



# Conceptual density functional theory: status, prospects, issues

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## Abstract

This paper results from a round table discussion at the CCTC2018 Conference in Changsha City, Hunan, China, in December 2018. It presents a report on the status, prospects, and issues of conceptual density functional theory (CDFT). After a short exposition on the history of CDFT, its fundamentals, philosophy, and successes are highlighted. Then ten issues for reflection on the future of conceptual DFT are formulated and discussed, ending with one or more summarizing statements on the present status of various concepts/principles/practices and proposed directions for future research. The issues include the further analysis of the energy functional,  $E[N, \nu]$ , extended to include effects of temperature, solvent, and mechanical forces, basic requirements for physically acceptable response functions as reactivity descriptors, the use of the grand canonical ensemble, the relevance of CDFT for chemical kinetics and thermodynamics, the domain of validity of CDFT-based principles, the combination of CDFT with reaction path calculations, information-theoretic descriptors, and the treatment of excited states and time dependence. The final issue advocates the transition of CDFT from an interpretative to a predictive mode; we believe this is of utmost importance for promoting CDFT as a viable alternative to wave function-based methods for the practicing chemist, a separate issue treated in the final section.

**Keywords** Density Functional Theory (DFT) · Conceptual DFT (CDFT) · CDFT history · CDFT philosophy · CDFT issues

## 1 Introduction

At the occasion of the CCTC2018 Conference (International Symposium on Chemical Concepts from Theory and Computation) in Changsha City, Hunan Province, China, from 9 to 11 December 2018), the conference's host and lead

organizer, Shubin Liu, proposed that an introductory paper for the Special Issue of *Theoretical Chemistry Accounts* devoted to this conference, on the present status, prospects, and challenges of conceptual DFT should be composed [1, 2]. The paper would be based on a round table discussion moderated by Paul Ayers, based on a draft text prepared by Paul Geerlings, which was duly convened at the beginning of the conference. After the conference, the text was revised

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(chiefly by Paul Geerlings, exploiting notes taken by Christophe Morell) to reflect the discussion, and then, the text was revised, amended, and approved by all co-authors.

Clearly, then, this contribution is not a review of the classical type, but a snapshot of the status of the field of CDFT and a measure of the volume of the CDFT literature at specific juncture in time. This seemed more valuable to the participants, as there are several authoritative reviews on CDFT from the last 2 decades, the first by Chermette [3], followed by Geerlings et al. [4], Ayers et al. [5], Gázquez [6], and Liu [7]. There are in-depth reviews on topical issues within CDFT like Higher-Order Response Functions [8], the retrieval of the Woodward Hoffmann rules [9], electrophilicity [10–12], the linear response function [13, 14]. Several books have also been published [15–17]. Recently, a special issue of *Acta Physico-Chimica Sinica*, devoted to Chemical Concepts in DFT with 30 contributions from all over the world, was edited by Shubin Liu with the intent to broaden the readership of CDFT [18]. The most extensive review, the 2003 *Chemical Reviews* paper by Geerlings and co-workers, has already been cited more than 2600 times; given that the review itself contains more than 800 references, the volume of the CDFT literature must exceed 4000 papers.

Clearly this subfield of density functional theory (DFT) has been the subject of intense intellectual activity in the last 40 years. However, the aim of the present paper is not to exhaustively review these efforts, but to provide a perspective on the current status and future prospects of CDFT. In assessing the current status of the discipline, many of the major accomplishments will be addressed, although, due to space limitations, generally only in a concise form, featuring only the most essential references.

The present paper is also an occasion to contemplate the basic principles and philosophy of CDFT and to assess its place in the broader discipline of theoretical chemistry. These fundamental facets of CDFT are sometimes mentioned, but usually very modestly, in the journal articles, but have been addressed in more detail in some book chapters which, as it is so often the case, are less widely read and cited. Therefore, in Sect. 2, after a short history of CDFT, we present the fundamental precepts of CDFT. Section 2 ends with a very rough, helicopter-type, overview of the types of accomplishments CDFT has made. This highly selective list of achievements is intended simply to illustrate the broadness of activity in the field and to help the reader situate the particular issues addressed in Sect. 3 (Issues for Reflections on the Future of CDFT).

In Sect. 3, we made a selection of ten topics that in our view merit particular attention for the future with all possible pitfalls of prejudice, limited interests, and knowledge of the co-authors. The topics were selected, in most cases, upon reflection on CDFT's accomplishments and taking into account the basic philosophy of CDFT espoused in Sect. 2.

To facilitate discussion, each topic was phrased as a concrete question, which was subsequently discussed at the meeting in Changsha. The conclusions/recommendations resulting from those discussions can be found in bold throughout the text.

We end this paper with a separate Sect. 4 on what we believe is the most salient topic of all: “Promoting CDFT for the Practicing Chemist”. We think that the enormous intellectual effort that has gone into the development of conceptual DFT and the realm of the applications addressed should find further recognition and greater use by a broader community of chemists. Some ideas on how to reach this goal are addressed here.

## 2 A short history of conceptual density functional theory (CDFT)

### 2.1 Fundamentals

Conceptual DFT, as a branch of DFT [19], can be considered to have its genesis in the ground-breaking 1978 paper by Parr et al. [20] leading to the identification of the Lagrangian multiplier  $\mu$  in the DFT variational principle (hereafter called the electronic chemical potential) with the first derivative of the ground-state electronic energy with respect to the number of electrons  $N$  retrieving the (negative of the) Iczkowski–Margrave expression for the electronegativity  $\chi$  [21]. Taking a finite-difference approximation, the Mulliken electronegativity [22] is obtained, thereby bridging the gap between DFT and classical chemical concepts. Soon after, in 1983, Parr and Pearson [23] identified Pearson's hardness [24, 25] with the second derivative of the energy with respect to  $N$ . In 1984, the Fukui function made its appearance in a paper by Yang and Parr [26], generalizing and extending Fukui's Frontier MO concept [27, 28]. One could say that at that moment the launching of conceptual DFT was complete, though the name “conceptual density functional theory” was only proposed a decade later, in 1995, in an *Annual Reviews of Physical Chemistry* review by Parr and Yang [2]. As stated in that early review, the mission of CDFT is to develop a chemical reactivity theory founded on DFT-based concepts, including the electron density  $\rho(\mathbf{r})$  itself, the chemical potential  $\mu$ , and other quantities and functions that appear in time-independent ground-state DFT [1]. Confusion and debate has arisen in later years about the description “conceptual”, as obviously also in other facets of DFT concepts are prominent starting with its fundamentals. In conceptual DFT, however, physical and mathematical concepts from DFT are repurposed and combined to form descriptors to elucidate chemical concepts, especially those related to reactivity. Conceptual DFT is clearly “conceptual” in both substance and purpose; then, as it is built upon

a hierarchy of rigorously defined response functions (vide infra), starting with the first-order responses,  $\mu$  and  $\rho(\mathbf{r})$ , that appear in the fundamental DFT variational principle. **The authors advise to keep the term “conceptual DFT” because it is now widely known, even though it might be confusing for some newcomers.**

Starting long before the advent of CDFT, chemical reactivity has been addressed with wave function techniques, an example par excellence being the Woodward Hoffmann rules [29]. However, the essence of conceptual DFT is to address chemical reactivity from a “density only” viewpoint. Note also that at the founding of CDFT, methods for the accurate calculation of reaction paths were not standard, making efforts to predict/interpret the course of a reaction based on the perturbational approach of the starting compound(s) extremely rewarding (vide infra).

Central to Parr’s perturbational strategy is the electronic energy, expressed as a function of the number of electrons and the external potential,  $E[N, v]$ . More precisely, the functional Taylor expansion [30] of the energy explains how a molecular system responds to changes in its number of electrons  $N$  and/or its external potential  $v(\mathbf{r})$  (the potential felt by the electrons). The coefficients in the Taylor series are the response functions,  $\partial^n \delta^m E / \partial N^m \delta v(\mathbf{r}_1) \delta v(\mathbf{r}_2) \dots \delta v(\mathbf{r}_m)$ , the simplest response functions being the electron density itself ( $n=0; m=1$ ), the electronic chemical potential ( $n=1; m=0$ ), and the hardness ( $n=2; m=0$ ). In a nutshell, the history of conceptual DFT can be summarized as the exploration of these and more complicated response functions (with all the mathematical intricacies and interpretation nuances associated thereto), their use to characterize molecular systems from the kinetic and thermodynamic points of view (vide infra), and the discovery of generalizing principles and rules-of-thumb that allow the CDFT ansatz to cover the broadest possible repertoire of molecules and their reactions. Some of these principles existed long before CDFT (the electronegativity equalization principle [31–33], the hard and soft acids and bases principle [34–36]), but had not been mathematically formulated or rigorously justified. Other principles, most notably the maximum hardness principle, came later and are scarcely even conceivable without the essential context provided by CDFT.

**Summarizing the latter sentences and extrapolating to the future, the aim of conceptual DFT is “to develop a nonempirical, mathematically and physically sound, density-based, quantum–mechanical theory for interpreting and predicting chemical phenomena, especially chemical reactions”.**

## 2.2 Philosophy

Looking back at the foundational papers of CDFT and subsequent developments, most CDFT researchers adopt some

common precepts although, it must be said, this “philosophy” is rarely explicitly written down. Some of the present authors tried to formulate these implicit rules in two book chapters [37, 38].

**In retrospect (as no philosophy was written down explicitly in the early years of CDFT, although it has always been implicit) the following philosophical basis can be put forward. Conceptual DFT is based on three fundamental precepts, which constitute its essential philosophy and which, in our opinion, should be followed in the years to come:**

1. **Observability:** Our understanding of chemical observations should be based on quantum mechanical observables (in casu the energy, density, and their derivatives).
2. **Universality:** the tools we use to understand the results of quantum mechanical calculations should not depend on the type of calculation that is performed.
3. **Mathematical Rigour:** the tools we use to understand chemistry should fit into a well-defined mathematical framework.

Recently, some specific work in this direction has been presented by Ayers et al. [39] whilst formulating an axiomatic approach to conceptual DFT.

Conceptual DFT is not the only theoretical framework based on the preceding precepts nor do we claim that every theory should be based on these axioms (vide infra). CDFT’s big advantage is that it is based on the density and the responses of the density and energy to changes in the number of electrons and the external potential, all of which are observables, unlike the wave function in the wave function-based approaches. Thus CDFT is in line with the observability precept. Considering “universality”, the wave function approach has the disadvantage that concepts used as interpretational tools sometimes, to quote Mulliken [40], “vanish into thin air” as the level of computation increases (e.g., configuration interaction calculations with millions of determinants or valence bond calculations leading to an astonishingly increasing number of (often chemically unrealistic) resonance structures). In conceptual DFT, the nature of the computed quantities like the electron density and the other response functions ensures unchanged transparency upon increasing level of computation; the values change, but their underlying complexity does not. This ensures the aforementioned universality: the tools we use are not dependent on the level of theory used to obtain them. Finally, perhaps the greatest advantage of conceptual DFT is that it provides a mathematically rigorous, formally exact, approach to understanding chemical changes. In essence, its appeal is its (striving towards) mathematical rigour,

physical/quantum–mechanical underpinning, combined with chemical insight and intuition. The perturbation expansion mentioned above plays a fundamental role in this context: each term is well-defined and probes the system's response to a particular type of perturbation at a given order. In this way, in principle, through analysis of their response functions, molecules can be designed to display particular reactive properties. Certainly mathematically intricate issues remain (as will be seen in Sect. 3), and there are challenges associated with turning the CDFT framework into a practical instrument for non-specialists (see Sect. 4).

A word of caution is in order: the three precepts formulated above are valuable guidelines and the observation that conceptual DFT adheres to these precepts does not mean that other approaches, which disregard one or more of these precepts, are not valuable. Wave function-based approaches predate CDFT and have been and remain immensely important to the chemical community. Neither do we dispute that some chemical phenomena are easier to explain within a wave function context (MO or VB), taking again the celebrated Woodward Hoffmann rules [29], or, in the early days of quantum chemistry, Hückel's  $\pi$ -electron theory [41–45] as paradigmatic example. Some of the present authors, however, showed that the WH results can be retrieved in a CDFT context without undue complexity [9, 46–50]. A temporary conclusion (elaborated upon in Sect. 4) is that both CDFT and traditional wave function-based approaches are highly valuable and that the choice of “when to use what” depends on both the system/phenomenon of interest and the preferences of the individual researcher. The use of observables is sometimes more demanding than a wave function-based approach, but sometimes their rigour is important. A precondition for making the correct decision is that the researcher can choose based on scientific considerations, and (s)he is not punished by the availability and usability of software tools. These considerations should be of primary concern for the CDFT community (see the separate discussion in Sect. 4).

### 2.3 Accomplishments

The literature on the development and applications of conceptual DFT is vast. Our focus is primarily on *fundamental developments/issues*; guidelines for the *users* of conceptual DFT is a major concern of all the authors and is addressed in Sect. 4. However, the bulk of the literature on conceptual DFT focusses on its broad *applications* across all branches of chemistry, from inorganic and materials chemistry, to organic and polymer chemistry, to biochemistry. As conveyed through the aforementioned review articles and books, CDFT has also been applied to the full scope of chemical reactions, from gas-phase reactions, to reactions in solution, to reactions/rearrangements in solids, to reactions at

phase boundaries; from acid–base complexation, to redox reactions, to pericyclic reactions, to coordination chemistry. CDFT has also been applied to a wide range of quantities from physical chemistry, from thermodynamic properties (binding energies, pKa) to kinetic properties (reaction rates, branching ratios).

We now provide a partial list of a few important fundamental/theoretical developments in the last ~ 15 years, emphasizing those developments that motivate the topics we shall consider in the next section. (As appropriate, we will indicate the researchers who have been most active in these developments, along with the sections of this article and/or references to which the reader may refer for further details.)

At the most fundamental level are various studies that explore, or apply, fundamental aspects of the energy  $E[N, v]$  functional. Yang extended the pioneering work by Perdew et al. [51] on the piecewise linearity of the energy functional at 0 K, including the “flat plane” conditions on density functionals [52, 53], thereby obtaining linearity and constancy conditions for a variety of CDFT indicators [54, 55]. Ayers, among others, concentrated on the related problem of  $N$ -differentiability [56–58]; these differentiability issues can be removed by including temperature in the description [59–65] (Sect. 3.1). Several workers have investigated the concavity of the energy functional with respect to the external potential and its consequences for the linear response function and higher derivatives (Helgaker [66], Geerlings [67], based on pioneering work by Lieb [68]). Higher derivatives have been advanced by many, especially through the introduction of the dual descriptor by Morell et al. [69, 70]. Geerlings and De Proft exemplified the computation and extraction of chemical information from the linear response function and the softness kernel [13, 54, 71–81]. Cardenas, Cedillo, Ayers, and Bultinck refined the calculation of the Fukui function and other descriptors for degenerate ground states [82–84]. New relations between nuclear and electronic density functional indices were presented by Torrent-Sucarrat et al. [85], with particular attention to the relation between electronic and nuclear Fukui functions, the latter being the  $N$ -derivative of the force on a given nucleus, used as a proxy to the response of nuclear positions to changes in the number of electrons [86–88]. The combined use of electronic and nuclear Fukui functions was explored by Cauët et al. [89] to investigate bond breaking patterns occurring upon low energy electron attachment to DNA fragments.

Although the concept of alchemical derivatives dates back to the pioneering work of Parr and Politzer [90], they were scrutinized and turned into nearly standard research tools through the work of von Lilienfeld [91–95], Balawender and Geerlings [96–100], and others (Sect. 3.2). Also dating back to pioneering work by Parr, Yang, and Nalewajski, the alternative perspective provided by the grand canonical ensemble (or “open-system picture”), where one uses  $\Omega$



$[\mu, \nu]$  instead of  $E[N, \nu]$  has been advanced by Gázquez et al. [65]. Chemical transferability has been found to have its physical origins in the concept of nearsightedness [101–104] (Sect. 3.3). The concepts of global and local electrophilicity have been greatly advanced, with an astonishingly broad range of applications, as summarized in Chattaraj's reviews and references therein [10–12] (Sect. 3.2). Existing reactivity principles (HSAB, MHP) were refined and critically examined [105–107], and some new ones have been introduced (e.g., the Minimum Electrophilicity Principle [108–111]) (Chattaraj, Ayers, etc.; Sect. 3.5). Following on the pioneering work by Ghanty, Ghosh, Galván, Gázquez, and Vela [112–114], the formalism for extending the  $E = E[N, \nu]$  functional into spin-polarized conceptual DFT has been developed in detail [115–123] and its calculability and utility has been demonstrated in practical applications. An extension of CDFT's framework to mechanochemistry is under development [124, 125] (Sect. 3.6). Toro-Labbé and his coworkers made an important step forward by connecting conceptual DFT with reaction path calculation using the reaction force [126–129] and identified the derivative of the chemical potential with respect to the reaction coordinate, the reaction electronic flux, as a key indicator for characterizing chemical reactions [130–132] (Sect. 3.7). While one might think that since DFT was originally formulated as a ground-state theory, CDFT would not be applied to excited-state (photo)chemistry, Morell et al. [133] and others have made advances along these lines, and the future of this aspect, along with the closely related time-dependent CDFT (Chattaraj), will be addressed in Sect. 3.8. Finally, the link between conceptual DFT and information theory that was pioneered by Parr and Nalewajski [134–137] has been extended and strongly promoted by Nagy [138, 139], Liu [140–146], and others, suggesting that tighter links between information-theoretic approaches and CDFT may open up entirely new research directions, both in the formal and the practical sense (Sect. 3.9).

In addition to the preceding topics, which are more topical, we will also discuss methodological, and even philosophical, aspects of CDFT. For example, we shall discuss the use of so-called “derived” descriptors which are not response functions (Sect. 3.2), reflect on whether CDFT is a theory of kinetics, thermodynamics or both (Sect. 3.5), and investigate whether CDFT is a theory of bonding (processes) or chemical bonds (structure) (Sect. 3.5). In Sect. 3.10, we reflect on whether CDFT, which until now has been essentially interpretative can and should be turned into a predictive theory and, (vide supra) how its position versus wave function theories should be assessed.

Finally, as stated above, Sect. 4 presents the authors' thoughts about how to increase the impact of conceptual DFT in the future.

### 3 The future of CDFT: issues for reflection

#### 3.1 The electronic energy functional, $E[N, \nu]$ : differentiability, temperature, and marrying mathematical rigour to practical utility

The electronic energy, expressed as a function of the number of electrons and a functional of the external potential,  $E[N, \nu]$ , has been the central quantity in conceptual DFT from its inception. The energy and its derivatives (including the electron density,  $\rho(\mathbf{r})$ , which is simply the functional derivative of the energy with respect to  $\nu(\mathbf{r})$ ) satisfy the condition (vide supra) of being quantum-mechanical observables. However, it was realized very early that differentiating the energy with respect to  $N$  was problematic due to derivative discontinuities. In the landmark paper by Perdew et al. [51], the form of the energy as “series of straight lines intersecting at integer  $N$ ” was derived as the zero-temperature limit of the (thermal) expectation value of the electronic energy. This led to acceptable working equations for the chemical potential and the electronegativity, but the hardness, being the second derivative of the energy with respect to  $N$ , became problematic since it becomes the derivative of a step function (with expressions of the type  $\eta = (\text{IP-EA}) \delta(\omega)$  where  $\delta(\omega)$  is the Dirac Delta Function [147]). This expression for the hardness is unusable and chemical meaningless, compared to the venerable result of Parr and Pearson obtained by assuming that  $E(N)$  is a simple quadratic interpolation between the energies at integer  $N$  [1] (or alternatively, similarly useful, results based on exponential [148] and rational [149] interpolants). The derivative discontinuity in  $E[N, \nu]$  therefore implies the disappearance not only of the chemical hardness as a useful concept, but also of other quantities involving second- or higher-order  $N$  derivatives including the hyperhardness [149, 150] (maybe less important), but also the dual descriptor [69, 70] (a mixed derivative) which has proved to be extremely useful for discussing reactivity since it gives a one-shot picture of both electrophilic and nucleophilic regions [101].

Are we trapped? Must we choose between the physically and mathematically correct intersecting straight lines model (but without useful definitions for the hardness, dual descriptor, etc.) and chemically (but not mathematically) reasonable smooth interpolation with flourishing chemistry in it? This problem has been addressed in the aforementioned series of papers by Franco-Pérez, Ayers, Gázquez and Vela by ensuring differentiability of the  $E[N, \nu]$  function by introducing temperature [59–65]. (See also the early work in [151] and a recent review [65].) Introducing the temperature (more-or-less) necessitates passing to an open system (and the concomitant switching

from the canonical ( $N, \nu$ ) ensemble to grand canonical ( $\mu, \nu$ ) ensemble) in which  $N$  represents the average number of electrons, and there are fluctuations in the number of electrons around integer values. The average electronic energy (and its derivatives) becomes the central quantities in the finite-temperature chemical reactivity theory, analogous in form/interpretation but different in evaluation to those from traditional approaches. The temperature values at which the deviation from the zero-temperature limit becomes chemically meaningful are usually so high (thousands, even tens of thousands, of degrees) that they typically exceed the temperatures of interest even in the so-called high-temperature chemistry. Since including thermal effects leads to negligible changes in the values of the response functions compared to their values at 0 K, the traditional, temperature-independent approach can therefore be retained if one wishes. However, in addition to its resolution of the differentiability problem, the temperature-dependent approach provides a new perspective and leads to new reactivity indicators, many of which are associated with response functions associated with temperature changes, like a heat capacity [152] and a local heat capacity [62]; these are important for energy transfer analysis. One also discovers subtleties in the mathematical framework of CDFT. For example, the inverse relationships between hardness- and softness-related quantities only holds at 0 K [60], indicating that in general the hardness and softness contain different chemical information. Although at finite temperature the hardness and the dual descriptor may be determined analytically, at low temperature their profiles revert to the (unchemical) Dirac delta type behaviour. The finite-temperature approach allows one, however, to define a new thermodynamic hardness and thermodynamic dual descriptor that retain their utility in the zero-temperature limit [59, 64]. Another approach to introducing an ensemble considers the system not as a finite-temperature open system interacting with a reservoir, but as a zero-temperature open system interacting with its chemical (other molecules, solvent, etc.) environment. By building a model for the interactions of a system with its environment, Miranda-Quintana and Ayers [58] presented a different way to (re)define the chemical potential and the hardness for interacting systems.

**We recognize a dichotomy between fundamental CDFT work, where the inclusion of temperature to ensure differentiability may be essential, and applied CDFT works where temperature effects can be neglected. Now that the mathematical framework of temperature-dependent CDFT is largely complete, more systematic studies about the effects of temperature, especially on the  $E(N)$  curve, are needed. At the applied level, the conventional, temperature-independent descriptors may be used with confidence. Indeed, recent work suggests that**

**the quadratic model is well-founded if it is considered a model for the free energy [63].**

For reactions in solution, treating a reagent as an open system in which the number of electrons fluctuates (as in the temperature-dependent theory) seems appropriate. Then, using the grand canonical ensemble, in the limit of infinite dilution, it seems reasonable to regard the solvent as an electron reservoir with a specified chemical potential (which could be tuned electrochemically or by acid/base titration), so that the number of electrons in the system will fluctuate [65]. While this is certainly the correct physical picture, for the practicing chemist the number of electrons at the *molecular* level, even in solution, is considered to be constant (with the obvious exception of the electron transfer reactions). The following issue then arises.

**Do we need to invoke different theoretical frameworks for gas-phase chemistry and solution-phase chemistry? Its necessity might be related to the magnitude of fluctuation of the number of electrons in real systems at temperatures, say up to 500 K, which is expected to be very small in many cases. On the other hand, the extension of the  $E[N, \nu]$  functional to include solvent effects, leading to a redefinition of reactivity descriptors, must be scrutinized. Systematic studies, analogous to the aforementioned studies on temperature dependence, are needed to provide clear guidelines to applied theoretical chemists (which framework to use?) and to experimentalists (how to interpret the results?).**

Two final notes: In a recent contribution by Heidar-Zadeh et al. [56], different interpolation models for  $E(N)$  models were scrutinized for the correct normalization of the electron densities and Fukui functions derived therefrom. Polynomial interpolation models and, in particular Parr and Pearson's quadratic  $E$  versus  $N$  model, yield normalized densities and density derivatives; other models, most notably the rational and exponential interpolants, do not. Second, we have not discussed higher-order derivatives with respect to the external potential. These derivatives are not formally problematic (for nondegenerate states) but can be cumbersome to evaluate. Nonetheless, the second derivative with respect to  $\nu$  (the linear response function) has been evaluated at various levels of approximation by the Brussels group [13], and in principle this strategy can be extended to higher-order derivatives [153]. The important chemical content encapsulated by the linear response function (inductive and mesomeric effects, delocalization, (anti)-aromaticity, molecular conductivity, etc.) has also been demonstrated by the Brussels group [74–81]. Along the same lines, it is known that (anti) aromatic systems are (softer) harder and (more) less polarizable and electrophilic [154]. The quadratic and higher-order response functions are certainly technically demanding, both to evaluate and to visualize/interpret, but they are not afflicted by the mathematical problems associated

by higher-order derivatives with respect to the number of electrons.

### 3.2 Response functions as CDFT's fundamental ingredients: basic requirements, selection, and subtleties

Inasmuch as CDFT is fundamentally a theory of chemical reactivity, the behaviour of the energy at the onset of a chemical reaction is of utmost importance. Klopman's rule [155], which holds when the reaction curves of similar reactions do not cross between the reactant and the transition state, indicates that smaller increases in energy at the onset of the reaction are associated with lower activation energy (and higher reaction rates). Therefore, studying how the energy changes at the onset of a chemical reaction gives information about (relative) rates. Information about reactivity can thereby be extracted from a perturbational ansatz by studying low-order derivatives of  $E[N, v]$ , that is, by studying the response functions  $\partial^n \delta^m E / \partial N^n \delta v(\mathbf{r}_1) \delta v(\mathbf{r}_2) \dots \delta v(\mathbf{r}_m)$  either directly or (better) multiplied by the perturbations in  $N$  and  $v(\mathbf{r})$  themselves ( $\Delta N$  and  $\Delta v(\mathbf{r})$ ). *Response functions are thereby established as the fundamental CDFT descriptors and, in accord with the precepts presented in Sect. 2.2, they are quantum-mechanical observables.*

Response functions are not the only acceptable descriptors, however. Other descriptors derived from  $E[N, v]$  and exploiting its characteristics (e.g., the universal presence of a minimum in a quadratic interpolation for  $E(N)$ ) are perfectly acceptable. The most important example is the electrophilicity, introduced by Parr et al. [156], which Chattaraj and his coworkers have shown to be exceptionally useful across a broad range of applications, both in its global and local forms [10–12]. For example, the (local) electrophilicity is very useful in QSAR models for toxicity [157] and other properties. Nucleofugality [158, 159] is also based on the quadratic  $E(N)$  model, still promising though less popular. Electrophilicity and nucleofugality are examples of the so-called “derived descriptors”, wherein response functions are combined using products, quotients, sums, etc. While some derived descriptors, as those mentioned above, arise from a well-formulated mathematical model, most have been proposed in an ad hoc fashion, and do not have any clear physical/chemical meaning. Given the proliferation of existing derived descriptors and the infinite flexibility one has in defining new derived descriptors, they are susceptible to “cherry picking”.

**We propose the following guideline: in order to have a unified approach to practicing CDFT, response functions and descriptors directly derived from the  $E[N, v(\mathbf{r})]$  should be preferred, and the “cherry picking” of “derived descriptors” should be avoided. All new**

**descriptors should be based on firm physical/mathematical grounds.**

In order to implement the preceding guideline, the following issues related to the evaluation of response functions should be kept in mind.

1. A clear statement should be made about how the partial derivatives with respect to  $N$  are to be evaluated, including mixed partials (e.g., the dual descriptor).
2. Although technically complex, second- and higher-order derivatives with respect to the external potential can be evaluated. However, the difficulty of computation/visualization/interpretation increases rapidly for higher-order responses.
3. The convergence of the perturbation series should be investigated. It seems that for alchemical derivatives, convergence in  $v(\mathbf{r})$  is faster than convergence in  $N$  [95, 160].
4. The method for condensing local descriptors to atoms and functional groups must be specified and for responses to the external potential, one must be wary of (near-)degeneracy as evidenced in Bultinck's and Cardenas' papers [82–84].

**A final issue: can a “derived descriptor”, even one that is well-motivated, be universal? [161–164] If the descriptor is constructed from (physically observable) response functions, then this question relates to the use of the complete perturbation series (to be addressed in Sect. 3.10).**

### 3.3 Passing from the canonical ensemble to the grand canonical ensemble: a more refined use of CDFT?

The grand canonical ensemble and its associated state function,  $\Omega[\mu, v]$ , has been present almost from the beginning of CDFT. The response functions  $\partial^n \delta^m \Omega / \partial \mu^n \delta v(\mathbf{r}_1) \delta v(\mathbf{r}_2) \dots \delta v(\mathbf{r}_m)$  lead in a natural way to key reactivity indicators including the global softness ( $S; n=2, m=0$ ), local softness ( $s(\mathbf{r}); n=1, m=1$ ), and the softness kernel ( $s(\mathbf{r}, \mathbf{r}'); n=0, m=2$ ), which are, respectively, the analogues of the hardness, Fukui function, and linear response function ( $\eta, f(\mathbf{r}), \chi(\mathbf{r}, \mathbf{r}')$ ) from the Canonical Ensemble [3, 165–167].

While the fundamental difference between  $N$  and  $\mu, \eta$  and  $S$ , and  $f(\mathbf{r})$  and  $s(\mathbf{r})$  has been fully recognized and exploited for a long time, the difference between the linear response function and the softness kernel, initially highlighted by Parr and Berkowitz [166], has only recently been studied in a quantitative way. Notably, Fias et al. [104] showed that the softness kernel is the key quantity associated with Kohn's nearsightedness of electronic matter principle, while the linear response function is not nearsighted.

Conceptually, the importance of the grand canonical ensemble arises from the chemical potential of the bath, which is an *independent* variable in  $\Omega$  and therefore different from the mathematically imposed choice for the electronic chemical potential in finite-temperature CDFT. This may be very important for electrochemical processes [60]. Nonetheless, practicing CDFT researchers often prefer working at constant number of electrons (using  $E[N, \nu]$ ) to working at constant electronic chemical potential (using  $\Omega[\mu, \nu]$ ). The use of the grand canonical ensemble is rooted in the idea that the number of electrons in a molecule can fluctuate, as occurs in solution. But this seems to force us to rethink CDFT, especially the tendency to think of electron transfer as a specific change in the (fixed, constant) number of electrons, rather than a shift in the average number of electrons. This raises the following question:

**Is, at the molecular level, dropping the idea of constant  $N$  contradictory to chemical intuition? These two visions can be reconciled when, as is usually the case, fluctuations in  $N$  due to solvent/temperature are small. Therefore, for most reactions in solution, the constant  $N$  condition is almost fulfilled. If electron transfer between the reagent and the solvent is significant, however, a treatment based on the grand canonical ensemble is strongly preferred [58].**

### 3.4 Kinetics or thermodynamics? Bonding or bond?

When it is used to investigate the onset of a chemical reaction perturbatively, CDFT is inherently a reactivity theory. As stated above, the preference of a reagent for one reaction or another in similar conditions (e.g., by analysing the product distribution) is based on kinetic considerations, implicitly using Klopman's non-crossing rule (cf. Sect. 3.2). Predictions for CDFT are not expected to be reliable for late transition states or multistep reactions. On the other hand, the derivations of the (global) HSAB and maximum hardness principles in CDFT are essentially thermodynamic. (With the HSAB principle, at the global level one addresses relative thermodynamic stabilities of different products, though the (more questionable theoretically) local HSAB principle is again more aligned with kinetics.)

In a one-step reaction, assuming the reaction-energy curves do not cross during the complete reaction pathway, thermodynamic and kinetic predictions should be aligned. Still, one may question whether investigations of relative thermodynamic stability fit within the perturbational approach of CDFT or are merely occasionally incidental by-products of its predictions of relative kinetics. *Relative stability* is often discussed and related to differences in certain descriptors, as when correlations between aromaticity and (relative) hardness [168, 169]. This is an inherently differently use for CDFT descriptors, and while it has been

discussed in the literature, it seems advisable to propound this usage clearly to the community. From the earliest days of CDFT, the theory was nurtured by analogies with thermodynamics, most notably in the early work of Nalewajski and Parr [170]. The shift to reactivity came a bit later (chiefly through the work of Yang and Parr). Nonetheless, the analogies between CDFT descriptors and thermodynamic potentials and their derivatives continue to be exploited [171, 172]. Early discussions on whether DFT reactivity descriptors were primarily thermodynamic or kinetic concepts were published by Fuentealba et al. [173] and Chattaraj et al. [174], the latter concentrating on electrophilicity.

**The fundamental issue how to reconcile the CDFT perturbative approach with interpretations/predictions of relative stabilities should be addressed for the community of CDFT users. Possible pitfalls should be addressed so that the distinction between thermodynamic and kinetic reasoning is clear.**

A similar issue is the use of CDFT to discuss bonding (processes) or bonds (structure). The phenomenon of chemical bonding is parallel to the onset of a reaction approach discussed above, so the process of bond formation is subject, *ex ante*, to a CDFT analysis [37]. One example is the use of Berlin's binding function [175] in combination with the electronic and the nuclear Fukui function [176, 177] (see Sect. 2.3), or combining the Berlin function with the reaction force [178]. Conversely, the analysis of a chemical bond as a structural motif is an *ex post* analysis that is comparable to thermodynamic stability. Bader's quantum theory of atoms in molecules (QTAIM) analysis [179] is the most venerable density-based approach to bonding but, aside from its use of the density as a key ingredient, QTAIM has little in common with CDFT. At first glance, then, bond analysis is outside the realm of CDFT: if the process of bond formation and its completion is described as "from becoming to being", the focus of CDFT is on "becoming". However, the reaction electronic flux (REF) elucidates the electronic rearrangements that take place along a chemical reaction path. Detailed analysis of the reaction electronic flux provides a quasi-dynamic perspective on the sequence of bond strengthening/forming and bond weakening/breaking processes that connect reactants to products (see Sect. 3.7). Reaction force analysis, then, can bridge the gap between the *ex ante* and *ex post* viewpoints and provides a quasi-dynamic description of the bonding processes.

**Insofar as the process of chemical bonding is inferred from an incipient interaction within a molecule or between molecules, CDFT can be used to describe it using, e.g., the nuclear Fukui function. Analysing the chemical bond as structural motif, *ex post*, seems to surpass the domain of validity of CDFT, although the reaction electronic flux provides a way to bridge the *ex ante* and *ex post* viewpoints.**



### 3.5 What is the domain of validity for CDFT principles? (EEM, HSAB, MHP, MEP, etc.)

The initial impetus for CDFT arose from its ability to simply and rigorously explain the origins of the electronegativity equality method/principle (EEM) [31–33]; this momentum was sustained by placing the hard/soft acid/base (HSAB) in this framework and the creation of the maximum hardness principle (MHP), which is inconceivable without the mathematical framework of CDFT [34]. These early principles are based on considerations of the energy as a function of the number of electrons or, better, by the realization that the electronic chemical potential (identified as minus the electronegativity) is equalized for a system in a stationary state, analogous to the way that thermodynamic chemical potential is equalized in macroscopic thermodynamics.

These principles are based on consideration of  $E(N)$  or  $\mu(N)$ , neglecting the dependence on the external potential. Early on, Nalewajski pointed out that  $\nu$ -dependence can and should be explicitly considered [180], and a (simplified) treating of  $\nu$ -dependence was already present in the EEM of Mortier et al. [181]. Subsequent refinements, by Bultinck et al. [182, 183] advanced EEM to the stage where it can be used for rough estimates of charge distributions in (large series of) large molecules; recent years have seen EEM adopted in popular molecular mechanics force fields programs.

**The electronegativity equalization method (EEM) should be further refined, essentially by improving its treatment of  $\nu$ -dependence by using CDFT ingredients. However, this rigorous, first principles, approach to EEM might substantially increase its computational cost, making EEM less useful for rapidly screening the properties of large molecules. So there may be conflict between increasing the domain of validity of EEM in terms of computational time and increasing the domain of validity of EEM in terms of accuracy/robustness.**

There is a broad literature of applications of the hard/soft acid/base (HSAB) principle, with many successes and some (probably underreported) failures, both at the global and local level. In Pearson's words, the HSAB principle states that "*all other things being equal, hard acids prefer binding to hard bases and soft acids prefer to bind to soft bases*" [106]. The "*all other things being equal*" caveat, often forgotten, can of course never be perfectly satisfied in real chemical reactions, but ignoring this caveat altogether is dangerous, as exemplified in the statistical analysis by Cardenas and Ayers on the reliability of the HSAB principle [105]. In particular, the HSAB principle is often thwarted by the tendency of strong acids to prefer strong bases thereby shedding some light on the reasons why the HSAB principle sometimes fails. It is desirable to convey a more nuanced

understanding of the HSAB principle as an easily applied set of guidelines for CDFT practitioners.

At the local level [184, 185], the HSAB principle is often used to discuss *regioselectivity* problems, thereby shifting the focus from thermodynamic *stability* [186] to *reactivity* [187]. Whereas the appropriate definition of the local softness in the HSAB context seems clear, the definition (even the existence) of a suitable definition for the local hardness is actively debated (for a critical account, see [188]). However, the fact that for  $T > 0$  global softness and global hardness are not inverses of each other suggests that one can formulate new definitions for the local hardness in temperature-dependent CDFT. Along these lines, Gázquez et al. [189, 190] have presented a procedure to establish local and nonlocal counterparts for global indicators and have analysed, in particular, different definitions for the local hardness. (See also the recent revisitations of the local hardness by Polanco-Ramírez and Morell [191, 192].)

**The HSAB principle has found a firm place not only in CDFT but also in the much broader "general chemistry" context and is widely used both by experimentalists and theoreticians. The CDFT community should put further effort in exploring the domain where the HSAB principle holds and establish the caveats that must be remembered when applying the HSAB principle at both at the global (stability) and local (reactivity) levels. The discussion of the local hardness should either converge towards a widely accepted and broadly useful definition or else this quantity should be discarded.**

The maximum hardness principle (MHP) has found less acceptance outside the CDFT community than the HSAB principle. However, the importance of MHP to CDFT is unquestionable (consider that Parr and Chattaraj's proof of the MHP has nearly 1000 citations [193]). We speculate that the limited acceptance of the MHP in the broader community of chemists arises because the constraints under which the MHP is rigorously true (constant temperature, constant chemical potential, constant external potential) are exceptionally restrictive. Note that it was shown by Torrent-Sucarrat et al. that even when the conditions of nearly constant  $\mu$  and  $\nu$  are fulfilled the MHP may fail as in the case of (small) displacements along non-totally symmetric vibrational modes [194, 195]. Pearson's verbal statement of the MHP "*there seems to be a rule of nature that molecules arrange themselves to be as hard as possible*"—does not acknowledge these restrictions, but is also vague, and difficult to apply in practical simulations [34]. Which system should be harder than another system when both are at their equilibrium geometry or how does the hardness of a given system varies under molecular rearrangements/transformations such as intra- and intermolecular reactions or internal rotations of a molecule? A recent statistical analysis for some selected reactions shed some light on this issue [107].

In practical cases, the MHP is usually applied by examining the hardness of a given system as a function of a transformation coordinate (in accord with Pearson's statement but in opposition to the mathematical requirement of constant external potential). At present, Pearson's hardness concept seems more useful for practical chemistry when applied using the HSAB principle than when applied using the MHP.

The minimum polarizability principle (MPP) was formulated by Chattaraj and Sengupta as a companion to the MHP. It states that "the natural direction of evolution of a system is towards a state of minimum polarizability" [196, 197]. It is expected from the inverse behaviour of hardness and polarizability [198] that one will mirror the other and that the MHP implies the MPP. A recent detailed statistical analysis in a case study (the comparison between the polarizability of a large number of molecules and the sum of polarizabilities of their constituent atoms) revealed a failure of the MPP, in this particular case, of only 2 to 3% of the cases [199].

**The domain of validity of the MHP needs to be clarified, especially by identifying situations where its application is meaningful/reliable based on its formulation within the mathematical framework of CDFT. This critical analysis should lead to a list of more-or-less explicit conditions that enable the thoughtful application of Pearson's MHP dictum.**

The minimum electrophilicity principle (MEP), proposed by Chattaraj et al. as a companion to the MHP [109–111], seems more successful than the MHP itself. The MEP was scrutinized in a statistical study of 101 exothermic reactions, where it was more reliable than the MHP, which was especially prone to fail in cases of very hard reactant molecules or in most cases of association reactions [108]. Extending the electrophilicity equalization principle [200] and Sander-son's geometric mean equalization expression, one has, after differentiation, equalization principles for the hardness and hyperhardness. These higher-order equalization principles seem useful for discussing formation and fragmentation reactions [201].

### 3.6 Extending the $E[N, \nu]$ functional to include additional variables: broadening applicability versus computational simplicity?

As mentioned previously, the first extension of the energy functional,  $E[N, \nu]$ , was to include temperature, and thereby address the problem of derivative discontinuity. The second extension was to include spin, either by including the spin polarization,  $E[N, N_S, \nu, B]$  (Galván, Vela, and Gázquez) or by resolving the number of electrons into its spin components,  $E[N_\alpha, N_\beta, \nu_\alpha, \nu_\beta]$  (Ghanty and Ghosh) [112–114]. In spin CDFT, one can consider how a system's energy changes when its spin state is perturbed, e.g., by a magnetic field or by spin transfer from its environment (or another reagent).

The response functions in spin CDFT all have spin labels, resulting in a proliferation in reactivity indicators (each  $n$ th-order response function has  $2^n$  spin components). Analogous to the electrophilicity, concepts like the spin-philicity and spin-donicity were introduced and evaluated by Pérez [202, 203] and Olah [204].

Adding spin variables to the energy functional not only increases the number of response functions, but also forces the CDFT practitioner to include additional *constraints* when evaluating response functions (e.g., changing  $N_S$  at constant  $N$  and vice versa); this sacrifices the computational and conceptual simplicity of spinless CDFT. This may be one reason why spin CDFT is much less applied. However, treating transition metal chemistry and radical reactivity (domains in which CDFT could and should be more active) in the CDFT framework would seem to necessitate the inclusion of spin. While the mathematical framework of spin DFT is directly analogous to that of traditional spin-free CDFT, the peculiar nature of the spin in density functional theory itself means that the interpretation and evaluation of spin CDFT quantities is not entirely trivial [205].

**Despite its computational demands, spin CDFT should be thoroughly explored, especially for phenomena like transition metal catalysis, radical reactions, and singlet–triplet gaps in low-valent main-group chemistry.**

Extending the energy functional in CDFT by magnetic and electric fields was pioneered by Chattaraj. Based on the response of a system to an external magnetic field [206], he identified a correlation between softness and magnetizability [207] and proposed a minimum magnetizability principle (analogous to the minimum softness/maximum hardness principle) [208]. The response to an external electric field was also pioneered by Chattaraj and coworkers [209, 210] and is more straightforward computationally than the magnetic field case. These responses may be useful for elucidating nonlinear optical properties of molecules and materials.

A fundamentally different extension of the energy functional, not addressed until very recently, is the inclusion of an external force, different in nature than an electromagnetic force. This issue is at stake in mechanochemistry which although existing in its "macroscopic" form for centuries (grinding, etc.) has in recent years been downscaled to the molecular level. Treating mechanochemistry with CDFT necessitates a fundamentally different change in the energy functional, as one must include a mechanical force (or potential) in the ansatz, rather than an electromagnetic one. A salient example of the chemical relevance of mechanochemistry is that an external mechanical force perturbation is able to overrule some of the celebrated Woodward–Hoffmann rules for pericyclic reactions [211] (for a recent review, see [212]). This rewriting of fundamental chemical rules seems prominent and originates (at least in part) in the directionality that arises from the vector character of the mechanical

force. The Brussels group extended CDFT to mechanochemistry by extending the energy functional,  $E[N, v, F_{\text{ext}}]$ , where  $F_{\text{ext}}$  denotes the external force. It is straightforward to write down response functions, though evaluating them requires a particular ansatz (e.g., Beyer's COGEF approach [213]). This allowed a series of rules characterizing the influence of an external force on the energetic and geometrical variables of diatomics to be expressed in the framework of CDFT [124]. More recently, an extension to bending external forces has been presented [125].

**It is important to extend the CDFT to cope with recent evolutions in chemistry by extending the energy functional. Mechanochemistry is one exciting example, which involves a new type of variable. Other additional variables (e.g., specifying a variable in the external potential as in an alchemical transformation where nuclear charges are changed, applying a voltage difference to study molecular conductivity) are being or should be explored.**

### 3.7 CDFT along reaction paths: the reaction electronic flux as the guiding ansatz?

Conceptual DFT is generally considered with a molecule's intrinsic reactivity, that is, the reactivity of the molecule in isolation, without consideration of specific features of its molecular environment (e.g., solvent) or possible reaction partners. The susceptibility of the molecule to various types of reactions is then assessed through its response functions, evaluated at the equilibrium geometry. CDFT, therefore, in principle, addresses the onset of the reaction. At first sight evaluating these response functions along the reaction path may seem contradictory to the initial aim of CDFT, as the reactivity of a system is now probed when the system is already perturbed by the reaction partner. However, evaluating these response functions along the reaction path, or in the presence of a specific reaction partner, can provide important additional information. Specifically, studying how global and local reactivity indicators change along a reaction path can help locate transition states, reveal mechanistic insights, and connect reactivity, bonding, and kinetics [214, 215].

The power of this strategy has been realized most impressively through the work of Toro-Labbé and co-workers in the Reaction Force ansatz [126–132]. They have shown how depicting the evolution of reactivity descriptors provides entirely new information, far beyond what can be obtained by applying CDFT to the reactant(s) alone. In this way, reaction force analysis introduces the reaction coordinate in CDFT and bridges the world of reaction path calculations and conceptual DFT, providing detailed mechanistic insights.

Among the many descriptors that can be and have been explored along reaction force profiles, the electronic chemical potential is among the most useful. Differentiating the electronic chemical potential with respect to the reaction coordinate defines the reaction electronic flux (REF; [130–132]), which indicates how electrons move during the reaction. (Further differentiation with respect to the external potential can reveal *where* the electrons move during the reaction.) The REF therefore reveals the essential stages of bond formation/strengthening and bond weakening/breaking. There is a strong analogy to the macroscopic thermodynamic chemical potential, written as a function of Dedonder's "degré d'avancement/extent of reaction" (see for example I. Prigogine and R. Defay's famous textbook on Chemical Thermodynamics [216]) and the way the molar Gibbs energy emerges as the driving force for the conversion of reactants to products at the macroscopic level. Recent collaborative efforts between the Chilean and several French groups have resulted in analytical expressions for the REF in both in the Canonical and Grand Canonical ensemble, so that the systematic and routine use of the REF to reveal electron density reorganization along reaction paths is now possible [132]. A symmetry-adapted version of the REF has also been formulated; this is appropriate when following reactions that preserve a specific symmetry throughout the chemical transformation [131].

**The reaction electronic flux (REF) is a powerful tool that exploits CDFT (specifically, the chemical potential) along a reaction pathway to provide detailed characterization of reaction mechanisms, including the electron rearrangements that drive changes in molecular structure (e.g., bonding processes).**

### 3.8 Can CDFT be extended to excited states? What about time dependence?

The theory and applications of CDFT for excited states is limited. This is not unexpected since DFT, and by extension CDFT, was originally formulated as a ground-state theory and ground-state reactivity is already subtle, without the additional complications associated with excited-state potential energy surfaces, conical intersections, etc. However, Morell et al. [133] have probed chemical reactivity and regioselectivity in excited states by exploiting the fact that the chemical potential of an excited state is local ( $\mathbf{r}$ -dependent) when it is evaluated with the ground-state energy functional. Then, together with De Proft, Morell used excited states' densities to investigate electron density changes at the onset of a chemical reaction, specifically by invoking the state specific dual descriptor [217, 218]. Exploiting the result that traditional DFT is also valid for the lowest state of a given spin, the Brussels group treated the reactivity of triplet states using spin-dependent reactivity indicators [219,

220] (see also Sect. 3.6). Chattaraj and co-workers have presented useful rules of thumb, e.g., that systems are harder and less polarizable in their ground state than in excited states [221]. They also considered the ensemble version of excited-state DFT, where the Hohenberg–Kohn theorems can be proved [222].

**Excited-state reactivity is a new frontier for CDFT and requires both fundamental exploration and practical applications. Applying CDFT to the broad range of photochemical phenomena pervading many subfields of chemistry is important. It is possible, however, that this is a domain where wave function-based approaches, despite its complexity, may be more facile than CDFT.**

Like excited-state CDFT, time-dependent CDFT is complicated because it is inherently an out-of-equilibrium theory. Nonetheless, important contributions have been made by the Chattaraj group (for reviews, see [223, 224]), especially for ion–atom (molecule) collisions and (molecule-) atom–field interactions [197, 225]. Certainly physico-chemical processes are inherently dynamic in nature, and the global and local reactivity indicators change during the process. In order to follow a chemical reaction from “start” to “finish”, the time evolution of various CDFT-based descriptors, written as time-dependent density functionals and involving both ground and excited states, can be studied within the framework of quantum fluid density functional theory framework [196]. Various associated electronic structure principles manifest themselves in a dynamical situation [226]. For example, regioselectivity can be understood in a dynamical context [227] and atom-centred density matrix propagation shows that aromaticity can be the driving force for structural relaxation [228].

**Time-dependent (dynamical) variants of CDFT are important, not only for providing a direct representation of molecular dynamics, but also for exploring time-dependent quantum phenomena (quantum transport, energy dissipation and flow, etc.). Time-dependent CDFT also provides a way to treat reactions that occur on both ground- and excited-state potential energy surfaces.**

### 3.9 Information theory (IT) and CDFT: the best of both worlds?

As mentioned in the introduction, Parr introduced information theory (IT) to DFT in the early 1980s, concomitant with the seminal early years of conceptual DFT [134]. More recently, IT has led to deeper insights into the Hirshfeld atoms-in-molecules (AIM) partitioning. Specifically, it was shown that Hirshfeld AIM resemble neutral ground-state atoms as much as possible in the information-theoretic sense [135]. More recently, Nagy showed that the Shannon entropy, written as a functional of the electron density, suffices *on its own* to completely describe any Coulombic

system [139, 229]. This means that the Shannon entropy, just like the density, “determines everything”, and places IT alongside DFT as rigorous approaches to molecular structure and reactivity. Other density functionals have also been advanced in an IT context, including the Fisher information [230], Rényi entropy [231], and the Onicescu information energy [232]. Much of the current interest in the IT approach stems from the early work of Liu, linking the steric effect (omnipresent in organic chemistry, but hardly quantified and heretofore unexplored in CDFT) to the Fisher information, allowing steric effects to be quantified alongside the venerable reactivity concepts (electronegativity, aromaticity, hardness, electrophilicity, etc.) that CDFT has treated so successfully [140, 233]. Within the context of IT, the information conservation principle has proven useful for quantifying electrophilicity, nucleophilicity, and regioselectivity [141]. In light of these results and the close links between IT and (conceptual) DFT, it is tempting to link the IT density functionals to the CDFT functionals, identifying exact and approximate relations of the form  $Q[\rho] = Q\{\text{IT}\}$  where  $Q$  is any electronic property of a Coulombic system and  $\{\text{IT}\}$  stands for a set of information-theoretic quantities (which are all density functionals too, i.e.,  $\{\text{IT}\} = \{\text{IT}[\rho]\}$  [141]. Such investigations may impart additional *chemical* meaning to IT functionals. In the same vein Liu and De Proft recently used IT-based descriptors to quantify aromaticity (another ubiquitous concepts of chemistry for which no precise definition has been put forward—or at least widely agreed upon—yet for which myriad descriptors exist, among others the (relative) hardness) [234–238].

**IT-based density functionals should be explored and their chemical relevance/applicability should be scrutinized. If possible, IT-based descriptors should be connected to CDFT-based descriptors, thereby combining the best of both worlds, information theory and conceptual DFT.**

### 3.10 Can we move from interpretation to prediction?

In nearly all computational studies using CDFT, the aim is to *interpret* the results of experiments and/or computations. Of course, it would be more useful to experimentalists and more impressive to theorists if *predictions* of unknown chemical phenomena could be made routinely. Most predictions in the literature, however, are qualitative and/or semiquantitative correlations (in the style of QSAR and QSPR); the authors cannot think of any case where entirely new chemical phenomena were predicted from CDFT.

There is, in principle, no obstacle to using CDFT to make predictions. The framework is available (*vide supra*) and the  $E[N, v]$  or  $\Omega[\mu, v]$  functional Taylor expansion can be written to arbitrarily high order in principle (though mathematical



issues in higher-order derivatives with respect to  $N$  and the cumbersome evaluation of higher-order derivatives with respect to  $v(\mathbf{r})$  cannot be ignored). If the Taylor series are assumed to converge, then predictions are mathematically possible. However, studies of alchemical transformations seem to indicate that convergence in  $v(\mathbf{r})$  may be faster than convergence in  $N$  [100, 160]. (This is not surprising: in a mathematically rigorous sense the derivative discontinuity in  $N$  limits the radius of convergence of the Taylor series; when an interpolated formula is used for  $E(N)$  the first- and second-order derivatives with respect to  $N$ ,  $\mu$  and  $\eta$ , are comparable in magnitude, indicating slow convergence of the Taylor series.)

The main problem, however, is that evaluating the perturbation expansion requires knowledge of  $\Delta N$  and  $\Delta v(\mathbf{r})$ , which requires (at least a crude model about) the second reactant. Pragmatically, one may use one's chemical intuition and, based on the nature of the reaction partner, choose to consider only the terms in the Taylor series that are expected to be most important. (This, however, biases the results towards the effects one intuitively expects, and imperils the predictivity of the model). For example, one often eliminates the Fukui function for hard/hard interactions, or chooses a specific Fukui function,  $f^+(\mathbf{r})$ ,  $f^-(\mathbf{r})$ , or  $f^0(\mathbf{r})$ , based on the perceived nucleophilic, electrophilic, or radical character of the second reactant [1]. A more explicit modelling of the second reactant could/should be envisaged; however, at the cost of increasing computational burden and veering away from predictivity and towards traditional computational modelling and supermolecule-type approaches. In this spirit, one could, for example, treat the two reactants as an association complex (or even, as advocated by Toro-Labbé, all along the reaction path). If one analyses the interaction energies in the association complex, insights into the essential chemical interactions can be gleaned. For example, key driving forces behind chemical reactivity can be gleaned from Morokuma-type partitioning [239] or its DFT-based analogue [240, 241] and Bickelhaupt's activation strain model [242]. The advantage of CDFT over this approach lies in its alternative identification and quantification of all terms in the perturbation expansion in terms of observables, and the possibility to deduce how chemical interactions can be fine-tuned by changing/adjusting the nature of the reactants (as captured by the perturbations  $\Delta N$  and  $\Delta v(\mathbf{r})$ ). This two-reactant approach to CDFT was pioneered by Berkowitz [243] and extended in the two-reactant charge sensitivity analysis of Nalewajski [244]. Importantly, an element of predictivity can be recovered by building coarse-grained models for the reactants [37, 162].

**It seems difficult to make predictions solely from the one-reactant picture of CDFT, but the one-reactant picture can be effective when coupled with chemical intuition that identifies which term(s) in the perturbative**

**expansion of the energy are most likely to be significant. In addition, recent advances have made evaluating higher-order responses feasible, so that the traditional second-order truncation of the expansion is no longer required. In our view, the full expansion should be studied, as a proof-of-concept, for a series of well-chosen reactions, so that (less ad hoc) rules for selecting the most important coefficients can be formulated. Alternatively, the second reactant can be explicitly introduced, with varying levels of refinement for the associated perturbation  $\Delta N$  and  $\Delta v(\mathbf{r})$ . If the second reactant is fully and explicitly included and the reaction path followed, then this reduces to Toro-Labbé's "CDFT along the reaction path" approach.**

#### 4 Promoting CDFT to practicing chemists

While there are hundreds of papers each year employing CDFT, this number is appreciably smaller than the number of papers that use wave function theory (essentially techniques based on the orbital picture (MO) or resonance structures (VB)) to interpret and predict chemical events at the molecular level. *Why isn't CDFT as popular as wave function-based approaches?*

The first answer is practical: with readily available software packages, a plethora of wave function theory-based properties can be calculated and visualized. Accordingly, there are countless articles from experimentalists using valence orbitals, and in particular the highest-occupied molecular orbital (HOMO) and lowest-unoccupied molecular orbital (LUMO) to interpret reactivity trends. It is not so easy for people who want to interpret their results using CDFT. At this moment, most CDFT researchers have cobbled together their own homebuilt code, which is then coupled to an existing major quantum chemistry code (e.g., GAUSSIAN [245]). This presents a major obstacle to non-specialists. It is a pity that no joint effort has been launched to provide CDFT users with a flexible, user-friendly, and well-documented software package that can be coupled to all (or at least most) quantum chemistry codes. In this regard, a major step has been taken by the Heidar-Zadeh and Ayers groups, with the ChemTools package, which incorporates arbitrary-order energy and grand potential derivatives, the electron density, and higher-order response functions, and which is interoperable with molecular quantum chemistry packages based on Gaussian orbitals [153, 246]. ADF uses Slater-type orbitals and is not supported by ChemTools, but it now contains native support for CDFT, written in part by Joubert and Tognetti [247]. This effort should be continued, refined and intensified. An extension towards periodic calculations should be planned, although this is complicated by

the difficult of defining CDFT reactivity indicators in bulk (due to degeneracy).

**The CDFT community should strive to create/refine CDFT software that can be coupled to all major quantum chemical codes. This software should be highly documented, with prescriptive user guides and tutorials suitable for the novice user, and advanced scientific documentation to aid the expert in interpreting the output. It would be highly advisable to agree upon a common set of standards. A joint venture would be ideal, though we recognize that getting funding for software programming and its documentation is difficult to get, at least in Europe and the Americas.**

A more fundamental reason is that CDFT is still mainly a reactivity theory, with a beachhead in thermodynamics. As such, CDFT is less general than the orbital picture where; taking MO theory as an example, the same theory can be used to characterize kinetics, thermodynamics, and molecular structure. If the community can clearly delineate the domain of applicability of CDFT, this drawback can be mitigated. In addition, we should strongly advocate for the advantages attendant to CDFT (working with observables, insensitivity to level of theory, the tight integration with useful reactivity principles, etc.) and contrast them with orbital-based approaches (arbitrary phases, sensitivity to level of theory, etc.).

Can CDFT compete with wave function theory? We do not see it as a competition, but instead recommend adopting the best tool for each chemical problem, thereby exploiting the best of both worlds. As a follow-up to the present paper, rules for the correct use of CDFT should be formulated, so that “the right answer for the right reason” can be obtained therefrom.

**The publication of a set of rules governing the correct use of CDFT should be commissioned, e.g. as a sequel to the present paper. Also simple rules of thumb may be formulated for a broad readership, including undergraduate students. One strategy to do this is to note that all chemists are familiar with the concept of electronegativity, which is first (chronologically, and arguably also in terms of importance) among the CDFT response functions. This can be leveraged to introduce chemists to other CDFT-based response functions and the principles associated thereto.**

As a final answer to the opening question of this section, the theory and application of CDFT is intimidating. It is undeniable that a relatively high level of mathematical sophistication is required to grok the theoretical foundations of CDFT, and the usual computational protocols for evaluating CDFT response functions are relatively complicated. In our experience, it takes practicing chemists less time to look at and interpret a molecular orbital diagram than to draw meaningful conclusions from CDFT descriptors. All

these issues can be mitigated by providing suitable software packages and tutorials on how to use them and interpret their output.

**Even if the intellectual effort required is larger, it is our opinion that CDFT will lead in some cases to a deeper understanding than wave function alternatives. CDFT has to live with its own DNA, including the deep physical/quantum–mechanical basis and often intricate mathematical framework it inherits from DFT. Perhaps uniquely, CDFT entwines mathematical/physical rigour with qualitative chemical intuition. In the long run, this DNA must be preserved, as it is the *conditio sine qua non* upon which future achievements of CDFT, to understand, support and contribute to tomorrow’s chemistry, relies.**

## 5 Conclusions

Over the last 4 decades, conceptual DFT has blossomed into a mature, but—as evidenced by a few thousand papers published in the last decade—by no means stagnant discipline. The present paper is intended to be both reflective (presenting the fundamentals of CDFT, overviewing its history and achievements, and presenting its underlying philosophical tenets) and prospective (looking at the issues and challenges that may define the future of this approach).

To this end, we present ten issues for reflection on the future of CDFT. The concluding statements, summarizing the outcome of a round table discussion at the CCTC2018 Conference in Changsha, are intended to be a guideline for future theoretical research and computational applications. These issues encompass deepening and broadening the theory (e.g., the nature of the energy functional and its extension to include temperature, solvent, and mechanical forces; the extension to time-dependent phenomena and excited states; the coupling of CDFT with reaction force and information theories). We also present guidelines for formulating physically acceptable CDFT-based reactivity descriptors and identify the need for a critical analysis and delineation of the domain of validity for CDFT-based reactivity principles like the HSAB rule.

We devoted particular attention to the need for formulate simple rules so that the non-expert user (both theorists and experimentalists) can reliably and appropriately use CDFT as an interpretational tool, with the ambition that CDFT can segue from its current predominately interpretative role into a more powerful predictive tool. We strongly feel that CDFT should be recognized as an alternative for wave function-based approaches, with the proviso that each problem should be approached, after thoughtful consideration, by the most appropriate road. The future of CDFT strongly depends on this endeavour.

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