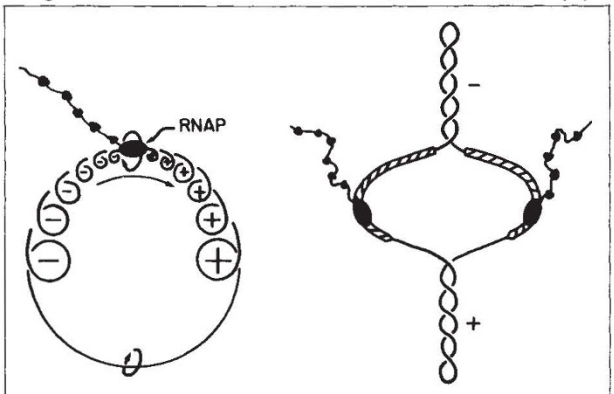
Gene transcription

Waves of DNA supercoiling

Maxim Frank-Kamenetskii

IF YOU walk to the window and rotate the double string used to draw the blind in a clockwise direction long enough to obtain a double helix, then insert a pen between the two strands and push it ahead without rotation, you would be making a mechanistic model of the transcription process: the pen, or RNA polymerase, moves along DNA, the interwound double string. From this experiment, it can be seen that while RNA polymerase translocates it should overwind DNA in front of itself and underwind DNA behind itself. In other words, DNA becomes positively supercoiled in front of RNA polymerase and negatively supercoiled behind it (see figure). Though an inevitable consequence of the DNA helical structure, this wave of supercoiling which moves with RNA polymerase seems fantastic. However, the elegant recent experiments by J. C. Wang and co-workers demonstrate that these waves of supercoiling actually exist both in prokaryotic and eukaryotic cells (Wu, H.-Y. *et al. Cell* **53**, 433–440; 1988; Giaever, G.N. & Wang, J.C. *Cell* **55**, 849–856; 1988). These data will surely change the general attitude to the biological significance of DNA supercoiling and to the importance of DNA topology.

Continuing the experiment with the string and pen, very soon the pen stops because the double string cannot be overwound any more. Thus, one has to suppose either that DNA and RNA polymerase rotate around each other, or that the cell can eliminate both positive and negative supercoils. One can hardly expect that a very long DNA molecule and a very bulky transcription machinery loaded in prokaryotes with an even bulkier translation machinery could rotate around each other. On the other hand, topoisomerases are known to be able to change DNA supercoiling. On the basis of these simple reasons, L. F. Liu and Wang put forward the concept of waves of supercoiling (*Proc. natn. Acad. Sci. U.S.A.* **84**, 7024–7027; 1987). But how can the wave of supercoiling be measured? Extraction of DNA from the cell, ridding it of proteins, causes the memory of the wave to be lost, as the wave of supercoiling does not change the overall DNA linking number. Although Wang and co-workers could not directly observe the wave of supercoiling *in vivo*, they unambiguously demonstrated its existence in experiments involving the inhibition of different DNA topoisomerases. Their most striking piece of evidence is the formation of positively supercoiled plasmid DNA in *Escherichia coli* when DNA gyrase is inhibited. In this case, topoisomerase I continues to remove negative supercoils, while positive supercoils, which are normally removed by DNA gyrase, are accumulated in DNA.



Formation of twin supercoiling domains during transcription. Left, a single RNA polymerase (RNAP) transcribing along a plasmid. Translocation generates a positively supercoiled domain (+) in front of RNAP and a negatively supercoiled domain (−) behind it. Right, when two opposing transcripts are present on the same circular DNA, the two supercoiled domains cannot merge by rotating the DNA alone; one of the transcription ensembles must be rotated as well. (From Wu, H.-Y. *et al. Cell.* 53, 433; 1988.)

In contrast with the prokaryotic case, one cannot selectively cut off the topoisomerase activities which relax positive and negative supercoils in eukaryotes. Giaever and Wang overcame this difficulty by using yeast temperature-sensitive (*ts*) strains transformed by a plasmid expressing *E. coli* DNA topoisomerase I. This enzyme relaxes negative supercoils but cannot relax positive ones. In full agreement with the model, an endogenous plasmid extracted from cells grown under nonpermissive temperature when yeast endogenous topoisomerase was inactive, turns out to be significantly positively supercoiled.

These findings throw a totally new light on the biological significance of DNA supercoiling. Specifically, people had thought that DNA gyrase in *E. coli* serves as an enzyme which introduces negative supercoils into DNA. Competing with topisomerase I, it supports the native level of DNA supercoiling in the cell. Some held that by changing DNA supercoiling, gene expression could be regulated.

Now it can be seen that this picture, which was almost generally accepted, is really upside down. Indeed, DNA gyrase seems to eliminate positive supercoils rather than to create negative ones in *E. coli*. Native supercoiling is an irrelevant notion because actual local supercoiling may be highly positive, highly negative or negligible depending on the position of promoters, on the current position of RNA polymerase and on the relationship between the rate of RNA polymerase translocation and the efficiency of supercoil removal by the topoisomerases. Supercoiling depends on transcription to a far greater extent than transcription depends on supercoiling.

The findings of Wang and his colleagues emphasize the significance of the unusual structures in DNA (open regions, cruciforms, Z and H forms and so on) which form *in vitro* under negative supercoiling. These structures can form transiently in the negative domain of the wave of supercoiling (behind a moving RNA polymerase) and be trapped by specific proteins. Among other things, this could explain the transcriptional activation of replication and recombination. □

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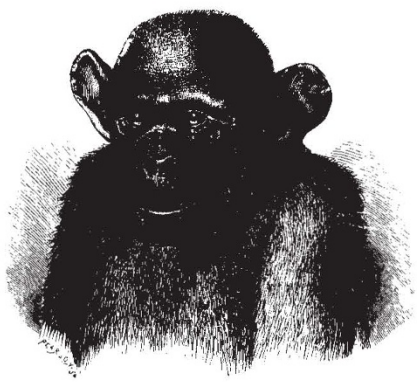
100 years ago

THE BALD-HEADED CHIMPANZEE



THERE is no longer any room for doubt amongst naturalists as to the complete distinctness of the larger anthropoid ape of tropical Africa, the gorilla, from its smaller brother, the chimpanzee. But, on the question whether there is only one chimpanzee over the African continent, there is still much difference of opinion. The acquisition of the fine female specimen, known by the name of "Sally", by the Zoological Society in 1883, caused me to change my views. There can be no doubt that this animal, when compared with specimens of the ordinary chimpanzee, presents very essential points of distinction. The uniform black face and nearly naked forehead, render "Sally" conspicuously different from the many specimens of the common chimpanzee that the Society has previously received.

From *Nature* **39**, 254; 10 January 1889.