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How round is a protein? Exploring protein structures for globularity using conformal mapping

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ABSTRACT

We present a new algorithm that automatically computes a measure of the geometric difference between the surface of a protein and a round sphere. The algorithm takes as input two triangulated genus zero surfaces representing the protein and the round sphere, respectively, and constructs a discrete conformal map f between these surfaces. The conformal map is chosen to minimize a symmetric elastic energy $E_S(f)$ that measures the distance of f from an isometry. We illustrate our approach on a set of basic sample problems and then on a dataset of diverse protein structures. We show first that $E_S(f)$ is able to quantify the roundness of the Platonic solids and that for these surfaces it replicates well traditional measures of roundness such as the sphericity. We then demonstrate that the symmetric elastic energy $E_S(f)$ captures both global and local differences between two surfaces, showing that our method identifies the presence of protruding regions in protein structures and quantifies how these regions make the shape of a protein deviate from globularity. Based on these results, we show that $E_S(f)$ serves as a probe of the limits of the application of conformal mapping to parametrize protein shapes. We identify limitations of the method and discuss its extension to achieving automatic registration of protein structures based on their surface geometry.

Keywords: proteins, genus zero surfaces, conformal mapping, diffeomorphism, triangular mesh

1 INTRODUCTION

Proteins, the end products of the information encoded in the genome of any organism, play a central role in defining the life of this organism. They catalyze most biochemical reactions within cells and are responsible, among other functions, for the transport of nutrients and for signal transmission within and between cells. As a consequence, a major focus of bioinformatics is to study how the information contained in a gene is decoded to yield a functional protein (Pevsner (2009)). The overall principles behind this decoding are well understood. The sequence of nucleotides that forms a gene is first translated into an amino acid sequence, following the rules encoded in the genetic code. The corresponding linear chain of amino acids becomes functional only when it adopts a three-dimensional shape, the so-called tertiary, or native structure of the protein. This is by no means different from the macroscopic world: most

28 proteins serve as tools in the cell and as such either have a defined or adaptive shape to function, much as
29 the shapes of the tools we use are defined according to the functions they need to perform.

30 Protein structures come in a large range of sizes and shapes. They can be divided into four major groups,
31 corresponding to *fibrous* proteins, *membrane* proteins, *globular* proteins, and *disordered* proteins. Fibrous
32 proteins are elongated molecules in which the secondary structure forms the dominant structure (**Fraser**
33 (2012)). They are insoluble, play a structural or supportive role in the cell, and are also involved in
34 movement (such as in muscle and ciliary proteins). Membrane proteins are restricted to the phospho-
35 lipid bilayer membrane that surrounds the cell and many of its organelles (**White and Wimley** (1999)).
36 These proteins cover a large range of shapes, from globular proteins anchored in the membrane by means
37 of a tail, to proteins that are fully embedded in the membrane. Globular proteins, also referred to as
38 *spheroproteins*, due to their compactness, have a unique structure derived from a non-repetitive sequence.
39 They range in size from one to several hundred residues, and adopt a compact structure **Lim** (1974); **Levitt**
40 **and Chothia** (1976); **Branden et al.** (1991). While proteins belonging to these three groups illustrate the
41 shape-defines-function rule mentioned above, intrinsically disordered proteins form a significant group of
42 exceptions, as they lack stable structures (**Dyson and Wright** (1999, 2005); **Dunker et al.** (2008)). Shape
43 remains important for those proteins, although it is its flexibility and plasticity that is of essence, as shown
44 for example in the case of P53 (**Oldfield et al.** (2009)).

45 The overall importance of shapes for proteins underlines the importance of being able to study,
46 measure and compare those shapes. The most relevant mathematical fields for this topic are Topology
47 and Geometry. One of the first questions that arise in these fields is what distinguishes a space from
48 the simplest and most symmetric shape, the sphere (**Bryant and Sangwin** (2011)). The 3-dimensional
49 Poincare conjecture for example, recently proved by Perelman (for review see **Morgan** (2005)), states
50 that if a closed 3-manifold is simply connected then it is homeomorphic to the 3-sphere. In differential
51 geometry, a main focus is how the local geometry of a space, as measured through its curvature, differs
52 from the local geometry of a sphere, and how that difference affects global properties of the space.
53 The Sphere Theorem of differential geometry states that a simply-connected smooth manifold whose
54 curvatures are sufficiently close to those of a sphere is itself a sphere (**Brendle and Schoen** (2009)).

55 The fundamental question that arises is how to describe the geometry of a shape such as a protein. The
56 configuration of atoms that constitute a protein can be explicitly obtained by high-resolution experimental
57 methods such as X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, or cryo-
58 electron microscopy. As of September 2014, the geometries of over 100,000 proteins are available in the
59 Protein Data Bank (PDB) (**Bernstein et al.** (1977); **Berman et al.** (2000)). The PDB file corresponding
60 to a protein contains the coordinates of all its atoms. This representation has its limitations. Indeed, it
61 corresponds to a rigid representation of a protein, while proteins have dynamic structures, a key feature
62 that explains their functions, over a large range of time scales, from the nanosecond to the minute
63 time scales (**Henzler-Widman and Kern** (2007); **Henzler-Widman et al.** (2007); **Vendruscolo and**
64 **Dobson** (2011)). This means that modeling them with a single rigid representative in 3-space $\mathbb{R}^3$ can be
65 problematic.

66 One approach to overcoming the challenges raised by flexibility is to work with the geometry of a
67 2-dimensional surface that encloses the protein, rather than with the 3-dimensional atomic coordinates.
68 Following the space-filling models such as those of Corey-Pauling-Koltun (CPK; **Corey and Pauling**
69 (1953); **Koltun** (1965)), a protein is represented as the union of balls, whose centers match with the
70 atomic centers and radii defined by van der Waals parameters. The structure of a protein is then fully
71 defined by the coordinates of these centers, and the radii values. One option for generating a 2-dimensional
72 surface that encloses a protein is to consider the geometric surface or boundary of its union of balls, the
73 vdW surface of the protein. Note that other definitions are possible, such as the accessible surface (**Lee**
74 **and Richards** (1971)), the molecular surface (**Richards** (1977)), and the skin surface (**Edelsbrunner**
75 (1999)). While the dynamics of a protein can cause some distortion of its surface, the geometry of this

76 surface is generally well preserved under motions, much more so than the occupied solid region in 3-
77 space. Focusing attention on the surface of the boundary of a protein is also biologically reasonable, since
78 the main biological functions of a protein take place at its surface.

79 Within this framework, the basic question about protein shape resemblance asks for a measure of the
80 similarity of two protein surfaces. With this paper, we begin an investigation of this question. Our eventual
81 aim is to get a meaningful measurement of the relative similarity of any pair of proteins. It seems useful
82 however to first compare protein geometries to a single well understood benchmark. We could take some
83 fixed protein as a benchmark, but the results we obtain would then be dependent on a rather arbitrary
84 choice of a reference protein. To develop our method in a geometrically meaningful framework, we use
85 the round sphere as a base shape to compare to a range of proteins. The sphere is the most symmetrical
86 surface in 3-space, and the resemblance of a protein to a sphere reflects the symmetry, convexity, and
87 globularity of the protein. With this in mind, we focus on the following question: How round is a protein?
88 A suitable answer would assign a nonnegative number to each protein that indicates how far away it is
89 from being round. This number should be stable under small perturbations, and not change significantly
90 for different poses of a single flexible protein. We also choose it to be independent of scale.

91 Ideally, shape comparison techniques aim at defining directly a map between any two shapes that is
92 as close to an isometry as possible. This is however a difficult problem, as the space of possible near-
93 isometric maps is extremely large and not straightforward to characterize mathematically. Despite these
94 difficulties, there have been many methods developed to find such mappings, including one for mapping
95 bio-molecular surfaces onto the sphere (**Rahi and Sharp** (2007)). These methods rest on the definition
96 of a distance measure that evaluates how close the map is to an isometry, on choices of sets of points on
97 the two shapes, and on an algorithm for finding the mapping between these sets of points that minimizes
98 this distance measure. The harmonic or Dirichlet energy (**Eck et al.** (1995); **Alliez et al.** (2002)), the
99 Procrustes distance and its continuous variant (**Lipman et al.** (2013a)), the Gromov-Hausdorff distance
100 and variants (**Bronstein et al.** (2006); **Mémoli** (2007)), and the conformal Wasserstein distance (**Lipman**
101 **and Daubechies** (2011); **Lipman et al.** (2013b); **Boyer et al.** (2011)) are popular distance measures used
102 in this context. The closest to-isometric mapping is then found by exhaustive evaluation of the chosen
103 distance measure over all permutations of the landmark points on the two surfaces (**Mémoli and Sapiro**
104 (2005)), by direct optimization, such as the generalized multi-dimensional scaling algorithm proposed by
105 Bronstein and colleagues in **Bronstein et al.** (2006), or through conformal parametrization of the surfaces
106 (**Gu and Yau** (2003); **Gu et al.** (2004)).

107 In this paper we introduce a new method for measuring the similarity between a protein and the sphere
108 that is based entirely on intrinsic geometry. It compares the two shapes by measuring the distortion of
109 an optimal conformal mapping of the surface of one to the surface of the other. A preliminary report of
110 this method was published in **Koehl and Hass** (2014). We assume that the surface of the protein is a
111 surface of genus zero in $\mathbb{R}^3$. This allows us to look for optimal diffeomorphisms (differentiable maps with
112 differentiable inverses) between the surface and the sphere. The restriction to genus zero is appropriate for
113 a wide variety of natural surface comparison problems, including facial recognition (**Wang et al.** (2005)),
114 alignment and comparison of brain cortical surfaces (see for example **Gu et al.** (2004); **Hurdal and**
115 **Stephenson** (2009)), and geometric identification and comparison of bones (for example **Boyer et al.**
116 (2011)), in addition to protein surfaces (**Rahi and Sharp** (2007)). Compared to the other techniques
117 for comparing genus zero surfaces mentioned above, the method we describe here has the advantage of
118 being both computationally efficient and dependent only on the intrinsic surface geometry of the protein.
119 Computational efficiency allows for comparisons with large collections of shapes, such as those found
120 in the Protein Data Bank. Dependence on the intrinsic surface geometry makes our method well suited
121 for modeling geometric similarities of flexible shapes, shapes that can bend over time to realize varying
122 configurations in space. A substantial number of proteins demonstrate substantial flexibility, and thus our
123 method seems well suited to their study.

124 As mentioned above, this paper is an extension of a previous study (**Koehl and Hass** (2014)). It differs
125 mainly in that we have modified the elastic energy used to measure the difference between the optimal

conformal mapping designed to map a surface onto another and an isometry, and we justify why. We also introduce a new quantitative measure of the similarity between protein surface and the round sphere, and describes how this measure allows to set the limits of the applications of conformal mapping to analyzing protein shapes. The paper is organized as follows. Section 2 provides the mathematical background for our algorithm: conformal geometry and measures of similarity between surfaces of genus zero. In Section 3, we provide the details of its implementation on discrete surfaces, as well as a description of the test cases used in the Results section. Section 4 presents and discusses the results obtained by our algorithm first on simple test cases to show the validity and power of the approach, then on a large dataset of proteins that are compared to the round sphere. We conclude the paper with a brief discussion on future developments.

2 MATHEMATICAL BACKGROUND

2.1 BASIC IDEA: FINDING AN OPTIMAL CONFORMAL MAPPING BETWEEN TWO SURFACES OF GENUS ZERO

Let F_1 and F_2 be two surfaces of genus zero. Our goal is to define a map $f : F_1 \rightarrow F_2$ that is as close as possible to an isometry, i.e. that minimizes the distortion of pairwise geodesic distances between points. When $F_2 = S^2$, i.e. the unit 2-sphere in $\mathbb{R}^3$ and F_1 and F_2 are scaled to have the same area, then f gives a measure of the roundness of F_1 . We always in this paper scale two surfaces to have the same area, which we can take to be 4π , the area of the unit sphere. We then say that F_1 is round if f is an isometry. For a surface that is not round, some metric distortion is found in any map to or from the sphere.

We now fix $F_2 = S^2$ to be isometric to the unit sphere. A deep result, the *Uniformization Theorem*, states that given any smooth genus zero surface F , there is always a conformal diffeomorphism from F_1 to S^2 (see **Bers** (1972)). Such conformal maps are not unique. Each conformal diffeomorphism $f : F_1 \rightarrow S^2$ is part of a family of conformal diffeomorphisms. The space of conformal diffeomorphisms from S^2 to itself forms the group $\text{PSL}(2, \mathbb{C})$, called the *Möbius* or *Linear-Fractional* transformations. Any conformal map $C : F_1 \rightarrow S^2$ can be composed with a conformal Möbius transformation $\phi : S^2 \rightarrow S^2$ to give a new conformal map $\phi \circ C : F_1 \rightarrow S^2$, and this construction gives all orientation-preserving conformal maps from F_1 to S^2 .

Given two surfaces F_1 and F_2 and a conformal mapping f between them, f can be understood as the composition of three conformal mapping functions, C_1 , m and C_2^{-1} (see Figure 1). In this composition, m is a Möbius transformation that may arise through composition with transformations ϕ_1 and ϕ_2 as described above. We can choose m among the six-dimensional space of Möbius transformations to yield minimal distortion.

2.2 DISTORTION FROM AN ISOMETRY

At a point $p \in F_1$, a conformal map $f : F_1 \rightarrow F_2$ stretches the metric of F_1 uniformly in all directions by a positive factor $\lambda(p)$. A conformal diffeomorphism then defines a real valued function $\lambda : F_1 \rightarrow \mathbb{R}^+$ that measures this point-wise stretching. The function $\lambda > 0$ is called the *dilation* and is defined by the formula

$$f^*(g_2) = \lambda^2 g_1 \quad (1)$$

where g_1, g_2 are the metrics on F_1, F_2 respectively. Since $\lambda > 0$, it can be represented in the form $\lambda = e^u$, where $u : F_1 \rightarrow \mathbb{R}$ is a real-valued function.

We use the following energy function to measure the distortion of a conformal map $f : F_1 \rightarrow F_2$ from an isometry. Recall that we have scaled all surfaces to have area equal to one.

Definition. The *symmetric elastic energy* of a conformal diffeomorphism $f : F_1 \rightarrow F_2$ with dilation function $\lambda = e^u$ is given by

$$E_S(f) = E_n(f) + E_n(f^{-1}) = \int_{F_1} u(x)^2 dA + \int_{F_2} u(y)^2 dA. \quad (2)$$

In Koehl and Hass (2014), we considered a different distortion energy function:

$$E(f) = \int_{F_1} (\lambda(x) - 1)^2 dA. \quad (3)$$

Equations 2 and 3 differ at two levels. First, the distortion over a whole surface is computed using either the logarithm u of the dilation function λ , or λ directly. The latter varies between 0 and $+\infty$, with values smaller than 1 corresponding to compression and values larger than 1 corresponding to expansion. As such, large compressions can contribute less to the total distortion than large dilations. In contrast, the function $u = \ln(\lambda)$ varies between $-\infty$ and 0 for compression, and between 0 and $+\infty$ for expansion, leading to a more balanced contribution for the two types of distortion. Second, $E_S(f)$ is symmetric and treats equally the distortions induced by f and those induced by f^{-1} . In contrast, $E(f)$ only accounts for the distortions induced by f . For these two reasons, we believe that $E_S(f)$ may be a better measure of distortion from an isometry.

The symmetric elastic energy defined in Equation 2 has the following properties (Hass and Koehl, in preparation):

1. For any pair of genus zero surface there is a smooth conformal homeomorphism between them that minimizes the symmetric elastic energy.
2. The symmetric elastic energy of a map is zero if and only if the map is an isometry. (Recall that we are assuming that all surface areas are equal to 4π .)

3 MATERIAL & METHODS

3.1 A GENERAL ALGORITHM FOR MAPPING TWO SURFACES OF GENUS ZERO

The algorithm described below is derived from our initial study of conformal mapping of genus zero surfaces described in Koehl and Hass (2014), which gives a comprehensive description. We focus here on the general concepts and on the differences with the original algorithm.

Let F_1 and F_2 be two surfaces of genus zero, represented by the meshes $\mathcal{M}_1$ and $\mathcal{M}_2$, respectively. Both meshes are taken to be triangular, with $\mathcal{M}_i = (V_i, E_i, T_i)$, $i = 1, 2$, where $\{V_i, E_i, T_i\}$ denote the vertices, edges and triangles, respectively. We note that these two meshes are completely independent of each other, and are likely to have different combinatorics.

As illustrated in Figure 1, we rely on the idea that a conformal mapping f between two surfaces F_1 and F_2 of genus zero can be written as the composition of two discrete conformal mappings C_1 and C_2 that parametrize S_1 and S_2 onto the sphere, and a Möbius transformation m . In optimizing the map produced from this composition, C_1 and C_2 are fixed, while m is variable and depends on six degrees of freedom, summarized in a parameter vector $\vec{h}$. The key to our approach is to choose the transformation m to minimize the sum of the distortions between the mesh $\mathcal{M}_1$ representing F_1 and its image $W_m(\mathcal{M}_1)$ warped by f onto F_2 , and between the mesh $\mathcal{M}_2$ representing F_2 and its image $W_m^{-1}(\mathcal{M}_2)$ warped by f^{-1} onto F_1 . The total distortion is a discrete version of the symmetric elastic energy given by Equation

2 and is computed as a sum over all edges of the two surface meshes:

$$E_S(f) = \sum_{e_{ij} \in E_1} \left(\ln \frac{l'_{ij}}{l_{ij}} \right)^2 \frac{A_{ijk} + A_{ijm}}{3} + \sum_{e_{kn} \in E_2} \left(\ln \frac{l'_{kn}}{l_{kn}} \right)^2 \frac{A_{knp} + A_{knq}}{3} \quad (4)$$

Here E_1, E_2 denote the set of edges in the meshes on F_1 and F_2 respectively, l_{ij} denotes the length of the edge $e_{ij} \in E_1$ that connects vertices v_i, v_j and l'_{ij} the distance from $f(v_i)$ to $f(v_j)$. Similarly l_{kn} denotes the length of the edge $e_{kn} \in E_2$ that connects vertices v_k, v_n and l'_{ij} the distance from $f^{-1}(v_k)$ to $f^{-1}(v_n)$. The areas of the two triangles adjacent to the edge e_{ij} are given by A_{ijk} and A_{ijm} . When f maps a pair of vertices v_i, v_j of F_1 to arbitrary points in F_2 , the distance between these points is computed by extending the metric on the edges of F_2 to a flat Euclidean metric on each 2-simplex of the triangulation.

We have developed all the tools we need to search for a conformal map between two surfaces of genus zero that has minimal distortion, as defined by Equation 4.

- (i) An algorithm for computing the discrete conformal mappings C_1 and C_2 :
While Riemann's Uniformization Theorem guarantees that any smooth genus zero surface F can be mapped conformally to the unit sphere, the theoretical underpinnings of the theory of discrete conformal maps are still being developed. Many methods have been developed to compute them in practice. We follow the approach proposed by Springborn and colleagues, which introduces a notion of discrete conformal equivalence (**Springborn et al. (2008)**). In this method, the mesh $\mathcal{M}$ representing a genus zero surface F is first made topologically equivalent to a disk by removing a vertex v_0 and its star. The transformed mesh is projected conformally on a plane through an optimization procedure (**Springborn et al. (2008)**). The planar mesh is then warped onto the sphere by stereographic projection. Vertex v_0 is reinstated on the North pole of the sphere and connected back to the mesh. Finally, we apply a Möbius normalization to ensure that the center of mass of all vertices is at the origin of the sphere. Full details on the implementation of this algorithm are provided in **Koehl and Hass (2014)**.
- ii) An algorithm for generating the warping of a discrete mesh onto a surface for a given Möbius transformation $m : S^2 \rightarrow S^2$:
This algorithm works as follows. A vertex v_i in $\mathcal{M}_1$ has image $v'_i = C_1(v_i)$ in the spherical mesh $C_1(\mathcal{M}_1)$. We locate the image $v''_i = m(v'_i)$ on the spherical mesh $C_2(\mathcal{M}_2)$, namely we identify the triangle t of $C_2(\mathcal{M}_2)$ that contains v''_i and compute barycentric coordinates (α, β, γ) of v''_i in t . Finally, we compute the position of $v'''_i = f(v_i)$ on the surface F_2 by propagating the barycentric coordinates (α, β, γ) onto the triangle t' in $\mathcal{M}_2$ that corresponds to t . Full details on the implementation of this method are provided in **Koehl and Hass (2014)**.

To simplify the notation, we write $E_S(f) = E_S(m(\vec{h})) = E_S(\vec{h})$ as the map f is determined by m which in turn is determined by the six parameters of $\vec{h}$. Simple calculations provide the analytical expressions for the symmetric elastic energy function $E_S(\vec{h})$ and its gradient with respect to $\vec{h}$. This allows us to apply a steepest descent algorithm to search for an optimum for the Möbius transformation m . Our general algorithm for comparing the two surfaces F_1 and F_2 represented with the discrete meshes $\mathcal{M}_1$ and $\mathcal{M}_2$ respectively, is then:

The scaling of the surface meshes in step (1) makes our comparison method insensitive to global changes of scale. While not necessary, this step is appropriate to measure scale invariant properties such as roundness. It is also appropriate when the global scale used to describe the vertex positions of the input surfaces is unknown. The damping parameter α_n in step (6) is obtained by solving the equation $E_S(\vec{h}_n + \alpha_n \nabla E_S(\vec{h}_n)) \leq E_S(\vec{h}_n)$ using a line search method. The value of TOL is set to a small constant related to machine error.

Algorithm 1 Conformal mapping with minimal distortion between discrete surfaces of genus zero

Initialization. (1) Scale $\mathcal{M}_1, \mathcal{M}_2$ to have total area one.
 (2) Find C_1 and C_2 that conformally map $\mathcal{M}_1$ and $\mathcal{M}_2$ onto the sphere, using the method described above.
 (3) Initialise Möbius transformation $m_0 = m(\vec{h}_0)$.
for $n = 0, \dots$ until convergence **do**
 (4) Generate $f(\mathcal{M}_1)$ and $f^{-1}(\mathcal{M}_2)$ using the warping method described above, where $m = m(\vec{h}_n)$.
 (5) Compute $E_S(\vec{h}_n)$ and its gradient $\nabla E_S(\vec{h}_n)$ with respect to $\vec{h}_n$.
 (6) Update $\vec{h}_{n+1} = \vec{h}_n - \alpha_n \nabla E_S(\vec{h}_n)$.
 (7) Check for convergence: if $E_S(\vec{h}_{n+1}) < \text{TOL}$, stop.
end for

238 We have implemented the whole procedure outlined in Algorithm 1 into a Fortran program,
 239 RoundProtein. The results of a run of this program include a warping of the mesh $\mathcal{M}_1$ onto the surface
 240 F_2 , $\mathcal{W}_2(\mathcal{M}_1)$ and its corresponding inverse, a warping of the mesh $\mathcal{M}_2$ onto the surface F_1 , $\mathcal{W}_1(\mathcal{M}_2)$,
 241 that minimizes distortion from an isometry among nearby conformal maps, as measured by the symmetric
 242 elastic energy. In addition, it gives a numeric measure of the geometric difference between $\mathcal{M}_1$ and $\mathcal{M}_2$
 243 based on Equation 4. When the surfaces F_1 and F_2 are isometric, any energy minimizer is an isometry.

244 When F_2 is set to be the round sphere, $d(F_1, S^2)$ is a measure of the roundness of the surface F_1 .

3.2 TRIANGULAR MESHES FOR REGULAR SHAPES

245 To compare surfaces of genus zero to the round 2-sphere S^2 , we need a triangular mesh $\mathcal{M}(S^2)$. We
 246 generate $\mathcal{M}(S^2)$ by positioning N points uniformly on the sphere and forming a triangulation from these
 247 N points.

248 Distributing points uniformly on the 2-sphere is one of eighteen unsolved mathematics problems
 249 proposed by the mathematician **Smale** (1998). We adopt the Thompson formulation of this problem and
 250 define it as the problem of determining the minimum electrostatic potential energy configuration of N
 251 electrons on the surface of a unit sphere, that repel each other with a force given by Coulomb's law,
 252 **Thomson** (1904). The total electrostatic potential energy of a N -electron configuration is expressed as the
 253 sum of all its pair-wise interactions,

$$U(N) = \frac{1}{4\pi\epsilon_0} \sum_{i < j} \frac{1}{\|r_i - r_j\|} \quad (5)$$

254 where ϵ_0 is the vacuum permittivity and r_i is the coordinate vector of electron i . A minimum value of
 255 $U(N)$ over the configurations of N distinct points is found by numerical minimization. We used for this
 256 the Matlab package “Uniform sampling of the sphere” available from **Semeshko** (2012). Once a minimum
 257 configuration is obtained, a triangular mesh is generated using QHull (**Barber et al.** (1996)). We note that
 258 the optimization of $U(N)$ is computationally intensive. To generate a mesh that is dense enough on the
 259 sphere, we have used the method described here for $N = 1000$ and subdivided the corresponding mesh
 260 recursively using triangular quadrisection (in this process, a triangle is subdivided into 4 triangles by
 261 adding the three edges that join the midpoint of its three sides).

262 In parallel, we have generated dense triangular meshes of the surfaces of the Platonic solids using a
 263 similar procedure. Starting from the vertices of a platonic solid, we generate a triangular mesh using
 264 QHull. This mesh is then subdivided recursively using triangular quadrisection.

265 Table 1 summarizes the characteristics of the triangular meshes generated for the sphere and the five
 266 Platonic solids.

Table 1. Characteristics of the discrete meshes of regular shapes

Shape	Vertices	Faces	Vertices in fine mesh	Faces in fine mesh
Tetrahedron	4	4	8194	16384
Cube	8	6	6146	12288
Octahedron	6	8	16386	32768
Dodecahedron	20	12	18434	36864
Icosahedron	12	20	10242	20480
Sphere			15970	31936

3.3 DATA SET OF PROTEIN STRUCTURES

The set of structures considered in this study is extracted from the database of 2930 sequence-diverse CATH (Orengo et al. (1997)) v2.4 domains used in a previous study (Kolodny et al. (2005)). As we focus on three-dimensional structures, we consider the first three levels of CATH, Class, Architecture and Topology, to give a CAT classification. We refer to a set of structures with the same CAT classification as a *fold*. We selected five of the most populated folds in the database of 2930 structures as the test set for all computational experiments run in the studies presented in this paper, including at least one fold from each CATH class: CATH fold 1.10.10, a fully α fold (arc repressor, 55 representatives), CATH fold 2.60.40, a fully β fold (immunoglobulin-like, 156 representatives), and three mixed $\alpha - \beta$ folds: 3.20.20, (TIM-like, 52 representatives), 3.30.70, (two layer sandwich, 85 representatives) and 3.40.50 (Rossmann fold, 185 representatives). These five folds include a total of 533 proteins.

We represent the surface of each protein by its skin surface (Edelsbrunner (1999)), given as a triangulated mesh that surround the atoms of the protein. We use the standard model in chemistry of representing a protein structure as a union of balls, with each ball corresponding to an atom. The skin surface of a protein is then computed from the boundary of the union of these balls, where the center of a ball is given by the coordinates of the corresponding atom, and its radius is set to $2^{1/6}\sigma + R_{H_2O}$, where σ is the vdW parameter for the atom in the AMBER94 force field (Cornell et al. (1995)) and R_{H_2O} is the radius of the solvent probe, set to 1.4 Å.

We generated high quality meshes for the skin surfaces of all 533 proteins using the program smesh, described in detail in Cheng and Shi (2004, 2009). Briefly, the algorithm implemented in smesh uses a Delaunay-based method to generate quality mesh for the skin surface incrementally. In particular, points are sampled one by one on the skin surface using a front advancing method. The Delaunay triangulation of the sample points is maintained using an incremental flipping algorithm developed by Lawson (1972). A subset of the Delaunay triangulation is extracted that defines candidate surface triangles. These candidate surface triangles form a partial mesh and guides the subsequent point samplings. The procedure is applied iteratively until an ϵ -sampling of the whole surface is obtained. The corresponding surface triangles define the skin surface mesh. The corresponding triangular meshes have similar sizes for all proteins, with approximately 25,000 vertices and 50,000 triangles on average. We checked that all the meshes have genus zero.

4 RESULTS AND DISCUSSION

4.1 HOW ROUND ARE THE PLATONIC SOLIDS?

We first consider the surfaces formed by the boundaries of the five Platonic solids: the tetrahedron (4 faces), the hexahedron, or cube (6 faces), the octahedron (8 faces), the dodecahedron (12 faces), and the icosahedron (20 faces). These highly symmetric surfaces serve as a collection of coarse to fine discrete

representations of the sphere, with known measures of the quality of the approximation. As such, they provide natural test cases for the effectiveness of our approach to measure surface roundness.

Figure 2 illustrates the quality of the optimal mapping obtained with RoundProtein between the sphere and the icosahedron, both represented with fine discrete triangular meshes whose characteristics are given in Table 1. The resulting warping of the icosahedron mesh onto the surface of the sphere shows 12 dense spots, corresponding to the 12 vertices of the icosahedron (left panel). In contrast, the warping of the discrete mesh representing the sphere onto the surface of the icosahedron shows smaller distortion. It represents the icosahedron surface well, with relatively large dilation at the vertices (red spots on the right panel of Figure 2). These dilations are expected as the mesh of the sphere needs to adapt to the angle defect at these vertices. Similar results were observed for the four other Platonic solids (results not shown).

Two common measures of the roundness of a surface $F \subset \mathbb{R}^3$ can also be computed analytically for the Platonic solids:

- i) The *sphericity* of a surface measures how efficiently the surface encloses volume. It is given as the ratio of the surface area of a sphere (with the same volume enclosed by the surface F) to the surface area of F :

$$Sph = \pi^{1/3}(6V)^{2/3}/A,$$

where V is the volume enclosed and A is the surface area. The sphericity is at most one, and equals one only for the round sphere.

- ii) The ratio R_{IC} of the radii of inscribed and circumscribed spheres. This is often used as a measure of roundness for convex surfaces, but is less useful for general shapes.

We will compare these roundness measures with E_S . Note however that these measures are *extrinsic*, depending on the particular embedding of a surface into $\mathbb{R}^3$. They will not be preserved under flexing and bending, unlike E_S .

In addition, we can measure local deformations between a Platonic solid and the sphere by computing the solid angle Ω at each vertex. The solid angle Ω is given by

$$\Omega = q\theta - (q - 2)\pi, \quad (6)$$

where

$$\sin \frac{\theta}{2} = \frac{\cos(\pi/q)}{\sin(\pi/p)}. \quad (7)$$

θ is the interior angle between any two face planes of the solid, p is the number of edges of each face, and q is the number of faces meeting at each vertex.

In Table 2 we report the values of these measures of roundness for all five Platonic solids as well as the minimal symmetric elastic energies obtained when computing the conformal mapping between the solids and the sphere using RoundProtein. As expected, the sphericity, R_{IC} , and the solid angles Ω increase as the number of faces of the solid increases, i.e. as the solid becomes a better approximation of the sphere. In parallel, E_S decreases, i.e. the differences between the conformal mapping constructed between the solid and the sphere and the isometry become smaller as the number of faces increases. The decrease in E_S is highly correlated with the increases in sphericity, R_{IC} , and solid angles, with Pearson's correlation coefficients of -0.92, -0.92, and -0.84, respectively.

We note that the order of the different measures of roundness does not precisely coincide. Sph and R_{IC} increase monotonically as the number of faces increases. These two measures capture the global shape of the solid. In contrast, the solid angle Ω shows a non-monotonic behavior, illustrated in Figure 3. Ω is a

Table 2. Roundness of the Platonic solids

Surface	# of faces	Sphericity, S_{ph}	R_{IC}	Solid angle, Ω	E_S
Tetrahedron	4	0.671	$\frac{1}{3} \approx 0.333$	0.551	0.96
Cube	6	0.806	$\frac{1}{\sqrt{3}} \approx 0.577$	1.571	0.12
Octahedron	8	0.846	$\frac{1}{\sqrt{3}} \approx 0.577$	1.360	0.24
Dodecahedron	12	0.910	0.795	2.962	0.02
Icosahedron	20	0.939	0.795	2.635	0.04
Sphere	Not defined	1.000	1.000	Not defined	0.00

measure of local differences with the sphere, as it measures how the local shape around a vertex of the solid differs from a round sphere. While the octahedron has more faces than the cube, its vertices have a smaller solid angle, i.e. they have less local resemblance to the sphere. The same difference in ordering is observed between the dodecahedron and the icosahedron. Interestingly, the symmetric elastic energy E_S captures these local differences between the shapes, while still decreasing as a shape gets closer globally to the sphere. As such, E_S is able to capture both local and non-local differences between a surface and a sphere.

4.2 HOW ROUND IS A PROTEIN?

Proteins come in a wide variety of sizes and shapes. Fibrous proteins, such as collagens that are important for structuring cellular tissues, have elongated shapes while globular spheroproteins that are responsible for catalyzing chemical reactions within cells adopt a compact structure. Understanding the relationship between a protein sequence, its shape, and its function is one of the fundamental problem in biology. Here we address a very specialized question within this problem, namely the characterization of the globularity of a protein, or a quantification of its roundness. A protein structure can be depicted in many different ways, each emphasizing different features of the protein. We focus on the geometry of a 2-dimensional surface that encloses the protein, as defined by the skin surface (Edelsbrunner (1999)).

We use CATH533 as our data set of proteins to assess our approach to measuring the roundness of a surface. CATH533 is a database of 533 protein structures that covers the three main classes of CATH: one fully α fold, one fully β fold, and three $\alpha - \beta$ folds (the TIM fold, an α/β plait, and the Rossmann fold) (see Material and Methods section above for details). We generated a mesh for each protein in CATH533 using the program smesh (Cheng and Shi (2004, 2009)) and computed the optimal conformal mapping between this corresponding mesh and the discrete mesh representing the 2-sphere using RoundProtein. In Figure 4, we show the distribution of corresponding optimized symmetric elastic energies E_S .

All proteins included in CATH533 are enzymes and therefore they are expected to be globular. Indeed, we observe that computing the optimal mappings f between these proteins and the sphere leads to mappings that are close to isometries, as measured by $E_S(f)$, the symmetric elastic energy of the optimal mapping given in Equation 4. Of the 533 proteins, 352 have an optimized $E_S(f)$ below 1, and 106 of those have an optimized $E_S(f)$ below 0.5. The “best” mapping, i.e. the one closest to an isometry, is observed for the protein with CATH code 1gci00. The latter corresponds to PDB code 1gci which contains the ultra-high resolution (0.78 Å) of *B. Lenti* subtilisin, a serine protease that is known to form a very compact beta barrel at its core (Kuhn et al. (1998)). The corresponding optimized symmetric elastic energy of 0.24 would make this serine protease similar to an octahedron when compared to the sphere (see Table2). The “worst” mapping, i.e. the least similar to an isometry, with an optimized symmetric elastic energy of 23.0, is observed for the protein with CATH code 1wwcA0. This is chain A from the PDB file 1wwc that contains the crystal structures of the neurotrophin-binding domains TrkA, TrkB, and TrkC, with chain A corresponding to TrkA. The TrkA domain is known to fold into an immunoglobulin-like structure, with

a core of β -sheet and two long loops at the N and C termini (Ultsch et al. (1999)). It is the presence of these two long loops that makes the structure deviate significantly from the sphere (see insert in Figure 4). Interestingly, the next to worst comparison of a protein surface with the 2-sphere is observed for the protein with CATH code 1hcrA0. This is chain A from the PDB file 1hcr, corresponding to the complex of a prokaryotic Hin recombinase bound to DNA. The recombinase adopts a 3 helix-bundle conformation, with two long flanking extended polypeptide regions that contact bases in the minor groove of the DNA (Feng et al. (1994)). As we only consider the structure of the recombinase, these two regions stand aside from the core helix bundle, leading to a less compact structure (see insert in Figure 4).

In Figure 5, we compare the optimized symmetric energy $E_S(f)$ of the mapping f between a protein surface and the sphere with the sphericity of the protein surface, computed using Equation 6, for all proteins in CATH533. Just as for the Platonic solids, $E_S(f)$ and the sphericity S_{ph} are correlated: as the sphericity increases, the mapping between the protein surface and the sphere improves, and $E_S(f)$ decreases. Interestingly, the correlation coefficient between $E_S(f)$ and S_{ph} for protein surfaces, -0.64, is significantly lower than the corresponding correlation coefficient for the Platonic solids, -0.92. We assign this difference to the fact that the latter are convex while the geometry of even globular proteins is more diverse, with more significant local differences to a round surface that are not captured by sphericity.

Figure 4 illustrates that the optimal conformal mapping between a protein surface that has long protruding regions and the sphere deviates significantly from an isometry. To help understand why this is the case, we compare in Figure 6 the surfaces of the three representative proteins identified in Figure 4 with the surfaces generated from the corresponding warping $f^{-1}(\mathcal{M}(S^2))$ of the mesh represented the sphere onto the surfaces of the three proteins, where the warping is generated with RoundProtein.

If the conformal mapping between a protein surface and the sphere is close to an isometry, it is expected that $f^{-1}(\mathcal{M}(S^2))$ closely follows the surface of the protein. This is indeed observed for the very compact protein 1gci00. The main distortions observed in the warped mesh occur at bumps in the surface (which correspond to the spherical representations of the atoms at the surface of the protein). In the case of the less compact proteins 1hcrA0 and 1wwcA0 however, the warped surfaces generated from $f^{-1}(\mathcal{M}(S^2))$ deviate significantly from the actual surfaces of the proteins. Most of the distortions occur at the protruding regions that are not present in the images of the spheres on the protein surfaces. The discrete conformal mappings of these protruding regions to the sphere introduce very large negative conformal factors on their vertices, which in turn lead to infinitesimally small edge lengths in the projected meshes and consequently large numerical errors. We have observed similar behaviors when computing conformal mappings between generic genus zero surfaces (Koehl and Hass (2014)). This problem is not specific to our method, as it appears in many conformal mapping procedures. In some cases approximating by a conformal map appears to be too restrictive. One solution is to introduce cone singularities in the regions with the worst distortions (see for example Springborn et al. (2008)).

Figure 6 illustrates that the distortions introduced by the restrictive condition that the mapping between the protein surface and the sphere be conformal lead to an image $f^{-1}(\mathcal{M}(S^2))$ of the mesh of the sphere onto the surface of the protein that does not capture well the geometry of this surface. One approach to measuring these distortions is to compute the ratio of the surface area A_W of $f^{-1}(\mathcal{M}(S^2))$ to the surface area A_P of the source mesh representing this protein. We plot this ratio against the symmetric elastic energy of the refined mapping f , $E_S(f)$, in Figure 7 for all 533 proteins in CATH533. If the mapping f is close to an isometry, there should be minimal distortion and $f^{-1}(\mathcal{M}(S^2))$ should be a good representation of the surface of the protein (as illustrated in Figure 6 for 1gci00). The ratio A_W/A_P should then be close to 1. This is indeed observed for the majority of the proteins in CATH533. We find that A_W/A_P is greater than 0.99 for 226 proteins, greater than 0.98 for 471 proteins, and greater than 0.95 for 512 proteins. This ratio decreases significantly as f deviates more and more from an isometry, with a minimal value of 0.79 for protein 1wwcA0. Interestingly, A_W/A_P and $E_S(f)$ are strongly correlated with a Pearson's coefficient of correlation of 0.95. This indicates that $E_S(f)$ has value as a tool to test whether a conformal map is accurately representing a given surface.

5 SUMMARY AND CONCLUSIONS

We have developed a new method for quantifying the compactness of a protein structure. In this new approach we compute the conformal map f between the surface of the protein (required to be of genus zero) and the 2-sphere that has minimal distortion, where distortion is defined as a symmetric elastic energy $E_S(f)$ that measures the distance between f and an isometry. It leads to flexible registration of the two surfaces and accurate measurements of their geometric dissimilarities. Its implementation within the program RoundProteins is based on fast and robust numerical methods, making surface comparisons feasible for large data sets of proteins. We have illustrated its use for quantifying the roundness of the Platonic solids and of 533 diverse protein structures. We have demonstrated that the elastic energy $E_S(f)$ captures both global and local differences between two surfaces. We have shown that our method identifies and measures the presence of protruding regions in protein structures that make them deviate from a compact shape.

This paper is a first step towards achieving automatic registration of protein structures based on their surfaces. The method described here is an extension of the approach described in **Koehl and Hass (2014)** and suffers from similar limitations. We note that it only applies to surfaces of genus zero and that it works best for surfaces that have uniform geometry, without long protrusions **Koehl and Hass (2014)**). In this paper, we have shown that this limitation can be used to generate valuable information. The difficulty that RoundProtein encounters in finding a conformal mapping f between a highly non-spherical protein surface and the 2-sphere translates into a high value for the symmetric elastic energy E_S of f . Such a high value measures the extent of the deviation of the protein from being approximately round. It also indicates the limits of the application of conformal mapping to parametrize protein shapes, as high values for E_S correspond to significant deviations between the representations of a surface given by its source mesh and the representation given by the parametrization formed by the target mesh (see Figure 6). For the limitation to genus zero surfaces, we note that the concept of discrete conformal structures can be extended to surfaces with arbitrary topology, either through the introduction of cone singularities (**Springborn et al. (2008)**), or through the definition of a discrete conformal equivalence between a Euclidean triangulation on the surface and a flat or hyperbolic triangulation (**Bobenko et al. (2010)**; **Tsui et al. (2013)**). Finding closest-to-isometric mappings for surfaces with genus greater than zero remains a topic for future studies.

Finally, we note that while the symmetric elastic energy of a conformal mapping between two surfaces F_1 and F_2 defined in Equation 2 is useful for measuring the differences between these two surfaces, it is not clear that it establishes a distance on the space of genus zero shapes. A number of important applications would benefit from an actual metric on the space of genus zero surfaces.

DISCLOSURE/CONFLICT-OF-INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

The two authors contributed equally to the work, as well as to the draft and following revisions of the manuscript.

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FIGURES

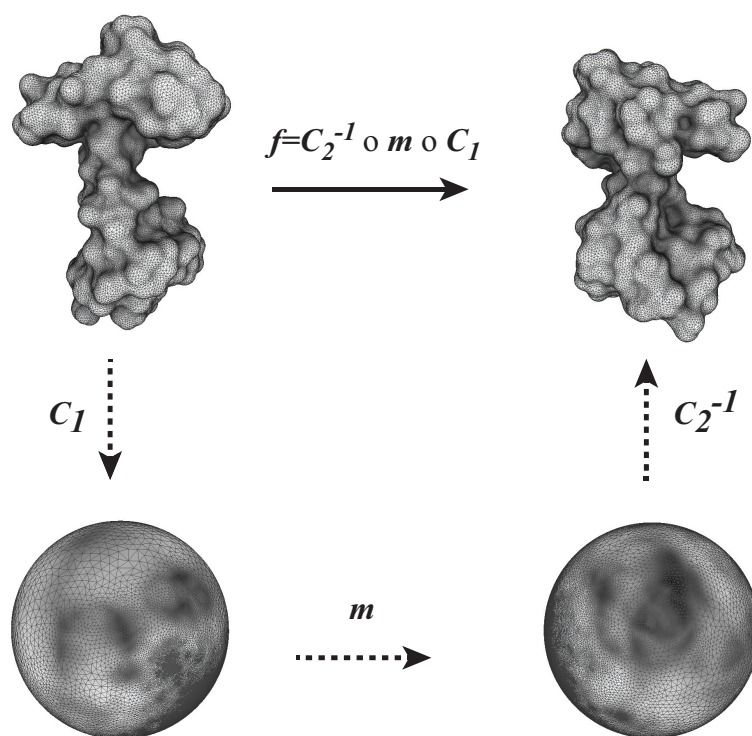


Figure 1. Globally optimal conformal mapping. The direct comparison of two surfaces S_1 and S_2 relies on the existence of a mapping f between these surfaces. In general a closed form for f is not known. When the two surfaces are of genus zero, it is however possible to construct f as a composition of three mappings C_1 , m , and C_2 , where C_1 and C_2 are conformal mappings from the surfaces S_1 and S_2 to the sphere and m is a bijective conformal mapping of the sphere to itself. The key to our approach is that the group of conformal self-mappings of the sphere is known: it is the group of Möbius transforms. As such, m is defined by six parameters that are optimized to yield minimal distortion (see text for details).

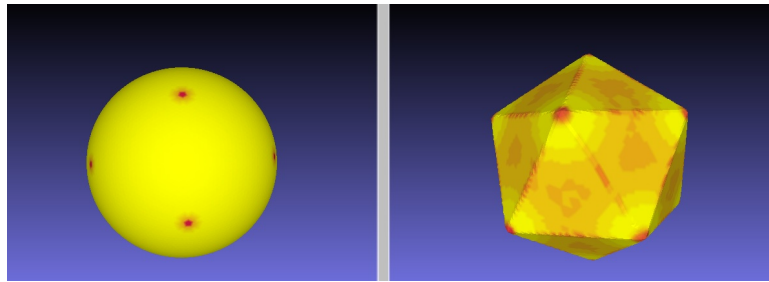


Figure 2. An E_S minimizing map between the sphere and the icosahedron. We computed the minimal distortion conformal map between the discrete mesh $\mathcal{M}_1$ representing the icosahedron and the discrete mesh $\mathcal{M}_2$ representing the sphere, where distortion is defined by the symmetric elastic energy given by Equation 4. The left panel shows the warping of the mesh $\mathcal{M}_1$ onto the surface of the sphere, while the right panel shows the warping of the mesh $\mathcal{M}_2$ onto the surface of the icosahedron. Red on the target indicates large dilation in the source.

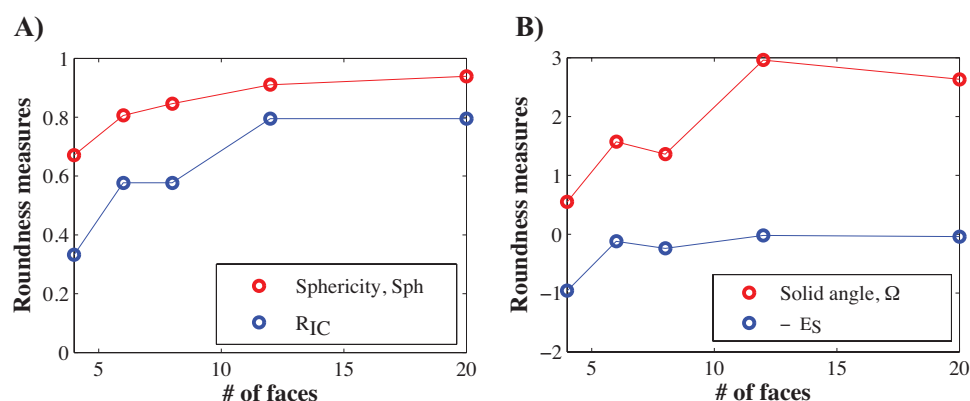


Figure 3. Global and local measures of roundness for the Platonic solids. We computed the sphericity, Sph , ratio of the radii of the inscribed and circumscribed sphere, R_{IC} , solid angle Ω at the vertices, and symmetric elastic energy E_S of minimal distortion conformal map between the Platonic solids and the sphere. A) Both Sph and R_{IC} vary monotonically with the number of faces of the solid, slowly converging to the expected value of 1 for a sphere. B) For both Ω and E_S (shown as $-E_S$ for clarity), we observe two inversions (i.e. non monotonic behavior) when compared to the number of faces: the cube and the octahedron, and the dodecahedron and icosahedron.

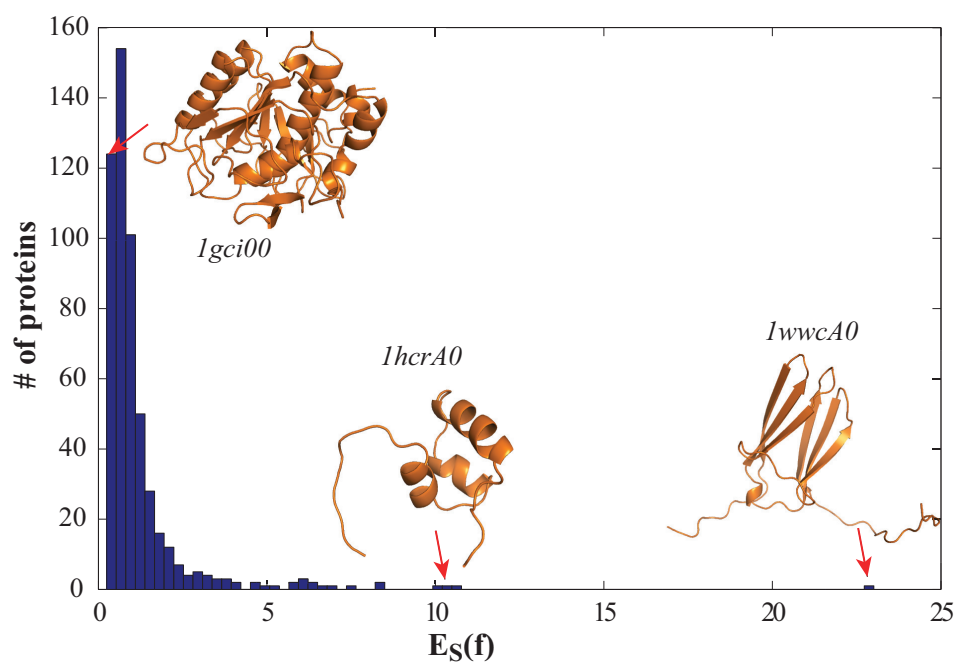


Figure 4. The distribution of the optimized symmetric elastic energies E_S for the 533 proteins in CATH533. Proteins *lgci00*, *lhcrA0* and *lwwcA0* are highlighted as they correspond to the proteins with the lowest (0.24), second to highest (10.2) and highest (23.0) symmetric elastic energies, respectively.

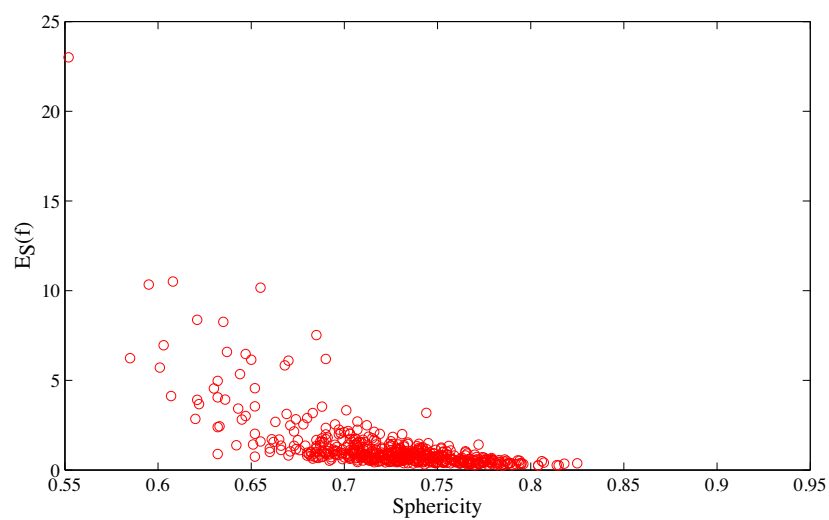


Figure 5. The optimized symmetric energy of the conformal mapping between the surface of a protein and the round sphere, E_S , versus the sphericity of the protein surface, for all 533 proteins in CATH533.

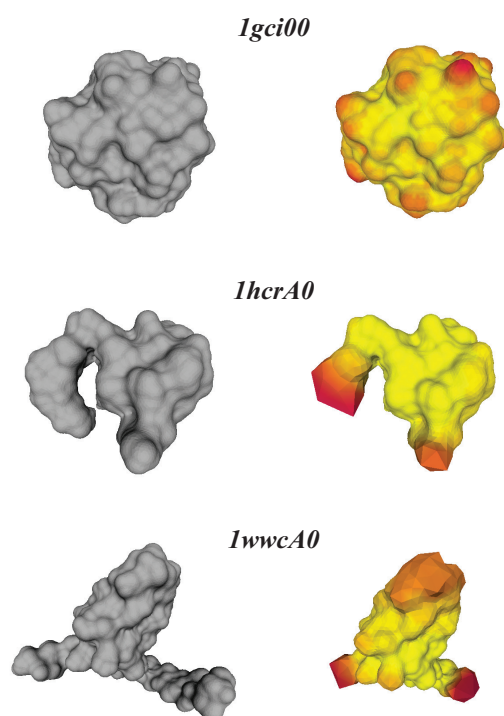


Figure 6. Distortions in the conformal maps between protein surfaces and the sphere. For the three proteins 1gci00, 1hcrA0, and 1wwa0 (see text for details), we compare their discrete skin surfaces (left panels), with the optimized surfaces generated from the conformal warping of the mesh representing the sphere onto the skin surfaces (right panels). Red on the warped surface indicates large distortions of the source mesh.

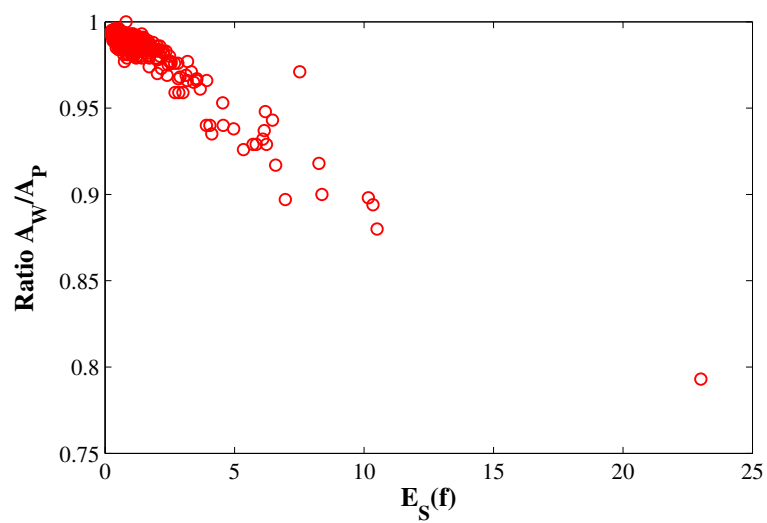


Figure 7. The estimated distortion of the image $f^{-1}(\mathcal{M}(S^2))$ of the mesh of the sphere onto the surface of a protein, measured as the ratio of the surface area of this image and the surface area of the mesh representing the protein is plotted against the optimized symmetric energy of the conformal mapping f , $E_S(f)$.

Figure 1.JPEG

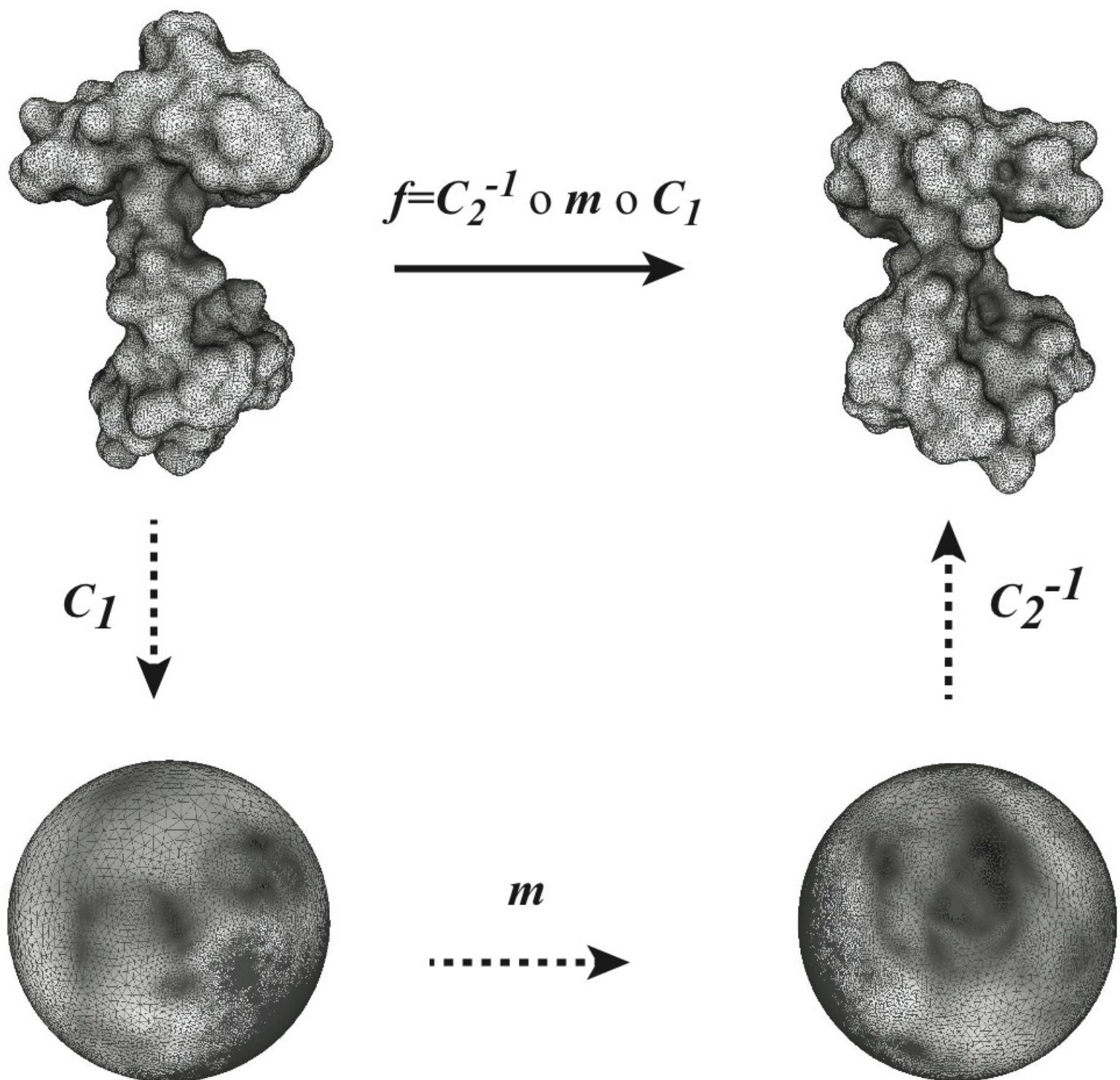


Figure 2.JPEG

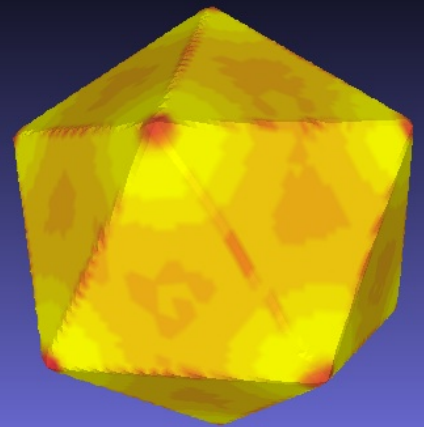
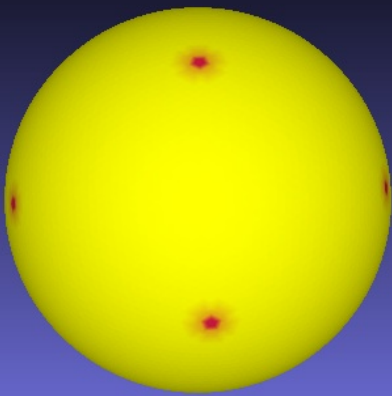


Figure 3.JPEG

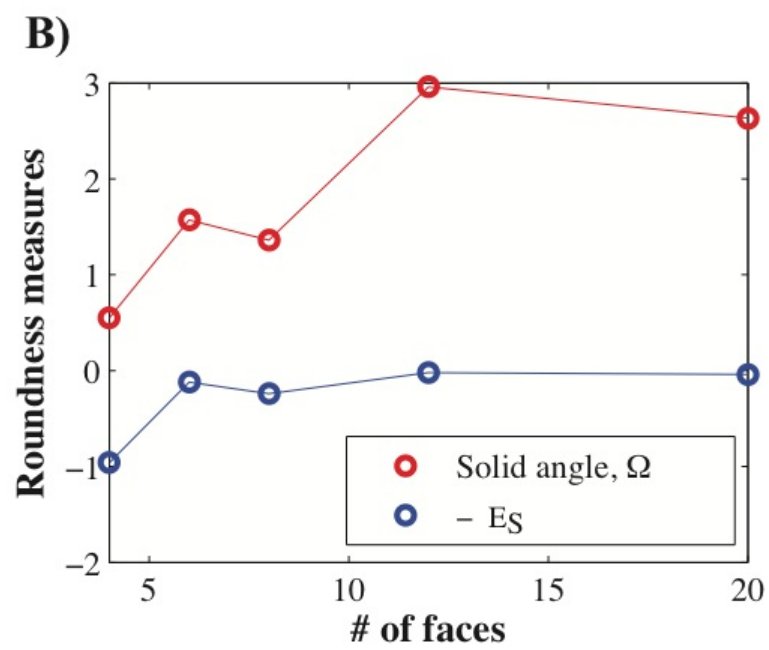
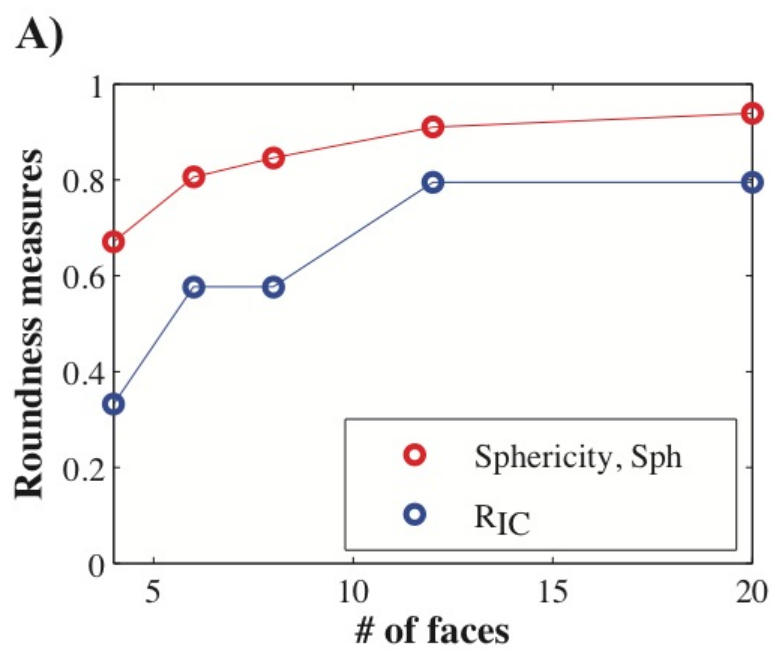


Figure 4.JPEG

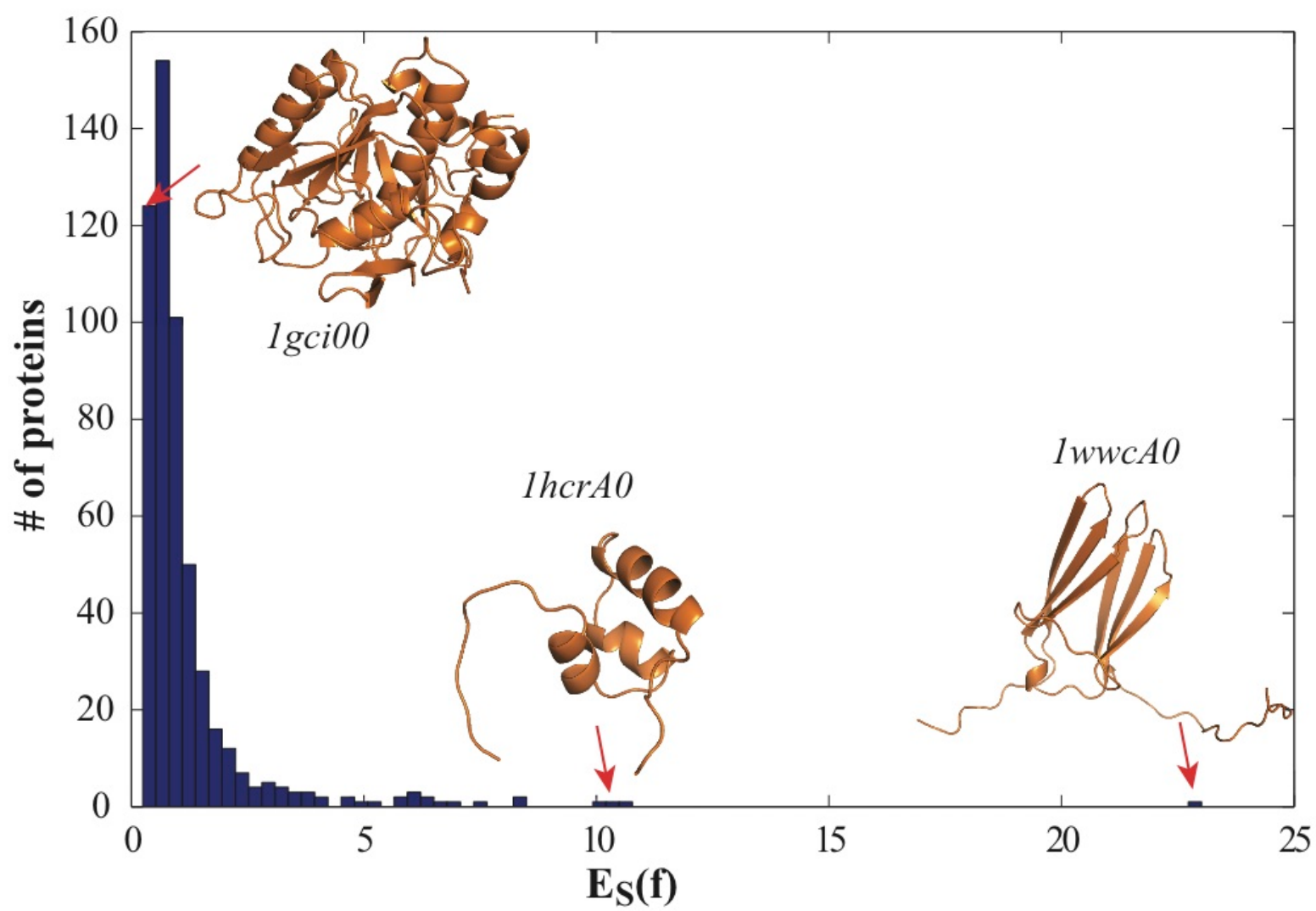


Figure 5.JPEG

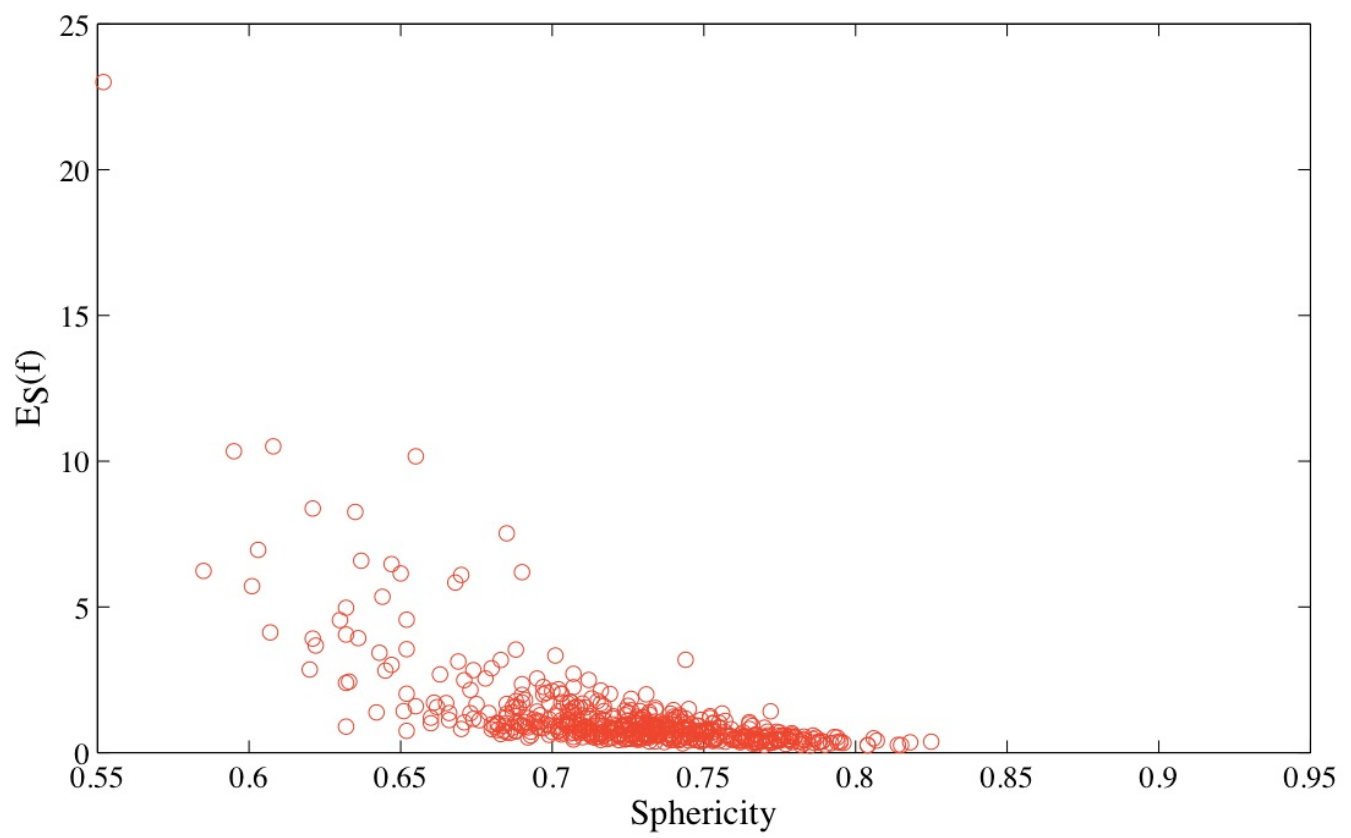
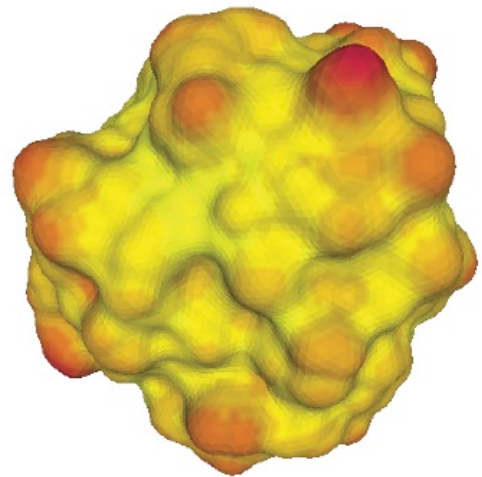
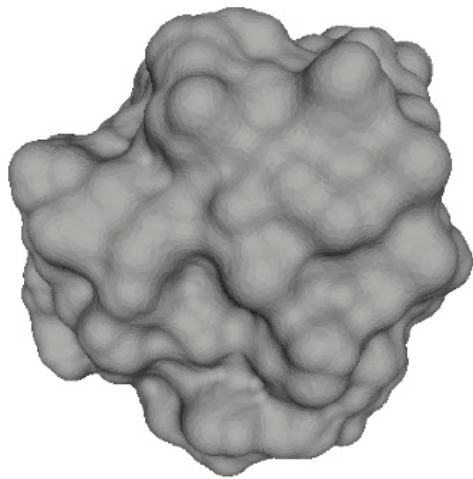
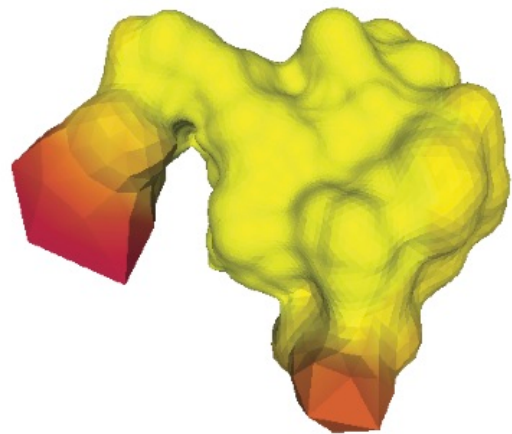
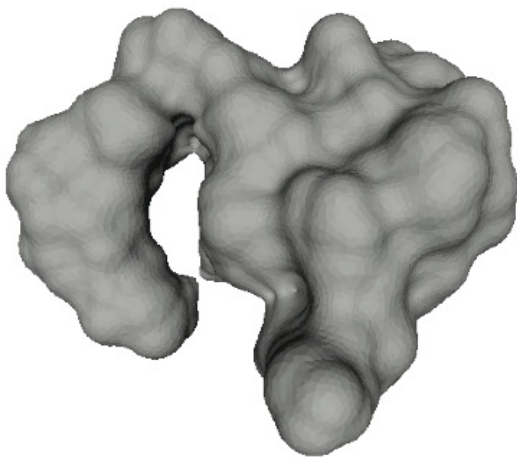


Figure 6.JPEG

1gci00



1hcrA0



1wwcA0

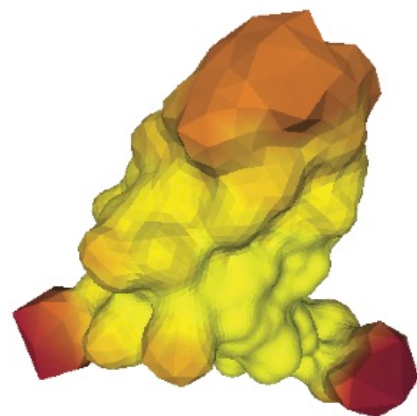
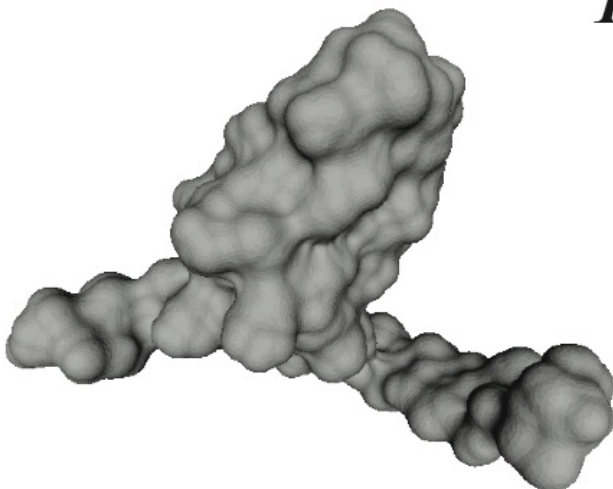


Figure 7.JPEG

