J Biosci Vol. 42, No. 4, December 2017, pp. 523–525
DOI: 10.1007/s12038-017-9720-7

Commentary

Irregular designs and Darwinism in biology: Genomes as the test case

Designs and functions are highly interlinked, perhaps much more so in living rather than in non-living systems. Interestingly, designs are largely non-Euclidian and irregular across several length scales in the biological world. It is intriguing to fathom how irregular shapes, bestowed with high dynamic properties, end up exhibiting robust biological functions, so much so that Euclidian idealized designs are rendered almost non-existent in biological schemes, almost at every length scale. It is no wonder that artistically oriented human minds have invariably been drawn to creating their own exquisite Euclidian designs for satiating their inner urge towards engaging with regular and periodic patterns of designs drawn entirely from the Euclidian geometry.

Are irregular design shapes aesthetically (and therefore functionally) so hopeless? Not really. It is very enlightening to learn that Nature (both in living as well as non-living worlds) in fact has created a mid-way solution to this 'quandary' of irregular designs by offering recursive periodicity and/or symmetry even within 'irregular shapes'. While symmetry in irregular designs was long appreciated by mankind, it is only recently that periodicity in irregular designs was first realized by Mandlebrot, who invented the word 'fractal' in 1975 (Mandelbrot 1975) to connote a design, which is 'a rough or fragmented geometric shape that can be subdivided in parts, each of which is (at least approximately) a reduced-size copy of the whole'. This property is referred to as self-similarity and the term 'fractal' was derived from the Latin word *fractus* meaning 'broken' or 'fractured'.

Fractals being self-similar structures exhibit similar features when examined at increasing magnifications (*http://homepages.ulb.ac.be/∼dgonze/TEACHING/fractals.pdf*). Several natural objects approximate to fractals, including clouds, mountain ranges, lightning bolts, coastlines, snowflakes, etc. (Mandelbrot 1982). Interestingly, the converse need not be true: not all self-similar objects are fractals: for example, a straight Euclidean line is formally self-similar but has no fractal characteristics. In the fractal world, objects besides being self-similar are *too irregular* to be easily described with any characteristic scale for their description. They obey a nonlinear, power law relationship. In non-mathematical parlance, a power law relationship simply means that a log–log diagram where log of the scale size when plotted against the values of a variable measured at respective scales shows a slope of a linear regression, which defines the fractal dimension (Metze 2010). In other words, the chosen variable exhibits scale-independent behaviour. It is really not intuitive as to why Nature chose a linear regression in such log–log relationships (the very basis of fractal designs). This relationship could well have been nonlinear too! Perhaps, this then forms an example of design principles in Nature where even in irregularity, there is a deep sense of regularity. Intuitively, such a design is highly scalable without requiring any additional assumptions and therefore must be fairly robust.

The fractal designs, though not obvious, seem ubiquitous in the living world too. This has *not* been well recognized even by the most celebrated biologists, unfortunately. In fact, the extension of fractal design concept in biology has significantly impacted our conceptual understanding of the underlying design principles that govern highly complex biological behaviours, a realization which is highly under-appreciated in biology. Fractality is discernible not only in the anatomy of the vascular and pulmonary systems but also in functional processes such as regulation of blood pressure, ion channel kinetics, heart rate variability, allometric scaling growth, allosteric enzyme kinetics, metabolic rates in mammals and population genetics, etc. (Losa 2009; McNally and Mazza 2010; Thamrin *et al.* 2010). It is even aesthetically very pleasing to recognize that fractal designs underscore the principle that biological structures could be built by rather simple, iterative schemes such that complex designs could result merely out of simple recursive steps, applied across all scales, a theme that Darwinian selection has successfully adapted in Biology. I am tempted to even go as far as speculating that Darwinian selections between two biological functions/features could in fact be bound by the log–log linearity of regression. I shall now take an example from comparative genomics system to illustrate this point. But before I go there, I want to emphasize

that more recent high-throughput analysis performed across the whole human genome for quantitatively assaying contact frequencies of a portion of the genome with any other portion of the same (Hi-C assay) (Lieberman-Aiden *et al.* 2009) has elegantly uncovered fractal nature of genome organization with an average fractal dimension of $\sim$ 1.08 in fibroblast cells of *Homo sapiens*. The same technique has been subsequently extended to probe several other genomes as well where again fractal nature of the genomes has become evident, except that the fractal dimension of different genomes seems to vary significantly (Hacker *et al.* 2017; Lebedev *et al.* 2005) (Why such definite variation is observed among different genomes is an exciting but separate topic of discussion, which I might take up later). Even 3D rheology-based biophysical experiments have revealed that the mammalian interphase nuclei show fractal organization in the genomes (Bancaud *et al.* 2009).

Let me now return back to the example of comparative genomics data that seem to suggest that Darwinism functions strictly under the bounds of log–log linear regressions (provocatively, put)! Syntenic chromosomes across different species oftentimes exhibit very different chromosomal sizes, so much so that a lot of extraneous sequences 'butt in' or 'extrude out' of a syntenic chromosome rather rampantly (vis- à-vis the syntenic partner being compared with) (Bolshakov *et al.* 2002; Zdobnov *et al.* 2002). However, interestingly, when one computes the fractal dimension of such syntenic chromosomes, one observes that extraneous sequences are only so chosen that they do not destabilize the overall fractal dimension that was intrinsic to the original syntenic chromosome. The acquisition or extrusions of extraneous sequences, which are obviously not related to syntenic sequences, seem to be under the leash of fractal geometry rules. Detailed sequence analyses across genomes suggest that large-scale sequence changes occurring during evolution are under the confines of power law distributions, which relate to genome fractal dimensions (Klimopoulos *et al*. 2012; Polychronopoulos *et al.* 2016).

This brings me to one final, again a relatively under-appreciated, aspect of genome design: genomes seem to be much more than a linear sequence of chemical information: Supra-chromosomal spatial organization of chromosomes within an interphase nucleus is maintained by concerted set of interactions not only across various intra- and inter-chromosomal contacts, but also across several non-chromatin-based sub-compartments (e.g. nuclear envelope, pore-complex, nuclear matrix, nuclear speckles, Cahal bodies, nucleoli, etc.) within the context of 'nucleography' (Gruenbaum 2015; Berger and Geyer 2016). Such intensely dynamic, but highly concerted cross-talk converts the genome into an epigenome, which functions as a system within the cellular nucleus, where chemical sequence of a genome plays only the role of a blueprint, with relatively a minor role in shaping the overall genome homeostasis.

References

Bancaud A, Huet S, Daigle N, Mozziconacci J, Beaudouin J and Ellenberg J 2009 Molecular crowding affects diffusion and binding of nuclear proteins in heterochromatin and reveals the fractal organization of chromatin. *EMBO J.* **28** 3785–3798

Berger F and Geyer PK 2016 Editorial overview: Genome architecture and expression: Connecting genome composition and nuclear architecture with function. *Curr. Opin. Genet. Dev.* **37** iv–vi

Bolshakov VN, Topalis P, Blass C, Kokoza E, della Torre A, Kafatos FC and Louis C 2002 A comparative genomic analysis of two distant diptera, the fruit fly, *Drosophila melanogaster*, and the malaria mosquito, *Anopheles gambiae*. Genome Res. **12** 57-66

Gruenbaum Y 2015 Nuclear organization. *Annu. Rev. Biochem*. **84** 61–64

Hacker WC, Li S and Elcock AH 2017 Features of genomic organization in a nucleotide-resolution molecular model of the *Escherichia coli* chromosome. *Nucleic Acids Res.* **45** 7541–7554

Klimopoulos A, Sellis D and Almirantis Y 2012 Widespread occurrence of power-law distributions in inter-repeat distances shaped by genome dynamics. *Gene* **499** 88–98

Lebedev DV, Filatov MV, Kuklin AI, et al. 2005 Fractal nature of chromatin organization in interphase chicken erythrocyte nuclei: DNA structure exhibits biphasic fractal properties. *FEBS Lett.* **579** 1465–1468

Lieberman-Aiden E, van BerkumNL, Williams L, Imakaev M, Ragoczy T, Telling A, Amit I, Lajoie BR, et al. 2009 Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science* **326** 289-293

Losa GA 2009 The fractal geometry of life. *Riv. Biol.* **102** 29–59

Mandelbrot BB 1975 Stochastic models for the Earth's relief, the shape and the fractal dimension of the coastlines, and the number-area rule for islands. *Proc. Natl. Acad. Sci. USA* **72** 3825–3828

Mandelbrot BB 1982 The fractal geometry of nature (Times Books: Henry Holt and Co. 08/15/1982)

McNally JG and Mazza D 2010 Fractal geometry in the nucleus. *EMBO J.* **29** 2–3

Metze K 2010 Fractal dimension of chromatin and cancer prognosis. *Epigenomics* **2** 601–604

Polychronopoulos D, Athanasopoulou L and Almirantis Y 2016 Fractality and entropic scaling in the chromosomal distribution of conserved noncoding elements in the human genome. *Gene* **584** 148–160

Thamrin C, Stern G and Frey U 2010 Fractals for physicians. *Paediatr. Respir. Rev.* **11** 123–131

Zdobnov EM, von Mering C, Letunic I, Torrents D, Suyama M, Copley RR, Christophides GK, Thomasova D, et al. 2002 Comparative genome and proteome analysis of *Anopheles gambiae* and *Drosophila melanogaster*. *Science* **298** 149–159

B J Rao

Department of Biological Sciences, Tata Institute of Fundamental Research, Mumbai 400 005, India

(Email, bjrao@tifr.res.in)