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Large-scale simulations of nucleoprotein complexes: ribosomes, nucleosomes, chromatin, chromosomes and CRISPR

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Abstract

Recent advances in biotechnology, such as Hi-C, CRISPR/Cas9, and ribosome display, have place nucleoprotein complexes at center stage. Understanding the structural dynamics of these complexes aids in optimizing protocols and interpreting data for these new technologies. The integration of simulation and experiment has helped advance mechanistic understanding of these systems. Coarse-grained simulations, reduced-description models and explicit solvent molecular dynamics simulations yield useful complementary perspectives on nucleoprotein complex structural dynamics. When combined with Hi-C, cryo-EM, and single molecule measurements, these simulations integrate disparate forms of experimental data into a coherent mechanism.

Introduction

Due to the large size of the nucleoprotein complexes (e.g., ~3 million atoms in for the ribosome in explicit solvent) and long time scales involved (~seconds), computational studies must use various approximations, often requiring compromises between force field accuracy and the time scale sampled. One is reminded, however, that simplified models can sometimes be powerful. For example, in the case of the orbits of the planets around the Sun, the Earth and every organism on it are approximated by a single point particle; yet the resulting model produces highly accurate predictions for the Earth's orbit. As often occurs in molecular dynamics simulations, high levels of detail in the force field are typically attained at the cost of the time scale sampled, and in turn, accuracy of the entropic contribution to the free energy. Similarly, enhanced sampling techniques that produce exhaustive sampling either (1) reduce the level of detail in the force field or (2) simulate portions of the macromolecular complex. Each technique, however, is quite useful on its own right and provides new insight and new perspectives into dynamics that were previously unexplored experimentally. In many cases, the beginning and end states of conformational changes are known from cryo-EM, along with rates determined by single molecule FRET. Molecular simulation provides a powerful way to merge available experimental data into a single, integrated movie, yielding a highly useful perspective unavailable from experimental data alone. In this review, we summarize many of the various computational techniques used to

study nucleoprotein complexes. While the review is by no means entirely comprehensive, it serves as a starting point for researchers in the field.

Structural modeling of the ribosome

Early computational studies of the ribosome concentrated on structural modeling of the bacterial ribosome, before higher resolution x-ray crystallography structures were solved [1–6]. RNA homology methods were used to construct predictive models of the *E. coli* 30S ribosomal subunit and the *T. thermophilus* 70S ribosome highly consistent with cryo-EM data and used for phasing x-ray crystals [7,8]. After X-ray crystallographic structures of ribosomal subunits were solved, it was possible to perform molecular dynamics simulations of important functional regions [9,10], normal mode calculations [11] and Poisson-Boltzmann analysis on the intact ribosome[12]. In a very interesting use of explicit solvent molecular dynamics simulation, Frank and co-workers performed simulations of the tRNA in solution and selected conformations with very close correlations to their tRNA cryo-EM density inside the ribosome [13].

Computational studies of intact ribosomes: coarse-grained and reduced description simulations

Normal mode analysis and elastic network models have described overall global motions of the ribosome at nucleotide resolution [11,14,15]. These studies reproduced intersubunit rotation, movement of the small subunit head and large-scale motions of the L1 stalk and L7/L12 stalk in bacteria. This technique was also used to perform some of the first automated molecular fitting of cryo-EM reconstructions [16,17]. Further elastic network models have depicted the coupled motions of tRNA and mobile domains of the ribosome [18]. Jernigan and co-workers also examined dynamics of the mRNA channel on the ribosome, a key player in tRNA translocation through the ribosome, suggesting that the entry clamp may assist in base recognition to ensure proper selection of the incoming tRNA [19]. In addition to elastic network models, early electrostatic calculations determined charged regions on the ribosome [12], showing the surface of the ribosome to be mostly negative with scattered positively charged regions corresponding to ribosome proteins.

Reduced-model molecular dynamics simulations have explored larger regions of configurational space and longer time scales. Trylska and co-workers performed coarse-grained molecular dynamics of the entire ribosome on a half a microsecond time scale, accounting for large-scale motions by implementing a Morse potential function, observing intersubunit rotation and stalk motion[20]**. Here, large-scale collective motions such as the rotation of the subunits were produced. In addition, the anti-correlated movement of the ribosomal stalks positioned on the opposite sides of the large subunit was observed. Studies performed by Trylska *et al.* also enabled the investigation of large-scale conformational changes coupled with electrostatic effects.

All-atom reduced model simulations based on a structure-based potential have enabled systematic studies of spontaneous large-scale conformational changes with atomistic detail [21]. Here, reversible excursions of tRNAs into and out of ribosomal binding sites were

observed, consistent with recent single molecule FRET experiments. These simulations produced sampling on the order of ~200 milliseconds for the ribosomal complex in atomistic detail.

In studies of intersubunit rotation of the entire ribosome, Whitford and co-workers, by accounting for molecular flexibility, demonstrated that rotation likely involves asynchronous movement of the bridges, where the transition state is associated with partial rotation and the full displacement of bridge B8 [22].

Noller and co-workers have performed a very interesting computational study on ribosome dynamics, where they use translation-libration-screw (TLS) constraints to refine atomistic models based on x-ray diffraction data [23]. Here, they examine the mobilities of the peptidyl transferase center, the Shine-Dalgarno helix, as well as the 30S rotation relative to the 50S subunit. This was followed by an innovative study placing the head swivel movement in the context of nearly every structural study of translocation, showing that a two-hinge mechanism enables head-swivel [24].

In the first molecular simulations of the eukaryotic ribosome, experimentally determined SHAPE chemical probing data was integrated into a structure-based force field to determine conformational hotspots during translocation [25,26].

Computational studies of intact ribosomes: explicit solvent molecular dynamics simulations

Explicit solvent molecular dynamics simulations of the entire ribosome have examined large-scale conformational changes of the ribosomal complex. One of the more tractable conformational changes is movement (accommodation) of tRNA from its partially bound state (A/T) to its fully bound state (A/A) that occurs during tRNA selection. Targeted molecular dynamics simulations correctly predicted the regions of the large subunit that interact with the tRNA during this conformational change (accommodation corridor) [27]. These simulations are consistent with snoRNA deletion studies in yeast, producing ribosomes with unmodified nucleotides in the accommodation corridor[28,29]. The resulting ribosomes displayed fidelity phenotypes including defects in −1 frameshifting, peptide bond formation and misreading [29]. Mutational studies by the same group demonstrated that mutations of the predicted three-dimensional gate (A2556, 2492 and 2483) are viable for normal ribosomes, but dramatically effect growth when treated by antimicrobials [30]. The Dontsova lab also performed mutations on the same three nucleotides [31,32], finding that two of the nucleotides impair peptide release while the third is lethal and acts to block peptide bond formation, presumably by impeding tRNA accommodation into the fully bound (A/A) conformation. Simulation molecular simulation studies delineated the corridor (hybrid corridor) that facilitates movement of tRNAs from the classical state (A/A, P/P) to the hybrid state (A/P, P/E) [33] [34]. Molecular dynamics simulations of the intact ribosome have also examined dynamics of the L1 stalk and the ribosome exit tunnel in the large subunit of the ribosome [35–37]. Explicit solvent simulations of the 70S ribosome have connected measured kinetic rates of accommodation, intersubunit and head swivel motions to free energy barriers [38] [39]*. These microsecond simulations of the ribosome (3.2

million atoms) measure the diffusion of tRNA inside the ribosome, intersubunit rotation and head swivel, producing an estimate of the pre-factor in the Ahrenius equation for this process. The first simulations of ribosome-EF-P interactions, combined with cryo-EM, showed that EF-P modification and absence of EF-P protein result in the peptidyl-tRNA moving away from the A-site tRNA, generating a geometry that is incompatible with peptide bond formation [40]. A similar study of ErmBL-stalled ribosomes also examined movement in the peptidyl transferase center [41]. The studies nicely integrated simulations of the peptidyl transferase center with simulations of the full ribosome.

Computational studies of functional regions of the ribosome:

Another class of ribosome simulations focuses on localized regions of the ribosome that are critical for protein synthesis. Quantum mechanical studies of the peptidyl transferase center have explored reaction mechanisms [42,43]. Warshel an co-workers examined the mechanism of GTP hydrolysis by EF-Tu during tRNA selection, concluding that the critical residue H84 contributes to an allosteric effect [44]. Wieden and co-workers have performed extensive studies on the mechanism of EF-Tu, including one very interesting investigation that combines molecular dynamics simulations with rapid kinetics studies [45]. Aqvist and co-workers have also examined the mechanism of the peptidyl transferase reaction, combing an empirical valence bond description with molecular dynamics simulations, concluding that an acid-base catalysis method is unlikely, favoring a proton-shuttling mechanism that does include the P-site adenine O2’ oxygen [42,46]. Aqvist and co-workers have also applied quantum chemical methods to termination [47].

Short time scale simulations of the decoding center complexed with mRNA and tRNA anticodon stem loops have examined the stability of the decoding center hydrogen bond network for a wide range of cognate, near-cognate and non-cognate mRNA-tRNA combinations [48], suggesting that ribosomal RNA had a stabilizing effect on cognate codon-anticodon interactions and a destabilizing effect on certain non-cognate combinations. Aqvist and co-workers performed a similar study with longer aggregate sampling, estimating binding free energies [49]. They applied a similar method to study stop-codon recognition [46] and studied the interaction between the L7/L12 stalk, showing that complementary charge-based interaction between L12-CTD and IF2 is important for fast subunit association [50]. Aqvist and Green studied the mechanism of peptide release, finding that the 2’ OH of the P-site substrate is critical for orienting the nucleophile in a hydrogen-bonding network productive for catalysis [51].

Several studies investigated the dynamics of the decoding center helix [52–55]. Explicit solvent simulations of the decoding center complexed with antibiotics examined the stability of the drug-ribosome interactions [53]. Exhaustive sampling simulations (replica exchange molecular dynamics simulations) show a high degree of convergence after one microsecond in the absence of antibiotics and 15 microseconds the presence of gentamicin. These studies show the decoding center bases (A1492 and A1493) flipping in and out of helix 44 in absence of drug [52,53], while in the presence, the equilibrium shifts towards the flipped out state with time scales consistent with 2-aminopurine fluorescence studies of the decoding helix. The studies produced the first energy landscapes of the ribosome, and suggest that an

entropy shuttling mechanism may move the drug from local minimum to local minimum until the binding site is reached. Brooks and co-workers performed studies suggesting that flipping of the decoding bases can distinguish between cognate and near-cognate tRNAs [51].

Trylska and co-workers performed explicit solvent molecular dynamics simulations of decoding introducing various mutations, finding differences in the internal mobility of the A-site, as well as in ion and water density distributions inside the binding cleft, between the prokaryotic and mutated RNA [54]. They also examined the effect of A2058G on clindamycin activity[56]. In an important study, Trylska and co-workers used Brownian dynamics simulations to examine antibiotic binding to the 30S subunit, showing that electrostatic steering is not the sole factor directing the aminoglycosidic antibiotic toward the binding site on the 30S ribosomal subunit. The simulations explain why paromomycin overstabilizes the 70S ribosome complex and precludes its dissociation into 30S and 50S subunits. The study unveiled other binding clefts in ribosomal RNA and explained the physical mechanisms of aminoglycoside diffusion and binding to the ribosomal RNA [57]*. A number of additional studies of localized ribosomal regions have focused on drug-ribosome interactions [53–55,58].

Sponer and co-workers have explicit solvent simulations of three-way junctions present in the ribosome, demonstrating that the junctions contribute to functional fluctuations of the ribosome, including 5S rRNA, A-site finger, and L7/L12 stalk RNA [59]*. Sponer, Frank and co-workers performed studies of the A-site finger [60]. Several groups have used molecular simulations to study dynamics and peptide folding within the exit tunnel of the large subunit of the ribosome [61–66]. O’Brien an co-workers identified a new source of mechanical force acting on the ribosome by combining experimental measurements of changes in nascent-chain extension in the exit tunnel in conjunction with all-atom and coarse-grained simulations, observing that the route of force transmission is shown to be through the nascent polypeptide’s backbone, not through the wall of the ribosome’s exit tunnel [67].

Nucleosomes, di-nucleosomes, tri-nucleosomes, and tetra-nucleosomes

A wide range of single and multiple nucleosome simulations have been performed, both at atomistic and coarse-grained levels of detail. Simulations of single nucleosomes have studied the flexibility of DNA and histone tails in the context of nucleosomes[68]. In the context of a comprehensive multiscale study, multimicrosecond explicit solvent molecular dynamics simulations of dinucleosome, including histone tails were performed with three different state-of-the-art force fields and validated by experimental NMR measurements. Takada and co-workers have examined the effect of histone acetylation on trinucleosome dynamics [69]. Coarse-grained simulations of unrolling have been studied by Langowski and co-workers [70]. The SIRAH force field extension for protein-DNA complexes has been used to perform coarse-grained simulations of tetranucleosomes to study DNA dynamics within the context of this system[71]. Many coarse-grained models of DNA itself have been described previously[72].

Coarse-grained simulations of chromatin: nucleosome arrays and intact gene loci

Schlick and co-workers have developed a coarse-grained model for polynucleosome systems over the past 15 years, that captures the physics of nucleosome-nucleosome interactions and sterics, electrostatics, flexible DNA and histone tails, consistent with many forms of experimental data [73–76]. Because the model has much more detail than full chromosome bead polymer models, but less detail than atomistic models, the model is referred to as mesoscale. The model includes different coarse-grained representations for linker DNA, flexible histone tails, linker histone, and nucleosomes [74–79]. The mesoscale model [80–86] has reproduced properties related to internucleosome distances, entry/exit angles, sedimentation coefficients, diffusion contacts, fiber curvature, force versus extension measurements, and cross linking data [73,74,84,87–89]. More recently tools related to electrostatics, Langevin dynamics, Monte Carle and enhanced sampling have been added [82,84,90–92] [87,93,94]. Recently, the mesoscale model was used to study HOXC, producing the first folded gene structure that was defined from first principles (nucleosome positions, epigenetic marks, linker histones) [95]. A second mesoscale model uses a globular histone core and flexible histone tails described by one particle per each amino acid, taking into account their net charge. DNA wrapped around the histone core is approximated at the level of two base pairs represented by one bead (bases and sugar) plus four beads of charged phosphate groups. Simulations of this model reproduced experimental results and the structure of the nucleosome-nucleosome contacts [96].

Intact gene loci: explicit solvent simulations

Recently, the first explicit solvent molecular dynamics simulations of an intact gene locus were performed (GATA4), consisting of 427 nucleosomes and 83 kb of DNA, requiring approximately one billion atoms [97]. Here coarse-grained models of GATA4 from Schlick and co-workers [97,98] were remodeled to construct an all-atom model. This was solvated with water and ion excess ions, minimized and run in molecular dynamics mode with particle mesh Ewald using the GENESIS molecular dynamics code. Scaling past 500,000 processor cores was achieved.

Coarse-grained simulations of intact chromosomes and genomes

The advent of high resolution chromatin capture technology (Hi-C) has produced intense interest in 3-D modeling of chromosomes. By crosslinking distal regions of chromosomes and sequencing them at high resolution, Hi-C allows one to map interactions between chromosome regions, enabling approximate 3-D reconstructions of chromosomes. A working model of chromatin architecture resembling a fractal globule has been proposed [99,100]. Early Hi-C studies demonstrated that chromosomes tend to be organized into large-scale (~5 Mb) A/B compartments and smaller topologically associating domains (TADs) within the compartments (0.3–0.8 Mb). While the TADs entail modular, locally isolated interactions, the compartments form a checker board pattern in the contact map, depicting longer-range interactions that segregate active, A/T rich regions from less active, G/C rich regions [99,100]. The A/B compartments can be extracted by Eigen-vector analysis

(*i.e.,* principal component analysis). Interestingly, in the X chromosome in females, one of two X chromosomes is inactivated, whereby a long non-coding RNA (Xist RNA) effectively coats the chromosome, ultimately resulting in a massive reorganization of the chromosome architecture: A/B compartments are replaced by a different set of compartments (S1/S2) [101–103]. Here, the interactions are segregated according to their interactions with the Xist RNA. That is, during X chromosome inactivation, the inactive X chromosome is partitioned into Xist-rich S1 and Xist-poor S2 compartments, which are eventually merged into a single compartment by the SMC protein, SMCHD1[101–103].

Using a very coarse-grained (typically 1 bead > 50 kB) homopolymer model, one can use Monte Carlo [100,104–108] or Langevin dynamics simulations [109–115] to mimic the structure and dynamics of chromatin. These and other simulations often display raindrop shaped features analogous to the topologically associating domains (TADs) characteristic of Hi-C maps [112–116]. More recently, knowledge-based potential terms directly incorporate Hi-C and other data to obtain contact maps quite similar to experimentally measured Hi-C maps [107,109–111,113–115]. Regarding Langevin dynamics, Onuchic and Wolynes have constructed a quasi-equilibrium homopolymer model (MiChroM) including interchromosomal interactions, loop extrusion factors (e.g., CTCF and cohesion), and a maximum entropy term to incorporate interactions observed in Hi-C experiments [114,115]. Their quasi-equilibrium energy landscape studies were used to demonstrate that the confinement of crowding effectively slows diffusion, consistent with experimentally observed diffusion, viscoelasticity and spatial confinement. The model is highly extensible, allowing the authors to construct an excellent model incorporating ChIP-seq data, enabling the study of a variety of epigenetics marks [113].

Innovative coarse-grained methods

Several interesting coarse-grained methods have been developed recently that can be applied to interesting aspects of nucleoprotein complex mechanism. Wu and co-workers developed a Monte Carlo simulation algorithm which incorporates both molecular factors including conformational changes of cellular adhesion molecules and cellular factors including fluctuations of plasma membranes to approach the physical process of adhesion [117]. A highly effective method that combines molecular simulation with SAXS and hydroxyl-radical probing experiments has been developed by Yang and co-workers [118]. Zheng and co-workers developed an interpolated elastic network model (iENM) protocol to construct a transition pathway for large macromolecular complexes such as SNARE [119]. Several other methods are described in a comprehensive review by Kolinski and co-workers [120].

Molecular simulations of the CRISPR-Cas9 and related complexes.

In terms of biotechnology, one of the most exciting areas of molecular simulations of nucleoprotein complexes is the CRISPR-Cas9 system used in gene editing. McCammon and co-workers have performed a number of pioneering studies, incorporating the latest experimental data to shed light on the mechanism of CRISPR-Cas9 [121,122]. Using Gaussian-accelerated molecular dynamics, they reveal the conformational dynamics of Cas9 during activation toward catalysis and find the conformational transition of Cas9 from its

apo form to the RNA-bound form. Interesting coarse-grained studies of CRISPR mechanism have been recently performed by Zheng [123].

Single molecule and other in vitro studies

Single molecule studies often reveal the dynamics of a system, connecting structural studies to computer simulations. As a result, a comprehensive picture of mechanism is constructed that integrates multiple experimental perspectives of the same phenomena. For ribosomes, nucleosomes and chromatin, single molecule experiments have played key roles in advancing mechanism.

Regarding larger regions of chromatin, a number of interesting studies have produced new insight into the compaction of chromatin architecture within a rigorous, *in vitro* setting. Nordenskiold and co-workers recently performed single molecule studies of a 165 kb mimic of chromatin, reconstituting chromatin from T4 phage DNA (165 kb) and recombinant human histone octamers. In this exciting study, the authors probed the compaction of chromatin as a function of magnesium and spermine ions using single molecule fluorescence microscopy and dynamic light scattering, identifying ~250–400 nm condensates, comparable to the compaction observed *in vivo*. In addition, the authors performed transmission electron microscopy (TEM) and atomic force microscopy to clearly identify single nucleosomes, beads-on-a-string formations and aggregrated nucleosomes [124]. Fierz and co-workers use single molecule FRET to measure the time scales of nucleosome-nucleosome stacking, revealing that even tightly packed nucleosomes undergo reshuffling of configurations, exhibiting a hierarchy of dynamics of micro- to milliseconds [125]. Specifically, they examine an array of twelve nucleosomes organized into three tetranucleosome units, where Alexa 568 donors and Alexa 647 acceptors are placed on the DNA of neighboring nucleosomes, directly measuring nucleosome-nucleosome stacking. Discrete tetranucleosome units exchange nucleosome stacking partners (register interconversion) on the order of hundreds of microseconds. Distorted and open configurations are also sampled. They examine compaction caused by HP1a, a factor that cross bridges H3K9me3-modified nucleosomes. When HP1α is added, causing even more compaction, significant dynamics persist. Dekker and co-workers used flow through microfluidic chambers to dynamically image the process of DNA loop extrusion by yeast condensing, extruding ~10kb of DNA at 1.5 kb/s using ATP hydrolysis[126]. Bulk FRET studies of show that the chromatin architectural factors, linker histone (H1) and MeCP2 (Rett Syndrome) produce compaction by trapping the nucleosomes in more tightly wrapped states[127]. In combination with restriction enzyme accessibility studies for 17-mer nucleosome arrays, the study suggests that linker histone and MeCP2 may create higher-order chromatin structure susceptible to remodeling by ISWI. In small angle X-ray scattering studies (SAXS), Luger and co-workers show that nucleosomes with extra-nucleosomal DNA engage additional binding sites in MeCP2, resulting in a compact higher-order complex[128]. Time resolved SAXS experiments by Pollack and co-workers examined salt-induced disassembly of nucleosome particles, demonstrating that histone protein dimers are released sequentially, with the first H2A-H2B dimer released only after the DNA has formed a teardrop-shaped conformer[129]. Lastly, a large number of single molecule studies

of nucleosomes have been performed, gaining insight into nucleosome wrapping, sliding, and dynamics, among other aspects of nucleosome function[130–133].

Conclusions: Outstanding issues and future outlook:

A wide variety of computational techniques have been used to capture the dynamics and mechanisms of nucleoprotein complexes, ranging from the highly detailed explicit solvent molecular dynamics simulations of nucleosomes and ribosomes to coarse-grained polymer bead models used to visualize Hi-C data for entire chromosomes. While the ribosome represents one of the most well-studied biophysical systems, where workers are computing free energies of transitions, chromosomes represent the next frontier, where emerging fundamental questions are arising. The vast array of diverse techniques provides one with a myriad of perspectives, whether it be global motions on long time scales or conformational changes of single residues that are crucial for biological function. Overall, computational methods allow one to synthesize a wide range of different experiments into a more coherent mechanism of the nucleoprotein complex. In one sense, movies generated by molecular simulation produce a more realistic view of macromolecular function because they include the constant background of small and large thermal fluctuations that give rise to conformational changes, painting a vivid picture of, for example, the stochastic Brownian motion required for ribosome conformational changes [134]. In contrast, movies accompanying X-ray crystallography or cryo-EM studies can sometimes be over simplified, showing (i) tractor-beam like behavior of one protein being mysteriously guided in a bee line to its target on a macromolecular complex, (ii) linear morphing between states with no fluctuations whatsoever, or (iii) flashing between two single snapshots. Inexpensive simulators, such as SMOG and others, provide a convenient method to visualize stochastic conformational changes [135].

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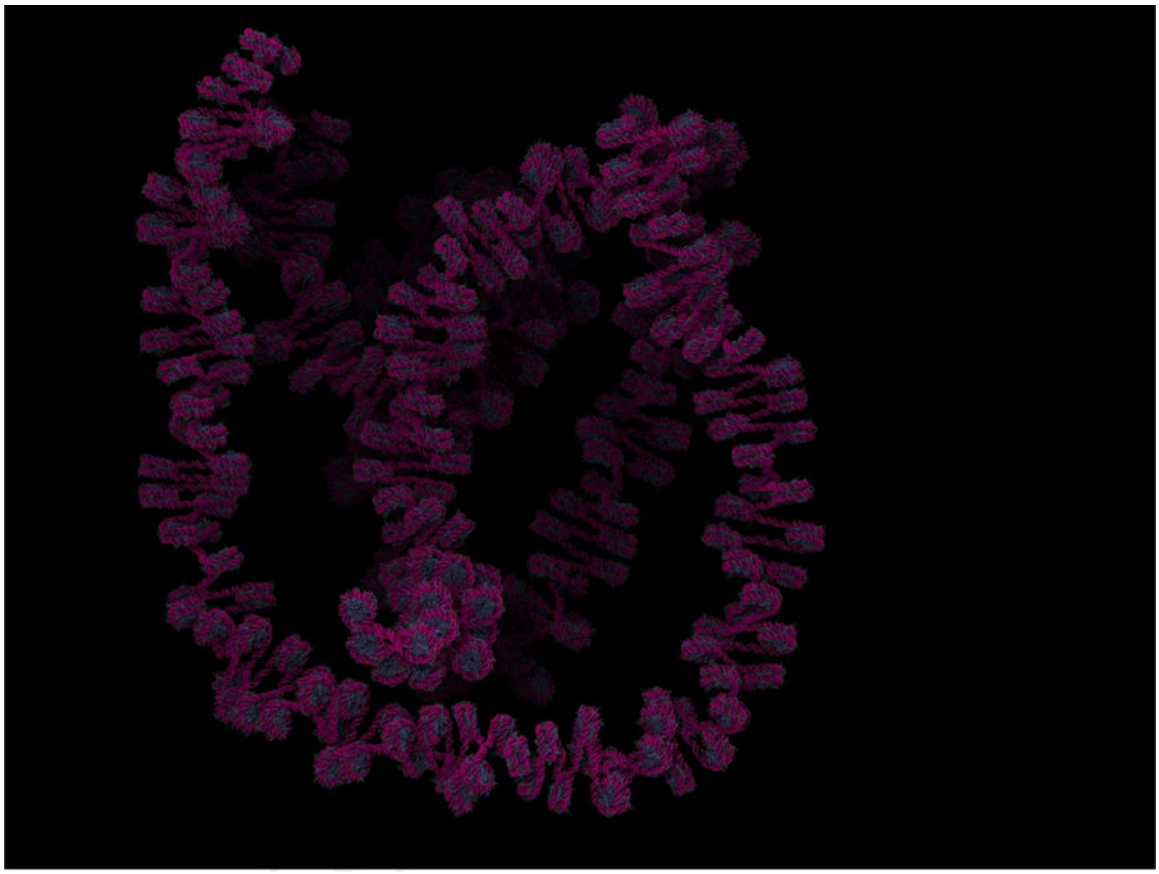

Figure 1.
Explicit solvent simulations of the GATA4 gene locus, including 427 nucleosomes, 83 kb and 1 billion atoms. Magenta, DNA; blue, proteins (histone octamers).