DNA Packing in Chromatine, a Manifestation of the Bonnet Transformation

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The packing of DNA is described using the formalism of differential geometry. Winding of the DNA double helix around the histone 2–5 octamer forming a nucleosome and the condensation of the so-formed bead-on-a-string chromatine aided by histone 1 is interpreted as two consecutive isometric, i.e. Bonnet, transformations. The DNA double helix can be approximated to a helicoid which can be transformed isometrically to a catenoid, an approximation of the nucleosome. Owing to the organization of the histone octamer the extended chromatine takes a helicoidal shape allowing a second Bonnet transformation to consummate the condensation into a chromatine fibre.

"The screw constitutes the most general one-parameter group of motion in space". (Hilbert and Cohn-Vossen, 1952).

The fact that the uncoiled DNA of an eucaryotic organism, e.g. a human, is approximately 2 m long, albeit split up in ~5 cm strands in each chromosome, yet is contained in a nucleus of ~5 μm diameter, represents a formidable packing problem. Not only must allowance be made for the total confinement of such a giant molecule, but also for fast and easy access to different segments thereof, coupled with the obvious necessity of maintaining structural integrity. In other words the folding–packing mechanism should ideally be adiabatic, thereby ensuring maximum velocity in both directions and avoiding the establishment of chemical and/or thermal gradients that could be impairing to the molecule.

According to common belief, DNA is packed along hierarchic levels of rising complexity.[1] The lowest level is of course the DNA double helix itself. This is then transformed to the nucleosome, i.e. chromatine, level where the double helix is wound around a highly specific protein cluster creating the so-called bead-on-a-string form of chromatine. At the next level the bead-on-a-string is condensed to a chromatine fiber, once again aided by a specific protein, which is further compacted to the final metaphase chromosome.

In a number of recent papers, the role of differential geometry and, as a consequence, minimal surfaces in chemistry has been firmly established. It has been convincingly shown that such different areas of chemistry as transformations in the solid state,[2] equi- or zero-potential surfaces of solids,[3,4] structure and reactivity of zeolites,[5,6] structure of starch,[7] composition of membranes,[8,9] and protein/enzyme structure and reactivity[10] can be explained by the presence and intervention of minimal surfaces. In this paper we will show how the application of differential geometry, especially the so-called Bonnet transform-

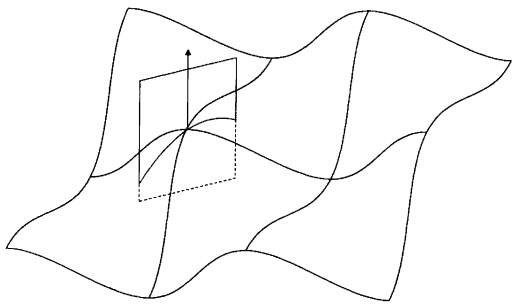

Fig. 1. Normal curvature at a point on a surface.

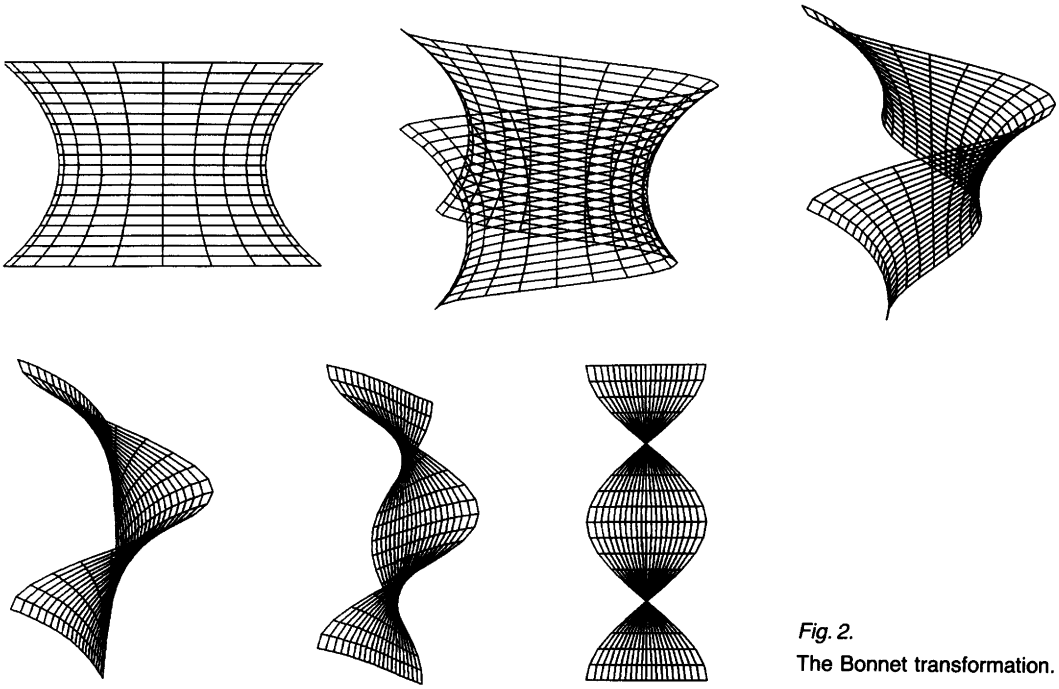

Fig. 2.
The Bonnet transformation.

ation, can explain the necessary conversions in DNA packing up to at least the chromatine fibre level.

To understand the Bonnet transformation[11] we need to explore the concept of curvature a little more deeply. The curvature of a plane curve is rather simple to grasp. At any regular point it is defined as the inverse of the radius of the circle that most closely approximates the curve in that point. Thus, for a straight line-segment the closest approximation is a circle with infinite radius and the curvature is zero.

In the case of curves and surfaces in three-dimensional space the problem is somewhat more complex. The notion of normal curvature is closely related to that of plane line curvature. The normal curvature at a point on a surface is the curvature of the plane line of intersection between a plane through the surface normal and the surface itself (Fig. 1).

As the plane is rotated around the surface normal, the value of the normal curvature will change smoothly. During a full turn it will have to attain a maximum and a minimum value. These values are known as the principal curvatures (in concordance with principal tensions in mechanics etc.). By combining the principal curvatures in different ways we can develop other curvature concepts.

The arithmetic mean of the principal curvatures is known as the mean curvature (H). The hallmark of a minimal surface is that $H = 0$ at all points. Minimal surfaces are further characterized by the property that for any closed curve on that surface, the surface with the smallest area spanned by that curve is the enclosed element of the minimal surface.

The Gaussian curvature (K) is the product of the principal curvatures and hence is always negative for a minimal surface. It is a measure of the local metric of the surface. Two surfaces with K equal at corresponding points can be deformed into each other by simple bending, while surfaces with different K require stretching or shrinking at some points to coincide. An example of the first case is the ease with which a plane can be rolled into a cylinder, an example of the other case is the difficulty of making a sphere out of a plane.

The unique property of the Bonnet transformation is that it preserves both K and H. It is the most restrictive of all transformations and thus isometric, i.e. lengths and angles are preserved.

It operates on minimal surfaces and converts them continuously into other minimal surfaces, e.g. helicoid to catenoid (Fig. 2), without stretching or tearing. In the deformation of a chemical structure these properties are of great importance. The preservation of mean curvature, and thereby also of minimality, means that solvent−solvate interactions are minimized and the number of solvating bonds to be broken during conversion is negligible. The preservation of Gaussian curvature, and hence of local metric, has the result that all bond lengths in the converted molecule remain constant during the conversion. As a combined result of the invariance of both K and H, the Gaussian curvature and the mean curvature of any parallel surface are also invariant.

A surface y, parallel to a surface x, is defined as

$$y(u,v) = x(u,v) + aN(u,v)$$

in some local coordinate system $[u,v]$. N is the surface normal and a is the distance between x and y. Since the gradients of N with respect to u and v are contained in the plane tangent to x they can be written as

$$N_u = \alpha_{11}x_u + \alpha_{21}x_v$$

$$N_v = \alpha_{12}x_u + \alpha_{22}x_v,$$

where the indices u and v indicate differentiation with respect to these variables. These are called the equations of Weingarten. Evidently the differential form dN is given by the matrix α_{ij} in the base $[x_u,x_v]$. By comparing this expression with that of the second fundamental form for a surface we obtain

$$K = \det(\alpha_{ij})$$

$$H = -1/2\ \mathrm{trace}(\alpha_{ij}).$$

K can be viewed as the ratio between the area of the Gauss map of a particular surface element and the area of that element. Since corresponding elements of x and y have identical Gauss maps, the ratio between K_y and K_x will be equivalent to the ratio between the area of the x surface element and that of the y surface element. These areas are proportional to the outer products of the gradients of the surfaces with respect to u and v, and hence

$$K_x/K_y = y_u \Lambda y_v / x_u \Lambda x_v,$$

since

$$y_u = x_u + aN_u$$

$$y_v = x_v + aN_v.$$

This combines with the equations of Weingarten to give

$$K_x/K_y = 1 + a(\alpha_{11}+\alpha_{22}) + a^2(\alpha_{11}\alpha_{22}-\alpha_{12}\alpha_{21})$$

$$= 1 - 2aH_x + a^2K_x.$$

This must be true for the reverse situation as well (viewing y as the original surface, and x as the parallel), and hence

$$(1 - 2aH_x + a^2K_x) = 1/(1 + 2aH_y + a^2K_y).$$

Solving for K_y and H_y yields

$$K_y = K/(1-2H+K\cdot a^2)$$

$$H_y = (H-K\cdot a)/(1-2H+K\cdot a^2).$$

The effect of this is that not only the first solvation shell, but also the more loosely associated solvent layers (all of which are contained within successive parallel shells) will remain quite unperturbed during the transformation. It is necessary to realize that when applied to complete surfaces, the Bonnet transformation will always yield self-intersecting surfaces. This is, however, not true for strip-like sections of surfaces. All these features should greatly facilitate conformational change.

Capitalizing on the teachings of differential geometry, we can easily recognize the DNA double helix as helicoid-like. As such, given the necessary driving force, it will enter the Bonnet series of transformations towards the catenoid-like state.

The driving-force in this case is the winding around the protein cluster (*vide supra*). This protein, an octamer of histones, has been characterized in detail by X-ray diffraction.[12] The eight discrete proteins (i.e. four pairs) of the cluster

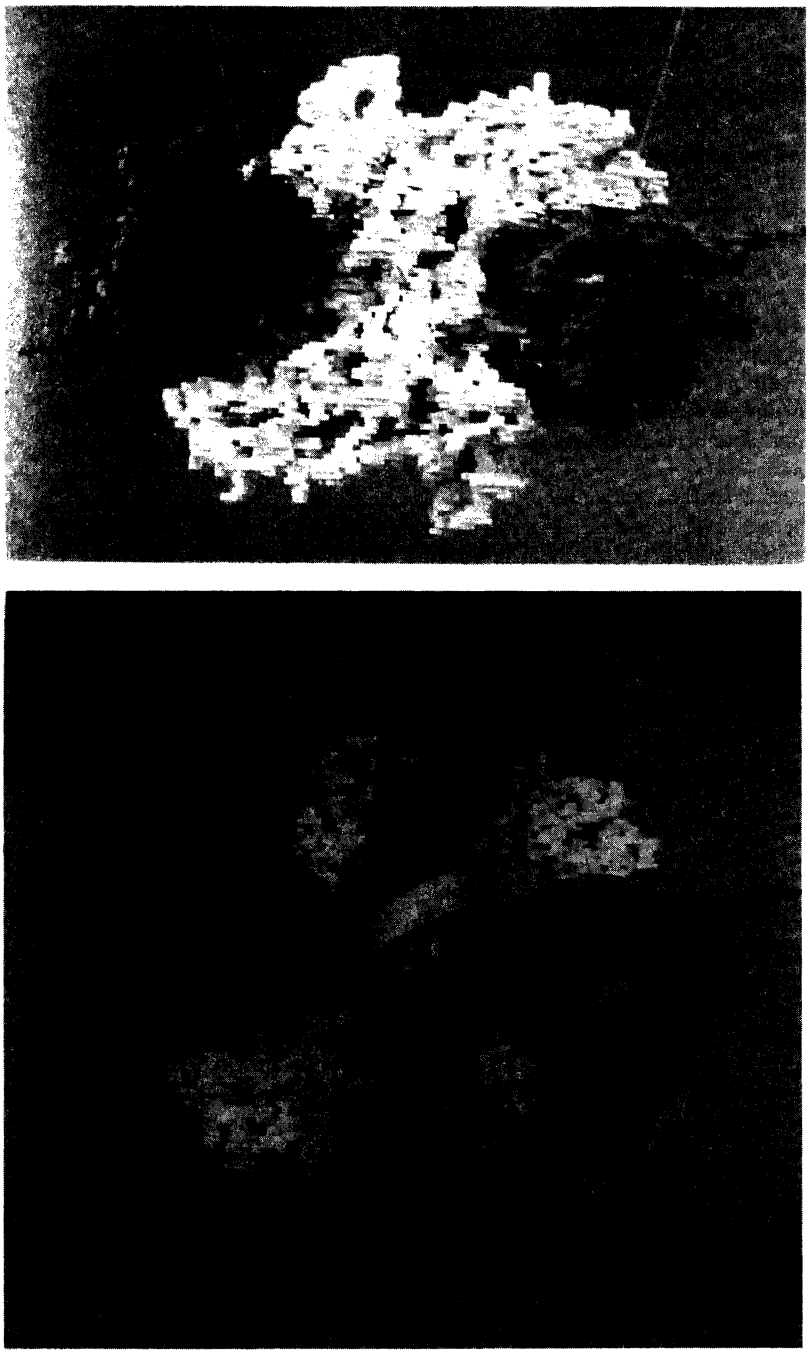

Fig. 3. (a) Model of the nucleosomal histone-octamer. (b) Same as in (a) but with DNA model fitted. Reproduced from Ref. 12 with permission. Copyright AAAS 1985.

are arranged so as to form a screw-shaped groove along the cluster body. The groove constitutes an arbitrary part of a minimal surface, and, according to Blum *et al.*,[10] focuses positive charges, enabling a potent interaction with the negatively charged DNA. In other words, the DNA helix is

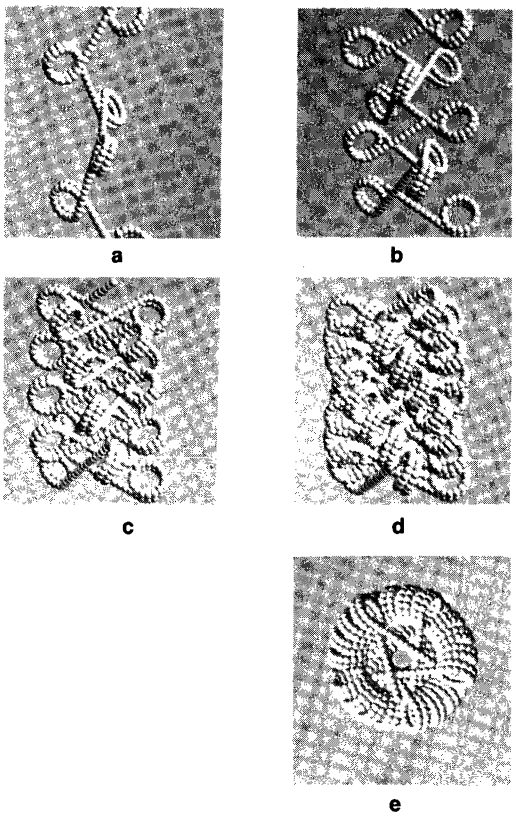

Fig. 4. (a) Maximally extended chromatine showing the helicoidal space arrangement. (b)–(d) Condensation of chromatine with final catenoidal space arrangement shown in (d). (e) View down the central cavity in (d). Reproduced from Ref. 13 with permission. Copyright Springer Verlag 1986.

intercepted by the templating protein cluster whereupon the helix is forced into the screw-shaped groove, accomplished by attraction by means of negative Gaussian curvature of the surface of the groove, thereby forming the nucleosome (Fig. 3). Formation of nucleosomes, spaced by "linker" DNA units, continues along the entire helix, forming the bead-on-a-string chromatine.

The chromatine, forced by the organization of the nucleosome core proteins, assumes a spatial arrangement in which the nucleosomes are placed on a strip-like section of a helicoid. A recent X-ray diffraction investigation fully validates this statement[13] (Fig. 4a). Thus, once again we have a situation where a Bonnet transformation may be induced. Quite analogously to the formation of the nucleosomes, the drive to enter the Bonnet transformation is provided by a protein. In this case it is the so-called histone 1, the topological features of which are surprisingly little known. Nevertheless, the "globular" part of the protein has been fairly well investigated[14] and it exhibits a screw-like topology, i.e. is part of a helicoid. Thus, interception of linker DNA strands by the surface of histone 1 in the uncondensed chromatine, in combination with internucleosomal attraction due to mass-concentration in the nucleosomes, initiates the Bonnet transformation (Figs. 4a–e).

This process, which is extremely fast, <0.5 ms,[15] results in the formation of a highly condensed chromatine fibre, resembling a corncob. The inside of the fibre consists of a stack of histone 1 proteins with linker DNA strands aligned in a spiral fashion with the helicoidal surface of the protein core. The surface of the fibre is built up of a compact spiral of nucleosomes. The structure of condensed chromatine, the endpoint of the Bonnet transformation, has been confirmed by X-ray diffraction.[12] One may well assume that the further condensation of chromatine fibers into the final metaphase chromosome will follow a similar mechanism.

In conclusion we would like to take the opportunity to quote a recent review on chromatine structure in which the authors state, concerning the condensation of chromatine: *"Der Strukturumformung muss also ein möglichst einfacher und rasch ablaufender Mechanismus zugrunde liegen"*.[15,*] To us it seems obvious that the Bonnet transformation fulfils these requirements.

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*The structure transformation must rest on a mechanism which is simple and which allows for rapid kinetics.

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