Global-To-Local Representation and Visualization of Molecular Surfaces Using Deformable Models

Nicolay Postarnakevich[1], Rahul Singh[2]
[1]Department of Mathematics, San Francisco State University, San Francisco, CA
[2]Department of Computer Science, San Francisco State University, San Francisco, CA
npost@sfsu.edu, rsingh@cs.sfsu.edu

ABSTRACT
Macromolecules such as proteins and enzymes are responsible for most of cellular functionality. Many molecular interactions, such as protein-protein interactions or protein-ligand binding, occur at what can be defined as the molecular surface. The topology of the molecular surface is often complex, containing various geometric features such as clefts, cavities, tunnels, and flat regions. These geometric features coupled with non-geometric physicochemical properties influence surface-based molecular interactions. Consequently analysis of molecular surfaces is crucial in elucidating structure-property relationships of molecules. In this paper we propose a method for visualizing a molecular surface in a manner that preserves and elucidates salient features. The method involves mapping of a molecular surface to a standard spherical coordinate system. The ability to map arbitrary molecular surfaces to a standard coordinate system aids in comparison of surface features across different molecules. The mapping is accomplished by enclosing the molecular surface by a sphere, and then iteratively deforming the sphere until it converges by wrapping the entire molecular surface. This allows a one-to-one relationship to be established between points on the molecular surface and points on the surface of the sphere. The presence of discontinuities such as tunnels in the molecular surface can be identified by detecting collision between patches of the deforming sphere. Subsequently, the deformable surface is restored back to the sphere, retaining the mapping. Features and properties defined at the molecular surface are then mapped and visualized in the standard spherical coordinate system. The proposed approach has several key advantages. First, it allows a global-to-local visualization of molecular surfaces. Second, it facilitates comparison of specific features as well as collection of features within and across molecules by mapping them to a common coordinate system. Third, the method allows visualization of both geometric and non-geometric surface properties. Fourth, specific molecular characteristics can be visualized individually or in combination on-demand. Finally, and crucially the advantages offered by the proposed visualization do not involve simplification of the surface characteristics thereby ensuring that no loss of potentially important information occurs.

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Categories and Subject Descriptors
J.3 [**Life and Medical Sciences**]: *Biology and genetics*. H.5.2 [**Information Interfaces and Presentation (e.g., HCI)]**: User Interfaces – *Graphical user interfaces (GUI)*. I.3.8 [**Computer Graphics]**: *Applications.*

Keywords
Molecular surfaces, molecular visualization, deformable models, surface mapping.

1. INTRODUCTION
The structure of a molecule can have direct influence on how the molecule behaves biologically. A mechanistic elucidation of the structure-property relationship of macromolecules requires an appropriate representation of structure. This problem is critical given the rapid increase in the availability of structural molecular data. In this context it should be noted, that protein function, in particular of enzymes, is often intimately related to the recognition and chemical modification of endogenous ligands such as agonists, antagonists, effectors, or substrates [21]. This recognition usually occurs in well characterized patterns on protein surfaces such as clefts and cavities (see for instance, [7, 21, 22] and references therein). It can be argued [16], that if a group of evolutionarily related proteins is known to have divergent functional characteristics, then techniques that focus on similarity based on functionally relevant characteristics such as surface features, should be able to perform better than those that consider overall similarity. At the state-of-the-art, comparing surface features is therefore an active area of investigation [3, 9, 13, 20, 18, 23]. Research in this area, typically involves various types of surface representation such as van-der-Waals surfaces, where each atom is treated as a solid ball and the surface determined from the intersection of such balls. Other methods compute solvent contact surface [6] and solvent accessible surface [17], which is obtained by rolling a probe-atom over the van-der-Walls radii. It may be noted that given the basic parameters (atomic coordinates, radii, and radius of the probe atom) these representations are inferable from each-other.

Molecular surfaces typically contain protrusions, pockets, tunnels, and flat regions. Several of these features are biochemically significant. For instance, ligand binding occurs at pockets, many protein-protein interactions occur at flat surfaces, and tunnels facilitate solvent ion conductance. These geometric features are complimented by the distribution of physicochemical properties such as electrostatics and polarity on the molecular surface. The interplay of geometric and physicochemical attributes ultimately defines surface-based molecular interactions. Consequently, a

molecular surface can be thought of as a collection of multi-attribute points.

The complexity of molecular surfaces poses severe challenges for their analysis and assessment. Consequently design of surface representation and visualization techniques is critical to the area. There are a variety of problems that have to be addressed in providing a comprehensive solution. These include:

- *Global-to-local nature of surface characteristics*: Protein surfaces are characterized by local features such as active sites/cavities as well as by the overall pattern of such localized features across the entire protein surface. Effective representation/visualization therefore needs to capture not just specific local features but also topological relationships between all such features.
- *Presence of non-geometric attributes*: In addition to geometric features, it is important to represent/visualize distribution of physicochemical surface characteristics, especially in context of geometric features of interest. This requires a unified framework for representing geometric and non-geometric properties.
- *Presence of non-extremal surface features*: While surface discontinuities, protrusions, and cavities are important, regions of the surface that are flat or have slowly varying curvature also play a critical role in protein function. It is therefore important to design representation/visualization schemes that can effectively and simultaneously capture both extremal and non-extremal surface features.
- *Multi-attribute nature of molecular surfaces*: The multi-attribute nature of molecular surfaces requires that researchers be able to visualize specific attributes or combination of specific attributes flexibly and on-demand.
- *Facilitating comparative reasoning*: In many cases molecular features are studied not in isolation but in comparative settings. For instance, in drug discovery, identifying whether a potential lead-molecule is promiscuous requires comparing the binding site characteristics of its target with (potential) binding sites on other proteins/enzymes. However, these molecules may have vastly different surfaces. Such comparisons require that the molecular surfaces are represented in a standard representation (coordinate) framework.

In this paper we make a fundamental departure from current approaches and propose a new method, based on deformable surfaces to map arbitrary molecular surfaces to a standard spherical coordinate system. Our approach allows a one-to-one relationship to be established between points on the molecular surface and points on the surface of the sphere. The presence of discontinuities such as tunnels in the molecular surface is identified by detecting collision between patches of the deforming sphere. Based on the obtained correspondences, geometric and non-geometric properties of the molecular surface are mapped to the sphere and visualized. The proposed method addresses all the critical challenges described above. The rest of the paper is structured as follows: in the next section we cover background pertaining to surface generation, as well as analyze related research in this area. In Section 3 the proposed method is presented. In Section 4 various rendering techniques to show global and local surface features on the spherical map are presented. Finally, in Section 5 we discuss several case studies that show the advantages of using spherical maps.

2. RELATED WORK

Many software packages specialize in molecular visualization, including Jmol, KiNG, PyMol, and Chimera [10, 8]. Most of these packages offer various visualization options, including abstractions such as viewing the secondary structure of the molecule. However, none of these packages (and underlying methods), provides a good abstraction of surface-based molecular characteristics, especially in context of the criteria discussed above. Surface visualization is directly addressed in [5, 8, 19] from a purely visualization perspective. These works reduce the complexity of the molecular surface by mesh reduction and/or use of stylized elements. While such methods are useful when important surface features are known a priori, in general they are less suited to exploratory scenarios since important features may not be known ahead of time and could be removed during the simplification process. Several methods have been developed for identifying/representing/visualizing pockets, cavities, and tunnels in proteins: SURFNET [12] finds cavities by fitting spheres between atoms and CAST [14] uses Delaunay tessellation of protein residues, with empty triangles identifying cavities. In [13] the protein is first voxelized and the fraction of directions not blocked by protein atoms computed for each voxel. Group of voxels having visibility below a threshold are then identified as pockets. In [23] a level-set marching method is used to identify pockets and hollows.

The key distinction of these methods from our approach lies in that they focus primarily on detection/representation/visualization of critical local features on protein surfaces as opposed to a global-to-local representation. While [13] provides such a representation, the visibility criteria used in it is defined on a discrete rectangular grid. The rectangular grid introduces an undesired anisotropy and its discrete nature implies that the visibility measurements can be significantly impacted by the choice of grid spacing and consequently may not represent the intrinsic geometry of the molecular surface. The spherical mapping proposed in [20] is in certain respects most similar to our work and addresses many of the issues identified by us. In [20] the molecule is encapsulated by a sphere and rays drawn from the center of the sphere at predefined angular separation are used to map the corresponding point on the molecular surface to the sphere. Unfortunately, the predefined linearity of such a mapping implies that regions of non-uniformly varying surface curvature are not guaranteed to be captured. Furthermore, there is no way to correlate the angular separation to local curvature variations. The method proposed by us, in contrast, uses a non-linear mapping based on the idea of deformable models that adjusts automatically to surface features in a data-driven manner. The number of nodes on the sphere can be selected based on the number of triangulations of the underlying surface which is known a priori, thus obviating any sampling issues.

3. METHOD

3.1 Deformable Surfaces

The central idea of the proposed method involves mapping and visualizing the molecular surface as a map on a sphere. Some of

the more obvious ways of achieving such a map involve either projecting surface normals onto the sphere, or similarly projecting rays from the center of the molecule onto the sphere. These methods have several inherent drawbacks. One of the biggest problems is shown in Figure 1(a) where both of the above strategies map multiple points of the molecular surface onto the same point on the sphere, due to the non-convexity of the surface. This can lead to improper representation of surface features. Hence, a desired method should map a unique point on the molecular surface to a unique point on the sphere. Our approach uses the idea of deformable models [11, 14] to map the molecular surface to the sphere to meet this requirement. Deformable models were developed in computer vision to extract desired features from images. The goal is to continuously deform an elastic contour until it settles on the salient features. This is accomplished by minimizing the energy of the contour until it converges. The energy functional can be formulated as:

$$E_{model} = \int E_{internal} + E_{external} d\gamma \quad (1)$$

Where the integral gives the total energy of the model, $E_{internal}$ and $E_{external}$ are internal and external energies of the model. The internal energy is usually driven by internal forces of the model surface. The internal forces have traditionally been defined in terms of spring forces, twisting forces, and bending forces. Internal forces restrict undesired local deformations, and force the model to converge initially. The external energy is usually derived from external image driven forces, which usually are derived from the image intensity. The method seeks to minimize the energy of the contour by iteratively deforming it in a way that eventually reaches an energy minima.

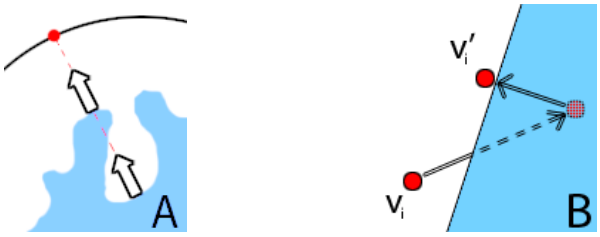

Figure 1. A) Example where simply mapping surface normals to a sphere can create problems. B) The motion of the vertex is projected onto the molecular surface, simulating skidding on the surface.

Based on the idea of deformable models, in our approach a sphere encapsulating the molecule is iteratively deformed until the sphere converges onto the molecular surface, tightly wrapping it. Once the sphere converges on the molecular surface, any characteristic of interest (such as electrostatic forces, or local curvature) that can be computed at the surface can be transferred to the corresponding point on the sphere. In this paper, we characterize molecular surfaces using curvature (obtained from Connolly's code) and electrostatic distributions generated using APBS [1]. Special consideration is taken when the molecule is non-genus zero. In this case first the tunnels and holes are identified by detecting intersection between patches of the deforming sphere, as they meet, having entered the tunnel/holes from different sides. Next, these discontinuities are mapped to the sphere.

3.2 Deforming the Sphere

We represent the deformable sphere by a discrete connected set of points. We chose to use a subdivided icosahedron [14]. It consists of triangular subdivisions which make it easier to render and work well in approximating the triangulated molecular surface. The sphere is initialized outside the molecular surface.

Typically, a three dimensional deformable model is formulated in terms of its energy as in equation (2). The total energy of the deformable model depends on internal forces intrinsic to the deformable model and external forces usually derived from the image. Parameters α_i, β_j control elasticity of the material; tension, bending rigidities, and twisting. The internal forces cause the deformable model to converge initially as well as restricting undesired local deformations such as twists. The deformation process itself is iterative, and is repeated until the deformable model converges to a desired degree. Our deformable model formulation is simpler than what is normally encountered in computer vision applications due to two main points. Firstly we do not have to deal with image noise. Furthermore, since the implementation of the model is usually a discrete approximation of a continuous surface, many algorithms subdivide/merge vertices of the deformable surface during the deformation process. This is unnecessary (and undesirable) in our case since we want a one-to-one mapping between points on the molecular surface and points on the sphere.

$$\varepsilon_p(x) = \iint \alpha_1 \left|\frac{\partial x}{\partial u}\right|^2 + \alpha_2 \left|\frac{\partial x}{\partial v}\right|^2 + \beta_1 \left|\frac{\partial^2 x}{\partial u^2}\right|^2 + \beta_2 \left|\frac{\partial^2 x}{\partial u \partial v}\right|^2 + \beta_3 \left|\frac{\partial^2 x}{\partial v^2}\right|^2 du dv \quad (2)$$

The deformation process is performed iteratively. An iteration consists of two main parts. First, each node of the sphere is moved to the intended position based on the sum of acting forces. Second, once all the intended destination positions of each node are computed, the sphere is checked and possible corrected for self intersections. Then the process is repeated until the model converges on the surface. In the first step, forces are applied to each node v_i of the sphere separately, computing the displacement of the node for that iteration. The nodes are driven by a combination of two forces, an internal force and external force. The internal force (3) is computed as approximate spring force minus the node normal vector:

$$F_{internal} = \left(\sum_{n=1}^{NN} (v_n - v_i) \right) - N(v_i) \quad (3)$$

$$F_{external} = -pN(v_i) \quad (4)$$

$$v_i' = F_{internal} + F_{external} \quad (5)$$

In Eq. (3) above, *NN* denotes the number of neighbors of the current node, which for a subdivided icosahedron is either five or six, v_n is the n^{th} neighbor of v_i and $N(v_i)$ is the surface normal vector at v_i. The external force $F_{external}$ (4) is approximated as the pressure force, where there is a pressure drop from exterior of the sphere to the interior: here p is a positive constant. The total displacement for a node is then given by Eq. (5). Once v_i' is calculated, a check against the surface of a molecule is made to ensure that the node does not cross into the molecular surface.

This is done by considering the line segment $v_i v_i'$, where v_i is assumed to be outside of the molecular volume. This segment can then be checked for intersection against triangles of the molecular surface. If there are no intersections, then v_i' is accepted as a valid destination point. Otherwise, from the calculated point of intersection of the segment and the surface we subtract the vector component responsible for crossing into the molecule. This effectively simulates the sliding of the node v_i on the molecular surface, as illustrated in figure 1(b). Similarly, if during the iteration, node v_i starts on the surface of the molecule, then we first subtract the component responsible for pushing v_i' into the surface. This is done to ensure that a node of the sphere that lies on the surface can skid on it, ensuring better uniformity of the final node distribution on the surface. To increase the efficiency of the check, we use a space partitioning technique (Octal Tree).

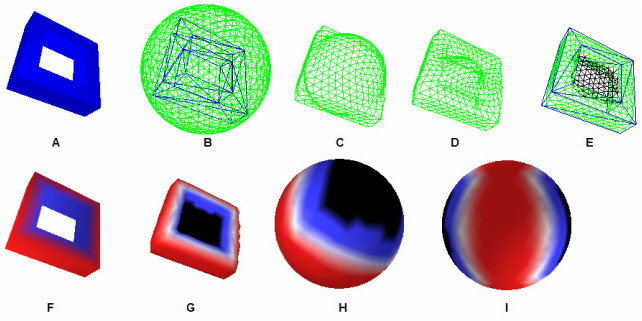

Figure 2. A) Test surface. B) Sphere initialized around the surface, depicted as a wire frame. C,D) Sphere during the iterative deformation. E) Sphere converged onto the surface, self-collided triangles are drawn black. F) Arbitrary property denoted by the red and blue colors are assigned and rendered at the surface. G) Properties transferred to the converged sphere. H) Sphere expanded to the original form. I) Rotated view of the sphere, note how the symmetry of the surface is reflected on the spherical map. Two black regions signify the hole on the original surface.

For the second step of the iteration, once all intended motion destinations are computed and the molecular surface collisions are checked for all the nodes of the sphere, a check is made to ensure that no self collision occurred. Self collisions can occur when the molecular surface has a hole. This is because in our deformation scheme the sphere is allowed to collide with itself, but is not allowed to cross over into itself. Self collision is handled in the following way. Every triangular tessellate of the sphere consists of three nodes that might have moved during the iteration. We consider the volume that is traced by the deforming triangle, and check it against a line segment $v_i v_i'$ of the current node. This is accomplished by considering the position of the triangle and the current vertex in terms of time variable t which varies from zero (beginning of iteration) to one (end of iteration). By expressing each vertex as a linear function of t, the triangle in equation defines a plane, which then is also expressed in terms of t. Solving plane equation and the line equation for vertex motion $v_i v_i'$ for t, we get all possible times when a collision could have occurred. Then it remains a simple check to verify that the collision indeed did occur. If collision is found, then all participating vertices are backtracked to the linearly interpolated position at the time of collision t. These steps are repeated for all the nodes of the sphere. The deformation process is iterated until the sphere converges by settling on the surface of the molecule. At this point triangulated molecular surface is covered by the triangulated surface of the now deformed sphere. Therefore, to properly sample the molecular surface the sphere should have as many tessellates (triangles) as the molecular surface. Since we are using a subdivided icosahedron, the number of triangles of the sphere is defined by the number of subdivisions of the icosahedron. Given that the triangulation of the molecular surface is known, we choose the level of subdivision of the icosahedron that gives equal or more triangles than on the molecular surface. At this point the appropriate molecular surface characteristics can be mapped to the sphere, see figure 2. During the mapping, special consideration is taken to represent the self collided vertices. They are flagged so then specific rendering can be done on the resulting sphere (a simplified example is presented in figure 2).

3.3 Visualization of Molecular Surface Properties on the Sphere

Once the deformed sphere converged onto the surface of the molecule, any property that can be calculated at the molecular surface can be mapped to the sphere. Then, a choice has to be made as to how to render the information on the sphere. One of the possible ways to represent the global topology in our visualization framework is shown in figures 3(b) and 3(d). Figure 3(b) shows the molecular surface of porin rendered by using computed distance from each point of the molecular surface to the centeroid of the molecule. In this display points farther away from center are colored purple and points closer to the center are colored green. Mapping of this information on the sphere using the same color scheme is shown in Fig. 3(d). To further help in visualizing the intricacies of the molecular surface, bump mapping [4] is applied to the final rendering. As part of this step, the sphere is rendered with ambient and diffuse light sources. The surface normals from the deformed state of the sphere are retained and used on the restored spherical shape, creating a bump map effect that helps to elucidate the underlying topology of the molecular surface. It is now possible to visualize both global surface properties as well as local features simultaneously on the spherical map.

4. CASE STUDIES AND DISCUSSION

In this section we go over several case studies, including a comparative discussion of the figures for which coloring schemes where discussed in previous section. Figure 3(a) shows a rendering of porin, with two accompanying spherical maps. The first map, figure 3(c) focuses on local curvature of the molecular surface. A number of interesting features can be observed with ease on the spherical map, whereas same features are barely visible on the three dimensional rendering of surface in fig 3(a). Specifically, a patch of locally concave surface (reddish region), highlighted by an oval, can be observed on the sphere. This geometric feature is not easily seen in 3(a). A closer observation of the molecular surface, as shown in figure 3(e), shows the pocket of interest.

The previous example focuses on local geometric feature presentation. An example capturing global geometric features of the molecular surface can be seen in Figure 3(b) and 3(d). As

shown in Fig. 3(d), the black patch on the sphere, representing the hole through the center of the molecule, lies in a green region. Since green points are close to the center of the molecule, it can be easily deduced that tunnel runs through the center of the molecule. On the other hand, the pair of black patches on the lower left of the spherical map is surrounded by purple region. This short tunnel lies on the peripheral of the molecular surface and the two patches are separated by a short distance on the sphere; this shows that the tunnel they map to is short. The reader can compare this visualization with the standard display in Fig 3(a), there the short tunnel is difficult to discern. Unlike the geometric properties visualized in this example, Figure 4 shows visualization of electrostatic field values computed using [1] from Crambin (PDB ID: 1CRN). The correlation between the distribution of electrostatic field values on the molecular surface and the sphere can be discerned from a side-by-side comparison.

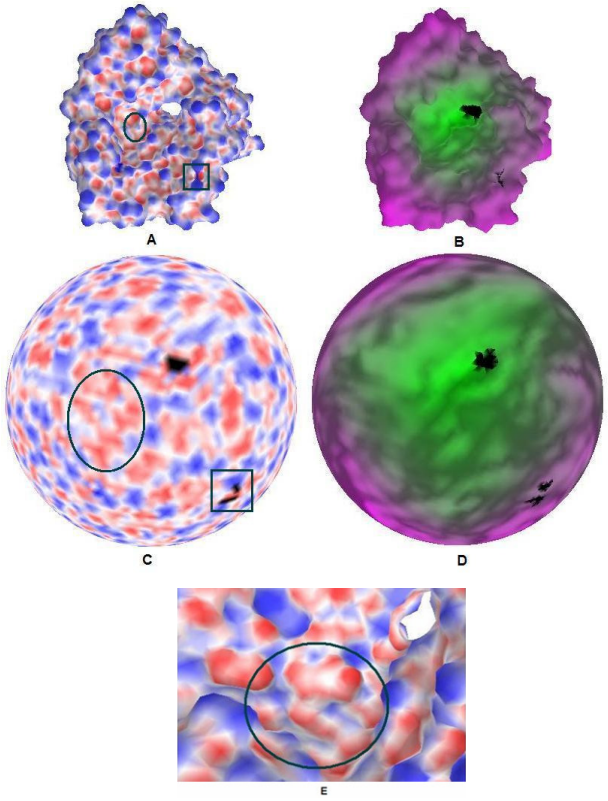

Figure 3. 2POR surface and two maps, for detailed discussion of coloring schemes, see section 4. For comparative discussion of highlighted regions of interest see section 5 A) Molecular surface, colored by local curvature: blue convex, red concave. B) Converged sphere, colored by distance to center. C) Spherical map of figure A. D) Spherical map of figure B. E) Zoomed in view of the pocket highlighted by oval in A and C.

Another example of this rendering scheme can be seen in figure 5. Fig 5(a), rendered with PyMOL, shows a molecular surface of hen egg-white lysozyme (PDB code 1HEL). Figure 5(b) shows a spherical map of 1HEL, colored by distance to center and oriented the same way as figure 5(a). On a spherical map a bright green region is clearly visible, surrounded by purple regions. This suggests a possible pocket. Even though this pocket is located in plain sight in the center of the molecule in figure 5(a), it's not as easily visible as it is on the spherical map. The existence of a binding site as indicated using our method is confirmed by a search of PDB. In figure 5(c), a co-crystallized structure with a ligand bound to this very binding site (PDB code 1HEW) is shown (the rendering is done with PyMOL).

5. CONCLUSION

Molecular surfaces are rich with information, which, owing to their innate complexity, often hinder analysis. In this paper we have proposed a method for representation and visualization of arbitrary molecular surfaces. Our method elucidates features of interest without potentially lossy simplification of surface characteristics. Other salient advantages of the method include representation of the surface in a standard coordinate system and simultaneous support for visualizing local-to-global molecular surface characteristics. The cornerstone of our method involves mapping the molecular surface to a standard spherical coordinate system. The mapping is achieved via a notion of deformable surfaces, where we iteratively deform the sphere until it converges on the surface. We also proposed several different strategies for presenting/visualizing information on the spherical coordinate system. Case studies presented in the paper demonstrate how this method can be used to visualize local, global, and non-geometric characteristics of molecular surface and instances where such visualizations provide better avenues to reason about surface characteristics than other methods at the state of the art. Owing to the conceptual novelty of the method and its advantages, it can be expected to play an important role in structural biology, molecular informatics, and applied areas like pharmaceutical drug discovery.

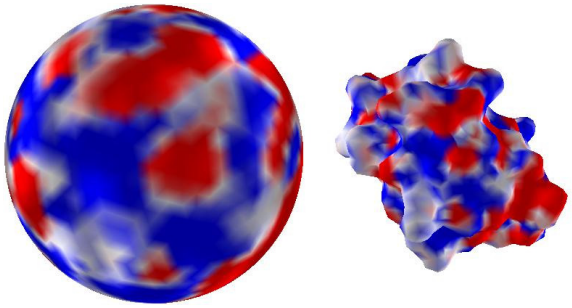

Figure 4. CRAMBIN (1CRN) Left) Spherical map of the electrostatic field values. Right) Surface rendered with electrostatic field.

6. ACKNOWLEDGMENTS

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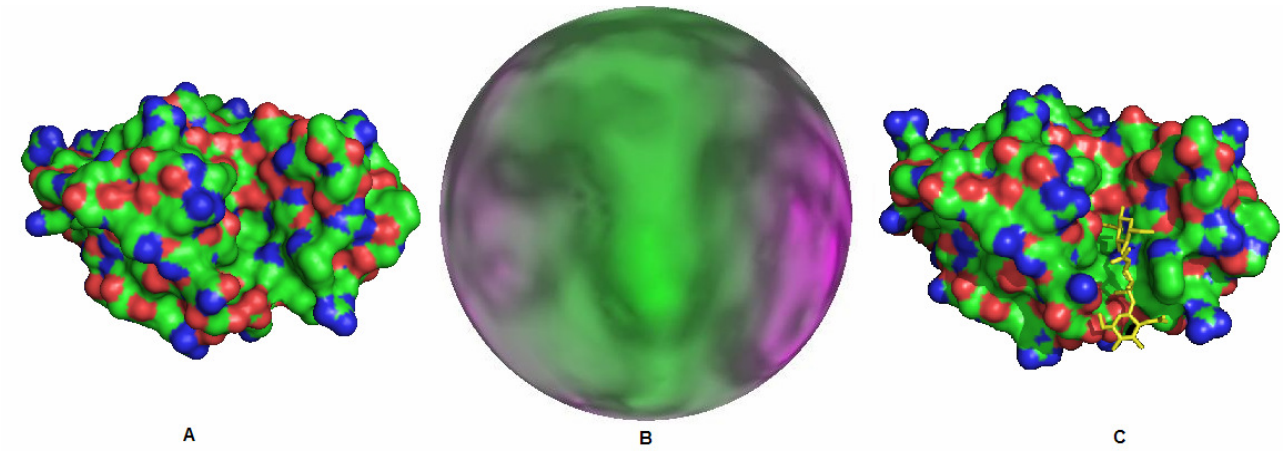

Figure 5. A) PyMOL rendering of 1HEL, note large pocket right in the middle is not clearly visible. B) Spherical map of 1HEL, note the large green region in the center, surrounded by purple regions, indicating a pocket. C) 1HEW (same molecule as 1HEL), PyMOL Rendering, with a bound ligand in the pocket.

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