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The organization of bacterial genomes: Towards understanding the interplay between structure and function

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Abstract
Genomes are arranged in a confined space in the cell, the nucleoid or nucleus. This arrangement is hierarchical and dynamic, and follows DNA/chromatin-based transactions or environmental conditions. Describing the interplay between local genome structure and gene activity is a long-standing quest in biology. Here, we focus on systematic studies correlating bacterial genome folding and function. Parallels on organizational similarities with eukaryotes are drawn. The biological relevance of hierarchical units in bacterial genome folding and the causal relationship between genome folding and its activity is unclear. We discuss recent quantitative approaches to tackle these questions. Moreover, we sketch a perspective of experiments necessary to iteratively and systematically build, test and improve structure−function models of bacterial chromatin.

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Introduction

Genomes of all organisms, bacteria, archaea and eukaryotes, are arranged in the cell in a confined space, the nucleoid or nucleus. This arrangement is dynamic allowing for DNA transactions such as replication, transcription and repair to occur at appropriate times. A spectrum of mechanisms is involved in physically compacting and functionally organizing genomes in cells. Although at first sight the organization of the genomes of bacteria and eukaryotes may appear diverse, common principles are recognized [1]. The proteins providing structural and functional organization are generally not conserved at the protein sequence level. Nevertheless, several types of conserved structural features are evident [1]. Bacterial H-NS-family proteins, SMC proteins, and eukaryotic insulator proteins bridge DNA to form loops at different length scales [2–4]. In bacteria DNA decorated with architectural proteins is folded in looped structures [5], whereas in eukaryotes nucleosomal fibres, in which DNA is wrapped around histone proteins, are arranged into loops [6]. Although in eukaryotes much of genome regulation occurs at the level of nucleosomes (via histone tail modifications and nucleosome density) [7,8], at a coarse grained, structural level such molecular details are irrelevant. At a larger scale both in bacteria and eukaryotes, loops are arranged into structural domains, defined by genome activity [1,9]. An understanding of the interplay between structural and functional organization is emerging. The field is further advanced in eukaryotic organisms compared to bacteria, yet in both cases a lot of unanswered questions remain. Here, we discuss recent advancements in understanding bacterial genome organization, linking chromatin structure to function. Our focus is on systematic approaches aimed at determining characteristics of the dynamic organization of bacterial genomes, and lessons learned from similar studies in eukaryotic model systems.

State of the art

Most bacterial model organisms harbour a single circular chromosome. The bacterial chromosome has been primarily studied in *Bacillus subtilis*, *Escherichia coli* and *Caulobacter crescentus*, and unless otherwise indicated the information summarized here applies to these organisms. Bacteria have a cell cycle with a duration on the order of tens of minutes. As a consequence, genome folding and transcription are intimately coupled with genome replication. Current key question is to understand the structure−function relations within the

bacterial chromosome, specifically the interplay between genome structure and gene activity.

The first systematic studies of bacterial chromosome structure aimed at defining the positioning of genomic loci within the cell. Two approaches based on fluorescence microscopy were used: *i*) fluorescent *in situ* hybridization (FISH) labelling of endogenous loci in fixed cells [10] and *ii*) fluorescent repressor-operator systems (FROS) involving binding of e.g. LacI-GFP to exogenous *lacO* operator sites integrated in the genome in living cells [11,12]. These studies have revealed that regions proximal to the initiation (*oriC*) and termination (*ter*) site of replication are not distributed randomly in the nucleoid but exhibit specific localization patterns throughout the cell cycle [12–14]. Visualizing the locations of up to about 100 defined genomic loci relative to *oriC* reveals a linear relationship between genomic and physical location, indicating a linear ordering [15–17]. The reproducible positioning of genomic loci at specific subcellular positions in individual cells and their linear organization appear as fundamental features of chromatin organization in bacteria.

In *E. coli*, *oriC* and *ter* are part of two distinct structural domains, the Ori and Ter macrodomains [18]. In addition, the *E. coli* genome contains two other structural domains flanking the Ter domain, called the Right and Left macrodomains, and two non-structured (NS) regions, flanking the Ori domain [19,20] (see Figure 1). The Ter domain stretches along the length of the cell to connect the two chromosomal arms, with an estimated packing density of only 1/10 compared to the rest of the genome [16]. Genome packing density may correlate with genome activity. The chromosome is organized as a dense nucleoid scaffold wherefrom large 'plectonemic' loops of negatively supercoiled DNA protrude. Such loops are probably formed by binding of a group of proteins called 'nucleoid-associated proteins' (NAPs) [21–23]. But these proteins only provide part of the answer.

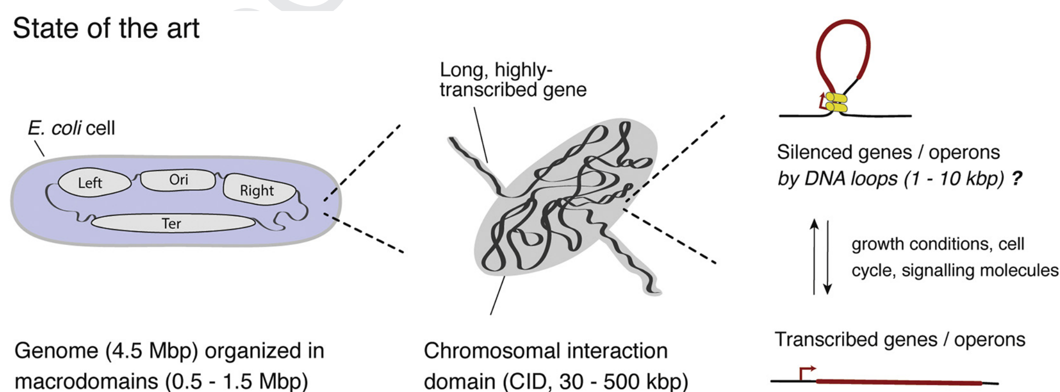
What is the relevance and evolutionary conservation of the different levels of organization? How are the different organizational units and their borders defined, and what are their dynamics upon DNA transactions? Below we discuss recent advances on quantitative approaches aiming to find answers to these fundamental questions.

Chromatin structure: organization in domains

Since the early 2000's chromosome conformation capture (3C), developed by Dekker and colleagues [24], and derivatives of the method, have promoted large advances in understanding genome folding and function [25–28]. These techniques yield maps of relative interaction frequency between different pairs of genomic sites averaged over a population of cells. The technique relies on chemical cross-linking, digestion, religation of digested fragments, followed by identification of the hybrid DNA molecules [24]. A large-scale variant, Hi-C [29], has been used to produce genome-wide contact matrices in several organisms. These matrices, structurally interpreted by modelling approaches, provide insight in global and local features of genome structures [28,30].

Among bacterial species, currently, Hi-C contact maps are available for *C. crescentus* [31–33], *B. subtilis* [34–36] and *Mycoplasma pneumoniae* [37]. Different genome features have been identified in these studies. In the *C. crescentus, B. subtilis, V. cholera and M. pneumoniae* genome-wide contact maps, several tens of chromosomal interaction domains (CIDs) have been identified [31,34,35,37,38] (see Figure 1). CIDs are highly self-interacting genomic regions. These regions vary in size from about 20 to 400 kbp, and they are analogous to so-

Figure 1



State of the art. The bacterial genome is organised at different length scales. At the smallest length scales it has been hypothesised that genome folding is directly affected by environmental signals which are translated into a transcriptional response.

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