The protein topoisomerase can change the knot type of circular DNA by breaking a segment of DNA, allowing a second segment to pass through the break before resealing the break. This results in a crossing change. Recombinases are another family of proteins which can knot circular DNA. Their operation is mathematically equivalent to smoothing a crossing. A skein quadruple is a set of four knot diagrams which differ at exactly one crossing. In the quadruple, \((K_+, K_-, K_D, K_I)\), the knots \(K_+\), \(K_-\) differ by a crossing change which may represent topoisomerase action. The knots \(K_D\) and \(K_I\) are obtained by the oriented and unoriented smoothings, respectively, of that crossing which represents recombinase action. Both recombinases and topoisomerases have been used in an experimental technique called difference topology to probe the topological conformation of DNA bound by proteins of interest. The types of knots produced by topoisomerase and recombinase will differ depending on whether the DNA is bound by other proteins. This difference is used to solve for the shape of DNA bound by proteins of interest. The skein quadruple can be used to determine what is the most efficient experimental set-up for difference topology experiments. Two published experiments will be analyzed. (Received August 18, 2016)