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How to use the bacteriophage system to analyze the structure and phase transitions of DNA in and out of the capsid

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The DNA molecule is known to form multiple ordered phases (mesophases or 3D crystals) in solution, whose nature depends on its concentration and ionic environment [1]. Similar organizations were found *in vivo* in chromosomes, sperm nuclei and virus capsids [2]. We focus here on bacteriophage DNA. Bacteriophages are complex macromolecular machineries that deliver their genome into the bacteria while their capsid and tail remain outside. DNA ejection is triggered by specific interactions of the extremity of the tail with a receptor inserted in the wall of the bacteria. DNA, initially at a concentration close to 500 mg/ml in the full capsid, progresses in the tail and is injected into the cytoplasm. In a few cases, the bacterial receptor has been isolated and DNA can be ejected in solution [3]. This simplified system can be used to investigate the underlying mechanisms of bacteriophage ejection [4] and also to study the condensed states of DNA inside and outside of the capsid. We used the T5 bacteriophage with a 80 nm diameter capsid containing 113.9 kbp DNA (almost 40 µm long).

Using cryoElectron microscopy (cryoEM), we follow the organization of DNA inside the capsid at different steps of the ejection process. The DNA chain decreases in length and reorganizes to occupy the total volume of the capsid. The structure goes from 3D hexagonal to 2D hexagonal, cholesteric and isotropic, following the sequence reported for solutions of short DNA fragments [5]. After partial ejection of DNA, multivalent cations (polyamines) were added to the solution. Ions diffuse freely through the protein capsid and induce the collapse of each individual DNA chain (3000 to 55000 bp i.e.1.4-18 µm long) inside each capsid. Toroidal DNA structures are formed. We show how the frustration arising between chirality and hexagonal packing combined with the strong curvature imposed by the small volume of the capsid impose phasing of the helices and variations the DNA helical pitch [6].

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