A Curved Panel Integration Technique for Molecular Surfaces

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ABSTRACT

In this paper we present a surface formulation and curved panel integration method for computing the van der Waals interaction energy between a molecular solute and aqueous solvent. This modeling problem arises in computational drug design, where one wishes to understand the energetic tradeoff between a trial drug's interactions with solvent and its interactions with the target. We use the divergence theorem to convert a volume integral to an integral over the solute–solvent boundary. Validation of the surface formulation reveals strong dependence on the accuracy of the boundary representation; to improve the surface discretization quality, we define a type of curved panel called a generalized spherical triangle. A straightforward extension of an earlier curved panel integration method allows us to integrate functions over the curved surfaces. Numerical results demonstrate the accuracy of the improved surface representation and the integration technique.

1 INTRODUCTION

A key step in computational drug design is the calculation of binding free energies between drug candidates and their target; candidates with the most favorable binding free energies are selected and subjected to more computationally demanding processes of optimization and testing. The binding free energy calculation can be decomposed into desolvation, interaction, and solvation terms, and the solvation term can be further decomposed into electrostatic and nonpolar components. The nonpolar component is the sum of an unfavorable cavity formation term and a favorable van der Waals (vdW) interaction energy, and finding an efficient approach to computing the vdW interaction energy is the subject of this paper.

Levy *et al.* [1] introduced a continuum model for calculating the solute–solvent van der Waals interaction energy in the nonpolar term of the solute solvation energy. The vdW interactions with solvent can be computed as a sum of integrals over the semi-infinite exterior solvent region, where each integral models the vdW energy due to one atom in a solute molecule. The Levy *et al.* approach to evaluating the integrals over the solvent region is numerically challenging because the boundary of the integration is a complicated domain with sharp corners.

In this work we present a surface integral-based method for computing the vdW interaction energy. Since the accuracy of the surface method is strongly dependent on the accuracy of the surface representation, we compute the integrals by discretizing the boundary into small curved panels and develop formulas for efficiently evaluating integrals of curved panels. As will be shown below, the use of curved panels results in energy calculations that are substantially more accurate than using the flat-panel discretizations that are popular in many boundary element method simulations. To make the curved panel integral calculation efficient, we exploit the union of spheres property of the solute–solvent interface and introduce generalized spherical triangles (GSTs) as an efficient, accurate way to represent the interface. To compute integrals over GSTs, we have extended a recently developed curved panel integration technique [2].

Section 2 of this paper briefly introduces the continuum van der Waals model and the definition of the solute–solvent interface. Section 3 presents the surface formulation of the continuum van der Waals model and motivates the use of curved panel surface discretizations. In Section 4, we introduce generalized spherical triangles (GSTs) as an improved way to discretize the surfaces of interest and present an approach to integrating functions on GSTs. Section 5 illustrates the accuracy of the new surface representation; Section 6 summarizes the paper.

2 SURFACE FORMULATION

2.1 Continuum van der Waals Model

Levy *et al.* express the solute–solvent van der Waals interaction energy as a volume integral over the solvent [1],

$$U_{vdW} = \sum_{i=1}^{n} \left(\int_{solvent} \rho_w u_{vdW}^{(i)}(|r' - r_i|) dr' \right), \qquad (1)$$

where n is the number of solute atoms, ρ_w is the bulk number density of water, and $u_{vdW}^{(i)}(r)$ is the van der Waals potential due to atom i at a distance r from the solute's i^{th} atomic center r_i. The van der Waals potential fields are modeled using the Lennard-Jones 6/12 functional form [3]:

$$u_{vdW}^{(i)}(r) = \frac{A^{(i)}}{r^{12}} - \frac{B^{(i)}}{r^{6}}. \qquad (2)$$

Here, $A^{(i)}$ and $B^{(i)}$ are parameters dependent on atom i's type. The boundary between the molecular interior and the solvent volume is defined by the solvent-accessible surface [4].

2.2 Definition of the Molecule-Solvent Interface

Figure 1 is an illustration of the Lee and Richards [4] definition of the solvent-accessible surface as the boundary of a union of spheres. Each sphere corresponds to one atom in the solute molecule, and each sphere radius is equal to the corresponding atom's van der Waals radius plus the radius of a spherical probe molecule. The resulting surface then defines how closely the probe center can approach the solute atoms. This surface definition is chosen because the van der Waals potential is defined as a function of the distance between atom centers.

It is difficult to accurately evaluate the integral in (1) defined by the solvent-accessible surface. The volume is too irregular to use high order volume quadrature, and low-order methods require an enormous number of integrand evaluations due to the rapid variation of the vdW potential.

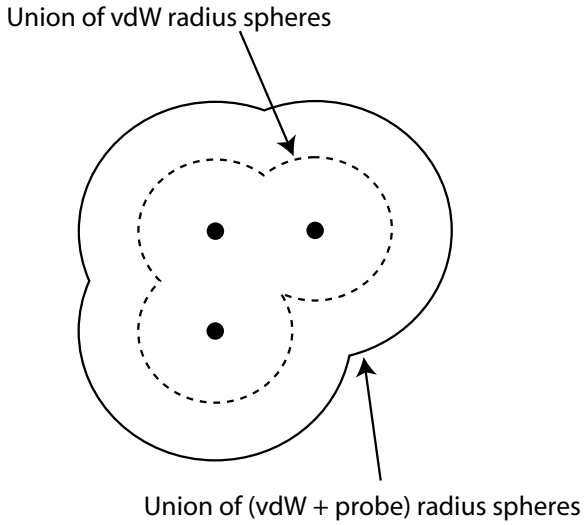

Figure 1: Definition of the solvent-accessible surface.

3 SURFACE FORMULATION

The divergence theorem can be applied to show that

$$\int_V \frac{A}{r^{12}} - \frac{B}{r^6} dV = \int_S \frac{\partial}{\partial n} \left(\frac{A}{90r^{10}} - \frac{B}{12r^4} \right) dS. \qquad (3)$$

We validated the surface formulation in (3) by numerically calculating the van der Waals surface integrals using flat panels for several systems and comparing the results to either analytic answers or converged results from numerical volume integration. Figure 2 is a plot of the convergence with flat panel refinement of a spherical test case to the analytic answer. Note that convergence is linear with the number of panels used, and that almost one million panels are required for five digits of accuracy.

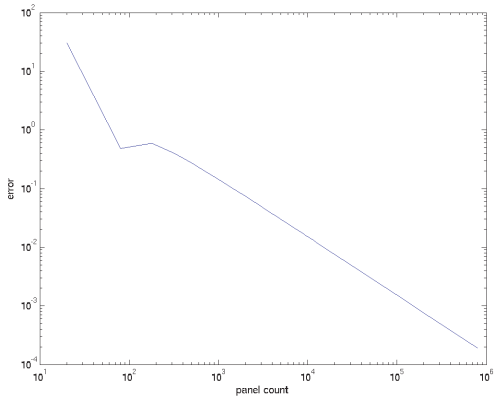

Figure 2: Linear convergence is observed for flat-panel discretizations of the accessible surface.

3.1 Curved Panel Surface Integrals

The above slow convergence with panel refinement motivated the introduction of curved panel surface representations. Since the solvent-accessible surface is defined by a union of spheres, we first attempted to discretize the surface using spherical triangles and then use the mapping technique in [2] to evaluate the curved panel integrals. When the above method is used for spherical test cases, the method converges superlinearly with panel refinement and achieves excellent accuracy for coarse discretizations. In all other test cases, however, the method exhibited only linear convergence. As explained in the next section, spherical triangle discretizations do not accurately resolve the boundaries between spheres.

Wang *et al.* [2] presented a technique to calculate $\int G(r;r')dr'$ over a curved panel, where r is an evaluation point and $G(r;r')$ is a Green's function. First, a coordinate transformation is found that maps a carefully-sized flat polygon F to the curved domain C. The integral is then computed as

$$\int_C G_C(r;r')dr' = \int_F G_F(r;r') \left(\frac{G_C(r;r_C)}{G_F(r;r')} |J(r')| \right) dr', \quad (4)$$

where r_C is the image of r' under the transformation, and J is the transformation Jacobian. If the flat polygon is chosen carefully, the expression in parentheses is smooth and can be fit with a low order polynomial. Then (4) becomes

$$\int_C G_C(r;r')dr' \approx \sum_{i,j} \alpha_{i,j} \int_F x^i y^j G_F(r;r')dr', \qquad (5)$$

where the $\alpha_{i,j}$'s are the polynomial coefficients. The integrals involving monomials and the Green's function can be found using numerical quadrature or analytic methods [5, 6].

4 GENERALIZED SPHERICAL TRIANGLES

4.1 Definition

A standard spherical triangle is a three-sided region of a sphere's surface whose edges are formed by three major arcs, each of which passes through two of three vertices. For a generalized spherical triangle (GST), the edges are formed from three arcs which can be arbitrary circular arcs. Figure 3 is an illustration of a diatomic molecule; the intersection between the spheres is a circle whose center lies on the axis between the sphere centers. In the figure is a GST with one edge on this circle of intersection. Note that if the same three vertices were used to define a spherical triangle, part of the resulting region would extend beyond the circle of intersection and lie within the molecular interior rather than on the surface. For this reason, GSTs are needed to accurately represent the intersections between spheres.

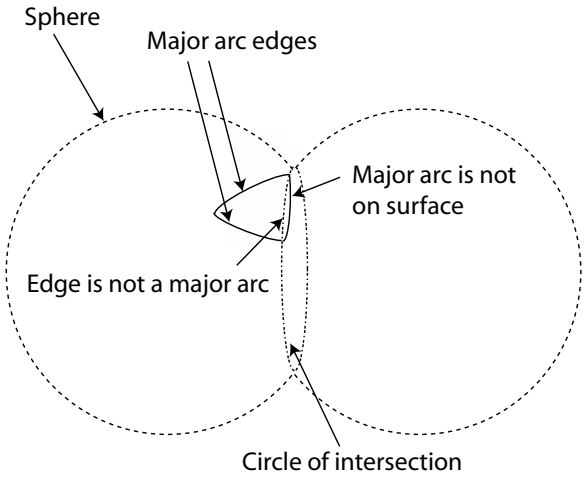

Figure 3: Generalized Spherical Triangle definition.

4.2 Modifying Curved Panel Integration

The spherical triangle panel, under perspective projection from the sphere center, becomes a planar triangle. The generalized spherical triangle under the same transformation has the same vertices, but the non-major arcs are conic curves instead of straight lines. Figure 4 illustrates the flat domain Γ_1 that maps to a GST with one non-major arc, the flat domain Γ_2 that maps to the standard spherical triangle with the same vertices, and the difference Γ_3 between the two domains. We can compute the required polynomial integrals by

$$\int_{\Gamma_1} x^i y^j G(r;r')dr' = \int_{\Gamma_2} x^i y^j G(r;r')dr' - \int_{\Gamma_3} x^i y^j G(r;r')dr'. \quad (6)$$

This is substantially simpler than finding a coordinate transformation that maps directly from a straight edged triangle to

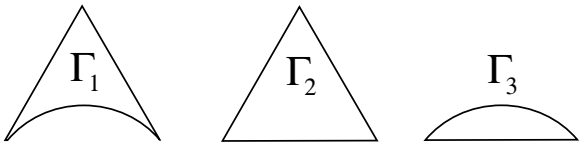

Figure 4: GST integration is accomplished by decomposing the integral into multiple domains.

an arbitrary GST. To find the curved section of the boundary of Γ_3, we first apply the inverse coordinate transformation to several points on the non-major arc. A least squares fit then determines the coefficients of the conic curve

$$ax^2 + 2bxy + cy^2 + dx + ey + f = 0. \quad (7)$$

Once these coefficients are specified, the polynomial integrals over Γ_3 can be computed in polar coordinates using numerical quadrature.

5 NUMERICAL RESULTS

For numerical examples, we used the MSMS [7] program to generate flat-panel surface discretizations; postprocessing scripts based on Connolly's work [8] then transformed the flat-panel discretizations into GST discretizations.

5.1 Spherical cap

We first computed the surface area of a spherical cap, where the elevation angle ϕ for the cap varies from 0 to $3\pi/4$. We used flat panels, spherical triangles, and generalized spherical triangles to discretize the surface, and compared the calculated areas to the analytic answer. Figure 5 is a plot of the results; observe that the GST integrals converge superlinearly with panel count.

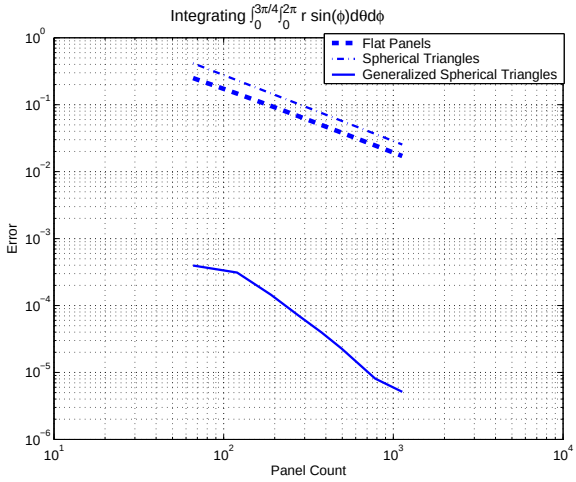

Figure 5: Convergence of the surface area calculation for a spherical cap.

5.2 Propanoic Acid

Figure 6 is a plot of the convergence of the continuum van der Waals surface integral for propanoic acid. When answers are compared to volume-based van der Waals integrals, panel counts as low as 932 suffice to give better than five digits of agreement.

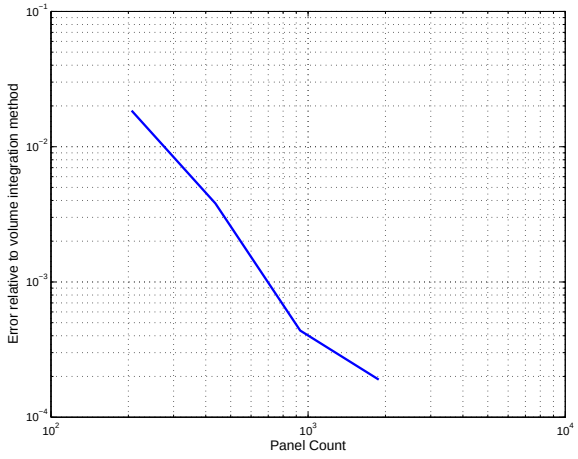

Figure 6: Convergence of the continuum van der Waals integral for propanoic acid.

6 SUMMARY

In this paper we have introduced a surface formulation for the continuum van der Waals model of the interactions between a molecule and solvent. Numerical implementation requires an accurate representation of the molecule–solvent interface, and the generalized spherical triangles (GSTs) introduced in this work are significantly more accurate than flat panels or spherical triangle panels. Our numerical results demonstrate superlinear convergence with discretization refinement, and surprisingly coarse discretizations suffice to achieve good agreement with volume integration methods. Current work focuses on applying the continuum van der Waals model to structure-based design of therapeutic molecules. In the future, the GST integration technique may be extended for surface generalized Born calculations [9] or BEM simulations of molecular electrostatics [10, 11].

7 ACKNOWLEDGMENTS

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