

length. The measured dependence of inter-locus positioning on genomic distance singles out intra-nucleoid interactions as the mechanism responsible for chromosome organization, from which we infer the existence of an as-yet-uncharacterized higher-order DNA organization in prokaryotic cells. We demonstrate that both the stochastic and average structure of the nucleoid is captured by a fluctuating elastic filament model. This organization is shown to be dependent on a number of structural genes. The quantitative analysis of the deletion phenotypes of these genes, in the framework of the nucleoid model, reveals new insights into the mechanisms by which these genes effect cellular-scale organization.

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I-Switch: A DNA Nanomachine that Maps Spatial and Temporal pH Changes Inside Living Cells

Souvik Modi.

National Centre For Biological Sciences, Bangalore, India.

DNA nanomachines are synthetic assemblies that switch between defined molecular conformations upon stimulation by external triggers. Previously, the performance of DNA devices has been limited to *in vitro* applications. Here we report the construction of a DNA nanomachine called the I-switch, which is triggered by protons and functions as a pH sensor based on fluorescence resonance energy transfer (FRET) inside living cells. It is an efficient reporter of pH from pH 5.5 to 6.8, with a high dynamic range between pH 5.8 and 7. To demonstrate its ability to function inside living cells we use the I-switch to map spatial and temporal pH changes associated with endosome maturation. The performance of our DNA nanodevices inside living systems illustrates the potential of DNA scaffolds responsive to more complex triggers in sensing, diagnostics and targeted therapies in living systems.

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Chromosomal Loci Move Subdiffusively Through a Viscoelastic Cytoplasm

Stephanie C. Weber, Julie A. Theriot, Andrew J. Spakowitz.

Stanford University, Stanford, CA, USA.

Tracking of fluorescently labeled chromosomal loci in live bacterial cells reveals a robust scaling of the mean square displacement (MSD) as $\tau^{0.39}$. We use Brownian dynamics simulations to show that this anomalous behavior cannot be fully accounted for by the classic Rouse or reptation models for polymer dynamics. Instead, the motion seems to arise from the interaction of the Rouse modes of the DNA polymer with the viscoelastic environment of the cytoplasm. To demonstrate these physical effects, we present a general analytical derivation of the subdiffusive scaling for a monomer in a polymer within a viscoelastic medium. The time-averaged and ensemble-averaged MSD of chromosomal loci exhibit ergodicity, and the velocity autocorrelation function is negative at short time lags. These observations are most consistent with fractional Brownian motion and rule out a continuous time random walk model.

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The Epigenetic Code and Algorithms: Complementary Biomolecular Imprint Interaction of Functional Non-Coding ncRNA, A "Rosetta Stone" for Hermeneutics of Genome Episcryption

Josef H. Wissler.

Arcons Institute for Applied Research & Didactics, Postfach 1327, D-61231 Bad Nauheim, jhw@arcons-research.de, Germany.

OBJECTIVE: The genome orchestrates genetic [Mendelian] and epigenetic [non-Mendelian] information of same genotype into different organized or mess-chaotic [tumor] phenotype variations. By genetic complementary and triplet base codes, only ~2% total DNA transcription output [RNA] are translated into proteins. In entangled epigenetic cancer-angiogenesis-tolerance remodeling of cells activated by extrinsic [environmental] factors, functions of residual ~98% ncRNA transcripts were investigated what governs genome episcryption [greek: "overscript"]: Chance or necessity for structural codes and algorithms? **METHODS:** Ann.N.Y.Acad.Sci.1022:163-184,2004; 1137:316-342,2008. **RESULTS:** Nascently formed functional redox- and metalloregulated small hairpin ncRNA [$<200n$] as bioaptamers in RNP complexes were isolated and sequenced. Some are genomic DNA derivatives which are not base-complementary to protein-coding gene sequences. They may address defined conserved homologous helix-nucleating domains shared in epigenetic regulator proteins entangled in tolerated growth, vascularization, metabolic syndromes, cancer, epigenetic and genetic information indexing of the epigenome. At variance to usual interpretation in genetic complementary and triplet base codes, ncRNA are not "non-coding", if read in another "language alphabeth" [complementary biomolecular imprint interaction]. They code algorithmic [necessity] rather than stochastic [chance] and heuristic [trial/error] regulatory processes. **CONCLUSIONS:** The results suggest the

epigenetic code consists of different associated intrinsic and extrinsic interactive complementary biomolecular imprints and factors: [1] Non-Mendelian nucleic acid 3D-episcrypts in helix-nucleating complementary interaction with [2]: Conserved Mendelian genotype-originated homologous domains in epigenetic regulator protein and nucleic acid matrices, comprising variant, mutational, infectious [viral] and heritable disease implications. [3] Extrinsic and intrinsic factors upon which formation of [1] and interaction with [2] depends [e.g. redox-and metalloregulation]. Thus, the epigenetic code comprises more diversity, complexity and plasticity repertoires than genetic codes. It implies Darwin-Mendel's genetic principles in synergism with some environmental [Lamarck's] influences for epigenetic [phenotype] imprinting and inheritance.

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Epigenetics of Self-Organization of Biomolecules

Okan Gurel¹, Demet Gurel².

¹IBM, New York, NY, USA, ²Touro College, New York, NY, USA.

The Genetic Code table does not reveal the hidden pattern in the structure of the table. The only observed structural pattern reported is *asymmetry*, [1]. **C. H. Waddington** pointed out that "*Selection does not impinge directly on genotypes, but on phenotypes*.", [2]. In the case of the Genetic Code, the codons form the genotypes and amino acids phenotypes. The pattern of synthesis of the different groups in amino acids is observed in terms of Fibonacci sequence, 1 1 2 3 5 8. The asymmetric form of the Genetic Code table, the Genetic Tableau, has a pattern formed by the six right-hand Fibonacci spirals, 1 1 2. A similar pattern for the six Fibonacci spirals 1 1 2 3 5 8 is observed by matching the elements of the DO_{GU} group of *polyhedra* classifying proteins, [3]. This precision in pattern formation is *intrinsic* in the Fibonacci sequence, ($F_n = F_{n-2} + F_{n-1}$). Unlike the *cardinal* numbers, x_n , $n = 1, 2, 3, \dots$, or *complex* numbers $z_n = x_n + iy_n$, **Fibonacci numbers** are *hexagonal*; therefore, six rotationally symmetric positions on the surface (2D) are possible. This creates *congruence (mod 6)*. In addition, two consecutive ones (F_{n-2} and F_{n-1}) represented by two hexagons are rotated from each other by $\pi/6$. This rotation can be $+\pi/6$ or $-\pi/6$, creating the *right-handedness* or *left-handedness* of 2D (surface) tessellation by *spirals*. The size of the edges of each hexagon corresponding to a Fibonacci number is equal to F_n . For example, $F_6 = 8$. Covering surface (2D) can be *symmetric* or *asymmetric*. The 3D tessellation is accomplished by the formation of a *helix*. The expanding surface forms a *hyperboloid* obeying the golden ratio (F_n/F_{n-1}). This is the **Waddington-Thom Epigenetic Landscape** [3]. [1] *Biophys J.* February (1969); A-254 [2] *Annals NYAS* 231 (1974)32-42. [3] *Biophys J.* January (2009); (3038-Pos).

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Biophysical Features of Non-Coding Genome Sequences

Juan A. Subirana¹, Ezequiel Anokian¹, Tadeo Moreno¹, Joan Pous², Xavier Messegue¹, J. Lourdes Campos¹.

¹Universitat Politècnica de Catalunya, Barcelona, Spain, ²Institute for research in biomedicine (IRB), Barcelona, Spain.

Non coding sequences of DNA represent most of the genome in eukaryotes. Such sequences are complex and probably include features which are essential for chromosome structure, such as chromosome condensation, axis formation, homologous chromosome pairing in meiosis, etc. It is unlikely that coding regions (exons) play a significant role in chromosome structure, since they have evolved to optimize protein synthesis. We are trying to determine by computational methods the presence of frequent sequences, which might play a role in chromosome structure. Such frequent sequences should also be considered as potential targets for drug binding. We have analyzed the occurrence of short words (2-4 nucleotides), as well as the distribution of frequent longer words (9-14 nucleotides) and of microsatellites (long repeats of short words). We have found that some sequences, such as (AT)_n and (AG)_n, have a distribution in most eukaryotic genomes which suggests a structural role. Analysis of longer words shows the presence of many frequent sequences which contain clusters of purines/pyrimidines such as GGAA, TTT, CCC, etc. We have studied in more detail the genome of *Caenorhabditis elegans*: we have found words with a similar sequence which punctuate the whole genome and provide structural marks. Surprisingly very few structural data are available on such frequent sequences, as obtained by biophysical methods (x-ray crystallography, NMR): further work is required. Their eventual influence on nucleosome structure should also be established. As an example we present the structure of some (AT)_n sequences which are polymorphic and frequently present Hoogsteen instead of the standard Watson-Crick base pairing. Interaction with pentamidine, for example, presents novel features when compared with highly studied sequences such as d(CGCGAATTCGCG). It is worth noting that the latter sequence is not frequent in most genomes.