

The H₂O Helix: The Chiral Water Superstructure Surrounding DNA

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Chiral vibrational sum frequency generation spectroscopy reveals a chiral water superstructure surrounding DNA and suggests that new biophysical insights are just around the bend.

The double helix structure of DNA comes as close as it gets in science to a household brand. Results reported by Petersen and co-workers uncover a new structure buried just at the surface of DNA: a chiral, helical superstructure of water molecules (Figure 1).¹ The authors applied second-order nonlinear optical spectroscopy to observe the collective orientation of these waters. They propose that DNA shapes weakly bound water molecules into a right-handed helix that follows the contours of the DNA minor groove. The findings represent the first observation of a chiral water superstructure under ambient conditions, marking a new chapter in experimental studies of the DNA hydration shell.

In the 1980s, X-ray crystal structures showed that all waters in the hydration shell of DNA do not behave the same, giving the first hint of a non-bulk-like ordering of water around DNA.² This study and later NMR experiments³ revealed a “spine of hydration”: highly ordered water molecules in the minor groove of DNA with residence times of several hundred picoseconds. Nonetheless, the hydrated water molecules had not been observed using optical methods under ambient conditions. The major challenge comes from the background of a much larger population of water molecules in bulk solution.

To make the observations, Petersen and co-workers relied on chiral vibrational sum frequency generation (SFG) spectroscopy. Chiral SFG does not require spectroscopic labels that could perturb the sample. While conventional SFG has long been used to probe structures and dynamics at interfaces,⁴ chiral SFG has recently emerged as a powerful method in probing chiral biomacromolecules.⁵ Under the dipole approximation, the second-order chiral SFG signal originates from an electric dipole response described by a

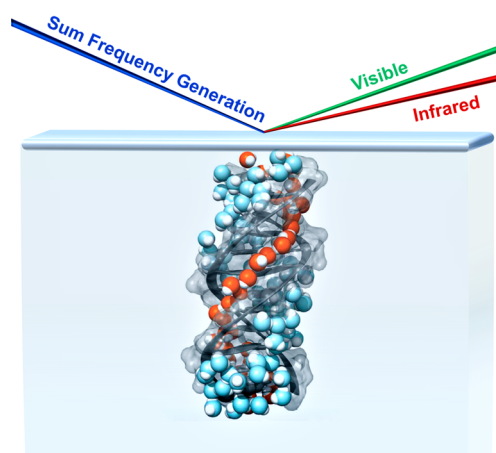


Figure 1. Observation of a chiral water superstructure surrounding DNA by chiral sum frequency generation (SFG) spectroscopy. Water molecules form helical superstructures following the contours of the DNA in the minor groove (red) and major groove (light blue). DNA was bound at the glass/bulk water interface and probed by chiral SFG. Chiral SFG is a nonlinear chiral optical spectroscopic method, relying on a visible beam at frequency ω_{vis} and an infrared beam at frequency ω_{IR} to generate an SFG signal at frequency $\omega_{\text{vis}} + \omega_{\text{IR}}$. Figure modified with permission from ref 1. Copyright 2017 American Chemical Society.

third-rank ($3 \times 3 \times 3$) tensor. Hence, this response inherits enough dimensions and does not rely on relatively weak magnetic dipole and/or electric quadrupole to specify structural chirality.⁶ Thus, nonlinear chiral SFG provides higher sensitivity than conventional linear chiral optical methods (e.g., circular dichroism and Raman optical activity). This point is key to Petersen’s success in observing DNA’s chiral waters.

The ability to observe—without labels or interference from the bulk—a chiral helix of ordered waters around DNA presents new research potential into the real-time dynamics, structures, and functions of hydrated DNA molecules.

When Watson and Crick first proposed the double helix structure in 1953, they already predicted the delicate relationship between DNA structure and aqueous environments.⁷ Upon partial dehydration, the iconic “B-form” of DNA (with a minor groove of ~ 7.3 Å and a major groove

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of ~ 15 Å) spontaneously converts to the less common “A-form”, which features tilted nucleotide bases and a widened minor groove. Single-molecule spectroscopy has shown that the double helix is only possible if the water hydrogen bonds are neither too weak nor too strong, but occupy some “Goldilocks” regime.^{8,9} The ability to see chiral hydrated waters by chiral SFG *in situ* and in real time will offer a handle to probe the fundamental dependence of DNA and water structures.

Water molecules that follow the contours of double helix DNA likely participate in energy dissipation, playing a role in shielding DNA from excess heat and UV photodamage.

Water molecules in the chiral superstructure must be important in the site-specific recognition of DNA. These water molecules need to be released or become part of the interaction interface, thus contributing to enthalpy and entropy of the activation barrier. For instance, Pal et al. showed that binding of small-molecule drugs is mediated by the entropic remodeling of “ordered” water molecules in DNA’s minor groove.¹⁰ Moreover, Mayer-Jung et al. obtained crystal structures to show that epigenetic modifications (e.g., methylation of cytosines) on DNA can change the hydration patterns in the major groove.¹¹ In addition, protein-mediated shape change of DNA by histones and other large DNA–protein complexes, like CRISPR/Cas9, involves hydrating waters around DNA.¹² At large, evolution of our biological world hinges on the fidelity of DNA functions. The capacity to characterize the structures and dynamics of chiral water in DNA by optical methods should prove fruitful in uncovering the detailed mechanisms behind the biomolecular machineries for propagating genetic information.

Furthermore, photodamage of DNA is central in cancer research. Previous 2-dimensional infrared spectroscopy experiments have shown that excitation of the phosphate backbone of DNA is relaxed through energy transfer processes involving surrounding waters.¹³ Water molecules that follow the contours of double helix DNA likely participate in energy dissipation, playing a role in shielding DNA from excess heat and UV photodamage. Since the chiral hydration shell of waters is invisible to most spectroscopic methods due to huge background from bulk waters, the ultrafast dynamic response of these waters during vibrational energy redistribution remains almost unexplored. Following the work of Petersen and co-workers,

the significance of chiral water superstructures for vibrational energy propagation may now be investigated by chiral SFG.

Computer simulations have provided insights into heterogeneous water dynamics in the hydration shell of DNA. Molecular dynamics (MD) simulations show three vastly distinct water dynamics in the minor groove, major groove, and sugar–phosphate backbone regions.¹⁴ Several studies have concluded that surface topology of DNA is the overriding factor for water dynamics.^{14,15} Fluctuations in DNA structures that slightly widen the corridor of the minor groove can indeed give rise to faster water dynamics (closer to bulk water). The findings of Petersen and co-workers may impose new constraints on future MD simulations.

The work of Petersen and co-workers introduces many research opportunities. However, some questions remain to be addressed. For instance, the authors interpret that the chiral SFG signal arises from minor but not major groove or sugar–phosphate backbone waters. This interpretation, although supported by MD simulations, may require further experimental validation. Moreover, the authors propose that a chiral spine of hydration will be present regardless of DNA sequence, but that a sequence-specific “fine structure” is likely to exist. Future work can be extended to pin down how the formation of the chiral water superstructure relates to nucleotide sequence. The results can potentially shift the paradigm of our current understanding of DNA’s sequence-specific interactions.

We think it inevitable that future biophysical research will raise the matter of the biological relevance of confined waters at biomolecular surfaces. The discoveries reported in this issue of *ACS Central Science* emphasize the centrality of this concept for biophysical experiments and simulations.

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