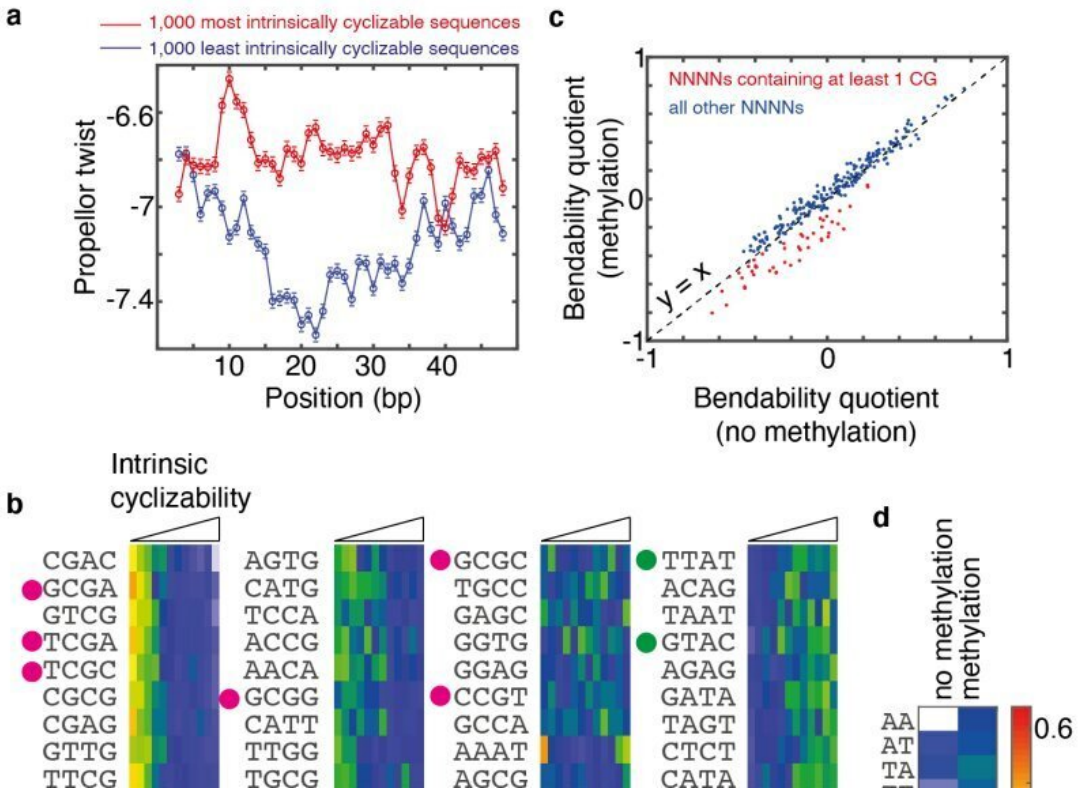
Scientists decrypt the 'mechanical code' of DNA

December 5 2022



(a) Mean propeller twist as a function of position averaged over those 50 bp DNA fragments in the random library that had the most (red) and least (blue) values of intrinsic cyclizability. Sequences were tiled as a series of pentamers and the associated propeller twist of the central base in the pentamer was assigned on the basis of earlier reports27. (b) The 12,472 sequences in the random library were sorted according to increasing intrinsic cyclizability and grouped into 12 bins with 1,039 sequences each. 4 remaining sequences were ignored. Within each bin, the normalized number of times each of the 256

tetranucleotides occur is color coded and depicted (Supplementary Note 7). Tetranucleotides containing a CG in the middle (ie of the form NCGN) are indicated by a magenta circle, while those containing a TA in the middle are indicated by a green circle. (c) Bendability quotients for all 256 NNNNs obtained from the measured values of intrinsic cyclizability of the 12,472 sequences in the random library vs those obtained from the measured values of intrinsic cyclizability of the sequences in the methylated random library (which contain the identical set of 12,472 sequences, except all occurring CpG are cytosine methylated). Dashed line represent x=y. NNNNs are marked in red if at least one CG occurs in it (such as ACGA, CGCG, CGAC, etc). Other NNNNs (such as AAGC, GGGC, etc) are marked in blue. (d) Heatmap representing the contributions of all NN-CG dinucleotide pairs towards intrinsic cyclizability, obtained by considering the intrinsic cyclizability values of sequences in the random library (first column, identical to the 15th column in figure 1f except for the color scale), and obtained from measurements on the methylated random library (second column). Contribution towards intrinsic cyclizability of a NN-CG pair is calculated as done in the case of figure 1f. Credit: *Nature Structural & Molecular Biology* (2022). DOI: 10.1038/s41594-022-00877-6

A new study has deciphered the mechanical code of DNA to reveal previously unknown ways in which nature encodes biological information in DNA sequence.

Led by Durham University, UK, an international team of researchers used a next-generation DNA-sequencing based technology called loop-seq, which they had developed, to show that the local sequence of bases along a region of DNA determines the local bendability of DNA.

Via a large number of measurements, coupled with computational analysis and machine learning, they determined the mechanical code, i.e., the mapping between local sequence and the local deformability of DNA.

Additionally, the researchers found that the mechanical code of DNA can be modified by "methylation," which is a known chemical modification that DNA bases are routinely subject to at various stages in an organism's development. Aberrant methylation has been linked to several cancers.

The discovery that methylation alters the mechanical code presents the possibility that biological development programs, or diseases such as cancer, could be achieving a part of their effects on cells by altering the information encoded via the mechanical code.

The research was carried out along with colleagues from Johns Hopkins University, U.S., Barcelona Institute of Science and Technology, Spain, and the University of Barcelona, Spain. It has been published in the journal *Nature Structural & Molecular Biology*.

Lead author of the study, Dr. Aakash Basu of Durham University, said, "DNA is a book containing instructions that cells need to survive. But it's a very special kind of book, where your ability to turn a page, repair a tear in the page, or fold a page, depend on the words written on the page. This is because in the book of DNA, those words somehow also control the mechanical properties of the paper."

They point out that it is well known that, reading, copying, packaging, and repairing the genetic information stored in the sequence of bases (the As, Ts, Gs, and Cs) along DNA routinely involves processes that require local mechanical deformations of DNA.

The researchers provide evidence that in diverse organisms ranging from mammals to bacteria, nature and evolution has taken advantage of the mechanical code to locally control DNA deformability, and thus in turn, control critical biological processes that require mechanical distortions of DNA.

The researchers expect this knowledge to guide future therapeutic and bioengineering developments.

More information: Aakash Basu, Deciphering the mechanical code of the genome and epigenome, *Nature Structural & Molecular Biology* (2022). DOI: 10.1038/s41594-022-00877-6.
www.nature.com/articles/s41594-022-00877-6

Provided by Durham University