New Born-Oppenheimer molecular dynamics based on the extended Hückel method: first results and future developments

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Computational chemistry at the atomic level has largely branched into two major fields, one based on quantum mechanics and the other on molecular mechanics using classical force fields. Because of high computational costs, quantum mechanical methods have been typically relegated to the study of small systems. Classical force field methods can describe systems with millions of atoms, but suffer from well known problems. For example, these methods have problems describing the rich coordination chemistry of transition metals or physical phenomena such as charge transfer. The requirement of specific parametrization also limits their applicability. There is clearly a need to develop new computational methods based on quantum mechanics to study large and heterogeneous systems. Quantum based methods are typically limited by the calculation of two-electron integrals and diagonalization of large matrices. Our initial work focused on the development of fast techniques for the calculation of two-electron integrals. In this publication the diagonalization problem is addressed and results from molecular dynamics simulations of alanine decamer in gas-phase using a new fast pseudo-diagonalization method are presented. The Hamiltonian is based on the standard Extended Hückel approach, supplemented with a term to correct electrostatic interactions. Besides presenting results from the new algorithm, this publication also lays the requirements for a new quantum mechanical method and introduces the extended Hückel method as a viable base to be developed in the future.

I. INTRODUCTION

The development of atomistic computational methods for chemistry, biology and physics has a long and notable tradition, having evolved from pure academic curiosities to indispensable tools of great economic value. Notable examples where computational methods take a central role include the development of new drugs [1, 2] and the design of new enzymes and catalysts [3, 4]. Innumerable methods have been developed spanning very different approximations and targeting different systems and systems sizes. They can typically be grouped into certain levels, each one corresponding to a certain complexity and functionality. Each level is typically inter-related to the levels below and contributes to the levels above. At the lowest level, there is Quantum Mechanics (QM), with progress in algorithms and computer hardware making possible to model systems with a few thousand atoms [5], although simulations of systems with millions of atoms have been reported [6]. Those calculations required sophisticated super-computers with tens of thousands of processors and are not generally accessible to most academic and industry users. Highly accurate calculations are also possible for up to a few dozen atoms, for example using coupled-cluster techniques [7]. The next level of simulation methods can handle systems with up to millions of atoms and are based on classical Newtonian mechanics and empirical Force Fields (FFs) [8]. At the upper end, the mesoscale describes systems of billions of atoms using very approximate methods that still reflect molecular effects. The level of accuracy of each computational methodology decreases significantly on moving from the quantum level to the mesoscale. This work reports the initial steps in the development of new methodologies for fast and accurate methods at the quantum level for large systems on commodity hardware. Next, the need for atomistic methods based on QM is described, due to known problems of classical FFs. Then the Extended Hückel (EH) method is briefly described since it is a good base for the new computational method. Finally, results from gas-phase molecular dynamics simulations of alanine decamer, (Ala)_{10}, are presented and discussed.

II. NEED OF NEW COMPUTATIONAL METHODS BASED ON QUANTUM MECHANICS

Quantum Mechanical methods are in general generic and applicable to most problems in chemistry and biology. The major problem of QM based methods is their limitation to small systems, which typically excludes most of the large systems in biology, physics and chemistry. FF methods, on the other hand, were designed to be fast and applicable to very large systems. In 2006, for example, the first molecular dynamics simulation of a system with more than a million atoms was reported [9]. FFs abandoned the QM principles and the energy function is purely classical. The harmonic nature of empirical FFs does not allow the study of systems with breaking and formation of chemical bonds and since FFs are parametrized for certain classes of compounds their applicability is limited. Besides reactivity studies, classical FFs have other limitations that impart their effectiveness. One notorious problem is the difficulty of FFs in describing systems with transition metals. This is a very
significant area since according to some sources approximately half of all proteins are metalloproteins [10], meaning that approximately half of all proteins cannot, or are incorrectly studied, with classical FFs. Another limitation of classical FFs is the description of polarization and Charge-Transfer (CT) effects. Methodologies to describe polarization effects have been incorporated into classical FFs with notable examples being AMOEBA [11, 12] and the Drude polarizable Force Field (polFF) [13, 14]. Charge-transfer, being a pure quantum effect, is considerably more difficult to describe with classical methods. It remains a severe issue with empirical FFs. QM studies have shown that CT effects account for approximately one-third of the binding energy in a neutral water dimer [17], and a similar amount (22-35% depending on the semi-empirical method) in protein-protein interactions [18]. Ab initio molecular dynamics studies of BPTI in water and vacuum also revealed significant CT between the solvent and the protein. Furthermore, for the simulations in vacuum a very significant intra-molecular CT was found between the neutral and charged residues. Interestingly, upon solvation the formally neutral residues remained neutral [19]. The reliance of classical FFs on parameterization has positive and negative aspects. On the positive side, classical FFs can be made very accurate in reproducing properties in gas and condensed phases. For example, classical water models [20, 21] are able to reproduce the structure of liquid water considerably better than pure Density Functional Theory (DFT) [22, 23]. On the negative side, development of classical FFs is a painstaking process that includes multiple fittings and careful judgment to obtain the best compromise in reproducing the experimental and ab initio target data [24].

The problem is exacerbated with polFFs where transferability of the electrostatic parameters can be lost due to cooperative effects, as was the case with the Drude polFF (see references [13] and [22] for an example). The ideal parameterization scheme for polFFs would require reliable reference data for large systems, in gas and condensed phase, from large scale QM calculations, that is difficult to compute using current methods. Development of more accurate polFFs will clearly benefit from availability of fast and accurate large scale QM methods. There have been many attempts to remedy the deficiencies of classical FFs. Illustrative examples are the development of reactive FFs and development of theories to quantify effects of d-electrons. Reactive FFs have been developed to describe chemical bonding without expensive QM calculations, thus allowing studies of reactive events [25]. Deeth and co-workers added energy terms from d-electrons derived from ligand-field theory to classical FFs to study systems with transition metal complexes [27]. These efforts, despite improving traditional classical FFs are not effective replacements for a full QM description. From the discussion above it is clear that there is a great and urgent need to develop fast and accurate QM methods capable of studying large and complex systems across multiple scientific areas. Although such a computational methodology can be understood as a direct competitor to classical FFs, it is better to see it as another element of the multiscale ladder with potential close integration with classical FFs. In our vision, the new QM method will be reserved to study systems, or parts of systems, where quantum effects are preponderant, leaving the remaining parts for classical FFs. Because studies of very large systems will be possible, the new QM methods will also be used in the parameterization of very accurate polFFs. The quantum and classical approaches will also be interfaced together in ways reminiscent of QM/MM methods.

III. A VISION FOR THE FUTURE BUILT STEP BY STEP

The problems limiting the development of fast QM methods for large systems are well known. Calculation of two-electron integrals scales formally as N^4, due to the four different functions in the integral. Several techniques that include integral screenings and fittings to decrease the dimensionality of the integral have been proposed (see [28] for appropriate references), but computation of two-electron integrals remains a formidable task. Another limitation of typical QM methods is diagonalization of the Hamiltonian, which has a N^3 scaling. Much effort has been put into developing alternatives to diagonalization. For electronic structure calculations several alternatives to formal diagonalization have been developed including partitioning of a larger problem into smaller more amenable problems [29, 30] and direct minimization of the density matrix [31, 32]. Development of novel QM algorithms for physics, chemistry and biology has to, invariably, address both problems. Recently, we developed a fast algorithm to compute two-electron integrals by approximation, using nested bi- and single-dimensional Chebyshev polynomials [33]. This algorithm is not a direct replacement to standard methodologies, since it is limited to a fixed basis due to parameterization. It is, however, very fast and for the basis set of choice, allowing development of Hartree-Fock (HF) or DFT methods that are able to describe very large systems. A new methodology for pseudo-diagonalization has also been recently developed, and the first results are show in this publication (see below). A full description of the methodology will be presented in a dedicated publication. When both of our most recent works are combined, they will allow development of a new generation of fast and accurate QM methods for large and complex systems. The goal is to develop a fast and accurate QM method that is capable of studying the dynamics of systems with 10-100,000 atoms on commodity hardware. Ideally, the new computational method needs to have several distinct features:

- Be applicable to a wider range of large systems, over greater time scales, including gas phase, liquid and solid state.
• Be flexible and rely on standard optimized libraries, for example optimized implementations of Blas and Lapack. This means the method will benefit from high level optimizations without incurring further development costs, and will be fully inter-operable between various computing platforms and operating systems.

• Be affordable and capable of running on workstations or lower-cost parallel systems, not only expensive supercomputers. For this purpose it has to take advantage of new computing paradigms such as Graphical Processing Units (GPUs).

• Be able to reproduce experimental gas and condensed phase properties. This is, perhaps, the most important factor in the success of classical FFs and the same concepts need to be incorporated in the development of the new method. To my best knowledge, this is the first time that this important concept for classical FF development is being used in QM methods development.

IV. HIGHLIGHTS OF THE EXTENDED-HÜCKEL METHOD. POSSIBLE BASIS FOR FUTURE COMPUTATIONAL METHOD

The desirable features for the new QM computational method outlined above find a good match on existing tight-binding approaches, such as the EH. The EH method is conceptually very simple, which tend to yield faster algorithms, and has been connected to the standard HF algorithm, showing a clear path for optimization and enhanced accuracy. It is very interesting that in two very different periods, spanning a period of fifty years, and enhanced accuracy. It is very interesting that in two very different formulations of the parameter \( K_{ij} \), and (2) addition of nuclear repulsion and nucleus-electron attraction terms. Several formulas were suggested to correct the Hamiltonian including parameterizations by Cusachs et al. \[43\], Kalman \[44\], Anderson \[45\], and Ammeter et al. \[46\]. The latest parameterization of the Hamiltonian due to Calzaferri et al. \[47–50\] introduced a distance dependent formula for \( K_{ij} \), in order to make it larger than 1 for intermediate and large inter-atomic separations,

\[
K_{ij} = \{1 + \kappa_{ij} \exp(-\delta (R_{ij} - d_0))\} \tag{IV.2}
\]

with \( \kappa_{ij} \) and \( \delta \) being positive parameters, and \( d_0 \) a parameter defined by Calzaferri as the sum of orbital radii. In reference \[47\] formulas for \( \kappa_{ij} \) and \( d_0 \) are given.

Additional nuclear repulsion and nucleus-electron attraction corrections were added initially by Anderson and Hoffmann \[51\]. Carbó et al. \[52\] also introduced electrostatic corrections to the EH method. Lastly, Calzaferri and co-workers \[47–50\] defined the electrostatic terms as

\[
E_{corr}(\vec{R}) = \sum_{A,B} A \sum_{A \neq B} \left\{ Z_A Z_B \frac{\rho_B (\vec{r})}{R_{AB}} - \frac{1}{2} \left[ Z_A \int \frac{\rho_B (\vec{r})}{|R_{AB} - \vec{r}|} \, dr + Z_B \int \frac{\rho_A (\vec{r})}{|R_{AB} - \vec{r}|} \, dr \right] \right\} \tag{IV.3}
\]

with the integrals being computed as

\[
\int \frac{\rho (\vec{r})}{|\vec{R} - \vec{r}|} \, dr = \frac{1}{R} \sum_{n,l} b_{n,l} \left[ 1 - \exp\left(-2\zeta_{n,l} R\right) \sum_{p=1}^{2n} \frac{p}{(2n - p)!} \right] \tag{IV.4}
\]

The coefficients \( b_{n,l} \) are the occupation numbers of the corresponding AOs with exponents \( \zeta_{n,l} \), and \( n,l \) are the
Table I. Optimized parameters of the atomic orbitals in a single-\(\zeta\) representation of Slater type functions (STFs). \(\varepsilon_s\) and \(\varepsilon_p\) are the s and p orbital energies and \(\zeta_s\) and \(\zeta_p\) are the corresponding exponential parameters of the STFs.

| Atom | \(\varepsilon_s\) | \(\zeta_s\) | \(\varepsilon_p\) | \(\zeta_p\) |
|------|-----------------|-------------|-----------------|-------------|
| H    | -16.2866        | 1.2784      |                 |             |
| C    | -25.6725        | 1.6958      | -13.6697        | 1.8884      |
| N    | -21.5711        | 1.8000      | -13.5185        | 2.5758      |
| O    | -25.8400        | 1.9867      | -13.5413        | 2.5942      |

Figure V.1. Identification of relevant atoms of (ALA)\(_{10}\) (A) and NMA (B) used in the analysis.

In order to demonstrate the capabilities of the newly developed algorithms for fast density optimization and pseudo-diagonalization and the performance of the basic EH Hamiltonian, Born-Oppenheimer molecular dynamics simulations were performed. The test system is (Ala)\(_{10}\) in gas phase. The system was deliberately kept small to allow extensive monitoring of the calculated energies relative to the true values obtained by diagonalization along the trajectory. The Hamiltonian was based on the EH approach with the standard Hamiltonian (Eq. [IV.1]) with additional nuclear repulsion and nuclear-electronic attraction terms described by Eq. [IV.3]. All calculations were performed on a single AMD Ryzen 1700X processor. The initial goal is to establish the baseline performance of the method without speed boosts due to multiprocessing and parallelization. The scalability of the algorithms is an important feature of the development process though, and all algorithms are being developed considering parallelization using standard CPU and emerging computer architectures such as GPUs.

V. TESTING THE PSEUDO-DIAGONALIZATION METHOD: BORN-OPPENHEIMER MOLECULAR DYNAMICS SIMULATIONS
Table II. Selected bond distances and angles of alanine decamer from the simulations and experiment

| Angles (degrees)   | Cβ-Cα-C  | N-Cα-Cγ | Cα-C-O | Cα-C-N+1 | O-C-N+1 | C1-Cα-Nα |
|--------------------|-----------|---------|--------|----------|---------|----------|
| MD                 | 111.1±4.1 | 106.7±3.8 | 121.3±3.1 | 118.2±3.6 | 120.2±2.8 | 123.2±4.0 |
| Exp. [55]          | 109.7±1.5 | 110.9±1.4 | 120.4±0.9 | 116.4±1.1 | 123.2±0.9 | 122.5±1.3 |

| Distances (Å)      | Cα-C     | N-Cα     | C-N+1   | C-O      | Cα-Cβ   |
|--------------------|----------|---------|---------|----------|---------|
| MD                 | 1.503±0.021 | 1.479±0.021 | 1.338±0.027 | 1.199±0.012 | 1.618±0.022 |
| Exp. [56]          | 1.525, 1.531 | 1.456, 1.461 | 1.332, 1.336 | 1.232, 1.235 | 1.525, 1.531 |
| HF/cc-pVDTZ        | 1.514 | 1.447 | 1.352 | 1.199 | NA |

* Values of non-Gly/non-Pro residues in β-structure
# Average values for different (ϕ,ψ) regions
** Optimized values for NMA. See Figure V.4 for naming of the atoms

Initially, the values of each $\varepsilon_i$, Slater exponents $\zeta_i$ and the $K_{ij}$ value were optimized based on fittings to potential energy surfaces for bond stretching and shortening around the equilibrium in N-methyl acetamide (NMA). NMA is the smallest molecule prototyping a chemical bond and is used extensively in the development of classical FFs [57–58]. Six bond lengths were fitted in total: C(sp$^2$)-N, C-O, N-C(sp$^3$), N-H, C(sp$^3$)-H and C(sp$^3$)-C(sp$^3$). The C(sp$^3$)-C(sp$^3$) bond in alanine was deliberately not fitted to test transferability of the C parameters. The target potential energy surfaces were obtained at the HF/cc-pVDTZ and restricted to the vicinity of the minimum. Since this work is only illustrative of the capabilities of the new algorithm for pseudo-diagonalization and of the EH method, there is no need for higher level ab initio target data. The parameters were fitted freely using the same simulated annealing procedure used to develop the Drude polFF [20, 25]. In Figure V.2, the plots of the reference and fitted potential energy surfaces are show (see the fitted parameters in Table I). For each plot, the agreement between the target and the computed energies is nearly perfect. This adds to the great potential of the basic EH method to be a suitable basis to develop a new class of methods for computational quantum chemistry.

After suitable parameters have been developed, MD simulations were performed. The test system was (ALA)$_{10}$ in gas phase. These results come with an important disclaimer since the EH parameters were not fitted taking into consideration the relative energies of different conformers. Thus, there is no guarantee that sampling is appropriate, for example as a function of the $\phi$ and $\psi$ torsions. The Newton’s equations of motion were integrated using the velocity Verlet algorithm with 1 fs timestep and the temperature (300 K) was maintained using the Berendsen thermostat [59]. In Figure V.3, the total energy is plotted for two simulations of 30 ps each. The second simulation (in blue) started from the last frame of the first simulation (in red) with randomized velocities. The energy is well conserved and there is no apparent drift. It has been reported that with methods dependent on self-consistent iterations significant drifts of the total energy can occur due to incompleteness of optimization [60]. Niklasson and co-workers have proposed the XL-BOMD method to remedy this problem [61–63]. In the present case, the EH Hamiltonian is immune due to its
torsions from the simulations will be analyzed. The Cα behavior will be analyzed thoroughly.

Next, sampling of selected bond distances, angles and torsions are considered for non-self consistency.

Despite the important feature of the total energy not drifting, it is important to understand how the potential energies (and the forces) from the pseudo-diagonalization algorithm compare with the true energies obtained from diagonalization. In Figure V.3 the differences of potential energies between the new pseudo-diagonalization and true diagonalization are plotted. Remarkably, the energy difference shows a continuous decrease for both simulations. At 30 ps the difference is very small relative to the optimized values. The largest deviations are for N-Cα-Cβ and O-C-N+1, with 4.2 and 3.0°, respectively. It is interesting to note that the largest deviation for the bond angles also involves Cβ. The planarity of the peptide bonds is maintained along the simulation with the out-of-plane torsions of 180.4° for O-Cα-Cβ-N+1 and 179.7° for H-N+1-Cα+1.

VI. CONCLUSIONS

The outcome of this work largely exceeded the initial expectations. One goal was to test the performance of the simple EH algorithm (Eq. IV.1) and evaluate its suitability for further development to create new algorithms for simulation of large and heterogeneous systems. The second objective was testing of the new algorithm for pseudo-diagonalization in realistic conditions.

The simple EH approach (Eq. IV.1) supplemented with the nuclear-nuclear and nuclear-electronic term of Calzaferri (Eq. IV.3) performed remarkably well. In the MD simulations the structural parameters (bond distances, angles and torsions) compared very well with their experimental equivalents. The EH parameters were optimized based on fitting of the potential energy surface for each bond of NMA around the minimum. NMA provides a similar, although not the same, chemical environment and the parameters proved transferable. Transferability is a key concept in the development of approximated computational methodologies allowing high quality target data from smaller systems to be used in the parameterization. The largest discrepancy to the experimental values was with the Cα-Cβ bond that was not included in the parameterization. These results are very encouraging considering the simplicity of the electronic Hamiltonian and the electrostatic corrections. There is a direct connection between the extended Hückel and HF methods, meaning that suitable approximations of the HF, or related correlated methods such as DFT, will be possible. Our previous work on the computation of two-electron integrals will be fundamental to derive computationally fast and accurate approximations.

The algorithm for pseudo-diagonalization also performed very well. Due to its iterative nature, it showed continuous improvement during the MD simulations differing by ~0.18 kcal/mol relative to the true diagonalization result. This is the first generation of the algorithm compared with experimental values from high-resolution crystal data. Starting with the bond distances, it is apparent that the simple EH Hamiltonian reproduces outstandingly well all bonds with the exception of the Cα-Cβ bond. For the Cα-Cβ bond the equilibrium value is ~1.53 Å whereas the averaged value from the MD simulations is 1.618 Å. In the polypeptide some distances increase, while others decrease, relative to the optimized values from NMA. In future works the target geometries will be derived from geometry optimizations at a higher level of theory with correlation. The bond angles also remain very close to the experimental values. The largest deviations are for N-Cα-Cβ and O-C-N+1, with 4.2 and 3.0°, respectively. It is interesting to note that the largest deviation for the bond angles also involves Cβ. The planarity of the peptide bonds is maintained along the simulation with the out-of-plane torsions of 180.4° for O-Cα-Cβ-N+1 and 179.7° for H-N+1-Cα+1.
and the main purpose was testing its usability. Subsequent revisions will update the underlying optimization algorithms to faster and more robust methods. The pseudo-diagonalization algorithms and a detailed analysis of their performance will be the subject of a dedicated publication.

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