DISCRETE DIFFERENTIAL GEOMETRY OF PROTEINS: A NEW METHOD FOR ENCODING THREE-DIMENSIONAL STRUCTURES OF PROTEINS

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Abstract. In nature the three-dimensional structure of a protein is encoded in the corresponding gene. In this paper we describe a new method for encoding the three-dimensional structure of a protein into a binary sequence. The feature of the method is the correspondence between protein-folding and “integration”. A protein is approximated by a folded tetrahedron sequence. And the binary code of a protein is obtained as the “second derivative” of the shape of the folded tetrahedron sequence. With this method at hand, we can extract static structural information of a protein from its gene. And we can describe the distribution of three-dimensional structures of proteins without any subjective hierarchical classification.

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1. Overview

In nature the three-dimensional structure of a protein is encoded in the corresponding gene. In this paper we describe a new method for encoding the three-dimensional structure of a protein into a binary sequence (Fig. 1).

In the method a protein is approximated by a tetrahedron sequence. For example, approximation Fig. 1(b) is obtained by folding tetrahedron sequence Fig. 1(c), where three tetrahedrons are assigned for each amino-acid. We would obtain more precise approximation if we use more tetrahedrons.

The feature of the method is the correspondence between protein-folding and “integration”. And the binary sequence is obtained as the “second derivative” of the shape of the folded tetrahedron sequence.

With this method at hand, we can extract static structural information of a protein from its gene. And we can describe the distribution of three-dimensional structures of proteins without any subjective hierarchical classification.

2. Basic idea: encoding of two-dimensional objects

For simplicity we shall explain the basic idea behind the paper in the case of two-dimensional objects, where we use triangle sequences for approximation.

2.1. Triangle sequence. Consider a unit cube in the three-dimensional Euclidean space \( \mathbb{R}^3 \) whose vertices are given by \( v_1, v_x, v_y, v_z, \ldots, \) and \( v_x, v_y, v_z := (l, m, n) \in \mathbb{Z}^3 \) (Fig. 2(a)). And draw lines \( v_1v_x, v_1v_y, \) and \( v_1v_z \). Then, each of three upper faces is divided into two slant-triangle-tiles. For example, \( v_1v_xv_yv_z \) is divided into two slant-tiles \( v_1v_xv_y \) and \( v_1v_yv_z \).

Firstly, by piling up these unit cubes in the direction from \( v_x, v_y, v_z \) to \( v_1 \), we obtain “peaks and valleys” with a “drawing” on it. The drawing is uniquely determined by its peaks and divides the surface into a collection of slant-triangle-tile sequences. For example, the drawing of Fig. 2(b) is determined by two peaks, left \((2, 0, -1)\) and right \((0, 0, 0)\). And we denote the drawing by \( Cone^* \{x^2/z, 1\} \).

![Diagram](image)

**Figure 1.** Overview. (a): Schematic diagram of 2HIU chain A (Insulin, human). (b): Approximation of 2HIU by a tetrahedron sequence. (c): The \( U/D \) sequence of approximation (b). (d): The amino-acid sequence of 2HIU. (The figure (a) is prepared using **WebLab Viewer** (Molecular Simulations Inc.).)
Figure 2. Basic idea. (a): Unit cube in $\mathbb{R}^3$ and its projection on $H$. (b): Slant-tile sequences and flat-tile sequences defined by $Cone^*\{x^2/z, 1\}$. (c): Slant-tiles over a flat-tile on $H$.

Secondly, by the projection onto the hypersurface $H := \{(a, b, c) \in \mathbb{R}^3 | a + b + c = 0\}$, we obtain a division of $H$ into a collection of flat-triangle-tile sequences. For example, the gray slant-tile sequence is projected onto the gray flat-tile sequence on $H$ in Fig.2(b). We write $a[uv]$ for slant-tile $v_1v_2v_3v_4v_5v_6$ and $|a[uv]|$ for the corresponding flat-tile. For example, $1[xy]$ for $v_1v_2v_3$. Note that there are three types of slant-tiles over a flat-tile (Fig.2(c)). We shall see in the appendix that “peaks and valleys” specifies a “discrete vector field” of flat-tiles on $H$.

Finally we obtain a binary code of the shape of a flat-tile sequence by arranging up ($U$) and down ($D$) of the corresponding slant-tile sequence. For example, the gray flat-tile sequence in Fig.2(b) is encoded into $U/D$ sequence $U - U - D - D - U - U - U - D - D - D - D - D$. In general we need more than one drawing to encode a flat-tile sequence because of overlaps among its peaks (Fig.3(c)). Each drawing encodes a part of the flat-tile sequence and its code is obtained by patching those “local codes” together.

2.2. Encoding of two-dimensional objects. Now let’s encode the two-dimensional object shown in Fig.3(a). First of all we should give a flat-tile sequence which approximates the object (Fig.3(b)).

Then, using encoding table Table I(a), we obtain a binary code of the object (Fig.3(c)). The process is going on as follows:

Step 1. Choose an initial value, say $U$,
Step 2. By the second row of the table, the second value is $U$,
Step 3. By the fourth row of the table, the third value is $D$, ....

As the result we obtain $U/D$ sequence

$$(1) \quad U - U - D - D - U - U - D - D - U - D - D - D - D - D.$$ 

Fig.3(c) shows the corresponding slant-tile sequence. In this case we need two drawings because of the overlap between two peaks $z^2/(y^2x)$ and $z^3/x^2$. The left drawing $Cone^*\{1, z/y^2, z^2/(xy^2), z^3/x^2\}$ corresponds to the first sixteen tiles and the right drawing $Cone^*\{z^3/x^2\}$ to the last five tiles.
Figure 3. Encoding of a two-dimensional object. (a): Two-dimensional object. (b): Approximation by a triangle sequence. (c): Two drawings $\text{Cone}^*\{1, z/y^2, z^2/(xy^2), z^3/x^2\}$ and $\text{Cone}^*\{z^3/x^2\}$ which encode approximation (b).

Table 1. Tables for two-dimensional objects. (a): Encoding table. (b): Decoding table. (The gray tile is the current one.)

2.3. Decoding of $U/D$ sequences in $\mathbb{R}^2$. To decode $U/D$ sequences in $\mathbb{R}^2$ we use decoding table Table 1(b). For example, decoding process of $U/D$ sequence $\text{I}$ is going on as follows:

Step 1. Choose an initial flat-tile, say $[x[yx]],$
Step 2. By the fourth row of the table, the second flat-tile is $[1[xy]],$
Step 3. By the third row of the table, the third flat-tile is $[1[xz]], \ldots$.

As the result we obtain the flat-tile sequence shown in Fig 3(b).

3. Encoding of three-dimensional objects

If we consider unit cubes in the four-dimensional Euclidean space $\mathbb{R}^4$, we shall obtain a three-dimensional drawing made up of slant-“tetrahedron”-tiles. And we approximate a three-dimensional object by a tetrahedron sequence (Fig 1(c)), where

(1) each tetrahedron consists of four short edges and two long edges, where the ratio of the length is $\sqrt{3}/2$ and
(2) successive tetrahedrons are connected via a long edge and have the rotational freedom around the edge.
Figure 4. Encoding of three-dimensional objects. (a): Unit cube in $\mathbb{R}^4$ and its projection on $H$. (b): Slant-tile sequence and flat-tile sequence defined by three peaks $P_1 = 1$, $P_2 = z^2/(x^3yw)$, and $P_3 = z^2/(x^2y^2w)$. (c): Slant-tiles over a flat-tile on $H$. (In the figures arrows indicate the direction of “down”.)

3.1. Tetrahedron sequence. Consider a unit cube in the four-dimensional Euclidean space $\mathbb{R}^4$ whose vertices are given by $v_1, v_x, v_y, v_z, v_w, \ldots$, and $v_{xyzw}$, where $v_{x'y'z'w'} := (l, m, n, k) \in \mathbb{Z}^4$ (Fig. 4(a)). And divide each of four upper three-dimensional faces into six slant-tetrahedron-tiles. For example, the face defined by $v_1, v_x, v_z, v_w$ is divided into six slant-tiles $v_1v_xv_zv_{xyzw}$, $v_1v_yv_zv_{yxzw}$, $v_1v_xyv_zv_{xzyw}$, and $v_1v_zv_xv_{xzyw}$.

Firstly, by piling up these unit cubes in the direction from $v_{xyzw}$ to $v_1$, we obtain four-dimensional “peaks and valleys” with a three-dimensional “drawing” on it. The drawing is uniquely determined by its peaks and divides the three-dimensional surface into a collection of slant-tetrahedron-tile sequences. For example, the drawing of Fig. 4(b) is determined by three peaks $P_1, P_2$, and $P_3$. And we denote the drawing by $\text{Cone}^*\{P_1, P_2, P_3\}$.

Secondly, by the projection onto the hypersurface $H := \{(a, b, c, d) \in \mathbb{R}^4 \mid a + b + c + d = 0\}$, we obtain a division of $H$ into a collection of flat-tetrahedron-tile sequences. For example, Fig. 4(b) shows a slant-tile sequence and its projection onto $H$. We write $a[uvw]$ for slant-tile $v_1v_xv_yv_{xyzw}$ and $a[uvw]$ for the corresponding flat-tile. Note that there are four types of slant-tiles over a flat-tile (Fig. 4(c)). For example, $|1[xyz]| = |x[yzw]| = |xy[zwx]| = |xyz[wxy]|$.

Finally we obtain a binary code of the shape of a flat-tile sequence by arranging up ($U$) and down ($D$) of the corresponding slant-tile sequence. For example, the flat-tile sequence shown in Fig. 4(b) is encoded into $U/D$ sequence

$$U^6 - D^4 - U^7 - D - U - D.$$  

3.2. Encoding of three-dimensional objects. To encode three-dimensional objects we use encoding table Table 2(a). For example, encoding of the flat-tile sequence shown in Fig. 4(b) proceeds as follows:

- Step 1. Choose an initial value, say $U$,
- Step 2. By the second row of the table, the second value is $U$,
- Step 3. By the second row of the table, the third value is $U$, . . .

As the result we obtain $U/D$ sequence (2).
3.3. **Decoding of U/D sequences in** $\mathbb{R}^3$. To decode $U/D$ sequences in $\mathbb{R}^3$ we use decoding table Table 2(b). For example, decoding of $U/D$ sequence $2)$ proceeds as follows:

- **Step 1.** Choose an initial flat-tile, say $[xw^2z^2xz]$.
- **Step 2.** By the fourth row of the table, the second flat-tile is $[xwz^2wz]$,.
- **Step 3.** By the fourth row of the table, the third flat-tile is $[xwz^2zw]$, . . . .

As the result we obtain the flat-tile sequence shown in Fig.4(b).

### 4. Examples

#### 4.1. Double helix.

Here let’s consider the double helix shown in Fig.5(a) which has 12 tiles per turn. (Cf. DNA has an average of 10.9 (type A) or 10 (type B) nucleotide pairs per turn ([1]).) To encode the shape of the helix, it is enough to consider the flat-tile sequence shown in Fig.5(b).

Using Table 2(a) with initial slant-tile $y[zxy]$, we obtain two drawings of Fig.5(c). $Cone^*\{P_1, P_2\}$ (left) encodes the first ten tiles. And $Cone^*\{P_2, P_3\}$ (right) encodes the last ten tiles. By patching these local codes together, we obtain the $U/D$ code of helix Fig.5(b):

$$U - U - D - D - D - D - D - U - U - D - D - D - U - U - D - D.$$

#### 4.2. 2HIU chain A (Insulin, human).

Next let’s consider the three-dimensional structure of 2HIU chain A (Fig.1). Using Table 2(a) with initial slant-tile $zw[xyz]$,
we obtain eight drawings:

- $Cone^*(\{z/y, 1/(x^2w), 1/(x^2z)\})$ for [1, 14],
- $Cone^*(\{1/(xy), 1/(x^2w), 1/(x^2z)\})$ for [7, 18],
- $Cone^*(\{1/(xy), 1/(x^3zw), 1/(x^3z^2), w/(xyz)\})$ for [13, 29],
- $Cone^*(\{1/(xyz^2), 1/(x^3zw), 1/(x^3z^2), xw/y^2\})$ for [16, 42],
- $Cone^*(\{xw^2/(yz), w/y, xw/y^2\})$ for [36, 45],
- $Cone^*(\{xw^2/(yz), 1/y^2, x/y^3\})$ for [40, 51],
- $Cone^*(\{x/(y^4z), 1/y^2, x/(y^4w)\})$ for [45, 57],
- $Cone^*(\{x/(y^4z), 1/(y^4w^2)\})$ for [52, 63].

([n, m] denotes the part of the sequence from the n-th tile to the m-th tile.) By patching these local codes together, we obtain the $U/D$ code of the three-dimensional structure of the protein (Fig. 1(c)):

$$U - U - U - D - U - U - U - D - U - U - D - D - U - D - D - D - U - D - U - U - D - U - U - D - U - D - U - D - U - U - D - D - D - U - U - D - U - U - D - U - U - D - U - U - D - U - U - D - D - D - U - D - D - U - U - D - U - U - D - U - U - D - U - U - D - U - U - D - D - D - U - U - D - U - U - D - U - U - D - D - D - U - U - U - D - D - D - D - D - U - U - D - D - D - U - U - D - U - U - D - U - U - D - U - U - D - D - D - U - U - D - U - U - D - D - D - U - U - U - D - D - D - D - D - U - U - D - U - U - D - U - U - D - D - D - U - U - U - D - U - U - D - D - D - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - U - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D - D - D - D - U - U - U - D - D -
Table 3. U/D code and the amino-acid sequence of 2HIU chain A. (0 denotes D − D − D, 1 denotes D − D − U and so on.)

| No. | Amino-acid | U/D code |
|-----|------------|----------|
| 1   | GLY        | 7        |
| 2   | ILE        | 3        |
| 3   | VAL        | 6        |
| 4   | GLU        | 3        |
| 5   | GLN        | 1        |
| 6   | CYS        | 3        |
| 7   | CYS        | 6        |
| 8   | THR        | 3        |

| No. | Amino-acid | U/D code |
|-----|------------|----------|
| 9   | SER        | 0        |
| 10  | ILE        | 3        |
| 11  | CYS        | 4        |
| 12  | SER        | 0        |
| 13  | LEU        | 3        |
| 14  | TYR        | 1        |
| 15  | GLN        | 3        |
| 16  | LEU        | 6        |

| No. | Amino-acid | U/D code |
|-----|------------|----------|
| 17  | GLU        | 3        |
| 18  | ASN        | 6        |
| 19  | TYR        | 3        |
| 20  | CYS        | 6        |
| 21  | ASN        | 0        |

Appendix A. Differential geometry of N-hedron tiles

A.1. Space of N-hedron tiles. Let $L_N^*$ be the collection of all integer points of the N-dimensional Euclidean space $\mathbb{R}^N$:

$$L_N^* := \{ x_1, x_2, \ldots, x_N | l_i \in \mathbb{Z} \text{ for all } i \}.$$ 

And consider the collection $S$ of all “slant” N-hedrons defined by $L_N^*$:

$$S := \{ a [x_{\rho(1)} \cdots x_{\rho(N-1)}] | a \in L_N^*, \rho \in S_N \},$$

where $S_N$ is the $N$-th symmetric group and $a [x_{\rho(1)} \cdots x_{\rho(N-1)}]$ denotes the convex hull $\text{conv}[a_0, a_1, \ldots, a_{N-1}]$ of $N$ points $a_0 = a, a_1 = ax_{\rho(1)}, \ldots, a_{N-1} = ax_{\rho(1)}x_{\rho(2)} \cdots x_{\rho(N-1)}$ in $\mathbb{R}^N$:

$$a [x_{\rho(1)} \cdots x_{\rho(N-1)}] := \left\{ \prod_{0 \leq i < N} a_i^{\lambda_i} | 0 \leq \lambda_i \in \mathbb{R} \text{ s.t. } \sum_{0 \leq i < N} \lambda_i = 1 \right\}.$$ 

The collection $B$ of all “flat” N-hedrons is defined as the quotient of $S$ by “shift operator” $\sigma$ on $S$ (Fig.1(a)). That is, $B := S/\sigma$, where

$$\sigma (a [x_{\rho(1)} \cdots x_{\rho(N-1)}]) := ax_{\rho(1)} [x_{\rho(2)} \cdots x_{\rho(N)}].$$

A.2. Differential structure on $B$. “Tangent bundle” $T[B]$ on $B$ is defined as the quotient of $S$ by $\sigma^N$:

$$T[B] := S/\sigma^N,$$

$$\pi : T[B] \to B, \pi (s \mod \sigma^N) := s \mod \sigma.$$ 

We identify $T[B]$ with $B \times \{ e/x_1, e/x_2, \ldots, e/x_N \} (e = x_1x_2 \cdots x_N)$ by one-to-one correspondence

$$s \mod \sigma^N \sim (s \mod \sigma, Ds),$$

where the “gradient” $Ds$ of $s \in S$ is defined by

$$Da [x_{\rho(1)} \cdots x_{\rho(N-1)}] := x_{\rho(1)} \cdots x_{\rho(N-1)} = e/x_{\rho(N)}.$$
Let $s = a \left[x_{\rho(1)} \cdots x_{\rho(N-1)}\right] \in S$. Then $s \mod \sigma^N \in T[B]$ specifies “local trajectory” $\{s_u \mod \sigma, s \mod \sigma, s_d \mod \sigma\}$ at $s \mod \sigma \in B$ (Fig.6(b)), where

$$
\begin{align*}
    s_u &:= a \left[x_{\rho(1)} \cdots x_{\rho(N-2)}x_{\rho(N)}\right], \\
    s_d &:= a x_{\rho(1)} \left[x_{\rho(2)} \cdots x_{\rho(N-1)}x_{\rho(1)}\right].
\end{align*}
$$

And we shall obtain a flow on $B$ by patching these local trajectories together.

**A.3. Cones and their boundary surfaces.** Let $\mathbb{PH}\mathbb{N}^N := \{\text{Cone}^*A \mid A \subset L_N^*\}$, where

$$
\text{Cone}^*A := \{px_1^{l_1}x_2^{l_2}\cdots x_N^{l_N} \in L_N^* \mid p \in A \text{ and } 0 \leq l_i \in \mathbb{Z} \text{ for all } i\}.
$$

That is, $\mathbb{PH}\mathbb{N}^N$ is the collection of all “cones” defined by $L_N^*$. And we denote the “boundary surfaces” of $w \in \mathbb{PH}\mathbb{N}^N$ by $d_{sw}$:

$$
d_{sw} := \{\text{conv}[a_0, a_1, \ldots, a_{N-1}] \in S \mid l_w(a_i) = 0 \text{ for all } i\},
$$

where $l_w(z) := \max_{p \in w} \left\{\min_{1 \leq i \leq N} \left\{l_i \in \mathbb{Z} \mid \prod_{1 \leq i \leq N} y_i^{l_i} = z/p\right\}\right\}$ for $z \in L_N^*$.

The boundary surfaces of a cone induce a vector field on $B$.

**A.4. Vector field on $B$.** Let $w \in \mathbb{PH}\mathbb{N}^N$. Then $d_{sw}$ specifies a unique $N$-hedron $s \in d_{sw}$ over each $t \in B$, which we denote by $\Gamma_w(t)$:

$$
\Gamma_w(t) := \text{the unique } N\text{-hedron } s \in d_{sw} \text{ s.t. } t = s \mod \sigma.
$$

And $\Gamma_w$ induces vector field $X_w$ over $B$:

$$
X_w(s \mod \sigma) := D\Gamma_w(s \mod \sigma).
$$

Let $\{t[i]\} \subset B$ be a trajectory defined by vector field $X_w$. And we define the “second derivative” $D^2\Gamma_w(t[i])$ of $\Gamma_w$ along $\{t[i]\}$ as a $\{U, D\}$-valued function by

$$
D^2\Gamma_w(t[i+1]) := \begin{cases} 
    D^2\Gamma_w(t[i]) & \text{if } X_w(t[i+1]) = X_w(t[i]), \\
    -D^2\Gamma_w(t[i]) & \text{else},
\end{cases}
$$

where $-D := U$ and $-U := D$ (Fig.6(c)).

Then we can encode the $N - 1$-dimensional structure of any trajectory by the second derivative along the trajectory, i.e., an $U/D$ sequence.
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