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Power Transformations Improve Interpolation of Grids for Molecular Mechanics Interaction Energies

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Abstract

A common strategy for speeding up molecular docking calculations is to precompute nonbonded interaction energies between a receptor molecule and a set of three-dimensional grids. The grids are then interpolated to compute energies for ligand atoms in many different binding poses. Here I evaluate a smoothing strategy of taking a power transformation of grid point energies and inverse transformation of the result from trilinear interpolation. For molecular docking poses from 85 protein-ligand complexes, this smoothing procedure leads to significant accuracy improvements, including an approximately twofold reduction in the root mean square error at a grid spacing of 0.4 Å and retaining the ability to rank docking poses even at a grid spacing of 0.7 Å.

Graphical abstract

A simple smoothing procedure based on power transformation is shown to improve the interpolation of nonbonded molecular mechanics interaction energies for a set of molecular docking poses.

Keywords

Molecular Mechanics; Nonbonded Interactions; Grid Interpolation; Power Transform; Molecular Docking

INTRODUCTION

A simple power transformation procedure was tested and found to be successful in improving accuracy of interpolating molecular mechanics interaction energy grids - which are useful for molecular docking and other applications with a large rigid region.

A considerable fraction of compute operations in molecular mechanics energy calculations are spent on van der Waals (vdW) and electrostatic interactions between nonbonded pairs of atoms. For larger systems, the computational expense of nonbonded interactions is even more pronounced; while the number of bonded interactions grows roughly linearly with the number of atoms in a system, N , the number of pairwise interactions increases as N^2 . One strategy to address this issue is to cut off the potential energy at a specified distance and only consider pairs within a neighbor list. When a large fraction of the system is treated as rigid, an even more efficient strategy is based on precomputing nonbonded interaction energies between the rigid region and points on three-dimensional grids. Subsequently, interaction energies between the rigid region and a flexible region can be estimated by interpolating the grids instead of evaluating force field terms for every atom pair. The strategy is highly scalable with receptor size because after the initial grid calculation, compute time no longer depends on the size of the rigid region.

Grids are suitable for representing force field terms in which the interaction energy between atom i and the rigid region has the general form [1, 2],

$$\Psi_{gen,i} = \gamma_i \sum_{j \in R} \gamma_j V(r_{ij}), \quad (1)$$

where the sum is over the rigid region and $V(r_{ij})$ is a function of the distance r_{ij} between atoms i and j . For example, the electrostatic energy may be expressed as,

$$\Psi_{ELE,i} = q_i \sum_{j \in R} q_j \frac{1}{r_{ij}}, \quad (2)$$

where q_i and q_j are atomic partial charges; thus, $\gamma_i = q_i$, $\gamma_j = q_j$ and $V(r_{ij}) = 1/r_{ij}$. As described in the methods section, the vdW interaction energy may also be represented in the form of Equation 1 by specifying the Lennard-Jones (LJ) potential based on using the geometric (opposed to the arithmetic) mean to combine the well depth of two atoms. Values on the grid are based on the sum in Equation 1,

$$G_R(\mathbf{x}) = \sum_{j \in R} \gamma_j V(\|\mathbf{r}_j - \mathbf{x}\|), \quad (3)$$

where $\mathbf{x}$ is the position vector of a grid point. The interaction energy between atom i and the rigid region is obtained by interpolating the grid to estimate $\sum_{j \in R} \gamma_j V(\|\mathbf{r}_j - \mathbf{x}_i\|)$ at the atom position $\mathbf{x}_i$ and then multiplying by γ_i .

Precomputed nonbonded interaction energy grids are primarily but not exclusively used for molecular docking. Scoring functions for docking programs usually include vdW and electrostatic interaction energies [3, 4]. (They may employ empirical weighting factors and include other terms such as desolvation and hydrogen bonding). In the context of grid-based vdW and electrostatic interaction energy calculations, the rigid region is the receptor and flexible region the ligand [1, 2, 5–7]. In protein [8–10] and fragment [11, 12] docking, it is also popular to discretize the ligand onto a corresponding set of grids and compute interaction energies at many translational positions using a fast Fourier transform. A related approach has also been used to estimate the excess chemical potential of a protein in a crowded solution [13, 14]. Because these Fourier approaches do not involve a grid interpolation, however, the interpolation results presented here are not relevant to them. Another application of a grid-based potential has been in steered molecular dynamics simulations where a molecule is driven through a nanopore [15]. Finally, my research group uses grids in our main program to estimate the binding potential of mean force (BPMF), the binding free energy between a *flexible* ligand and *rigid* receptor [16]. After I proved that BPMFs can be used to *rigorously* estimate noncovalent association free energies between *flexible* binding partners [17], we have demonstrated the approach on host-guest [17] and protein-ligand systems [18].

There are numerous ways to interpolate a three-dimensional grid. The simplest approach is to use the energy of the nearest grid point [1, 2]. More accurate results are available with trilinear interpolation [19] and B-splines [20]. Because vdW potentials are highly nonlinear, however, straightforward trilinear interpolation of vdW grids provides energies that poorly match directly calculated energies [20]. To address this problem, Venkatachalam et al. [6] proposed a smoothing algorithm based on a transformation, trilinear interpolation, and inverse transformation procedure: If $f(\mathbf{x}_c)$ is the vdW attractive or repulsive energy at $\mathbf{x}_c$, a position vector on a grid corner, then $g(\mathbf{x}_c) = f(\mathbf{x}_c)^{1/m}$ is evaluated for all grid corners. To estimate $f(\mathbf{x}_i)$ at a desired atom position $\mathbf{x}_i$, $g(\mathbf{x}_i)$ is obtained by trilinear interpolation of $g(\mathbf{x}_c)$ for the eight $\mathbf{x}_c$ surrounding $\mathbf{x}_i$ and $f(\mathbf{x}_i) = g(\mathbf{x}_i)^m$. They found that using $m = -2$ for both attractive and repulsion led to a significant reduction in interpolation error.

As I was developing methods for protein-ligand BPMF estimation [16, 18], I decided to investigate the influence of power transformations on the accuracy of molecular mechanics nonbonded energies more carefully. Venkatachalam et al. [6] apparently restricted their search space to negative integers (in the present notation) and to using the same transformation power for both attraction and repulsion. Here, aside from looking at a different dataset and applying different accuracy metrics, I also consider positive integers for

m and the use of a different transformation power for each vdW term. While it is possible for m to be any real number, I considered only integers because their power transformations are less computationally expensive. Using a different power for attraction and repulsion could also lead to improved accuracy or computational savings, as different powers vary in computational expense.

As an illustration of the possible benefits of this smoothing procedure, consider a linear interpolation of a LJ repulsive potential (Figure 1). While a standard linear interpolation ($m = 1$) clearly deviates from the r_{ij}^{-12} curve, the interpolated curve based on $m = 4$ is much closer.

METHODOLOGY

Molecular Docking

Molecular docking calculations were performed on the Astex diverse set, a subset of the Protein Data Bank carefully curated for quality and diversity [21]. Each of 85 complexes in the set was prepared using AmberTools 16 [22]. Proteins and ions (from protein.mol2) were parameterized using the AMBER ff14SB force field. Zinc parameters were also used for iron, mercury, and magnesium. Non-standard amino acid residues were converted to their standard counterparts. Using the python wrapper to the OpenEye OEChem Toolkit, all crystallographic ligands were parameterized with the Generalized Amber Force Field 2 [23] and AM1BCC charges [24, 25]. Every atom not part of the main ligand in ligand.mol was considered to be part of the receptor. Noncrystallographic atoms in each receptor were minimized for 2500 steps in gas and 2500 steps in GBSA solvent using NAMD 2.9 [26].

Docked poses were obtained using the anchor and grow algorithm in UCSF DOCK 6 [27] to redock ligands into their respective proteins. First, sphgen was run with default parameters: dotlim = 0.0, radmax = 4.0 Å, and radmin = 1.4 Å. DOCK was run with 20000 maximum orientations, using internal energy with an exponent of 12, a flexible ligand, an a minimum anchor size of 40. Pruning was performed with clustering, 1000 maximum orientations, a clustering cutoff of 1000, and conformer score cutoff of 25.0. A bump filter was used with max_bumps_anchor = 12 and max_bumps_growth = 12. Final conformations were clustered with a root mean square deviation threshold of 1.0 Å.

Nonbonded Interaction Energies

As a reference, the interaction energy between each receptor and every atom in the binding poses of corresponding ligands were directly evaluated with a custom python script. The set of binding poses included the crystallographic pose and all the predicted docking poses in which every atom was contained in the grids (see below). vdW interactions were based on the LJ potential energy between atoms i and j , $V_{LJr,i,j} = V_{LJr,i,j} + V_{LJa,i,j}$ where,

$$V_{LJr,i,j} = \epsilon_{i,j} \left(\frac{R_{min,i,j}}{r_{i,j}} \right)^{12} \quad (4)$$

$$V_{LJa,i,j} = -2\varepsilon_{i,j} \left(\frac{R_{min,i,j}}{r_{i,j}} \right)^6 \quad (5)$$

The vdW radii $R_{min,i,j}$ were calculated by two methods: the arithmetic and geometric mean. The former, $R_{min,i,j} = (R_{min,i} + R_{min,j})/2$, is the canonical approach in the AMBER force field. The latter, $R_{min,i,j} = \sqrt{R_{min,i} R_{min,j}}$, is compatible with Equation 1. In both cases, the LJ well depths were based on the geometric mean, $\varepsilon_{i,j} = \sqrt{\varepsilon_i \varepsilon_j}$. Electrostatic interactions were evaluated using Equation 2.

To clarify how using the geometric mean for $R_{min,i,j}$ makes the LJ terms compatible with Equation 1, it is helpful to express the terms as,

$$\Psi_{LJr,i} = \varepsilon_{i,i}^{\frac{1}{2}} \sigma_{i,i}^6 \sum_{j \in R} \frac{\varepsilon_{j,j}^{\frac{1}{2}} \sigma_{j,j}^6}{r_{i,j}^{12}}, \quad (6)$$

for the repulsive component and,

$$\Psi_{LJa,i} = -2\varepsilon_{i,i}^{\frac{1}{2}} \sigma_{i,i}^3 \sum_{j \in R} \frac{\varepsilon_{j,j}^{\frac{1}{2}} \sigma_{j,j}^3}{r_{i,j}^6}. \quad (7)$$

for the attractive component.

For every receptor, LJ and electrostatic interaction energy grids were calculated with grid spacings of 0.2, 0.25, 0.3, 0.35, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.0 Å. Grids spanned at least $10 + 1.5 d_{max}$ Å in each dimension surrounding the ligand center of mass in the crystallographic binding mode, where d_{max} is the maximum distance from any ligand atom to its center of mass. A slice of a representative grid is shown in Figure 2.

Interpolation-based interaction energy terms were evaluated based on the power transformation procedure pioneered by Venkatachalam et al. [6]. LJ grids were transformed with powers of

$$m \in \{-12, -11, \dots, -1, 1, 2, \dots, 12\}.$$

The electrostatic grid was not transformed because it contains both positive and negative numbers, and the transformation procedure loses memory of the original sign.

RESULTS AND DISCUSSION

The LJ energy based on the geometric mean accurately reproduces the energy based on the arithmetic mean

For the vast majority of ligand atom positions, the LJ energy based on the geometric mean and the arithmetic mean for the vdW radii are nearly identical. Because Figures 3 (a) to (c) give equal weight to points on and off the diagonal, they somewhat exaggerate the extent of distinction between the directly evaluated interaction energies. Figure 3 (d) clarifies that the distribution of absolute differences are dominated by small differences. The modes of the histograms are at $\exp(-3.94) = 0.0195$, $\exp(-3.53) = 0.0291$, and $\exp(-4.34) = 0.0130$ kcal/mol for the repulsive, attractive, and total energies respectively. In rare cases, the geometric mean underestimates the repulsive energy and overestimates the attractive energy compared to the arithmetic mean. In these cases, because the magnitude of the repulsive energy is greater, the overall energy is underestimated. The rarity of these cases verify that using the geometric mean for vdW radii in the LJ potential is a reasonable approximation for the canonical form of the potential.

The power transform enables accurate estimates of LJ energies at larger grid spacings

Direct and interpolated energies were then compared for atoms in which the total LJ energy is less than 25 kcal/mol, which do not have a large steric clash with the receptor. Energies were compared by the root mean square error (RMSE). For two series of data points $\{x_1, x_2, \dots, x_N\}$ and $\{y_1, y_2, \dots, y_N\}$, the RMSE is,

$$\varepsilon = \sqrt{\frac{1}{N} \sum_{n=1}^N [x_n - y_n]^2}. \quad (8)$$

With standard trilinear interpolation ($m = 1$), the RMSE between direct (based on the arithmetic mean) and interpolated LJ energies for all atoms in the docking poses increases rapidly with grid spacing (Figure 4). For trilinear interpolation with a power transform, the RMSE also increases with grid spacing, but at a much slower rate.

For all grid spacings, the RMSE significantly decreases as $|m|$ increases, leveling off by around $|m| = 4$. At a grid spacing of 0.40 Å, the RMSE of the repulsive energy with $m = 4$ is approximately half the RMSE with $m = 1$. At a grid spacing of 0.5 Å, the RMSE of the repulsive energy with $m = 4$ is 0.56 kcal/mol, within “chemical accuracy” of 1 kcal/mol, but at 1.86 kcal/mol, the RMSE with $m = 1$ is significantly larger than chemical accuracy. The improvement is even more dramatic with larger grid spacings, with RMSE reductions being slightly more significant for negative m than for positive values of m .

Compared to the repulsive interaction energy, the magnitude of the RMSE (note that the bottom panel of Figure 4 is multiplied by 100) and the benefits of grid interpolation are significantly reduced for the attractive energy. Because the LJ attractive term is much smoother, decaying slowly as a function of distance compared to the repulsive term, linear

interpolation is a better approximation. Thus, the smoothing effect of the power transformation is less beneficial.

The described qualitative trends hold for the RMSE between interpolated and LJ interaction energies based on a geometric mean (Figure 7).

Electrostatic energy errors are relatively insensitive to grid spacing

The magnitude of the RMSE for the electrostatic energy is much smaller than for the LJ repulsive energy and comparable to the LJ attractive energy (Figure 5). As with the LJ terms, the error in the electrostatic term monotonically increases with grid spacing, but more slowly than for the LJ attractive energy. The slow increase in RMSE makes sense because the Coulomb potential decays even more slowly than the LJ attractive energy, as a function of r_{ij}^{-1} instead of r_{ij}^{-6} .

Interpolation accuracy influences the interaction energy of reasonable binding poses

I then looked into how much interpolation accuracy affects the energy of not only individual atoms, but binding poses. In the subsequent analysis, I only considered binding poses that were fully contained within their respective grids and for which the total LJ energy is negative (excluding poses with a significant steric clash). The binding pose energy was based on the sum of the LJ and electrostatic energies. I chose to compare $m = 1$ versus $m = 4$ for the LJ repulsive energy, and to use to standard trilinear interpolation for the electrostatic and LJ attractive energy because these choices provide a good balance between accuracy and computational expense. Performing the back transformation (which is the operation repeated for every ligand atom) for $m = 4$ is computationally simple because it is simply the square of the square. Furthermore, $m > 4$ does not lead to much better accuracy (Figure 4). Because the error is substantially smaller for electrostatic and LJ attractive energies and is not significantly reduced by the power transformation, the standard linear transformation was used for this term.

The RMSE between direct and interpolated binding pose energies increases more slowly with $m = 4$ than $m = 1$ (top panel of Figure 6). Without the power transformation, the RMSE exceeds 2 kcal/mol at a grid spacing of 0.35 Å. On the other hand, with $m = 4$, the RMSE only exceeds 2 kcal/mol near a grid spacing of 0.6 Å.

Grid accuracy influences the ranking of binding poses

Finally, I looked into whether improving interpolation accuracy has practical benefits to the ranking of binding poses. The quality of binding pose prediction was assessed by the average (1) ranking of the lowest-scoring native pose and (2) energy gap between the lowest-scoring native and non-native poses. A binding pose was considered native if its heavy-atom root mean square deviation with the crystallographic pose was less than 2 Å. The rank is the number of non-native poses with lower scores than the native pose; for an ideal pose scoring function, the rank is zero. For both ranking and energy gap calculations, I only considered complexes in which the energy gap is less than 25 kcal/mol. Large energy gaps are likely indicative of more serious force field or model deficiencies, such as missing water molecules.

By both metrics, as the grid spacing goes up, the quality of binding pose ranking deteriorates (Figure 6). At a grid spacing of 0.2 Å, the interpolated and direct energies have comparable quality. With larger grid spacings, distinctions between the pose ranking metrics for $m = 1$ and $m = 4$ are immediately apparent. For $m = 1$, the ranking metrics become qualitatively worse beyond 0.5 Å but for $m = 4$ this breaking point does not occur until beyond 0.7 Å.

CONCLUSIONS

A simple power transformation, originally proposed by Venkatachalam et al. [6], is found to make trilinear interpolation of nonbonded molecular mechanics energies significantly more accurate. The transformation is more beneficial and necessary for LJ repulsive energies than LJ attractive energies. The inverse transformation power $m = 4$ provides a good balance between accuracy and computational expense. (This inverse power was used in my group's recent BPMF-based protein-ligand binding free energy calculations [18].) The power transformation reduces the rate at which molecular docking scores deteriorate with increased grid spacing.

The algorithm is computationally inexpensive and simple to implement. Its key benefit is to allow larger grid spacings, which reduces computer memory usage and grid computation times. Reduced memory usage can be especially useful when a large grid is required, such as when docking to the entire surface of a receptor. Even if a large grid is not required, a smaller memory profile can allow more jobs to be run in parallel or reduce the load on computing clusters and other computing platforms. Reduced grid computation times can be important when many calculations are required, e.g. when computing an ensemble average over many receptor structures in BPMF-based protein-ligand binding free energy calculations.

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Figure 1.

LJ repulsive energy as a function of distance between two gaff ca atoms. The energy is evaluated every 0.005 Å (Reference, solid line), linearly interpolated with a grid spacing of 0.25 and $m=1$ (Linear, dashed line) or $m=4$ (Transformed, dotted dashed line). Data points being interpolated are shown with squares.

Figure 2. Slice of the LJ repulsive grid for PDB ID 1ke5. The grid spacing is 0.2 Å. Receptor heavy atoms are shown as sticks and the ligand is shown with vdW radii.

Figure 3. Comparison of LJ repulsive (a), attractive (b), and total (c) energies using radii based on the arithmetic mean (x-axis) and geometric mean (y-axis) for all atoms from docking poses to the Astex Diverse Set (1973498 total positions). (d) Histogram of the absolute differences between LJ energies for repulsive (right arrows), attractive (left arrows), and total (squares) interactions.

Figure 4. RMSEs (kcal/mol) between the direct and interpolated LJ repulsive (top) and attractive (bottom) energies as a function of grid spacing (x-axis) and inverse transformation power (y-axis) for atoms from docking poses to the Astex Diverse Set in which the total LJ energy is less than 25 kcal/mol (1971671 total positions). RMSE annotations for attractive interactions are multiplied by 100. LJ radii for the direct calculations are based on the arithmetic mean of the two atoms. For a similar figure comparing interpolated to direct calculations based on the geometric mean, see Figure 7.

Figure 5. RMSEs (kcal/mol) between the direct and interpolated electrostatic energies as a function of grid spacing (x-axis) for atoms from docking poses to the Astex Diverse Set in which the total LJ energy is less than 25 kcal/mol (1971671 total positions).

Figure 6.

RMSE between direct and grid-interpolated binding pose energies (top), average energy gap (middle), and average native pose rank (bottom) as a function of grid spacing, with $m = 1$ (diamonds) and $m = 4$ (circles) as the inverse transformation power for interpolation of LJ repulsive energies. Statistics are reported based on 30928 binding poses that are fully contained within their respective grids and for which the total LJ energy is negative. In the top panel, the dashed line at 2.0 kcal/mol is drawn for reference. In the middle and bottom panels, the dashed line is the value for direct energy evaluation.

Figure 7. RMSEs (kcal/mol) between the direct and interpolated LJ repulsive (top) and attractive (bottom) energies as a function of grid spacing (x-axis) and inverse transformation power (y-axis) for atoms from docking poses to the Astex Diverse Set in which the total LJ energy is less than 25 kcal/mol (1971671 total positions). RMSE annotations for attractive interactions are multiplied by 100. LJ radii for the direct calculations are based on the geometric mean of the two atoms. For a similar figure comparing interpolated to direct calculations based on the arithmetic mean, see Figure 4.