CUSA and CUDE: GPU-Accelerated Methods for Estimating Solvent Accessible Surface Area and Desolvation

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ABSTRACT

It is well-established that a linear correlation exists between accessible surface areas and experimentally measured solvation energies. Combining this knowledge with an analytic formula for calculation of solvent accessible surfaces, we derive a simple model of desolvation energy as a differentiable function of atomic positions. Additionally, we find that this algorithm is particularly well suited for hardware acceleration on graphics processing units (GPUs), outperforming the CPU by up to two orders of magnitude. We explore the scaling of this desolvation algorithm and provide implementation details applicable to general pairwise algorithms.

Key words: desolvation, GPU computing, NVIDIA CUDA, protein docking, solvent accessible surface area (SASA).

1. INTRODUCTION

THE PREDICTION OF THE BOUND CONFIGURATION OF TWO PROTEINS is an important problem in computational biology. One approach involves defining and globally minimizing a function that describes the various energetic interactions between intermolecular pairs of atoms (Totrov et al., 1997; Rarey et al., 1996; Caflisch et al., 1992; Given et al., 1998; Goodsell et al., 1990; Hart et al., 1992; Mitchell et al., 1999; Marcia et al., 2005; Klepeis et al., 1998; Gray et al., 2003). One way to account for the hydrophobic effect in such a function is to exploit the strong linear relationship between accessible surface area and the desolvation energy of binding. Energetic methods attempt to define and optimize functions for which the native solution produces the global minimum energy. In addition to terms describing electrostatic and van der Waals interactions, the inclusion of a desolvation term can significantly improve predictions (Camacho et al., 1999; Horton et al., 1992; Eisenberg et al., 1989; Cummings et al., 1995; Eisenberg et al., 1986; Juffer et al., 1995).

Most global optimization algorithms require many evaluations of the associated energy function. Thus, it is crucial that the function evaluation be as efficient as possible. Graphics processing units, referred to as GPUs, are emerging as high-performance parallel coprocessors able to greatly speed certain types of calculations. This paper describes our efforts at developing CUSA and CUDE, codes that compute solvent

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accessible surface area and desolvation using the CUDA programming language (NVIDIA, 2007), which will be described in Section 2.2.2.

1.1. Solvent accessible surface area

Many different approaches have been applied to the approximation of the accessible surface area of Lee and Richards, which in concept rolls a sphere of average solvent radius over the surface of a macromolecule. The solvent probe's boundary traces out the molecular surface, while its center traces out the solvent accessible surface (Lee et al., 1971).

The solvent accessible surface area (SASA) method of Hasel et al. that we implement is one of a class of pairwise, twice differentiable approximate algorithms for computing SASA developed by the group of W. Clark Still (Weiser et al., 1999a,b,c). A later method in this class—the method of linear combinations of pairwise overlaps (LCPO) of Weiser et al. (1999a)—utilizes more parameters than the algorithm we implement, and to improve runtime performance, it uses a pre-computed list of atomic overlap information. These neighbor lists are compiled through the application of an atomic model based on Gaussian distributions (Weiser et al., 1999b).

Exact methods for the rapid calculation of SASA are also widely available. The first differential geometry-based analytic model published by Connolly (1983) has been made more efficient (Fraczkiewicz et al., 1998; Sanner et al., 1996). As a benchmark for our own SASA calculations we have used NACCESS, a near-exact method for computing SASA that slices the macromolecule to obtain 2D exterior boundaries, adds the solvent probe radius to the boundaries of each slice, and interpolates the surface between slices to compute SASA (Hubbard et al., 1993).

Because our goal is to devise a surface area calculation that is ideal for GPU computing, we avoid models having a large number of parameters or which implement inhomogeneous calculations. By applying a pairwise model with a minimal set of atom parameters, we achieve up to two orders of magnitude speedup. Moreover, the model is twice differentiable, making it well-suited for use in optimization schemes. These requirements led us to choose the SASA model of Hasel et al. (1988), which is described in Section 1.1.2.

1.1.1. Buried surface area. The buried surface area (BSA) of a complex between two bound proteins is the total surface area of both proteins that is removed from solvent upon binding. If the proteins have individual surface areas A_1 and A_2 , and if the area of the complex itself exposed to solvent is A_C , then

$$A_1 + A_2 = A_C + \text{BSA} \quad (1)$$

Rearranging this relationship gives a convenient formula for buried surface area:

$$\text{BSA} = A_1 + A_2 - A_C. \quad (2)$$

Rewriting the formula for BSA in terms of per atom changes in solvent accessibility, we see that

$$\text{BSA} = \sum_{i=1}^{N_1} (-\Delta A_i) + \sum_{j=1}^{N_2} (-\Delta A_j) \quad (3)$$

The negative signs arise due to the fact that BSA is a positive quantity, while $\Delta A_i < 0$ for atoms in the interface.

In this study we use buried surface area to fit the parameters of the SASA algorithm of Hasel et al. (1988). We use the computed areas along with the Eisenberg-McLachlan atomic solvation parameter set (Eisenberg et al., 1986) to compute binding desolvation energy.

1.1.2. Pairwise accessibility calculation. A key element of our desolvation energy algorithm is the geometrically intuitive method of Hasel et al., for approximating the accessible surface area of Lee and Richards (Hasel et al., 1988; Lee et al., 1971). They showed that a good approximation to the SASA of atom i in a protein of N atoms is

$$A_i = S_i \left(\prod_j^N f_{ij} \right) \quad (4)$$

where

$$f_{ij} = 1 - \frac{p_i p_{ij} b_{ij}}{S_i} \quad (5)$$

$$S_i = 4\pi (r_i + r_s)^2 \quad (6)$$

$$b_{ij} = \pi (r_i + r_s)(r_i + r_j + 2r_s - d_{ij}) \left(1 + \frac{r_j - r_i}{d_{ij}} \right) \quad (7)$$

Intuitively, S_i is the SASA of atom i in the absence of overlaps, and b_{ij} is the factor for reduction in surface area due to atom j overlapping with atom i . However, the SASA reduction from multiple overlaps is not additive, so p_i is an atom-wise parameter used to reduce the magnitude of b_{ij} across multiple overlaps. Finally, $p_{ij} < 1$ is a parameter dependent on whether or not atoms i and j are covalently bound. In the auxiliary formulas, r_i is the radius of atom i , r_s is the radius of the solvent probe whose center traces out the accessible surface (typically $r_s = 1.4 \text{ \AA}$ is used), and d_{ij} is the distance between atoms i and j .

Equation (4) allows us to compute the change in SASA during binding of proteins P_1 and P_2 as

$$\Delta A_i = S_i \left(\prod_{j=1}^{N_1} f_{ij} \right) \left(\prod_{k=1}^{N_2} f_{ik} \right) - A_{i, \text{initial}} \quad (8)$$

where

$$A_{i, \text{initial}} = S_i \left(\prod_{j=1}^N f_{ij} \right) \quad (9)$$

for $N = N_1$ or $N = N_2$, depending on whether atom i belongs to P_1 or P_2 respectively.

Note that to allow for flexible docking, formula (8) cannot be easily simplified. In this equation, the products of f_{ij} and f_{ik} terms represent the atomic overlap after binding, while the product of f_{ij} 's included in the $A_{i, \text{initial}}$ term represents overlap before binding. Conformational changes during binding imply that these terms will generally not be equal.

1.2. Desolvation energy

The linear relationship demonstrated by Eisenberg and McLachlan (1986) between the accessible surface area of Lee and Richards (1971) and experimentally determined solvation energy of transfer provides a way to approximate hydrophobic effects. More recent work (Wagoner et al., 2006) shows that introducing solvent accessible volume information improves model accuracy at the cost of more complex computations.

Eisenberg and McLachlan showed that, for a solvated protein consisting of N atoms, the energy of solvation can be estimated as:

$$\Delta G_{\text{solv}} = \sum_{i=1}^N \gamma_i A_i, \quad (10)$$

The γ_i are constant values that depend on atom type. These atomic solvation parameters, or ASPs, are frequently written as $\Delta \sigma_i$, as they represent the Gibbs free energy ΔG associated with the solvation of individual atoms.

In this work, we use formula (10) to characterize the energetic contribution of the hydrophobic effect in protein binding:

$$\Delta G_{\text{bind, solv}} = \sum_{i=1}^{N_C} \gamma_i \Delta A_i. \quad (11)$$

Here, $\Delta G_{\text{bind, solv}}$ describes the energetic effect of desolvating the atoms at the active sites of the proteins during binding, and ΔA_i can be computed from formula (8). This sum is taken over all atoms in the protein-protein complex of N_C total atoms—that is, if the individual proteins are comprised of N_1 and N_2 atoms, then

$$\begin{aligned}\Delta G_{\text{bind,solv}} &= \sum_{i=1}^{N_c} \gamma_i \Delta A_i \\ &= \sum_{i=1}^{N_1} \gamma_i \Delta A_i + \sum_{j=1}^{N_2} \gamma_j \Delta A_j.\end{aligned}\quad (12)$$

Note that the change ΔA_i in area for atom i may be affected by conformational changes in addition to binding events.

1.2.1. Atomic solvation parameters. Many sets of ASP values γ_i have been published. Juffer et al. (1995) provide an overview and comparison of several such sets. This study found poor and often contradictory performance among various ASP sets. They suggest that the Eisenberg ASPs (Eisenberg et al., 1986) are most consistent in systems with strong hydrophobic interactions which led to their use in our study.

In 1995, Cummings et al. (1995) presented a comprehensive study of ASPs derived for use in protein docking simulation. The study took three widely used SASA sets—those reported in Eisenberg et al. (1989); Wesson and Eisenberg (1992); and Lesser and Rose (1990)—and regressed them on three sets of transfer energy data: those of Fauchere and Pliska (1983); Radzicka and Wolfenden (1988); and Wolfenden et al. (1993). Of these pairings, they found that the ASP set that best discriminated between correct and incorrect protein docking results as a complement to their own energy function—comprised of an electrostatic and Lennard-Jones potential—was that derived from the regression of the SASA set of Lesser and Rose on the transfer energy set of Fauchere and Pliska (Cummings et al., 1995).

A more recent study by Zhou and Zhou (2002a,b) takes an entirely different approach to deriving ASPs. They derive a mutation experiment-based amino acid residue stability scale to determine the degree to which various residues are hydrophobic, and show that the experimentally determined free transfer energy of the most hydrophobic portion of this scale has excellent correlation with octanol-to-water transfer free energy. ASPs for the atoms in these hydrophobic residues are taken from the correlation (Zhou and Zhou, 2002a,b).

1.3. Computation on GPUs

Researchers have exploited graphics hardware for general purpose scientific computation since the 1970s (Owens et al., 2007). Within the past half decade, commodity desktop graphics processing units (GPUs) have become progressively more capable, most importantly in terms of programmability and key hardware features necessary for general purpose GPU, or GPGPU, computation (Owens et al., 2008).

Initially, programmable GPUs had to be accessed through a graphics programming library such as OpenGL or DirectX. Use of these complex libraries required a substantial graphics programming background. Particularly laborious was the reinterpretation of a nongraphics problem in the language of 3D visualization, and a significant amount of work was invested into understanding how fundamental scientific computing algorithms, such as general matrix/vector arithmetic, map to the GPU (Krüger and Westermann, 2005). These early results were promising, but they also required significant technical skill and impressive knowledge of graphics programming. For instance, Krüger and Westermann (2005) discusses the performance benefits of mapping a vector to a 2D texture, and Yang et al. (2007) describe the efficiency improvements of using OpenGL frame buffer objects.

For our work, the most significant advancement in GPU computing is the recent proliferation of software tools (and accompanying hardware support) targeted at easing GPGPU programming (NVIDIA, 2007; ATI, 2007; Buck et al., 2004). These tools greatly simplify scientific computing on GPUs, all but eliminating the type of requisite graphics programming knowledge described in the above referenced literature. However, as we discuss in Section 3.3, GPUs are not always the answer—care is required to design GPU algorithms for optimal scaling and speedup.

Several recent articles describe the evolution and technical implications of modern GPU computing in greater detail (Owens et al., 2007, 2008; Stone et al., 2007).

2. METHODS

We develop a pairwise parametric atomic algorithm for computing desolvation energy based on the algorithm for accessible surface area of Hasel et al. (1988) and the energy of solvation of Eisenberg and

McLachlan (1986). To address the computational complexity of the accessibility calculation, we use the CUDA language for NVIDIA graphics processing units (GPUs) to greatly speed up batched desolvation calculations. The resulting CUDA algorithms for solvent accessible surface area (CUSA) and desolvation (CUDE) are well-suited for applications in computational structural biology.

2.1. CUSA and CUDE models

The solvation energy model proposed by Eisenberg and McLachlan (1986) provides atomic solvation parameters for five groups of atoms: $\gamma_C = 30.5$, $\gamma_S = 21.0$, $\gamma_{NO} = -0.9$, $\gamma_{N+} = -38.5$, and $\gamma_{O-} = -15.0$, all in units of $\text{cal } \text{\AA}^{-2} \text{ mol}^{-1}$. These values were computed from a linear least-squares fit of equation (10) against experimentally determined transfer free energies taken from Fauchere and Pliska (1983) and Eisenberg and McLachlan (1986). The SASAs used in this regression were computed by Shrake and Rupley (1973) using the atomic radii of Pauling (1960). To remain consistent with these varied initial studies, we use a united atom model with radii taken from Pauling (1960).

The desolvation model outlined above can be implemented as a simple algorithm that first computes solvent accessibility and then desolvation energy. The accessibility computation must iterate over each pair of atoms in the complex, combining p_i parameters with separation information to obtain the per atom accessible surface areas. This per-atom accessibility information is then scaled by the relevant ASP values and summed to complete the desolvation calculation.

Using accessible surface area to calculate the solvation energy in this fashion is computationally expensive. This cost is further compounded in a minimization setting, where many function evaluations may be required to achieve convergence to a local or global minimum. The most expensive portion of the outlined algorithm is the accessibility calculation, which requires a pairwise comparison of all atoms in a complex and scales as $O((N_1 + N_2)^2)$. Furthermore, since SASA is a function of atomic positions, a minimization application must ensure all accessibilities are properly updated at each iteration. Reducing the runtime cost of the desolvation calculation will allow a minimization algorithm to more rapidly predict near-native structures.

2.1.1. Solvent accessible surface model. The method of Hasel et al. described in Section 1.1.2 provides p_i parameters and atomic radii for a united atom model that includes polar hydrogens. Atoms are grouped into 23 types according to hybridization and binding partners. In order to align the SASA algorithm with the united atom model dictated by the ASPs of Eisenberg and McLachlan (1986), we reduce the number of atom types to 12, excluding parameter values for polar hydrogens, carbon atoms with hybridization types not commonly found in proteins, and the elements F, Cl, Br, and I, which do not occur in the systems we study. We perform a new fit of the p_i values to minimize the square error over a benchmark set of M known receptor/ligand complexes. The optimization of the parameters is described succinctly as:

$$p_i^* = \underset{p_i}{\operatorname{argmin}} \sum_{j=1}^M \left(\text{BSA}_j^{\text{NACC}} - \text{BSA}_j^{\text{CUSA}}(p_i) \right)^2 \quad (13)$$

For this new regression, we use the Mintseris et al. (2005) protein docking benchmark. Benchmark files in PDB format (Berman et al., 2000) were obtained from the Weng group's website. 1ML0 was excluded from the benchmark because the available complex PDB file did not include all the chains present in the Mintseris et al. (2005) PDB files.

For each known complex in the training set, we used NACCESS (Hubbard et al., 1993) to estimate the buried surface area $\text{BSA}_j^{\text{NACC}}$ from equation (2). We then iterated each of the 12 p_i 's individually over the range $0 < p_i < 5$ and computed $\text{BSA}_j^{\text{CUSA}}(p_i)$ at each step using equations (3) and (8). The search interval is based on the original p_i values derived by Hasel et al., In our search, we first used a coarse-grain step size of 0.1 and then performed a second refined search using step sizes of 0.001 in the $[x - 0.1, x + 0.1]$ interval around the coarse-grain minimum x . The resulting values are the new p_i^* parameters (Table 1) that approximately minimize equation (13).

Additionally, the p_{ij} factor that appears in formula (5) is based on whether atoms i and j are covalently bound (Hasel et al., 1988). Hasel et al. (1988) set this value to $p_{ij} = 0.8875$ if atoms i and j are covalently bound, and $p_{ij} = 0.3516$ otherwise. To simplify our calculations, we set $p_{ij} = 0.8875$ if atoms i and j are within $1.8\text{\AA}$ and $p_{ij} = 0.3516$ otherwise.

TABLE 1. RE-OPTIMIZED p_i^* PARAMETERS AND RADII USED FOR SASA COMPUTATION ACCORDING TO (HASEL ET AL., 1988)

Atom type	p_i^*	r_i
CH(sp ³)	0.416	2.0
O(sp ²)	0.507	1.4
CH ₂ (sp ³)	0.472	2.0
O ⁻	0.577	1.4
CH ₃ (sp ³)	0.544	2.0
N(sp ³)	0.620	1.5
C(sp ²)	0.356	1.5
N(sp ²)	0.411	1.5
CH(sp ²)	0.458	1.85
NH, =N-(sp ²)	0.411	1.5
O(sp ³)	0.518	1.4
S	0.568	1.85

Radii are due to (1960).

2.1.2. Desolvation model. We combine formulas (12) and (8) to create a parametric, pairwise algorithm for the desolvation energy $\Delta G_{\text{bind,solv}}$ for use in protein docking simulation. In Algorithms 1–3, we outline the formulation and implementation on both CPUs and GPUs. Algorithm 1 describes the basic CPU implementation of the pairwise surface area and desolvation calculation, and Algorithms 2 and 3 describe the GPU implementation. The CPU and GPU versions are close to numerically equivalent, with the anticipated single-precision floating point representation error averaging 2.26×10^{-6} over our benchmarking set.

Our algorithm computes the desolvation free energy of a protein complex by combining known atomic solvation parameters with computed solvent accessible surface areas. Profiling of an initial CPU implementation indicates that the majority of processing time is spent computing the SASA. This agrees with the expected computational complexity—the solvent accessibility computation scales as $O(n^2)$ whereas the desolvation sum is $O(n)$.

The problem of accessibility computation time is further compounded when one considers extending the application of the algorithm to search through conformational space for an energetic minimum—accessibility values are dependent on atomic positions, so each conformational change requires a potential re-evaluation of order n^2 . The desire to perform a large number of desolvation calculations motivates our application of hardware acceleration to this problem.

2.2. CUSA and CUDE implementations

Here, we present implementation details for the CUDA-based codes, CUSA and CUDE, along with their reference CPU implementations. The CPU implementations perform multicore calculations, while the GPU implementations perform multi-threaded calculations on NVIDIA graphics cards.

2.2.1. CPU implementation. The reference CPU implementation (Algorithm 1) consists of the previously described accessibility computation followed by a loop that uses the computed accessibility to determine the desolvation contribution of each atom. On lines 8 and 15 of Algorithm 1, atom i is assigned its SASA before overlaps—the factor S_i defined in formula (6). The overlap factor of atom j with atom i on lines 10, 17, 23, and 29 is the f_{ij} defined in (5).

The intra-molecular SASA computations performed in the loops beginning on lines 7 and 14 correspond to the product of f_{ij} terms in formula (8), and the inter-molecular computations performed beginning on lines 21 and 27 correspond to the product of f_{ik} terms in formula (8). The pairwise desolvation contributions due to changes in SASA during binding are summed on lines 35 and 38 of Algorithm 1.

Our CPU implementation used function inlining where appropriate, avoided string lookups, and tried to maximize re-use of commonly computed values. This implementation did not undergo additional optimization, such as intrinsic hints to reduce L2 cache misses or loop vectorization.

2.2.2. CUDA overview. Modern GPUs are cooperative processing platforms designed for the rendering of 3D graphics, an application that demands high-throughput parallel hardware capable of significant arithmetic density. Originally specialized for high-speed performance in specific graphics applications, the

Algorithm 1 CPU desolvation

```
1:  $A_{L,initial} \leftarrow$  ligand unbound accessibility
2:  $A_{R,initial} \leftarrow$  receptor unbound accessibility
3:
4: for each conformation  $c$  do
5:   transform all atoms according to  $c$ 
6:
7:   for each receptor atom  $i$  do
8:      $A_R[i] \leftarrow S_i$ 
9:     for each receptor atom  $j \neq i$  do
10:       $A_R[i] \leftarrow A_R[i] \times f_{ij}$ 
11:     end for
12:   end for
13:
14:   for each ligand atom  $i$  do
15:      $A_L[i] \leftarrow S_i$ 
16:     for each ligand atom  $j = i$  do
17:       $A_L[i] \leftarrow A_L[i] \times f_{ij}$ 
18:     end for
19:   end for
20:
21:   for each receptor atom  $i$  do
22:     for each ligand atom  $j$  do
23:       $A_R[i] \leftarrow A_R[i] \times f_{ij}$ 
24:     end for
25:   end for
26:
27:   for each ligand atom  $i$  do
28:     for each receptor atom  $j$  do
29:       $A_L[i] \leftarrow A_L[i] \times f_{ij}$ 
30:     end for
31:   end for
32:
33:    $\Delta G_d \leftarrow 0$ 
34:   for each receptor atom  $i$  do
35:      $\Delta G_d \leftarrow \Delta G_d + \gamma(A_R[i] - A_{R,initial}[i])$ 
36:   end for
37:   for each ligand atom  $i$  do
38:      $\Delta G_d \leftarrow \Delta G_d + \gamma(A_L[i] - A_{L,initial}[i])$ 
39:   end for
40:
41: end for
```

Algorithm 2 CUSA: CPU control code

```
1: GPU call: calculate unbound ligand accessibility
2: GPU call: calculate unbound receptor accessibility
3: for each conformation  $c$  do
4:   GPU call: transform ligand
5:   GPU call: calculate all-complex accessibility
6:   read accessibility from GPU memory
7:   compute desolvation for all atoms
8: end for
```

Algorithm 3 CUSA: GPU accessibility thread

```
1: derive atom index  $i$  from position in block and grid
2: accessibility  $\leftarrow 0$ 
3: for each block  $b$  in the molecule do
4:   load one atom's SASA parameters
5:   __syncthreads()
6:   for each atom  $j$  in block  $b$  do
7:      $\Delta A_j \leftarrow \Delta A_j \times f_{ij}$ 
8:   end for
9: end for
10:  $\Delta A_i \leftarrow \Delta A_i \times S_i$ 
```

modern GPU strikes a balance between maintaining a somewhat specialized high-speed architecture and exposing enough functionality to become a viable platform for general purpose scientific computing. For a more detailed description of the evolution of GPU programming interfaces, see Owens et al. (2007).

GPUs are high performance devices which, for certain categories of parallelizable problems, can greatly outperform a CPU. This is possible because of the data-parallel nature of the GPU's memory and arithmetic unit layout. A deep pipeline and scores of multi-processors executing uniform calculations allow a GPU to perform computation more frequently and at higher rates than on a general purpose CPU (Owens et al., 2008). With 256 streaming multiprocessors, an NVIDIA GeForce GTX 280 card has a theoretical maximum throughput of 933 GFLOPS, compared with a theoretical maximum throughput of under 50 GFLOPS for an Intel Quad-Core Xeon E5335.

NVIDIA, along with Advanced Micro Devices' ATI division and Intel Corporation are major world-wide suppliers of commodity GPUs. Using a graphics shader language and programming API such as OpenGL or DirectX, one can implement a scientific computing problem on several generations of ATI and NVIDIA cards. However, this approach is cumbersome: it requires a good deal of graphics programming knowledge, authoring multiple versions of shader code to account for generational and manufacturer hardware differences, and forces an unnatural re-interpretation of a problem in the language of 3D rendering.

In 2007, NVIDIA released CUDA (NVIDIA, 2007), a combination hardware/software platform that greatly simplifies the use of commodity GPUs for general purpose scientific computation. Using CUDA, parallel algorithms can be written for and executed on a GPU without any knowledge of graphics programming. CUDA is an NVIDIA product and only runs on modern CUDA-capable NVIDIA GPUs. ATI's Stream Computing (ATI, 2007) initiative plans to provide similar development tools for ATI GPUs, but was not yet fully available at the time this article was written.

On a CUDA-capable GPU, computation is performed by sets of streaming multiprocessors, each containing several compute units. Code is executed as a block of threads on a particular multiprocessor. Blocks of threads are grouped into a grid for distribution onto the GPU. Each multiprocessor contains a small shared memory store that can be accessed by all threads in a given block. Accessing the shared memory store is very cheap—on the order of register access (NVIDIA, 2007). Global memory provides a much larger storage space but is significantly slower to access. Structuring memory access with these capabilities in mind is an important consideration for good utilization of GPU resources.

2.2.3. CUSA and CUDE. Nested computations of order n^2 are common in scientific computing, and the literature describes several methods of implementing such computations on the GPU (NVIDIA, 2007; Stone et al., 2007; Schive et al., 2008). A common method we adopt is to factor the algorithm to perform n computations in each thread. We then have the GPU compute n of these threads to achieve the necessary n^2 comparisons. Each singleton thread collects the accessibility contribution from other atoms on a fixed atom.

CUDE (CUDA Desolvation) is our GPU implementation (Algorithm 2). It consists of four device kernel calls which compute accessibility information. First, we compute the prebinding SASA for both proteins. Then, for each conformation we transform the ligand and compute the accessibility of the complex. The algorithm is also capable of transforming the receptor molecule, in order to allow for flexible docking applications.

Our algorithm requires several parameters for each atom, and the parameter set for a reasonably sized molecule will not entirely fit into shared memory. Our device kernel (Algorithm 3) addresses this by dividing the molecule into blocks that are processed in parallel. Furthermore, to minimize the number of reads to global memory, we adopt an iteration pattern suggested by Schive et al. (2008). In their work on pairwise astrophysical systems, they suggest a method of block-based iteration to reduce global memory access. In this method, the threads in a given execution block iterate over the complex atoms one block-size chunk at a time. This allows the threads on a given multiprocessor to cooperatively load the the relevant data for one block's worth of atoms into shared memory. Each thread only reads one atom's parameter set from global memory and relies on the other threads in the block to provide the rest of the data. After the return of the synchronization call on line 5 of Algorithm 3, the multiprocessor's shared memory bank will contain all the atomic parameters needed by each thread in the current iteration. Furthermore, since threads within a block read parameter sets in adjacent memory, this access scheme can be coalesced by CUDA into one hardware read per parameter per block-size iteration.

3. RESULTS AND DISCUSSION

We have adapted a method for approximating the solvent-accessible surface area developed by Hasel et al. (1988) to a form suitable for parallel evaluation on graphics processing units. As an application of our method, we compute desolvation free energies using the ASP model of Eisenberg and McLachlan (1986).

We determined that CUDE, our GPU implementation, substantially outperforms our CPU version. Because the most computationally intensive part of CUDE is the solvent accessibility calculation, similar performance can be expected for CUSA. On average, our GPU based codes compute a given batch of desolvation energies two orders of magnitude faster than our CPU based code. Thus, GPU computation is a valuable tool for decreasing the runtime of our computational biology codes.

3.1. Model accuracy

Following the parameter fitting method described in Section 2.1.1 we derived the p_i values necessary for the SASA computation using Pauling united atom radii (Pauling, 1960). Table 1 lists our new p_i parameters along with the radii used for each atomic group. Compared against the buried area computed with NACCESS (Hubbard et al., 1993), our optimized p_i values yield a correlation of 0.95 with a relative error of 9.7%. This correlation was computed over the Mintseris et. al. protein docking benchmark (Mintseris et al., 2005) and is displayed in Figure 1. We withheld 9 randomly selected complexes for use as a test set, leaving the rest as a training set. The correlation on the withheld complexes was 0.96 with a relative error of 9.5%.

As an initial application of our CUSA algorithm, we implemented CUDE, an ASP-based desolvation model and compared with results presented by Weng et al. (1997), which we refer to as the WDV model. This work presents a comparison of experimental and computed free energies for 15 complexes, and lists ASP-computed ΔG_d 's. We noted that on the WDV benchmark, our computed ΔG_d values seem to systematically underestimate the WDV ΔG_d values proportionally to the surface area buried during binding. This suggests that we can compute a correction factor based on the ratio of error in ΔG_d and the buried surface area. Using a five-fold cross validation we trained a correction term $\varepsilon = 5.8376 \times \text{BSA}$. Adding ε to our desolvation energies (formula 12) yields a relative error of 9.1%. The average relative error on the withheld bins was 9.4% and the individual correction factors for each subset were comparable with the value ε given above. These relative errors are similar to those observed in other solvation energy models (Zhang et al., 1997).

3.2. Computational runtime

CUDE, described in Section 2.2.3, substantially outperforms our reference CPU implementation. Because the dominant cost of running CUDE is the solvent accessibility calculation, speedup results for CUSA are apt to be similar.

FIG. 1. Buried area correlation between CUSA and NACCESS.

TABLE 2. TIMING BENCHMARK SET

Large complex	1I9R	1DE4	1K5D
Large receptor	1KXQ	1BVN	1MAH
Large ligand	1I2M	1H1V	1B6C
Average complex	1JPS	1FSK	1DQJ
Average receptor	1BUH	1E6E	1A2K
Average ligand	1M10	1IB1	1FC2
Small complex	1QA9	1AY7	1CGI
Small receptor	1EZU	1D6R	1AVX
Small ligand	1UDI	1TMQ	2SNI

Timing numbers were computed over a protein set selected from the Mintseris et al. (2005) protein docking benchmark. To create our timing benchmark, we randomly selected 3 complexes in each of 9 categories: large complex, large ligand, large receptor, average complex, average ligand, average receptor, small complex, small ligand, and small receptor. The selection criteria for the categories was based on the number of atoms in the complex, ligand, and receptor, respectively. Complexes, ligands or receptors containing a number of atoms greater than one-half a standard deviation above the mean for the entire benchmark set were eligible to be selected into the large categories. Similarly, proteins within one-half a standard deviation of the mean were eligible for selection into average categories, and proteins below one-half of a standard deviation of the mean were eligible for selection into the small categories.

Table 2 lists the PDB identifiers (Berman et al., 2000) of the proteins selected for timing analysis. To simulate a minimization application, we evaluate desolvation energies for each of the complexes for 2000, 4000, 6000, 8000, and 10,000 randomly generated rigid body transformations of the ligand. The runtime reported is the wall-clock time averaged across three runs. For both the CPU implementation and the GPU implementation the measured runtime includes transforming the ligand and receptor, computing the SASA, and finally summing the atomic desolvation contributions. Additionally, both the CPU and GPU runtime numbers reported include relevant set-up such as memory allocation, system threading overhead, and data transfer to the GPU. For more information, please see our source code, available at <http://www.mitchell-lab.org>.

We compared three versions of the desolvation algorithm designated 2CPU, 8CPU and 2GPU. The 2CPU and 8CPU algorithm split the ligand conformations into two and eight CPU threads respectively. The 2GPU version split the ligand conformations into two CPU system threads, each one claiming one of the machine's GPUs. Our benchmark machine, listed in Table 3, contains a quad-core processor. Because of this, our 8CPU timings are CPU-limited and represent a "maximum load" case.

Table 4 contains the results of our timing analysis. For each complex in our timing benchmark we report 3-run averaged wall-clock times for 2000, 4000, 6000, 8000, and 10,000 ligand conformations. Additionally, for each complex we report the average speedup factor computed as the average of the speedup $\frac{2\text{CPU}}{2\text{GPU}}$ and $\frac{8\text{CPU}}{2\text{GPU}}$ for each set of transformations.

Our CUDE implementation substantially outperformed both of our CPU implementations. Because of the $O(n^2)$ complexity of the SASA calculation, the degree of improvement is correlated to the size of the complex—in general, larger complexes show greater speedup. Figure 2 shows a graph of average runtime over all transformation numbers versus complex size. Observed average runtime improvements range from $30\times$ (2GPU vs. 8CPU) for 1AY7, a 1466-atom complex, to $378\times$ (2GPU vs. 2CPU) for 1DE4, a 13,107-atom complex. In addition, the scaling results suggest that the use of careful massively-threaded calculations not only reduces the overall runtime considerably, but it also appears to decrease the effective order of the calculation, as witnessed by the different slope exhibited by the data points for the GPU timings in Figure 2 compared with those taken for calculations on the CPU.

TABLE 3. HARDWARE SPECIFICATIONS

CPU	Quad-core Intel Xeon E5335, 2.0 GHz
RAM	8,169,904 kB
GPU	2×NVIDIA GeForce GTX 280

TABLE 4. TIMING BENCHMARK RESULTS

		Timings for: 2CPU 8CPU 2GPU							
		Number of energy evaluations						Average speedup	
PDB name	Complex size	2000	4000	6000	8000	10000	2CPU 2GPU	8CPU 2GPU	
Large complex	1I9R	6573	1410	2818	4226	5626	7045	289	145
			705	1409	2113	2818	3521		
			6	10	15	19	24		
	1DE4	13107	5570	11136	16697	22229	27801	378	189
			2786	5568	8352	11130	13911		
			16	30	44	59	73		
	1K5D	5566	1004	2009	3013	4020	5024	271	136
			504	1007	1509	2011	2513		
			5	8	11	15	18		
Large receptor	1KXQ	4826	758	1515	2272	3029	3791	229	115
			380	759	1138	1517	1897		
			4	7	10	13	16		
	1BVN	4443	643	1285	1927	2569	3214	210	105
			323	644	965	1286	1607		
			4	7	9	12	15		
	1MAH	4576	685	1367	2053	2737	3420	219	109
			343	685	1026	1369	1710		
			4	7	10	13	15		
Large ligand	1I2M	4245	591	1180	1770	2360	2948	198	99
			296	591	886	1181	1476		
			4	7	9	12	15		
	1H1V	5414	954	1907	2859	3810	4762	268	134
			477	953	1430	1906	2382		
			4	8	11	14	18		
	1B6C	3433	386	771	1156	1541	1922	174	87
			193	386	578	770	963		
			3	5	7	9	11		
Average complex	1JPS	4858	769	1536	2303	3073	3837	234	117
			385	769	1154	1538	1922		
			4	7	10	13	16		
	1FSK	4577	683	1366	2052	2732	3410	218	109
			342	684	1025	1367	1708		
			4	7	10	13	15		
	1DQJ	4245	590	1177	1768	2355	2941	202	101
			295	589	884	1178	1472		
			4	6	9	12	14		
Average receptor	1BUH	2916	278	555	832	1109	1386	139	70
			139	278	416	555	693		
			3	5	6	8	10		
	1E6E	4377	625	1250	1873	2497	3123	211	105
			313	625	937	1250	1562		
			4	7	9	12	15		
	1A2K	3560	413	827	1240	1650	2066	178	89
			207	414	620	827	1033		
			3	5	7	9	11		

(continued)

TABLE 4. CONTINUED

			Timings for: 2CPU 8CPU 2GPU					Average speedup	
			Number of energy evaluations					2CPU 2GPU	8CPU 2GPU
	PDB name	Complex size	2000	4000	6000	8000	10000		
Average ligand	1M10	3688	445	888	1333	1776	2216	187	93
			223	444	666	888	1111		
			3	5	7	10	12		
	1IB1	5046	826	1650	2476	3305	4124	248	124
			414	827	1240	1652	2065		
			4	7	10	13	16		
	1FC2	2010	133	264	396	528	661	90	45
			67	133	199	265	331		
			2	4	5	6	7		
Small complex	1QA9	1622	87	173	259	345	430	68	34
			44	87	130	172	215		
			2	3	4	5	6		
	1AY7	1466	71	142	213	284	354	59	30
			36	71	107	142	178		
			2	3	4	5	6		
	1CGI	2239	166	331	496	661	826	101	51
			83	166	248	331	413		
			3	4	5	7	8		
Small receptor	1EZU	3854	485	969	1454	1938	2421	182	91
			243	485	727	969	1211		
			4	6	8	11	13		
	1D6R	2056	140	279	418	557	697	91	46
			70	140	210	279	349		
			2	4	5	6	7		
	1AVX	2916	280	559	838	1116	1395	141	71
			140	280	420	559	699		
			3	5	6	8	10		
Small ligand	1UDI	2472	200	400	600	801	1000	115	58
			101	200	300	400	500		
			3	4	6	7	8		
	1TMQ	4479	657	1312	1968	2623	3280	216	108
			329	657	984	1312	1640		
			4	7	9	12	15		
	2SNI	2451	199	398	597	796	995	111	55
			100	199	299	398	497		
			3	4	6	7	9		

3.3. GPU speedup analysis

Neither the CPU nor CUDE GPU implementations received extensive optimization. Both implementations are straightforward, although implementing CUDE certainly required more care to avoid performance pitfalls. Several goals can be summarized to help achieve good GPU performance with CUDA:

1. Factoring of the algorithm to maximize arithmetic operations on values stored in shared memory
2. Avoiding use of global memory in inner device kernel loops
3. Ensuring that global memory reads are coalesced when possible
4. Avoiding conditional statements that cause divergent thread execution pathways
5. Avoiding hardware-specific performance pitfalls described in (NVIDIA 2007), such as the mod operator

FIG. 2. Average runtime versus complex size.

Goal 1 is arguably the most important from a high level perspective. Algorithms that will see the greatest gain from GPU computation are parallelizable algorithms that perform a high number of arithmetic operations for each memory access. Algorithms that require more frequent access to global memory can still see good performance benefits but will require more effort to optimize. The remaining goals can be dealt with to a large extent during implementation. All are described in greater detail in (NVIDIA, 2007).

Careful analysis of a given problem is vital before pursuing a GPU implementation. The best problems will be those that can be implemented using many arithmetic computations for relatively infrequent memory access. In theory, the best performing CUDA algorithm would be one that does arithmetic computation without ever reading or writing to memory. Although CUDA has some capability to hide memory latency by performing independent instructions while memory requests complete, global memory access is slow and should be minimized. Consequently, a significant determining factor of the speedup of a GPU algorithm is achieving balance in the amount of data required for each individual algorithmic computation.

In our case, each pairwise desolvation contribution only depends on a small number of parameters, 24 bytes per atom. This allows many atoms to fit into shared memory and minimizes how often data needs to be read from global memory. Simultaneously, our algorithm has high enough arithmetic density to amortize the cost of inevitable global memory access.

Algorithms that perform simple calculations on large amounts of non-coherent data are less optimal candidates for GPU implementation, but can still yield speed ups with appropriate optimization. For example, we implemented a version of the popular DFIRE statistical potential (Zhou et al., 2002) for the GPU and observed a much more modest speedup. We believe this is likely due to the model's large number of parameters describing interactions between atom/residue-atom/residue pairs.

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No competing financial interests exist.

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