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The three-dimensional (3D) configuration of chromosomes within the eukaryote nucleus is an important factor for several cellular functions, including gene expression regulation, and has also been linked with many diseases such as cancer-causing translocation events. Recent adaptations of high-throughput sequencing to chromosome conformation capture (3C) techniques, allows for genome-wide structural characterization for the first time with a goal of getting a 3D structure of the genome. In this study, we present a novel approach to compute entanglement in open chains in general and apply it to chromosomes. Our metric is termed the linking proportion (Lp). We use the Lp in two different settings. We use the Lp to show that the Rabl configuration, an evolutionary conserved feature of the 3D nuclear organization, as an essential player in the simplification of the entanglement of chromatin fibers. We show how the Lp incorporates statistical models of inference that can be used to determine the agreement between candidate 3D configuration reconstructions. In the last part of our work, we present Smooth3D, a novel 3D genome reconstruction method via cubic spline approximation. (Received September 03, 2020)