J. Biomedical Science and Engineering, 2011, 4, 719-733 **JBiSE**
doi:10.4236/jbise.2011.411089 Published Online November 2011 (http://www.SciRP.org/journal/jbise/).

Structural features of the nucleotide sequences of virus and organelle genomes

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Received 8 July 2011; revised 9 September 2011; accepted 9 October 2011.

ABSTRACT

The four nucleotides (bases), A, T (U), G and C in small genomes, virus DNA/RNA, organelle and plastid genomes were also arranged sophisticatedly in the structural features in a single-strand with 1) reverse-complement symmetry of base or base sequences, 2) bias of four bases, 3) multiple fractality of the distribution of each four bases depending on the distance in double logarithmic plot (power spectrum) of L (the distance of a base to the next base) vs. P (L) (the probability of the base-distribution at L), although their genomes were composed of low numbers of the four bases, and the base-symmetry was rather lower than the prokaryotic- and the eukaryotic cells. In the case of the genomic DNA composed of less than 10,000 nt, it was better than to be partitioned at 10 of the L-value, and the structural features for the biologically active genomic DNA were observed as the large genomes. As the results, the base sequences of the genomic DNA including the genomic-RNA might be universal in all genomes. In addition, the relationship between the structural features of the genome and the biological complexity was discussed.

Keywords: Structural Features of Small Genome; Virus; Organelle

1. INTRODUCTION

Watson and Crick deduced that DNA had a double-helical structure with complementary and anti-paralleled strands [1] based on the equal amounts of adenine (A) and thymine (T), and guanine (G) and cytosine (C) by Chargaff [2], and the X-ray diffraction patterns of DNA fibers by R. Franklin and M. Wilkins [3,4]. After that, Chargaff and co-workers also observed that a single-strand of *Bacillus subtilis* DNA had the same amount of A + T and G + C ([5]; Chargaff's second parity-rule, 1968).

About fifty years later, the genome base sequences of many organisms described below have been determined, and an artificial bacterial genome (582,970 bp) was chemically synthesized based on *Mycoplasma genitalium* [6], although partial unreadable regions still remained in each genome. The structural analysis of the DNA based on the entire genome base sequence was necessary to understand living organisms. To do this, we had to characterize the structural features of genomic DNA.

Genome projects had been completed so far to obtain the base sequences of prokaryotic organisms, and eukaryotic organisms and so many organisms [7-9]. The base sequences of many viruses, plastids and organelle genomes were also revealed. Their genomes were essentially small and were diverse because in a part of viruses, RNA or a single-strand DNA/RNA was used as genomes.

As the Genome Project revealed, an individual gene was an integral part of a genome. There were many genes in a genome, and the associated regulatory regions that were expressed, replicated, transcribed and translated into proteins, and all participated in biological phenomena. Each gene could be converted to respective protein according to the maturation of mRNA and "Central Dogma" [10]. They might be organized based on the support the other regions in chromosome, so called, the non-coding region for the regulation of the gene-expression in living cells as a biological system. If so, we should be to face up to the entire genome as a molecule with three dimensions, not only the coding region, but also the non-coding regions. The genome might be organized in living cells as a biological system, including the coding- and the non-coding regions, which had grown with the passage of time. Therefore, we would have reported the entire genome as a systematized molecule to understand living cells [11].

The study for the entire genomic base sequences were not so much, because we had few effective tools, in-

cluding hard- and soft-ware, to analyze the large-scale molecule such as genome now. Some challenging bioinformatics papers [12-16] had reported on stem-loop structures, and the analyses of the whole-genome using the structural features of the genomic DNA, the specific base sequences [17-24].

In prokaryotic cells including viruses and bacteriophages, most regions of the genome were occupied in the coding regions, whereas in eukaryotic cells the coding regions were not so large in entire genome, and variable depend on the genome-sizes (base numbers composed of the genomic DNAs), for example, the coding regions was occupied only several percent in *H. sapiens* genomic DNA [25]. Furthermore, each gene on chromosome or genome had been arranged in the order, the direction using either the Watson-strand or the Crick-strand on the transcription, and the distance to the both-sides genes. When changed one of these three characters of gene on genome, the order, the direction, the distance, the living cells were become different ones. For instance, the changes of these characters might be occurred the chromosomal translocation [26-28], and they were forced to live the surroundings. Therefore, only the coding regions, *i.e.*, the genes could not be explained over the biological phenomena in living cells, especially the eukaryotic cells [11].

The genomic DNA might be also "a molecule with the aligned four bases, A, T, G, C, and with three dimensions" even if there was a huge. So, the large region was deleted, presumably they might become a molecule with different conformation affected the gene-expression and the activity to interact with the biological materials, bio-organic compound(s), protein(s), nucleic acid(s), sugar(s), fatty acid(s) or so on. To express the gene(s), the regulatory elements, the promoter (trigger), the SAR (scaffold), the insulator (boundary), the poly-A-signal (stability), ncRNAs (controller) etc on genomic DNA were all or some necessary [25,29-34]. Thus, both the coding- and the non-coding regions should be necessary to express gene(s) precisely, rapidly and stably to carry out the various biological phenomena.

The small genomes were compact because of the little, or the low non-coding regions, and questioned whether the structural features of the genomic DNA/RNA would have the same or not as those of the large genomes. If they would have so, the base sequences of their genomes might be a model of the genomic DNA [11,35,36].

In this paper, the author had analyzed the small genomic DNA/RNAs such as the virus, the mitochondrial and the chloroplast genomes were also arranged sophisticatedly in the same rules similar to the large genomes and chromosomes.

2. MATERIALS AND METHODS

2.1. Sequence Spectrum Method (SSM)

Sequence spectrum Method (SSM) was described previously [35].

2.2. Appearance Frequencies of Bases or Base Sequences

Appearance frequency of the base or base sequences (three successive base sequence = triplet) was described previously [11,35]

2.3. The Parameters "d"-, "m"-, "p"-, and "w"-Values of the SSM Analysis for the Interaction

The Controllable parameters in the sequence spectrum were the base size "d" of the key sequence, the average width "m", the skip base number (the size factor) "p" and the window width "w" of homology as described previously [35,36].

2.4. $f(\alpha)$ Spectrum Analysis [37,38]

The $f(\alpha)$ and α were calculated from the base distribution curve of adenine base(s) as follows. 1) L was 1 through 15 (the base distribution curve of adenine in for example, *S. cerevisiae* chromosome 1 was calculated as $y = ae^{-bx}$, x = L-value, a = 0.3736, b = 0.3365), and 2) L was 16 or more (the base distribution curve of adenine in *S. cerevisiae* was calculated as a = 0.2148, b = 0.2770).

When the L-value was between 1 and 15, bases in the genome were expressed as **Eq.1**, $y = ae^{-bx}$. Then, a derivative of both sides of **Eq.1** by x is as follows.

$$dy/dx = -abe^{-bx} = -ab/e^{bx} .$$

let $$-ab/e^{bx} = \alpha \text{ , (x is L-value).}$$

Here, the distribution curve P (L) correlated to $f(\alpha)$ is as follows,

$$P(L) = cL^{-f(\alpha)} \quad (3)$$

here *c* is constant in **Eq.3**.

In order to exclude the effect of c in this equation, let $P'(L) = P(L)/P(L)\,max$, and then use $P'(L)$ instead of P (L). P (L) max is the maximum value of P (L).

Therefore,

$$f(\alpha) = -\ln P'(L)/\ln L \quad (4).$$

In each case (L = 1 - 10, or 15, L = more than 11, or 16), the $f(\alpha)$ spectrum of the adenine (A) is calculated and plotted as α (x-axis) vs. $f(\alpha)$ (y-axis). When the $f(\alpha)$ varies as a function of α, the fractality must be multi-fractal (red-diamond, the linearly-decreased region of the "A" base in double logarithmic plot of L vs. P (L)); in contrast, when $f(\alpha)$ is constant at any given α-value,

the fractality must be unifractal (black-square, the exponential-decreased region of the "A" base in double logarithmic plot of L vs. P (L)).

A similar calculation was carried out for each base, T, G, or C in a single-strand of DNA in the genome from the genome database.

3. RESULTS AND DISCUSSION

Using the data-bases of NCBI [7], Sanger Institute [8], SGD [9] and MIPS [39] were useful to analyze, following structural features were revealed in a single-strand of genomic DNA.

3.1. The Genome Base Sequence Was Reverse-Complement Symmetry Even in a Single-Strand of DNA

Genomic DNA/RNA was composed of four different bases, A, T (U), G and C. The base number (nt) and GC contents of each genome and chromosome for virus, plastid and the mitochondiral (mt) DNAs were calculated as shown in **Table 1**. Although in viruses (DNA/RNA), mtDNA and chloroplast (ch) DNA, the symmetry of the base sequences was somewhat low because of the small genome-size (base numbers) of genomic DNA/RNA in comparison with the large genomes such as eukaryotic chromosomes. In other words, the numbers of base A was almost equal to those of T, and the numbers of G was equal to those of C, the symmetry of a single-strand of DNA maintained according to exactly would agree with Chargaff's second parity-rule and previously reported [**Table 1**, ref. 5, 11]. The results also indicated that a single-stranded genomic DNA might sometimes be had a closed structure with partial hydrogen-bonding (stem-loops) as seen with RNA secondary structure [13-16].

Table 2 was shown in the three successive base sequences (triplet) of *Simian virus* 40 (SV40, 5243 nt, DNA), *Human adenovirus A* DNA (34,125 nt), *Autographa California* virus (133,894 nt, DNA), *Fujinami sarcoma* virus (4711 nt, RNA), *Rous sarcoma* virus (RSV, 9392 nt, single-strandRNA), *Homo sapiens* mtDNA (16,570 nt), *Plasmodium fasciparum* mtDNA (5967 nt), *Saccharomyces cerevisiae* mtDNA (85,779 nt), *Arabidopsis thaliana* mtDNA (366,924 nt), *Arabidopsis thaliana* chDNA (154,478 nt), *Oryza sativa japonica* mtDNA (490,516 nt) and *Oryza sativa japonica* chDNA (134,525 nt). The *S. cerevisiae* chromosome 1 (230,203 nt) was a control genome.

Although the reverse complement base-symmetry in a single-strand of DNA/RNA was rather low in the virus genomes, and a part of mtDNAs, the structural feature of genome could be maintained regardless the genome-size, the GC-content and the form of the genomes as the larger genomes [11]. The appearance frequencies of three successive base sequences corresponded to the species-dependent genetic codon (triplets) [11,22,40], which in turn could be corresponded to the 20 amino acids. The structural feature of the genomes might be related the "peak" and "pocket" of the sequence spectra of the genomic DNAs and connected to identify the homology of the interactive-sites of proteins and DNAs [35,36].

The difference of the GC-content and the ratio of the base-symmetry between the nuclear chromosomes and the organelle, the chloroplast genomes might be caused of the origin of the symbiosis of these genomes in the host cells [41-43].

3.2. The Genome Base Sequence Was Localized

We calculated the distribution of the bases in 1) *Simian virus* 40, 2) *Autographa California* virus, 3) *Human immunodeficiency virus* 2, 4) *Arabidopsis thaliana* mtDNA, 5) *Plasmodium falciparum* mtDNA, 6) *Arabidopsis thaliana* chDNA (**Figure 1**). The artificial chromosomal sequences with the same appearance frequencies of the triplet (3 successive base sequences) and the same base numbers were generated using the random number as that of real sequence in each chromosome as previously reported [11]. The *S. cerevisiae* chromosome 1 (230, 203 nt, **Figure 1(g)**) was a control of the real- and the artificial chromosome. The window-length (w, base number, nt) in each genome was depend on the genomesize as described in the MATERIALS ANA METHODS.

Four bases were localized on each real genome of each species (**Figure 1**, left panels), whereas they were distributed uniformly on the artificial genomes (**Figure 1**, right panels). In contrast to the uneven distribution of four bases on the real genome, the "A", "T", "G" or "C" frequencies in each artificial genome sequence were distributed uniformly. In addition, the results that the frequency of "A" was similar with "T", and that of "C" was similar with "G" corresponded to the base symmetry, *i.e.*, the hydrogen bonding of A-T and G-C (GC-content) of each chromosome [11]. When the genome was AT-rich, the frequency of A (or T) was higher than that of C (or G) (**Figure 1**).

Similar results were also observed in base distribution between real chromosomes and their artificial genome sequences both in single- or double-stranded RNA used as a genome (**Figure 1(c)**). These results indicated that there might be many A-T (U for RNA) and G-C hydrogen bonding in a single-strand DNA of intra-chromosomal molecules regardless eukaryotes or prokaryotes. The artificial genome sequence of each genome or chromosome could observe the reverse-complement symmetry, but the four bases were distributed uniformly, corresponding with the same molar contents, A to T and

Table 1. Nucleotide (base) contents of small genomes.

	Genome	Form	Base number nt	A	T (U)	C	G	GC (%)	A/T (U)	C/G
(Virus)										
SV40	DNA	circular	5243	1518	1586	1100	1039	40.8	0.96	1.06
H.adenoA	DNA	linear	34,125	9330	8919	8012	7864	46.5	1.05	1.02
APSE-1	DNA	circular	36,524	10,357	10,138	7567	8462	43.9	1.02	0.89
Phage933	DNA	linear	61,670	15,964	15,261	14,057	16,388	49.4	1.05	0.86
Acid-two-tail	DNA	circular	62,730	17,978	18,891	13,166	12,695	41.2	0.95	1.04
S/Pnecro	DNA	linear	111,362	25,250	25,112	30,919	30,,081	54.8	1	1.03
A.calif.	DNA	circular	133,894	39,195	40,201	27,151	27347	40.7	0.97	0.99
HParvoV B19	DNA (ss)	linear	5594	1658	1482	1177	1277	43.8	1.12	0.91
V. phageVf12	DNA (ss)	circular	7965	2028	2299	1851	1787	45.6	0.88	1.03
Enterophage If1	DNA (ss)	circular	8454	2324	2435	1747	1948	43.7	0.95	0.9
Fujinami	RNA	linear	4788	1072	856	1302	1558	59.7	1.25	0.84
OSendornaV	RNA	linear	13,952	5209	4019	3541	3472	33.8	1.29	0.79
Newcastle	RNA	linear	15,186	4425	3748	3541	3472	46.2	1.18	1.02
VicfabaV	RNA	linear	17,635	5816	3421	4117	4281	47.6	1.7	0.96
RSV	RNA(ss)	linear	9392	2230	2080	2378	2704	54.1	1.07	0.88
HIV.ty2	RNA(ss)	linear	10,359	3506	2123	2132	2598	45.7	1.65	0.82
Nipah	RNA(ss)	linear	18,246	6176	5106	3326	3638	38.2	1.21	0.91
(Organelle)										
P. know. Mt	DNA	circular	5957	1968	2171	916	902	30.5	0.91	0.98
P. falc. Mt	DNA	linear	5967	1933	2149	936	949	28.2	0.9	0.99
C. elegans Mt	DNA	circular	13,794	4335	6179	1225	2055	23.8	0.7	0.6
H.sapiens Mt	DNA	circular	16,570	5123	4094	5182	2170	44.4	1.25	2.39
S. pombe Mt	DNA	circular	19,431	6652	7022	2783	3064	30	0.93	0.91
D. melano. Mt	DNA	circular	19,517	8152	7883	2003	1479	17.8	1.03	1.35
S. cerev. Mt	DNA	circular	85,779	36,169	34,934	6863	7813	17.1	1.03	0.88
A. thaliana Mt	DNA	circular	366,924	102,464	100,190	82,661	81,609	44.7	1.02	1.01
O. sativa Mt	DNA	linear	490,516	136,863	138,,549	107,346	107,758	43.8	0.99	1
O. sativa Ch	DNA	circular	134,525	41,248	40831	26,126	26,320	39	1.01	1
Zea mays Ch	DNA	circular	140,384	43,281	43,108	26,908	27,087	38.4	1	0.99
A. thaliana Ch	DNA	circular	154,478	48,546	49,866	28,496	27,570	36.3	0.97	0.97

Table 2. Appearance frequency of three successive base sequences.

Triplet	SV40 (5243 nt)		Hadeno-A (34,125 nt)		A.calif (133,894 nt)		Fujinami (4711 nt)		RSV (9392 nt)		HS mtDNA (16,570 nt)		Pfal mtDNA (5967 nt)		SC mtDNA (85,779 nt)		AT mtDNA (36,6924 nt)		AT chDNA (154,478 nt)		OSJ mtDNA (490,516 nt)		OSJ chDNA (134,525 nt)		SC chr.1 (230,203 nt)	
	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*	Frequency	ratio*
AAA	212		1086		5746		59		141		524		157		4982		10260		7118		14279		5586		8576	
TTT	240	0.88	1044	1.04	5762	1	26	2.27	119	1.18	251	2.09	282	0.56	4326	1.15	9605	1.07	7604	0.94	14815	0.96	5408	1.03	8845	0.97
AAT	111		633		4160		23		102		376		206		6950		6745		5449		9920		4180		6306	
ATT	128	0.87	648	0.98	4161	1	42	0.55	128	0.8	330	1.14	280	0.73	6620	1.01	6731	1	5390	1.01	10316	0.96	4158	1.01	6383	0.99
AAG	106		630		1680		95		180		209		80		1117		9714		3017		12173		2932		4960	
CTT	113	0.94	668	0.94	1869	0.9	48	1.98	139	1.29	319	0.66	100	0.8	874	1.28	9514	1.02	3190	0.95	12280	0.99	2920	1	4727	1.05
AAC	103		683		3079		52		122		494		105		689		5705		2324		7342		2058		4105	
GTT	98	1.05	556	1.23	3135	0.98	36	1.44	119	1.03	104	4.75	101	1.04	806	0.85	5329	1.07	2449	0.95	7277	1.01	1994	1.03	4195	0.98
ATA	71		438		2654		25		99		367		247		9734		6185		4621		8980		3378		5243	
TAT	84	0.85	438	1	2716	0.98	26	0.96	114	0.87	324	1.13	310	0.8	9427	1.03	5994	1.03	4400	1.05	9050	0.99	3366	1	5187	1.01
ATG	83		593		2217		60		151		162		157		878		5057		2468		7439		2155		4294	
CAT	104	0.8	584	1.02	2201	1.01	80	0.75	120	1.26	416	0.39	127	1.24	703	1.25	5254	0.96	2634	0.94	7580	0.98	2201	0.98	4264	1.01
ATC	67		383		1955		64		102		371		84		752		6312		3032		8257		2564		3849	
GAT	50	1.14	407	0.94	1910	1.02	62	1.03	144	0.71	114	3.25	125	0.67	904	0.83	6292	1	3027	1	8442	0.98	2504	1.02	4012	0.96
AGA	67		485		1507		69		160		178		100		947		8611		3080		10394		2992		4537	
TCT	94	0.71	488	0.99	1564	0.96	38	1.82	128	1.25	307	0.58	87	1.15	755	1.25	8512	1.01	3368	0.91	10884	0.95	2954	1.01	4424	1.03
AGT	87		502		1576		68		115		161		78		836		5963		2098		7910		1843		3697	
ACT	104	0.84	555	0.9	1608	0.98	37	1.84	115	1	412	0.39	114	0.68	660	1.27	5990	1	2041	1.03	7813	1.01	1834	1	3534	1.05
AGG	95		532		674		133		227		174		54		555		6543		1769		8146		1916		2707	
CCT	102	0.93	495	1.07	781	0.86	88	1.51	179	1.27	543	0.32	53	1.02	483	1.15	6482	1.01	1934	0.91	8114	1	1882	1.02	2456	1.1
AGC	96		604		1423		141		170		282		50		265		6368		1459		7766		1452		2684	
GCT	101	0.95	563	1.07	1582	0.9	121	1.16	183	0.93	179	1.58	53	0.94	233	1.14	6.049	1.05	1453	1	7607	1.02	1429	1.02	2698	0.99
ACA	130		683		3602		72		155		448		119		574		4652		1932		6114		1629		3924	
TGT	104	1.25	581	1.18	3336	1.08	50	1.44	133	1.17	100	4.48	128	0.93	555	1.03	4355	1.07	2057	0.94	6201	0.99	1601	1.02	4181	0.94
ACG	5		352		2529		40		105		119		38		193		2878		1056		3959		1015		2186	
CGT	5	1	312	1.13	2630	0.96	47	0.85	92	1.14	78	1.52	35	1.09	169	1.14	2840	1.01	1149	0.92	4044	0.98	1000	1.02	2105	1.04
ACC	53		523		1163		91		158		516		63		416		4776		1692		6054		1559		2849	
GGT	61	0.87	445	1.18	1210	0.96	64	1.42	150	1.05	80	6.45	70	0.9	631	0.66	4561	1.05	1622	1.04	6296	0.96	1557	1	2955	0.96
TAA	106		647		3169		37		93		414		202		7171		5915		3888		7821		2803		4787	
TTA	122	0.87	644	1	3105	1.02	31	1.19	125	0.74	329	1.26	262	0.77	6765	1.06	5838	1.01	3638	1.05	7793	1	2812	1	4693	1.02
TAG	66		361		1196		26		105		258		103		843		6186		2350		8187		2240		2925	
CTA	73	0.9	444	0.81	1172	1.02	27	0.96	108	0.97	523	0.49	100	1.03	701	1.42	6136	1.01	2342	1	8187	1	2213	1.01	2755	1.06
TAC	66		535		1804		36		111		377		139		654		4536		2021		6482		1820		3282	
GTA	56	1.18	455	1.18	1955	0.92	42	0.86	91	1.22	154	2.45	134	1.04	895	0.73	4472	1.01	2058	0.98	6580	0.99	1831	0.99	3490	0.94
TTG	107		649		3877		62		152		116		103		638		6566		3130		9626		2651		5451	
CAA	132	0.81	702	0.92	3659	1.06	53	1.17	139	1.09	465	0.25	104	0.99	618	1.03	7031	0.93	3044	1.03	9355	1.03	2698	0.98	5147	1.06
TTC	110		579		2183		33		108		308		116		898		9169		4261		12454		3609		5161	
GAA	82	1.34	597	0.97	2091	1.04	80	0.41	172	0.63	200	1.54	84	1.38	967	0.93	9218	0.99	3858	1.1	12259	1.02	3669	0.98	5437	0.95

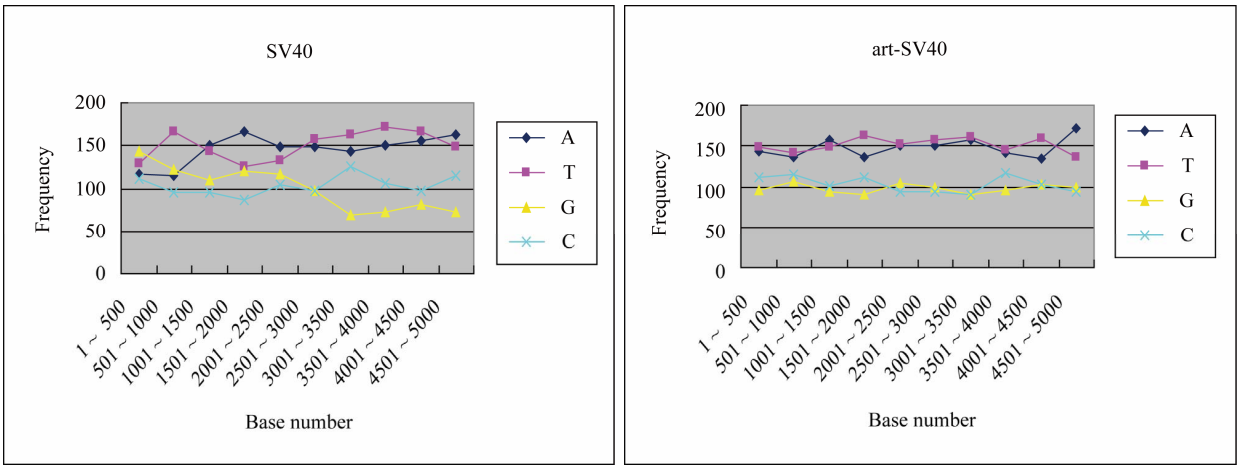
TGA	89		529		2157		82		137		190		82		776		6382		2854		8781		2189		4800	
TCA	103	0.86	470	1.13	2129	1.01	64	1.28	126	1.09	415	46	102	0.8	714	1.09	6489	0.98	2819	1.01	8606	1.02	2176	1.01	4611	1.04
TGG	93		620		1643		114		232		99		94		444		5099		1949		7269		1975		3691	
CCA	98	0.95	662	0.94	1578	1.04	114	1	176	1.32	464	0.21	74	1.27	287	3.48	5538	0.92	2144	0.91	7219	0.99	1997	0.99	3696	1
TGC	104		590		2241		121		166		123		53		196		4383		1314		6345		1322		2945	
GCA	94	1.11	609	0.97	2130	1.05	122	0.99	149	1.11	207	0.59	48	1.1	188	1.04	4644	0.94	1264	1.04	6239	1.02	1360	0.97	2993	0.98
TCG	4		275		2173		47		86		121		36		198		4411		1711		5775		1566		2200	
CGA	2	2	309	0.89	2077	1.05	47	1	105	0.82	122	0.99	25	1.44	214	0.93	4479	0.98	1654	1.03	5899	0.98	1576	0.99	2158	1.02
TCC	94		469		1145		63		86		361		61		573		6748		2501		8460		2338		2786	
GGA	81	1.16	570	0.82	1003	1.14	148	0.43	254	0.34	122	2.96	91	0.67	635	0.9	6614	1.02	2231	1.12	8356	1.01	2343	1	2983	0.93
GAG	61		472		1056		136		189		129		46		450		6482		1714		7828		1792		2645	
CTC	81	0.75	391	1.21	1123	0.94	59	2.31	142	1.33	419	0.31	50	0.92	352	1.28	6463	1	1876	0.91	7763	1.01	1752	1.02	2556	1.03
GAC	46		417		1688		68		151		170		43		251		4094		1220		4901		1135		2384	
GTC	37	1.24	349	1.19	1750	0.96	56	1.21	131	1.15	106	1.6	36	1.19	238	1.05	4216	0.97	1231	0.99	5251	0.93	1109	1.02	2455	0.97
GTG	66		480		1912		95		149		55		40		251		3676		1188		5343		1067		2798	
CAC	77	0.86	478	1	1791	1.07	85	1.12	149	1	454	0.12	47	0.85	249	1.01	3961	0.93	1156	1.03	5215	1.02	1024	1.04	2722	1.03
GGG	77		419		729		159		285		73		25		741		4934		1532		6573		1745		1592	
CCC	41	1.88	480	0.87	685	1.06	102	1.56	206	1.38	624	0.12	17	1.47	724	1.02	5007	0.99	1685	0.91	6416	1.02	1589	1.1	1620	0.98
GGC	57		486		1569		139		208		151		12		228		4124		966		5354		1009		1905	
GCC	59	0.97	514	0.95	1446	1.08	120	1.16	194	1.07	271	0.56	33	0.36	252	0.9	4077	1.01	1023	0.94	5454	0.98	1002	1.01	1960	0.97
GCG	12		523		2181		110		135		54		8		142		2827		734		3997		774		1259	
CGC	8	1.5	529	0.99	2106	1.04	71	1.55	116	1.16	155	0.35	27	0.3	126	1.13	2722	1.04	735	1	3832	1.04	782	0.99	1380	0.91
CAG	112		660		1248		154		198		199		65		193		5077		1325		6028		1239		3091	
CTG	134	0.84	598	1.1	1371	0.91	150	1.03	216	0.92	180	1.11	57	1.14	204	0.95	4920	1.03	1388	0.95	6188	0.97	1214	1.02	3074	1.01
CGG	11		350		1465		104		153		80		25		495		3656		1101		4591		1018		1446	
CCG	6	1.83	350	1	1395	1.05	72	1.44	140	1.09	141	0.57	30	0.83	471	1.05	3581	1.02	1138	0.97	4635	0.99	1021	1	1444	1

G to C, as in the genomic DNA molecule [11]. The low symmetry of A/T and G/C such as HIVtype2 (**Table 1**) or three successive base-sequences such as SV40 (**Table 2**) were affected on the distribution of the four bases (**Figure 1**). In addition, the low symmetry of four bases in HIVtype2-genome (**Table 1**) was affected to the distribution of bases (**Figure 1(c)**). Other small RNA-genome such as *Fujinami sarcoma virus* (RNA, 4788 nt) and RSV (ss-RNA, 9392 nt) maintained the base symmetry and the base distribution (**Table 1** and data not shown), therefore, the low symmetry of four bases in HIVtype2-genome might be not only reason that the genome was RNA, but also related to the origin and the evolution of the genome.

3.3. The Genome Bases Had Multiple Fractality

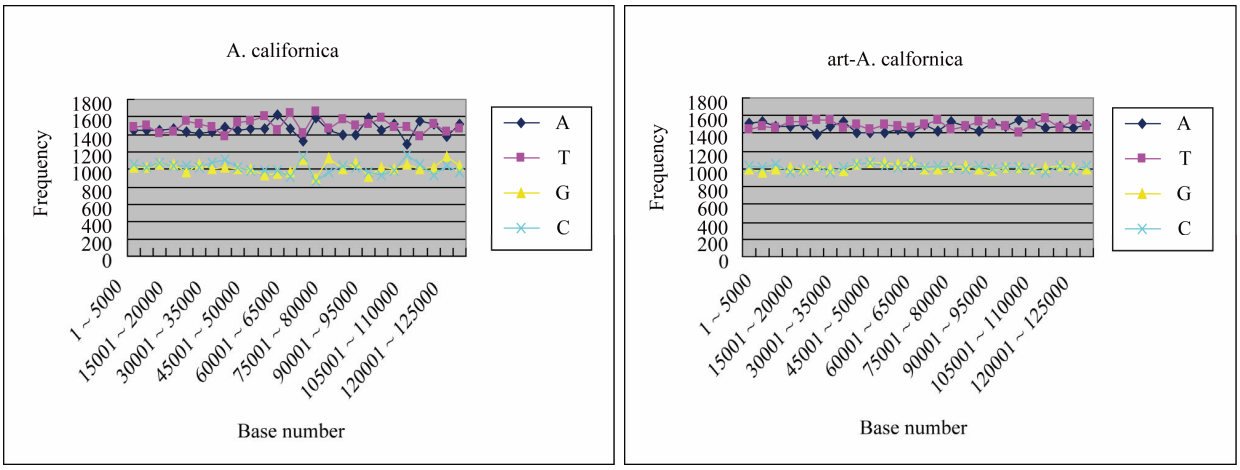
Figure 2 showed the distribution curve of adenine bases "A" in small genomes. Most genomes should be partitioned the "L" value at 15 to observe the multiple fractality, but in the very small genomes composed of 10,000 - 15,000 nt such as SV40 (a), HIV (c), and *P. falcipu arum* mtDNA (e) the linearly decreased region (power law-tail) at long distances could be observed when the L-value of the partition was favorable at 10, *i.e.*, L = 1 - 10, and more than 10 in double logarithmic plot of L vs. P (L).

Real chromosomes had the base-symmetry (the reverse-complement symmetry) as well as the base bias, whereas the artificial genome sequences had only the reverse-complement symmetry, but not the bias of the base-distribution. Based on the above results, how are the four bases, A, T (U), G, and C placed on a single-strand of DNA in a genome? In order to understand this issue we investigated the fractality characteristics of the real genomes and the artificial genomes based on the distribution of the base-distance (L). Each base-distribution curve P (L) expresses the distribution of the distance L between a base and the next base, for the base "A", the



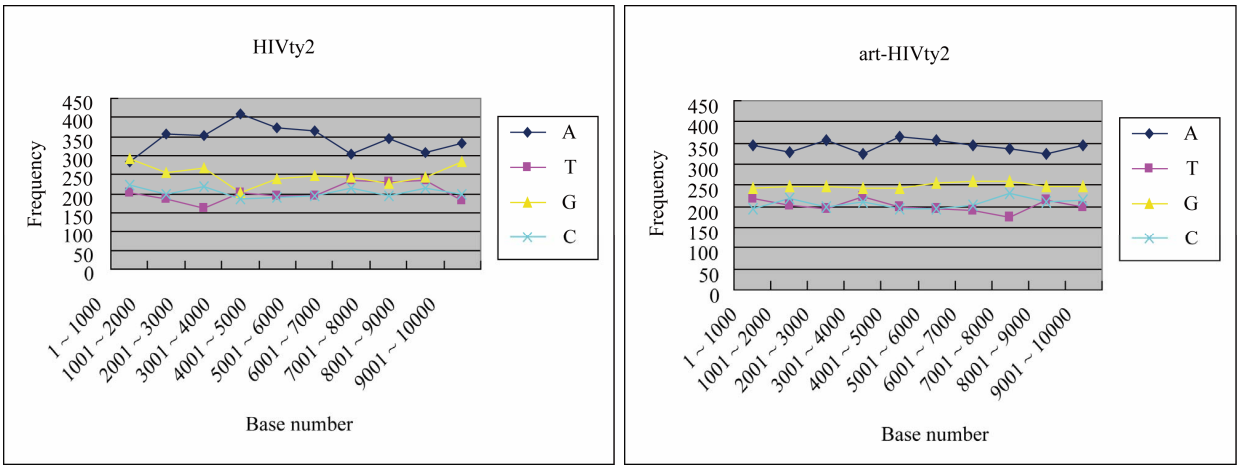
Real Artificial

(a)



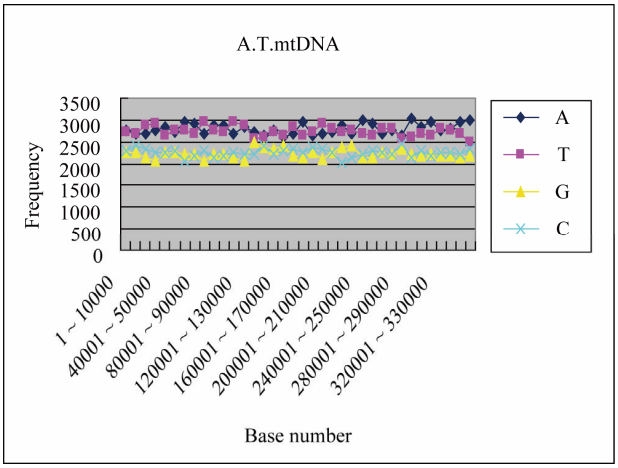
Real Artificial

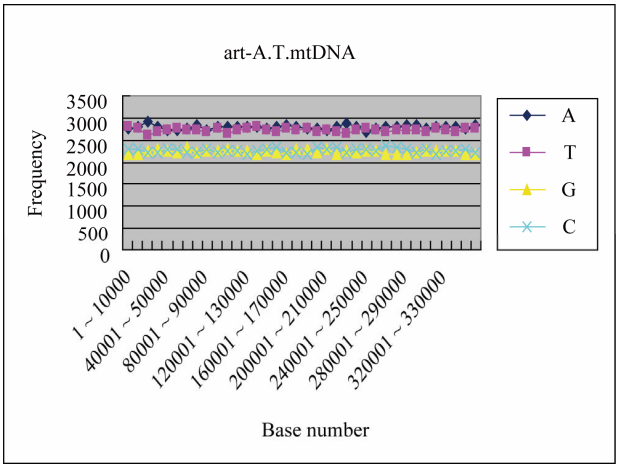
(b)



Real Artificial

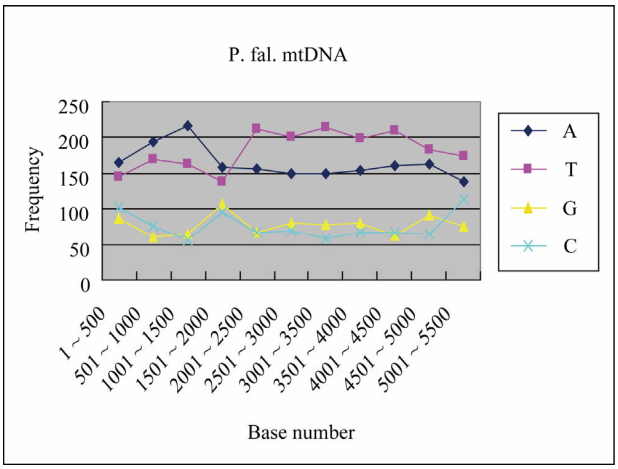
(c)

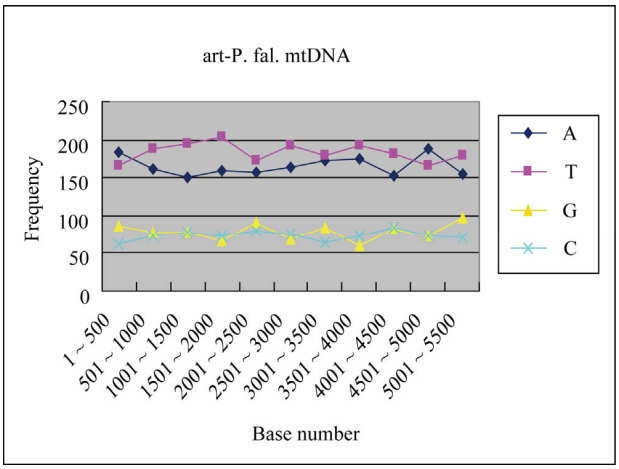




Artificial AT-mDNA.

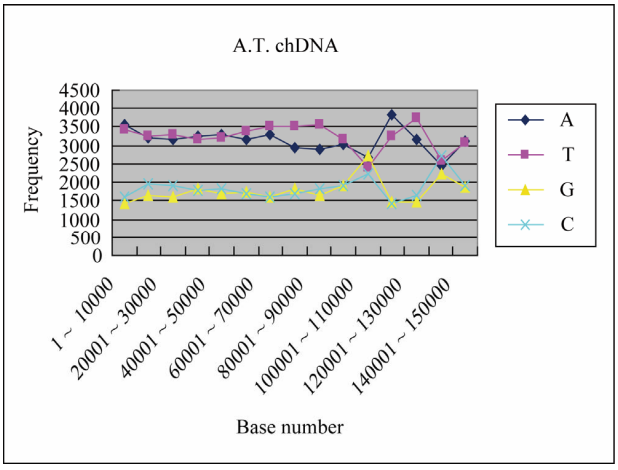
(d)

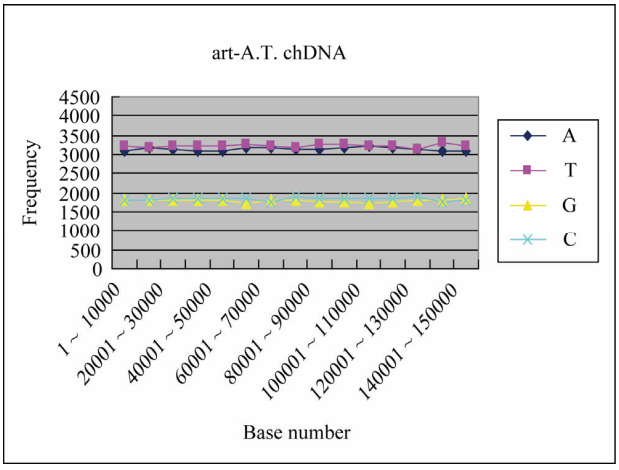




Real Artificial

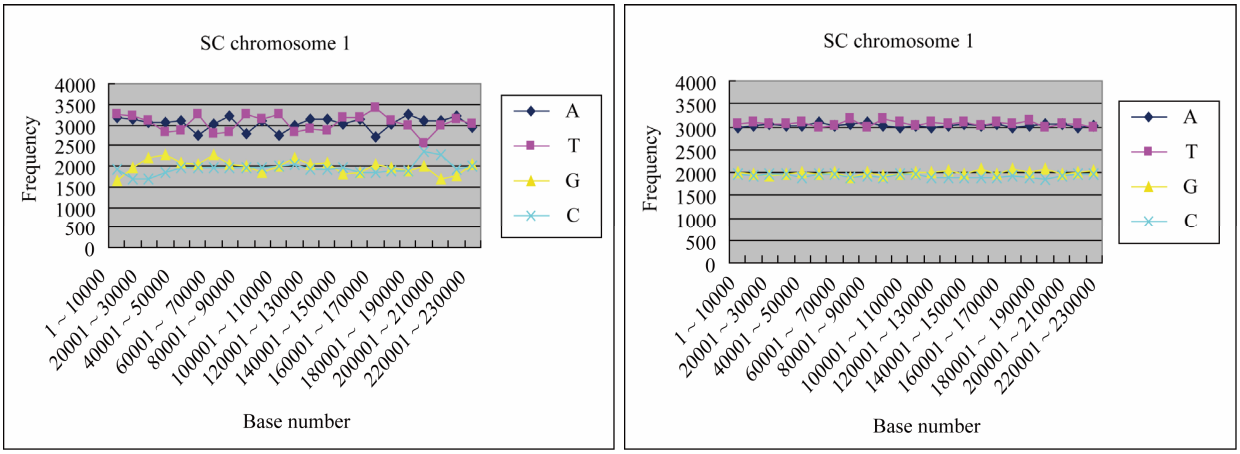
(e)





Real Artificial

(f)



Real Artificial

(g)

Figure 1. (a) *Simian virus* 40 (5243 nt), DNA, circular, GC = 40.8%, w = 500 nt; (b) *Autographa calfornica nucleopolyhedrovirus* (133,894 nt), GC = 40.0%, w = 5000 nt; (c) *Human immunodeficiency virus* 2 (10,359 nt), GC = 45.7%, w = 1000 nt; (d) *Arabidopsis thaliana* mtDNA (366,924 nt), GC = 44.7%, w = 10,000 nt; (e) *Plasmodium falciparum* mtDNA (5967 nt), GC = 28.2%, w = 500 nt; (f) *Arabidopsis thaliana* chDNA (154,478 nt), GC = 36.3%, w = 10,000 nt; (g) *Saccharomyces cerevisiae*, chromosome 1 (230,201 nt), linear, GC = 38.0%, w = 10,000 nt (control).

L-value was corresponded the base numbers from "A" to the next "A" in the genomic DNA, and P (L) is the sum of the L-value with the same base-distance in the genomic DNA [11].

A simple distinction of the multi-fractality (the linearly-decreased fractality = power-law-tail) or the uni-fractality (the exponential-decreased fractality) of the base distribution in a sequence was determined using by the fractal analysis described in the MATERIALS AND METHODS section.

For example, let us consider the case of adenine "A" in the SV40 genome. When the L-value was 1 through 10, the distribution curve P (L) of adenine (A) was fitted to an exponential equation, $y = ae^{-bx}$ (**Eq.1**, x = logL, y = logP(L); a and b are constant). In the case of adenine "A" in the SV40 genome, the a and b values were calculated from equation 1 (**Eq.1**) as 0.3819 and 0.3400, respectively (**Figure 2(a)**).

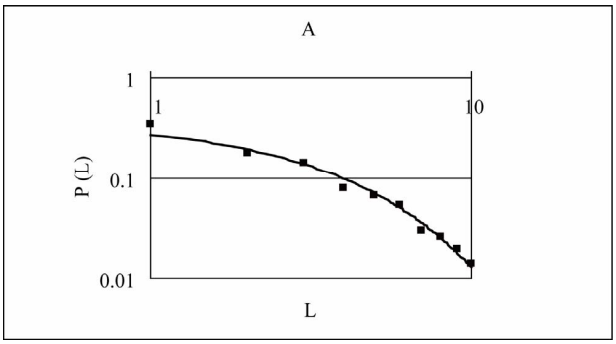
In contrast, when the L-value was more than 10, P (L) gave a straight line, $y = Ux + W$ (equation 2 = **Eq.2**; U is the slope and W was the intercept) with a slope of –0.00121 (expressed as –(1.21E-03)) (**Figure 2(a)**). Other small genomes, *A. calfornica*, HIVtype2, *A. thaliana* mtDNA, *P. falciparum* mtDNA, and *A. thaliana* chDNA were also showed the multiple fractality (**Figure 2**).

The identification of the multiple fractality in the base(s) in these genomes was also confirmed by the $f(\alpha)$ spectrum **Figure 3**. When $f(\alpha)$ varied as a function of α, the fractality must be multifractal (red-diamond, **Figures 2** and **3**); in contrast, when $f(\alpha)$ was constant at the α-value, the fractality must be unifractal (black-square, **Figures 2** and **3**).

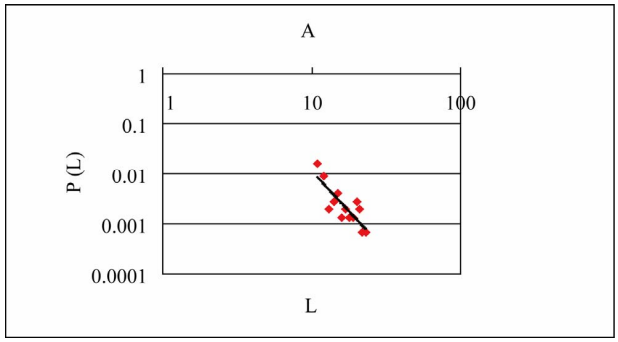
The other three bases, thymine "T", guanine "G", and cytosine "C" in the SV40 genome also behaved in a similar manner as "A", with the multiple fractality at the boundary of the L-value. In addition, the a and b values of A and T, and G and C were identical. These fractal characteristics of a single-strand of DNA of the genome were also obtained for other species (**Figure 1**, data not shown, ref. 11).

In contrast, in the artificial genome sequences, neither the bias of four bases on the genomes nor the multiple fractality were observed in the base(s) regardless of the distance in the base distribution (L-value = 10 or more). Thus, the bases of the artificial sequence of genomes were distributed only the exponentially decreased-fractality (**Eq.1**, uni-fractal) even when L was more than 10, and the multiple fractality of the base sequences in the real genomes was not observed throughout the sequences, although the base numbers (nt) and the appearance frequencies of the base sequences were the same in each genome described in the MATERIALS AND METHODS section (data not shown).

Many studies using a part of genomic DNA of *E. coli* and other model DNA sequences had been reported that genomic DNA had a fractality [44-47]. These studies might be analyzed based on the bacterio-phages, the prokaryotic genomes, because the fractality of large genome such *S. cerevisiae* and *H. sapiens* genomes had not been analyzed yet in those days, in addition, the multiple fractality might not be observed in the literatures previously published.

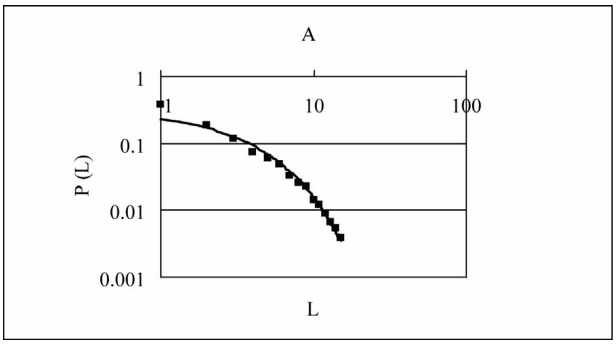


L = 1 - 10, $y = 0.3819\ e^{-0.34x}$

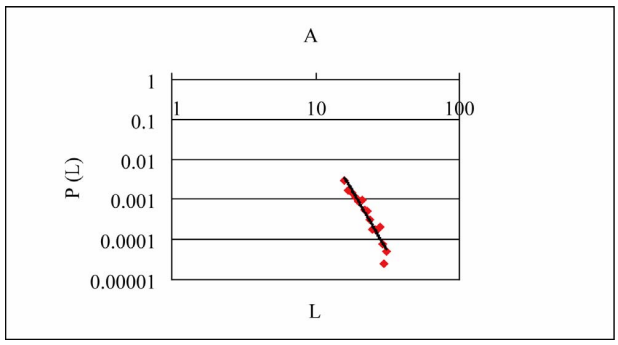


L = 11 - 23, y = –(1.21E-03) x + W

(a)

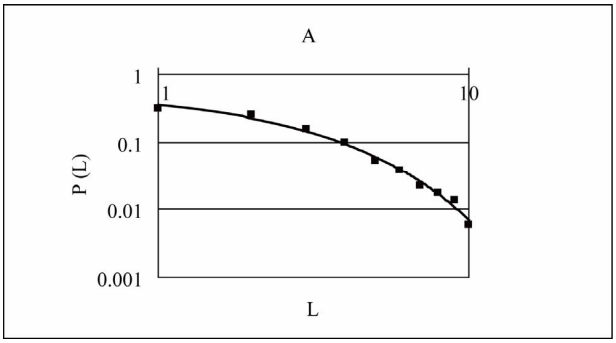


L = 1 - 15, $y = 0.3134\ e^{-0.3007x}$

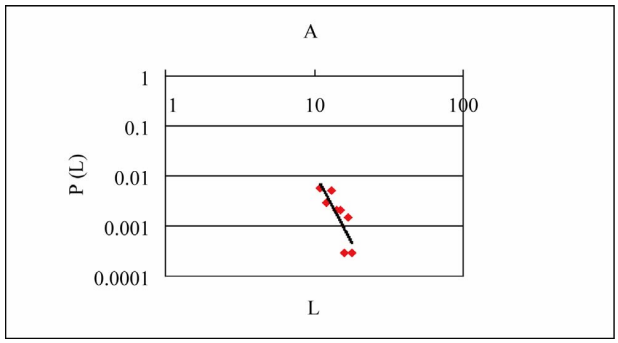


L = 16 - 31, y = –(1.75E-04) x + W

(b)

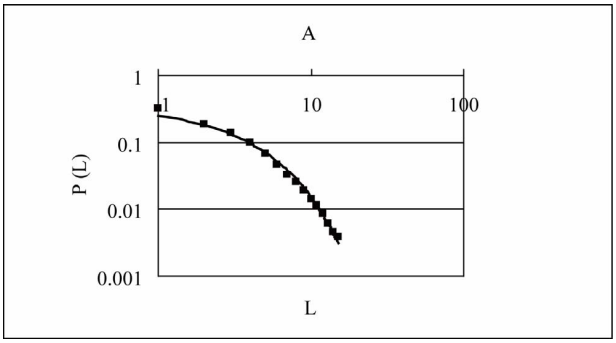


L = 1 - 10, $y = 0.5412\ e^{-0.4367x}$

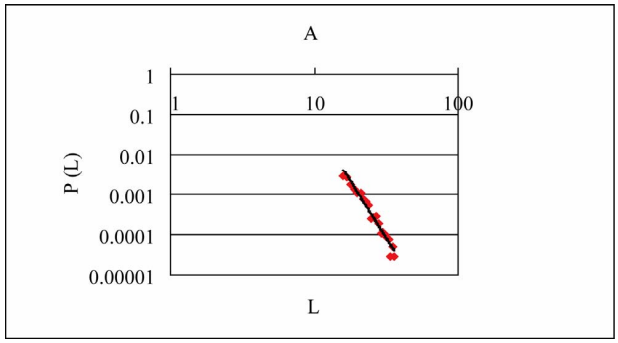


L = 11 - 18, y = –(6.77E-04) x + W

(c)

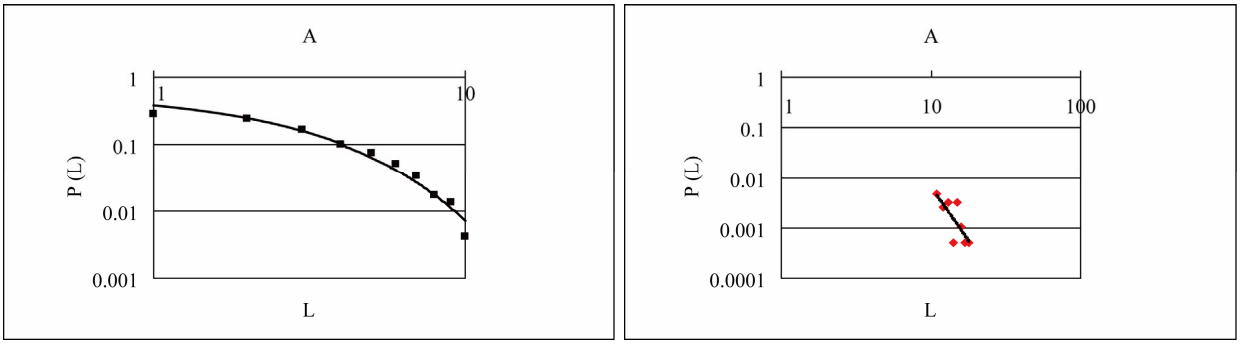


L = 1 - 15, $y = 0.3421\ e^{-0.3125x}$



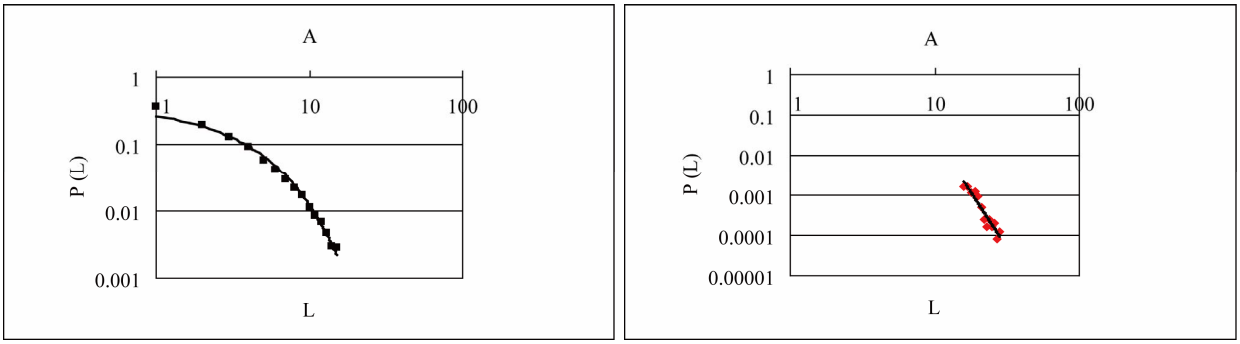
L = 16 - 36, y = –(1.35E-04) x + W

(d)



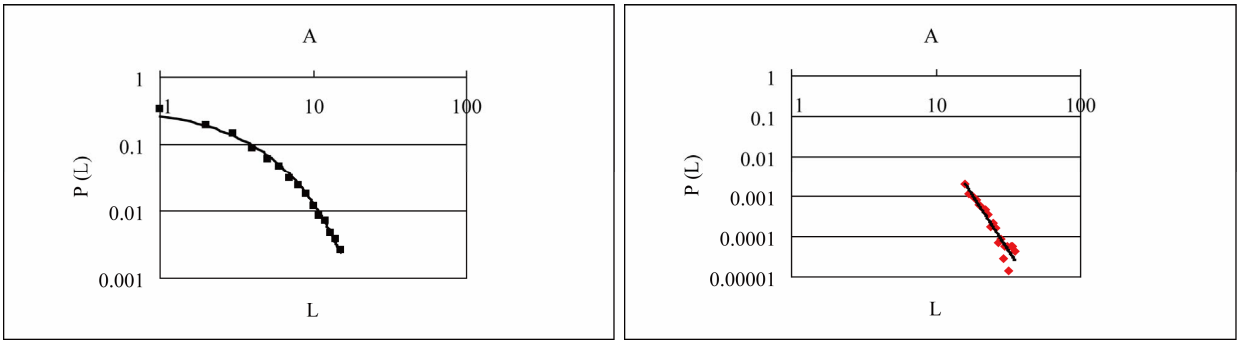
L = 1 - 10, y = 0.5929 $e^{-0.4431x}$ L = 11 - 18, y = –(5.17E-04) x + W

(e)



L = 1 - 15, y = 0.3682 $e^{-0.3403x}$ L = 16 - 28, y = –(1.12E-04) x + W

(f)



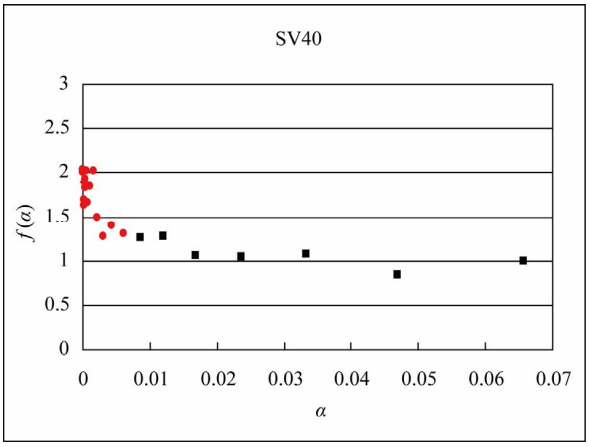
L = 1 - 15, y = 0.3736 $e^{-0.3369x}$ L = 16 - 35, y = –(9.81E-05) x + W

(g)

Figure 2. Fractality of adenine nucleotide (A). (a) *Simian virus* 40 (5243 nt); (b) *Autographa calfornica nucleopolyhedrovirus* (133,894 nt); (c) *Human immunodeficiency virus*2 (10,359 nt); (d) *Arabidopsis thaliana* mtDNA (366,924 nt); (e) *Plasmodium falciparum* mtDNA (5967 nt); (f) *Arabidopsis thaliana* chDNA (154,478 nt); (g) *Saccharomyces cerevisiae* chromosome 1 (230,203 nt, control).

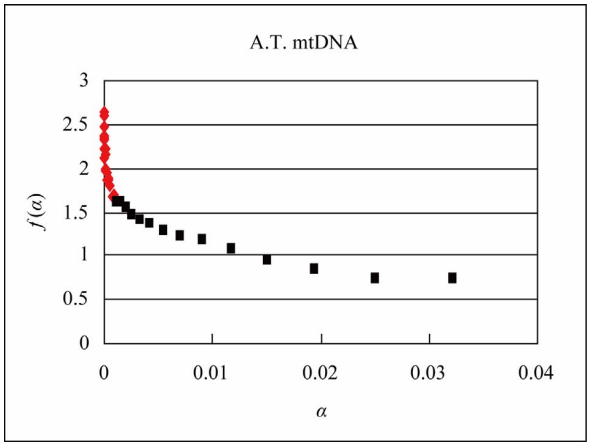
Essentially, all genomes or chromosomes might be three structural features, the co-existence of the reverse-complement symmetry, the bias, the multiple fractality in a single-strand of DNA [11].

These three structural features of the single-strand DNA of genomes were able to observe only in the real (active) genome, but not observed in the individual gene, the short DNA or the random-ordered DNA such as the artificial sequence of the genome [11]. When these three structural features were co-existed, the gene(s) on the genome could be able to express, and the resulted product(s) might be functioned timely and properly in the living cells even in the small genomes. The bases of genomes were not placed randomly, but seem to be placed sophisticatedly by the generation-rules as a single-strand of genomic DNA even in the small genomes. Presumably, two such structural-featured in a single-strand DNAs above described might be assembled to form the anti-



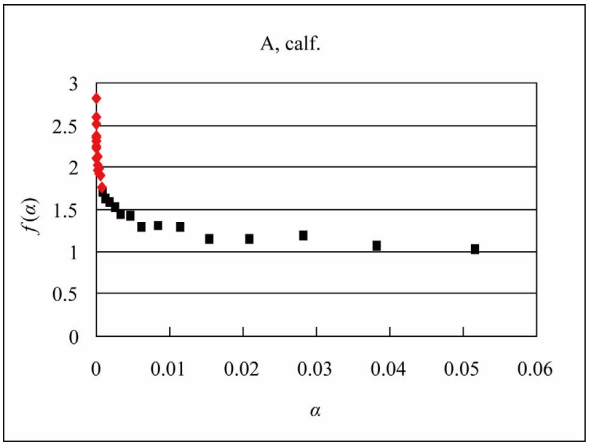
L = 1 - 10, (exponentially decreased region)
L = 11- 23, (linearly-decreased region)

(a)



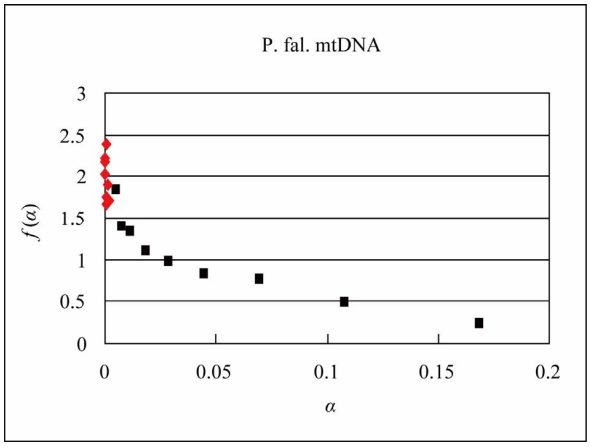
L = 1 - 15, (exponentially decreased region)
L = 16 - 36, (linearly-decreased region)

(d)



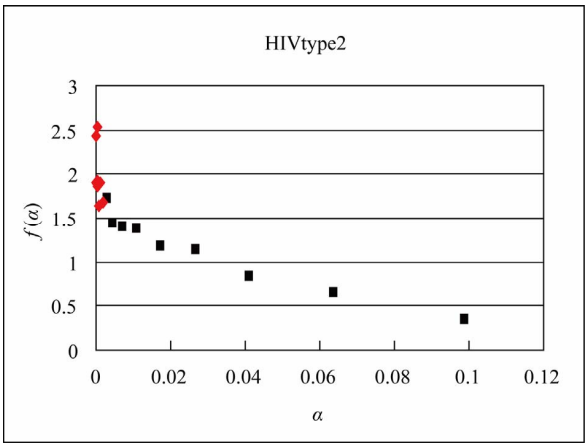
L = 1 - 15, (exponentially decreased region)
L = 16 - 36, (linearly-decreased region)

(b)



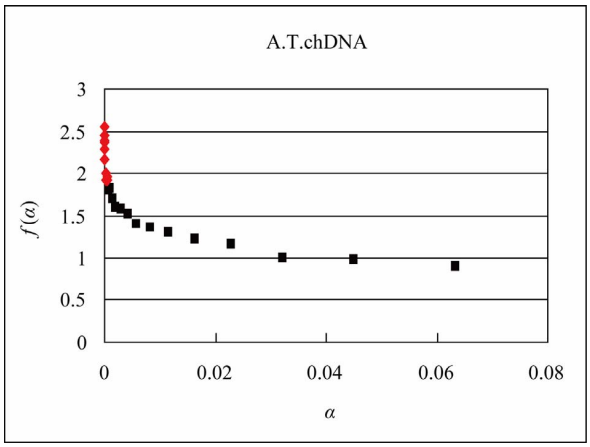
L = 1 - 10, (exponentially decreased region)
L = 11 - 18, (linearly-decreased region)

(e)



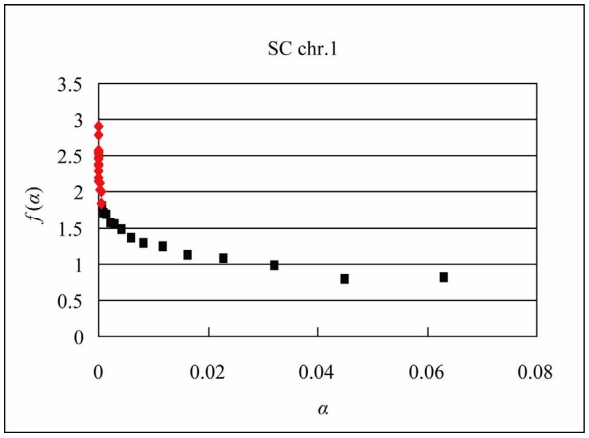
L = 1 - 10 (linearly-decreased region)
L =11 - 18 (exponential-decreased region)

(c)



L = 1 - 15, (exponentially decreased region)
L = 16 - 28, (linearly-decreased region)

(f)



L = 1 - 15, (exponentially decreased region)
L = 16 - 35, (linearly-decreased region)

(g)

Figure 3. $f(\alpha)$ analysis of virus, mitochondrial and chloroplast genomes. (a) SV40; (b) *Autographa California* virus; (c) *Human immunodeficiency* virus2; (d) Arabidopsis thaliana mtDNA; (e) *Plasmodium falciparum* mtDNA; (f) *Arabidopsis thaliana* chDNA; (g) *Sacchrmyces cerevisiae* chromosome 1 (230,203 nt, control).

paralleled, complementary, double-strand DNA as we know (**Table 2**).

The structural features of a single-strand of genomic DNA might have implications that affect DNA replication, transcription, translation, as well as other biological processes because the information might be present in genome base sequence [11].

Previously, Crick and his co-workers proposed a question about DNA structure [48,49]. They presented data to show that the base-sequence of the DNA was necessary to understand the detailed structure of DNA. Now we could speculate about the detailed structure of DNA molecules because the complete base sequences of several genomes were available. The structural features of the single-strand of the genomic DNA might also be suggested the process of the DNA replication.

Essentially, the reverse-complement symmetry in the base sequence should be observed on a single-strand of DNA in a genome. The base symmetry in a single-strand of DNA of a genome was presented; in other words, the DNA might be able to be closed, and possible to make stem-loop structures. Previously, the biological role of the non-coding sequences and stem-loop structures was discussed [12-16]. Now, the genome sequences of many organisms had been revealed, and we should analyze the genome to understand living organisms.

Therefore, to understand biological phenomena in living organisms, we needed new approaches to analyze genomes including both the coding- and the non-coding region as a large intact molecule.

Based on the above structural features of the genomic DNA, the Sequence Spectrum Method (SSM) was developed and proposed [35,36]. The SSM was a new analytical method of the entire genome based on the appearance frequencies of the nucleotides (bases) sequence of genome.

4. COMPLEXITY THROUGHOUT THE GENOME

When the distribution of each four bases depending on the distance in double logarithmic plot (power spectrum) of L (the distance of a base to the next base) vs. P (L) (the probability of the base-distribution at L), the exponentially decreased-fractality at short distances and the linearly decreased (power law-tail) at long distances, *i.e.*, the multiple fractality with the different fractality was observed. The genome was a "field" of the various genes as described above. In virus genomes, the genes were very crowded on the field like the prokaryotic cells; in addition, the intergenic region was smaller, and the multiple fractality was hard to be observed, specifically the multifractality was hidden behind the unifractality. In prokaryotic cells, most of the genome was occupied the coding regions, whereas in the organelle and the plastids (chloroplasts) genomes, the field was large, but not so large (base numbers) with the different bases-contents from the nuclear chromosomes. As a result, in the virus genomes, the mitochondrial- and the chloroplast-DNA, the multiple fractality, both the unifractality and the multifractality were also observed like in the large genomes. The non-coding regions of the genome were composed of promoter, MAR, insulator, poly (A) signal sequence, SINE, LINE, ncRNA, intron and so on [25,29-34]. These elements were known as regulation of the gene-expression for the biological phenomena. The more complex the organisms were, the more the non-coding regions might be in genome [25,34]. In genome, including these regulatory elements of the gene-expression, the base sequences of the genomic DNA would be maintained the structural features, the reverse-complement symmetry, the bias, and the multiple fractality in a single-strand [11,5,36].

Whereas, in small genomes, many genes were overlapped each other and compact to be expressed timely the regulation.

We could be tried to approach the studies targeted to the entire genome based on the appearance frequencies of the bases in genome, in other words, how to use the base sequence in genome. We had studied many, including the eukaryotes, prokaryotes, viruses, organelles and plastids genome sequences down-loaded from the data bases like NCBI [7] and so on. We had calculated the base frequencies of the chromosomes in numeric order

when there were several chromosomes in one organism. In addition, the reason for using chromosome in *H. sapiens*, the personal computer can not be calculated the sum of chromosomes 1 - 22, X and Y because of the limited capacity.

The genome data are draft as described above, but most of the unreadable area was very small part compared with the huge entire chromosome. So, when there was unreadable region in chromosome, we could skip the region to calculate the base frequencies of the chromosome or genome because the unreadable region of each chromosome was small number of bases to neglect in comparison to large number of genomic DNA. The complexity of the organisms might be dependent on the capacity of the non-coding region in the entire genome.

5. CONCLUSIONS

The structural features, 1) the reverse-complement symmetry of the base or three successive base sequences, 2) the bias of the four bases-distribution, 3) the multiple fractality of the four bases-distribution were the universal in a single-strand of genomic DNA or RNA genomes in a part of virus even in the small genomes such as virus, the plastids and the organelle genomes. These three characters were co-existed in the single-strand of DNA in all genomes. The molar ratio of the plastids and the organelle genomes were different from the nuclear chromosomes of the host cells because most of the plastids and the organelle genomes might be evolved under the process of the symbiosis in other organisms.

6. ACKNOWLEDGEMENTS

The author wishes to thank to Dr. Masatoshi Nakahara for his critical reading and advice of this manuscript, and to Mr. Yasuharu Mayama for his technical assistance.

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