Biophysical *Journal*
New and Notable

Self-assembled nucleoid proteins scaffold bacterial DNA

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Eukaryotic DNA is packaged in the repeating unit of nucleosome via histone proteins (1). Most Archaea also express histones that help to compact their genomes (2). However, in Bacteria, the organization and condensation of chromosomal DNA are possible, largely because of the many types of architectural nucleoid-associated proteins (NAPs) (3). These designated nucleoid proteins multimerize in different ways and typically exist in polymeric forms. At least 12 types of NAPs have been identified (4), including HU, IFS, H-NS, ParB, and so on. Although their interactions with DNA can be summarized as four common patterns (*right panel* in Fig. 1), the mechanism of how NAPs cooperatively condense DNA is poorly understood on the chromosomal scale. Besides DNA sequences, one common challenge to address this question is due to the architectural specificities of diverse NAPs. For example, bridges from different NAPs may affect DNA organizations by opposing ways (6). From a modeling perspective, methods like molecular dynamics with quantum-chemistry-based force fields may carry out accurate molecular details, but with impractical computational costs for studies that involve many NAPs and DNAs. One direct idea is to build a coarse-grained polymer model with flexible features reflecting various specificities of NAPs. In a recent issue of *Biophysical Journal*, Joyeux (5) developed such a polymer model to investigate the interplay of NAPs and DNA, especially focusing on how the self-association of nucleoid proteins affect the architecting properties of DNA. In this model, six beads represent one protein, and uniform beads constitute DNA (Fig. 1). Thereby, the total potential energy has four terms, $E_{total} = E_{DNA} + E_{protein} + E_{DNA\text{-}protein} + E_{protein\text{-}protein}$, which describe the energy of DNA, the total internal energy of individual proteins, the interaction energy between DNA and proteins, and the self-association energy among nucleoid proteins (details in Eq. S1, S8, S14, and S18 of (5)). An interesting difference of this work from previous modeling works (7,8) is that here the author aims to cover possible structural features from different types of NAPs. Thus, two protein models with flexible features were presented (Fig. 1, details in Fig. 1 of (5)). These two models share most features, except that model I has two self-association beads and model II has four (*green beads* in Fig. 1). 200 proteins and 2880 DNA beads (equivalent to 21,600 base-pairs) were modeled at room temperature through Brownian dynamics simulations.

By adjusting the Leonard-Jones potential depth $\boldsymbol{\varepsilon_{LJ}}$ in the $\boldsymbol{E_{protein\text{-}protein}}$ term (details in Eq. S18–S20 of (5)), these modeled proteins associate with different binding affinities (a range of 4–12 k_BT was tested). In this way, the impact of self-association of nucleoid proteins on architecting DNA was quantified. It shows that solely with the increasing of protein-protein-binding affinity, more proteins become occupied by DNA, characteristically in the state of bridging (Fig. 3 in (5)). A clear transition of protein occupancy occurs at $\boldsymbol{\varepsilon_{LJ}}$ equal to 7 and 8 k_BT, respectively, in model I and model II. DNA only starts to get compacted at $\boldsymbol{\varepsilon_{LJ}}$ of 7 k_BT (Fig. 4 in (5)), indicating the importance of protein multimerization in controlling DNA compaction. Similarly, filaments of model II proteins (at $\boldsymbol{\varepsilon_{LJ}}$ of 9 k_BT) significantly increase the persistence length of bound DNA, implying more rigidity (Fig. 4 in (5)). On the other side, the presence of DNA also enhances the bundling of nucleoid proteins (Fig. 1 in (5)). Lastly, these computationally measured properties of the two models demonstrate impressive consistencies with experiments on various nucleoid proteins such as Dps, CbpA, ParB (model I), and H-NS (model II).

Submitted January 22, 2021, and accepted for publication February 2, 2021.

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Editor: Yamini Dalal.
https://doi.org/10.1016/j.bpj.2021.02.001

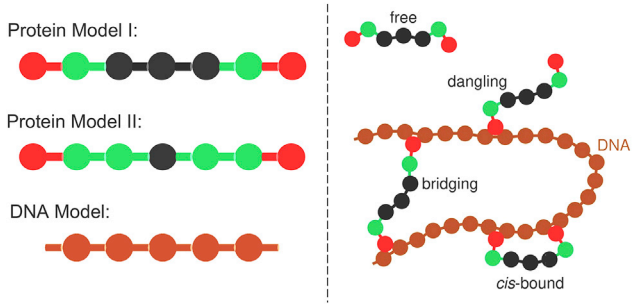

FIGURE 1 Cartoon representations of the nucleoid protein and DNA model, and their binding modes. Left: the two protein and one DNA models in (5) are shown. In the protein models, red beads can bind with DNA, green beads can self-associate, and neither applies to black beads. DNA model consists of uniform beads (*brown*). The right panel is taken from (5), showing four binding modes between nucleoid proteins and DNA. To see this figure in color, go online.

In all, this simple and neat model developed by Joyeux displays a clear picture of how the self-association of different nucleoid proteins influences the architectural properties of DNA. This model is promising for further developments and applications. For instance, more features, either geometrical or chemical, can be added to model the 12 types of NAPs and specific DNA sequences. Combined with other models by the same group (9), theory hypotheses (10,11), and experimental data (12–14), more complicated questions can be studied: 1) the comprehensive NAPs-DNA regulation network in DNA compaction and gene expression; 2) NAPs' responses to environmental stimuli and their possible consequences on stimuli-specific gene expressions; and 3) environmental stimuli may involve unfavorable physiological stress, concentration changes of NAPs, ionic conditions, solvent solubility, and so forth.

ACKNOWLEDGMENTS

The author thanks Dr. Daniël Melters for critical reading of this manuscript.

REFERENCES

1. Zhou, K., G. Gaullier, and K. Luger. 2019. Nucleosome structure and dynamics are coming of age. *Nat. Struct. Mol. Biol.* 26:3–13.
2. Henneman, B., C. van Emmerik, …, R. T. Dame. 2018. Structure and function of archaeal histones. *PLoS Genet.* 14:e1007582.
3. Browning, D. F., D. C. Grainger, and S. J. Busby. 2010. Effects of nucleoid-associated proteins on bacterial chromosome structure and gene expression. *Curr. Opin. Microbiol.* 13:773–780.
4. Verma, S. C., Z. Qian, and S. L. Adhya. 2019. Architecture of the *Escherichia coli* nucleoid. *PLoS Genet.* 15:e1008456.
5. Joyeux, M. 2021. Impact of self-association on the architectural properties of bacterial nucleoid proteins. *Biophys. J.* 120:370–378.
6. Song, D., and J. J. Loparo. 2015. Building bridges within the bacterial chromosome. *Trends Genet.* 31:164–173.
7. Dias, R. S. 2019. Role of protein self-association on DNA condensation and nucleoid stability in a Bacterial cell model. *Polymers (Basel).* 11:1102.
8. Dahlke, K., and C. E. Sing. 2019. Influence of nucleoid-associated proteins on DNA supercoiling. *J. Phys. Chem. B.* 123:10152–10162.
9. Joyeux, M. 2020. Bacterial nucleoid: interplay of DNA demixing and supercoiling. *Biophys. J.* 118:2141–2150.
10. Konto-Ghiorghi, Y., and V. Norris. 2020. Hypothesis: nucleoid-associated proteins segregate with a parental DNA strand to generate coherent phenotypic diversity. *Theory Biosci* Published online October 23, 2020. https://doi.org/10.1007/s12064-020-00323-5.
11. Hu, L., A. G. Vecchiarelli, …, J. Liu. 2017. Brownian ratchet mechanism for faithful segregation of low-copy-number plasmids. *Biophys. J.* 112:1489–1502.
12. Lioy, V. S., A. Cournac, …, R. Koszul. 2018. Multiscale structuring of the *E. coli* chromosome by nucleoid-associated and condensin proteins. *Cell.* 172:771–783.e18.
13. Remesh, S. G., S. C. Verma, …, M. Hammel. 2020. Nucleoid remodeling during environmental adaptation is regulated by HU-dependent DNA bundling. *Nat. Commun.* 11:2905.
14. Xiang, Y., I. V. Surovtsev, …, C. Jacobs-Wagner. 2020. Solvent quality and chromosome folding in *Escherichia coli*. *bioRxiv* https://doi.org/10.2139/ssrn.3650601.