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DNA CONDENSATION CAUSED BY LIGAND BINDING MAY SERVE AS A SENSOR

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1. Introduction

DNA is a promising construction material for the engineering of artificial nanostructured devices [1]. One of possible DNA implications in bionanodevices is detecting of metal ions. This possibility is based on the fact that metal ions may preferentially bind to definite DNA conformation and thus metal ion binding may give rise to transition between A-, B-, or Z-DNA [2]. Another approach based on utilizing the specific DNA sequence required to detect specific metals was reported recently [3]. In this method single-stranded DNA forms "pocket" that accepts only lead ions. Here we consider a potential DNA-based sensor detecting metal ions which is based on the phenomenon of DNA condensation.

DNA condensation *in vivo* is governed by complicated system containing polyamines, histones, regulatory proteins and metal ions. It is essential for DNA cyclisation [4],

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renaturation and recombination [5, 6] accelerating these processes in thousands times. Reversible condensation of DNA triggers gene silencing [7]. *In vitro* DNA condensation may be induced by addition of multivalent cations, for example metal ions [8]. This process is described as transition of the first kind from extended coil to compact globule. In some cases very small variation in cationic ligand concentration causes abrupt DNA condensation [9, 10].

We have shown previously that long-range interaction between ligands bound to a DNA molecule may give rise to adsorption with the character of phase transition [11]. This model may describe the process of DNA condensation. From the point of view of molecular electronics, such a system shows properties of a trigger and thus may be applied for sensor manufacturing.

Calculation shows that adsorption with the character of phase transition arises when the long-range potential is high enough. Here we derive the criterion for energy of ligand-ligand interaction necessary to give rise to a phase transition. Then we analyze data from literature on interactions between bivalent metal ions bound to DNA. The values for long-range potential corresponding to metal ions bound to DNA are recalculated on the basis of data from several papers. It is shown that absolute values of their interaction is enough to give rise to phase transition. Possible application of adsorption with the character of phase transition in DNA-based sensor for bivalent metal ions is discussed.

2. Method for calculating binding curves

Let us consider an ideal solution of ligands and DNA. The free energy of a ligand bound to DNA includes three constituents:

1) $\mathcal{G}_a$ -free energy of direct binding of a ligand to m base pairs that are covered by the ligand.

2) We include long-range interaction between *all* the adsorbed ligands in the frame of approach that was proposed by Scatchard [12] and updated by Nechipurenko [13] to

make it suitable for studies of DNA-ligand interactions. In the Scatchard [12] approach, it is assumed that the total free energy of every bound ligand is a linear dependence on relative concentration of all bound ligands. The dependence can be taken arbitrary in the Nechipurenko method. The approaches [12, 13] has been successfully used for description of ligand binding to the helical DNA molecules [3, 14-16] and single-stranded polynucleotides [16, 17]. In the frame of this approach the free energy term corresponding to long-range interaction equals to $-G(c^*)$, where $c^* = k/N$ is the relative concentration of bound ligands (degree of binding), k is the number of bound ligands, and N is the number of base pairs (units) in a DNA chain. As in [12, 13], it is supposed that $G(c^*)$ is independent of ligand distribution along DNA chain. It is obvious that $G(0)=0$.

3) The term corresponding to the entropy of adsorbed ligands was calculated according to [18-20].

Two methods were applied to calculate binding curves $c(c_o)$, where c - average degree of binding, c_o - concentration of free ligands in solution: method of the minimum of the free energy (equivalent to the method of the maximum of the entropy) and the Partition Function method. Method of the minimum of free energy gives S-shaped, Van-der-Vaals like curve $c(c_o)$ for large enough long-range potential (taken in form $G=Wc$, W being determined in units of $R\cdot T$). In this case the point c_{cr} exists at which transition from lower branch of binding curve to the higher branch occurs. At point c_{cr}, free energies corresponding to these two states are equal. The derivatives of free energies corresponding to different states are not equal. Thus this adsorption has a character of phase transition of the first kind. Calculations carried out using the Partition Function method which gives directly the binding curve and the probability of a given degree of binding proved that adsorption has the character of phase transition because degrees of binding corresponding to the central part of the curve are prohibited.

3. Results and Discussion

Calculation of binding curves demonstrates that adsorption with the character of phase transition arises when long-range interactions are strong enough. If long-range interaction is introduced in linear Scatchard form $G=Wc$, then W must reach the threshold value W_t, to allow adsorption with the character of phase transition. Calculation for parameters corresponding to binding of bivalent metal ions to DNA (one metal ion per one base pair at the saturation) gives $W_t=2$.

Are long-range interaction between ligands bound to DNA molecule strong enough to give rise to adsorption with the character of phase transition in real DNA-Me^{2+} systems? To answer this question we have analyzed data in literature on adsorption of bivalent metal ions on single- and double-stranded DNA. Data for interaction of Me^{2+} with single-stranded DNA suggest attractive linear Scatchard potential in the form $G=Wc$ with $W=2$ for Ca^{2+} (recalculated from [21]), $W=2$ for Cu^{2+} (recalculated from [17]), $W=1.55$ for Mg^{2+} (recalculated from [21]). These values indicate that the energetics of long-range interaction between bivalent metal ions bound to single-stranded DNA is at list of order necessary for adsorption with the character of phase transition to arise ($W_t=2$). Such a transition for single-stranded DNA would probably represent a trivial aggregation. Long-range potential between bound ligands is caused by crosslinking of different DNA strands in disordered structure by Me^{2+}.

Let us consider binding of bivalent metals to double-stranded DNA. Interaction between bound to DNA Mg^{2+} or Mn^{2+} may be well fitted by repulsive linear Scatchard potential with $W=-1.5$ (recalculated from [22]). Although repulsive potential can not give rise to cooperative transition, the absolute value is enough for it. Attractive potential between the all bound to DNA ligands might appear between tightly packed DNA molecules [23]. Attractive forces arise between DNA molecules if definite critical concentration of ligands in solution is reached. These forces are dependent on the adsorption of counterions [8, 23]. Thus long-range interaction between bivalent metal

ions bound to DNA may account for phase transition in DNA. It should be noted that in water solution ions with valence more then two are required to induce condensation. But bivalent ions may cause condensation if DNA is topologically constrained (condensation of supercoiled plasmid DNA by Mn^{2+} ions [8]), confined to two dimensions (2D-condensation of DNA molecules between lipid membranes by Ca^{2+}, Mg^{2+}, Mn^{2+} ions [10]), or dissolved in methanol-water mixture [24]).

From the experiments mentioned above of our particular interest is 2D-condensation. In the work [10] a sandwich-like structure was investigated: lipids are arranged in a lamellar stack of nearly flat bilayers with the DNA intercalated between each pair of bilayers. Upon addition of threshold concentration of bivalent metal a stepwise phase transition was observed. From the point of view of electronics, this system have a properties of electrical condenser. The capacity of such a sensor changes abruptly upon condensation transition and probably may be measured directly or inderectly by a various optical methods [8].

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