf{M}^{-1}\right)_{ia,jb}\phi_i^{(0)}(\mathbf{r})\phi_a^{(0)}(\mathbf{r})\phi_j^{(0)}(\mathbf{r}')\phi_b^{(0)}(\mathbf{r}') \tag{11}$$

where the $\mathbf{M}$ matrix elements are given by

- in HF:

$$(\mathbf{M})_{ia,jb} = (\varepsilon_a - \varepsilon_i)\,\delta_{ij}\delta_{ab} + 4(ia|jb) - (ib|ja) - (ij|ab) \tag{12}$$

- in KS:

$$(\mathbf{M})_{ia,jb} = (\varepsilon_a - \varepsilon_i)\,\delta_{ij}\delta_{ab} + 4(ia|jb) + 4(ia|f_{\mathrm{XC}}(\mathbf{r},\mathbf{r}')|jb) \tag{13}$$

The $\varepsilon_k$ stand for the orbital energies, indices $i$ and $j$ refer to occupied orbitals, $a$ and $b$ to unoccupied ones and the integrals between curly brackets are the two-electron repulsion integrals in the chemist's notation. In the KS expression the exchange-correlation term is defined in terms of the operator

$$f_{\mathrm{XC}}(\mathbf{r},\mathbf{r}') = \frac{\delta^2 E_{\mathrm{XC}}}{\delta\rho(\mathbf{r})\delta\rho(\mathbf{r}')} \tag{14}$$

where $E_{\mathrm{XC}}$ is the exchange-correlation energy. It can now easily be seen that three levels of approximation arise in the construction of the $\mathbf{M}$ matrix, both in Hartree Fock and Kohn Sham. In the Independent Particle Approximation (IPA) only the orbital energy dependent term is retained, $(\varepsilon_a - \varepsilon_i)\,\delta_{ij}\delta_{ab}$. It is the only term in Hartree Fock if the influence of the external potential perturbation on the first order correction to the Fock operator (through the perturbed orbitals) is neglected; in Kohn Sham it is the only remaining term if the influence of the potential perturbation on the Coulomb/Hartree and exchange-correlation potentials is dropped. In the Random Phase Approximation (RPA) the influence of this perturbation is maintained in the Coulomb terms resulting again in an identical expression for HF and KS: $(\varepsilon_a - \varepsilon_i)\,\delta_{ij}\delta_{ab} + 4(ia|jb)$. The third level uses the full expressions (11-13)) where now the RPA expression is supplemented with an exchange term in HF and an exchange-correlation term in KS. Note that, due to a misprint the HF exchange term in refs [24] and [26] is different, numerical results reported by our group hitherto being however correct. In fact the simplest approximation (IPA) has been the only one used until now in the studies mentioned in the Introduction, except for a few cases in Ref [45]. Its expression reduces to (dropping the superscripts to simplify the notation)

$$\chi(\mathbf{r},\mathbf{r}') = -4\sum_i\sum_a \left(\varepsilon_a-\varepsilon_i\right)^{-1}\phi_i^{(0)}(\mathbf{r})\phi_a^{(0)}(\mathbf{r})\phi_a^{(0)}(\mathbf{r}')\phi_i^{(0)}(\mathbf{r}') \tag{15}$$

which equals $\frac{\delta\rho(\mathbf{r})}{\delta v_{\mathrm{KS}}(\mathbf{r}')}$: the functional derivative of $\rho$ with respect to the KS potential $v_{\mathrm{KS}}$ [65, 66]

$$\chi_{\mathrm{KS}}(\mathbf{r},\mathbf{r}') = \frac{\delta\rho(\mathbf{r})}{\delta v_{\mathrm{KS}}(\mathbf{r}')} \tag{16}$$

In the present work the three levels of approximation are used offering the possibility to scrutinise the effect of the corrections to the IPA level from both quantitative and qualitative (trends in the results between different systems) point of view. The Independent Particle Approximation is straightforward to evaluate after a standard HF or KS calculation. The Random Phase Approximation only involves the standard manipulation of two-electron interaction integrals, as is the case for the full expression in HF . The evaluation of the exchange-correlation term in the KS approach is more demanding starting from a well-chosen exchange-correlation potential. Here, care should be taken at two points . Firstly, in the case of hybrid functionals (for recent, comprehensive and critical accounts of the different type of functionals see references [67, 68]) e.g. B3LYP [69, 70], where part of the exact exchange energy is introduced in the energy expression, an accordingly adapted version of the exchange correlation contribution in the $\mathbf{M}$ matrix element should be used, of the type,

$$(\mathbf{M})_{ia,jb} = \left(\varepsilon_a-\varepsilon_i\right)\delta_{ij}\delta_{ab}+4(ia|jb)+4(ia|f_{\mathrm{XC}}(\mathbf{r},\mathbf{r}';\ \alpha)|jb)+\alpha\left(-(ib|ja)-(ij|ab)\right) \tag{17}$$

where $\alpha$ denotes the percentage of exact exchange included in the energy-expression. Secondly the evaluation of the $f_{\mathrm{XC}}$ term should be looked upon with care. In the case of LDA functionals the exchange energy density $e_{\mathrm{XC}}$ defining $E_{\mathrm{XC}}$ via the relation

$$E_{\mathrm{XC}} = \int e_{\mathrm{XC}}(\rho, \nabla\rho, \ldots)(\mathbf{r}) d\mathbf{r} \tag{18}$$

contains only a $\rho$-dependence leading to a simple expression for $f_{\mathrm{XC}}$, namely

$$f_{\mathrm{XC}}(\mathbf{r}, \mathbf{r}') = \frac{\partial^2 e_{\mathrm{XC}}}{\partial\rho(\mathbf{r})\partial\rho(\mathbf{r}')} \delta(\mathbf{r} - \mathbf{r}') \tag{19}$$

which can be obtained e.g. directly from the libxc library [71] In the case of GGA functionals however, and in hybrid functionals containing them (e.g. B3LYP), $e_{\mathrm{XC}}$ also depends on $\nabla\rho$ resulting in much more complicated terms involving second order derivatives of both the $\left(\frac{\partial^2 e_{\mathrm{XC}}}{\partial\rho\partial\nabla\rho}\right)$ and $\left(\frac{\partial^2 e_{\mathrm{XC}}}{\partial\nabla\rho\partial\nabla\rho}\right)$ types. [72–76] Recently, in a study on diatomics and the ten electron molecules $NH_3$, $CH_4$, $H_2O$ and HF, we were however able to show that, not unexpectedly, these terms lead to corrections on the atom condensed LRF matrix-elements (vide infra) which are much smaller than the GGA correction (19). In the case of $H_2O$ for example, they amount to far less than 10 % for $\left(\frac{\partial^2 e_{\mathrm{XC}}}{\partial\rho\partial\nabla\rho}\right)$ and less than 1 % for $\left(\frac{\partial^2 e_{\mathrm{XC}}}{\partial\nabla\rho\partial\nabla\rho}\right)$ of the first GGA correction, obviously retaining the trends in the LRF values up to the first GGA correction.[77] As a result and in view of computational efficiency, we can safely neglect these corrections and stick, for GGA and Hybrid functionals, to the leading correction (19) . All calculations were done with the B3LYP functional with a 6-311++G** [78] basis-set where in the case of I a 6-311+G* basis set was constructed from the standard 6-311G basisset [79] by adding a soft L-type shell with exponent 0.02. Extensive comparisons in the parallel study mentioned above [77] show that the influence of the functional is minor and certainly does not influence trends in the atom-atom condensed LRF values. In view of the complexity of the systems, an atom-integrated LRF is used [35] resulting in an atom- condensed LRF matrix with elements

$$\chi_{\mathrm{AB}} = \int_{V_A} \int_{V_B} \chi(\mathbf{r}, \mathbf{r}') d\mathbf{r} d\mathbf{r}' \tag{20}$$

where the LRF is integrated in atomic basins in regions $V_A$ and $V_B$ associated to atoms A and B. Two techniques were applied: the Iterative Hirshfeld method (HI) starting from spherically averaged atomic densities [80, 81], and its extension using fractional orbital occupations (FOHI) [82] in which spherical atom densities are calculated at the same level of theory of the molecular calculations. All calculations were performed staring from a standard KS calculation with the GAUSSIAN 16 package [83] coupled to the BRABO (to calculate the inverted **M**-matrix) and STOCK (to atom-atom partition the inverted **M**-matrix) programs developed by one of the present authors [81, 84] in which the LRF matrix calculation as presented above was implemented.

## 2.3 Choice of the H-and X -Bond systems

The selection of the systems out of the S66 and X40 list was made as follows. In view of the LRF results being presented as an atom by atom matrix we selected those H or X bond systems which indeed can be characterised by a 1 to 1 contact between an H/X bond donor and acceptor atom eliminating for example complexes involving $\pi$- interactions as e.g. displayed by aromatics . In the same vein dispersion type complexes were not considered. Also complexes in which more than one H-bond interaction is present were eliminated in order to keep the interpretation of the results as simple as possible in this proof-of-concept paper. This led us to 25 H-bond complexes (cases 1-16 of the S66 set and 31 to 39 of the X40 set ) involving H-bonds with first row atoms (N,O,F

) and 11 X-bond complexes (cases 13-18 and 22-26 of the X40 set, involving Cl, Br and I as halogen bond donor and formaldehyde, trimethylamine and metanethiol as halogen-bond acceptor. Nine of these complexes involve a first row acceptor atom (O,N) and two a second row atom ( S). The complete set of systems with the results for the LRF at various levels of theory is given in Table S1 of the SI.

# 3 Results and Discussion

## 3.1 Overall trends

It is immediately striking that the results for the H-bond and X-bond complexes were of fundamentally different nature .The halogen bond values (consider for the moment the full expression in Table S1) are much larger, and show a much larger range than the H-bond cases: in the case of the H-bonds, out of the 25 LRF values 18 are situated between 0.005 and 0.015 whereas for the halogen bonds, the values are typically one order of magnitude larger and vary from 0.05 to 0.15. These ranges should be compared with the interaction strength values, which were our main instrument to test the capability of the LRF in describing non-covalent interactions. There, although, as well-known, the orders of magnitude are similar, the range of the interaction strength is larger for the H-bonds, varying from 3 kcal mol$^{-1}$ to some (exceptional) cases where it surpasses in absolute value 10 kcal mol$^{-1}$. In the case of Halogen bonds the range of the interaction energies is between $-1$ and $-6$ kcal mol$^{-1}$. This analysis immediately shows that in the case of H-bonds the LRF values are expected to fail in accounting for the wide range of interaction strengths on the basis of (very) small differences in their values. A satisfactory correlation can hardly be expected on the basis of this order of magnitude analysis and Figure S1 given in the Supplementary Information indeed shows that there is in fact no correlation.

The situation turns out to be completely different for the halogen bonds. In Figure 2 the plot of the interaction energy vs. the $\chi$ values (still the full expression) is given. An excellent correlation is observed for the 9 cases where a halogen bond is formed (Cl, Br or I) with a first row atom acceptor (O and N, the cases of $H_2CO$ and TMA respectively). The regression line for these points (in black) is drawn and shows an $R^2$ value of 0.952. The two outliers, given in red, are precisely the two cases where the accepting atom is a second row atom being the Sulfur atom of metanethiol.

<<< **INSERT FIGURE 2 HERE** >>>

Two questions arise: why this fundamental difference between the H and Halogen bond behaviour and why do the second row cases of the halogen accepting atoms deviate from the regression line? These questions will be addressed in the final part of the discussion after having discussed some more technical problems putting the results in a broader perspective now that with the halogen bond cases we apparently dispose of a series of data showing a fair range and apparently bearing interesting information. Also here two questions/issues are addressed: what is the influence of the level of theory and what is the influence of the condensation technique.

## 3.2 Methodological issues

Concentrating first on the influence of the level of theory (IPA, RPA or Full) the overall results in Table S1 for the halogen-bond cases on which we will concentrate in this section show that the orders of magnitude of the mostly used IPA approximation and the full expression are similar, though for the larger values the IPA approximation has more tendency to overestimate the correct “full value”. In Figure 3 an overall very satisfactory $R^2$ value of 0.890

is observed, the slope deviating however substantially from 1 (0.53). This is an important result as (vide supra) nearly all previous LRF calculations were, for computational simplicity, carried out at the IPA level. In view of the correlation sketched above and, importantly, in view of the comparative nature in all these studies (comparison of relevant LRF values between atoms in a given molecule or between different molecules) it can safely been said that the chemistry which was displayed in these values can be built upon as it stands. The values itself will change when adopting the full version of the theory, but the trends will be conserved.

<<< **INSERT FIGURE 3 HERE** >>>

<<< **INSERT FIGURE 4 HERE** >>>

We also display in Figure 4 the correlation between the RPA values and the IPA results, again for the 11 X-bond cases: the result is less satisfactory, with a appreciably smaller $R^2$ value of 0.753. The message is clear: the IPA model, the crudest approximation in the Coupled Perturbed approaches we described above, makes sense, in its consistency that it neglects all corrections due to the perturbed orbitals on the Coulomb, exchange-correlation operators. Correcting, as in RPA , only for the influence of polarisation in the Coulomb term, gives a somewhat imbalanced model, due to the neglect of exchange. Reintroducing exchange, together with correlation in the KS case, restores this balance yielding results which are qualitatively in line with the crudest approximation, be it quantitatively different. These results can be compared within the introductory results on benzene in Ref. [26], the only molecule for which comparative results in this context were published until now, where it was found that although the IPA values are now significantly higher than for the two other levels (cf. the overall much higher values in view of the intramolecular character of the comparison) and which among each other are quite close, the overall pattern at the three levels is identical. The zig-zag behavior of the (1,1), (1,2) , (1,3) and (1,4) benzene matrix elements (the number referring to the Carbon numbering in benzene) [36] prevails at all levels of theory, be it that the exact exchange term was evaluated in a different way (vide supra), which however was shown during the preparation of the present paper to have only minor numerical consequences. Based also on ample evidence given in Ref. [77] where tests were carried not only on e.g. aromaticity indicators in aromatic six-rings, but also on diatomics, the inductive and mesomeric effects in (un) substituted (un)saturated hydrocarbons, ... it can be decided that in the future, if computational timing is a burden, the IPA approximation can still be used in qualitative comparative work in discussing overall trends but that in quantitative studies the full option however derives to be used still neglecting however the contributions of the derivatives with respect to $\nabla\rho$ to $f_{\mathrm{XC}}$. Note that the timings are still unfavorable for the full option and that presently a much faster version of the LRF code is in preparation. [77] Finally we depict in Figure 5 the correlation between the Iterative Hirshfeld and FOHI results for condensation in the case of the LRF values for the halogen bond donor and acceptor atoms in the 11 X-bond systems considered. The high correlation coefficient ($R^2$=0.998) and the slope value 0.944 indicate that both techniques yield highly similar results, be it that the FOHI technique, in view of its more elegant/consistent way of calculating spherical atom densities way of treating the sphericalisation issue might, in our opinion, be the method of choice.

<<< **INSERT FIGURE 5 HERE** >>>

### 3.3 Deepening the discussion on the difference between hydrogen and halogen bonds and between halogen bonds internally

The first question formulated in Section 3.1 was the fundamentally different behaviour between hydrogen bonds (extremely small LRF values showing little or no variability) and halogen bonds (values typically one order of magnitude larger and showing a much higher variability). In our view the interpretation of this difference can be traced back to the definition of the Linear Response Function itself. Equation 2 clearly points out that the reactivity descriptor we treat pertains a perturbation only in the potential of the reference system, often called in CDFT a $\Delta v$ perturbation, as opposed to its alternative, a $\Delta N$ perturbation (cf. the nature of the $E = E[N, v]$ functional). These potential perturbations are directly related to polarization effects and finally the contribution of the polarization energy in intermolecular interactions. Indeed the latter effects originate from the perturbation of the electron density due to the change in potential , as opposed to electrostatic effects involving only the unperturbed density.[85] The LRF is now nothing else than the response function associated to the polarization phenomenon as it determines, together with the perturbing potential, the first order change in the density $\Delta\rho(\mathbf{r})$ upon a perturbation $\Delta v(\mathbf{r}')$ via Eq. 4. Via corrections to the density $\Delta V$ perturbations are in this way responsible for those energy corrections commonly termed as polarisation energy. The polarisability of the species then comes into play. When considering a $\Delta V$ perturbation due to an external field $\epsilon$, of interest in recent work on the inclusion of external fields in CDFT [86], the elements of the polarisability tensor can be written [87, 88]

$$\alpha_{ij} = \int\int \mathbf{r}_i \chi(\mathbf{r},\mathbf{r}')\mathbf{r}'_j d\mathbf{r}d\mathbf{r}' \quad (i,j = x,y,z) \tag{21}$$

which can be casted in a local form as

$$\alpha(\mathbf{r})_{ij} = \int\int \mathbf{r}_i \chi(\mathbf{r},\mathbf{r}')\mathbf{r}'_j d\mathbf{r}' \quad (i,j = x,y,z) \tag{22}$$

linking in this case in a direct way the (local) polarizability and the LRF . Note that in the past connections between the Grand Canonical Ensemble analogue of the LRF, the softness kernel, and the CDFT counterpart of the polarisability, the (global) softness, have been established. The global softness is simply obtained by twice integrating the softness kernel, the intermediate result being the local softness

$$S = \int s(\mathbf{r})d\mathbf{r} \quad \text{with } s(\mathbf{r}) = \int s(\mathbf{r},\mathbf{r}')d\mathbf{r}' \tag{23}$$

A cubic relationship was established between $\alpha$ and S in the case of isolated atoms. [89, 90].Taking all things together it can be expected that with increasing polarizability of e.g. the halogen partner in a X-bond (passing from Cl to Br and I) the LRF of the donor acceptor couple will increase, further finetuning being of course being taken care of by the other partner. On the other hand in hydrogen bonds the halogen is replaced by a hydrogen atom , of very low polarisabilty and on top of that usually involved in a covalent bond with a strongly electronegative atom (F, O, N, . . . considering here only first row atoms) so that the H-atom is further reduced in its electronic population. This further diminishes its polarisability. As moreover the bonding partners in the cases considered in this paper are also (the same) first atoms showing besides high electronegativity, a low polarisability (or softness), the polarisation effect, which we expect to be reflected in the LRF, can be expected to be (very) low. This should be compared with the electrostatic effect in which the unpolarised density is at stake as present in the Molecular Electrostatic Potential (MEP). [91] Several (H bond) interaction energy decomposition techniques are at present available, sometimes with deviating nomenclature, but simply referring to the early work by Morokuma in his first ab initio partitioning technique [92] our argumentation seems to consistent. Looking in more detail at the values for the halogen bonds it can be seen that the highest interaction energies for a given X bond acceptor always increase along the series Cl, Br and I, well known in the literature, reflecting increasing polarisability of the donor atom. Substantially increasing values of the LRF are thereby displayed stressing its capability to reflect the role of polarisation in X-bond formation . The role of polarisation and polarisability in a halogen bond has already been stressed by e.g. Politzer, Alkorta, Brink and Ibrahim and their coworkers,[93–96], the latter stating in 2019 that "polarisation plays a key-role in halogen bonding". [96] In globo and as a first conclusion it can be stated that, as opposed to the case of H-bonds, the LRF can be used to interpret the trends in these non-covalent interactions. Note that these findings are also in line with our recent work [77] showing for example an increase in the C-C LRF when passing from ethane, via ethene to acetylene, reflecting the increasing polarisability when passing from a single to a double and a triple bond (for early experimental work on bond polarisabilities revealing the same trend, see [97]). What about the outliers involving the presence of a second row atom (S) involved as halogen bond acceptor? The reason might be that we are deviating more from a homogeneous series and that, as we make intermolecular comparisons instead of intramolecular ones, or better comparisons between complexes instead of between different positions in a given complex, the next step, presently in preparation in our group, might be (vide supra) to refine the treatment by comparing softness kernel elements instead of LRF elements. Defined in the context of the Grand Canonical Ensemble with the $\Omega = \Omega[\mu, v]$ functional as counterpart of the $E = E[N, v]$ functional, the second functional derivative of $\Omega$ with respect to $v(\mathbf{r})$ at constant $\mu$ emerges as an analogue of the LRF. [4, 5] One of the most interesting properties of this kernel, is that upon integration it yields the local softness $s(\mathbf{r})$ [44, 98] which in its turn via the expression $s(\mathbf{r}) = Sf(\mathbf{r})$ yields the global softness (for a recent overview of the mathematical properties of both the LRF, and the softness kernel see [99]). In analogy with the role of the local softness, being more adapted for comparisons of reactivity between different systems than the Fukui function [5, 98], passing from the LRF $\chi(\mathbf{r}, \mathbf{r}')$ to its counterparts$s(\mathbf{r}, \mathbf{r}')$ may indeed be expected to be a next step in reactivity studies, at stake when making comparisons between different systems (vide supra). Converting LRF values to the softness kernel can be made via the famous Berkowitz-Parr relation [44]

$$\begin{aligned} s(\mathbf{r}, \mathbf{r}') &= -\chi(\mathbf{r}, \mathbf{r}') + \frac{s(\mathbf{r})s(\mathbf{r})}{S} \\ &= -\chi(\mathbf{r}, \mathbf{r}') + Sf(\mathbf{r})f(\mathbf{r}) \end{aligned} \tag{24}$$

where $f(\mathbf{r})$ is the Fukui function. Recently it was shown that, based on the convexity of $\Omega(v)$ [99, 100] as opposed to the concavity of $E(v)$ [2, 99–103], the following inequality holds

$$s(\mathbf{r}, \mathbf{r}) \geq \frac{s(\mathbf{r})^2}{S} \geq 0 \tag{25}$$

linking the three softness descriptors in another way. The diagonal elements of the softness kernel should thus be positive or zero as opposed to those of the LRF. In an atom-condensed form Eq. (24) can be rewritten as

$$-s_{\mathrm{AB}} = \chi_{\mathrm{AB}} - \frac{s_{\mathrm{A}}s_{\mathrm{B}}}{S} = \chi_{\mathrm{AB}} - f_{\mathrm{A}}f_{\mathrm{B}}S = \chi_{\mathrm{AB}} - \frac{f_{\mathrm{A}}f_{\mathrm{B}}}{\eta} \tag{26}$$

where $s_{\mathrm{A}}$ and $s_{\mathrm{B}}$ denote atom condensed local softness values. Only a single paper hitherto made a numerical comparison between LRF and softness kernel values. In the case of hexatriene (see SI of [45]), using analytical expressions for the Fukui function and the hardness [104] it was found that for all elements of the LRF matrix the correction when passing to the softness kernel-matrix is such that the overall sequence of the C1 Cn (n=1,2, 6) matrix elements does not change. The correction for the off-diagonal $\chi$ elements (at stake in the present study) , which are positive, is always negative with an overall tendency of reducing the (absolute value) of the $s_{\mathrm{AB}}$ matrix elements as compared to the $\chi_{\mathrm{AB}}$ values. Importantly, the correction is proportional to the product of the local softness values. Despite being divided by the total softness, this indicates that in a given system the correction will be more important for the heavier congeners of e.g. the halogen bonding acceptor atom. This might result in a tendency of the two S-containing outliers in Figure 2 (in combination with the two heavier, and thus more polarisable, halogens Br and I) to come closer to the overall correlation curve (indicated by the red arrows). The situation that the original deviation is much larger for the heavier halogen (I) than for its Br counterpart further supports the hypothesis that, when passing to a softness kernel a still more uniform picture might appear.

# 4 Conclusions

In an effort to extend the use of the Linear Response Function to interpret non-covalent interactions its implementation with Coupled Perturbed Hartree Fock or Kohn Sham theory was scrutinized, delineating the different levels of approximation, and establishing clear rules for an efficient evaluation of the LRF in the case of the full first order correction level for different types of exchange-correlation functionals. The intricacies in the evaluation of the exchange correlation term in the case of meta GGAs and Hybrid functionals were thereby highlighted. Based on a set of 25 hydrogen bonded and 11 halogen bonded systems, selected from Hobzas S66 and X 40 compilation, the correlation between the interaction energy and the LRF matrix element between the hydrogen/halogen bond donor and acceptor atom was investigated. The case of H bonding fails to yield a decent correlation in contrast with the excellent result for the halogen bonds where the sequence of increasing strength when passing from Cl to Br and I is retrieved. The correlation between the full first order correction and the Independent Particle Model is high, providing support for our previous work using the IPA approximation as is also the case for the previously used Iterative Hirshfeld condensation and the more advanced FOHI method making use of fractional occupation numbers. The fundamental difference between hydrogen and halogen bond behaviour and the retrieval of the stability sequence within the halogen bonds series are traced back to the nature of the LRF as a response function for perturbations in the external potential putting polarisation effects and the polarisability of the atoms of the donor- acceptor couple at the forefront. The extension to the use of the softness kernel is advocated and already used qualitatively to rectify the behaviour of two deviating complexes involving S as second row halogen bond acceptor atom.

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# 5 Figures

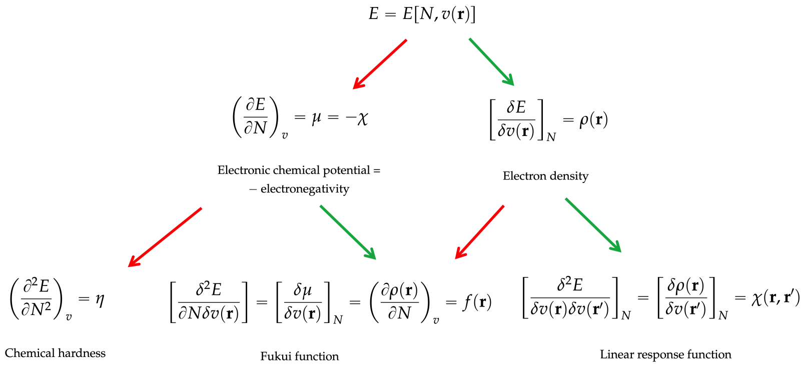

**Fig. 1** The Response Function Tree of the Energy vs. changes in the number of electrons N and the external potential $v(\mathbf{r})$, up to $n = 2$ (see text). Red arrows indicate differentiation with respect to $N$, and green arrows indicate differentiation with respect to $v(\mathbf{r})$ (see text).

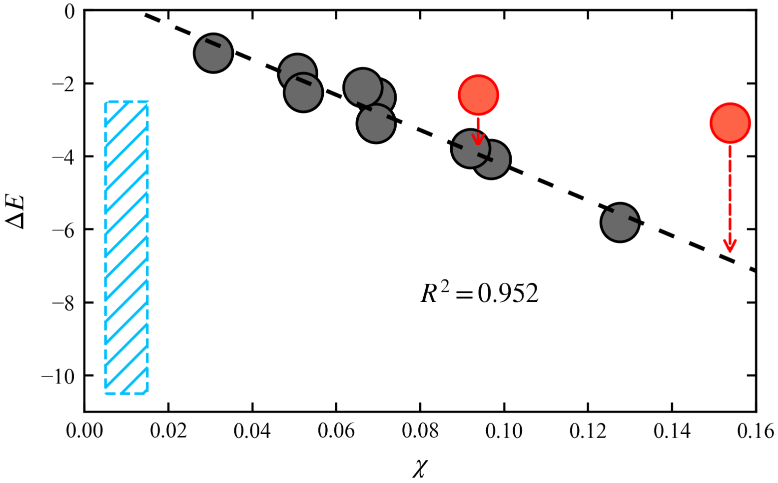

**Fig. 2** Correlation between the H- and X- bond interaction energy ($\Delta E$) (in kcal mol$^{-1}$) and the Linear Response Function atom-atom matrix element $\chi_{H/X\cdots B}$ (in a.u.) for hydrogen and halogen bonds, B denoting the acceptor atom. The H-bond cases are schematically represented in the vertical blue block showing no internal correlation (see text). The correlation for the X-bonds is shown for all complexes involving a first row acceptor atom B (in black). The two red points refer to halogen bond complexes involving a second row (S) atom as acceptor atom. The arrows represent the expected evolution when passing from the LRF to the softness kernel (see text).

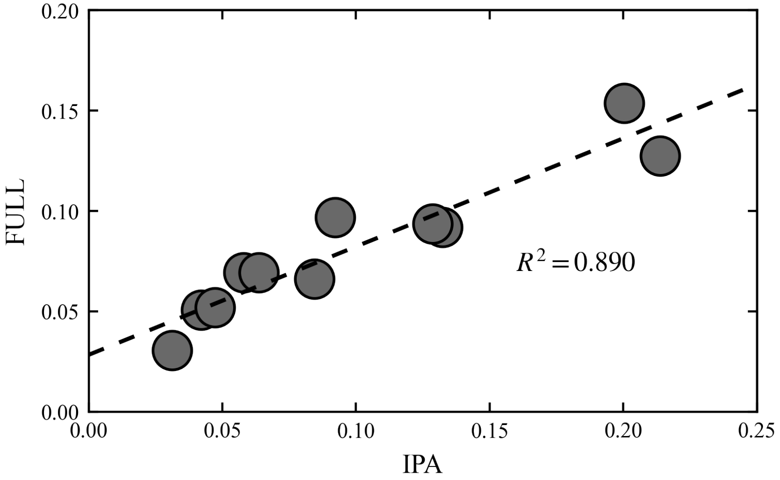

**Fig. 3** Correlation between Linear Response Function atom-atom matrix elements $\chi_{H/X\cdots B}$ (in a.u.) for halogen bonds at the IPA and “Full” level (all values in a.u.).

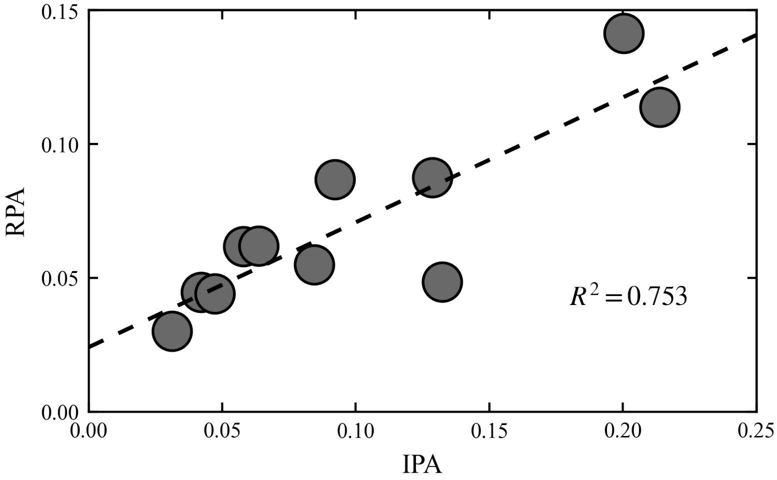

**Fig. 4** Correlation between Linear Response Function atom-atom matrix elements $\chi_{H/X \cdots B}$ (in a.u.) for halogen bonds at the RPA and IPA level (all values in a.u.).

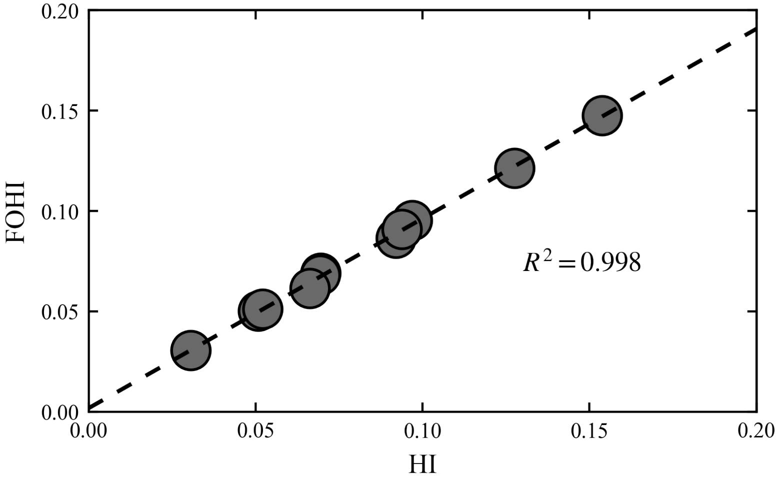

**Fig. 5** Correlation between the Iterative Hirshfeld (HI) and FOHI results for condensation: the LRF values for the halogen-bond donor and acceptor atoms (in a.u.).

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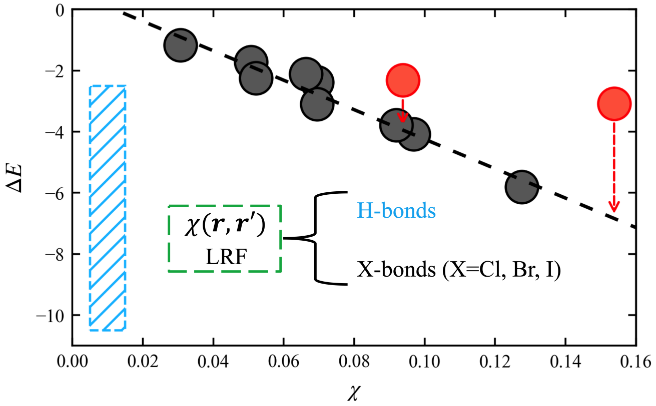
**Fig. 6** **Graphical abstract**



## Supporting information

- Table S1: H- and X-bonded complexes: numerical data.
- Figure S1: Correlation between the H-bond interaction energy ($\Delta E$) (in kcal mol$^{-1}$) and the Linear Response Function atom-atom matrix element $\chi_{H/X\cdots B}$ (in a.u.) for hydrogen bonds, B denoting the acceptor atom. Detailed version of part of Figure 2.