Genome folding and function: from DNA base pairs to nucleosome arrays and chromosomes

Abstract: Despite the astonishing amount of information now known about the sequential makeup and spatial organization of many genomes, there is much to learn about how the vast numbers of DNA base pairs in these systems contribute to their three-dimensional architectures and workings. The chemical structure of DNA contains information that dictates the observed spatial arrangements of base pairs within the double helix and the susceptibilities of different base sequences to interactions with proteins and other molecules. Our group has been developing software to analyze the spatial and energetic codes within known DNA structures and using these data in computational studies of larger nucleic acid systems. By representing the DNA bases as sets of geometric objects, we can capture the natural deformability of DNA as well as the structural details of ligand-bound interactions (1,2). There are now sufficient data to examine the influence of sequence context, i.e., the effects of immediate neighbors, on the apparent motions of the bases and to develop simple functions that capture this information. The observed behavior can be incorporated in computational treatments to improve our understanding of macromolecular systems in which DNA sequence and protein binding play important roles. For example, DNA elements that regulate gene expression often lie far apart along genomic sequences but come close together during genetic processing. The intervening residues form loops, mediated by proteins, which bind at the sequentially distant sites. We have developed methods that take account of both DNA and protein in simulations of loop formation and successfully captured experimental observations (3-5). Our recent studies of long-range communication between regulatory elements on short nucleosome-decorated DNA (6) provide a basis for linking the 'local' arrangements of nucleosomes in these systems to higher-order macromolecular structures, such as the looped architectures detected within chromosomes. We are developing new algorithms to characterize the spatial arrangements of nucleosomes and incorporating the collective information in nucleosome-level depictions of chromosomal DNA (7,8). The build-up of structural components in our treatment of DNA and chromatin offers new insight into the stepwise processes that underlie genome organization and processing.

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