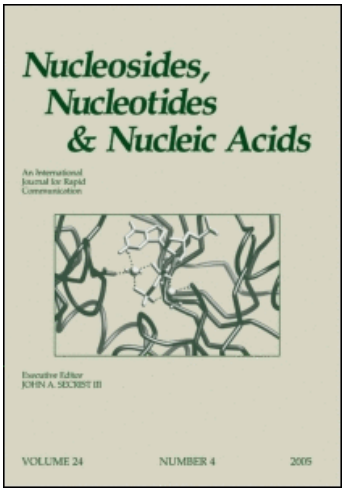

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Non-Linear Dynamics in Nucleic Acid Research Using Fractals Ulm Report 1996

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To cite this Article Kleinschmidt, Albrecht K.(1997) 'Non-Linear Dynamics in Nucleic Acid Research Using Fractals Ulm Report 1996', Nucleosides, Nucleotides and Nucleic Acids, 16: 5, 733 — 736
To link to this Article: DOI: 10.1080/07328319708002942
URL: http://dx.doi.org/10.1080/07328319708002942

NUCLEOSIDES & NUCLEOTIDES, 16(5&6), 733-736 (1997)

NON-LINEAR DYNAMICS IN NUCLEIC ACID RESEARCH USING FRACTALS ULM REPORT 1996

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Abstract: Chemical oligonucleotide syntheses give rise to short target and error sequences useful for measuring statistical synthesis efficiency in fractal dimensions. These are compared to fractals of template-supported DNA yields by polymerase chain growth of polynucleotides, and *in vivo* grown viral HSV-1-DNA. The report includes fractal packaging of coliphage T4-DNA in the intracellular prohead.

Fractals as coined by Benoit Mandelbrot [1] are measures with fractional power laws. The formalistic procedures [2] to work with were initially of mathematical, intrinsic nature, and first applied to physical objects and laws [2] (coast-line (Richardson), meteorological low (Lorenz), geometric and dynamic structure and its designs). In biomedicine and biotechnology [3, 4] we visualize spatial and temporal, non-linear, reiterative and scale-invariant patterns of biological systems demonstrating similarity within high complexity in structure or time. These patterns allow to use fractals in deterministic and statistical forms or processes either as parts of, or as whole biosystems. Fractals in nucleic acid research should be based on experiments before fitting models are developed [5, 6].

A first important successful application were the "landscape distributions" of natural DNA sequences of large primary DNA structures. Existing already in numerous "layers of information" [7, 8], the genomic sequences were arranged in a "DNA walk" (pyrimidines up, purines down in (x,y) coordinates) along a natural sequence. The long-range correlations were presented in similarity as a spectrum in double-log plots, revealing self-affine fractal properties in the DNA walk landscape. These new patterns also allow discrimination of exons and introns, and comparison of coding elements of the same protein in different species. Mountainous contour plots of DNA reading sequences are self-similar,

somehow scale-invariant, from, say 400 (lower limit) to 16,000 (upper limit) nucleotides e.g., while nucleotide intron sequences deviate individually from these fractal patterns.

DNA Growth: In this short Ulm report the fractal dimensions of DNA growth were analyzed by experiments of chemical synthesis of oligodeoxyribonucleotides, enzymatic growth *in vitro* polymerase chain reaction - (PCR), and *in vivo* grown DNA restriction enzyme patterns. They are modeled as practical applications of DNA growth controlled by experiments [9, 10, 11; 13, 14]. In addition, results of chemical, *in vitro* and *in vivo* syntheses were compared and differentially interpreted [12].

In our case, nucleic acid research in **target** and **error sequences** is the introduction of a fractal two-dimension D according to Mandelbrot (eq. 3 in [15] which is one-dimensional).

$$\lim_{N \to \infty} [\ln \{\Sigma_{l \in (1\ N)} M(l, N)\} / \ln (1/N)] = 2-D \qquad \text{(eq.1)}$$

where M (l, N) is the probability density of sequence variabilities (l) at truncation, deletion and point mutation sequences (N) in embedding space 2 [5, 10].

Applications of fractal dimension eq. 1: In a first consideration we studied the chemical single stranded DNA synthesis to find the amounts of error sequences and error propagation in chemically solid phase synthesized oligonucleotides and DNA sequences for biomedical application [17]. The result is that the longer the single stranded synthesis proceeds, the more errors are exponentially accumulated during synthesis as seen by high resolution chromatography [9, 11]. The chemical process included bonding of nucleoside-3'-phosphoamidites in cyclic repetition of steps of each detritylation, coupling, capping and oxidation in organic solvents [16], bound to solid phases of various proveniences. Limits for target nucleotide lengths are set for practical reasons (inefficiency and crowded error sequences) between 50 and 100 nucleotides with inequality of control experiments.

However, enzymatic growth *in vitro* (PCR) is indicative for much less errors. There are many examples for a combination procedure where point mutations, deletions, and other common errors are very rare [12]. *In vivo* growth of herpes simplex virus type 1 was analyzed in the junction (L - S) domain under standard conditions, where no errors within one strain were detected, and could be used for strain characteristics (standard strain F, strain AK and others) [12]. All these characteristics are found under improve-

ments of procedures. Thus, the fractality of PCR analyses of genes encoding cytoskeleton elements lies in the comparison of amplified and non-amplified actin encoding fragments. The multigene families of actin show variation in intron length [12].

T4 DNA packaging: Packaging of DNA of coliphage T4 [18] is an intracellular process exercised on processed proheads. It is shown that DNA advances from a replicated DNA pool in limited length into a vesicle via a terminase at the proximal opening of the prohead. Globules are formed under cellular ATP consumption supported by an intraphage active (capsomeric) enzyme, condensing further the fractal DNA segment to globules in a row. Globules are pseudo-fasces like showing highest condensation in uneven lengths of rods less than half the maximal inner diameter of the phage head. Globules are modeled to 1,246 and 55 μm total DNA length. The packaging is fractal through intermittent steps of prohead filling and can be described by Lévy statistics of anomalous diffusion

$$p(l,t) = a(t) / l^{\mu} \qquad \text{(eq. 2)}$$

where p is a probability distribution, a(t) is time dependent amplitude, and l the length of a globule. The fractal exponent μ determines the scaling exponent of the distribution. This model is an improvement of already existing T4-DNA packaging models [19,20].

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