



JOINT 12<sup>TH</sup> EBSA  
10<sup>TH</sup> ICBP-IUPAP  
BIOPHYSICS CONGRESS  
BIOPHYSICS FOR LIFE AND TECHNOLOGY



# JOINT 12<sup>th</sup> EBSA congress 10<sup>th</sup> ICBP – IUPAP congress

*July 20-24, 2019, Madrid, Spain*



This supplement was not sponsored by outside commercial interests. It was funded entirely by the publisher.

P-048

**Sequence-dependent regulation of the mechanical properties of double-stranded DNA and RNA at short length scales**A. Marin-Conzalez<sup>1</sup>, J.G. Vilhena<sup>2</sup>, F. Moreno-Herrero<sup>1</sup>, R. Perez<sup>3</sup><sup>1</sup>National Center for Biotechnology (CNB-CSIC), Madrid, Spain; <sup>2</sup>University of Basel, Basel, Switzerland; <sup>3</sup>Universidad Autonoma de Madrid, Madrid, Spain.

Sequence-dependent DNA conformation and flexibility play a fundamental role in specificity of DNA-protein interactions. Here we quantify the DNA crookedness: a sequence-dependent deformation of DNA that consists on periodic bends of the base pair centers chain. Using extensive 100 microsecond-long all-atom constant-force molecular dynamics (MD) simulations [1], we found that DNA crookedness and its associated flexibility are bijective: unveiling a one-to-one relation between DNA structure and dynamics [2]. This allowed us to build a predictive model to compute DNA stretch modulus from solely its structure. Sequences with very little crookedness show extremely high stiffness and have been previously shown to form unstable nucleosomes and promote gene expression. Interestingly, the crookedness can be tailored by epigenetic modifications, known to affect gene expression. Our results rationalize the idea that the DNA sequence is not only a chemical code, but also a physical one that allows to finely regulate its mechanical properties and, possibly, its 3D arrangement inside the cell.

Mechanical properties also play a key role in many biological functions of double-stranded (dsRNA) --like the interaction with proteins that regulate gene silencing--, but how sequence affects the global mechanical response has so far remained unexplored. Using the same MD protocol, we find that the nucleotide sequence affects in a strikingly different manner the overall stretching and twisting flexibility of RNA and DNA duplexes [3]. For instance, poly-CG sequences soften the stretching response in dsRNA but in contrast they make the dsDNA duplex stiffer. At the dinucleotide level such disparities between dsRNA and dsDNA disappear and both molecules show a similar sequence-dependent flexibility. Our extensive simulations unveil how similar local base-pair motions can lead to divergent sequence effects in the global mechanical properties of DNA and RNA duplexes.

[1] A. Marin-González et al, PNAS) 114, 7049 (2017).

[2] A. Marin-González et al, Phys. Rev. Lett. 122, 048102 (2019).

[3] A. Marin-González et al, submitted (2019).

P-049

**Non canonical interactions in artificial nucleic acids**C. Cabrero<sup>1</sup>, D. O'reilly<sup>2</sup>, I. Serrano<sup>1</sup>, N. Martin-Pintado<sup>1</sup>, A. Aviñó<sup>3</sup>, R. Eritja<sup>1</sup>, M. Damha<sup>2</sup>, C. González<sup>1</sup><sup>1</sup>Instituto de Química Física Rocasolano, CSIC, Madrid, Spain; <sup>2</sup>Department of Chemistry, McGill University, Montreal, Canada; <sup>3</sup>Institute for Advanced Chemistry of Catalonia, IQAC-CSIC, Barcelona, Spain.

Advances in synthetic chemistry afford new artificial nucleic acids with intriguing properties. In this poster, we present our structural studies on chemically modified nucleic acids carried out by NMR spectroscopy. In particular, nucleic acids analogs containing 2'-fluoro-arabino (2'F-ANA) and 2'-fluoro-ribose (2'F-RNA) are interesting compounds for their potential applications in antisense and interference RNA therapy. In addition, locked nucleic acid (LNA) has become attractive modification in which the ribose moiety is modified with an extra bridge connecting the 2' oxygen and 4' carbon. The preferential conformations of these three analogs are different. Whereas 2'F-ANA is considered to be a DNA analog, 2'F-RNA and LNA exhibit a strong tendency to adopt a 3'-endo (North) conformation and, consequently, are considered RNA analogs. By changing the pattern of incorporation of these analogs in a particular oligonucleotide sequence, structure and stability, as well as binding affinity for RNA targets may be tuned. We discuss here the three-dimensional structure of several chimeric hybrid duplexes, whose sequences combine different patterns of LNA, 2'F-ANA and 2'F-RNA nucleotides, as determined by combining <sup>1</sup>H and <sup>19</sup>F NMR spectroscopy.

We will also present results on 8-amino-substituted guanine quadruplexes. Base-modifications in G-tetrads are usually not well-tolerated and have a destabilization effect in G-quadruplexes. One of the few exceptions is the substitution by 8-amino-guanines. 8-amino-Gs (8g) stabilize triplexes and parallel-hairpins. However, its effect on the stability on G-quadruplexes is not clear, and depends on the quadruplex topology and the sequence context. In the case of tetramolecular parallel quadruplexes, such as that formed by d(TGGGGT), we have found that substitution of the first guanine by a 8-amino-guanine provokes the formation of an unusual interlocked quadruplex dimer, stabilized G:T:G:T and 8g:T:8g:T tetrads. Dimerization of the two quadruplexes occurs in an antiparallel orientation through their 5'-side.

P-050

**Sequence encoded DNA – DNA Interactions**A. Srivastava<sup>1</sup>, R. Timsina<sup>2</sup>, S.W. Dewage<sup>1</sup>, X. Qiu<sup>2</sup>, S. Kirmizialtin<sup>3</sup><sup>1</sup>Chemistry Program, New York University Abu Dhabi, Abu Dhabi, United Arab Emirates; <sup>2</sup>Department of Physics, The George Washington University, Washington, United States; <sup>3</sup>Chemistry Program, NYUAD, Abu Dhabi, United Arab Emirates.**Sequit encoded DNA – DNA Interactions**Amit Srivastava<sup>1</sup>, Raju Timsina<sup>2</sup>, Sajeewa W. Dewage<sup>1</sup>, Xiangyun Qiu<sup>2</sup>, Serdal Kirmizialtin<sup>1</sup>

1. Chemistry Program, Science Division, New York University Abu Dhabi, Abu Dhabi, United Arab Emirates

2. Department of Physics, The George Washington University, Washington DC USA.

Ion mediated interactions between nucleic acids helices are essential for their efficient packaging within tight spaces such as viral capsids, sperm heads, nucleosomes and cell nuclei. However, the underlying physical principles governing these interactions at the molecular level are still debatable. In this study, we investigate the role of Mg<sup>2+</sup> ions in DNA-DNA interaction within ordered dsDNA arrays, via an integrated approach of osmotic pressure measurements coupled with molecular dynamics simulations. Umbrella sampling simulations allowed computing the potential of mean force (PMF) between dsDNAs as a function of inter-DNA spacing and provided a direct comparison to osmotic pressure measurements. We studied poly(AT) and poly(A)-poly(T) sequences in varying cation concentrations. Our analysis revealed strong correlation between the structure of the counterion atmosphere and inter-DNA interactions. The interaction energy is found to be mediated by Mg<sup>2+</sup> ions that show differences in localization in sequences studied. We further partition the interaction energy into thermodynamic potentials. Results suggest sequence specificity for solvent entropy which can have important implications in governing DNA assembly.

P-051

**Conformational transitions in non canonical DNA structures.**I. Serrano Chacón<sup>1</sup>, B. Mir<sup>2</sup>, N. Escaja<sup>2</sup>, C. González<sup>1</sup>.<sup>1</sup>Instituto de Química Física Rocasolano CSIC, Madrid, Spain; <sup>2</sup>Departamento de Química Orgánica y IBUB, Universitat de Barcelona., Barcelona, Spain.

I-motif is a non-canonical DNA structure formed by intercalated C:C<sup>+</sup> base pairs. It is believed that i-motifs are formed in regulatory regions of the human genome, playing a role in the regulation of gene expression. Since formation of C:C<sup>+</sup> base pairs requires partial cytosine protonation, these kinds of structures are usually only stable at acidic pH. However, we have observed that i-motif can be formed at physiological pH provided the stack of C:C<sup>+</sup> base pairs are flanked by two minor groove tetrads. This kind of tetrads results from the association of two Watson-Crick or G:T base pairs through their minor groove side, forming G:T:G:T, G:C:G:T or G:C:G:C tetrads.

We have explored the stability of different i-motifs with repetitive sequences with a very low content in cytosines, all of them stabilized by minor groove tetrads. We have obtained their structures by NMR methods. Among them, the one with tetrads G:C:G:C affords the most significant stabilization versus pH, resulting in effective p*H*<sub>T</sub> values above 8.0. This peculiar structure requires the concurrent presence of neutral and protonated cytosines.

At pHs below 6.1 the cytosines involved in the G:C:G:C tetrads become protonated and are not able to form Watson-Crick pairs. However, the structure does not unfold but a drastic conformational change occurs, leading to an i-motif structure with four C:C<sup>+</sup> base pairs. Some of the thymines that were in the loops at neutral conditions form G:T base pairs at acidic pH, giving rise to two G:T:G:T minor groove tetrads. The neutral and the acidic structures as well as the transition between them are discussed in the presentation.