Hydration-dependent dynamics of human telomeric oligonucleotides investigated by inelastic neutron scattering.

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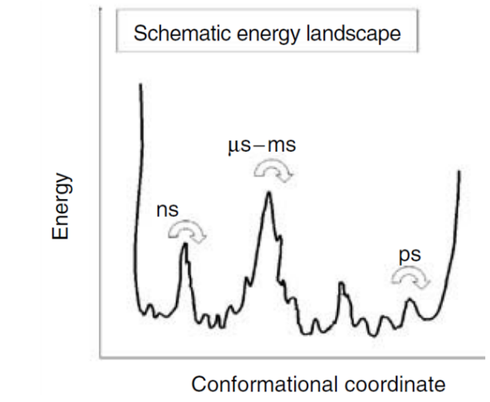
Introduction

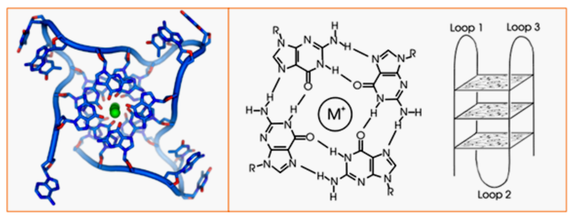
The functionality of biomolecules, such as DNA, is strongly related not only to the structural but also to the dynamical properties.



The activation of the fast structural fluctuations on the pico- and the nanosecond windows enables slower conformational rearrangements and provides a minimum degree of the flexibility to carry out the biological activity [1].

The study of guanine-rich sequences at the end of human telomeres is strongly increasing because of their potential therapeutic target for cancer [2].

This oligonucleotides can fold into a four-stranded structure called G-quadruplex and inhibit the activity of telomerase, an enzyme which is expressed in an abnormal way in cancers cells [3].



Goal: to single out the dynamics of the human oligonucleotide $d[AG_3(T_2AG_3)]$ as a function of the hydration and of the temperature.

Elastic Incoherent Neutron Scattering experiment

Goal: study the atomic mean square displacements (MDS) $\langle u^2 \rangle$ of the human sequence $d[AG_3(T_2AG_3)_3]$ as a function of the temperature and of the hydration $(0h, 0.2h, 0.4h, 0.7h)$, $[h = g_{water}/g_{DNA}]$.

Where? The high-resolution, wide-momentum-transfer backscattering spectrometer IN13 (ILL, Grenoble, France) ,

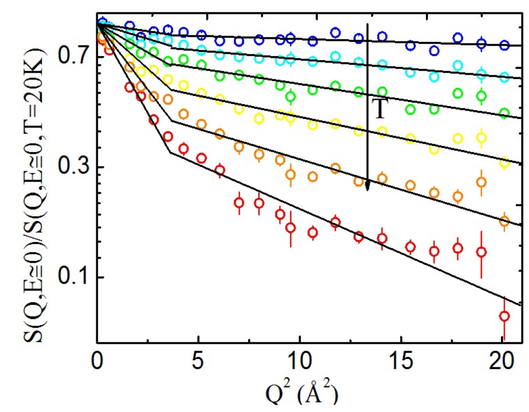


Figure 1: Normalized incoherent elastic intensities versus Q^2 of the oligonucleotides at $h = 0.4$ and at selected temperatures: 100, 200, 240, 260, 280, and 300 K . Lines: fits to the data.

$$S(Q,E) = \left\{ e^{<u>^2 Q^2} [A_0(Q)\delta(E)] \right\} \otimes R(Q,E)$$

	Q range	Explored λ_{av}	Explored region
High–Q	$2 - 4.48 Å^{-1}$	$\sim 2Å$	intra-molecular atomic motions
Low–Q	$0.5 - 1.86 Å^{-1}$	$\sim 5.5Å$	inter-nucleotides motions

Results:

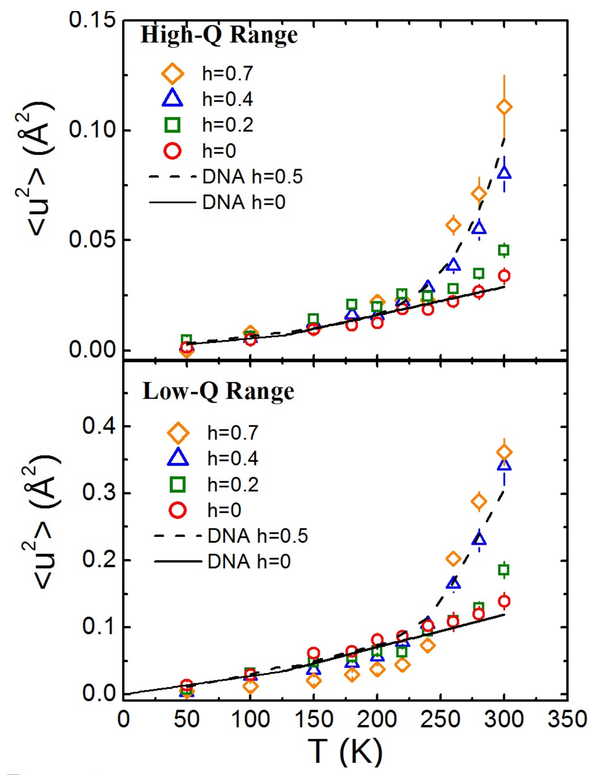


Figure 2: $< u^2 >$ vs T for oligonucleotides and for poligonucleotides DNA at different hydration degree

- CH_3 rotational dynamics contribution
- Dynamical transition
- T_D shifts from 240 K to 180 K as the water content increases.
- Low-Q: $\langle u^2 \rangle_{Oligo} > \langle u^2 \rangle_{Poly}$
- The intra-nucleotide motions in DNA poly- and oligo-nucleotides are not significantly affected by conformational properties.

Quasi Elastic Incoherent Neutron Scattering experiment

Goal: study of the characteristic time of the internal motions for the oligonucleotides sequence $d[AG_3(T_2AG_3)_3]$ (0.5h) and polynucleotides DNA (0.5h) as a function of the temperature.

Where? The backscattering spectrometer high-energy resolution SPHERES (FRM II, Garching, Germany).

$$S(Q,E) = \left\{ e^{<u>^2 Q^2} [A_0(Q)\delta(E) + (1 - A_0(Q))L(Q,E)] \right\} \otimes R(Q,E)$$

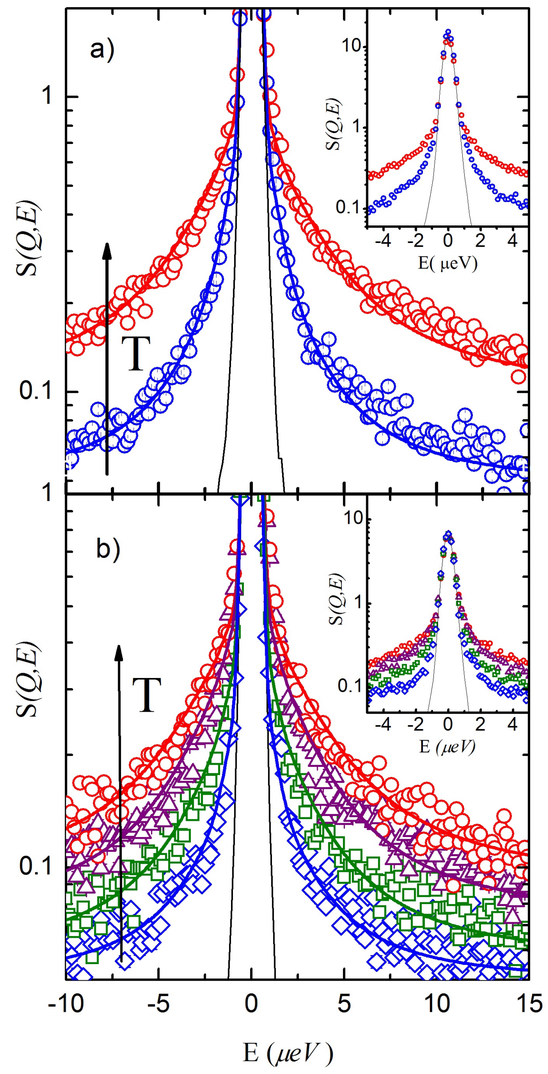


Figure 3: a): S(Q, E) of oligonucleotides at $0.55h$, at 250 K (blue diamonds), 270 K (green squares), 285 K (purple triangles), 300 K (red circles).b): S(Q, E) di DNA at $0.55h$, at250 K (blue diamonds)) and 300 K (red circles).i) .

$$L(Q,E) = \frac{1}{\pi} \frac{\Gamma(Q)}{E^2 + \Gamma(Q)^2}$$

$\tau = \frac{\hbar}{\Gamma}$ is the characteristic time of the relaxational motion sampled by Hydrogen atoms.

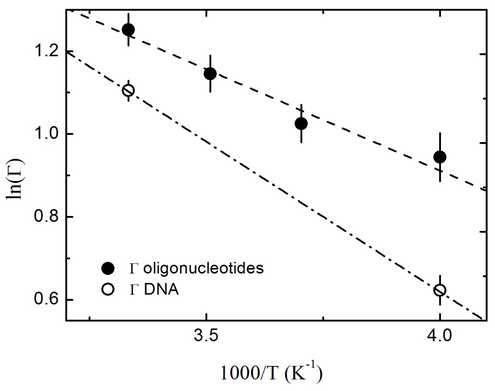


Figure 4: Temperature dependence of the half-width at half-maximum Γ obtained from fits of a single-Lorentzian function to the Q-averaged QENS spectra

	τ(ps) at 300K	ΔE $(\frac{kJ}{mol})$
DNA Oligonucleotides	190 ± 7	4.0 ± 0.5
DNA Polynucleotides	220 ± 5	6.0 ± 0.5

Results:

- $\Gamma_{Oligo-DNA} > \Gamma_{Poly-DNA}$ $\quad (\tau_{Oligo-DNA} < \tau_{Poly-DNA})$
- $\Delta E_{Poly-DNA} > \Delta E_{Oligo-DNA}$

Conclusions

- Hydration- and temperature-dependent dynamical activation
- DNA oligonucleotides exhibit a higher flexibility not only because they explore a larger conformational space (larger $\langle u^2 \rangle_{Oligo-DNA}$) but also because they do it in shorter times.
- The higher flexibility of $d[AG_3(T_2AG_3)_3]$ oligonucleotides should not be ascribed to their specific tertiary structure.
- The larger flexibility of oligonucleotides has to be ascribed to other **intrinsic properties**, such as sequence composition or chain length.

References

[1] A. J. Mc Cammon, S. C. Harvey, *Dynamics of Protein and Nucleic Acids*, (Cambridge University Press, Cambridge, UK, 1987).
[2] G. M. Parkinson, M. P. H. Lee and S. Neidle, *Nature*, **417**, 867-880 (2002).
[3] B. Akabayov, S. R. Akabayov, S. J. Lee, G. Wagner, C. C. Richardson, *Nat. Commun.*, **4**, 1615 (2013).

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