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Comment

Intrinsic structural variability of DNA allows multiple genomic encoding for nucleosomes
Comment on "Cracking the chromatin code: Precise rule of nucleosome positioning" by E.N. Trifonov

Arvind Marathe, Manju Bansal *

Molecular Biophysics Unit, Indian Institute of Science, Bangalore - 12, India

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The review by Trifonov [1] gives a fascinating account of the discovery of immense compaction of DNA in eukaryotic chromosomes and the consequent three-decade-long search for a *chromatin code*, to which the author himself contributed in no small measure. It culminates in the derivation of a sequence motif by the author that possibly represents the *code*. However, the story is rather one-sided, based as it is primarily on the author's own results, with no mention of the large number of experimental studies ([2], and several references therein) which indicate that sequence plays little or no role in the formation of nucleosome structure. It leaves no room for the possibility that maybe, just maybe, there is no *chromatin code*.

In this commentary, we would like to play the devil's advocate and focus on the ambiguities surrounding the existence of a *chromatin code*. The theoretical postdiction by Trifonov implicitly assumes that dinucleotide steps take up unique structures. However, analysis of high-resolution DNA crystal structures [3] and molecular dynamics studies [4] have shown that several dinucleotide steps not only show large variation in their structures within the same distribution, but also display multimodal distributions. Further, the structure of RR/YY and YR/YR steps is dependent on their immediate neighbors [4]. Large variation in dinucleotide level structure is also seen in an analysis of nucleosome crystal structures [5]. In fact, it has been shown that "DNA overall flexibility increases considerably upon particle formation" [6]. Thus the absence of unique dinucleotide structures is a serious impediment to sequence-based structure prediction algorithms.

An added complication is the presence of a large number of kinks in the nucleosome crystal structures [5]. Molecular dynamics studies have shown that kinks, similar to the ones observed in nucleosome structure, can spontaneously form in long, $\sim$ 90-mer oligonucleotides, and these kinks are stiff [7]. A linear elastic model does not apply to such stiff regions. Can one then really argue about which steps would (energetically) favor kinking into the major or minor grooves? For example, in free and other protein-bound DNA, the GG/CC step bends into the major groove, and almost never into the minor groove. However, in the nucleosome structure, several kinks into minor groove are observed at

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* Corresponding author.
E-mail address: mb@mbu.iisc.ernet.in (M. Bansal).

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GG/CC steps [5]. In the absence of a theoretical model for kinks, it is difficult to hypothesize that it is energetically more costly to form a minor groove kink at a GG/CC step, as against, say, a CG/CG or AT/AT step.

Finally, even if we assume that a *code* exists and the sequence motif derived by the author indeed represents the strongest possible nucleosome-forming sequence, it has very little biological relevance or predictive power. The author himself points out that the *chromatin code* is not observed *in toto*. This is understandable, because one does not want a nucleosome to be so stable that it cannot be disrupted. Most 'real' nucleosomes will tend to form only marginally stable structures, which can be disrupted as needed for free DNA access during transcription and replication, while preventing inappropriate access at other times. The small prevalence of minor groove bends in regions where the major groove faces the histone octamer, and vice versa [5], probably highlights the same tendency.

In such a scenario, identifying the sequences which are least likely to form nucleosomes, may be a more interesting and fruitful exercise. Then, if *in vivo*, one finds nucleosome formation at a very weak sequence, it will either indicate a lacunae in the theory, or that *that* region is the location for some interesting biological phenomenon.

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