Human Topoisomerase I Relaxes Positive and Negative DNA Supercoils Differently

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Topoisomerases are enzymes of quintessence to the upkeep of superhelical DNA, and are vital for replication, transcription and recombination. An atomic-resolution model for human topoisomerase I in covalent complex with DNA is simulated using molecular dynamics with external potentials that mimic torque and bias the DNA duplex downstream of a single-strand cut to rotate around the intact strand, according to the prevailing enzymatic mechanism. The simulations reveal the first dynamical picture of how topoisomerase accommodates large-scale motion of DNA as it changes its supercoiling state, and indicate that relaxation of positive and negative supercoils are fundamentally different. To relax positive supercoils, two separate domains (the ``lips'') of the protein open up by about 10-14 A, whereas to relax negative supercoils, a continuous loop connecting the upper and lower parts (and which was a hinge for opening the lips) stretches about 12 A while the lips remain unseparated.

Normal mode analysis is additionally used to characterize the functional flexibility of the protein. Remarkably, the *same* combination of low-frequency eigenvectors exhibit the dominant contribution for *both* rotation mechanisms through a see-saw motion.
The simulated mechanisms suggest mutations to control the relaxation of either type of supercoiling selectively and advance a hypothesis for the debated role of the N-terminal domain in supercoil relaxation.