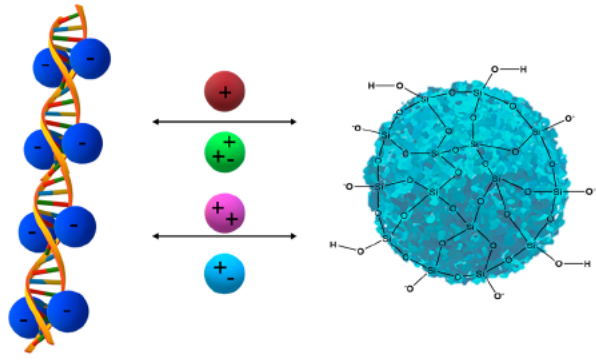
DNA Binding to the Silica: Cooperative Adsorption in Action

Saientan Bag,[#] Stefan Rauwolf,[#] Sebastian P. Schwaminger, Wolfgang Wenzel,[*] and Sonja Berensmeier[*]

ABSTRACT: The adsorption and desorption of nucleic acid to a solid surface is ubiquitous in various research areas like pharmaceutics, nanotechnology, molecular biology, and molecular electronics. In spite of this widespread importance, it is still not well understood how the negatively charged deoxyribonucleic acid (DNA) binds to the negatively charged silica surface in an aqueous solution. In this article, we study the adsorption of DNA to the silica surface using both modeling and experiments and shed light on the complicated binding (DNA to silica) process. The binding agent mediated DNA adsorption was elegantly captured by cooperative Langmuir model. Bulk depletion experiments were performed to conclude the necessity of a positively charged binding agent for efficient DNA binding, which complements the findings from the model. A profound understanding of DNA binding will help to tune various processes for efficient nucleic acid extraction and purification. However, this work goes beyond the DNA binding and can shed light on other binding agent mediated surface−surface, surface−molecule, molecule−molecule interaction.



I. INTRODUCTION

The adsorption of deoxyribonucleic acid (DNA), the carrier of genetic information, to a solid surface is of immense interest in pharmaceutics, nanotechnology, medicine, and recently in organic electronics.[1−4] Especially, in the last years, the purification of plasmids gained increasing scientific attention.[5] The extraction, separation, and purification of DNA, which nowadays is mostly done by solid phase extraction (SPE), relies on its adsorption capacity, where silica is primarily used as an adsorbent medium.[6−9] Silica is an abundant, low cost material that can be easily functionalized for purification processes and represents one of the standard materials for filtration, SPE and column chromatography.[8,10,11] Multiple approaches exist to investigate the interaction of silica with biomolecules and understand the complexity of silica surface chemistry.[12−14] The question, which arises, is how can DNA be extracted with silica based materials? Silica and DNA are both negatively charged over a wide pH range. DNA possesses a negatively charged[15] phosphate backbone, while silica's point of zero charge (PZC) lies in a range of pH 2−3.[13] At neutral pH, silica possesses[16] around one negative charge per nm^2. Hence, DNA should not bind to silica due to electrostatic repulsion.

A variety of techniques[1,17] have been devised in the past to make the DNA binding possible to the silica and even a standard procedure for DNA purification has been established. One of the possible ways in this direction is to alter the negative charge of the silica surface by controlling the pH.[15] Geng et al.[18] used an electrical switch to lower the solution pH facilitating the DNA binding to silica. The silica surface can also be functionalized with different groups to make the silica surface positive to allow DNA binding.[17,19−21] Forming layers of positive ions also enhances the DNA−silica interaction[22−24] on the silica surface by building a salt bridge between the silica surface and the DNA backbone.[25,26] In another approach, the DNA−silica interaction is enhanced by using a high concentration of chaotropic salt[27,28] in the solution which has the disadvantage of changing the DNA native structure. The usage of other molecular species in the solution together with DNA to tune the DNA−silica interaction has been recently reported in various experiments. Zhai et al.[29] studied the adsorption of environmental DNA on mica in the presence of a protein using atomic force microscopy. Vandeventer et al.[30] studied the adsorption and elution of DNA from the silica surface, in the presence of an amino acid (AA) buffer. During this experiment, a significant dependence of different AAs on the DNA−silica binding was observed. Both Zhai[29] and Vandeventer et al.[30] hypothesized the formation of a DNA−AA complex, which shows higher interaction to silica than

DNA itself. No theoretical understanding of these AA mediated interactions was accomplished. However, theoretical investigation exploring only DNA−silica interaction has been done in the past. Shi et al.[31] developed a silica model to study the interaction of both single strand DNA (ssDNA) and double strand DNA (dsDNA). They calculated the binding free energy and explored different binding modes of ssDNA and dsDNA to silica. Furthermore, no stable binding modes for the dsDNA were found.

Although there were numerous experiments conducted in the past studying the DNA binding to silica, there is no modeling work attempting to understand the binding agent mediated DNA adsorption. It is worth mentioning that there have been numerous modeling attempts[12,32−35] to understand other small molecule adsorption to various carbon and silica surfaces. The original version of the Langmuir model (noncooperative) has been extensively used[12,35,36] in the past to understand a variety of adsorption processes. However, the simple noncooperative Langmuir model, which does not consider the interaction between the adsorbates, fails when the adsorption is cooperative in nature.[12] In this paper, we employ the cooperative Langmuir model to understand the DNA binding in different aqueous environments. The influence of different metal ions and amino acids (binding agents) on the interaction was investigated with static bulk depletion experiments to understand the equilibrium binding capacity and affinity of DNA to silica surfaces. We found that DNA binds well to silica in the presence of metal ions and the positively charged amino acid arginine (R), while no binding was observed in deionized water or the noncharged reference amino acid glycine (G). DNA binding was also measured in the presence of two binding agents, where no significant change in binding was observed. The DNA binding both in the presence of one and two binding agents was satisfactorily understood using the cooperative Langmuir model.

We hope this work will significantly impact molecular biology, especially where nucleic acid extraction is one of the more essential processes. Our work, which provides a profound understanding of the binding agent mediated DNA binding, will also be of great interest in the field of high purity purification of DNA,[37,38] plasmids,[5] gene therapy,[39−41] and sensor chips.[42] Furthermore, our approach can improve the understanding of other binding agent mediated surface−surface, surface−molecule, molecule−molecule interactions.

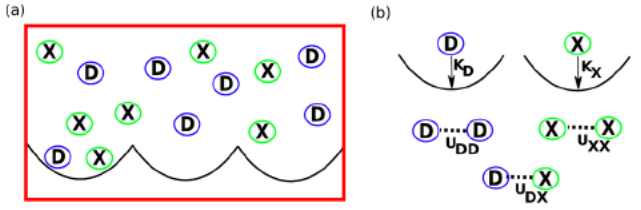


Figure 1. (a) Schematic diagram showing the cooperative Langmuir model. The adsorptive DNA (D) and the binding agents (X) bind and unbind to the silica adsorption sites, shown in black parabolas. (b) The parameters in the cooperative adsorption model are shown schematically.

II RESULTS AND DISCUSSIONS

A. DNA Binding to the Silica: One Binding Agent.

A.1. Modeling: The Cooperative Langmuir Model with One Binding Agent. DNA can not bind to the silica on its own because of the electrostatic repulsion of its negatively charged backbone with the negatively charged silica surface. Therefore, simple noncooperative Langmuir model cannot explain DNA binding. Hence, we propose the cooperative Langmuir model to understand the DNA binding to silica described as follows.

Assuming the binding affinities of the DNA and the binding agent to silica are K_D and K_X respectively. The interaction energy between the two DNAs is U_{DD}, between two binding agents is U_{XX}, between a binding agent and a DNA U_{DX}. Γ is the total number of available silica binding sites as shown as black parabola in Figure 1(a). Each binding site can hold a maximum of two adsorbates. The energetic parameters of the cooperative Langmuir model is shown schematically in Figure 1 (b).

In equilibrium, the average number of DNA bound to silica (N_{DNA}) per unit binding site (F_{DNA}) is given by[12]

$$<N_{DNA}>/\Gamma = F_{DNA} = \frac{2K_D\theta_D + 2\theta_D^2K_D^2e^{-\beta U_{DD}} + 2\theta_DK_D\theta_XK_Xe^{-\beta U_{DX}}}{1 + 2\theta_DK_D + \theta_D^2K_D^2e^{-\beta U_{DD}} + 2\theta_XK_X + \theta_X^2K_X^2e^{-\beta U_{XX}} + 2\theta_DK_D\theta_XK_Xe^{-\beta U_{DX}}} \quad (1)$$

Here, θ_D and θ_X are the concentrations of DNA and binding agent, respectively. For a complete derivation of the eq 1, see our earlier work[12] and the Supporting Information therein. The eq 1 above can also be rewritten in terms of the concentration ratio of the adsorbates $r_\theta = \theta_X/\theta_D$ and their ratio of the binding affinity $r_K = K_X/K_D$. $\beta = 1/k_BT$. Here k_B is the Boltzmann constant and T is the temperature.

$$<N_{DNA}>/\Gamma = F_{DNA} = \frac{2K_D\theta_D + 2\theta_D^2K_D^2e^{-\beta U_{DD}} + 2\theta_DK_Dr_\theta\theta_Dr_KK_De^{-\beta U_{DX}}}{1 + 2\theta_DK_D + \theta_D^2K_D^2e^{-\beta U_{DD}} + 2r_\theta\theta_Dr_KK_D + r_\theta^2\theta_D^2r_K^2K_D^2e^{-\beta U_{XX}} + 2\theta_DK_Dr_\theta\theta_Dr_KK_De^{-\beta U_{DX}}} \quad (2)$$

Now, we try to understand the behavior of the DNA binding fraction (F_{DNA}) as we tune different parameters of the eq 2 above. Since it was previously hypothesized[30] in the literature that the binding of the DNA with the binding agent initiates the DNA adsorption to silica, we first check how the F_{DNA} depends on the parameter U_{DX} (interaction energy between DNA and the binding agent) and the r_K (the ratio of adsorption affinity of the binding agent with respect to the DNA adsorption affinity). We compute F_{DNA} as a function of U_{DX} and r_K for different values of the U_{DD} (interaction energy between two DNA's) and U_{XX} (interaction energy between two binding agents).

As evident from the Figure 2 above, for the DNA to bind to the silica, the following conditions need to be satisfied:

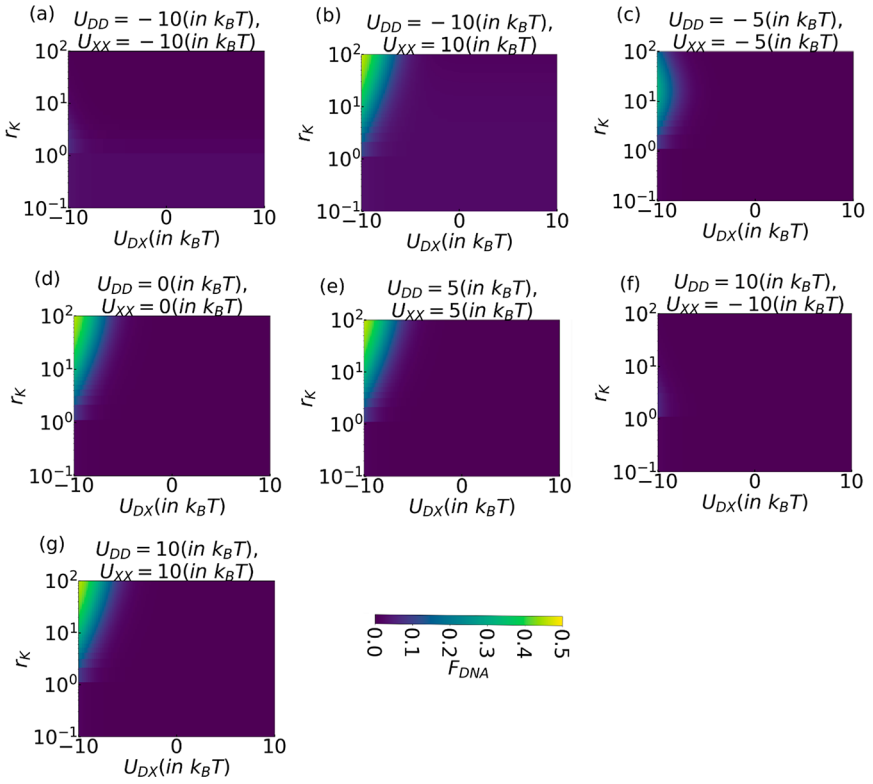


Figure 2. Binding fraction of the DNA (F_{DNA}) as a function of U_{DX} (interaction energy between DNA and the binding agent) and the r_K (the ratio of adsorption affinity of the binding agent with respect to the DNA adsorption affinity) as calculated using the cooperative Langmuir model (see eq 2). Interaction between two DNAs (U_{DD}) and interaction between the binding agents (U_{XX}) are also varied. The temperature (T) was assumed to be at 300 K and the concentration ratio of the binding agents to the DNA (r_θ) was fixed at 5. The color scale used for all the subfigures is shown in the inset.

1 The binding agents should have a high adsorption affinity to the silica.

2 There has to be an attraction between the DNA and the binding agents.

3 There should not be an attraction between two binding agents.

Please note that we have ruled out the possibility of an attraction between two bare DNAs ($U_{DD} < 0$) because of their high negative charge. These three conditions above can be physically understood as follows. Since DNA cannot bind to silica on its own, the attraction between the binding agent and DNA (condition 2) will ensure that the DNA sticks to the binding agent whereas the complex (DNA+binding agent) binds to silica. The binding agents have to bind to silica for this to happen (condition 1). However, if there is an attraction between two binding agents, it is energetically more favorable to form a complex between two binding agents, rather than a DNA binding agent complex (condition 3). This will decrease the DNAs binding probability to the silica.

It is worth mentioning here that the ranges chosen for the parameter sweep in this work were guided by our earlier works[12,43] where extensive unbiased and biased molecular dynamics simulation (umbrella sampling simulation) were done to evaluate the parameters. Here because of the complexity of the system, we could not evaluate the exact value of the parameters and therefore a parameter sweep was attempted.

In all the calculations described above, we have fixed the concentration ratio of the binding agents to the DNA (r_θ) as 5. We now check the effect of this concentration ratio on the DNA binding fraction (F_{DNA}) as shown in Figure 3 below.

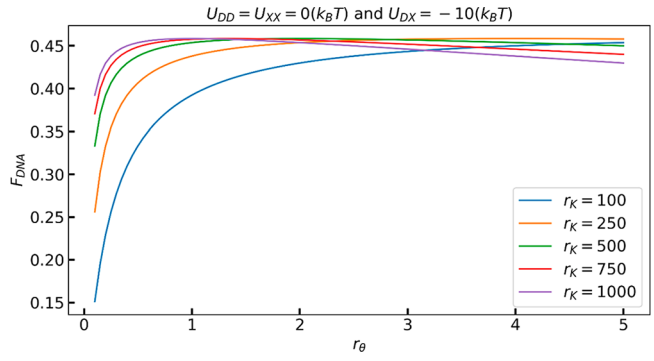


Figure 3. DNA binding fraction as a function of the concentration ratio (r_θ) of the binding agents to the DNA for different values of (r_K) as calculated using the cooperative Langmuir model (see eq 2). We have fixed the interaction between two DNA molecules (U_{DD}) and interaction between the binding agents (U_{XX}) at zero. Interaction energy of $-10\ k_BT$ between the DNA and the binding agent (U_{DX}) was assumed.

As mentioned in the previous paragraph DNA cannot bind to silica on its own, and needs a binding agent to form a complex to bind to silica. If the concentration of the binding agent is too low, the binding amount of DNA is also reduced. As one increases the concentration of binding agents, DNA binding also increases because of the formation of the complex (DNA+binding agent).[25,28] However, when there are many

more binding agents than the DNA, the complex (binding agent + DNA) has to further compete with the free binding agents. Since the complex will have low binding affinity compared to the free binding agent, an increase of free binding agents will reduce the chance of DNA binding to silica.

II.A.2. Experiment: DNA Binding to the Silica in the Presence of One Binding Agent. To validate the findings of the simulation, experiments were conducted where the amount of DNA bound to silica in the presence of different binding agents was measured. As shown in the Figure 4 below, the

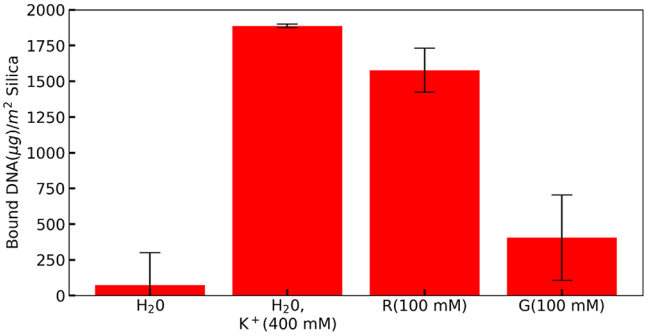


Figure 4. Amount of DNA bound to the silica for different solvation conditions. For the bulk depletion experiments ddH_2O, 400 mM KCl in H_2O (K^+), 100 mM arginine (R), and 100 mM glycine (G) were set to pH 5. 150 μL of 0.2 g/L of the DNA solution were then added to 250 μg MagPrep. The standard deviations result from three parallel experiments.

DNA does not bind to silica if deionized water (H_2O) or 100 mM glycine (G) is used, whereas binding increases in the presence of 400 mM potassium (K^+) ions or 100 mM arginine (R) in the solution. These results can be understood using the three main conditions (for the efficient DNA binding) concluded from the cooperative adsorption model (see Section II.A.1). While DNA is negatively charged, K^+ ions and R (binding agent) are positively charged. K^+ and R both bind to silica,[12] furthermore, show an attraction to DNA.[44] Due to the charge screening of negative loadings and the resulting salt bridging of positive charged ions with the silica surface, DNA binds to silica surface.[45,46] The glycine (G), due to its zwitterionic state binds only weakly to silica and the DNA and therefore, the adsorption of DNA to silica is relatively low. This indicates that the G has, in comparison, only a minor role in DNA binding. In the case of H_2O, none of the above conditions (see Section II.A.I) are satisfied, resulting in no DNA adsorption.

Next, the DNA binding as a function of the concentration of the binding agents (K^+/R) was measured (Figure 5). As found in our modeling described in the previous section (see Figure 3), the amount of bound DNA increases with the

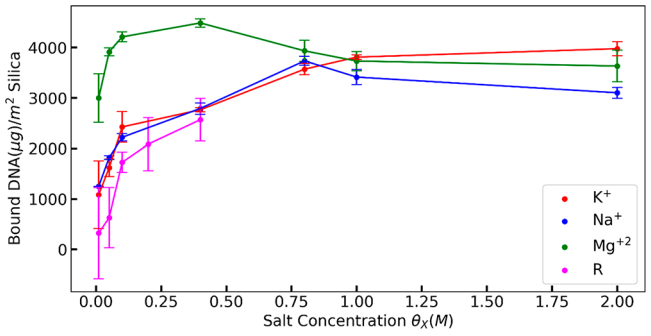


Figure 5. Amount of DNA bound to silica as a function of the concentration of the binding agents. For the bulk depletion experiments KCl, NaCl, $MgCl_2$, and arginine (R) were diluted in ddH_2O and set to pH 5. 150 μL of 0.2 g/L of the DNA solution were then added to 250 μg MagPrep. The standard deviations result from three parallel experiments.

concentration of the binding agents, as well as the valence of the cations.[25,28,47,48] It is worth noting (Figure 5) that for a very high (>1.5 M) salt concentration DNA binding slightly decreases, which was also well captured (see Figure 3) in our model.

So far, we have not discussed the effect of DNA length in our calculation. However, the information on the DNA length is encoded in the total number of binding sites Γ (see eqs 1 and 2). The longer DNA will certainly occupy more space on the silica than the shorter DNA. Therefore, for a given total surface area of the silica, there will be a higher number of binding sites (Γ) available for the shorter DNA than the longer ones. Since, we always report the number of DNA bound to silica per unit binding sites (F_{DNA}) (see eqs 1 and 2), all the theoretical predictions are independent of the actual value of Γ. We want to emphasize that the DNA used in all experiments does not have a specific size but ranges from 0.2 to 2 kbp. Hence, the DNA adsorption is independent of the DNA molecule's length.

II.B. DNA Binding to Silica: Two Binding Agents. *II.B.1. The Cooperative Langmuir Model with Two Binding Agents.* As already showed above the usage of a binding agent is necessary to bind DNA to silica. In the following section, we ask how the binding of the DNA changes in the presence of two binding agents. In this case, we assume that the DNA takes part in the cooperative adsorption separately with the two binding agents. If, F_{DNA1} is the binding fraction of the DNA which took part in cooperative adsorption with the binding agents *X1* and F_{DNA2} is the corresponding fraction in case of the binding agent *X2*. The total binding fraction is given by[12]

$$F_{DNA} = 1/2(F_{DNA1} + F_{DNA2}) \tag{3}$$

Where F_{DNA1} and F_{DNA2} are given by,

$$F_{DNA1} = \frac{2K_D\theta_D + 2\theta_D^2K_D^2e^{-\beta U_{DD}} + 2\theta_DK_Dr_{\theta 1}\theta_Dr_{K1}K_De^{-\beta U_{DX1}}}{1 + 2\theta_DK_D + \theta_D^2K_D^2e^{-\beta U_{DD}} + 2\theta_Dr_{\theta 1}\theta_Dr_{K1}K_D + r_{\theta 1}^2\theta_D^2r_{K1}^2K_D^2e^{-\beta U_{X1X1}} + 2\theta_DK_Dr_{\theta 1}\theta_Dr_{K1}K_De^{-\beta U_{DX1}}} \tag{4}$$

$$F_{DNA2} = \frac{2K_D\theta_D + 2\theta_D^2K_D^2e^{-\beta U_{DD}} + 2\theta_DK_Dr_{\theta 2}\theta_Dr_{K2}K_De^{-\beta U_{DX2}}}{1 + 2\theta_DK_D + \theta_D^2K_D^2e^{-\beta U_{DD}} + 2\theta_Dr_{\theta 2}\theta_Dr_{K2}K_D + r_{\theta 2}^2\theta_D^2r_{K2}^2K_D^2e^{-\beta U_{X2X2}} + 2\theta_DK_Dr_{\theta 2}\theta_Dr_{K2}K_De^{-\beta U_{DX2}}} \quad (5)$$

Here K_{X1} and K_{X2} are the binding affinity (to the silica) of the binding agent $X1$ and $X2$ respectively. θ_{X1} and θ_{X2} are the concentration of the binding agents. $r_{K1} = K_{X1}/K_D$ and $r_{K2} = K_{X2}/K_D$. $r_{\theta 1} = \theta_{X1}/\theta_{X2}$ and $r_{\theta 2} = \theta_{X2}/\theta_D$. $r_\theta = r_{\theta 1} + r_{\theta 2}$.

Among the various parameters in eqs 4 and 5, we first decided to tune the most significant ones (see Sections II.A.1 and II.A.II) and check their effect on DNA binding as shown in Figure 6. The results presented in Figure 6(a) can be understood physically as follows: if there are more than one type of binding agents present, both of the binding agents should be attractive toward DNA to achieve maximum DNA binding, provided the binding agents both favor silica. If one of the binding agents forms a complex with DNA while the other one does not, then the complex (DNA+one of the binding agents) has to compete with the free binding agent. As a result, the DNA binding will be hindered. In the end, we also check how the DNA binding fraction (Figure 6(b)) depends on the binding affinity of the individual binding agents. If both binding agents like DNA, both binding agents should have high adsorption affinity (compared to DNA) to silica, to maximize DNA binding. If the binding agent favors DNA, it forms a complex with it. However, the complex cannot further bind to silica if the binding agent does not have a high adsorption affinity (to silica). A quick comparison of Figures 2 and 6 reveals that in the best parameter regime (for maximum DNA binding), DNA binding efficiency remains unaltered in the presence of one and two types of binding agents.

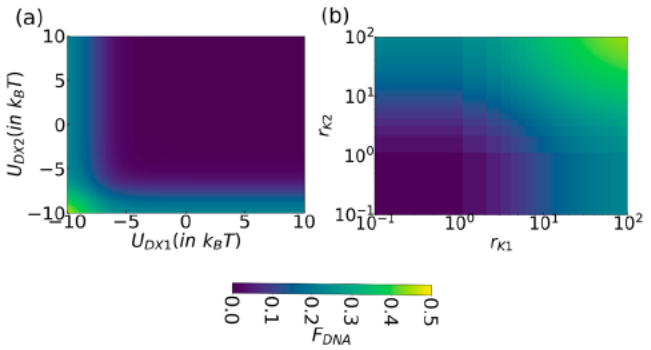


Figure 6. (a) The fraction of DNA bound (F_{DNA}) to silica as we vary the interaction of the DNA to the binding agents (U_{DX1}) and (U_{DX2}). The r_{K1} and r_{K2} were fixed at 100. The U_{DD}, U_{X1X1}, U_{X2X2} were kept at zero. (b) The DNA binding fraction as we tune the adsorption efficiency (r_{K1} and r_{K2}) of the binding agents. U_{DX1} and U_{DX2} were fixed at -10 (k_BT). The U_{DD}, U_{X1X1}, U_{X2X2} were kept at zero. The calculations are performed using eqs 3, 4, and 5. The color scale used for all the subfigures is shown in the inset.

II.B.2. Experiment: DNA Binding to Silica in the Presence of Two Binding Agents. Again, to validate the results from the simulation the amount of DNA binding to silica was measured, this time in the presence of two binding agents, R and K. For a particular amount of R (100 mM) in the solution, we change the amount of K^+ ions (0, 200, 400 mM) and measure the binding of DNA. We also kept the K^+ concentration at 400 mM and increased the R concentration to 500 mM. The binding of DNA remained unaffected for all changes, as shown in Figure 7 below. This behavior can be explained from our cooperative model, which infers that the presence of two binding agents does not increase the efficiency of DNA binding. However, the addition of K^+ ions to the G results in the DNA binding to the silica again, comparable to the conditions when only K^+ is in solution (Figure 4), simply because K^+ ions act as binding agents again.[49] This effect of K^+ ions on the binding behavior of DNA in the presence of glycine further verifies the cooperative model.

III. CONCLUSIONS

To conclude, in this contribution we have provided a profound understanding of adsorption of the negatively charged macromolecule DNA to the negatively charged surface silica using both modeling and experiments. DNA binding to silica is facilitated by a binding agent, which was nicely captured in the

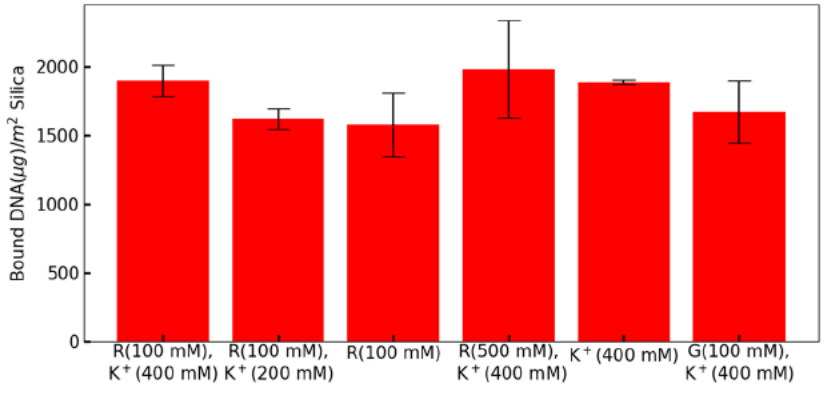


Figure 7. Amount of bound DNA to silica in the presence of both R and different amounts of K^+ ions. The case where the solution contains only 400 mM K^+ ions (without R), a higher R concentration (500 mM) and G with 400 mM K^+ ions are also shown for comparison. For the bulk depletion experiments, KCl (K^+) and arginine (R/G) were diluted in ddH_2O and set to pH 5. 150 μL of 0.2 g/L of the DNA solution were then added to 250 μg MagPrep. The standard deviations result from three parallel experiments.

cooperative adsorption model. In order to validate the findings of the models, bulk depletion experiments were performed and the DNA binding was measured for different chemical environments. We found that a positively charged binding agent (which forms a complex with DNA) needs to be present, for the DNA adsorption to occur, which aligned with the findings of the models. Although only one binding agent is necessary for the DNA binding, the usage of multiple binding agents increases the DNA binding efficiency. The understanding of DNA binding will significantly impact high purity purification of DNA, plasmids, gene therapy, and sensor chips where nucleic acid adsorption−desorption is an extremely important process. Furthermore, our work goes beyond the DNA binding and can shed light on any other binding agent mediated surface−surface, surface molecule, molecule−molecule binding.

MATERIALS AND METHODS

Experimental Details. *Reagents.* L arginine (Cellpure ≥98%) was purchased from Carl Roth, Germany. L glycine (analytical grade ≥98%) was purchased from SERVA, Germany. Sodium chloride and magnesium chloride hexahydrate were purchased from Carl Roth, Germany. Potassium chloride was purchased from Sigma Aldrich, Germany. The MagPrep silica particles used in the experimental part were purchased from Sigma Aldrich, Germany. For binding experiments, we used Invitrogen UltraPure salmon sperm DNA (double stranded DNA sheared to ≤2 kb).

Binding Experiments. All amino acid and salt test solutions (TS) were prepared in their respective concentration in deionized water and adjusted to pH 5 with HCl. For the binding experiment, 250 μg of MapPrep silica particles were added in an Eppendorf tube and washed with 150 μL of TS. The DNA was diluted in TS to 0.2 g/L and 150 μL were added to the tubes and were incubated for 2 h at room temperature with linear agitation at 1000 rpm using the Thermomixer comfort from Eppendorf. The particles were then removed from the solution magnetically, and the concentration of DNA in the supernatant was determined spectrophotometrically at 260 nm with an Infinite M200 Microplate Reader (Tecan Deutschland, Germany).

AUTHOR INFORMATION

Corresponding Authors

Wolfgang Wenzel − *Institute of Nanotechnology (INT), Karlsruhe Institute of Technology (KIT), 76344 Eggenstein Leopoldshafen, Germany*; Email: wolfgang.wenzel@kit.edu

Sonja Berensmeier − *Bioseparation Engineering Group, Department of Mechanical Engineering, Technical University of Munich (TUM), Munich 85748, Germany*; orcid.org/0000 0002 4943 848X; Email: s.berensmeier@tum.de

Authors

Saientan Bag − *Institute of Nanotechnology (INT), Karlsruhe Institute of Technology (KIT), 76344 Eggenstein Leopoldshafen, Germany*; orcid.org/0000 0003 1000 7719

Stefan Rauwolf − *Bioseparation Engineering Group, Department of Mechanical Engineering, Technical University of Munich (TUM), Munich 85748, Germany*

Sebastian P. Schwaminger − *Bioseparation Engineering Group, Department of Mechanical Engineering, Technical University of Munich (TUM), Munich 85748, Germany*; orcid.org/0000 0002 8627 0807

Author Contributions

#Sa. B and S. R. contributed equally to the work. So.B. and W.W. conceived the idea and designed the study. Sa.B. performed all the theoretical calculations. S.R. and S.P.S. performed all the experiments. The manuscript was written by Sa.B., S.R., S.P.S., So.B., and W.W.

Notes

The authors declare no competing financial interest.

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