New and Notable

The Ghost in the Machine: Is the Bacterial Chromosome a Phantom Chain?

Jian Liu[1,*]
[1]Biochemistry and Biophysics Center, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland

In the classic picture of bacterial genome organization, the bacterial chromosome is considered to be a disordered polymer, like spaghetti confined in a bag. Progress in high-resolution microscopy radically advanced our understanding of chromosomal organization and completely toppled this classic picture. Many experiments in recent years have revealed intriguing order in chromosomal structure at different length- and timescales (1,2). The questions that arise from these observations include: What is the origin of multiscale order? And what does it mean?

Addressing these questions raises a fundamental dichotomy: on the one hand, the chromosome is essentially a ring polymer that folds itself into a dense globule, a so-called nucleoid, which mainly consists of DNA, RNA, and nucleoid DNA binding proteins. It is thus tempting to apply our knowledge of polymer physics acquired over the past six decades (3,4) to understand the fundamental principles of chromosome organization in bacteria and cells in general. On the other hand, the chromosome is a special kind of polymer, inasmuch as its structural organization and dynamics are intricately coupled to, and tightly regulated by, fundamental energy-transducing biological processes, such as chromosome replication, segregation, and gene expression (1,2). This dichotomy blurs the line between physics and biology. Accordingly, it is a general belief that integration of physical and biological approaches is the future paradigm in this, as in many other, biological fields. In this issue of the *Biophysical Journal*, work from Lampo et al. (5) represents a good example of this integrated approach.

A series of seminal experiments tracking the position of the chromosome replication origin (*ori*C) over time in *Escherichia coli* demonstrated that the chromosome loci undergoes subdiffusive motion both at short timescales (1–100 s, shorter than a cell cycle) between consecutive rounds of chromosome replication, and at long timescales (1–100 min) encompassing chromosome segregation (6,7). That is, the mean-square displacement scales with time as $\sim t^{\alpha}$, where $\alpha < 1$, slower than an unbiased random walk. Further experiments suggested that this subdiffusive behavior is a common feature among different bacteria, although the specific value of the power-law exponent α varies with the species and the loci (6–9). Because the power-law exponent scaling is an indicator of the dynamic organization of the underlying structure, on which the motion takes place, one could extract a great deal of information on the material properties of the structure, in this case the nucleoid itself. The early analytic theory of Lampo et al. (5) considers the bacterial chromosome as a Rouse polymer, i.e., a "phantom" chain that can run across itself without volume exclusion between its segments (6). This Rouse model is perhaps the simplest polymer model for bacterial chromosomes. Interestingly, it reveals that the subdiffusive motion of *ori*C at the short timescales is most consistent with relaxation of the Rouse modes of the DNA polymer within the viscoelastic environment of the nucleoid, which itself exhibits a fractal dimension. It is an elegant theory and makes intuitive sense; the observed *ori*C motion should relate simply to the intrinsic polymer properties at short timescales, during which the contribution of chromosome segregation is negligible.

Lampo et al. (5) apply the same model to explain the scaling of the *ori*C dynamics at long timescales. One would have thought that concurrent processes of chromosome segregation at these long timescales should have major impacts on the *ori*C motion, because the nucleoid itself—the underlying structure that the *ori*C moves along—is undergoing dramatic remodeling. Instead, Lampo et al. (5) show that the same Rouse model of a DNA polymer driven by an external force fully recapitulates the subdiffusive scaling of *ori*C motion during chromosome segregation. This means, from the perspective of the chromosome replication origin, that the nucleoid, even through the process of segregation, provides an effectively static viscoelastic background environment similar to that between rounds of chromosome replication. In other words, the chromosome behaves like a phantom chain throughout the cell cycle. This exciting theoretical result thus comes as a surprise! In addition, the authors show that the ratio between the mean displacement (MD) and the variance of displacement (VarD) is linearly related to the driving force f:

$$\frac{MD}{\mathrm{VarD}} = \frac{f}{2k_{\mathrm{B}}T}.$$

This analytic formula is useful because it allows direct determination of chromosome segregation forces from experimental position-tracking data.

Like any good research that opens up more questions than it answers, this elegant theory provides a starting point for deeper understanding of the structural organization principles of bacterial chromosomes. As elaborated above, the top-down approach taken by Lampo et al. (5) disregards the dynamic changes in nucleoid during chromosome segregation. Although

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*Correspondence: liuj7@nhlbi.nih.gov

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this theory explains the subdiffusive motion of *ori*C at the long timescales, it remains a minimal model that provides guidance for future experiments following bottom-up approaches. In particular, the intriguing question is: Is the bacterial chromosome really a phantom chain?

Any physical polymer should have volume exclusion effects and other chromosome loci are known to exhibit different motions from that of *ori*C (8,9). The very finding that the chromosome could be considered as a phantom chain suggests that the chromosome-structure maintenance process by complexes such as topoisomerases is crucial in the polymer physics of the chromosome (10). The detailed mechanism of how structural maintenance integrates with chromosome loci motion is an exciting future direction. This quest also elicits further questions in a broader spectrum: How does the chromosome segregation machinery, together with that of chromosome replication, control chromosome loci motion? What role does the interplay among chromosome replication, segregation, and chromosome loci movement play in shaping the nucleoid structure? How does such chromosome structural remodeling coordinate with other process of the cell cycle?

Answering these questions will provide a deeper understanding in the fundamental principle of chromosome organization. It entails the close synergy between physics and biology, and this article provides a good starting point.

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