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Phys Life Rev. Author manuscript; available in PMC 2012 March 1.

Published in final edited form as:
Phys Life Rev. 2011 March ; 8(1): 62–63. doi:10.1016/j.plrev.2011.01.013.

Sequence determinants of histone-DNA binding preferences:

Comment on “Cracking the chromatin code: precise rule of nucleosome positioning” by Edward N. Trifonov

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DNA in eukaryotic cells is packaged into compact chromatin state. The fundamental unit of chromatin is a nucleosome, a highly conserved protein-DNA complex in which ~ 147 basepairs (bp) of DNA are wrapped around a histone octamer in a left-handed superhelix [1]. Histone-DNA binding affinity depends on the nucleotide sequence of the nucleosomal site: indeed, the ability of the DNA molecule to bend into the superhelix is mostly governed by dinucleotide base-stacking energies. The review by Trifonov [2] emphasizes the role of deformational properties of DNA in nucleosome positioning and energetics, proposing a novel sequence motif CGRAAATTTYCG that favors nucleosome formation. The motif is inferred from a large-scale map of *C.elegans* nucleosomes [3].

In building up the case for the 10–11 bp-periodic nucleosome positioning motif shown above, the author has chosen to focus mostly on his own work and the work of his colleagues. However, I find myself intrigued by how well the proposed pattern stacks up against some of the other models and datasets (nucleosome positioning determinants and the idea of the “nucleo-some code” have recently garnered a lot of interest in the chromatin field). The author argues that due to steric exclusion between neighboring particles only single-nucleosome conformations can be used to compare experiment with theory [4]. However, techniques similar to dynamic programming in computer science and transfer matrices in physics can be used to convert histone-DNA binding energies into probabilities of nucleosome formation at every bp, without any approximations related to the finite particle size (see *e.g.* [5]).

Furthermore, because the DNA bendability matrix proposed by the author is capable of placing nucleosomes with 1 bp resolution, only seven nucleosomes whose positions are known precisely from experiment have been chosen to test the model, with impressive success [4]. This seems to be too restrictive – certainly a high-resolution algorithm can predict lower-resolution data. Besides, the vast majority of the algorithms proposed in the literature also have 1 bp resolution and have nonetheless been used to predict genome-wide occupancy profiles for nucleosomes mapped with ~ 10–20 bp precision by micrococcal nuclease (MNase). Moreover, *C.elegans* data from which the model was inferred in the first place employed MNase digestion followed by 454 pyrosequencing [3], and therefore has the usual ~ 10 – 20 bp accuracy. It would be especially interesting to see whether the DNA bendability model proposed by Trifonov and colleagues has greater predictive power against

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large-scale nucleosome maps than simple models that assign the same scores to mono- and dinucleotides of the same type, regardless of their position with respect to the DNA helical repeat [6,7].

Finally, nucleosomes on which the analysis by Trifonov and colleagues is based come from *in vivo* chromatin in a mixture of *C.elegans* cells. The nucleosome positions in this sample are averaged over cell types and may have been affected, among other things, by chromatin remodeling enzymes and competition with other DNA-binding proteins. It would be reassuring to see the proposed motif also appear in two recent large-scale maps of nucleosomes positioned *in vitro* on genomic sequences from *S.cerevisiae* and *E.coli* [8,9].

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