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Review

Condensed DNA: Condensing the concepts

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ABSTRACT

DNA is stored *in vivo* in a highly compact, so-called condensed phase, where gene regulatory processes are governed by the intricate interplay between different states of DNA compaction. These systems often have surprising properties, which one would not predict from classical concepts of dilute solutions. The mechanistic details of DNA packing are essential for its functioning, as revealed by the recent developments coming from biochemistry, electrostatics, statistical mechanics, and molecular and cell biology. Different aspects of condensed DNA behavior are linked to each other, but the links are often hidden in the bulk of experimental and theoretical details. Here we try to condense some of these concepts and provide interconnections between the different fields. After a brief description of main experimental features of DNA condensation inside viruses, bacteria, eukaryotes and the test tube, main theoretical approaches for the description of these systems are presented. We end up with an extended discussion of the role of DNA condensation in the context of gene regulation and mention potential applications of DNA condensation in gene therapy and biotechnology.

Contents

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1. Introduction

Storage and processing of genetic information encoded in DNA is governed by a number of compounds, which bind, bend, loop, modify DNA and assemble on the double helix, recognize each other and target new DNA binders (Fig. 1). These events are further complicated by the fact that they happen *in vivo* in a highly compact, so-called condensed DNA state. Scientists have been dealing with condensed DNA since the discovery of nucleic acids. However, only recently with the development of adequate tools for the single-molecule and whole-genome analysis, it has became possible to connect classical bulk experiments to mechanistic details of gene regulation *in vivo*. This has led to a number of new concepts and the reevaluation of some of the old ones. The purpose of this review is to provide what we believe are the most exciting concepts, which obviously does not reflect the whole body of the literature. For more extensive data-oriented literature overview see the recent books with the focus on DNA condensation *in vitro* (Dias and Lindman, 2008) or *in vivo* (Rippe, in press) and older reviews devoted to DNA condensation (Bloomfield, 1996, 1997; Gelbart et al., 2000; Hud and Vilfan, 2005; Schiessel, 2003; Strey et al., 1998; Vijayanathan et al., 2002; Yoshikawa, 2001; Yoshikawa and Yoshikawa, 2002). We will start with biological concepts arising from DNA packing in viruses, bacteria and eukaryotes, then proceed to DNA condensation *in vitro* and its theoretical modeling, and finally discuss the role of DNA condensation in the context of gene regulation in living systems and its potential biomedical applications.

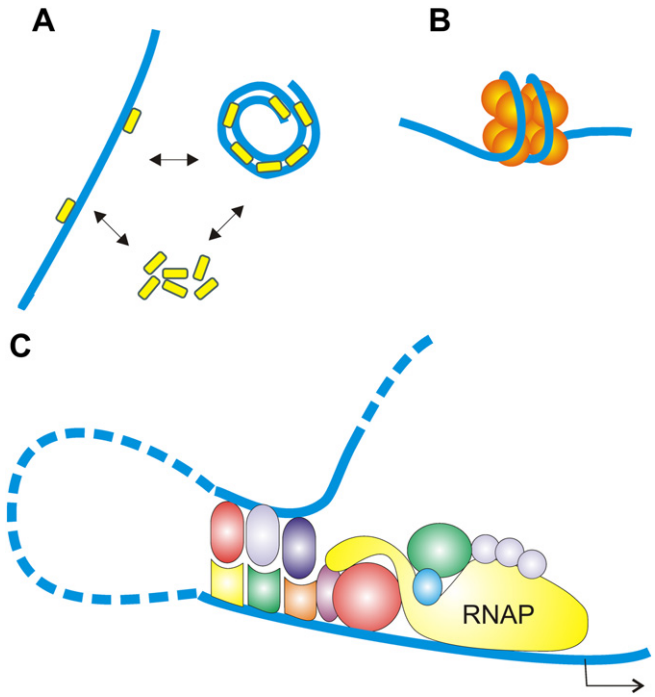

Fig. 1. Biological implications for DNA compaction. A) Small ligands (inorganic ions, polyamines, etc) may induce DNA condensation *in vitro*. This process is used to model DNA compaction in prokaryotes within the small volume of the bacterial nucleoid or viral capsid. B) In eukaryotes, DNA is wrapped around histone proteins to form the nucleosome. Further levels of compaction of the chromatin fiber are achieved with the help of divalent metal ions and proteins. C) Gene regulation in many cases involves DNA looping maintained by protein bridging at the promoter and enhancer regions. Precise spatial positioning of the DNA and DNA–DNA recognition might facilitate the multiprotein assembly and recruitment.

2. The concept of DNA condensation

DNA is a long and strongly charged heteropolymer. It bears on average one elementary negative charge per each 0.17 nm of the double helix. DNA diameter is about 2 nm, while the length of a stretched single-molecule may be up to several dozens of centimeters depending on the organism (Bloomfield et al., 2000). Many features of the DNA double helix contribute to its large stiffness, including the mechanical properties of the sugar–phosphate backbone, electrostatic repulsion between phosphates, stacking interactions between the bases of each individual strand, and strand–strand interactions (Guo et al., 2008). The measure of the DNA stiffness is the persistence length, which characterizes the length over which a tangent vector to the DNA axis becomes uncorrelated. The persistence length of the double-stranded DNA in physiological conditions is around 50 nm depending on the DNA sequence (Bloomfield et al., 2000; Brinkers et al., 2009; Zheng et al., 2010). Such a large persistence length makes DNA one of the stiffest natural polymers, yet this value is quite small in comparison with the typical DNA lengths. This means that at the distance much larger than the persistence length the DNA can be considered as a flexible rope, and on a short scale as a stiff rod. Like a garden hose, unpacked DNA would randomly occupy a much larger volume than when it is orderly packed. Mathematically, for a non-interacting flexible chain randomly diffusing in 3D, the end-to-end distance would scale as a square root of the polymer length. For real polymers such as DNA this gives only very rough estimate; what is important, is that the space available for the DNA *in vivo* is much smaller than the space that it would occupy in the case of a free diffusion in the solution. In order to cope with the volume constraints, DNA has a striking property to pack itself in the appropriate solution conditions with the help of ions and other molecules. Usually, DNA condensation is defined as “the collapse of extended DNA chains into compact, orderly particles containing only one or a few molecules” (Bloomfield, 1997). As detailed below, this definition applies to many situations *in vitro* and is also close to the definition of DNA condensation in bacteria as “adoption of relatively concentrated, compact state occupying a fraction of the volume available” (Zimmerman and Murphy, 1996). In eukaryotes, the DNA size and the number of other participating players are much larger, and a DNA molecule forms millions of ordered

nucleoprotein particles, the nucleosomes, which are just the first level of DNA packing, as detailed below. Thus, one can hardly develop a single definition for DNA condensation valid for all systems. Conceptually, it should be understood that DNA condensation refers to a concentrated macromolecular phase where neighboring DNA segments may be separated by just a few layers of solvent molecules. The local alignment of these segments is thus not the requirement, but rather a consequence of the condensed state.

3. DNA condensation in viruses

In viruses and bacteriophages, the DNA or RNA is surrounded by a protein capsid, sometimes further enveloped by a lipid membrane. Double-stranded DNA is stored inside the capsid in the form of a spool, which can have different types of coiling (Hud, 1995) leading to different types of liquid-crystalline packing (Earnshaw and Harrison, 1977; Hud and Downing, 2001; Knobler and Gelbart, 2009; Leforestier and Livolant, 2009). This packing can change from hexagonal to cholesteric to isotropic at different stages of the phage functioning (Leforestier and Livolant, 2010). Although the double helices are always locally aligned, the DNA inside viruses does not represent real liquid crystals, because it lacks fluidity. On the other hand, DNA condensed *in vitro*, e.g. with the help of polyamines which are also present in viruses, is both locally ordered and fluid (Sikorav et al., 1994). Highly symmetric DNA packing inside viruses is probably the only way to fill the small space of the symmetric viral capsid (Johnson and Chiu, 2007). When a virus is being assembled, motor proteins push the DNA inside the capsid, where it is stored under large pressures ~6 MPa (Evilevitch et al., 2008; Rickgauer et al., 2008; São-José et al., 2007). In order to infect the host cell, the virus needs to open up a small hole by a conformational transition in the portal gatekeeper proteins (Lhuillier et al., 2009). The DNA injection is then triggered by the differences in the osmotic pressure and ionic conditions, with the DNA ejecting as fast as 60 kbp/s (Grayson et al., 2007). The energy stored in the form of DNA compaction is enough to inject as much as 1/5 of the viral DNA before motor proteins start pushing the DNA (São-José et al., 2007). RNA packing in RNA-containing viruses is even more intricate: a recent analysis shows that the size of the optimally compacted RNA matches the size of the corresponding viral capsid, suggesting that there might be evolutionary pressure for the genome to have an appropriate size (Yoffe et al., 2008). Notably, organisms which do not have such strict packing constraints are easily increasing the genome size at the evolutionary timescale. Viral packing provides the most condensed state of genomic DNA. Scientists are trying to follow the Nature's way of delivering and releasing specifically synthesized nucleic acids for the purpose of gene therapy. Many effective DNA-packing strategies have been developed, but none as elegant as viruses.

4. DNA condensation in bacteria

Bacterial DNA is packed with the help of polyamines and proteins. Protein-associated DNA occupies about 1/4 of the intracellular volume forming a concentrated viscous phase with liquid-crystalline properties, called the nucleoid (Cunha et al., 2001; Wiggins et al., 2010). Similar DNA packaging exists also in chloroplasts (Sekine et al., 2002) and mitochondria (Friddle et al., 2004). Bacterial DNA is sometimes referred to as the bacterial chromosome (Saier, 2008). In fact, the bacterial nucleoid evolutionary represents an intermediate engineering solution between the protein-free DNA packing in viruses and protein-determined packing in eukaryotes (Luijsterburg et al., 2008). There are several main nucleoid-associated proteins, such as H–NS, HU, Fis, IHF and Dps, all of which contribute to DNA packing and also regulate gene expression (Dame, 2005; Pettijohn, 1988; Travers and Muskhelishvili, 2005). For example, H–NS has functions analogous to eukaryotic histones, while HU resembles eukaryotic high-mobility-group (HMG) proteins (Luijsterburg et al., 2008). Indeed, yeast HMGB proteins have been shown to be to some extent interchangeable with *Escherichia coli* HU proteins (Becker et al., 2008). In analogy to the eukaryotic chromatin, most of bacterial DNA is covered by H–NS and HU proteins, which bind cooperatively and form short protected DNA stretches (functionally analogous to eukaryotic nucleosomes) and larger DNA loops of ~10 kb length. The DNA in bacterial loops is confined to a small volume. The latter is achieved by coiling the loop and fixing the obtained superhelical structures by protein bridges. In such structures, the DNA is said to be in the supercoiled state. Supercoiling is another Nature's trick allowing energy storage combined with tight packing (Cozzarelli et al., 2006; Luijsterburg et al., 2008). The level of DNA packing in the bacterial nucleoid is also regulated by the macromolecular crowding, which is defined as excluded volume effects favoring compact molecular conformations (Zimmerman and Minton, 1993; Zimmerman and Murphy, 1996). However, nucleoid structure is determined not only by non-specific interactions. For example, H–NS proteins have a slight sequence-specificity, which adds even more to the analogy with eukaryotic histones (Fang and Rimsky, 2008; Navarre et al., 2006). Furthermore, a recent study has shown that specific bacterial genes are nonrandomly positioned in 3D within the nucleoid (Wiggins et al., 2010) in analogy with the concept of spatial positioning of genes in the eukaryotic genome (Lieberman-Aiden et al., 2009).

5. DNA condensation in eukaryotes

In comparison with bacteria or viruses, eukaryotic chromatin is the "state of the art" of DNA condensation, and also a large field of scientific efforts, which we will only briefly mention here. Eukaryotic DNA with a typical length of dozens of centimeters should be orderly packed to be readily accessible inside the micrometer-size nucleus. Thus DNA is always "condensed" in chromatin, but there are different states of DNA condensation. In primitive unicellular eukaryotes such as dinoflagellates, it is possible to distinguish liquid-crystalline chromosomal ordering similar to bacterial chromosomes, just with higher DNA density (Chow et al., 2010). However, this is the only exception in the eukaryotic world. In other eukaryotes, DNA is arranged in the cell nucleus with the help of histones (Van Holde, 1989). In this case, the basic level of DNA compaction is the nucleosome, where the double helix is wrapped around the histone octamer containing two copies of each histone H2A, H2B, H3 and H4. Linker histone H1 binds the DNA between nucleosomes and facilitates packaging of the 10 nm "beads on the string" nucleosomal chain into a more condensed 30 nm fiber (Rippe et al., 2008). Most of the time, between cell divisions, chromatin is optimized to allow easy access of transcription factors to active genes, which are characterized by a less compact structure called euchromatin, and to alleviate protein access in more tightly packed regions called heterochromatin. During the cell division, chromatin compaction increases even more to form the classical chromosomes, which can cope with large mechanical forces dragging them into each of the two daughter cells (Van Holde, 1989). The transitions between different states of chromatin compaction are regulated by the dynamic exchange of histones, as well as other proteins such as HMG-proteins competing for DNA binding with linker histones (Gerlitz et al., 2009), HP1 proteins recruited by the nucleosomal histone tails (Müller et al., 2009) and larger players such as CTCF proteins defining the boundaries between the regions with different nucleosome

arrangement (Ohlsson et al., 2010) and cohesines linking sister chromatids in meiosis (Suja and Barbero, 2009), to name just a few. Furthermore, specific energy-dependent molecular motors, so-called chromatin remodelers, reorder chromatin following the cell cycle, cell differentiation and external signals (Corpet and Almouzni, 2009). All transitions between the states of DNA compaction are precisely controlled. Damaging the integrity of DNA packing is lethal to the cell. Although morphological changes in chromatin during apoptosis (programmed cell death) are also described by the word "condensation" (Widlak et al., 2002), this transition is accompanied by DNA fragmentation as opposed to the reversible DNA condensation occurring in the normal cell. Several anticancer drugs also act through crosslinking the DNA, looping it and establishing condensed untranscribed structures (Hou et al., 2009; Kida et al., 2010). Transitions between different states of DNA compaction *in vivo* regulate a number of processes, from viral invasion to the cell cycle, differentiation, and apoptosis. Before we proceed to these biological processes, we have to make a step back and learn the basic physical properties of DNA condensation *in vitro*.

6. DNA condensation *in vitro*

6.1. Experimental methods

Most of our knowledge about condensed DNA states comes from comparatively simple *in vitro* experiments started in the 1970s (Gosule and Shellman, 1976; Lerman, 1971). In such experiments, DNA is compacted by adding different condensing agents, from simple inorganic ions to large macromolecules, which represent important model systems to understand DNA functioning *in vivo* and also to achieve controlled drug delivery in gene therapy. During four decades of such experiments, DNA condensation has been studied using a variety of methods including sedimentation (Jary and Sikorav, 1999), light scattering (Vijayanathan et al., 2001; Wilson and Bloomfield, 1979), viscometry (Slita et al., 2007; Slonitskii and Kuptsov, 1989), osmotic equilibrium (Parsegian et al., 2000; Strey et al., 1998), IR, UV and Raman spectroscopy (Marty et al., 2009), as well as electron microscopy (Hud and Vilfan, 2005) and atomic force microscopy (Hansma et al., 2004). More recently, capillary electrophoresis techniques have been added to the bulk experiments (Keyser et al., 2010). Today one can also use single-molecule optical and magnetic tweezers (Baumann et al., 2000; Besteman et al., 2007; Chien et al., 2007; Dias and Lindman, 2008; Todd et al., 2008).

6.2. Condensing agents

DNA condensation can be induced *in vitro* either by applying external force to bring the double helices together, or by inducing attractive interactions between the DNA segments. The former can be achieved e.g. with the help of the osmotic pressure exerted by crowding polymers, as is done in the case of the ψ-DNA compacted by adding neutral polymers in the presence of monovalent salts (Greek letter "psi" stands for "polymer-and salt-induced") (Evdokimov et al., 1972; Lerman, 1971). In this case, the forces pushing the double helices together are coming from entropic random collisions with the crowding polymers surrounding DNA condensates, and salt is required to neutralize DNA charges and decrease DNA–DNA repulsion. The second possibility can be realized by inducing attractive interactions between the DNA segments by multivalent cationic charged ligands (Gosule and Shellman, 1976), as detailed in the following sections. More exotic ways to induce attraction between DNA molecules also exist, including e.g. an external electrical field alternating at a certain frequency (Bruinsma and Riehn, 2009). However, typical biologically motivated DNA condensing agents are either neutral polymers such as polyethylene glycol plus Na^+, or multivalent counterions (ligands).

In water solutions, DNA condensation usually requires counterions with charge 3 + or higher (Bloomfield, 1996, 1997). Among typical ligands used in experiments are trivalent metal ions and inorganic cations such as $Co(NH_3)_6^{3+}$ (Kankia et al., 2001), naturally occurring polyamines and their analogs (Nayvelt et al., 2010), protamines (Balhorn, 2007), natural and synthetic peptides (Korolev et al., 2009; Saccardo et al., 2009), lipids and liposomes (Rao, 2010), bacterial nucleoid-associated proteins and eukaryotic chromatin proteins. Monovalent counterions such as Na^+ cannot induce DNA condensation unless under additional osmotic pressure exerted e.g. by neutral polymers such as PEG (Lerman, 1971; Parsegian et al., 2000; Zimmerman and Minton, 1993). Divalent metal ions provide a boundary case. They cannot induce condensation of linear DNA molecules in water solutions, but they can do so in the presence of lipids that partition DNA molecules in lamellar sandwich-like structures (Harries et al., 1998; Koltover et al., 2000; Mengistu et al., 2009), or under special conditions if the DNA is circular. In the latter case, DNA supercoiling is a factor favoring DNA condensation as suggested by experimental observations that Mn^{2+} is able to induce condensation of the circular but not linear DNA (Ma and Bloomfield, 1994), the conclusion also supported by the Brownian Dynamics simulations (Sottas et al., 1999). Not all metal ions of the same charge are equally effective: transition metals such as Mn^{2+}, which can interact both with DNA phosphates (electrostatically) and bases (e.g. forming chelate complexes) are stronger condensing agents in comparison with alkali metals, which can interact only with DNA phosphates. Similar considerations apply also to more complex ions such as divalent amines: their condensing efficiency strongly depends on the structure and the ability to form DNA–DNA bridges (Saminathan et al., 1999). Alcohols and condensing ligands may act synergistically to locally destabilize the double helix, permitting DNA foldbacks that can lead to a higher proportion of rod-like condensates (Bloomfield, 1996). Temperature elevation can help aggregate DNA in the presence of divalent ions (Andrushchenko et al., 2003; Bloomfield, 1996, 1997). A recent study has shown a reversible condensation of T4 genomic DNA in solutions of poly(N-isopropylacrylamide) upon a temperature increase from 30 to 35 °C (Chen et al., 2010).

6.3. Morphologies of condensed DNA

Upon addition of critical concentrations of condensing ligands, double-stranded DNA molecules condense from a random coil into toroids, rods, or more sophisticated structures (Bloomfield, 1997). The morphology of the condensates depends on the solution properties and condensing agent structure (Bloomfield, 1996, 1997). Depending on the DNA length, DNA condensation may happen either as a monomolecular collapse (Post and Zimm, 1979; Widom and Baldwin, 1983) or as a multimolecular aggregation (Post and Zimm, 1982). On the other hand, DNA molecules shorter than the persistence length form ordered liquid-crystalline phases (Rill, 1986; Schellman and Parthasarathy, 1984; Sikorav et al., 1994). With the help of specifically designed metallo-supramolecular cylinders, DNA coiling around the nucleosome core can be mimicked (Meistermann et al., 2002). Lipids or liposomes condense DNA in well-defined small particles, which can be used for the purpose of gene delivery (Rao, 2010; Vijayanathan et al., 2002). It should be noted, that DNA condensation is in many cases associated with precipitation of the condensed particles or aggregates. On the other hand, DNA precipitation by itself, e.g. the one achieved by adding large quantities of ethanol or a similar solvent as in classical DNA extraction techniques, is usually not called condensation.

6.4. Reentrant effects

Experimentally, DNA condensates are stable within a large interval of condensing ligand concentrations. If one continues increasing the ligand concentration, DNA condensation is followed by a reverse transition when the aggregates resolubilize (Pelta et al., 1996; Raspaud et al., 1998; Saminathan et al., 1999). In the case of a long DNA, resolubilization is associated with decondensation of individual molecules (Chien et al., 2007; Jary and Sikorav, 1999; Murayama et al., 2003). The effect of reentrant condensation has been observed for short or long DNA molecules, single- or double-stranded DNA, small or high DNA concentrations. Reentrant condensation may also be essential for the functioning of the eukaryotic chromatin (Poirier et al., 2002) and is conceptually related to the reentrant effect of DNA–protein–DNA bridge assembly and disassembly in gene regulation (Vilar and Saiz, 2006). The corresponding bell-shaped condensation–decondensation curves coupled to different biochemical processes have attracted much attention of the biophysical community (Chien et al., 2007; Murayama et al., 2003; Raspaud et al., 1998; Saminathan et al., 1999; Sikorav and Church, 1991; Sikorav et al., 1994; Teif, 2005; Todd and Rau, 2008; Yang and Rau, 2005).

7. Insights from physics

7.1. The coil–globule transition

Condensation of long double-helical DNAs is a sharp phase transition, which takes place within a narrow interval of ligand concentrations (Bloomfield, 1996, 1997; Yoshikawa et al., 1996). Unlike protein folding, the general features of the DNA coil–globule transition such as the topology of the condensate are mainly determined by the average polymer and solution properties (DNA length, concentration, solution content and temperature) and not by the DNA sequence. On the other hand, the DNA sequence determines local interactions and recognition between the double helices in the condensed DNA phase (Kornyshev and Leikin, 1998; Sitko et al., 2003). The thermodynamic basis for the coil–globule transitions was set by the classical polymer theories (Birshtein and Ptitsyn, 1964; Flory, 1969) and adopted later for DNA condensation (Bloomfield, 1997; Grosberg and Zhestkov, 1985, 1986; Grosberg and Khokhlov, 1994; Post and Zimm, 1979, 1982; Yoshikawa et al., 1996). For stiff long polymers, theory predicts that DNA condensation is a first-order transition. High stiffness of the DNA double helix is due to both its internal properties (sugar–phosphate backbone with stacked base pairs) and its charge (like-charged phosphates repel each other and resist DNA bending). Single-molecule microscopy has confirmed that DNA condensation appears either to be an all-or-none transition for a single long DNA molecule, or a continuous transition when an ensemble of DNA molecules is considered (Yoshikawa et al., 1996).

7.2. Hydration forces

Since the double helices come very closely to each other in the condensed phase, this leads to the restructuring of water molecules, which gives rise to the so-called hydration forces (Gelbart et al., 2000; Parsegian et al., 2000; Strey et al., 1998). Each water molecule (as well as many other molecules dissolved in the water) represents a dipole, which can be statistically oriented in the electrical field perturbed by the neighboring surface of the DNA. Such ordering would decrease exponentially with the distance from the DNA surface. Dipoles would predominantly orient in the solution perpendicular to the charged surface (Maset and Bohinc, 2007). Several approached allow one to study surface-induced structural perturbation of the solvent. For example, Mengistu et al. have incorporated a solvent of interacting Langevin dipoles into the PB theory (Mengistu et al., 2009). Ruckenstein et al. have showed that the solvent polarization spatially decays with increasing distance from the charged surface (Ruckenstein and Manciu, 2002). The influence of a finite volume of ions and water molecules was also studied. In this case the dielectric permittivity profile close to the charged surface is mainly determined by two mechanisms, i.e. the depletion of water dipoles at the charged surface due to accumulation and of counterions and decreased orientational ordering of water dipoles as a function of increased distance from the charged surface (Gavryushov, 2009; Iglic et al., 2010). In addition to water restructuring, the counterions dissolved in the water also rearrange in the vicinity of the charged DNA molecule, which gives rise to the counterion-correlated attraction discussed in the next sections. Despite many experimental efforts and theoretical studies the relative contributions of these constituents of attractive interactions still require a clarification (Todd et al., 2008).

7.3. Counterion condensation

DNA is a highly charged molecule, which cannot exist in solution without other ions. Although the abbreviation “DNA” means deoxyribonucleic *acid*, usually DNA comes as a *salt* of Na^+ or other alkali metals. Physiological solutions also contain large amounts of divalent metal ions, which are essential for functioning of enzymes and play structural roles in DNA, RNA and proteins. Finally, the DNA is surrounded by a variety of other charged molecules, from small polyamines to proteins. Most electrostatic approaches treat DNA counterions as point-like, sphere-like or rod-like, but real multivalent ions and molecules possess an internal structure with spatially distributed charges. The simplest examples of such ions are spermidine^{3+} and spermine^{4+} – naturally occurring polyamines, which are flexible linear molecules widely used as DNA condensing agents (Bloomfield, 1997; Gelbart et al., 2000). The distribution of multivalent ions in aqueous solutions close to the macroion is mainly determined by the competition between electrostatic interactions within the system and the entropy of the constituents in the solution. At a thermodynamic equilibrium the counterions are attracted to the charged surface, while co-ions are depleted from this region, and a diffuse electric double layer is created (McLaughlin, 1989).

In 1960s Gerald Manning described some of the properties of the ionic cloud around a charged cylindrical surface representing the polyelectrolyte in solution (Manning, 1969). Above a critical surface charge density, the counterions condense on the cylinder and reduce its charge density down to the critical value (Grosberg et al., 2002). Counterion condensation is the consequence of the victory of Coulomb potential energy over the entropy. In the Manning picture the condensed layer of counterions is limited to a macroscopically small region near the charged cylinder. The Manning condensation theory holds only for an infinitely long cylinder and low concentrations. Surprisingly, it has a number of successful applications even when these conditions are violated (Manning and Ray, 1998).

As follows from the counterion condensation concept, a ligand binding to the DNA has to replace several monovalent ions from the Manning layer. Therefore protein–DNA interactions depend on the concentration of the monovalent salt. The equation of Record and coauthors predicts the following logarithmic dependence (Record et al., 1978): $\partial(\ln(K))/\partial(\ln[Na^+]) = -\varphi \cdot Z$, where K is the binding constant of a protein or multivalent ligand of charge Z, $[Na^+]$ is the Na^+ concentration in solution, φ equals to the number of thermodynamically released Na^+ ions per phosphate upon ligand binding ($\varphi \approx 0.88$ for linear helical DNA). More advanced solutions to this

problem are also available in the literature (Rouzina and Bloomfield, 1997) taking into account e.g. divalent counterions, but they do not change the main trend. The logarithmic dependence on the counterion concentration is also maintained in the condensed DNA state (Teif, 2005). However, the number of thermodynamically released Na^+ ions is different for different DNA phases and should be determined experimentally or calculated by a more sophisticated Poisson–Boltzmann equation (Burak et al., 2003).

An alternative to the simplified Manning description is the Poisson–Boltzmann (PB) theory (Evans and Wennerström, 1994). In this theory the charges are taken as point-like; the only interactions to be considered between the charges are the Coulombic interactions. The surfaces are uniformly charged. The aqueous solution is considered as a continuous medium with the dielectric constant of 78. In this mean field theory the charge correlations and short-range interactions between charged particles are neglected. The distribution of the ions is given by the competition between the electrostatic interactions and the entropy of the ions in the solution which tends to disperse them. The electrostatics of the system is described by the Poisson equation whereas the ion number densities in the solution obey the Boltzmann distribution. This gives the Poisson–Boltzmann equation for the electrostatic potential. The boundary conditions (Evans and Wennerström, 1994; McLaughlin, 1989) demand a neutral overall charge for the system. PB theory does not predict attractive interactions between like-charged surfaces.

7.4. Counterion correlations

In order to understand DNA–DNA attraction, one has to take into account correlations between counterions. The fact that inter-ionic correlations can lead to attraction was realized early by Kirkwood and Shumaker (Kirkwood and Shumaker, 1952) and Oosawa (Oosawa, 1968), later studied by Monte-Carlo simulations (Guldbrand et al., 1986), and various other methods. A simple interpretation of the mechanism that leads to attraction can be given at zero temperature where counterions condense onto the charged surface. Coulomb repulsion between condensed counterions produces an alternation of positive and negative charges at the surface. Two such opposing patterns adjust complementarily to each other and give rise to short-range attractive forces (Grosberg et al., 2002; Levin, 2002) (Fig. 2A). The attraction between like-charged surfaces is also found in integral equation theories (Kjellander et al., 1992; Kjellander and Marčelja, 1984), modified Poisson–Boltzmann theories (Forsman, 2004; Outhwaite and Bhuiyan, 1983, 1991; Vlachy, 1999) and field theoretical methods (Moreira and Netz, 2001; Naji et al., 2004). Also, perturbative expansions around the PB solution (Attard et al., 1988b; Netz and Orland, 2000; Podgornik, 1990) and density functional theory (Diehl et al., 1999; Stevens and Robbins, 1990) are able to predict the existence of attractive interactions. At distances between the polymer surfaces such that the two double layers weakly overlap, the attractive interaction is obtained within the approximation of two-dimensional counterion layers by including in-plane Gaussian fluctuations (Attard et al., 1987, 1988a; Lau and Pincus, 2002; Lukatsky and Safran, 1999; Pincus and Safran, 1998) or plasmon fluctuations at zero (Lau et al., 2000) and at non-zero temperatures (Lau et al., 2001). Fluctuation-induced interactions between macroscopic objects constitute quite a general phenomenon, which takes place if objects couple to fluctuating background field (Kardar and Golestanian, 1999). Dielectric discontinuities have been taken into account by means of image charges. It was shown that image charges increase the attraction between like highly charged surfaces (Bratko et al., 1986). Forces between like-charged surfaces

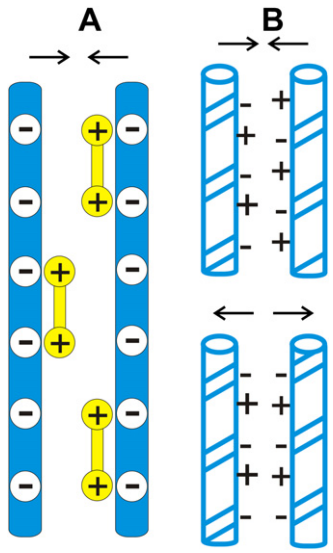

Fig. 2. Illustration of DNA–DNA interactions mediated by counterion correlations. A) DNA–DNA attraction arises due to correlated arrangements of bound ligands. B) The counterions bind DNA in a correlated way, as in Figure A, but now the helical nature of DNA is taken into account. The segments of DNA helices, which are in register, attract each other, while those out of register repel each other.

in the presence of polyelectrolytes were also considered (Åkesson et al., 1989; Miklavic et al., 1990). It was shown that strong attractive forces between charged surfaces were the result of the stretching of chains spanning the slit between the surfaces – the so-called bridging (Podgornik et al., 1995). It is strongest at a surface separation equal to an average monomer–monomer bond length (Åkesson et al., 1989). The studies were extended by the presence of simple salt of monovalent ions (Woodward et al., 1994). Fully flexible chains as well as semi-flexible chains have been introduced (Akinchina and Linse, 2003). Turesson and coauthors have considered charged stiff polyelectrolytes and their role in the inter-surface interactions (Turesson et al., 2006). They stated that in the limit of infinitely stiff chains the bridging attraction is lost and is replaced by a strong correlation attraction at short distances.

7.5. Counterion bridging

The above models deal with point-like charges or polyelectrolytes, while another biologically important type of ligands is a rod-like or a dumbbell-like particle with two individual point-charges separated by a fixed distance (Bohinc et al., 2004; Kim et al., 2008; Maset and Bohinc, 2007; Maset et al., 2009; May et al., 2008). The rod-like approximation could be relevant not only for small counterions, but also, as a first-order approximation, for DNA bridging proteins, e.g. H–NS and HU in bacteria, although these interactions are at least partially sequence-specific (Navarre et al., 2006). In the presence of rod-like ligands, the energetically most favorable distance between the charged surfaces of two DNA molecules would correspond then to the length of such a rod-like particle. At this distance, there are two most probable orientations of rod-like particles: either oriented in parallel or perpendicular to the charged surfaces (see Fig. 3). Other orientations are less pronounced. The parallel and perpendicular orientations indicate the tendency for the positive protein charges to be in contact with the negatively charged DNA surface. At high surface charge densities both orientations are more pronounced. The particles, which are oriented perpendicular to the charged surfaces, connect the surfaces and act as bridges. This bridging mechanism can lead to

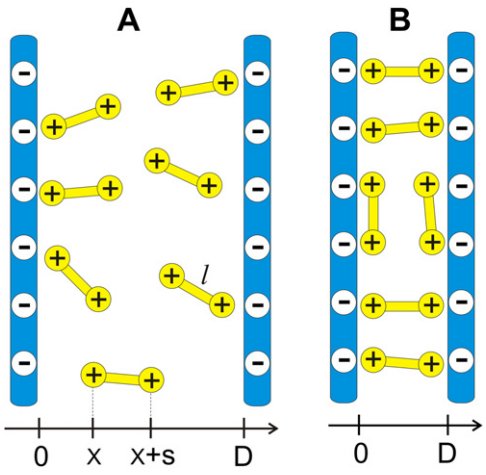

Fig. 3. Illustration of DNA bridging by rod-like counterions. (A) Two negatively charged surfaces are immersed in an electrolyte solution that contains positively charged rod-like divalent counterions. (B) The ions preferentially orient either parallel or perpendicular to the macroion surfaces. Those aligning perpendicular give rise to the bridging effect.

attractive interactions between DNA's as confirmed by Monte-Carlo simulations (Kim et al., 2008; Maset et al., 2009). At larger DNA–DNA separations, rod-like molecules tend to stay parallel to the charged surfaces and no bridging occurs (Fig. 3). Recently, the correlations between rod-like counterions embedded in the solution between two like-charged surfaces was studied (Hatlo et al., 2010). In the weak coupling regime, the interactions are only repulsive. At slightly higher couplings, there is a minimum in the variation of the free energy with distance at approximately the bond length of the dimers, which arises from bridging conformations of the dimmers. The bridging mechanism for sufficiently long dimers is confirmed, whereas at high electrostatic couplings charge correlations contribute to the attraction. Recently the influence of added monovalent salt on the bridging mechanism was studied (Bohinc et al., 2011).

7.6. DNA charge reversal

In nucleoprotein complexes containing DNA and histones, the negative DNA charge can, and in many cases is reversed by the positive charges of the bound proteins (Korolev et al., 2007). It is also quite easy to reverse the DNA charge by basic lipids or proteins *in vitro*. That the DNA charge may be reversed by diffusely bound small counterions is not that trivial. Several years ago, DNA charge reversal by counterions has been predicted theoretically (Shklovskii, 1999), and recent experiments have confirmed that simple polyamines may indeed induce DNA charge reversal (Besteman et al., 2007). DNA charge reversal by counterions can be understood with the help of the concept of charge fractionalization (Grosberg et al., 2002). It is based on an idea that long flexible counterions contacting DNA are not necessarily bound at a stoichiometric equilibrium, but may form brushes, etc, and their total charge can be more than the bare DNA charge (Fig. 5B).

7.7. DNA–DNA recognition

In a series of theoretical works of Kornyshev, Leikin and coauthors, it has been shown that the DNA helical symmetry can give rise to sequence-dependent DNA–DNA interactions (Kornyshev et al., 2007; Kornyshev and Leikin, 1998, 1999). For

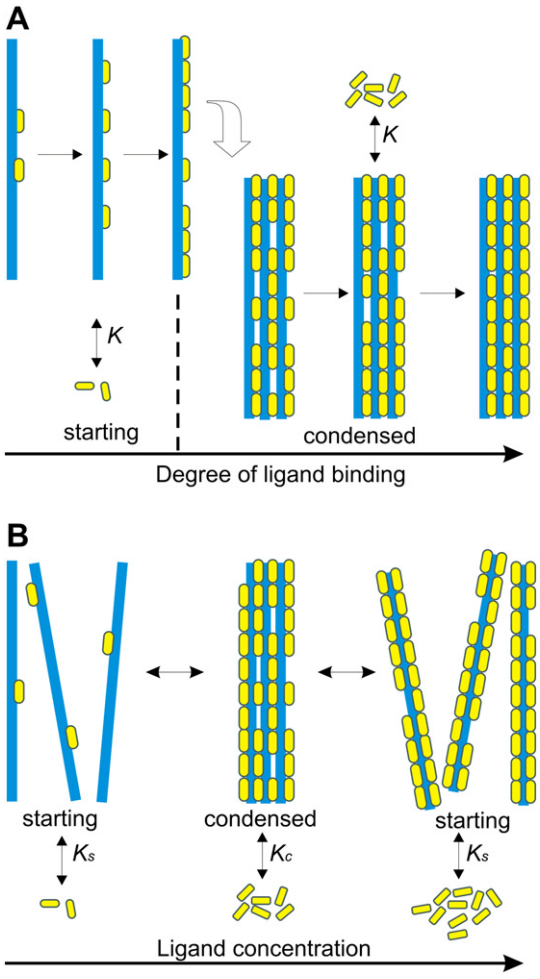

Fig. 4. Lattice models for ligand-induced DNA condensation. A) The threshold degree of binding model. DNA condenses when the degree of binding reaches a certain threshold value. B) The two-state lattice model for ligand-induced DNA condensation. The condensed and uncondensed DNA states bind ligands with different binding constants and stoichiometries. Ligand binding shifts the thermodynamic equilibrium, and at high enough ligand concentrations the condensed phase is favored. At much higher concentrations the condensates redissolve, because uncondensed DNA binds more ligands at saturation.

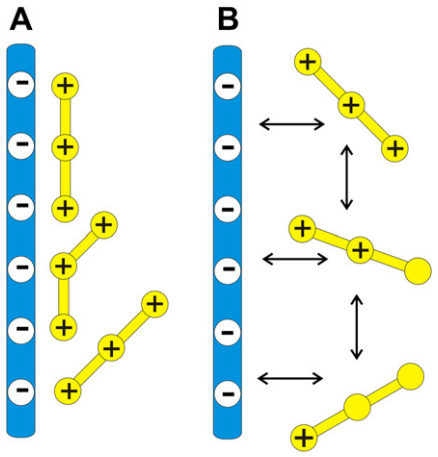

Fig. 5. Electrostatic mechanisms for DNA resolubilization. A) Incomplete ion dissociation. At different ionic strength multivalent salts may change their dissociation states. Competition for DNA binding between counterions of different charge determines whether DNA is condensed or not. B) DNA charge reversal by bound multivalent counterions.

homopolymers, this simply means that the DNA segments, which are in phase, are attracted, and those, which are out of phase, are repelled from each other (Fig. 2B). For heteropolymers, this means, that the forces between the segments of the double helices in addition depend on the DNA sequence. Recently it has been shown, that this mechanism indeed works *in vitro* (Baldwin et al., 2008). In these experiments, water–PEG–DNA–salt solutions were used to study the behavior of DNA condensates, spheroids containing short 176 bp double-stranded DNA molecules marked by different fluorescent dyes. Starting from the initial random distribution of DNAs in the spheroids, they have finally ended up with the color segregation indicating that double-stranded molecules were able to distinguish the sequence of their neighbors. The recognition of two double helices should be distinguished from the well-known concept of strand–strand recognition inside the double helix. The new concept of recognition of the double helices could explain precise spatial positioning of the DNA segments in the genome. A pair of functionally related DNA regions situated far from each other along the DNA can be positioned close to each other in 3D with the help of DNA–DNA interactions prior to sequence-specific protein bridging as is required e.g. in genetic recombination (Barzel and Kupiec, 2008).

7.8. Computer simulations

One way to proceed further to more complex systems is computer simulations. In the first models, only the DNA and counterions have been considered in order to understand the interaction forces. Monte-Carlo (MC) simulations confirmed the existence of attraction between equally charged surfaces immersed into the solution containing divalent ions in the limit of high surface charge density (Bratko et al., 1986; Grønbech-Jensen et al., 1997; Guldbrand et al., 1984, 1986; Kjellander and Marčelja, 1985). These and other (Moreira and Netz, 2001; Reščič and Linse, 2000; Svensson and Jönsson, 1984) MC simulations showed that attractive interactions between equally charged surfaces may arise for sufficiently high surface charge density, low temperature, low solution permittivity and multivalent counterions. Other model systems include surfaces with discrete charge distributions in a solution of multivalent ions (Khan et al., 2005), and like-charged surfaces in a solution of rod-like ions (Bohinc et al., 2004; May et al., 2008; Maset et al., 2009). Such simplified model systems continue to be the focus of systematic studies (Grime et al., 2010; Kim et al., 2008; Luan and Aksimentiev, 2008). One can also start from the known crystallographic structures and study the partitioning of small molecules and ions around the DNA double helix (Korolev et al., 2004) or between the nucleosomes (Yang et al., 2009). Nucleosomal DNA looping, unwrapping and stretching, as well as nucleosome–nucleosome interactions is now a subject of extensive studies using computer simulations (Diesinger and Heermann, 2009; Kepper et al., 2008; Korolev et al., 2010; Sereda and Bishop, 2010; Stehr et al., 2010; Wocjan et al., 2009).

7.9. Lattice models for chromatin

Available computer resources set an upper limit for the time/space resolution and the number of molecules in traditional computer simulations. Therefore, in order to study the multiplayer combinatorial protein binding encountered in gene regulation, one has to use more coarse-grained models. Within this framework, lattice models of statistical mechanics allow one to take into account both the condensed phase features and multiplayer complexity encountered in gene regulation. This approach is based on the accurate enumeration of all microstates allowed for each individual DNA unit (nucleotide, base pair, etc), each characterized by an individual statistical weight composed of the geometrical and thermodynamic parameters. The electrostatic contributions may be cast into the sequence- and content-specific binding constants. Fig. 6 shows basic lattice models for protein–DNA–drug binding, ranging from the sequence-specific binding of a single protein (Fig. 6A) to competition of several protein types (Fig. 6B) and multilayer protein binding (Fig. 6F). DNA loops formed by proteins can be divided into two calculable classes: the short loops which may be calculated directly taking into account all interactions within the loop (Fig. 6G), and large loops, which "forget" what happens deep inside the loop and only depend on the protein bridging at the loop start and end (Fig. 6F) (Teif, 2007).

Basic principles allowing formulating and solving statistical–mechanical DNA lattice-binding models have been described several decades ago (Hill, 1985; Poland, 1979). In mathematics, this field is known as "sequential adsorption" as well as "car parking" problems (Evans, 1993). In computational biology such models are formulated with the help of Markov chains (e.g. Hidden Markov Models, HMM), which go back to the works of the mathematician Andrei Markov (Markov, 1907). In biophysics they are usually known as Ising models historically arising from the work of Ernst Ising on the theory of ferromagnetism (Ising, 1925). Lattice models for DNA–ligand binding may be roughly divided into four classes: direct combinatorial methods (McGhee and von Hippel, 1974; Nechipurenko and Gursky, 1986; Rouzina and Bloomfield, 1997;

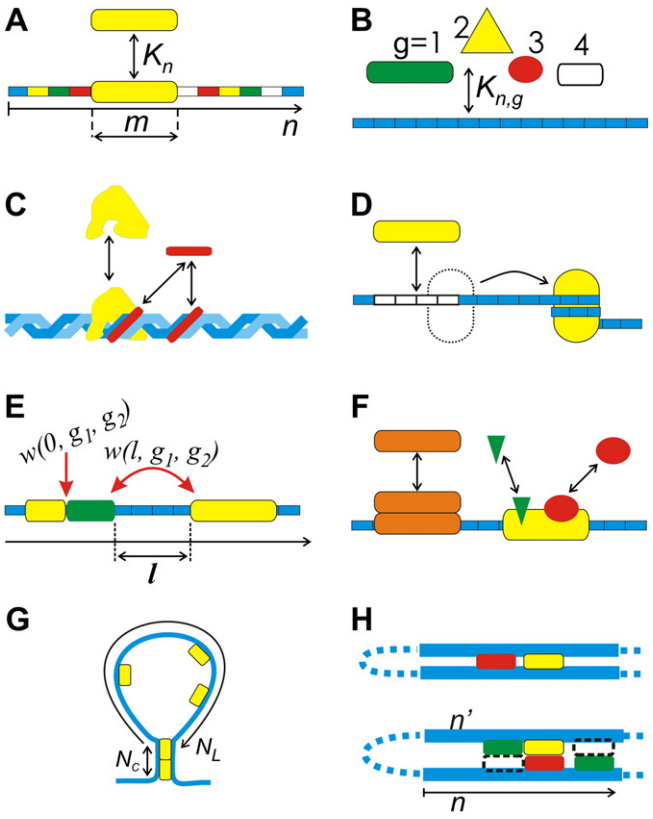

Fig. 6. Basic lattice models for DNA–protein–drug binding. A) Sequence-specific binding of a single protein. B) Competitive binding of several protein spices or several modes of binding of the same protein. C) Protein/small drug competition. D) Protein/nucleosome competition. E) Cooperative binding (includes contact interactions between the proteins bound to adjacent DNA units, and long-range interactions between the proteins separated by *l* DNA units). F) Multilayer binding (includes piggy-back binding of small ligands on the backs of DNA-bound proteins, and the multilayer assembly of proteins of similar size). G) Small DNA loops induced by protein cross-linking. H) Large DNA loops maintained by protein bridging.

Tsodikov et al., 2001; Wolfe and Meehan, 1992; Zasedatelev et al., 1971), generating functions methods (Chen, 1990; Lifson, 1964; Schellman, 1974), recurrent relations methods (also known as dynamical programming) (Granek and Clarke, 2005; Gurskii and Zasedatelev, 1978; Laurila et al., 2009; Nechipurenko et al., 2005; Segal et al., 2006; Wasson and Hartemink, 2009) and transfer matrix methods (Akhrem et al., 1985; Chen, 1987, 2004; Crothers, 1968; Di Cera and Kong, 1996; Gurskii et al., 1972; Hill, 1957; Teif, 2007; Teif et al., 2010b). The difference between computational algorithms lies mostly in the way they enumerate the states of the system and assign corresponding weights, as detailed in a recent review (Teif and Rippe, 2010).

In studying DNA condensation using lattice-binding approaches, we have to consider at least two coupled events: the DNA–ligand binding and DNA condensation. A third related event, the melting of the double helix, also comprises a process thermodynamically coupled to multivalent release and DNA condensation (Cherstvy and Kornyshev, 2005). Lattice models of DNA melting (Akhrem et al., 1985; Poland, 1979) could be easily integrated with lattice descriptions of DNA condensation as long as they are formulated in the frame of the same mathematical formalism (Teif, 2007), but usually only two coupled binding events are considered. The "threshold degree of binding" model assumes that ligand–DNA binding is non-cooperative and does not depend on DNA compaction (Nechipurenko and Gurskii, 2003; Porschke, 1984) (Fig. 4A). Here, DNA condenses when the degree of binding reaches a certain threshold value. On the other hand, the "two-state" models (Fig. 4B) assume that DNA may be in two states, starting or condensed, and the transition between the two states is governed by the modes of ligand binding to each state (Lando and Teif, 2002; Porschke, 1991; Sivolob and Khrapunov, 1989; Teif, 2005; Teif and Lando, 2001a; Wittmer et al., 1995). In the case of non-specific reversible binding, DNA condensation/decondensation may even be described analytically (Teif, 2005). Lattice approaches also allow descriptions of DNA condensation caused by irreversible binding (Maltsev et al., 2006), and a specific case of binding of flexible branched oligopolymers (Horsky, 2008; Nishio and Shimizu, 2005).

In the frame of the lattice models, DNA condensation at small ligand concentrations is believed to be due to establishing attractive DNA–DNA interactions, while the decondensation at high concentrations is thought to be caused by stoichiometric effects. These effects could be due to both electrostatic and entropic contributions. Electrostatic arguments include the elimination of ionic correlations (Allahyarov et al., 2004) or the DNA charge reversal (Grosberg et al., 2002). The entropic argument is that uncondensed DNA molecules can bind more ligands and have more possibilities for ligand rearrangements along the DNA (Lando and Teif, 2002; Porschke, 1991; Teif, 2005). The latter mechanism is likely to be the case for protein-induced DNA compaction/decompaction, while electrostatic mechanisms prevail in the case of small cationic ligands. In many cases, DNA decondensation at high ligand concentrations could be due to the incomplete counterion dissociation. This concept is explained in Fig. 5A. Consider a trivalent ion spermidine (Spd^{3+}), which can exist in solution in several forms depending on its concentration, e.g. Spd^{3+} and $SpdCl^{2+}$, each one with different DNA-binding properties. The DNA resolubilization at high ligand concentrations is then determined by the competition between counterions of different charges (Todd and Rau, 2008; Yang and Rau, 2005). For example, if divalent spermidine ions outcompete trivalent ones, then the DNA would be mainly bound by divalent ions, which cannot induce condensation, and that would lead to the decondensation. For the given DNA molecules, the condensation and decondensation concentrations can be predicted as a function of the corresponding binding constants, pH and the concentrations of DNA and monovalent salt.

8. DNA condensation in the context of gene regulation

Most nowadays descriptions of gene regulation are based on the approximations of equilibrium binding in dilute solutions, although it is clear that these assumptions are in fact violated in chromatin (Michel, 2010; Teif, 2010). The dilute solution approximation is violated for two reasons. First, the chromatin content is far from being dilute, and second, the numbers of the participating molecules are sometimes so small, that it does not make sense to talk about the bulk concentrations. Further differences from dilute solutions arise due to the different binding affinities of proteins to condensed and uncondensed DNA (Teif, 2005). Thus in condensed DNA both the reaction rates can be changed and their dependence on the concentrations of reactants may become nonlinear.

8.1. Non-enzymatic reaction rates

It was shown, that DNA-involving non-enzymatic reactions are accelerated in the condensed DNA state *in vitro*. In particular, these include the reaction of DNA renaturation (rebinding of two complementary DNA strands separated during genetic read-out) (Sikorav and Church, 1991) and DNA cyclization (rejoining of the complementary sticky ends of circular DNA) (Jary and Sikorav, 1999). It is believed that in this case the liquid-crystalline phase formed by the DNA helices facilitates their local adjustment required for the reactions mentioned above, while still keeping the high concentration and hence facilitating the collision rates (Sikorav et al., 1994). Some enzymatic reactions such as DNA catenation are also facilitated in the condensed DNA phase, probably due to the same arguments (Krasnow and Cozzarelli, 1982), although in general the effect on the rate of enzymatic reactions is more intricate (see below).

8.2. Protein binding site search

Before proceeding to enzymatic reactions, we have to clarify how proteins find their target sites on the DNA in the highly crowded environment of the cell nucleus. Firstly, positioning of genomic regions (and correspondingly protein localization) is to some extent spatially determined in chromatin (Kumaran et al., 2008; Lieberman-Aiden et al., 2009; Wiggins et al., 2010). 3D positioning of DNA in chromatin may involve several mechanisms including transcription factories (Cook, 2010), chromosome territories (Cremer and Cremer, 2010) and different types of fractal chromatin organization (Grosberg et al., 1993; McNally and Mazza, 2010), all leading to a substantial decrease of the search volume for protein binding. Secondly, transcription factors can be actively recruited with the help of other proteins and RNAs. In addition, local binding site search could be accelerated in the condensed phase due to the reduction of dimensionality. The latter concept implies that that diffusion of a protein in 1D along the DNA is faster than in 3D (Berg and von Hippel, 1985). Most DNA-binding proteins contact the negatively charged DNA backbone by positively charged binding domains. Furthermore, within their DNA-binding domains, charged residues are arranged so that to match sequence-dependent distances between the DNA phosphates (Cherstvy, 2009). Thus proteins can first bind DNA non-specifically and then travel along the DNA searching for a better match. 1D-diffusion might be further combined with hopping from strand to strand through DNA looping (Cherstvy et al., 2008; Givatya and Levy, 2009; Halford and Marko, 2004). In addition, condensed DNA double helices are locally aligned and frequently brought close to each other, so that

the formation of DNA–protein–DNA structures is facilitated even without formation of new loops (Lomholt et al., 2009). Furthermore, one can hypothesize that a protein which encounters a nascent RNA transcript might be directed to the transcribed DNA segment by a similar sliding and hopping along the RNA.

8.3. Enzymatic reaction rates

The effect of DNA condensation on enzymatic reactions depends on the nature of the reaction. For example, DNA condensation acts as a barrier to radiation-induced DNA damage (Levin-Zaidman et al., 2003; Lieber et al., 2009), as well as to the oxidative damage (Nayvelt et al., 2010); DNA condensation alleviates cell stress-induced DNA restriction in bacteria (Keatch et al., 2004); DNA condensation impedes gene expression *in vitro* DNA (Luckel et al., 2005). The radioprotective/oxiprotective effect is probably due to the acceleration of DNA repair in the high-density liquid-crystalline packing, while the suppression of expression in tightly condensed DNA is probably explained by the fact that tight DNA packing prohibits regulatory molecules access to the DNA. The latter is true also for the eukaryotic DNA inside a nucleosome. Nucleosome repositioning provides an intricate control of gene expression through the changes in DNA accessibility, which is now becoming a large area of research (Segal and Widom, 2009; Teif and Rippe, 2009). DNA condensation can also provide autoregulation to DNA-involving reactions through macromolecular crowding effects. Macromolecular crowding has been shown to affect reaction rates as a nonlinear bell-shaped function of concentrations of crowding macromolecules (Cayley and Record, 2004).

8.4. Condensation and origin of life

DNA condensation may play catalytic roles even in simpler systems. Since DNA condensation is associated with the dehydration of DNA, it could be considered as a complex coacervation (the phase separation between a phase rich on DNA and a phase poor on DNA). In a series of recent articles, it has been shown that single-stranded DNA molecules partition at a water–air interface and they perform Watson–Crick pairing more readily in the presence of aromatic molecules such as phenol, which also adsorb at the surface (Douarche et al., 2008; Goldar and Sikorav, 2004). These works provided a connection of DNA condensation to the Oparin's theory of the origin of life from coacervates (Oparin, 1924) and proposed a hypothesis of possible role of phenol substances in the biological activity of coacervates. An additional recent argument in support of this hypothesis is that the intercalation by phenol-like substances promotes polymerization of base-pairing oligonucleotides (Horowitz et al., 2010), which might act as a lacking force needed to create first nucleic acids from the trace amounts of suitable oligomers.

8.5. Epigenetic gene regulation

The DNA sequence stores only partial developmental information, since DNA is the same in all cells of the organism, while different cell types and different programs of cell functioning coexist. The information beyond that stored in DNA is called epigenetic, and potential candidates for such information storage are proteins (in particular, histones) and RNA. One of the levels of epigenetic regulation is achieved in chromatin, fine-tuning the elementary units of DNA compaction – the nucleosomes. A nucleosome-free DNA is more easily accessible to transcription factors. Several molecular mechanisms allow controlling the nucleosome positioning. Firstly, nucleosome positioning is to some extent determined by the DNA sequence. Secondly, transcription factors compete with nucleosomes and other chromatin proteins. Finally, molecular motors consuming ATP can context-specifically move the nucleosome along the DNA or completely remove it (Teif and Rippe, 2010). One of the options to deal with these problems is to introduce specific rules of action of molecular motors (remodelers), which complement to the equilibrium binding rules (Teif and Rippe, 2009). However, only reversible physical interactions are not enough to memorize the states of the cell, which can be inherited through the cell divisions. The latter requires chemical modifications of the macromolecules, the so-called language of covalent histone modifications. Histone modifications are altered chemical groups, such as methyl, phosphoryl or acetyl, added or deleted at histone tails or DNA nucleotides, which can affect the read-out from the given DNA segment. In many cases the effect of such modifications on DNA-binding is primarily electrostatic (Korolev et al., 2007). In addition, some histone modifications such as methylation do not change the charge but rather act as recognition sites for specific protein domains (Lu et al., 2009). In the frame of lattice models, covalent modifications may be taken into account through the changes in binding energies, assuming additive effects of epigenetic modifications on the binding affinity of unstructured protein domains (Teif et al., 2008, 2010a) (Fig. 7). Changes in the patterns of such histone modifications may explain the mechanisms of the epigenetic "memory" which can be described in the frame of the lattice models for DNA–protein binding (David-Rus et al., 2009; Dodd et al., 2007; Sneppen et al., 2008; Teif and Rippe, 2010). This is a very young field, and there are more questions than answers at the moment, but it might appear that epigenetic modifications are not less important than the DNA sequence. At least theoretically, the information capacity of histone modifications is comparable with that of the genomic DNA (Prohaska et al., in press).

9. Potential applications in medicine and biotechnology

The main potential application of DNA condensation in medicine is its use for gene delivery in gene therapy. The main problems in gene therapy are target recognition (what in the genome should be targeted by artificial DNA or RNA constructs), target modification (the way how the drug acts on the target), and the delivery of the DNA-targeted drug to the cell (here DNA condensation comes into play). Usually, the search for new drug delivery agents is performed by experimental screening of combinatorial libraries of cationic peptides, lipids, sugar derivatives, etc, that vary in length, density of charge, side-chain shape, hydrophobicity, and hence the DNA condensation efficiency (Murphy et al., 1998). Several robust methods of DNA condensation for gene delivery have already

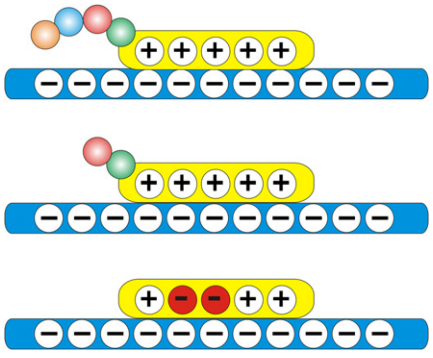

Fig. 7. Lattice models for covalent modifications of proteins and DNA, such as phosphorylation, acetylation, etc, which may modulate binding affinities through changes in the local charge pattern.

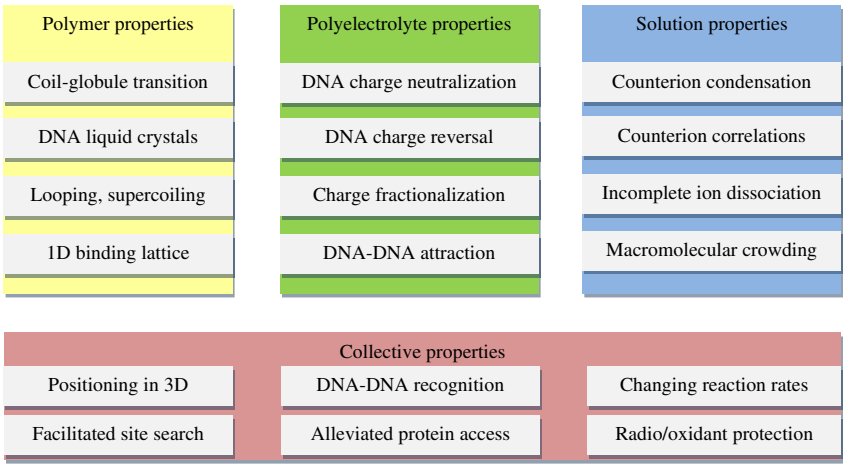

Fig. 8. A schematic list of concepts involved in the study of condensed DNA. DNA stiffness and flexibility determine its polymer properties (yellow box); DNA charge determines its polyelectrolyte properties (green box), which are affected by the molecules and ions in the solution (blue box). As a result of DNA compaction, new collective properties emerge (red box).

become an applied technology rather than science. However, gene therapy is still not a regular branch of medicine. Here is just one recent experimental puzzle: a commercially available DNA condensation agent was used in a study, which showed that it works fine with the circular DNA, but requires much higher concentrations or helper lipids to condense linear DNA (von Groll et al., 2006). This study suggests a connection to the basic DNA condensation experiments performed a decade ago, where Mn^{2+} ions were able to condense circular but not linear DNA (Ma and Bloomfield, 1994), explained by the additional energy of DNA supercoiling (Bloomfield, 1996, 1997). Thus, in order to get gene therapy working, rational drug design and delivery agent search should be probably combined in future with computational selection of a required drug/delivery/target combination. This subject has been recently noted: there are many important features of condensing agents beyond just being cationic (Rao, 2010).

Apart from delivery vehicles in gene therapy, DNA condensation can be utilized in the engineering of biosensors. The idea to use DNA condensation in sensor technologies has been in the literature for some time (Teif and Lando, 2001b; Yevdokimov, 2000), but first efficient realizations have been reported only recently. In one recent study, a sensor based on the effect of DNA condensation/decondensation is able to absorb more than 95% of the mercury ions from a 0.02–100 ppm (parts per million) solution (Zinchenko et al., 2009). In a technically different but conceptually similar way, the effect of closure/opening of a synthetic DNA Holliday junction can serve as a sensitive DNA-based nanosensor of metal ions (Ferapontova et al., 2008). On top of that, one can now chemically construct very sophisticated DNA-based nanostructures with almost any topology (Andersen et al., 2009). Combined with unique properties of condensed DNA, this has much to offer to future bionanotechnology.

10. Summary

The study of DNA condensation has already significantly enriched fundamental science by several new concepts (Fig. 8). We have studied above, how the properties of the DNA as a polymer and as a polyelectrolyte fine-tune its properties as a carrier of the genetic text, which results in the stepwise increase of the complexity and the appearance of principally new collective properties, which neither the elastic polymer nor the polyelectrolyte or the string of text would have on its own. Adding other players such as proteins further increases the complexity to achieve finally what the chromatin is – a unique biological computer, which is still far from being completely understood. Importantly, it is now clear that *all* processes *in vivo* happen in the condensed DNA phase and all binding events should be treated accordingly. An adequate description of DNA-binding processes in crowded macromolecular environments is a real challenge which will require merging existing biochemical, electrostatic, thermodynamic and bioinformatic approaches.

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