CSIAM Trans. Life Sci.
doi: 10.4208/csiam-ls.SO-2024-0003a

Vol. **1**, No. 2, pp. 258-279
June 2025

Modeling the Spatial Motion of Chromatin and the Whole Process of Gene Transcription

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Received 28 May 2024; Accepted 14 August 2024

Abstract. Biological experiments have verified that chromatin organization has importance influence on gene expression, but the conventional models of gene expression neglect this influence, in particular the effect of enhancer-promoter (E-P) communication on gene expression. Here we first review properties of the classical Rouse model that is a quite accurate description of chromatin as confirmed by microscopy experiments. Second, we extend this model to the polymer models with long-range interactions so that they include E-P communications that are typically long-range interactions. We also carry out theoretical analysis for the extended models. Third, we establish mathematical models for the whole process of gene transcription, which consider connections between upstream chromatin dynamics and downstream promoter kinetics. These connections consider two possible ways of regulation: The one via E-P encounter probability and the other via E-P spatial distance, both supported by a different experimental measurement. These models lay solid foundations not only for the deep study of gene-expression dynamics but also for the statistical inference of experimental data.

AMS subject classifications: 92C42, 82D60

Key words: Gene transcription, polymer model, chromatin dynamics, E-P communication, encounter probability.

1 Introduction

It is undoubted that the regulation of gene expression is at the center of intracellular processes. Correctly understanding the whole process of gene expression must consider chromatin organization and its function. In a cellular nucleus, chromatin consists of the DNA and its hierarchy of interacting molecules [5], whereas chromosomes are comparatively a higher order of DNA organization. Live cell microscopy data suggest that chromosomes are organized in distinct geographical territories possibly with different shapes

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and sizes [15]. Changing upstream chromosomes organization, e.g. by clustering several parts of different chromosomes together, can activate or repress downstream gene expression. This reorganization could allow the simultaneous regulation of multiple loci (i.e. nucleosomes) in specific substructures, although the existence of these substructures is still under debate [14, 57]. Gene expression is modulated by DNA regulatory elements on the chromatin, e.g. enhancers [47], which are often located far away from their target genes along the DNA line but are thought to associate with promoter sites on the DNA molecule that they regulate. Biological experiments have verified that mRNA or protein levels are related to the proximity between enhancer and promoter (E-P). These general descriptions constitute a coarse-grained scenario of chromatin dynamics, but lay a foundation for mathematical modeling of the whole gene-expression process.

Physical models and polymer models at different length or time scales or both [30] can be used to describe DNA and chromatin molecules [40,51], chromatin fibers, aggregation-dissociation with a finite number of particles [31], the encounter of chromatin loci, and the time for a Brownian particle to find its small target [29]. In turn, the theoretical analysis of these quantitative models can be used to estimate short- and long-time behaviors of rare molecular events, e.g. molecular binding, DNA looping, DNA repositing to the small location, and DNA searching for homology [5]. In particular, the asymptotic analysis of the models can reveal how key physical parameters control the spatial or time scales of chromatin organization [3, 5]. Although local changes in chromosomes organization are often difficult to resolve spatially, they can be studied using polymer models and analyzed using stochastic process theory [23]. In fact, the existed studies indicate that mathematical models are a powerful tool for studying chromatin organization and function. In spite of this, accounting for the forces driving these changes is still challenge for polymer physics and for the interpretation of data since chromatin is constantly moving driven by various cellular sources leading to random fluctuations inside confined nuclear sub-domains and restricted by the nuclear envelope in eukaryotes.

On the other hand, conventional models of gene expression, such as common ON-OFF models [21, 45, 54] and multi-state models [48, 68, 69] as well as queuing models [33, 37, 46, 55], have apparent shortcomings since they neglect the influences of chromatin configuration and E-P communication, two important factors that can modulate mRNA and protein levels. As an important step of establishing a biologically reasonable mathematical model for the whole process of gene expression, modeling chromatin dynamics has received extensive attentions in recent years. From the view of physics, chromatin can be modelled as a polymer discretized into monomers (representing nucleosomes) connected by springs. In fact, live-cell imaging of the chromatin and polymer models are now converging. If chromatin loci can be routinely tracked at a spatial scale of tens of nanometer resolution and at a time resolution of hundreds of milliseconds or less [9, 12, 42], polymer models and their numerical simulations are constantly increasing their accuracy by incorporating physical and mechanical properties of the chromatin structure to reproduce its local organization [5, 43, 44, 49, 50, 59, 60, 66]. Fortunately, chromosome conformation capture data provide an unprecedented chance for the reconstruc-