of individual dislocations have been possible for almost 30 years, albeit in a rather crude manner owing to the lack of refinement of the interatomic potentials. It is only recently that atomistic studies reached a sufficient level of sophistication to really start becoming quantitative.

Similarly, until a few years ago, it was simply impossible to study the other atomistic aspects of dislocation mechanics, namely, cross-slip and dislocation intersection. Both processes have now been tackled. Last year, an elegant atomistic modeling technique was applied to model cross-slip in copper (*7*). More recently, Zhou *et al.*, in this issue (*1*), and Bulatov *et al.* (*8*) have presented studies of dislocation intersections. These atomistic simulations encompass millions of atoms and generate such a vast amount of information (some 10^4 configurations of 10^6 atoms) that one of the most important steps is to discard most of it, namely, all the atomistic information not directly connected to the cores of the dislocations. What is left is a physical picture of the atomic configurations in such a dislocation intersection and even some quantitative information about the stresses required to break the junction.

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This atomistic study focuses on one of many different dislocation intersections in only one particular material, pure copper. Nevertheless, it exemplifies where atomistic modeling could in the near future contribute to the understanding of the mechanics of materials. Properly quantified, the atomistic simulations may contribute the last missing bits of information for the direct DDD simulation of macroscopic deformations based exclusively on physically transparent "rules." Such a comparison would mean directly calculating, as compared to empirically adjusting, the governing constitutive equations of continuum mechanical models of the deformation of materials.

Atomistic simulations still have a long way to go if they are to capture the full complexity of the dislocation core mechanisms contributing to the mechanical behavior of model materials, not to mention more complicated alloys. However, the present developments hold great promise that a link can eventually be achieved between atomic scale and macroscopic large-scale deformation.

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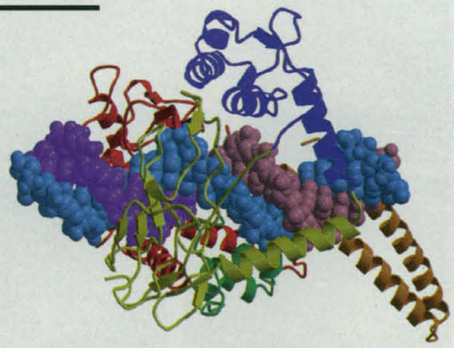
PROTEIN STRUCTURE

Topological Nuts and Bolts

Howard A. Nash

Most enzymes do chemistry—catalyzing reactions that change the covalent structure of a substrate. But with some enzymes that work on polymeric substrates, the end result is a mechanical rather than chemical change. Among these are the topoisomerases, which can untwist superhelically coiled DNA. Starting with the first example some 25 years ago (*1*), these enzymes that can change the topology of DNA have been the subject of elegant mechanistic and biological studies (*2*). On pages 1504 and 1534 of this issue, we get a first but very informative look at the structure of human topoisomerase I (*3*, *4*), whose importance is highlighted by its identity as the target of an important class of anticancer drug.

In a molecule of DNA without free ends, the number of times two polynucleotide strands wind around each other is fixed. This topological invariance is the inevitable consequence of the continuous DNA backbone, which forbids the two chains to pass through one another. Accordingly, an enzyme that alters DNA topology must break at least one strand. And, to restore the physical continuity of the DNA after the ensuing change in interwinding, the enzyme must also seal the break. Exactly as predicted in the initial study (*1*), this reversible breakage is achieved because topoisomerases maintain the high-energy status of the phosphodiester bond during unwinding. Nucleases, another class of DNA-cleaving enzymes, hydrolyze a phosphodiester in the backbone of DNA to a phosphomonoester. In contrast, topoisomerases use an enzyme residue (typically a tyrosine) to break DNA. A new enzyme-DNA phosphodiester is formed in the process. Since the new bond is of comparable energy to the original phosphodiester, the covalent DNA-enzyme intermediate can be readily attacked by the previously liberated end of DNA to restore free enzyme and produce intact, rejoined DNA.



REDINBO, STEWART, CHAMPOUX, AND HOL

Topoisomerase I ready to unwind DNA. The intact DNA strand is in cyan, and the strand transiently nicked by the enzyme as part of the relaxation event is in magenta and pink. The polypeptide backbone of the catalytic core of the protein is shown as a ribbon.

Reversible cleavage is an artifice that has arisen in nature more than once. In eukaryotes there are at least three major types of topoisomerases—nonhomologous enzymes that are distinguished biochemically by the number of strands cleaved and whether the liberated end comes from the 3′ or 5′ side of the phosphodiester (*2*). All three are important: Disruption of any one is either frankly lethal or causes substantial defects in DNA metabolism. Topoisomerases appear to be especially important in growing cells, presumably to deal with the topological complexities arising from replication, and several potent anticancer therapies achieve their effects by pharmacological inhibition of either topoisomerase I or II (*5*).

Scientists have been fascinated with the detailed mechanism of these enzymes. Not only is phosphodiester catalysis of interest in itself, topoisomerases somehow let DNA strands change their interwinding. In doing this, the enzyme must permit (or even encourage) the transiently unshackled strands to move with respect to each other, but not so far as to preclude subsequent rejoining. In recent years, structural information has become available for two of the topoisomerase families (*6*, *7*); the present work completes the picture.

The author is at the Laboratory of Molecular Biology, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA. E-mail: nash@codon.nih.gov

The structure of topoisomerase I, determined by crystallography, is the fruition of a Herculean effort (*3*, *4*). Indeed, the authors present three separate structures, each of which is of a complex between the human protein and a segment of duplex DNA. Two of these show how DNA is bound noncovalently by an enzyme that is rendered inactive by mutation of the active site tyrosine. The third complex uses active enzyme but a modified duplex that is made with a bridging phosphorothioate, a diester that can be cleaved by the enzyme to yield fragments that are defective in rejoining (*8*); this strategy results in a cocrystal of the covalent complex. In all three cocrystals the protein completely encircles the duplex like a nut around a bolt. Within this cavity, the amino acids in contact with the scissile phosphodiester are exactly as would be expected for the active site of a topoisomerase: Basic residues are positioned around the phosphate to enhance its reactivity and a tyrosine hydroxyl is positioned to attack it. The protein also contacts several nucleotides that flank the scissile phosphate. Perhaps because almost all the interactions are with the backbone and not the bases, the DNA is largely undistorted, closely resembling standard B-form DNA. Most important, the contacts to one side of the broken phosphodiester are neither numerous nor intimate. This suggests to the authors that topoisomerase I transiently loses hold of this "downstream" segment and that topological change occurs as this loose strand rotates relative to the "upstream" duplex. This mechanism is quite different from that deduced from biochemical and structural experiments for topoisomerase II (*7*) and the prokaryotic homolog of topoisomerase III (*6*). Here, both ends of the break are held by the enzyme, which then opens like a pair of jaws to let another DNA pass through the break before it is resealed.

Although the overall structure of topoisomerase I is novel, parts of the protein look like portions of other proteins. For example, two of the subdomains that encircle the DNA closely resemble structures found in bacteriophage integrases (although the sequence similarity is vanishingly small between these families). Integrases are biologically distinct from topoisomerases; they act on pairs of duplexes and transfer strands from one to another. Nevertheless, the basic chemistry of strand cleavage and rejoining is identical for integrases and topoisomerase I (*9*) and, not surprisingly, the conservation of structure is restricted to the subdomains of the catalytic site. A more unexpected structural homology is to another prokaryotic protein, Rop, that forms a prominent coiled coil. In topoisomerase I, such a coiled-coil structure juts away from the body of the protein and, although it has a positively charged surface, does not make extensive contact with the DNA duplex. Its intertwined α helices, which constitute a "linker" region between two subdomains of the catalytic core, form a notable protuberance from the body of the enzyme. Stewart *et al.* (*4*) propose that the linker acts like a brake that interacts with the DNA as it rotates during the interval between cleavage and rejoining. A similar function is also proposed (*4*) for a pair of helical "nose cones" that protrude from a different surface of the core.

Thus, topoisomerase I is expected to promote the untwisting of only a few superhelical turns of DNA in a single cycle. The number of supercoils relaxed in a single cycle has recently been measured for a viral topoisomerase that lacks a linker domain (*10*), setting the stage for a comparison with topoisomerase I. The issue is significant because the proposed braking would imply that excess (or deficient) interwindings between strands are of sufficient biological value to prompt selection for an enzymic design that removes them gradually.

These two reports will certainly stimulate a new round of experiments on enzyme mechanism, but perhaps the most important lead for biomedicine concerns structural implications for agents that inhibit topoisomerase I. The founding member of this promising family of anticancer agents is camptothecin (*5*), and Redinbo *et al.* (*3*) present a model for the way this drug binds to the topoisomerase I–DNA covalent complex. Their model nicely accounts for many of the mutations known to render topoisomerase I resistant to camptothecin and for the effect of various chemical modifications on the potency of camptothecins. In the model, the drug stacks onto the base downstream of the scissile phosphate, a feat that requires this base to flip around its glycosidic bond (*11*), thereby disrupting its Watson-Crick pairing. It seems certain that this model will stimulate a new wave of pharmaceutical design for better inhibitors of this fascinating enzyme.

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SEARCH

WEBWATCH

Genetic rolodex

http://bioinformatics.weizmann.ac.il/cards/index.html

GeneCards integrates subsets of information stored in big genetic databases and presents this in the form of a concise screen of data, including gene name and synonyms, gene locus, protein products, and associated disease data. With the help of "siftware," the GeneCards system automatically mines the databases to extract entries useful for quick navigation; wider or deeper searches can then be done with existing engines. Each card has a button to generate related cards, and future developments may include automated suggestions to help guide the search.

Changing landscapes

http://edcwww.cr.usgs.gov/Earthshots/

Since 1972, images from the Landsat satellite have been archived at the Earth Resources Observation Systems center of the U.S. Geological Survey. To make them available to the public, the Earthshots site has started posting these images of different locations around the world, taken at different times. A 1972 view of the Kara-Bogaz-Gol lagoon in Turkmenistan can be compared directly with the same region in 1987 to see the dramatic changes caused by decreasing water levels. Explanations of the Landsat maps are provided along with links to other sites.

The language of cells

http://www.mblab.gla.ac.uk/~julian/Dict.html

The Dictionary of Cell Biology (DCB) Web site is an Internet edition of the reference book of the same name. Hosted by the University of Glasgow, the DCB contains the entries and cross-references of the second edition print version, along with enhancements and new entries scheduled for the third edition. Users can search its 5450 entries with a keyword query or browse keywords from a simple graphical map. Returned definitions are further hyperlinked to other entries.

Edited by David Voss

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