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Perspective on Simplified Quantum Chemistry Methods for Excited **States and Response Properties**

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absorption for large systems with hundreds to thousands of atoms. The recently introduced spin-flip simplified time-dependent density functional theory (SF-sTD-DFT) variant enables an ultrafast treatment for diradicals and related strongly correlated systems. A few drawbacks were also identified, specifically for the computation of 2PA cross sections. We propose solutions to this problem and how to generally



improve the accuracy of simplified schemes. New possible simplified schemes are also introduced for strongly correlated systems, e.g., with a second-order perturbative correlation correction. Interpretation tools that can extract chemical structure-property relationships from excited state or response calculations are also discussed. In particular, the recently introduced method-agnostic RespA approach based on natural response orbitals (NROs) as the key concept is employed.

INTRODUCTION

Due to the complexity of the studied systems, the fate of molecular quantum mechanics has always been related to computing technology since its very beginning.¹ Until the 1990s, traditional semiempirical methods² were the workhorse of quantum chemistry. Then, it reached the point where sufficient computing power was available to run calculations with ab initio methods on chemically interesting systems, replacing little by little their semiempirical counterparts. Ab initio wave function theory $(WFT)^3$ and density functional theory $(DFT)^{4-6}$ methods are now the new busy bees of molecular quantum mechanics. System-size-wise, usually a hierarchy of methods with different degree of sophistication is applied to balance cost/accuracy, meaning that small systems are usually treated more accurately than larger ones. Ab initio excited-state calculations, e.g., at a standard time-dependent density functional theory (TD-DFT)⁷⁻¹¹ level, are currently limited to systems sizing up to a few hundreds of atoms, far from large systems such as fluorescent proteins or molecular aggregates that are of current interest.

Excited state calculations are challenging in general because essentially all of them are dealing with open-shell states (with several unpaired electrons) 12,13 and some are even multiconfigurational. The electronic states are often classified into three classes: (i) valence excitation that involve localized orbitals, (ii) Rydberg states that involve transitions from

localized to diffuse orbitals, and (iii) charge-transfer excitations in which net charges in different parts of the system change to a significant degree. A universally accurate method should be able to cope with all types of excitations in vertical and adiabatic (relaxed) mode, but such a method does not exist, at least for systems with more than a few atoms. In practice, TD-DFT has emerged as the workhorse of quantum chemistry for the calculation of excited-state properties and electronic spectra. Although, TD-DFT with many standard exchangecorrelation (XC) functionals yields large errors for excited states with substantial charge-transfer, double excitation, and Rydberg character, it is expected to work well for many lowlying valence states,¹⁴ where the only remaining problem is the choice of the XC functional. High accuracy and including the subtle details of many individual states is often not necessary for spectra or response calculations. A simple but physically reasonable model involving the most important single excitations can be sufficient to describe the very high density

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Figure 1. Schematic representation of the sTD-DFT/sTDA methods theoretical workflow.

of electronic states in a large system. Note that some of the TD-DFT problems come from the wrong asymptotic behavior of the XC potential and the self-interaction-error (SIE) that may lead to artificial "ghost" states.

While (TD)DFT methods can efficiently treat medium-size systems, larger ones involving thousands of atoms are still out of the reach, at least for a routine full ab initio treatment. Over the past, INDO/S (intermediate neglect of differential overlap using configuration interaction with singles (CIS)) method^{2,15,16} was favored to compute excited states. It describes vertical excitations relatively well but is not suited to characterize potential energy surfaces (PES).¹⁶ The INDO/S scheme was used in various QM/MM (quantum mechanics/ molecular mechanics) studies, tackling biological systems, e.g., the bacteriochlorophyll b dimer and aggregates of bacteriochlorophylls.² The OM1, OM2, and OM3 series of methods, 17,18 for which the NDDO (neglect of diatomic differential overlap) one-electron term includes orthogonalization correction, are more geared for PES explorations because they describe well the ground and excited states.² In particular, the OM2/MRCI (multireference configuration interaction) method was used for excited-state dynamics of large biological structures such as the photostability of DNA strands or the photocycle of the green fluorescent protein showing relatively good results with respect to experiment and high-level calculations.² The past 3 decades gave also rise to the DFTB (density functional based tight-binding) class of semiempirical methods.^{19,20} The time-dependent DFTB (TD-DFTB) method²¹ and its other flavors (DFTB2, DFTB3, and LC-DFTB2)²¹⁻²⁶ are cheap methods to compute excited states. For a set of 30 organic molecules, Fihey and Jacquemin²⁷ recently benchmarked the performance of TD-DFTB methods with respect to higher level calculations as well as experiment. They showed that while average errors are usually larger than for B3LYP and CC2 methods, in some cases DFTB3 and LC-DFTB2 outperform these methods. Note that a spin-flip

version of the TD-DFTB method was introduced last year by Inamori et al. $^{\rm 28}$

In this context, Grimme and co-workers^{29,30} developed a simplified version of TD-DFT, called sTD-DFT and a related variant termed sTDA employing the Tamm-Dancoff approximation. The idea behind these methods is to decrease the computational cost by applying approximations for computationally demanding steps while keeping the essential physics of the electronic interactions. In the case of the sTD-DFT/sTDA methods, these approaches approximate the two-electron integrals and massively truncate the single-excitation expansion space, leading to orders of magnitude speed-up at a minor loss of accuracy and even partially improving the SIE problem in DFT. Figure 1 summarizes the sTD-DFT/sTDA workflow. In a typical sTD-DFT calculation, the user only provides molecular orbitals and energies from a Kohn-Sham SCF (or tight-binding (TB) calculation). The first approximation concerns the computationally very demanding calculation of four-index two-electron integrals needed to construct TD-DFT matrix elements. A simple, damped transition density monopole (atomic charge) scheme approximates these twoelectron integrals in the simplified methods. The Mataga-Nishimoto-Ohno-Klopman (MNOK)³¹⁻³³ Coulomb operator is adapted according to the integral type, either Coulomb or exchange, by two respective empirical parameters, which are dependent on the amount of exact Hartree–Fock exchange a_x in the XC functional. Thus, both globally fitted parameters are determined by simple linear relations in the a_r range from 0 to 1. The second main approximation neglects response terms involving the exchange-correlation functional in the TD-DFT equations. The third, main approximation concerns the massive truncation of the configuration space because most electron correlation effects are already captured by the ground state calculation. This truncation is based on the diagonal Hamiltonian matrix elements of single excitations and selects those below a given threshold, typically the spectral energy range of interest. Then, a second-order perturbation theory



Figure 2. Singlet—triplet energy gaps for nine benchmark compounds obtained at SF-TD-DFT and simplified levels with collinear and noncollinear exchange-correlation kernels in comparison with the sTD-DFT method. Experimental absorption spectra for a μ -hydroxo-bridged dimer of corrole tape Ga(III) complexes derivatives are compared to SF-sTD-DFT/B5050LYP/cc-pVDZ and SF-sTD-DFT-xTB calculations. Reprinted with permission from ref 50. Copyright 2019 American Chemical Society.

scheme treats the single excitations disregarded by the first step. Note that the molecular orbital (MO) space was truncated according to the energy range of interest prior to these steps in order to avoid computational overhead in integral transformation steps.

The sTD-DFT/sTDA schemes were originally designed as fast methods to screen large sets of compounds or large systems allowing the interpretation of their UV–visible and CD spectra. The theoretical key points are (i) a general formulation for hybrid XC functionals, (ii) the inclusion of only two globally fitted parameters for the description of twoelectron integrals, (iii) two electron integrals having an asymptotically correct 1/R behavior, and (iv) an efficient truncation of the CI space for a given energy threshold. Designed for hybrid XC functionals, Grimme and co-workers³⁴ extended the sTD-DFT parametrization to range-separated hybrid (RSH) functionals.

The computational bottleneck of sTDA and sTD-DFT methods is the determination of the ground state Kohn–Sham orbitals and eigenvalues, limiting their application to systems up to around 1000 atoms. Grimme and Bannwarth³⁵ proposed to solve this problem by using a specially designed semiempirical TB procedure as a replacement for the DFT step. These ultrafast methods are called sTD-DFT-xTB and sTDAxTB where the "x" denotes an extended atomic orbital basis set. The accuracy of these models is roughly that of TD-DFT/ hybrid functional quality for molecules with not too complicated electronic structures. They can be used in complete (unfragmented) routine treatment for systems up to a few thousands of atoms, e.g., proteins.^{36,37} The sTD-DFTxTB parametrization was recently extended to 4d and 5d metals as well as 4p, 5p, and 6p elements.³⁸

This Perspective aims to present the current status of these methods and recent progress and developments as well as future challenges for new method developments to improve accuracy and extend its range of application. This includes extension of the sTD-DFT scheme to the computation of linear and nonlinear molecular response properties, developments for strongly correlated systems, new tools to interpret optical properties using simplified methods, and a discussion of basic approximations in sTD-DFT.

DISCUSSIONS

Simplified Methods for Large Strongly Correlated Systems. Because of the linear-response/adiabatic approximation, TD-DFT only considers singly excited configurations relative to the ground state KS-DFT determinant which drastically reduces the configuration interaction (CI) space. Note that the Kohn-Sham DFT ground state is normally a single reference state accounting only implicitly for static correlation effects.^{39,40} A simple way to account for the missing static correlation is the spin-flip (SF-)TD-DFT method⁴¹⁻ following the spin-flip scheme proposed by Krylov.45-48 It starts with a well-behaved high-spin reference state. Then, the target open-shell state is obtained by spin-flipping excitations. This allows the inclusion of a doubly excited configuration when the reference state is a high-spin triplet. This doubly excited configuration is important for strongly correlated systems such as diradicals with two nearly degenerate frontier molecular orbitals. For low-lying excited states formed within the complete SF active space, the SF-TD-DFT method yields excitation energies⁴¹⁻⁴⁴ with a similar accuracy to what is usually achieved by highly correlated methods such as equation-of-motion coupled-cluster.44 Outside this space, excited states are often strongly spin-contaminated. The interested reader about the spin-flip may refer to the excellent review on the topic by Casanova and Krylov.49

In this context, we developed the simplified SF-sTD-DFT method and its ultrafast tight-binding counterpart SF-sTD-DFT-xTB.⁵⁰ Our implementation considers only collinear XC functionals and the Tamm-Dancoff approximation. Note that the difference between collinear and noncollinear XC kernels is that the noncollinear formulation allows mixing of α and β orbitals while this is not the case for the collinear one. In the SF-sTD-DFT procedure, only $(i_{\alpha}j_{\alpha}|a_{\beta}b_{\beta})$ two-electron integrals are evaluated. Analogous to the sTD-DFT method, these integrals are approximated by short-range damped Coulomb interactions of transition density monopoles. Because these two-electron integrals consider $\alpha \rightarrow \beta$ single excitations, the sTD-DFT effective Coulomb operator was adjusted and reparametrized. This approach takes advantage of the sTD-DFT massive truncation of the single configuration space but now for $\alpha \rightarrow \beta$ single excitations. To simulate absorption spectra considering the first spin-flip states as the ground state, the sTD-DFT state-to-state transition dipole moment expression⁵¹ was adapted to the SF case and scaled by a factor of $\sqrt{2}$, approximately accounting for missing excitations in the α space. Figure 2a presents singlet-triplet energy gaps for a benchmark set⁵¹ of nine diradicals. SF-sTD-DFT values are compared to SF-TD-DFT values considering collinear and noncollinear exchange-correlation kernels. The agreement between the simplified method and the full scheme with the more accurate noncollinear kernel is very good, with a maximum averaged deviation of 0.076 eV and a root-meansquare deviation of 0.101 eV. In comparison to the experimental absorption spectra, the SF-sTD-DFT method even outperformed the full scheme while drastically reducing the computational time. The μ -hydroxo-bridged dimers of corrole-tape Ga(III) complexes were the largest compounds studied in this context. In only 8 min on a standard desktop computer (Intel Core i7-6700, 3.40 GHz), we were able to calculate the absorption spectrum for this system at the SFsTD-DFT/B5050LYP/cc-pVDZ level of theory (see Figure 2b), obtaining a relative good agreement with respect to experiment. Hence, we stated that the SF-sTD-DFT and SFsTD-DFT-xTB methods provide a very cheap way to recover the most important static correlation effects by including one doubly excited CSF. They also yield reasonable spin symmetry for states that are usually not well treated by unrestricted DFT, at least within the SF active space. These encouraging results open new horizons for the development of new simplified schemes for the treatment of strongly correlated systems. The obvious follow-up of the SF-sTD-DFT implementation is to improve the treatment of states outside the SF active space by removing the spin contamination. Recent approaches here are spin-adapted (SA-)SF-TD-DFT⁵² and mixed-reference (MR-)SF-TD-DFT⁵³ methods that may be easily "simplified" in the same manner as was done for the SF-sTD-DFT method. The very recent spin-flip pair-density functional theory proposed by Meitei and Mayhall⁵⁴ may also be investigated

The double-hybrid XC functionals⁵⁵ applied to excited states may be an interesting route to go beyond the standard approximation employed in sTD-DFT. One of us and Neese⁵⁶ proposed a scheme that adds a second-order perturbative correlation correction to excited states analogously to the CIS(D) method in WFT proposed by Head-Gordon.⁵⁷ Inclusion of nonlocal electron correlation effects implying virtual orbitals could solve inherent TD-DFT problems for excited states with ionic, charge transfer, double excitation, or Rydberg character. Note that the (D) correction not only includes double excitations but also effects from disconnected triple excitations.⁵⁷ As a perspective, computationally efficient "simplified" second-order correction for TD-DFT excited states could be developed. Another option is to add one or a few doubly excited configurations as in the so-called dressed (d-)TD-DFT method.^{58–60} More ambitious developments are a simplified version of the GW and Bethe–Salpeter equation (BSE) formalisms⁶¹ and/or the DFT/MRCI method^{62–64} They may require an improved approximate treatment of the two-electron integrals. This is currently under investigation. The development of such simplified methods for large, strongly correlated systems could represent a breakthrough for future applications in materials and life sciences where optical properties of large systems are at stake.

Linear and Nonlinear Molecular Optical Response **Properties.** During the last 3 years, we expanded the range of application of the sTD-DFT method to linear and nonlinear molecular optical response properties by implementing the linear and quadratic response functions at the sTD-DFT level. This enables fast computations of the polarizability, optical rotation (OR),⁶⁵ first hyperpolarizability,⁶⁶ two-photon absorption (2PA), and excited-state absorption⁵¹ for large systems. To evaluate the polarizability,⁶⁶ the sTD-DFT equations are solved for the electric dipole perturbation without any additional approximations while for the first hyperpolarizability two extra approximations are applied.⁶⁶ Note that because of the "(2n + 1)" theorem, only linear response vectors are needed. The first approximation neglects the computationally involved Hartree exchange-correlation kernel that accounts for orbital relaxations. The second approximation neglects exchange-correlation parts in the quadratic response avoiding the computation of the third derivative of the exchange-correlation functional. We showed for two typical push-pull π -conjugated systems that these two approximations have almost no impact on the response (see Figure 5 in ref 66).

For a set of eight push-pull π -conjugated systems,⁶⁶ the sTD-DFT method performed particularly well for hyperpolarizability values below an excitation energy of 1 eV. Above that value, resonance and double-resonance enhancements are somewhat shifted by the simplified theory. Note that the sTD-DFT method was primarily parametrized to reproduce excitation energies^{29,30} and not response properties. A reparametrization may improve response properties, but it cannot be expected that the monopole type two-electron integrals is appropriate to describe all types of excitation/ deexcitation processes at high energies. Nonetheless, computation times are drastically reduced (see Figure 3) and static first hyperpolarizability values are particularly well described. The sTD-DFT-xTB variant provided excellent results for large systems such as fluorescent proteins and a collagen model structure (see Figure 4) at drastically reduced computational cost. Concerning the chromophore pocket inside the protein (~500 atoms) for eGFP, SHardonnay, and DsRed, reference ONIOM MP2:HF static first hyperpolarizabilities were wellreproduced by the sTD-DFT-xTB method. Note that it took about 6 months for each reference calculation to be completed compared to only a few hours with the actual version of the stda program.⁶⁷ For the collagen PPG10 model structure, the sTD-DFT-xTB frequency dispersion is very similar to the reference ONIOM LC-BLYP:HF one while the static value is only 8% down-shifted. These results show the suitability of the



Figure 3. Computation times for the evaluation of the first hyperpolarizability at both TD-DFT and sTD-DFT levels using the BHandHLYP functional and the 6-31G(d) basis set as a function of the number of basis functions. The number of basis functions after truncation of the CI space by the sTD-DFT method is also provided. All the calculations were done on the same 8 cores desktop computer (Intel core i7-6700, 3.40 GHz). Reprinted with permission from ref 66. Copyright 2018 AIP Publishing.

sTD-DFT-xTB method for an ultrafast treatment of large biological systems.

Since 2018, two projects were initiated to evaluate the second-harmonic generation (SHG) property for biological systems. One concerned the dynamic structural effects on SHG of tryptophane-rich peptides and gramicidin A.⁶⁸ It was shown for nonrigid molecular structures that all significantly populated conformations at room temperature should be

accounted for to provide reliable total first hyperpolarizability values. This exploration was done fully quantum mechanically via the recently proposed meta-dynamics based on efficient GFN2-xTB calculations with the crest code.⁶⁹⁻⁷¹ In ongoing work, we have tried to establish a fully quantummechanical workflow for the SHG of fluorescent proteins with up to 4000 atoms, which is only possible at the sTD-DFT-xTB level of theory. To reduce memory requirements in the stda program,⁶⁷ we will introduce a dual threshold method that includes a larger configurations space for more important parts of the protein (chromophore) compared to spectator residues. This should enable a reasonably accurate and robust treatment of the SHG of large biological systems such as biotags used for second-harmonic imaging microscopy.⁷² The ultimate goal of these future studies is to provide new design guidelines to finetune the hydrogen-bond network and steric hindrances within the protein cavity to create new fluorescent proteins with improved SHG brightness.

The evaluation of 2PA cross sections is a "by-product" in the determination of the quadratic response function, for which only its single residue is needed. In 2018, we implemented this feature in the stda program.⁶⁷ Figure 5 shows 2PA transitions computed for water and toluene at TD-DFT and sTD-DFT levels of theory (BHandHLYP/6-31G(d)). One can observe that while energies are shifted, transitions are well reproduced for toluene except for excitation energies higher than 7.5 eV. Unfortunately, for larger organic molecules, the quality of 2PA electronic transitions becomes more erratic, limiting the general use of the sTD-DFT 2PA implementation. To calculate 2PA transitions, one needs first to compute excited states and their eigenvectors. Then, linear response vectors are computed at half of the transition energy for each excited state. Both eigenvectors and linear response vectors are



Figure 4. Static β_{HRS} values for eGFP, SHardonnay, and DsRed chromophores (shown with their first shell of surrounding residues) obtained at the sTD-DFT-xTB level of theory and compared to ONIOM MP2:HF/6-31+G(d) reference values. Frequency dispersion of β_{HRS} for PPG10, calculated at the sTD-DFT-xTB level of theory and compared to ONIOM HF/6-31+G(d):HF/6-31G(d) and LC-BLYP/6-31+G(d):HF/6-31G(d) results. Reprinted with permission from ref 66. Copyright 2018 AIP Publishing.



Figure 5. 2PA transitions of water and toluene at TD-DFT and sTD-DFT levels (BHandHLYP/6-31G(d)).



Figure 6. Transient ESA spectra of s-cis- β -carotene in *n*-hexane following a 498 nm pump excitation recorded after 60 and 300 fs compared to sTD-DFT/ ω B97X-D3/6-311+G(d,p) calculations for their first and second singlet excited-state absorption spectra. Transient absorption of PYP in 10 mM Tris-HCl buffer solution at pH 8.1, 1.5 ps after a 370 nm actinic excitation, compared to sTDA-xTB first singlet excitation, absorption, "fake" stimulated emission, and the simulated transient spectra. Reprinted with permission from ref 51. Copyright 2019 AIP Publishing.

then combined to calculate 2PA cross sections. As observed for the first hyperpolarizability frequency dispersion,⁶⁶ the quality of the response vectors seems to worsen at higher energies. This is not very relevant for first hyperpolarizabilities because experimental dynamic values are mostly extrapolated to zero frequency prior to a comparison to theory. However, 2PA transitions are less forgiving with that respect. One future challenge is to cure this problem. Two possible solutions are currently investigated. First, we propose to improve the approximate two-electron integrals by using a multipolar expansion as it was introduced by one of us for GFN2xTB.⁷¹ There, all electrostatic interaction and exchangecorrelation energies include terms up to second-order in the multipole expansion using cumulative atomic multipole moments.⁷³ Second, we suggest the reintroduction of an approximated exchange-correlation kernel, as was done, e.g.,

for the DFTB method.⁷⁴ Note that all molecular response properties may benefit from these developments.

Another "by-product" of the quadratic response function is the excited state absorption (ESA) which is derived from its double residue to compute expectation values of the (unrelaxed) state-to-state transition dipole moment. Due to both approximations in the sTD-DFT quadratic response function, only excited state transition amplitudes are needed, which is computationally inexpensive compared to usual excited state calculations. This implementation enables the ultrafast evaluation of ESA spectra.⁵¹ Figure 6a presents the transient ESA spectra of s-cis- β -carotene following a 498 nm pump excitation recorded after 60 and 300 fs. The comparison to sTD-DFT ESA calculations shows that the second excited state is first populated. Then, it relaxes to the first excited state after 300 fs. In this formalism, the extremely efficient sTD-



Optical rotation

Figure 7. Comparison of experimental and theoretical optical rotations at the sodium D-line (589.3 nm) for a set of substituted helicenes obtained at the sCAM-B3LYP/aug-cc-pVDZ level of theory in the velocity representation, except for compounds **1d1**, **3a**, and **3b** including transition metals for which we used the def2-SV(P) basis set. Reprinted with permission from ref 65. Copyright 2020 AIP Publishing.

DFT-xTB and sTDA-xTB³⁵ methods can be applied as well to treat systems of a few thousands of atoms. Employing the sTDA-xTB scheme, we determined the ESA spectrum of the photoactive yellow protein (PYP) composed of 1931 atoms and explained main features of the corresponding pump/probe experiment (see Figure 6b).⁵¹ Recently, we extended the linear response sTD-DFT method to the evaluation of frequencydependent optical rotation (OR).65 We took benefit of the existing implementation for the polarizability and adapted it for the evaluation of the electric dipole-magnetic dipole polarizability. In this case, the antisymmetric linear response vector needs to be computed. For systems with a valence statedominated response, the sTD-DFT method provides good quantitative agreement with experiment. This is especially true for substituted helicenes as shown in Figure 7. These results showed that the sTD-DFT method could be quite useful for the design of new helicenes with enhanced chiroptical properties, e.g., new chiral bilayer nanographenes.⁷⁵

For smaller molecules, with a Rydberg state-dominated response, the agreement of the sTD-DFT and TD-DFT results is less good but still acceptable. Because optical rotations are usually evaluated at 589.3 nm, sTD-DFT values are affected by the worsening of the response at higher frequency as was observed for other optical properties. However, linear response properties are less affected than nonlinear ones, for which double resonances come into play. Nevertheless, sTD-DFT optical rotation values should also benefit from future method developments. Note that, for optical rotations, the sTD-DFTxTB method gives poor results, probably because the basis set used is too small to treat such a complicated (signed) response property correctly. To improve the entire sTD-DFT-xTB scheme, we propose to replace the existing model by a new general tight-binding (gTB) method based on a nonselfconsistent mean-field electronic structure theory. The basic idea here is to generalize the existing TB schemes-which are limited to a mostly minimal valence atomic orbitals basis setto a general (double- or triple- ζ) basis set as usually used in

standard DFT or WFT methods. Work in this direction is in progress in our laboratory. This implementation will also be beneficial for the evaluation of 2PA cross sections that usually need larger basis sets.

For direct comparisons to experiment, an implicit solvation model is crucial to treat large systems such as fluorescent proteins because including explicit solvent molecules is computationally prohibitive. While the ground state includes implicit solvation terms self-consistently, nonequilibrium solvent effects are not accounted for in the stda program.⁶⁷ An implicit model such as the polarizable continuum model (PCM)⁷⁶ treats the solvent as a polarizable cavity around the solute. In solution, the solvent environment is polarized when an electronic (virtual) transition occurs. Considering equilibrium effects means that the solvent has the time to adiabatically adjust to the perturbation. Then, solvent electrons and nuclei are acclimated to the new solute electronic state. In a nonequilibrium regime, due to a fast perturbation, only the solvent electrons have the time to adjust themselves to the perturbation. This is the typical case for experimentally recorded optical spectra. Two approaches exist to treat nonequilibrium effects: the linear response method^{77,78} and a state-specific scheme,⁷⁹⁻⁸² which both may be implemented in the stda program.

Interpretation Tools. We took special care in developing tools for the interpretation of excited state and response calculations in the stda program. To characterize excited states, natural transition orbitals (NTOs) were recently added. They are particularly important to provide a method-independent orbital picture to electronic transitions as it was stressed again recently by Krylov.⁸³ NTOs were also used to describe spin-flip excitations⁸⁴ as it was proposed by Orms et al.⁸⁵ Two types of NTOs are defined in this case; i.e., type-I SF-NTOs describe SF transitions from the reference to the target SF state while type-II SF-NTOs are related to transitions between SF states. They are particularly useful when the first SF state is the ground state. Our first application was to

interpret absorption spectra of a set of conjugated expanded indenofluorene and diindeno[n]thiophene derivatives with possible diradical character.⁸⁴

To provide a method-agnostic, chemically intuitive interpretation of molecular optical response properties, we introduced the RespA approach.⁸⁶ This strategy includes two interrelated schemes that describe response properties in terms of newly introduced natural response orbitals (NROs) and chemical fragment response. Both quantities are extracted from the frequency-dependent perturbed one-electron transition/ current density matrix obtained from any quantum mechanical response function calculation. It is currently only implemented in the stda program but should be also available in other quantum chemistry codes in the future. NROs provide a compact virtual exciton picture by decomposing the response in few hole and electron NRO pairs. Moreover, on-site and between-site fragment responses partition the property in a chemically intuitive manner. The first application of the RespA approach was to interpret the optical rotation of particularly difficult cases. For example, Figure 8 presents the decom-



Figure 8. Molecule coordinate system for norbornenone as well as the hole and electron NRO pair for the largely weighted contribution to the β_{zz} component of the OR tensor. The weight is provided above the arrows while the response of NRO pairs are shown below. Fragment definitions for norbornenone as well as important on-site (red) and between-sites response (green for A < B and blue for A > B) for the β_{zz} component of the OR response tensor are also shown. Reprinted with permission from ref 86. Copyright 2020 American Chemical Society.

position of the dominant β_{zz} component of the optical rotation tensor of (1*S*,4*S*)-norbornenone into NROs and fragment response. The dominant NRO pair characterizes conveniently the virtual transition that results from the coupling between the $\pi \to \pi^*$ from the C=C bond and $n \to \pi^*$ from the C=O bond. This was further confirmed by the fragment analysis. An interesting future scope here is the use of the compact NRO basis to evaluate response properties for large aggregates of (supra)molecules using a virtual exciton coupling model. This will render the treatment of systems such as protein oligomers or large dye clusters possible.

An Extra Challenge Ahead. Last year, Ochsenfeld and coworkers⁸⁷ employed sTD-DFT/sTDA methods combined with the Hammes-Schiffer–Tully model and GPU-based integral routines to reduce the cost of nonadiabatic molecular dynamics

(NAMD) simulations. However, they evaluated exactly twoelectron integrals because derivatives of simplified two-electron integrals with respect to nuclear coordinates were not available. They concluded "For all investigated systems ranging from small organic molecules to proteins, excited-state properties and dynamics are described qualitatively correctly with a significantly reduced computational cost." This promising result suggests further development of the simplified methods for NAMD and related dynamical calculations. This requires implementation of two-electron integral derivatives with respect to nuclear coordinates in the simplified framework. A properly developed code for nuclear derivatives additionally enables computation of emission spectra and vibrationally resolved band shapes. Most computed excitation energies for large systems are vertical transitions implying that the geometry of the molecule does not change upon excitation. While this is a reasonable approximation for some excited-state properties, it does not provide rigorous observables directly comparable to experiment.^{12,88} An accurate comparison should include computations of the 0-0 energy that involve excited state geometry optimizations, calculations of the zero-point vibrational energy (ZPVE) for both states, and optionally, the vibrationally resolved band shape.⁸⁹⁻⁹³ As a perspective for sTD-DFT/sTDA/SF-sTD-DFT methods, one should implement both excited-state analytical gradient and finite-difference Hessian including a special treatment for the configuration truncation procedure. This future implementation could characterize nonadiabatic coupling in particular with the spin-flip method and respective spin-adapted and/or mixedreference versions. Note that the SF-TD-DFT method has become a very important tool to explore potential energy surfaces for photochemistry,94 especially for medium-sized systems.

CONCLUSIONS

In this Perspective, we reviewed recent developments in the sTD-DFT framework as well as future challenges ahead. For strongly correlated systems, we discussed the ultrafast SF-sTD-DFT method that provides good spin symmetry for (large) systems usually not well treated by standard DFT. This result suggests a way for the development of new simplified methods to treat strongly correlated systems, including (i) simplified versions of SA-SF-TD-DFT or MR-SF-TD-DFT methods, (ii) the inclusion of nonlocal electron correlation effects with the (D) correction to the sTD-DFT scheme, and (iii) the simplified version of the d-TD-DFT method.

We recently extended the range of application of the sTD-DFT method to a range of molecular optical response properties: polarizability, optical rotation, first hyperpolarizability, 2PA cross sections, and excited state absorption. We also identified some drawbacks for the characterization of frequency dispersions at small wavelengths that directly impact the usability of the 2PA part of the stda program. To cure this, we propose to replace the monopole approximation for the evaluation of two-electron integrals by a multipole scheme and to restore the exchange-correlation kernel in an approximate way. Concerning large systems, we are currently investigating the development of a new and more flexible tightbinding scheme than the actual sTD-DFT-xTB method.

We provide interpretation tools for excited states but also for response properties with the new method-agnostic RespA approach. We introduced the concept of natural response orbitals that may be used in the future in a virtual exciton

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coupling model to characterize optical response properties of large systems such as protein oligomers or clusters of dyes. Finally, the development of both excited-state analytical gradient and finite-difference Hessians with simplified methods is a viable option.

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The authors declare no competing financial interest.

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Marc de Wergifosse is a theoretical chemist who finished his Ph.D. on the theoretical characterization of nonlinear optical properties of complex systems in 2014, in the group of Prof. Benoît Champagne, at the University of Namur. After a postdoc with Prof. Anna Krylov at the University of Southern California on two-photon absorption properties of molecular switches, he joined Prof. Stefan Grimme's group in 2017 to work on simplified quantum chemistry methods for excited states and response properties of large systems. He was recently recognized by the editors of *Physical Chemistry Chemical Physics* as an Outstanding Reviewer for 2020. He is the stda program main developer. His main research interests are nonlinear optics, large biological systems such as fluorescent proteins, and the development of quantum chemistry methods to evaluate and interpret molecular optical response properties as well as excited states of large systems.

Stefan Grimme studied Chemistry and finished his Ph.D. in 1991 in Physical Chemistry on a topic in laser spectroscopy. He did his habilitation in Theoretical Chemistry in the group of Sigrid Peyerimhoff. In 2000, he became the C4 chair for Theoretical Organic Chemistry at the University of Münster. In 2011, he accepted an offer as the head of the Mulliken Center for Theoretical Chemistry at the University of Bonn. He has published more than 530 research articles and is the recipient of the 2013 Schrödinger medal of the World Organization of Theoretically Oriented Chemists (WATOC). In 2014 he was further awarded the "Gottfried Wilhelm Leibniz-Preis" of the DFG. His main research interests are the development and application of quantum chemical methods for large molecules, density functional theory, and noncovalent interactions and their impact in chemistry.

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