

# An extrapolation method for the efficient calculation of molecular response properties within Born–Oppenheimer molecular dynamics

Cite this: *Phys. Chem. Chem. Phys.*, 2013, **15**, 9392

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Received 16th January 2013,  
Accepted 11th April 2013

DOI: 10.1039/c3cp50204j

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The calculation of molecular response properties in dynamic molecular systems is a major challenge that requires sampling over many steps of, e.g., Born–Oppenheimer molecular dynamics (BO-MD) simulations. We present an extrapolation scheme to accelerate such calculations for multiple steps within BO-MD trajectories or equivalently within other sampling methods of conformational space. The extrapolation scheme is related to the one introduced by Pulay and Fogarasi [*Chem. Phys. Lett.*, 2004, **386**, 272] for self-consistent field (SCF) energy calculations. We extend the extrapolation to the quantities within our density matrix-based Laplace-transformed coupled perturbed SCF (DL-CPSCF) method that allows for linear-scaling calculations of response properties for large molecular systems. Here, we focus on the example of calculating NMR chemical shifts for which the number of required DL-CPSCF iterations reduces by roughly 40–70%.

## 1 Introduction

The reliable description of dynamic effects on molecular response properties represents a major challenge for quantum chemistry. It entails a huge computational effort to calculate response properties in following, e.g., Born–Oppenheimer molecular dynamics (BO-MD) trajectories or in scanning the change in properties by relevant variations of the molecular structure, e.g., in particular individual binding modes within supramolecular systems. This renders the restriction to just a few snapshots often mandatory, which typically leads to insufficient sampling for reliable predictions. The difficulties of sufficient and efficient sampling for the *ab initio* simulation of, e.g., NMR spectra characterized by chemical shieldings, spin–spin coupling constants, chemical shift anisotropies (CSA), and nuclear spin relaxation<sup>1–5</sup> are abundant, so that increased efficiency by transferring information between sampling points in order to speed up calculations is important and the focus of the present paper.

While there has been much progress in calculating molecular response properties for larger systems by the introduction of linear- or even sublinear-scaling quantum-chemical methods

(see, e.g., ref. 6 for a recent review), there is much need to reduce the prefactors for performing calculations on molecular systems, in particular, in following MD trajectories or in scanning, e.g., interaction domains in complex systems. Although there has been some progress in reducing the necessary quantum-chemical (QM) sphere by combination with simple empirical molecular-mechanical (MM) methods in so-called QM/MM schemes,<sup>7–10</sup> it has been shown crucial to systematically converge the QM sphere and to typically include large QM spheres of more than 300–1000 atoms for reliable results,<sup>11–15</sup> so that the prefactors of the calculations still remain large.

In our present work, we focus on how to speed up the calculation of molecular response properties within consecutive time steps in MD simulations for the example of NMR chemical shieldings. Here, calculating the response of the one-particle density matrix with respect to the magnetic field<sup>16</sup> or alternatively to the nuclear-magnetic moment is required,<sup>17</sup> which is obtained by solving the so-called coupled perturbed self-consistent field equations (CPSCF).<sup>18–21</sup> This holds for the response both within Hartree–Fock (HF) and Kohn–Sham density functional theory (KS-DFT) including exact exchange (hybrid functionals) that are solved for in a very similar fashion. In the molecular-orbital (MO) basis the solution of the CPSCF equations scales as  $\mathcal{O}(M^5)$  with molecular size  $M$ , since a transformation of the atomic-orbital (AO) four-center two-electron integrals into the MO basis is necessary. For NMR shieldings this effort can be conventionally reduced to  $\mathcal{O}(M^3)$  by a direct contraction of AO-integrals.<sup>22,23</sup>

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Despite this reduction, the application to larger molecular systems is strongly hampered in these schemes due to the steep cubic increase of the computational effort. In order to overcome these limitations, several alternative methods have been introduced in recent years to reduce the computational effort for the calculation of molecular response properties to linear<sup>21,24–28</sup> or even sublinear<sup>17</sup> (*i.e.*, to be asymptotically independent of molecular size in the rate-determining steps); see also ref. 6 for a recent review.

While the linear- and sublinear-scaling methods allow for tackling new molecular systems with more than a 1000 atoms, sampling over molecular-dynamic (MD) simulations or scanning surfaces in general is still a major challenge. The ultimate goal is to perform sufficient sampling for the reliable prediction of molecular properties for complex and dynamic molecular systems. This also includes the highly challenging description of solvent effects. At the same time the calculations should be feasible on simple workstations or cheap workstation clusters instead of supercomputer applications that are accessible in a dedicated fashion only for a few benchmark calculations in general.

Therefore, we focus in our present work to make another small step towards this goal by introducing an extrapolation method for accelerating response calculations in consecutive time steps of BO-MD simulations (or similarly in scanning properties depending on structural arrangements). While we currently focus on the calculation of NMR chemical shieldings, we expect our method to be useful also for other response properties that require the solution of the CPSCF equations. In order to exploit information of previous time steps, we develop an extrapolation scheme closely related to the one for extrapolating Fock matrices between consecutive SCF energy calculations introduced by Pulay and Fogarasi in 2004.<sup>29</sup> By adapting the extrapolation within our linear-scaling DL-CPSCF theory, we are able to significantly reduce the number of iterative cycles for converging the DL-CPSCF (or analogously the equivalent CPSCF) equations. After a brief description of our DL-CPSCF extrapolation method, we present the first results for analyzing the efficiency gains for various molecules.

## 2 An extrapolation method for response quantities

For calculating molecular response properties of dynamical systems, the CPSCF equations need to be solved for many points in conformational space, which represents the rate-determining step. The sampling points for describing dynamic molecular systems can be accessed either by molecular dynamics (MD) simulations, Monte Carlo methods (MC), or other conformational sampling techniques. Here, a very successful pathway is provided by MD simulations within the Born–Oppenheimer approximation (BO-MD) – for an introduction

and overview see, *e.g.*, ref. 30. By solving the CPSCF equations in all steps within BO trajectories, in principle, the complete time evolution of response properties due to conformational changes is accessible (see, *e.g.*, ref. 1–5, 31, and 32).

In order to exploit information of previous time steps efficiently for computing response properties, we employ our linear-scaling DL-CPSCF method introduced earlier<sup>26</sup> and adopt an extrapolation scheme closely related to the one for extrapolating Fock matrices between consecutive energy calculations introduced by Pulay and Fogarasi.<sup>29</sup> The original scheme allows for accelerating SCF energy calculations and has been further studied by Herbert and Head-Gordon,<sup>33</sup> see also related work for calculating energies within BO-MD by Niklasson *et al.*<sup>34</sup>

The original Fock matrix dynamics approach by Pulay and Fogarasi<sup>29</sup> is based on a polynomial expansion of order  $M$ , yielding a linear equation system for  $N$  preceding Fock (or Kohn–Sham) matrices  $F(n)$ :

$$\begin{aligned} F(1) &= K_0 + 1 \cdot K_1 + 1 \cdot K_2 + \cdots + 1 \cdot K_M \\ F(2) &= K_0 + 2 \cdot K_1 + 4 \cdot K_2 + \cdots + 2^M \cdot K_M \\ &\vdots \\ F(N) &= K_0 + N \cdot K_1 + N^2 \cdot K_2 + \cdots + N^M \cdot K_M \end{aligned} \quad (1)$$

The coefficient matrices  $K_m$  are determined by solving the corresponding matrix equation

$$f = X \cdot k, \quad (2)$$

with  $f = \begin{pmatrix} F(1) \\ \vdots \\ F(N) \end{pmatrix}$ ,  $k = \begin{pmatrix} K_0 \\ \vdots \\ K_M \end{pmatrix}$ , and  $X_{nm} = n^{m-1}$  ( $1 \leq n \leq N$ ;  $1 \leq m \leq M+1$ ;  $M < N$ ). Accordingly, the matrix  $F(N+1)$  for the time step  $N+1$  can be extrapolated as:

$$F(N+1) = K_0 + (N+1) \cdot K_1 + (N+1)^2 \cdot K_2 + \cdots + (N+1)^M \cdot K_M \quad (3)$$

The coefficient matrices  $K_m$  contain individual coefficients for all elements  $F_{\mu\nu}$  of the matrix  $F$ . However, the matrix  $X$  is independent of basis set indices  $\mu$  and  $\nu$ . Therefore the equation system has to be solved only once (independently of indices  $\mu$  and  $\nu$ ), which makes the extrapolation procedure very efficient. In our present work, we adopt this extrapolation approach for calculating response properties within our linear-scaling density matrix-based Laplace-CPSCF (DL-CPSCF) formalism.<sup>26</sup> While our approach is expected to be quite generally applicable to response properties, we currently focus on NMR shieldings (by calculating the response with respect to components  $B$  of an external magnetic field) and extrapolate an initial CPSCF guess by a similar polynomial expansion, such that the number of iterations in solving the DL-CPSCF equations is reduced. Here, the iterative procedure consists of solving the following linear-equation system:<sup>17</sup>

$$\underbrace{F \tilde{P}_{\text{vo}}^B S - S \tilde{P}_{\text{vo}}^B F}_{A_1} + \underbrace{G_{\text{vo}} [\tilde{P}_{\text{ov}}^B + \tilde{P}_{\text{vo}}^B]}_{A_2} = \underbrace{-F_{\text{vo}}^{(B)} + S_{\text{vo}}^B P F + F(PQ^B)_{\text{vo}} S - S(PQ^B)_{\text{vo}} F + G_{\text{vo}} [PS^B P + (PQ^B)_{\text{ov}} + (PQ^B)_{\text{vo}}]}_{b^B} \quad (4)$$

Within the iterative solution, the terms on the left hand side can be split into terms that involve only simple (and sparse) matrix multiplications (denoted  $A_1$ ) and terms that require a contraction of the perturbed one-particle density matrix  $\tilde{P}_{\text{vo}}^B$  with the two electron integrals leading to the  $G$  matrix. The latter terms are labelled  $A_2$  and are the computationally most intensive parts, since besides the fairly cheap  $A_1$  part, the computation of the right-hand side needs to be performed only once.

Therefore, in order to reduce the computational prefactor by an extrapolation from previous time steps, we propose an extrapolation employing the perturbed two-electron matrix  $A_2$  from preceding BO-MD steps. Here, the notation  $A_2$  refers to the Laplace-based DL-CPSCF equations as specified in eqn (13) of ref. 17 (see eqn (4) above). In this way, the matrix  $A_2(N+1)$  within the BO-MD step  $N+1$  can be extrapolated from previous  $A_2$  matrices by solving the matrix equation analogous to eqn (2),

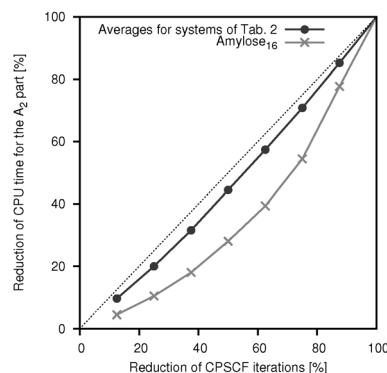
$$a_2 = \begin{pmatrix} A_2(1) \\ \vdots \\ A_2(N) \end{pmatrix} a_2 = Xk, \quad (5)$$

with  $a_2 = \begin{pmatrix} A_2(1) \\ \vdots \\ A_2(N) \end{pmatrix}$ . The form of  $k$  and  $X$  is unchanged compared to the Fock matrix extrapolation. By directly extrapolating the  $A_2$  matrix, the time-consuming formation of the Fock-like term  $G_{\text{vo}}[\tilde{P}_{\text{ov}}^B + \tilde{P}_{\text{vo}}^B]$  can be omitted, which would not be the case, if the perturbed one-particle density matrix was extrapolated (cf. the advantage of extrapolating the Fock matrix instead of the one-particle density matrix within SCF energy calculations).<sup>29,33</sup>

The proposed extrapolation method was implemented in a development version of the program package Q-Chem<sup>35</sup> based on the DL-CPSCF method.<sup>17,26</sup> All NMR shielding calculations were performed with sufficiently tight thresholds for SCF convergence, integral threshold, and verified accuracy for the chosen Laplace expansion.

### 3 Results and discussion

In the following, we study the efficiency of the extrapolation method in the context of solving the CPSCF equations for calculating response properties. Similar to the earlier studies for extrapolating between consecutive SCF energy calculations,<sup>29,33</sup> where the reduction of required SCF iterations was investigated, we list the reduction of the number of required  $A_2$ -builds (see discussion above), which are the dominant calculation step in converging the CPSCF equations.<sup>17</sup> The correlation between the number of CPSCF iterations and the CPU time for the  $A_2$ -part is exemplarily shown in Fig. 1 for the molecular systems that are investigated in Table 2 and in addition for a larger amylose system consisting of 16 glucose units.<sup>25</sup> Here, we always used incremental  $A_2$ -builds, which leads to a reduction of the computational time in later iterations. While there is a near linear correlation between the iteration number and CPU time for the systems studied in Table 2, there are some deviations from linear for the larger amylose system. It is worth noting that we observe almost exactly the same correlation behavior for the use of incremental Fock-builds in SCF iterations.<sup>36–38</sup> The data in Table 1 illustrate



**Fig. 1** Reduction of the total CPU time for the dominating  $A_2$  formation vs. the reduction of CPSCF iterations. For all calculations incremental builds of the  $A_2$  part (integral threshold of  $10^{-10}$ ) were employed. With circles averages over all molecular systems listed in Table 2 are shown (method and basis set according to Table 2); with crosses the results for a larger amylose<sub>16</sub> system<sup>25</sup> are shown (HF/SVP). The reduction of the number of CPSCF iterations refers to 8 CPSCF iterations (100%).

the efficiency of the proposed method for a simple test case that was also investigated in the context of Fock matrix extrapolation:<sup>29,33</sup> a tetrafluoroethylene molecule with time steps of 0.5 fs in the MD simulation. The table compares the required number of CPSCF iterations by different extrapolation choices ( $N/M$ :  $N$  preceding steps, polynomial of order  $M$ ) with both the most simple case of starting the CPSCF from the pure  $B^x$  part as an initial guess (which would correspond to no transfer of information between time steps), as well as the most obvious (and often conventional) exploitation of the previous perturbed one-particle density matrix  $P^B$  for the first DL-CPSCF iteration.

All calculations are based on an adaption of the DIIS method<sup>39</sup> for improving the CPSCF convergence (for details see Appendix A) and results for three different DIIS norms as convergence criteria (a)  $10^{-6}$ , (b)  $10^{-8}$ , and (c)  $10^{-10}$  are listed. The convergence criteria yield maximum errors for all atoms and all approaches of (a)  $2.2 \times 10^{-1}$  ppm, (b)  $1.8 \times 10^{-2}$  ppm, and (c)  $2.4 \times 10^{-3}$  ppm (in comparison to the approach with no transfer of information between time steps and a DIIS error norm of  $10^{-14}$ ).

**Table 1** Mean number of required CPSCF iterations without transfer from previous steps, using the perturbed one-particle density matrix  $P^B$  from the previous time step, and with different extrapolation choices  $N/M$  for DIIS error norms  $\epsilon_{\text{DIIS}}$  of  $10^{-6}$ ,  $10^{-8}$  and  $10^{-10}$  as a convergence criterion, respectively. Averages for all steps in five trajectories are given (each 0.5 ps,  $T = 500$  K, time step 0.5 fs, GIAO-HF/6-31G\*\*<sup>40,41</sup>)

Extr. choice	Number of required CPSCF iterations		
	$\epsilon_{\text{DIIS}} = 10^{-6}$	$\epsilon_{\text{DIIS}} = 10^{-8}$	$\epsilon_{\text{DIIS}} = 10^{-10}$
No transfer	6.00	7.24	8.96
$P^B$ prev.	4.01	5.84	7.01
1/0	3.35	4.97	6.61
2/1	<b>2.00</b>	3.68	5.03
4/2	<b>2.00</b>	2.30	4.22
6/3	<b>2.00</b>	<b>2.00</b>	3.66
8/4	<b>2.00</b>	<b>2.00</b>	2.49
12/6	<b>2.00</b>	<b>2.00</b>	<b>2.02</b>
16/8	<b>2.00</b>	<b>2.00</b>	2.03
20/10	<b>2.00</b>	2.01	2.04
22/11	<b>2.00</b>	3.92	5.17
24/12	5.00	6.36	7.96

All results in Table 1 are averaged over 1000 steps and five independent trajectories.

Already the simple direct reuse of the  $A_2$  matrix from the previous BO-MD step (formally a 1/0 extrapolation) while employing a convergence criterion of  $10^{-8}$  reduces the average number of CPSCF iterations from 7.24 (where just the one-electron part is employed as an initial guess – i.e., no data transfer between time steps) to 4.97. In case the previous perturbed one-particle density matrix ( $P^B$  prev.) would have been employed, the number of iterations is 5.84. By employing the more elaborate extrapolation using the higher-order polynomials the number of required iterations reduces further to only 2.00. At the same time deviations with respect to the case of no transfer between time steps are below  $1.8 \times 10^{-2}$  ppm.

For the tested convergence criteria ( $10^{-6}$ ,  $10^{-8}$ ,  $10^{-10}$ ) the number of required iterations decrease with enlarging the  $N/M$  values (as shown in Table 1) and reach a minimum before increasing again (a similar behavior is also observed for the Fock matrix extrapolation in ref. 33). For the DL-CPSCF case the  $N/M$  combinations 4/2, 6/3, 8/4, and 12/6 result in the largest savings regarding the number of DL-CPSCF iterations.

Further examples for the efficiency of the new extrapolation for the CPSCF initial guess are presented for various other molecular systems in Table 2. The BO trajectories at the HF/6-311G\*\*<sup>40,41</sup> level were all started from minimum structures as obtained at the same level, except for the glycine pentamer Glycine<sub>5</sub>, which was described by HF/6-31G\*\*.

The results are based on averages for three trajectories each over 50 fs and a DIIS error norm of  $10^{-8}$  as convergence criteria (errors of all NMR shieldings are below 0.05 ppm). For all molecular systems a similar trend for the reduction of the

required number of iterations is observed as for the C<sub>2</sub>F<sub>4</sub> system, even though the reduction may vary to some extent depending on the system and, e.g., the different flexibilities of the structures. While reuse of the perturbed density matrix from preceding iterations reduces the required number of iterations by 14–32% (20% on average), the optimal extrapolation scheme reduces the number of iterations by 31–74% (61% on average). An analogous evaluation for a looser CPSCF convergence criterion of  $10^{-7}$  (maximum error 0.2 ppm) yields a reduction of 3–34% (22% on average) for the reuse of the perturbed density matrix from preceding iterations and 40–75% (63% on average) for the optimal extrapolation scheme.

## 4 Conclusion

We have introduced an extrapolation scheme between consecutive Born–Oppenheimer molecular dynamics steps for accelerating the solution of the CPSCF equations being the rate-determining step in calculating response properties. The extrapolation scheme is closely related to the Fock-matrix extrapolation introduced by Pulay and Fogarasi<sup>29</sup> for the calculation of successive energies. Here, we extend the extrapolation to the quantities of relevance in our linear-scaling Laplace-based CPSCF theory (DL-CPSCF),<sup>26</sup> where we employ the perturbed two-electron part of preceding MD steps based on the simple polynomial expansion. For the example of calculating NMR chemical shieldings, the simple reuse of the perturbed density matrix from the preceding steps saves roughly 10–30% of iterations, whereas with an optimal choice of the investigated extrapolation schemes roughly 40–70% of iterations can be saved.

## A DIIS acceleration for DL-CPSCF

In our present work, the convergence of the CPSCF method is accelerated by employing the DIIS method<sup>39</sup> for the DL-CPSCF run. In line with the SCF DIIS error matrix

$$\epsilon_{\text{SCF}} \equiv \text{FPS} - \text{SPF}, \quad (6)$$

the DL-CPSCF DIIS error matrix is determined starting from the ansatz

$$\epsilon_{\text{CPSCF}} \equiv \frac{\partial}{\partial B} \epsilon_{\text{SCF}}. \quad (7)$$

Within the framework of DL-CPSCF theory as specified by eqn (4) (eqn (13) of ref. 17) the ansatz of eqn (7) results in

$$\epsilon_{\text{CPSCF}}^{(n)} = A_2^{(n)} - \underbrace{(b^B - A_1^{(n)})}_{A_2^{(n-1)}} \quad (8)$$

for the  $n$ -th DL-CPSCF iteration (the curly brace holds within the limits of the accuracy of the chosen Laplace expansion).

## Acknowledgements

C. O. acknowledges financial support from the Volkswagen Stiftung within the funding initiative ‘New Conceptual

**Table 2** Mean number of required CPSCF iterations without transfer from previous steps, using the perturbed one-particle density matrix  $P^B$  from the previous time step, and with different extrapolation choices  $N/M$ . Averages over all steps in three trajectories are given (each 50 fs,  $T = 300$  K, time step 0.5 fs, GIAO-HF/6-311G\*\*<sup>a</sup>, DIIS error norm  $10^{-8}$  as a CPSCF convergence criterion)

Molecule	No transfer	$P^B$ prev.	1/0	2/1	4/2	6/3	8/4	12/6	16/8
CH <sub>4</sub>	5.88	5.00	4.28	3.93	3.60	3.02	2.41	<b>2.29</b>	2.32
CH <sub>3</sub> CH <sub>3</sub>	6.00	5.07	4.80	3.98	3.79	3.34	2.71	<b>2.06</b>	2.13
CH <sub>3</sub> F	7.00	5.57	4.88	3.93	3.30	2.56	2.29	<b>2.06</b>	2.09
CH <sub>3</sub> OH	7.00	5.92	5.04	4.23	3.96	3.71	3.45	<b>2.95</b>	2.98
CH <sub>3</sub> NH <sub>2</sub>	7.00	5.93	5.00	4.12	3.97	3.69	3.35	<b>2.65</b>	2.68
CH <sub>3</sub> CHO	9.00	7.06	6.61	4.80	3.88	2.95	2.47	<b>2.32</b>	2.37
CH <sub>3</sub> COCH <sub>3</sub>	8.58	6.95	5.99	4.74	4.17	<b>4.12</b>	4.23	4.65	5.26
CH <sub>3</sub> CN	8.00	6.25	5.64	4.00	3.60	2.86	2.39	<b>2.32</b>	2.48
CO <sub>2</sub>	7.00	4.97	4.08	2.78	<b>2.11</b>	2.15	2.19	2.33	3.41
CF <sub>4</sub>	6.34	5.01	4.22	2.75	<b>2.00</b>	<b>2.00</b>	<b>2.00</b>	<b>2.00</b>	2.22
HCN	7.97	6.65	5.99	4.08	3.36	2.72	2.29	<b>2.11</b>	2.16
CH <sub>2</sub> CH <sub>2</sub>	7.00	6.00	5.45	4.16	3.87	3.44	2.95	<b>2.55</b>	2.63
CHCH	7.97	6.74	5.97	4.56	3.95	3.67	3.37	<b>3.33</b>	3.60
C <sub>6</sub> H <sub>6</sub>	7.13	6.00	5.63	4.94	<b>4.93</b>	4.99	5.00	5.10	5.79
CH <sub>2</sub> O	8.84	7.18	6.31	4.49	3.54	2.94	2.66	<b>2.60</b>	2.74
CH <sub>2</sub> CCH <sub>2</sub>	8.00	6.00	5.53	4.26	3.98	3.72	3.19	<b>2.89</b>	3.14
Thymine	9.00	6.16	5.79	4.47	<b>4.44</b>	4.76	5.05	5.36	5.76
Ribose	7.95	6.02	5.32	<b>4.93</b>	5.00	5.05	5.12	5.51	6.00
Glycine	8.55	6.19	5.61	4.30	<b>4.18</b>	4.23	4.33	4.85	5.36
Glycine <sub>5</sub> <sup>a</sup>	9.43	6.98	6.02	4.93	4.21	<b>4.15</b>	4.34	5.00	5.17

<sup>a</sup> The calculations for the glycine pentamer were performed with a 6-31G\*\* basis set.<sup>40,41</sup>



Approaches to Modeling and Simulation of Complex Systems', from the SFB 749 'Dynamik und Intermediate molekularer Transformationen' (DFG), and the DFG cluster of excellence EXC 114 'Center for Integrative Protein Science Munich' (CIPSM).

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