Partial multidimensional grid generation method for efficient calculation of nuclear wavefunctions

Tzvetelin Iordanov, Salomon R. Billeter, Simon P. Webb, Sharon Hammes-Schiffer *

Department of Chemistry, 152 Davey Laboratory, The Pennsylvania State University, University Park, PA 16802, USA
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Abstract
A partial multidimensional grid generation method for the efficient calculation of nuclear wavefunctions is presented. This method substantially decreases the number of potential energy calculations by avoiding this calculation for grid points with high potential energy. The application of this method to the calculation of three-dimensional hydrogen nuclear wavefunctions for hydride transfer in the enzyme liver alcohol dehydrogenase is presented. The results indicate that the partial multidimensional grid generation method is nearly as accurate as and significantly faster than the standard full grid method. © 2001 Elsevier Science B.V. All rights reserved.

1. Introduction

The efficient calculation of nuclear wavefunctions is critical to many areas of computational chemistry and biology. This Letter pertains to grid-based methods in which the potential energy and wavefunction are calculated directly on a multidimensional grid representing the coordinates of the nuclei [1–8]. Grid-based wavefunction calculations require two main steps: (1) the kinetic and potential energy must be calculated at the grid points, (2) the time-independent Schrödinger equation must be solved numerically to determine the wavefunctions. The method presented in this Letter is aimed at grid-based wavefunction calculations for which the evaluation of the potential energy at the grid points (i.e., the generation of the grid potential) is the most computationally expensive step. This method substantially reduces the number of potential energy calculations by avoiding this calculation for grid points with high potential energy.

The specific type of system investigated in this Letter is the calculation of hydrogen nuclear wavefunctions for the simulation of proton and hydride transfer reactions in solution and enzymes. In mixed quantum/classical molecular dynamics simulations of these systems, the transferring hydrogen nuclei are treated quantum mechanically, while the remaining nuclei are treated classically [9]. Typically the hydrogen nuclear wavefunctions must be calculated at each molecular dynamics time step. Often grid-based wavefunction methods are utilized to avoid the calculation of multidimensional integrals over basis functions [10,11]. The bottleneck of these grid-based simulations is often the evaluation of the potential energy for the large number of grid points.
points. Mixed quantum/classical simulations of many proton and hydride transfer reactions in solution and enzymes would be computationally prohibitive with standard methods requiring the evaluation of the potential energy for the full multidimensional grid. The partial multidimensional grid generation method presented in this Letter removes this bottleneck.

The details of the partial multidimensional grid generation method are presented in Section 2. The application of this method to hydride transfer in the enzyme liver alcohol dehydrogenase is described in Section 3. In this application, the transferring hydrogen nucleus is described as a three-dimensional wavefunction. For this system, the bottleneck of the nuclear wavefunction calculation is the evaluation of the potential energy on the three-dimensional grid. The grid method presented in this Letter decreases the computational expense of the nuclear wavefunction calculation enough to allow mixed quantum/classical molecular dynamics simulations on this system.

2. Method

In grid-based calculations of wavefunctions, the potential energy depends on coordinates represented on a multidimensional grid. The partial multidimensional grid generation method is designed to avoid the evaluation of the potential energy for grid points with potential energy higher than a specified cutoff, which is defined relative to one of the lower energy grid points. Specifically, grid points for which the potential energy can be identified as higher than the cutoff without explicit calculation of the potential energy are set equal to this cutoff. This method is useful if the potential energy at a significant number of the grid points is higher than the cutoff. The grid size should be chosen large enough such that the potential energies are larger than the cutoff for all grid points on the outer surfaces of the grid (i.e., on the four edges of a two-dimensional grid or on the six faces of a three-dimensional grid). The algorithm requires that all relevant grid points are contiguous (i.e., there should not be isolated regions of grid points with low potential energy). Note that for potential energy surfaces with multiple minima, the cutoff should be chosen to be higher than all barriers connecting the relevant minima.

First consider a two-dimensional grid in the x- and y-directions with $N_x$ and $N_y$ grid points, respectively. For simplicity, in this Letter the grid is assumed to be fixed with equal spacing between grid points. The grid points in the x-direction correspond to x-coordinates $x_1$ through $x_{N_x}$ and those in the y-direction correspond to y-coordinates $y_1$ through $y_{N_y}$. A general grid point on the two-dimensional grid is denoted by a pair of coordinates $(x_i, y_j)$. A line of points in the x-direction with y-coordinate $y_n$ is indicated by $y_n$ [i.e., grid points $(x_1, y_n), (x_2, y_n), \ldots, (x_{N_x}, y_n)$]. The extension to higher dimensions is discussed at the end of this section.

An interval of the line $y_n$ is defined as a set of contiguous grid points along this line. Intervals are represented by the arrays Pstart and Pend, which specify the indices of the grid points corresponding to the start and end of the intervals, respectively. For example, $Pstart(1, n)$ and $Pend(1, n)$ are the indices representing the start and end of the first interval in the line $y_n$. The goal of this algorithm is to determine the intervals for which the potential energy is lower than the cutoff for each line $y_n$. Upon completion of this algorithm, if $Pstart(1, n) = i$ and $Pend(1, n) = j$, then the potential energies for grid points between and including the grid points $(x_{i+1}, y_n)$ and $(x_{j-1}, y_n)$ are lower than the cutoff. The same is true for all intervals, and all points that are not contained in an interval are greater than or equal to the cutoff.

The fundamental step of the partial multidimensional grid generation algorithm is a line generation, which consists of a sequence of the following four basic elements:

1. An interval projection projects the interval arrays Pstart and Pend from a line $y_n$ to a neighboring line $y_{n+1}$ or $y_{n-1}$. For example, for the line $y_{n+1}$, $Pstart(1, n + 1)$ is set to $Pstart(1, n)$, $Pend(1, n + 1)$ is set to $Pend(1, n)$, and so forth.

2. An interval adjustment increases the size of the interval arrays for a line $y_n$ if necessary after an interval projection. The potential energy is
evaluated for grid points corresponding to the start and end of the intervals indicated in $P_{\text{start}}$ and $P_{\text{end}}$. If the potential energy is lower than the cutoff for an index in $P_{\text{start}}$, the index is decreased until the potential energy is above the cutoff, at which point the new index is stored in $P_{\text{start}}$. For example, if $P_{\text{start}}(1,n) = i$ after a projection to the line $y_n$, and the potential energy for the grid point $(x_i, y_n)$ is lower than the cutoff but the potential energy for the grid point $(x_{i-1}, y_n)$ is greater than the cutoff, then $P_{\text{start}}(1,n)$ is changed to be $i - 1$. The analogous procedure is performed for each index in $P_{\text{end}}$, where the index is increased until the potential energy function is above the cutoff, at which point the new index is stored in $P_{\text{end}}$. 

3. An interval evaluation involves the evaluation of the potential energy for relevant grid points along a line $y_n$ based on the intervals indicated in arrays $P_{\text{start}}$ and $P_{\text{end}}$. The potential energy is evaluated for all grid points that are within the intervals and have not been previously evaluated. All grid points that are outside of the intervals and have not been previously evaluated are set to the cutoff value. For example, if $P_{\text{start}}(1,n) = i$ and $P_{\text{end}}(1,n) = j$ then the potential energy is evaluated for grid points between and including grid points $(x_{i+1}, y_n)$ and $(x_{j-1}, y_n)$.

4. An interval search identifies the intervals along the line $y_n$ for which the potential energy is lower than the cutoff. The grid points are assumed to have been previously initialized, evaluated, or set to the cutoff value. The search starts at the first grid point $(x_1, y_n)$ of the line $y_n$. The index for the x-direction is incremented until the value of a grid point $(x_{i+1}, y_n)$ is lower than the cutoff, at which point $P_{\text{start}}(1,n)$ is set to $i$. The index for the x-direction is incremented further until the value of a grid point $(x_j, y_n)$ is higher than the cutoff, at which point $P_{\text{end}}(1,n)$ is set to $j$. Note that the potential energies for grid points between and including the grid points $(x_{i+1}, y_n)$ and $(x_{j-1}, y_n)$ are lower than the cutoff. This process continues until the grid point $(x_{N_n}, y_n)$ at the end of the line $y_n$ is reached. A line generation determines the intervals and relevant potential energies for a line $y_n$ by following a specific sequence of the four basic elements described above. First, an interval projection is performed to obtain a set of intervals for the line $y_n$ from a known set of intervals for a neighboring line. (An upward line generation corresponds to an interval projection from $y_{n-1}$ to $y_n$, while a downward line generation corresponds to an interval projection from $y_{n+1}$ to $y_n$.) Second, an interval adjustment is performed to increase the size of the intervals for the line $y_n$ if necessary. Third, an interval evaluation for the line $y_n$ is performed. Fourth, an interval search is performed to obtain a new set of intervals, which may differ from the projected ones due to overlapping intervals or to grid points within the projected intervals that are higher than the cutoff.

Prior to describing the overall algorithm, a schematic illustration of a line generation will be presented for clarification. Fig. 1 illustrates an upward line generation from $y_n$ to $y_{n+1}$ for a system with a cutoff value of 15. In Fig. 1a, the grid is initialized by setting all grid points to zero and evaluating the potential energy for grid points on the line $y_n$. An interval search is performed to determine that $P_{\text{start}}(1,n) = 2$ and $P_{\text{end}}(1,n) = 6$. After this step, the line generation for the line $y_{n+1}$ begins. Fig. 1b depicts the grid after an interval projection is performed so that $P_{\text{start}}(1,n+1) = 2$ and $P_{\text{end}}(1,n+1) = 6$. Fig. 1c depicts the grid after an interval adjustment is performed for line $y_{n+1}$ so that $P_{\text{start}}(1,n+1) = 1$ and $P_{\text{end}}(1,n+1) = 6$. Note that the value of $P_{\text{start}}(1,n+1)$ changed since the potential energy of grid point $(x_2, y_{n+1})$ is below the cutoff. Fig. 1d depicts the grid after an interval evaluation is performed for line $y_{n+1}$ so that the potential energy is evaluated for all grid points within the interval, and the values for all grid points outside the interval are set to the cutoff of 15. Fig. 1e depicts the grid after an interval search is performed for line $y_{n+1}$ so that $P_{\text{start}}(1,n+1) = 1$ and $P_{\text{end}}(1,n+1) = 5$. Note that the value of $P_{\text{end}}(1,n+1)$ changed since the potential energy of grid point $(x_5, y_{n+1})$ is above the cutoff.

The overall algorithm for evaluating a two-dimensional grid is based on a series of upward and
downward line generations. The grid is initialized by setting all grid points to zero and evaluating the potential energy for the grid points in the initial line \( y_n \). Note that at least one of the grid points in this initial line must be within the relevant region with potential energy below the cutoff. An interval search is performed for the line \( y_n \). Starting at the line \( y_n \), a series of upward line generations are performed until reaching a line \( y_k \) for which all grid points are set to the cutoff. At this stage all grid points for the lines between and including \( y_{k-1} \) and \( y_N \), are set to the cutoff. Then, starting at the line \( y_{k-1} \), a series of downward line generations are performed until reaching a line \( y_m \) for which all grid points are set to the cutoff. At this stage all grid points for the lines between and including \( y_1 \) and \( y_{m-1} \) are set to the cutoff. This procedure is continued until the number of intervals in each line does not change for two consecutive scans of the entire two-dimensional grid. (We have programmed this algorithm recursively [12,13].) The multiple scanning procedure ensures that the entire relevant region will be evaluated as long as at least one of the grid points in the initial line is in this relevant region. The efficiency of the algorithm is maximized if this initial line passes through or is close to the minimum of the potential energy surface. Upon completion of this algorithm, all grid points higher than the cutoff are set to the cutoff to avoid numerical instabilities in the calculation of the wavefunctions. Thus, the resulting potential energy surface is simply truncated at the cutoff value.

Fig. 2 is a schematic illustration of the results of the first series of upward and downward line generations. The bold contour line indicates the coordinates at which the potential energy is equal to the cutoff value. The upward scan is initiated at the line \( y_n \) and is terminated at the line \( y_k \), and the subsequent downward scan is initiated at the line \( y_{k-1} \) and is terminated at the line \( y_m \). Note that many lines, including \( y_n \), exhibit multiple intervals. More importantly, this figure shows that a single scan through the two-dimensional grid is inadequate. During the first upward scan starting at the line \( y_n \), a portion of the grid corresponding to potential energies lower than the cutoff is missed and thus set to the cutoff value. This portion of the grid is evaluated properly during the subsequent downward scan through this region. A third scan would be required if there were another similar region of the potential separated by regions of high cutoff. (Note that this algorithm requires that all relevant regions are contiguous.)

The three-dimensional extension of this algorithm involves repeating this entire procedure \( N_z \) times in the \( z \)-direction, starting at each line corresponding to \( y_n \), \( n = 1, \ldots, N_y \). In this case the upward and downward line generations occur in the \( z \)-direction rather than the \( y \)-direction. In order to ensure complete sampling, a similar procedure may be carried out \( N_z \) times in the \( y \)-direction, starting at each line corresponding to \( z_n \), \( n = 1, \ldots, N_z \). (Note that typically this additional
3. Application

We have applied this partial multidimensional grid generation method to hydride transfer in the enzyme LADH, which catalyzes the reversible oxidation of alcohols to the corresponding aldehydes or ketones. This enzyme reaction is vital to metabolism. Fig. 3 depicts the hydride transfer from the alkoxide substrate (i.e., the deprotonated alcohol substrate) to the NAD$^+$ cofactor in the active site of LADH. Note that $C_D$ and $C_A$ denote the donor and acceptor carbon atoms, respectively.

Our molecular dynamics simulation of this reaction requires the combination of many different types of methods [14]. Our simulations include the entire solvated LADH dimer, which involves more than 75,140 atoms. We developed an empirical valence bond (EVB) potential [15] based on the GROMOS [16] molecular mechanical forcefield to describe this hydride transfer reaction. This potential energy depends on the coordinates of all nuclei in the system. In our mixed quantum/classical simulations, the transferring hydrogen nucleus is described as a three-dimensional quantum mechanical wavefunction, and the remaining nuclei are treated classically. In order to treat the

procedure does not require many, if any, new evaluations of the potential energy.) As for the two-dimensional case, upon completion of this algorithm all grid points higher than the cutoff are set to the cutoff to avoid numerical difficulties. Extensions to higher dimensions are similarly straightforward.

Fig. 2. Schematic illustration of a two-dimensional grid after (a) a series of upward line generations initialized at line $y_n$ and (b) a series of downward line generations following (a). The bold contour line indicates the coordinates at which the potential energy is equal to the cutoff value. For simplicity, the grid points are assumed to be at the centers of the squares rather than at the intersection points. White squares indicate grid points still with the initial value of zero, scalloped squares indicate grid points that have been evaluated and found to have potential energy lower than the cutoff, and diagonally striped squares indicate grid points that have been either evaluated and found to have potential energy higher than the cutoff or set to the cutoff during an interval evaluation step. The bold arrow in (a) indicates the region of low potential energy that is missed during the first upward scan.

Fig. 3. Illustration of the location and orientation of the three-dimensional grid representing the hydride nucleus transferring from the alkoxide substrate to the NAD$^+$ cofactor for the reaction catalyzed by the enzyme LADH. The grid is centered at the midpoint between the donor and acceptor carbon atoms ($C_D$ and $C_A$, respectively) with the $x$-axis oriented along the $C_D$-$C_A$ internuclear axis.
transferring hydride quantum mechanically, the kinetic and potential energies are represented directly on a three-dimensional grid, and the hydrogen vibrational wavefunctions are calculated with the Fourier grid Hamiltonian multiconfigurational self-consistent-field (FGH-MCSCF) method [10]. All details of these simulations are given in [14]. This Letter focuses on the multidimensional grid potential generation portion of these simulations. The three-dimensional grid representing the transferring hydride is shown in Fig. 3. The grid is centered at the midpoint of the donor and acceptor carbon atoms with the $x$-axis oriented along the C-D-C$_A$ internuclear axis. The grid is cubic with sides of length 4.763 Å.

In order to test the partial multidimensional grid generation method, we compared this method to a full multidimensional grid method for a large number of configurations of the LADH system. We used an EVB mapping potential to obtain a representative set of configurations. The EVB mapping potential is defined as

$$V_{\text{map}} = \lambda V_1 + (1 - \lambda) V_2,$$

where $V_1$ and $V_2$ are the potential energies of the two valence bond states (representing the hydride bonding to its donor and acceptor carbon, respectively). The parameter $\lambda$ is used to drive the potential from reactant to product. We obtained configurations in the reactant, transition state, and product regions using $\lambda = 0.05$, $\lambda = 0.5$, and $\lambda = 0.95$, respectively. In each case, classical molecular dynamics simulations with a time step of 1 fs were performed, and configurations were obtained every 25 time steps (i.e., every 25 fs) for a total simulation time of 20 ps. In this way, we obtained 800 configurations for each of the three regions. Two-dimensional slices of representative potential energy surfaces for reactant, transition state, and product configurations are shown in Fig. 4. Note that the potential energy has a single minimum near the donor carbon or the acceptor carbon for the reactant or product, respectively, while the potential energy has two minima separated by a barrier close to $x = 0$ for the transition state.

Table 1 presents the results for a cubic grid with 32 grid points per side. Three cutoff values (94, 63, and 31 kcal/mol) for the partial multidimensional grid generation were investigated and were compared to the full multidimensional grid generation. (In our calculations, for each configuration these cutoff values are relative to the potential energy with the transferring hydride in the position obtained during the classical molecular dynamics
governed by the mapping potential.) The root-mean-square deviation \((\Delta E)^{1/2}\) and the maximum deviation \(\Delta E_{\text{max}}\) between the partial and full grid methods are given for the ground and excited hydrogen vibrational states. This comparison is shown with both the FGH-MCSCF method [10] (including five states per spatial dimension) and a Davidson iterative diagonalization scheme [17] utilized for calculating the hydrogen vibrational wavefunctions. The results with the Davidson scheme are included to allow a distinction between errors due to the FGH-MCSCF approach and those due to the cutoff in the partial multidimensional grid generation method. For the larger two cutoff values, the error due to the grid cutoff is smaller than the error due to the FGH-MCSCF approach (i.e., the average energy deviations due to the grid cutoff are less than \(10^{-4}\) kcal/mol). For the smaller cutoff value, the error due to the grid cutoff dominates, leading to nearly identical energy deviations for both the FGH-MCSCF and Davidson approaches. The ratio of the number of grid point evaluations of full to partial grid generation methods is given to indicate the average speed-up factor due to the partial multidimensional grid generation (excluding overhead from other functions). Note that a speed-up factor of \(\sim 50\) is obtained while maintaining the accuracy of all energies (calculated from 2400 different configurations) better than 0.03 kcal/mol.

Table 2 presents the analogous quantities for a cubic grid of the same length but with 64 grid points per side. In this case, the full multidimensional grid generation was prohibitively expensive, so the energies calculated with the partial multidimensional grid generation with cutoffs 63 and 31 kcal/mol are compared to those generated with the partial multidimensional grid generation with the higher cutoff 94 kcal/mol. The speed-up is still calculated with respect to a full multidimensional grid generation with 262144 (i.e., \(64^3\)) grid points. The results from the FGH-MCSCF and Davidson approaches behave as in Table 1. In this case, a speed-up factor of \(\sim 80\) is obtained while maintaining the accuracy of all energies better than 0.03 kcal/mol.

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As expected, for all cases both the error and the speed-up increase as the cutoff value is decreased. The appropriate balance between accuracy and speed must be determined for each application. Typically the excited state energies exhibit larger deviations than the ground state energies since excited states involve regions of higher potential energy. In addition, the speed-up is greater for a smaller spacing of the grid points due to a more accurate determination of the cutoff contour line. Although not shown in these tables, we also investigated the overlap of the wavefunction for the full to that for the partial multidimensional grid generation for several representative configurations (with the smaller grid size). For all cases studied, this overlap deviated from unity by less than $10^{-8}$.

4. Concluding remarks

This Letter presented a partial multidimensional grid generation method for the efficient calculation of nuclear wavefunctions. This method substantially decreases the number of potential energy calculations by avoiding this calculation for grid points with high potential energy. The application of this method to the calculation of three-dimensional hydrogen nuclear wavefunctions for hydride transfer in the enzyme LADH was presented. The results indicate that with an appropriate cutoff the partial multidimensional grid generation method is nearly as accurate as (generating ground state energies to within a hundredth of a kcal/mol) and significantly faster than (typically by more than an order of magnitude) the standard full multidimensional grid generation method for this system. A greater increase in speed could be attained by decreasing the cutoff (at the expense of some accuracy). Moreover, this approach could facilitate the reduction of the Hamiltonian matrix, leading to greater computational efficiency in the calculation of the wavefunctions.

This approach is extremely general and is applicable to a wide range of other types of systems. The method is easily extended to cases of uneven grid spacing and higher dimensions and may be used in conjunction with the powerful discrete variable representation (DVR) [1,5]. It may also be applied to the solution of the time-dependent Schrödinger equation [2]. Other possible applications include Car–Parrinello ab initio molecular dynamics calculations with plane-wave basis sets [18,19], the quantum dynamical simulation of scattering processes [1–8], and the simulation of electron and hole wavepackets in semiconductors [20].

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