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New and Notable

Pack it up, Pack it in: Unraveling H-NS Mediated Genome Packaging

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How are bacterial genomes compacted? Nucleoid-associated proteins have been discovered that bind to the circular genome in either a sequence-dependent or sequence-independent manner, thereby resulting in a compact nucleoid that can be confined within the bacteria and be accessed by the cellular machinery required to transcribe the genome (1,2). Dame and co-workers performed a number of key experiments that elucidated the binding behavior of a particular nucleoid-associated protein, histone-like nucleoid structuring protein (H-NS), and its role in confining the genome. Their work provided a model for nucleoid condensation in which H-NS protein binds randomly to one strand and, upon meeting another strand of DNA, induces condensation through *trans* binding (3). Through optical-tweezer experiments, they were able to further characterize the kinetics and thermodynamics of this process (4). However, open questions remained as the work demonstrating condensation of DNA by H-NS was performed in two dimensions on a mica surface and neither the effect of this spatial confinement nor the nature of the DNA-surface interaction itself were fully addressed.

Seeking to better understand the experimental findings of Dame et al., in their article Joyeux and Vreede (5) develop a representation of DNA and H-NS dimers consisting of bead-spring constructs. Through a careful choice of parameters, they closely reproduce the experimentally observed binding behavior of H-NS to DNA. They are able to then use this simple model to help elucidate the rich physics observed in experiments probing H-NS mediated genome condensation. In particular, their work gives insight into the nature of the H-NS dimer itself and its effect on genome condensation. In the work of Wiggins et al. (6), protein-mediated bridging is discussed in the context of two possible structural motifs, an H-NS linker domain (residues 65-89) that is either rigid or flexible. In the language of Joyeux and Vreede, this corresponds to an H-NS with a large or small value of G (the H-NS dimer bending rigidity), respectively. Coarse-grained simulations enable Joyeux and Vreede to test a hypothesis such as that of Wiggins et al. by simply assigning the dimer different physical parameters and observing the resulting change in behavior. They are able to demonstrate that a difference of ~20% in binding affinity in the *cis* configuration (the result of a factor of two change in the H-NS bending rigidity) is sufficient to fundamentally change the dynamics of the condensed nucleoid, with the more flexible case resulting in a fluctuating, dynamic structure exhibiting open loops (more *cis* binding) whereas the less flexible case results in a more compact globular structure that changes little over time (increased *trans* binding). Joyeux and Vreede do not propose a precise value for the H-NS bending rigidity, as the experimental data to which they compare are difficult to interpret (primarily nucleoids condensed on a two-dimensional mica surface (3)); their work, however, is of fundamental significance in that it points the way toward experiments that might better elucidate the true nature of H-NS and its role in nucleoid condensation. Indeed the marked difference in the radius of gyration of three-dimensional condensed nucleoids reported in their work, driven by differences in *cis* binding affinity, represents a quantity that can be directly accessed in experiment to make progress in the problem of H-NS mediated genome condensation and the role played by H-NS flexibility and binding affinity therein.

Looking forward in terms of developing molecular-level models to further understand protein-mediated genome compaction, the growing availability of advanced sampling techniques and reliable models provides the biophysics community with tools at every level of molecular description. The coarse-grained representation adopted by Joyeux and Vreede has provided valuable insights. Building on their results, future studies should aim to address potentially interesting details of the interaction between H-NS and DNA. Experimental data indicate that this interaction is not, in fact, entirely sequence-agnostic (as the Joyeux and Vreede representation assumes), but instead exhibits a preference for AT-rich genomic regions (7). Specifically, the minor groove width in these AT-rich regions is thought to be optimal for H-NS binding. Coarse-grain DNA (8,9) and protein (10) models have been developed that are capable of exploring such shape-dependent protein-nucleic acid interactions; approaching the problem at this scale may yield rich information regarding H-NS/DNA interactions. A particular detail that remains to be addressed is the effect of the ionic environment on the interaction of H-NS with the genome. In earlier work, Vreede and Dame used molecular simulations to demonstrate that the conformation of the dimerization domain of H-NS may indeed be sensitive to ionic conditions, with the parallel dimer increasing in stability with increasing salt (11). Experimental

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evidence also indicates that altering the ionic environment can fundamentally change the nature of the resulting H-NS/DNA complexes and promote either the *cis* or *trans* binding regime (12,13). Coarse-grained molecular models are uniquely suited to explore this wide range of environmental conditions and assess their impact on the mechanism of H-NS mediated nucleoid condensation.

A particularly exciting idea that could now be addressed is that AT-rich sequences that promote H-NS bridging behavior act as domain barriers in bacterial genomes (1,14). Interestingly, the acquisition of genomic islands, generally AT-rich, is believed to potentially disrupt the three-dimensional structure of the nucleoid through the recruitment of H-NS proteins and decrease the fitness of the bacterial cell (14). This notion that stochastic addition of H-NS binding domains may drastically alter the organization of the genome could be directly probed in coarse-grained simulations in which sequence-specificity in H-NS binding is taken into account.

In their work, Joyeux and Vreede provide a compelling example of how a simple and elegant molecular model can be used to provide profound insight into an otherwise complex biophysical problem. In addition to highlighting the large impact that small changes in DNA-protein interactions can have, their work suggests key experiments that, in due course, will provide a clearer picture of H-NS mediated genome condensation.

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