

New and Notable

Self-Assembly in Vivo

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The apparent complexity of cellular architecture can be reduced to the relative simplicity of self-assembled structures. By virtue of the machinery that produces copious quantities of identical molecules, some natural structures are the inevitable consequence of packing constraints enforced by van der Waals, hydrophobic, and electrostatic forces. The cell lipid bilayer is the classic example of such a two-dimensional structure. However, three-dimensional liquid-crystalline arrangements of biomolecules have been known since the pioneering work of Bouligand (1972). Since that time it has been an outstanding question whether those *in vitro* motifs that appear *in vivo* play any significant role in cellular form or function. Of particular interest is the packing of the genetic material into a cell. In some cases a millimeter of DNA is packed into a micron-sized region. While this can lead to a variety of mesophases *in vivo* (Livolant, 1991) for cells without nuclei, it is well known that in the nucleus DNA is wound up onto successive nucleosome core particles, forming a “beads on a string” complex. It has been an open question whether nuclear structure is affected by these same packing considerations.

In a technically challenging work, Livolant and Leforestier (2000) employed a combination of optical microscopy and freeze-fracture electron microscopy to show that nucleosome core particles (NCPs) form complex

self-assembled structures, even when the DNA linkers have been cut. Freeze-fracture electron microscopy involves slamming delicate liquid crystalline NCP samples at several meters per second onto a copper block cooled to 10K, followed by etching of the cleaved surface, and finally producing a replica. Such steps certainly distort the structure, but over the past 15 years Livolant and co-workers have developed techniques to control and characterize these artifacts (which actually are rather small for the NCP but are more significant for pure DNA phases). Optical and electron microscopy are complementary techniques; the former provides low resolution but three-dimensional structure in equilibrated samples, while the latter provides detailed glimpses of structure on the molecular scale. This work is a masterful example of how to combine successfully these two microscopies and raises hope that details of chromosomal structure will be elucidated by extensions of these same methods.

When macromolecules are in suspension at high densities, such as those typically found in the cytoplasm or nucleus, packing constraints lead to self-assembly of macromolecules, which then have a tendency to form orientationally or positionally ordered structures to maximize entropy. The seemingly paradoxical result of entropy inducing order has been extensively studied theoretically in the biological milieu (Herzfeld, 1996). What Livolant and Leforestier have shown is that in equilibrium at cellular concentrations the NCPs are in complex, self-assembled structures. Of course, the cell is far from equilibrium, but to understand cellular structure it is necessary to first understand the thermodynamic ground state, which is dictated by minimizing the free energy of the intracellular matrix and which then acts as a scaffolding on which cellular biochemistry functions and evolves.

The principles of entropically driven parallel ordering of achiral, rodlike molecules has been understood since

Onsager’s seminal work in the 1940s. However, NCPs are cylinders wrapped in several turns of DNA, which renders the NCPs chiral. When the molecules are chiral, intermolecular torques create a tendency for the local orientation to twist in space, frustrating this order. Often this competition is resolved via the introduction of topological defects. Livolant and Leforestier (2000) have found that NCPs form germs with a hexagonally ordered cross section. However, the hexagonal direction appears to twist along the perpendicular axis. Such twisting of crystalline order implies the presence of topological defects and suggests a novel equilibrium structure, the moiré 233 phase (Kamien and Nelson, 1995).

Livolant and Leforestier have found that *in vitro* the isolated, cylindrical NCPs stack face-to-face. This is in contrast to the proposed solenoidal packing, which is thought to occur when the NCPs are strung together in association with 30-nm chromatin fibers and H1 histone. Thus, like the liquid-crystalline arrangement of biomolecules *in vivo* and *in vitro*, the relevance of this new mesophase to biological function is unclear. The contrast between this liquid-crystalline state and the native chromatin structure suggests that there is further and profound frustration between the geometric constraints imposed by the continuous DNA strand or H1 and the natural packing of the NCPs. Comparing the results of this study with ordering in chromatin with and without H1 is next on the list of the beautiful experiments we can expect from this group that will move us one step closer to the goal of understanding chromosomal structure. Indeed, a physical approach to this problem may help in the resolution of the question of whether the chromatin is composed of solenoidal or zigzag fibers.

But further studies of the NCP system may lead to a deeper understanding of a fundamental, unsolved problem in physics. The relationship between molecular chirality and its macroscopic manifestation as chiral

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ordering in liquid crystals remains poorly understood. There is no theory that can take as input the structure of a chiral molecule and predict the magnitude, or even the sign, of the chiral pitch of a liquid crystal. But this system may be an excellent probe of the connection between intermolecular orientational correlation and the strength and sign of chiral interactions (Harris et al., 1999). In this system the DNA can be used to hinder or enhance these correlations. Because NCPs at-

tached to a single DNA strand have relative orientations different from those of NCPs in solution, it should be possible by considering finite chains to probe the effect of biaxial correlations (considered to be influential) on the resulting mesoscopic chiral pitch.

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