stimuli that are of moderate frequency or duration may alter the levels of cAMP throughout a large region of the neuron; however, they probably produce only limited changes in the cell body. But prolonged or repeated synaptic activation can result in elevated levels of cAMP in the cell body, and produce a series of cAMP-regulated transcriptional events[9,10].

The time course of decay of the cAMP signal is long and the spread of the signal large, so intracellular levels of cAMP could serve as a temporal and spatial integrator[5]. In other words, intracellular cAMP levels can be viewed as a 'memory trace in time and space' of the previous history of synaptic activation. ☐

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GEOMETRY ——————————————————————————————

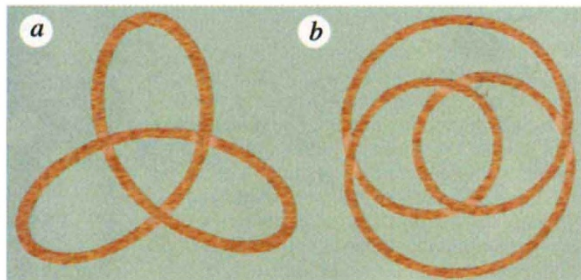# Pulling the knot tight

H. K. Moffatt

IF a complicated knot in a piece of string is pulled tight, it seems likely that it should always achieve roughly the same geometrical configuration, with a minimum length of string within the knot. If the string is strongly twisted first, the tightening processes may result in an unpleasant tangle; but otherwise, as every boy or girl scout knows, the operation can proceed with a predictable and repeatable result at every trial. How, then, can the 'ideal' ultimate configuration of a knot be defined and determined? Vsevolod Katritch *et al.* on page 142 of this issue[1] (see also Andrzej Stasiak *et al.*[2] on page 122) have found an ingenious approach to this problem. The resulting ideal configurations are remarkably similar to equilibrium configurations of knotted DNA molecules, so in some sense it would appear that DNA chains are pulled tight, and that they do not like to adopt highly convoluted configurations.

Knots are usually treated as closed curves, by simply joining the loose ends of the piece of string. The knot is then characterized by the topology of this curve, two knots being topologically equivalent if one can be obtained from the other by continuous deformation of the piece of string. Thus, the trefoil knot $T_{3,2}$ is topologically equivalent to the trefoil knot $T_{2,3}$ (see figure), but the granny knot is not equivalent to the reef knot.

Given two complicated knots, it may be extremely difficult to decide whether they are topologically equivalent (the same knot) or not. So mathematicians have developed increasingly sophisticated techniques for discriminating between them. For example, for every knot, one can construct an Alexander polynomial[3] based on the knot crossings when viewed in any plane projection, and this polynomial is invariant under any continuous deformation of the knot. Thus, two knots having

The trefoil knot, in different configurations $T_{2,3}$ (*a*) and $T_{3,2}$ (*b*). The trefoil is a special case of the torus knot $T_{n,m}$ which winds *n* times round a torus the long way, and *m* times the short way.

different Alexander polynomials are certainly distinct. More subtle discrimination is provided by the Jones polynomial[4], but as yet there is no complete classification of knots of very high complexity.

Suppose now that we have a knotted closed curve C, and that we place around it a tube of small constant radius r so that the curve becomes a string. If, for a given configuration of C, r is gradually increased (the tube is inflated), then we mimic the process of knot tightening. There are two limiting factors in this process: first, r cannot increase above the minimum radius of curvature of C, as otherwise the tube would locally intersect itself; second, more remote parts of the tube may come into contact with one another. If the initial configuration of C is varied, keeping its length constant, then the maximum value of r will also vary. Katritch *et al.*[1] have devised a numerical technique whereby r_{max} may be systematically increased; the corresponding configuration of C is then described as 'ideal'.

This technique is closely related to a different one involving the concept of 'knot energy'[5,6]. The knot is identified with an imaginary magnetic flux tube, which is allowed to contract in response to Maxwell tension, with a corresponding increase in cross-section to maintain total tube volume. The process of contraction is again arrested when the tube comes into contact with itself, and a minimum-energy equilibrium state is attained. The process is dis-

tinct from that envisaged by Katritch and colleagues in that the tube cross-section may, and in general does, deform from a circle during the final stage of contraction. But one may seek minimum-energy states within the family of constrained uniform tube configurations[7], and then the similarity with the purely geometrical construction of Katritch *et al.* becomes more apparent.

In the previous work, it was by no means clear that the minimum-energy configuration for a given knot is uniquely determined. It seems likely that the trefoil knot, for example, may end up in either the $T_{2,3}$ or $T_{3,2}$ configuration, each at a local energy minimum. By contrast, Katritch *et al.* have found that every knot investigated 'flows' to a uniquely determined ideal configuration[1]. Even the Perko pair. two different representations of a knot of ten crossings that were thought to be distinct until 1974, are shown to flow to the same ideal configuration. It would be interesting to test the algorithm on the simpler $T_{3,2}$ and $T_{2,3}$ configurations of the trefoil; it is not clear to me how $T_{3,2}$ could flow to $T_{2,3}$ through the process described.

Two properties of the ideal configuration appear to have physical significance: crossing number and writhe. The averaged crossing number has been shown by Freedman and He[6] to provide a lower bound on knot energy. Katritch and colleagues demonstrate a remarkable linear relationship between the length-to-diameter ratio in the ideal configuration and the average crossing number, which provides a useful measure of knot complexity.

But it is in modelling equilibrium configurations of knotted DNA molecules that this work is at its most thought-provoking. Averaging over an ensemble of millions of configurations for each knot type, the authors found that the mean writhe (an average over all projections of the number of crossings, with positive and negative signs according to handedness) is very close to that of the ideal configuration, and the mean average crossing number is linearly related to that of the ideal configuration. This is for molecules that are 'nicked' (having no torsional stress), a condition that must have a bearing on the writhe. One is led to speculate that the DNA molecule seeks to attain a minimum energy state. But what precisely is the energy that is minimized? ☐

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