

Self-similarity limits of genomic signatures

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Abstract

It is shown that metric representation of DNA sequences is one-to-one. By using the metric representation method, suppression of nucleotide strings in the DNA sequences is determined. For a DNA sequence, an optimal string length to display genomic signature in chaos game representation is obtained by eliminating effects of the finite sequence. The optimal string length is further shown as a self-similarity limit in computing information dimension. By using the method, self-similarity limits of bacteria complete genomic signatures are further determined.

I. INTRODUCTION

Along with an increasing amount of DNA sequences extracted from experiments, it is important to develop methods for extracting meaningful information from the one-dimensional symbolic sequences composed of the four letters ‘A’, ‘C’, ‘G’ and ‘T’ (or ‘U’). To detect similarity in DNA sequences, scatter plots [1] are introduced to make classification of cytochromes and illustrate a dendrogram. From a comparison of a pair of duplicated genes by a distance matrix, evolutionary relationship of three primary kingdoms of life is inferred [2]. Due to investigating relative abundances of short oligonucleotides in subsequences, genomic signature phenomenon and derivation of partial-ordering relationships among bacterial genomes are proposed [3]. The genomic signature describes that the difference of

dinucleotide relative abundance values within a single genome is larger than that between distinct genomes. Chaos game representation (CGR) [4], which generates a two-dimensional square from a one-dimensional sequence, provides a technique to visualize the composition of DNA sequences. By composing the CGR and short-sequence representation methods, the evolution of species-type specificity in mitochondrial genomes is analyzed [5]. In terms of the CGR method, it is shown that the main characteristics of the whole genome can be exhibited by its subsequences [6]. The genomic signature is extended to describe characteristics of CGR images. By making a Euclidean metric between two CGR images, classification of species in three primary kingdoms is discussed.

Recently, metric representation (MR) [7], which is borrowed from the symbolic dynamics, makes an ordering of subsequences in a plane. The MR method is an extension of CGR. Suppression of certain nucleotide strings in the DNA sequences leads to a self-similarity of pattern seen in the MR of DNA sequences. In this paper, first, we show that the MR is one-to-one. Due to the MR method, we determine suppression of nucleotide strings in DNA sequences. Then, eliminating effects of finite sequences on suppression of nucleotide strings, we give an optimal string length to display genomic signature. Moreover, we plot information function versus string lengths to determine self-similarity limits in MR images. Using the method, we present self-similarity limits of bacteria complete genomic signatures.

II. SUPPRESSION OF NUCLEOTIDE STRINGS

For a given DNA sequence, we have a one-dimensional symbolic sequence $s_1 s_2 \cdots s_i \cdots s_N$ ($s_i \in \{A, C, G, T\}$). In a two-dimensional MR, we take the correspondence of symbol s_i to number μ_i or $\nu_i \in \{0, 1\}$ and calculate the values (α, β) of all subsequences $\Sigma_m = s_1 s_2 \cdots s_m$ ($1 \leq m \leq N$). The number α represented in base 3, between 0 and 1, is defined as

$$\alpha = 2 \sum_{j=1}^m \mu_{m-j+1} 3^{-j} + 3^{-m} = 2 \sum_{i=1}^m \mu_i 3^{-(m-i+1)} + 3^{-m}, \quad (1)$$

where μ_i is 0 if $s_i \in \{A, C\}$ or 1 if $s_i \in \{G, T\}$. Similarly, the number β is defined as

$$\beta = 2 \sum_{j=1}^m \nu_{m-j+1} 3^{-j} + 3^{-m} = 2 \sum_{i=1}^m \nu_i 3^{-(m-i+1)} + 3^{-m}, \quad (2)$$

where ν_i is 0 if $s_i \in \{A, T\}$ or 1 if $s_i \in \{C, G\}$. According to (1) and (2), the one-dimensional symbolic sequence $s_1 s_2 \cdots s_N$ is partitioned into 4 kinds of subsequences, which correspond to points in 4 fundamental zones A, C, G and T of Fig. 1. Under left or right shift operators, each zone can be further shrunk to less zones with a factor of $1/3^2$. For an infinite sequence, this procedure can be defined as a fractal [8], which has a self-similarity. The subsequences with the same ending k -nucleotide string are labeled by $\Sigma_{(k)}$. All subsequences $\Sigma_{(k)}$ correspond to points in the zone encoded by the k -nucleotide string.

Lemma 1 $(\alpha, \beta)\{S(\Sigma_m)\} = 2(\mu_{m+1}, \nu_{m+1})/3 + (\alpha, \beta)\{\Sigma_m\}/3$. S is a left shift operator.

PROOF: Note that for the left shift operator, $S(\Sigma_m) = \Sigma_m s_{m+1}$. From the definition (1) and (2), we can immediately obtain the result.

Lemma 2 $(\alpha, \beta)\{\Sigma_m\} = (\alpha, \beta)\{G^\infty \Sigma_m\}$.

PROOF: When $m = 1$, $\Sigma_1 = s_1$ and $G^\infty \Sigma_1 = S(G^\infty)$. By the Lemma 1, we can obtain $(\alpha, \beta)\{G^\infty \Sigma_1\} = 2(\mu_1, \nu_1)/3 + (\alpha, \beta)\{G^\infty\}/3 = 2(\mu_1, \nu_1)/3 + (1, 1)/3 = (\alpha, \beta)\{\Sigma_1\}$. Suppose when $m = i$, we have $(\alpha, \beta)\{\Sigma_i\} = (\alpha, \beta)\{G^\infty \Sigma_i\}$. For $m = i + 1$, we have $\Sigma_{i+1} = \Sigma_i s_{i+1} = S(\Sigma_i)$ and $G^\infty \Sigma_{i+1} = S(G^\infty \Sigma_i)$. By the Lemma 1, we obtain $(\alpha, \beta)\{\Sigma_{i+1}\} = 2(\mu_{m+1}, \nu_{m+1})/3 + (\alpha, \beta)\{\Sigma_i\}/3$ and $(\alpha, \beta)\{G^\infty \Sigma_{i+1}\} = 2(\mu_{m+1}, \nu_{m+1})/3 + (\alpha, \beta)\{G^\infty \Sigma_i\}/3$. So, using the supposition $(\alpha, \beta)\{\Sigma_i\} = (\alpha, \beta)\{G^\infty \Sigma_i\}$, we can lead to $(\alpha, \beta)\{\Sigma_{i+1}\} = (\alpha, \beta)\{G^\infty \Sigma_{i+1}\}$.

By the Lemma 2, each finite subsequence Σ_m has a correspondent infinite sequence $G^\infty \Sigma_m$. Here, we define a set of the infinite sequences as Σ .

Theorem 1 $(\alpha, \beta) : \Sigma \rightarrow \Lambda$ is one-to-one. Λ is a set of points in the (α, β) plane.

This means that given $\Sigma^1, \Sigma^2 \in \Sigma$, if $\Sigma^1 \neq \Sigma^2$, then $(\alpha, \beta)\{\Sigma^1\} \neq (\alpha, \beta)\{\Sigma^2\}$. We give a proof by contradiction. Suppose $(\alpha, \beta)\{\Sigma^1\} = (\alpha, \beta)\{\Sigma^2\}$ and is marked as P in the the (α, β) plan. For the zone including the point P , we encode it as two subsequences Σ_1^1 and Σ_1^2 with the same mononucleotide. Then, enlarge the zone by a area factor of 3^2 , we can obtain two encoding subsequences Σ_2^1 and Σ_2^2 with the same dinucleotide. Each

enlarging process provides a right shift to two subsequences. At the same time, the point P is only included in one of four enlarged zones. So, two shifting subsequences are the same. Following the enlarging process in an infinite step, we can obtain $\Sigma^1 = \Sigma^2$, contradicting our original assumption. This contraction is due to the fact that we have assumed $(\alpha, \beta)\{\Sigma^1\} = (\alpha, \beta)\{\Sigma^2\}$; thus, $\Sigma^1 \neq \Sigma^2$, then $(\alpha, \beta)\{\Sigma^1\} \neq (\alpha, \beta)\{\Sigma^2\}$.

For the DNA sequence, some zones in CGR are replenished by points, so that a pattern appears. In CGR, there exists an correspondence of more subsequences with different ending k -nucleotide strings to the same points in bounds of zones. For examples, subsequences $G^\infty A$ in the zone A , $T^\infty C$ in the zone C , $A^\infty G$ in the zone G and $C^\infty T$ in the zone T have the same points in CGR $(1/2, 1/2)$. Under left shift operators, the corresponding relation between points and subsequences can preserve in zones with small enough lengths. For example, subsequences $G^\infty AC$ in the zone AC , $T^\infty C^2$ in the zone C^2 , $A^\infty GC$ in the zone GC and $C^\infty TC$ in the zone TC have the same points in CGR $(1/4, 3/4)$. In MR of DNA sequences, each zone in CGR is shrunk and clearly divided by four bands. There exists a one-to-one correspondence between zones and ending k -nucleotide strings of subsequences. Frequency of points in the zone can be determined by using MR method as follows. In order to compute frequencies in zones encoded by k -nucleotide strings, we need to determine partition lines of MR in Fig. 1. For mononucleotides, there exist 2×2 zones in the MR. We have $n_1 (= 3)$ partition lines $b_0^1 = 0$, $b_1^1 = 1/2$ and $b_2^1 = 1$ along the α axis. For dinucleotides, there exist 4×4 zones in the MR. We have $n_2 (= 5)$ partition lines $b_0^2 = b_0^1 = 0$, $b_1^2 = b_1^1/3 = 1/6$, $b_2^2 = b_1^1 = 1/2$, $b_3^2 = 1 - b_1^2 = 5/6$ and $b_4^2 = 1 - b_0^2 = 1$ along the α axis. In general, for $k-1$ -nucleotide strings, if knowing $n_{k-1} (= 2^{k-1} + 1)$ partition lines $b_i^{k-1} (i = 0, 1, \dots, n_{k-1} - 1)$ along the α axis, we can obtain $n_k (= 2^k + 1 = 2n_{k-1} - 1)$ partition lines $b_i^k (i = 0, 1, \dots, n_k - 1)$ for k -nucleotide strings as follows. For the k -nucleotide strings, there exist $2^k \times 2^k$ zones in the MR. The left half ($0 \leq i \leq n_{k-1} - 1$) of partition lines along the α axis are described as follows

$$\begin{aligned} b_i^k &= b_{i/2}^{k-1}, & \text{if } i \% 2 = 0; \\ b_i^k &= b_i^{k-1}/3, & \text{if } i \% 2 = 1. \end{aligned} \quad (3)$$

From (3), the right half ($n_{k-1} \leq i \leq n_k - 1$) of partition lines along the α axis can be determined immediately

$$b_i^k = 1 - b_{n_k-1-i}^k. \quad (4)$$

For example, for trinucleotides, 9 partition lines along the α axis are $0, \frac{1}{18}, \frac{1}{6}, \frac{5}{18}, \frac{1}{2}, \frac{13}{18}, \frac{5}{6}, \frac{17}{18}$ and 1. We can obtain 17 partition lines $0, \frac{1}{54}, \frac{1}{18}, \frac{5}{54}, \frac{1}{6}, \frac{13}{54}, \frac{5}{18}, \frac{17}{54}, \frac{1}{2}, \frac{37}{54}, \frac{13}{18}, \frac{41}{54}, \frac{5}{6}, \frac{49}{54}, \frac{17}{18}, \frac{53}{54}$ and 1 along the α axis for tetranucleotides. Partition lines along the β axis are the same to those along the α axis. Each zone in the MR can thus be surrounded by the combined partition lines along the α and β axes.

Using the MR method, we determine suppression of k -nucleotide strings in HUMHBB (human β -region, chromosome 11) with 73308 bases and YEAST1 (yeast chromosome 1) with 230209 bases in Table I, respectively. In order to check efficiency of the method, we also determine the number of disappearing strings in all strings for a giving string length in HUMHBB and YEAST1, respectively. The results are identical with those in Table I, respectively. So, the MR method is effective to determine suppression of nucleotide strings in DNA sequences.

In CGR of DNA sequences, self-similarity patterns change more obscurely as lengths of sequences increase. A grey plot describes frequency values in small zones, which sizes ($2^{-k} \times 2^{-k}$) can be given by lengths of strings encoding the zones (k). Along with increase of string lengths, the self-similarity patterns in CGR are more clear. A high and low frequent zones are redivided to smaller and described by a grey scale. Some empty zones may appear in the patterns of CGR, i.e., some nucleotide strings are suppressed in the sequences. In the procedure of decreasing zone sizes, more and more empty zones emerge in the patterns of CGR. For example, evolution of a self-similarity pattern in CGR of the archaebacteria *Archeoglobus fulgidus* is shown in Fig. 1 of Ref. [6]. If DNA sequences are infinite, the

compositional structure can be displayed in small enough zones. Empty zones are a part of the global feature in CGR. But the DNA sequences are finite. A finite sequence, even a random sequence, may also lead to suppression of strings. Along with increase of string length, more and more strings are suppressed in the finite sequences.

In Table I, we compare the suppression of nucleotide strings between DNA and random sequences with the same length. Suppression of nucleotide strings for HUMHBB starts at $k=5$. For a random sequence with the same length, which is given by using a random number generator [9], suppression of nucleotide strings is delayed to start at $k=7$. The number of suppressed nucleotide strings for the random number is 5.67% of that for HUMHBB. The finite sequence of HUMHBB effects on the suppression of 7-nucleotide strings. Along with increase of k , numbers of suppressed nucleotide strings for the random number more increase and approach those for HUMHBB. At $k=10$, the number of suppressed nucleotide strings for the random number is 99.3% of that for HUMHBB. In this case, suppression of nucleotide strings in HUMHBB is mainly caused by the finite length of sequence. Moreover, suppression of nucleotide strings for YEAST1 starts at $k=7$. For a random sequence with the same length, which is given by using a random number generator [9], suppression of nucleotide strings is delayed to start at $k=8$. The number of suppressed nucleotide strings for the random number is 22.7% of that for YEAST1. The finite sequence of YEAST1 effects on the suppression of 8-nucleotide strings. At $k=10$, the number of suppressed nucleotide strings for the random number is 97.5% of that for YEAST1. Due to the comparison of suppression of nucleotide strings, we can thus obtain that HUMHBB and YEAST1 have shorter suppressed nucleotide strings than random sequences with the same lengths, respectively. Along with increase of string lengths, the finite sequences take stronger effects on suppression of nucleotide strings.

In order to display genomic signature, we must eliminate effects of finite sequences on suppression of nucleotide strings. For a DNA sequence, we take the longest string length before suppression of nucleotide strings in a random sequence with the same lengths as an optimal option of string lengths. According to the definition, string lengths 6 and 7 can be

chosen as optimal options for genomic signatures of HUMHBB and YEAST1, respectively.

III. LIMITS OF SELF-SIMILARITY SCALES

Suppression of certain nucleotide strings in the DNA sequences leads to a fractal pattern seen in the MR of DNA sequences. To quantify the fractal feature in the MR of DNA sequences, we introduce information dimension. For a given length k of nucleotide strings, we have $M (= N - k + 1)$ subsequences $\Sigma_i (i = k, k + 1, \dots, N)$, which end with M k -nucleotide strings. The subsequences are corresponding to M points in a MR. In the MR, the length of a zone and the total number of zones are $\epsilon = 3^{-k}$ and $Z = 4^k$, respectively. The numbers of points falling in the i -th zone and of non-empty zones are labeled by $m_i(\epsilon)$ and $Z(\epsilon)$, respectively. Dividing the number $m_i(\epsilon)$ by the total point number M yields a probability $p_i(\epsilon)$ for the i -th zone. Information function and dimension for the points in MR are respectively defined [10] as

$$I(\epsilon) = - \sum_{i=1}^{Z(\epsilon)} p_i \log p_i, \quad (5)$$

and

$$D_1 = \lim_{\epsilon \rightarrow 0} \frac{I(\epsilon)}{\log(1/\epsilon)}. \quad (6)$$

The information function $I(\epsilon)$ during a range of $\log(1/\epsilon)$ has a scaling region. The scaling region reflects the self-similarity of pattern in the MR. The information dimension D_1 can be found from the slope in scaling region $I(\epsilon)$ versus $\log(1/\epsilon)$. When the length ϵ of a zone in MR increases from 3^{-k} to 2^{-k} , MR of DNA sequences changes to CGR. Information dimension in CGR can thus be determined as $(\log_2 3) D_1$. We compute information function $I(\epsilon)$ with different sizes ϵ for HUMHBB and draw in Fig. 2. A linear part of the curve $I(\epsilon)$ versus $\log(1/\epsilon)$ emerges between $\log(1/\epsilon) = \log 3 = 1.10$ and $\log(1/\epsilon) = 6 \log 3 = 6.59$. A fitting line is also drawn in Fig. 2. The point for $\log(1/\epsilon) = 7 \log 3 = 7.69$ is started leaving from the line. Along with the decrease of $\log(1/\epsilon)$, farther and farther the points leave

from the line. Since points in the zones correspond to k -nucleotide strings, we can obtain that the self-similarity of pattern in the MR preserves approximately from mononucleotides to 6-nucleotide strings, as well as the suppression of many nucleotide strings emerges at 7-nucleotide strings. Using the least-squares fit method [9] for the liner part, we determine its slope, i.e., information dimension D_1 , to 1.20. It is less than the information dimension 1.26 for random sequence with the same length. Moreover, in Fig. 3, we draw information function $I(\epsilon)$ versus $\log(1/\epsilon)$ for YEAST1. A linear part of the curve $I(\epsilon)$ versus $\log(1/\epsilon)$ exists between $\log(1/\epsilon) = \log 3 = 1.10$ and $\log(1/\epsilon) = 7\log 3 = 7.69$. We can obtain that the suppression of many nucleotide strings in YEAST1 emerges from 8-nucleotide strings. Using the least-squares fit method [9] for the liner part, we also plot a fitting line in Fig. 3 and determine its slope, i.e., information dimension D_1 , to 1.22. It is less than the information dimension 1.26 for random sequence with the same length. The limits of self-similarity in MR of HUMHBB and YEAST1 are equivalent to the optimal string lengths for genomic signatures, respectively. Thus, for presenting genomic signature, a self-similarity limit as an optimal string length can be determined in computing information dimension.

Using the MR method, we determine suppression of k -nucleotide strings of bacteria complete genomes in Table II, where we put suppression of k -nucleotide strings in the order of decrease. For each of the bacteria complete genomes, a linear part exists in the plot of information function $I(\epsilon)$ versus $\log(1/\epsilon)$. From the linear parts, we determine self-similarity limits of genomic signatures in Table II. Keeping in the order, we find the suppression of bacteria complete genomes does not necessarily depend on the lengths of sequences. The common optimal string length for the bacteria complete genomic signatures can be chosen as 7.

IV. CONCLUSION

In summary, we have shown MR of DNA sequences is one-to-one. Due to the MR method, suppression of nucleotide strings in the DNA sequences is determined. For a DNA

sequence, an optimal string length to display genomic signature is obtained by eliminating effects of the finite sequence. The optimal string length is further shown as a self-similarity limit in computing information dimension. By using the method, self-similarity limits of bacteria complete genomic signatures are further determined.

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REFERENCES

- [1] A. J. Gibbs and G. A. McIntyre *Eur. I. Biochem.* **16**, 1 (1970).
- [2] N. Iwabe, K. Kuma, M. Hasegawa, S. Osawa, and T. Miyata *Proc. Natl. Acad. Sci. USA* **86**, 9355 (1989).
- [3] S. Karlin, J. Mrazek, and A. M. Campbell *J. Bacteriol.* **179**, 3899 (1997).
- [4] H. J. Jeffrey *Nucleic Acids Res.* **18**, 2163 (1990).
- [5] K. A. Hill and S. M. Singh *Genome* **40**, 342 (1997).
- [6] P. J. Deschavanne, A. Giron, J. Vilain, G. Fagot, and B. Fertil *Mol. Biol. Evol.* **16**, 1391 (1999).
- [7] Z.-B. Wu *Electrophoresis* **21**, 2321 (2000).
- [8] B. B. Mandelbrot *The Fractal Geometry of Nature*. (Freeman and Company, New York, 1983).
- [9] W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery *Numerical Recipes in C*. 2nd ed. (Cambridge University Press, 1992).
- [10] J. D. Farmer *Physica D* **4**, 366 (1982).

FIGURES

Fig. 1 Metric representation of HUMHBB. Its boundary and partition lines are labeled by solid lines and dash lines, respectively.

Fig. 2 A plot of information function $I(\epsilon)$ versus $\log(1/\epsilon)$ labeled by dots and its fitting line for HUMHBB.

Fig. 3 A plot of information function $I(\epsilon)$ versus $\log(1/\epsilon)$ labeled by dots and its fitting line for YEAST1.

TABLES

Table I. Suppression of k -nucleotide strings in HUMHBB, YEAST1 and random sequences. The total numbers of nucleotide strings for a length k and suppressed k -nucleotide strings, are labeled by Π_k and Λ_k , respectively.

k	5	6	7	8	9	10
Π_k	1024	4096	16384	65536	262144	1048576
$\Lambda_k^{HUMHBB}/\Lambda_k^{Random}$ (73308)	4/0	244/0	3667/208	32909/21402	209280/198219	985222/977852
$\Lambda_k^{YEAST1}/\Lambda_k^{Random}$ (230209)	0/0	0/0	110/0	8897/2021	134302/109290	863555/842246

Table II. Suppression of k -nucleotide strings and self-similarity limits of bacteria complete genomes labeled by Λ_k and k_l , respectively.

k	6	7	8	9	10	k_l
$\Lambda_k^{mgen}(580074)$	14	851	14189	126690	776767	7
$\Lambda_k^{mjan}(1664970)$	3	318	7656	84937	612138	8
$\Lambda_k^{hpyl}(1667867)$	2	192	4290	58661	538051	8
$\Lambda_k^{hpyl99}(1643831)$	1	130	3977	58033	538512	8
$\Lambda_k^{bbur}(910724)$	0	232	8139	101444	712552	8
$\Lambda_k^{rpxx}(1111523)$	0	71	4778	79792	643520	8
$\Lambda_k^{hinf}(1830138)$	0	12	1077	33859	442423	8
$\Lambda_k^{pNGR234}(536165)$	0	10	2881	76649	699974	7
$\Lambda_k^{mpneu}(816394)$	0	7	2329	66513	638786	8
$\Lambda_k^{mthe}(1751377)$	0	5	665	26669	408030	8
$\Lambda_k^{aqua}(1551335)$	0	4	840	33972	468735	8
$\Lambda_k^{pyro}(1738505)$	0	4	708	26863	403468	8
$\Lambda_k^{aful}(2178400)$	0	4	365	16382	330488	8
$\Lambda_k^{mtub}(4411529)$	0	3	595	20793	306071	9
$\Lambda_k^{pabyssi}(1765118)$	0	3	291	18803	367742	8
$\Lambda_k^{tmar}(1860725)$	0	2	594	24329	399932	8
$\Lambda_k^{cpneu}(1230230)$	0	2	452	28569	468992	8
$\Lambda_k^{ecoli}(4639221)$	0	1	173	5595	150409	9
$\Lambda_k^{synecho}(3573470)$	0	1	149	8058	214433	9
$\Lambda_k^{ctra}(1042519)$	0	0	562	34004	510293	8
$\Lambda_k^{aero}(1669695)$	0	0	137	20084	401256	8
$\Lambda_k^{tpal}(1138011)$	0	0	118	20912	453066	8
$\Lambda_k^{bsub}(4214814)$	0	0	4	2919	156165	9





