Local Refinements in Classical Molecular Dynamics Simulations

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Abstract. Quantum mechanics provide a detailed description of the physical and chemical behavior of molecules. However, with increasing size of the system the complexity rises exponentially, which is prohibitive for efficient dynamical simulation. In contrast, classical molecular dynamics procure a coarser description by using less degrees of freedom. Thus, it seems natural to seek for an adequate trade-off between accurateness and computational feasibility in the simulation of molecules. Here, we propose a novel method, which combines classical molecular simulations with quantum mechanics for molecular systems. For this we decompose the state space of the respective molecule into subsets, by employing a meshfree partition of unity. We show, that this partition allows us to localize an empirical force field and to run locally constrained classical trajectories. Within each subset, we compute the energy on the quantum level for a fixed number of spatial states (ab initio points). With these energy values from the ab initio points we have a local scattered data problem, which can be solved by the moving least squares method.

1. Introduction

In the last few decades the simulation of biomolecules by classical molecular dynamics as well as quantum mechanical methods have been developed with great success. However, the huge computational complexity is still a burden. With the objective of coping with this problem, multiscale methods have been developed, combining quantum mechanical simulations with classical molecular simulation in order to reach a convenient trade off between precision and complexity. These multiscale methods are referred to as QM/MM methods, which have their origin in the pioneering work by Warshel and Levitt [1]: The molecule is geometrically decomposed into at least two parts, where the usually smaller part is calculated by quantum methods and the other (larger) domain by classical molecular dynamics or molecular mechanics (cp Fig 1). The corresponding Hamiltonian of this decomposed method is called effective Hamiltonian ($H_{\text{eff}}$) and is the sum of a pure quantum Hamiltonian, a pure classical Hamiltonian and a QM/MM Hamiltonian, whereas the latter is accounting for the interaction between the two scales. Since the pioneering work in 1976, different applications and variants have been developed e.g.[2, 3, 4, 5]. However it is well known, that special care has to be taken for the QM/MM boundary, i.e. the junction of the QM- and the MM-region.

2. Local Quadratic Approximation Algorithm

In order to abandon this boundary problem, we propose a method which abstains from a spatial decomposition of the molecule by considering its conformation space. Instead of decomposing
the geometry of the molecule, we aim at a pointwise evaluation of ab initio energies and a local quadratic approximation, which is, thus, leading to a decomposition of the state space. More precisely, we seek for a decomposition of the potential energy surface \( V(q) \) of a molecule with \( d \) atoms being at position \( q \in \mathbb{R}^d \) into \( n \) local subsets \( V_i \), i.e.

\[
V_i = V - \beta^{-1} \ln(\varphi_i) \quad \text{such that} \quad \sum_{i=1}^{n} e^{-\beta V_i} = e^{-\beta V}
\]  

(1)

where \( \beta = 1/(k_B T) \) is the inverse temperature and \( k_B \) the Boltzmann constant and \( \{ \varphi_i \} \) is a partition of unity \([6, 7]\), i.e. \( \sum_{i=1}^{n} \varphi_i(q) = 1 \) and \( \varphi_i \geq 0 \) \( \forall i \). In order to obtain such a partition a set of nodes \( x_i \) has to be selected such that to each \( x_i \) a radial basis function \( W_i \) can be given, i.e.

\[
W_i(x) = \|x_i - x\|^2, \quad i = 1, ..., n,
\]  

(2)

for which the Euclidean norm of a vector \( v = (v_1, ..., v_s) \) is given by \( \|v\| = \sqrt{v_1^2 + ... + v_s^2} \). We remark that also other choices for the norm are possible.

Since these functions do not form a partition of unity, we follow Shepard’s approach \([8]\):

\[
\varphi_i := \frac{W_i}{\sum_{j=1}^{s} W_j}, \quad i = 1, ..., n.
\]  

(3)

to gain a partition of unity.

Closely related to this decomposition scheme is the question of the approximation quality. For certain regions in the conformation space, a classical MM force field is quite a good approximation, whereas other regions can be found where the classical and the ab initio description differ. As a consequence, a decomposition in the above fashion for coupling QM and MM, should account for this aspect. We therefore suggest a method, which designs a decomposition with regard to the approximation quality. The following algorithm is not restricted to QM/MM coupling strategies, it can also be used as an initial decomposition in the context of meshfree methods in a pure classical context \([9]\).

We assume, that the potential energy surface is twice differentiable. This seems to be a strong requirement, since it excludes poles. However, most sampling schemes, like the Metropolis Hasting Monte Carlo explicitly avoid these regions. More precisely, these regions are not or very rarely visited and can, thus, be excluded. Let \( \varepsilon \in \mathbb{R} \) be a positive number (tolerance), \( n \) the maximum number of sampling points and \( x \) be an initial state. Then in each step of a ”for-loop” from 1 to \( n \), we compute:
Let us now give some comments on the algorithm. At the beginning the energy on the quantum level has to be computed for $n$ states (ab initio points). Starting from one of these points ($x_{\text{old}}$) we generate a new point $x_{\text{new}}$. Let $x_i$ be the closest ab-initio point to $x_{\text{new}}$ with a distance smaller than $\varepsilon$. Then we evaluate the Taylor expansion of $x_i$ at $x_{\text{new}}$ to obtain $f_{\text{new}}$ and apply the Metropolis criterion [10] on the approximated energy $f_{\text{new}}$. If this candidate fails we generate a new starting point outgoing from this failed candidate. If $\{x_j||x_j - x_{\text{new}}|| < \varepsilon, j = 1, \ldots, n\} = \emptyset$, candidate $x_i$ becomes a new ab initio point, that is the energy, gradient and the hessian have to be computed on the quantum level and the number of ab initio points increases ($n = n + 1$). We can interpret this algorithm as a discretization method for a partition of unity.

3. Example
We apply the method to a synthetic energy landscape [11] which is given by the potential energy function for $q = (q_1, q_2)$

$$e(q) = 3 \exp\left(-q_1^2 - \frac{1}{3}q_2^2\right) - 3 \exp\left(-q_1^2 - \frac{5}{3}q_2^2\right) - 5 \exp\left(-(q_1 - 1)^2 - q_2^2\right) - 5 \exp\left(-(q_1 + 1)^2 - q_2^2\right) + 0.2q_1^4 + 0.2(q_2 - \frac{1}{3})^4. \hspace{1cm} (4)$$

From Fig. 2 it can be seen that the two dimensional energy landscape has two basins of equal depth centered at $(-1, 0)$ and $(1, 0)$ and a smaller basin centered at $(0, 5/3)$. This 2-dimensional energy landscape should be considered as the “true” potential, which has be approximated locally by quadratic functions. In the end we checked the quality of our approximation method by testing the symmetry of the sampling: positive and negative $x$-values should be sampled with the same probability due to the symmetry of the potential energy function. See Table 1 for the results. The finer the discretization the better this symmetry is reproduced. We also checked the maximal deviation of the true function value from the approximated ones (again Table 1). A discretization parameter of $\varepsilon = 0.1$ leads to good results. The good results also depend on an adequate number of sampling points. About 40000 sampling points are needed to reproduce symmetry (blue/tiny points Fig. 3). Note, that the ab initio points in Fig 3 are given a priori and are thus not distributed according to the potential. With our method, we could reduce the number of 40000 function evaluations on the “ab initio level” to only about 580 (red/bold points in Figures 3).

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Algorithm 1 Local Quadratic Approximation of the ab-intio Points

**Require**: ab-initio points ($x_1, \ldots, x_n$), energy values ($e_1, \ldots, e_n$), gradients ($g_1, \ldots, g_n$), Hessians ($h_1, \ldots, h_n$), sampling point $x_{\text{old}}, f_{\text{old}}$

$x_{\text{new}} := x_{\text{old}} + r$

find closest ab-initio point $x_i$ to $x_{\text{new}}$

if $\|x_i - x_{\text{new}}\| < \varepsilon$ then

$f_{\text{new}} = e_i + g^T(x_i - x_{\text{new}}) + \frac{1}{2}(x_i - x_{\text{new}})^T h_i(x_i - x_{\text{new}})$

else

add $x_{\text{new}}$ to ab initio points and compute $f_{\text{new}} = e(x_{\text{new}}), g_{\text{new}} = \nabla e(x_{\text{new}}), h_{\text{new}} = H(e(x_{\text{new}}))$

$n = n + 1$

end if

if $\exp(-\beta(f_{\text{new}} - f_{\text{old}})) < \text{rand}$ then

$x_{\text{old}} = x_{\text{new}}$

$f_{\text{old}} = f_{\text{new}}$

end if
ε | % error
---|---
0.1 | 49.82 | 0.1053
0.2 | 47.47 | 0.6381
0.3 | 45.77 | 1.935

Table 1. Different tolerances ε, measure for symmetry and error.

Figure 3. Schematic sketch: Left: Ab initio points \( \{ x_i \} \) being the center of the local approximation spaces \( \{ V_i \} \). Right: Blue: Sampling points according to the local approximation. The potential Fig. 2 could be reproduced.

4. Summary

We have proposed a method which aims at an efficient coupling between the quantum and the classical scale via the ab initio points and a local quadratic approximation. The approach claims that the potential energy surface is twice differentiable. For an artificial potential we could show, that our scheme reduces the number of ab initio points. In the future we plan to apply our scheme to real world applications like the conformational space of a peptide or receptor ligand binding system.

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