The ancestral role of ATP hydrolysis in type II topoisomerases: prevention of DNA double-strand breaks

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The archetypal bacterial type IIA topoisomerase, DNA gyrase, transduces the free energy of ATP hydrolysis into negative supercoiling, passing one double helix (the T-segment) though a transient double-stranded break in another (the G-segment). The homologous type IIA enzymes (topoisomerase IV, eukaryotic topoisomerase II) and the archaeal type IIBs also hydrolyse ATP, despite only carrying out the ostensibly favourable reactions of decatenation and relaxation. The demonstration by Rybenkov *et al.* in 1997 that the IIA enzymes drive these reactions beyond equilibrium, using free energy to simplify DNA topology, suggested a resolution of this issue. However, our recent work shows that the simplification reactions are very energetically inefficient, and indeed, active topology simplification may not be a physiological requirement.

Instead, we propose that the ancestral role of ATP in all type II enzymes is to allow the strand-passage reaction to occur while minimising the formation of permanent cytotoxic double strand breaks. Specifically, we suggest that binding and hydrolysis of ATP drives a cycle of concerted formation and breakage of strong monomer-monomer protein interactions, such that a tight protein-protein dimer is maintained throughout the reaction cycle, particularly during the double-strand breakage and separation of the G (gate) DNA segment. We will consider this proposal in the light of a number of features of type II enzymes and their homologues.