

Effect of mono-/divalent metal ions on the conductivity characteristics of DNA solutions transferring through a microfluidic channel

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SPECIAL TOPIC — Celebrating the 100th Anniversary of Physics Discipline of Northwest University

Effect of mono-/divalent metal ions on the conductivity characteristics of DNA solutions transferring through a microfluidic channel

Jie Zhu(朱洁), Jing Xue(薛菁), Wei Zhao(赵伟), Chen Zhang(张琛), Xiaoqiang Feng(冯晓强), and Kaige Wang(王凯歌)†

State Key Laboratory of Cultivation Base for Photoelectric Technology and Functional Materials, Key Laboratory of Optoelectronic Technology of Shaanxi Province, National Center for International Research of Photoelectric Technology & Nano-functional Materials and Application, Institute of Photonics and Photon-Technology, Northwest University, Xi'an 710069, *China*

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Interactions between deoxyribonucleic acid (DNA) and metal ions are vital for maintaining life functions, however, there are still unsolved questions about its mechanisms. It is of great practical significance to study these issues for medical chip design, drug development, health care, etc. In this investigation, the conductivity properties of λ-DNA solutions with mono-/divalent metal ions (Na^+, K^+, Mg^{2+}, and Ca^{2+}) are experimentally studied as they are electrically driven through a 5 μm microfluidic channel. Experimental data indicate that the conductivities of λ-DNA solutions with metal ions (M^+/M^{2+}) basically tend to reduce firstly and then increase as the voltage increases, of which the turning points varied with the metal ions. When the voltage surpasses turning points, the conductivity of λ-DNA-M^+ solutions increases with the concentration of metal ions, while that of λ-DNA-M^{2+} solutions decrease. Moreover, the conductivity of λ-DNA-M^{2+} solutions is always smaller than that of λ-DNA-M^+ solutions, and with high-concentration M^{2+}, it is even smaller than that of the λ-DNA solution. The main reasons for the above findings could be attributed to the polarization of electrodes and different mechanisms of interactions between metal ions and λ-DNA molecules. This investigation is helpful for the precise manipulation of single DNA molecules in micro-/nanofluidic space and the design of new biomedical micro-/nanofluidic sensors.

Keywords: microfluidics, interaction between deoxyribonucleic acid (DNA) and metal ions, conductivity-voltage relations, asymmetric electrodes

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1. Introduction

It is of vital importance for life science research, clinical medicine, new drug development and human health, to study, analyze and comprehend the basic life process at the level of a single molecule. Deoxyribonucleic acid (DNA), as the most important genetic material for eukaryotic organisms, is an essential factor to maintain the propagation and development of species. DNA molecules are responsible for a variety of life functions,[1–4] which are always inseparable from the participation of metal ions. That is, organic life relies on inorganic elements to perform various life processes.[5,6] The study of interactions between DNA and metal ions at the single molecule level has profound meaning.

DNA molecules have a delicate and complex spatial structure, which is crucial for maintaining the structure and function of organisms. Under physiological PH conditions, DNA is a negatively charged polymer, which needs to be combined with metal ions (e.g., Na^+, K^+, Mg^{2+}, Ca^{2+}, etc.) to stabilize its spatial structure and maintain normal functions. In addition, metal ions are essential for a variety of cellular responses and various metabolic and physiological functions in life. For instance, a slight deviation of metal ion concentration from the normal level could lead to malfunction of diseases of living organisms, such as the lack of Mg^{2+} or Ca^{2+} results in cardiovascular disease and osteoporosis, and Na^+, K^+, Mg^{2+}, Ca^{2+} play crucial roles as neurotransmitters in cells.[7,8] However, excess metal ions *in vivo* are toxic to life, such as an overabundance of Cu^{2+} and Fe^{2+} in patients with hepatolenticular degeneration and thalassemia. Moreover, some metal ions also affect the spatial structure of DNA.[9,10]

Since the 1990s numerous single-molecule research techniques have been developed,[11–13] and the electrokinetic (EK) method is one of the most effective tools for manipulating and analyzing DNA molecules.[14] However, the conductivity of DNA is quite low, e.g., the genome of bacteriophage, λ-DNA is almost an insulator with one-dimensional conductivity less than $\sim 10^{-16}$ S/cm, whose length is 48502 base pair, it is a commonly used substrate for restriction endonucleases and generating DNA size marker.[15] It is found that DNA modification with metal ions effectively enhanced the manipulation of DNA molecules.[16] The interaction between metal ions and DNA molecules changes their configuration and conformation, thus affecting the conductivity of DNA molecules. Previous studies have found that there are several factors that affect the electrical characteristics of mixed solutions of DNA and metal ions as they pass through a micro-/nanochannel, such as

†Corresponding author. E-mail: wangkg@nwu.edu.cn

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the concentration and PH values of the electrolyte, the material and inner diameter of the micro-/nanochannel, etc.[17–19] Further research indicates that the interaction between DNA molecules and metal ions promotes or inhibits the concentration or mobility of the charged particles in the mixed solution, leading to different electrical characteristics,[20] however, how the interaction works remains unclear.

In this investigation, we systematically studied the conductivity-voltage relationship of the λ-DNA solutions with different metal ions as they were electrically driven by a low voltage ($\leq$ 100 mV) through the microchannel. The interaction between λ-DNA and metal ions with different valance states and concentrations was theoretically explained, which provided information for exploring the dynamics of DNA molecules in an electric field. Also, explorations of the effect of different (monovalent/divalent) metal ions on λ-DNA solution brought insight into manipulating λ-DNA molecules through the EK method, which is of great importance for the electrophoresis-based DNA detection. We hoped this research is helpful for the precise manipulation of single biological molecules with micro-/nanofluidic devices.

2. Experimental setup

The experimental setup is shown in Fig. 1, containing a potentiostat (EA 162, eDAQ, Australia), a micro-current detector (e-corder 401, eDAQ, Australia), a homemade sample reservoir, and a computer to control the equipment and process experimental data. The reservoir consists of two symmetric chambers defined as cis and trans respectively, and only connect by the capillary (3 mm in length, 5 μm in diameter). Due to the performance of the polytetrafluoroethylene (PTFE), the sample reservoir possesses excellent insulation, corrosion resistance, and high-temperature resistance.

A three-electrode measurement system was used to improve the accuracy of potential control. All the electrodes in this research were made of platinum, and the working electrode (W) and the reference electrode (R) were inserted into the cis chamber, while the counter electrode (C) was dipped in the trans chamber. Notably, the surface area of the counter electrode (cathode) was 20 times than that of the working electrode (anode). Duan *et al.* found that utilization of this three-electrode system reduces the recovery time in the current response of the detector, and improves the stability of the measurements.[17,18,21] Moreover, this integrated system was fixed in a grounded Faraday cage to shield external electromagnetic interference. The potentiostat could provide external voltages ranging from −10 V to 10 V with an accuracy of 1 μV, which was connected to the electrodes to provide stable and accurate voltage. The micro-current detector, whose optimal detecting accuracy is up to femtoampere order, was used to monitor the responding current in the microchannel of different solutions with a sampling frequency of 2 kHz. The current signal was transferred to the professional analysis software e-DAQ chat in the computer in real-time for further processing and analysis.

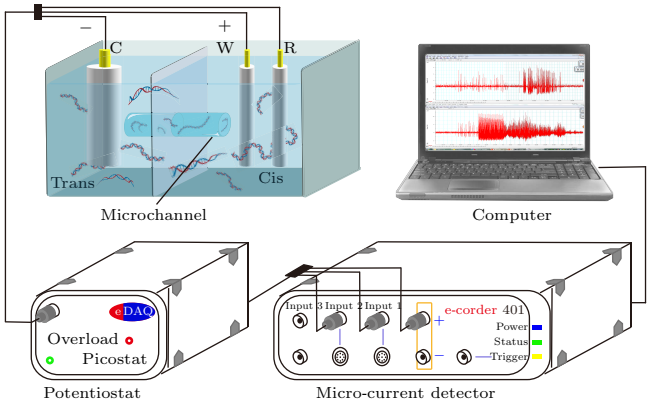


Fig. 1. Schematic illustration of the experimental setup.

The details of experimental conditions are listed in Table 1. λ-DNA solutions with four kinds of metal ions that commonly exist in life, i.e., Na^+, K^+, Mg^{2+}, Ca^{2+}, were studied. Tris(hydroxymethyl) aminomethane buffer solution with a concentration of 0.01 M was used as a solvent to mimic the physiological environment, and the concentration of λ-DNA was 0.018 nM. In the mixed solutions of λ-DNA and metal ions, the concentration of metal ions was set in three groups as 0.01 M, 0.05 M, and 0.25 M, respectively. The applied external voltage ranged from 0 mV to 100 mV with an interval of 10 mV, for the characteristic potential difference in normal life phenomena is generally on the order of 10 mV. The temperature was kept at 25 °C throughout the experiments excluding the influence of temperature fluctuation. The conductivity (G) of each kind of solution was acquired by differentiating the measured current value with respect to the external voltage. To ensure the reliability of the results, the measurements of responding current signals were repeated 5 times at each external voltage in each solution, and took the average of these 5 calculated conductivities as the final result. After completing each round of measurement, the microchannel system and electrodes were thoroughly cleaned for later use.

Table 1. Experimental conditions.

Parameters	Values
Inner diameter	5 μm
Voltage (mV)	0, 10, 20,…, 90, 100
Metal ion types	K^+, Na^+, Mg^{2+}, Ca^{2+}
Concentration of metal ions (M)	0.01, 0.05, 0.25

3. Results

3.1. The *G*–*U* relations of the λ-DNA solution

Firstly, the conductivity characteristics of the λ-DNA solution (0.018 nM) are investigated. Figure 2 shows the conductivity (G)–voltage (U) relations of the λ-DNA solution. As a

non-Newtonian fluid, the *G–U* relations of the λ-DNA solution follow nonlinear relationships, and the conductivity of the λ-DNA solution generally increases with the external voltage.

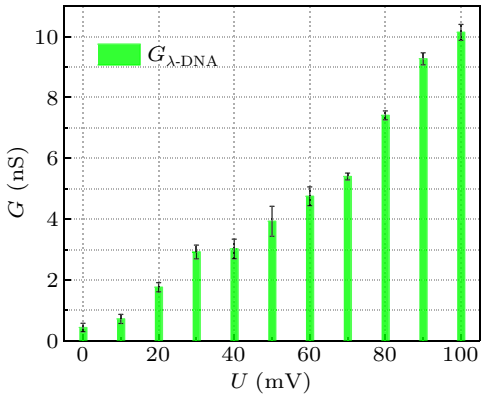


Fig. 2. The *G–U* relations of the λ-DNA solution.

3.2. The *G–U* relations of λ-DNA-M^+ solutions

Figure 3 shows the *G–U* relations of λ-DNA solutions with different monovalent metal ions, i.e., Na^+, K^+, as the concentration of metal ions is 0.01 M, 0.05 M and 0.25 M, respectively. Figure 3(a) depicts the *G–U* curves of λ-DNA-Na^+ solutions. It can be seen that as the external voltage increases, the conductivity of λ-DNA-Na^+ solutions (with Na^+ concentration is 0.01 M and 0.05 M) decreases at the beginning but increases as $U > 20$ mV. When Na^+ concentration is 0.25 M, the conductivity always increases with the external voltage. Moreover, the conductivity of λ-DNA-Na^+ solution increases with Na^+ concentration as $U \geq 30$ mV, and the conductivity of the mixed solution with Na^+ concentration of 0.05 M is the biggest one in this research when $U < 30$ mV. Similar results are presented in Fig. 3(b) for λ-DNA-K^+ solutions, and a little difference is that the conductivity of λ-DNA-K^+ solutions increases with K^+ concentration as $U \geq 20$ mV, and the conductivity of the mixed solution with K^+ concentration of 0.05 M is the biggest one in this research when $U < 20$ mV.

3.3. The *G–U* relations of λ-DNA-M^{2+} solutions

Figure 4 shows the *G–U* relations of the λ-DNA solutions with different concentrations (0.01 M, 0.05 M or 0.25 M) of divalent metal ions, i.e., Mg^{2+}, Ca^{2+}. Figure 4(a) shows the *G–U* relations of the λ-DNA-Mg^{2+} solutions. As the external voltage increases, the conductivity of λ-DNA-Mg^{2+} solutions (with Mg^{2+} concentration is 0.01 M, 0.05 M and 0.25 M) decreases at the beginning but increases as $U > 10$ mV, $U > 30$ mV, $U > 40$ mV, respectively. In addition, the conductivity of λ-DNA-Mg^{2+} solutions decreases with Mg^{2+} concentration as $U \geq 40$ mV, and the conductivity of the mixed solution with Mg^{2+} concentration of 0.05 M is the biggest one in this research when $U < 40$ mV.

In the λ-DNA-Ca^{2+} solutions with Ca^{2+} concentrations of 0.01 M, 0.05 M, and 0.25 M, as shown in Fig. 4(b), the conductivity of the mixed solutions increases with the external voltage as $U > 10$ mV, $U > 20$ mV, $U > 30$ mV, respectively. And the conductivity of λ-DNA-Ca^{2+} solutions decreases with Ca^{2+} concentration as $U \geq 20$ mV, and the conductivity of the mixed solution with Ca^{2+} concentration of 0.25 M is the biggest one in this research when $U < 20$ mV.

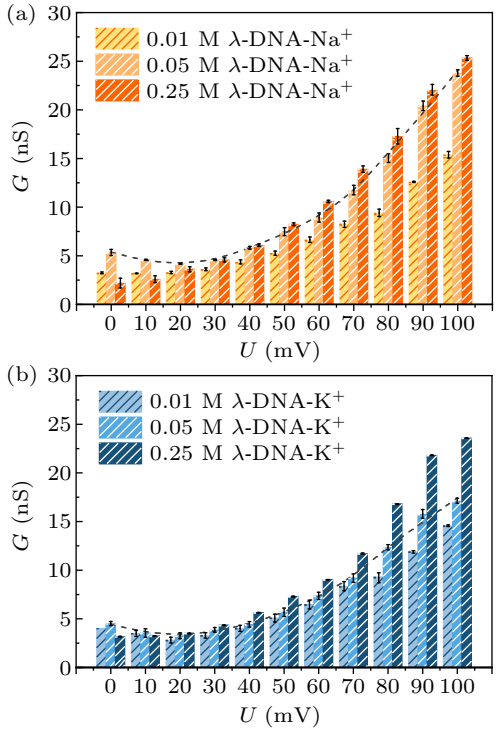


Fig. 3. The *G–U* curves of λ-DNA solutions with different monovalent metal ions. (a) λ-DNA-Na^+ solutions. (b) λ-DNA-K^+ solutions.

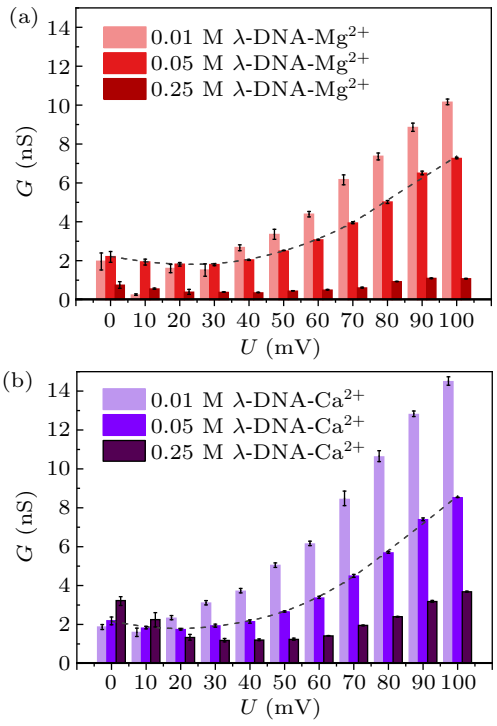


Fig. 4. The *G–U* curves of λ-DNA solutions with different divalent metal ions. (a) λ-DNA-Mg^{2+} solutions. (b) λ-DNA-Ca^{2+} solutions.

It can be found from Figs. 3 and 4 that the conductivities of λ-DNA solutions with metal ions basically have a tendency to reduce firstly and then increase as the external voltage increases. And the conductivity of λ-DNA solutions with monovalent metal ions is always higher than that with divalent metal ions, and when the external voltage reaches a certain threshold (turning point of the *G*–*U* curve), the conductivity of λ-DNA solutions with monovalent metal ions increases with the concentration of metal ions, while that of λ-DNA solutions with divalent metal ions decrease.

Comparing Figs. 2–4, it is worth noting that the conductivities of λ-DNA solutions with high-concentration (0.25 M) divalent metal ions are less than that of the λ-DNA solution. As Fig. 5 shows, the conductivity of the λ-DNA-Mg^{2+} solution is less than that of the λ-DNA solution when $U \geq 10$ mV. And the conductivity of the λ-DNA-Ca^{2+} solution is less than that of the λ-DNA solution when $U \geq 20$ mV. That is to say, in the λ-DNA solutions with a high concentration of divalent metal ions the conductivity of the mixed solutions is weaker than that of the λ-DNA solution when the external voltage reaches a threshold.

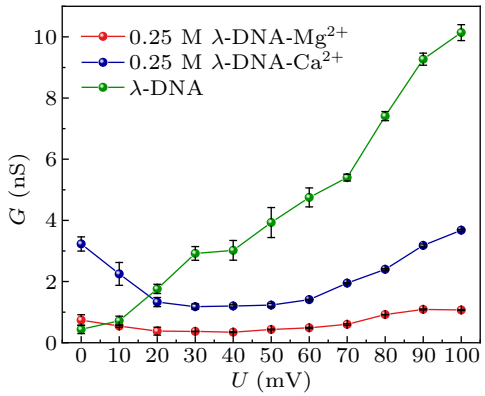


Fig. 5. *G*–*U* relations of λ-DNA solutions with or without Mg^{2+}, Ca^{2+}.

The *G*–*U* relations of λ-DNA solutions with metal ions are affected by the experimental conditions and equipment, and also significantly influenced by the interactions between DNA and metal ions. The conductivity of solutions is determined by the properties of charged particles (e.g., DNA and metal ions) in solutions. And the electrophoretic mobility of particles is related to the radius and charge of itself and the strength of the external voltage. In λ-DNA solutions with metal ions, the interaction between λ-DNA and metal ions varies for the type of metal ions and applies different effects on DNA structure, thus resulting in changes in the mobility of charged particles in the solution, and showing different electrical characteristics.

4. Discussion

4.1. Effect of interactions between metal ions and DNA

Interactions between DNA and different metal ions are quite complex and have varied effects on the configuration and conformation of DNA molecules, thus resulting in diverse characteristics of the mixed solutions of DNA and metal ions. It is essentially due to the distinct interaction mechanisms between λ-DNA and different metal ions that the conductivity of λ-DNA with mono-/divalent metal ions features quite differently. The conductivity of λ-DNA solutions with metal ions is mainly determined by the charges, concentration, and electrophoretic mobility of the charged particles in solutions. Interactions between λ-DNA molecules and metal ions alter the conformation or even break the strands of λ-DNA, which causes changes in the properties of charged particles in the mixed solutions thus affecting the conductivity. The λ-DNA solutions with or without metal ions are non-Newtonian fluids, and their *I*–*U* curves follow the nonlinear relationship[20]

$$I = A\,(q,b,C)\,U^{k+1} + I_0, \tag{1}$$

where I is the steady current, I_0 is the initial current as the applied external voltage is 0, U is the applied external voltage. The coefficient $A\,(q,b,C) = \sum_i q_i^2 b_i C_i$ is determined by the charge, mobility and ionic concentration of ions in solutions, and q_i, b_i, C_i are the charges, mobility, and ionic concentration of the i-th ion, respectively. The exponent k can be used to evaluate the sensitivity of the solutions' current variety to the applied voltage. According to $G = \mathrm{d}I/\mathrm{d}U$ and Eq. (1), the conductivity of the mixed solutions of λ-DNA and metal ions follows:

$$G = \sum_i q_i^2 b_i C_i U^k + G_0, \tag{2}$$

where G_0 is a constant related to the electrical properties of the solution.

The DNA molecule usually exists in a physiological environment in a structure of a double helix, resembling a ladder that's been twisted along its length as Fig. 6 shows, and in the mixed solutions, the DNA molecule is considered as a negatively charged polyelectrolyte and attracts surrounding metal ions. Deoxyriboses and bases in DNA molecules contain oxygen and nitrogen, and phosphoric acid is negatively charged. Positively charged metal ions prefer binding in these sites. Metal ions bond directly with the oxygen atom of the phosphate group and the hydroxyl group of ribose, and the oxygen and nitrogen atoms on the bases, or cooperation of the atoms aforementioned. Moreover, metal ions can bind to DNA through their coordinated water molecules in an indirect way.[22–24] Besides, bindings between metal ions and π electrons of the atoms on the bases disturb the stability of DNA structure and even lead to a break of DNA chains.[25]

Metal ions with different valences have distinct binding preferences for DNA molecules.[26,27] In the mixed solutions of λ-DNA and monovalent metal ions, metal ions prefer binding to the adenine–thymine (A–T) riched segments at minor grooves, and the width of the minor groove gets narrowest when the metal ions are connected to the phosphate groups.

The structure of the λ-DNA molecule has been compressed enhancing its particle property, and the mobility of the charged species improves to show a higher conductivity. Besides, when the concentration of the metal ions further increases, the insertion in bases destroys the hydrogen bonds between base pairs, resulting in a break of λ-DNA chains.[26] The conductivity of λ-DNA solutions with monovalent metal ions increases as more charged species have been released into the solution. Unlike the monovalent metal ions, bivalent metal cations tend to bind to the guanine–cytosine (G–C) riched segments at major grooves accompanied by the bending of DNA strands or even the agglomeration of DNA. Moreover, divalent metal ions interact with DNA molecules most frequently via water molecules in their first solvation shell,[26] which improves the particle properties of DNA and enhances the mobility of particles in the mixed solutions leading to an increase in the conductivity.

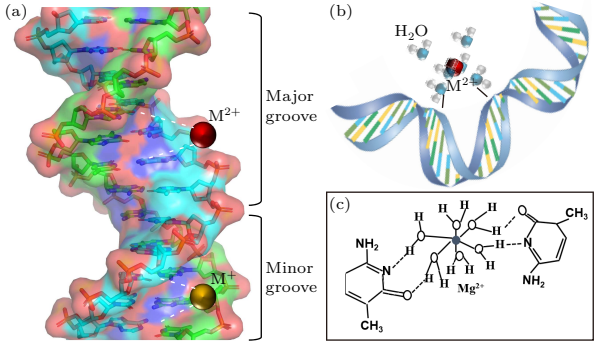


Fig. 6. Interactions between DNA and metal ions.[28,29] (a) Schematic structure of DNA double helix showing minor and major grooves. In DNA, guanine–cytosine (G–C) and adenine–thymine (A–T) pairs are connected through hydrogen bonds. Metal ions can bind to the sites on the same or the opposite strands, and also in a complex form with bases. The binding of metal ions can result in DNA strand break. (b) Hexahydrated divalent metal cation binding to DNA through hydrogen bonding. (c) Molecular structures of magnesium nucleic bases with hydrogen bonded.

In addition, molecular dynamics simulation results indicate that the ratio of the neutralized charge to the original charge on the λ-DNA molecule is $\gamma = 1 - 1/Z\xi$ when there is only one type of counterion with the valance of Z in the solution, and ξ is the Manning coefficient.[30] λ-DNA molecules usually exist in the B-type structure at 25 °C and $\xi = 4.2$. As only monovalent metal ions are added to the λ-DNA solution, $Z = 1$ and $\gamma = 0.76$, that is, 76% of charges on λ-DNA molecules have been neutralized in λ-DNA solutions with Na^+ or K^+, there are only 24% of charges on λ-DNA molecules retained. Similarly, residual charges on λ-DNA molecules in λ-DNA solutions with Mg^{2+} or Ca^{2+} are 12%. The charges of λ-DNA molecules in λ-DNA solutions with monovalent metal ions are higher than that of λ-DNA solutions with divalent metal ions.

4.2. Effect of DNA charge reversal

It is notable that different from cases in λ-DNA solutions with monovalent metal ions, the conductivity of λ-DNA solutions with Mg^{2+} or Ca^{2+} decreases with the metal ion concentration. The concentration of λ-DNA (48502 bp) is 0.018 nM carrying negative charges of around 1.75 μM in this research, which is much less than the positive charges carried by divalent metal ions. Therefore, the decrease of the conductivity in λ-DNA solutions with divalent metal ions is not only caused by the neutralization between λ-DNA and metal ions. A possible explanation is that the coordinated water molecules of divalent metal ions interact with the oxygen atoms on the phosphate group of λ-DNA forming a solvation shell, which reduces the repulsive force between λ-DNA molecules and enhances the particle property of λ-DNA molecules. Thus, the mobility of charged species in λ-DNA solutions with divalent metal ions increases and makes the conductivity of the mixed solution greater than that of the λ-DNA solution.[31] When the concentration of divalent metal ions continues to increase, the radius of the λ-DNA-metal ions complex increases leading to weakened mobility of the particles. Therefore, the conductivity of λ-DNA solutions with divalent metal ions decreases with metal ions concentration.

Besides, in λ-DNA-Mg^{2+} and λ-DNA-Ca^{2+} solutions, the hydrated metal ions adsorbed around the λ-DNA and shielded the charge of λ-DNA gradually as the concentration of divalent metal ions further increases. The electrostatic repulsion between λ-DNA molecules decreased, resulting in the condensation of DNA molecules and the decrease of the species mobility in the solution. Besteman *et al.*[32] found that multivalent metal ions formed a strongly associated fluid structure on the surface of DNA, which attracts more metal ions adsorbed on DNA molecules. When the total charge of the metal ions adsorbed on DNA molecules was greater than the charge of DNA in absolute value, the sign of the total net charge of DNA reversed. In this research, when the concentration of divalent metal ions exceeded a threshold (e.g., 0.25 M), the total charge of the counter ions adsorbed on λ-DNA was greater than the charge of DNA in absolute value, and the total net charge of some λ-DNA molecules reversed from negative to positive. There existed both negatively charged and positively charged λ-DNA molecules in the solution at that time, which further intensifies the condensation of λ-DNA molecules, causing a significant decrease in the species mobility. Thus, the conductivity of the mixed solutions decreased rapidly, even smaller than that of the λ-DNA solution.

4.3. Effect of the electrode polarization

Due to charge separation, there is a potential difference between the Pt electrodes and the interface of the mixed solutions forms an electric double layer (EDL), which could be evaluated by the ζ potential.[33–36] The three-electrode system we used in this investigation has an area ratio of the cathode to the anode of 20:1, that is, the area of the cathode is much larger than that of the anode. Therefore, the potential of the

cathode that charges accumulate on the surface of electrodes forming EDLs is higher than that of the anode, and a shielding electric field $\boldsymbol{E}_s$ is generated in the opposite direction to the external field $\boldsymbol{E}$. Thus, the initial electric field direction is opposite to the external electric field. As shown in Fig. 7, with the increasing of the external voltage, the direction of the total electric field is finally in keeping with $\boldsymbol{E}$ and the steady current value turns from negative to positive.

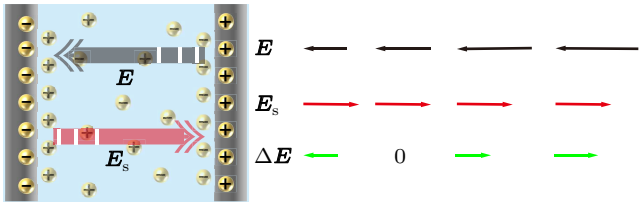


Fig. 7. Competition between $\boldsymbol{E}$ and $\boldsymbol{E}_s$ ($\Delta\boldsymbol{E}$ denotes the total electric field).

Besides, the thickness of the EDL is related to the concentration and valence of species in the solution, and evaluated by the Debye length

$$\lambda = \sqrt{\varepsilon k_B T / 4\pi \sum_i v_i^2 e^2 C_i}, \tag{3}$$

where $\varepsilon = \varepsilon_0 \varepsilon_r$ is the electric permittivity of the solution, ε_0 and ε_r are the vacuum and relative permittivities, respectively, k_B is the Boltzmann constant, T is the temperature, e is the electric charge, q_i and C_i are the charges and the ionic concentration of the i-th ion, respectively. It can be seen that increasing the concentration of species thinned the EDL, and the ζ potential is also reduced, leading to a reduction of $\boldsymbol{E}_s$.

In λ-DNA solutions with monovalent metal ions (Na^+, K^+), more charged species are released after the break of λ-DNA chains as the metal ions concentration increases. And the potential of the electrodes reduced, for the increase of species concentration, so does $\boldsymbol{E}_s$. Therefore, the absolute value of the I_0 in λ-DNA-Na^+ and λ-DNA-K^+ solutions decreases with the concentration of metal ions. In contrast, in λ-DNA-Mg^{2+} and λ-DNA-Ca^{2+} solutions, the increase of Mg^{2+} or Ca^{2+} leads to a decrease of species in the solutions with shielding electric field strength increases. Hence, the I_0 in λ-DNA-Mg^{2+} and λ-DNA-Ca^{2+} solutions gets more negative as metal ions concentration increases. On the other hand, the external field is weaker than the shielding electric field $\boldsymbol{E}_s$ in the initial stage. However, as the applied external voltage increases the external field gradually increases and overcomes $\boldsymbol{E}_s$. Therefore, the net potential difference between the electrodes decreases first and then increases with increasing voltage, and the conductivity of the mixed solution follows the same variation.

5. Conclusion

In order to reveal the effect of metal ions on the conductivity characteristics of DNA molecular solution as it passes through a microchannel, the conductivity–voltage relations of λ-DNA solutions with different metal ions (different valent states and concentrations) are systematically investigated.

In the mixed solutions of λ-DNA and metal ions, monovalent metal ions (Na^+, K^+) render the compression of DNA structure at low concentrations, which enhances the mobility of species in DNA solutions. As the concentration of Na^+ or K^+ increases, the break of DNA chains results in an increase in species concentration in the solution. All of that helps to improve the conductivity of the λ-DNA solutions.

On the other hand, divalent metal ions (Mg^{2+}, Ca^{2+}) mainly interact with DNA through coordinated water molecules to form a solvation shell. The adsorbed hydrated metal ions shield the charge of DNA molecules and reduce the repulsion force between them, which enhances the mobility of species when the concentration of metal ions is low, and the conductivity of the solution is improved. As divalent metal ions concentration increases, the mobility of charged species in the solution is reduced, for the reason of enlarged complex radius and effect of DNA charge reversion, thus the conductivity of the λ-DNA solutions is weakened. In a word, divalent metal ions strengthen the conductivity of λ-DNA solutions at low concentrations, but weaken it at high concentrations.

This investigation is meaningful for designing electrophoresis-based DNA detection devices and improving the accuracy of detection and manipulation of a single biomacromolecule.

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