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# Preparation of a new nanobiosensor for the determination of some biogenic polyamines and investigation of their interaction with DNA

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ABSTRACT

Biogenic polyamines are small organic polycations involving in a variety of biological processes. They form high affinity complexes with DNA. Here, we have followed two different novel approaches, either fabrication of an electrochemical nanobiosensor for determination of three of the most important biogenic polyamines; spermine (SPM), spermidine (SPD) and putrescine (PUT), or electrochemical investigation of their interaction with DNA. Strong binding of polyamines to DNA makes the DNA a suitable recognition element for construction of a sensitive biosensor. The fabricated biosensor responded to SPM, SPD and PUT over an extended dynamic range of 0.04–100 μM, 0.01–24 μM, and 0.08–100 μM respectively, with low detection limits of a few nM. We also studied the interaction of polyamines with three different DNA sequences with base composition of 100% AT, 80% AT and 100% GC in the presence of $[Ru(NH_3)_6]_3^+$ as a redox probe. The highest $k_b$ values were obtained in the interaction of polyamines with 80% AT (mixed) DNA sequence. The $k_b$ values were $5.24 \times 10^5$, $4.17 \times 10^5$ and $1.46 \times 10^5$ $M^{-1}$ for SPM, SPD and PUT, respectively, which correlated well with their increasing number of amino groups. In addition, competition study showed the impotence of SPD to replace with histone H1 in histone H1-DNA complex, which indicates the more potent interaction of histone H1 with DNA. In this proof-of-principle study, we have proposed an approach for simple, cost-effective, miniaturizable, and direct-readout detection of polyamines, as well as the understanding of the modes of interaction between polyamines and DNA.



## 1. Introduction

Biogenic polyamines, also known as natural amines, are nitrogenous bases localized in the nucleus of eukaryotic cells. They are usually synthesized by the decarboxylation of ornithine amino acid or by the amination and transamination of the aldehydes and ketones (Silerme et al., 2014). Spermine (SPM), spermidine (SPD) and putrescine (PUT) are three essential aliphatic polyamines that are involved in multiple cellular processes (Scheme 1). Biogenic polyamines are implicated in cell proliferation and differentiation, regulation of nucleic acids, synthesis of proteins, stabilization of lipids, brain development, nerve growth, regeneration and protection from external agents in all living organisms (Ramani et al., 2014). It has also been reported that polyamines interact with DNA and induce condensation or changes in its secondary structure (Kabir and Kumar, 2014). In addition, elevated levels of biogenic polyamines in body fluids are associated with different types of cancers (Bachrach, 2004). The analytical methods frequently used for quantification of polyamines are mainly chromatographic methods with precolumn or postcolumn derivatization techniques (Fiechter et al., 2013; Mayer et al., 2010; Yang et al., 2014; Zotou and Notou, 2012), since polyamines do not show absorption in UV–vis region. So preparation of a sensitive biosensor for determination of the biogenic polyamines is very important.

Interaction of polyamines and DNA have been studied by various methods such as Raman spectroscopy (Ruiz-Chica et al., 2001a, 2001b), mass spectrometry (Wen and Xie, 2013), calorimetry (Kabir et al., 2013; Kabir and Suresh Kumar, 2013), capillary electrophoresis (Ouameur and Tajmir-Riahi, 2004), UV–vis spectroscopy (Pérez-Flores et al., 2005) and circular dichroism (CD) spectroscopy (Ruiz-Chica et al., 2005). Some of these studies have shown that electrostatic interactions are the main mode of interactions between polyamines and oligonucleotides while the others have suggested that minor/major groove binding, as well as a mobile binding with no specific site of interaction are of major importance (Kabir and Suresh Kumar, 2013; Qi et al., 2014). The above mentioned reports indicated that all parameters including: the oligonucleotide structure, base composition and sequence, as

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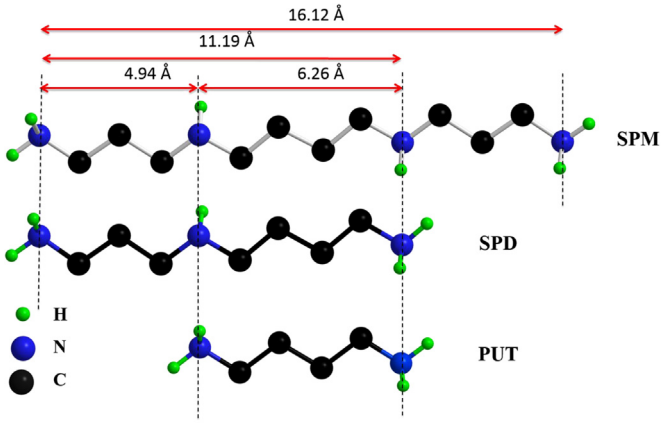



**Scheme 1.** Schematic representation of the three polyamines, PUT, SPD and SPM and the intramolecular distances derived from the Chimera software.

well as the polyamine type have an important role in the mechanism of DNA-polyamine interaction.

Electrochemical sensing methodologies, in general, have various advantages including fast response time, low cost, high sensitivity and the possibility of miniaturization. Alongside, the unique chemical and physical properties of nanomaterials have been of considerable interest to the electrochemists. Especially, in recent years nanotechnology as a promising technique has greatly help researchers to develop much fascinating strategies in diverse area of research. Our research group involved employing nanostructured materials for surface modification of the electrodes for different applications including interfacing biological recognition events (Elahi et al., 2011; Ilkhani et al., 2015; Mehdinia et al., 2008; Moradi et al., 2013), and fabrication of energy storage devices (El-Kady et al., 2015; Moosavifard et al., 2015; Pendashteh et al., 2015; Shao et al., 2015; Wang et al., 2015). Among various nanoscale material, carbon nanotube (CNT) has stimulated interest in the fabrication of electrochemical biosensors, due to their unique combination of excellent mechanical, chemical and electrical properties (Fotouhi and Bahmani, 2013; Mei and Ouyang, 2010; Niu et al., 2008; Shamsipur et al., 2012; Wang and Lin, 2008; Zhu et al., 2010). In addition, pretreated CNTs, which contain different functional groups, pave the way for covalent immobilization of biomolecules to the electrode surface (Elahi et al., 2012; Jacobs et al., 2010).

There are just a few reports on the electrochemical investigation of the interaction of DNA with polyamines (Corduneanu et al., 2010; Salvatore et al., 2012; Salvatore et al., 2013). Oliveira-Brett research group has reported electrostatic interaction of palladium chelates of SPD and SPM, as well as the free ligands, with calf thymus DNA by following the changes of the guanine and adenine oxidation peak currents at high overpotentials of $E_{pa(G)} = +1.03$ V, and $E_{pa(A)} = +1.30$ V (Corduneanu et al., 2010). Ulstrup research group has also reported that the interaction of SPD with a ssDNA is different from that with a dsDNA probe (Salvatore et al., 2012; Salvatore et al., 2013). We also have previously studied the interaction of SPD with dsDNA, and fabricated electrochemical SPD biosensors (Ghanbari et al., 2008; Mehdinia et al., 2009). Understanding the mechanisms of action of biogenic polyamines and their interaction with DNA is very important for setting up a quantitative structure-activity relationships that paves the way for the development of more sophisticated approaches for diverse biomedical applications.

The present study, is an important step forward in the journey to electrochemically find the mode of interactions that are involved in DNA-polyamines binding, as well as the impact of base composition in their interaction. We quantitatively analyzed the DNA-polyamines binding interaction with determination of a number of parameters including the stoichiometry of binding, equilibrium binding constants, and specificity of the binding interaction (by comparing the binding affinities to three different DNA sequences with varying base composition). In addition, we designed and fabricated a new electrochemical nanobiosensor for sensitive detection of the biogenic polyamines. We also studied the role and strength of electrostatic interaction in DNA-polyamines complex by comparing the competition between SPD and histone H1 for interacting with a DNA, since it is known that histone H1, as a protein that involves in packaging and ordering the DNA into nucleosomes, interacts only electrostatically with DNA (Dootz et al., 2011). Except our previous studies on SPD-calf thymus DNA interactions, to the best of our knowledge, this is the first report on electrochemical quantitative analysis of DNA-polyamines binding interactions, and using DNA as a recognition element for electrochemical biosensing of the three of the most important biogenic polyamines.

## 2. Experimental

Detailed description on chemicals and reagents, apparatus, and procedures for fabrication of the biosensor including; pretreatment of CNTs, modification of the electrode, DNA probe immobilization and hybridization, and interaction of DNA with polyamines, are given in the Supporting information (see SI, Experimental section).

## 3. Results and discussion

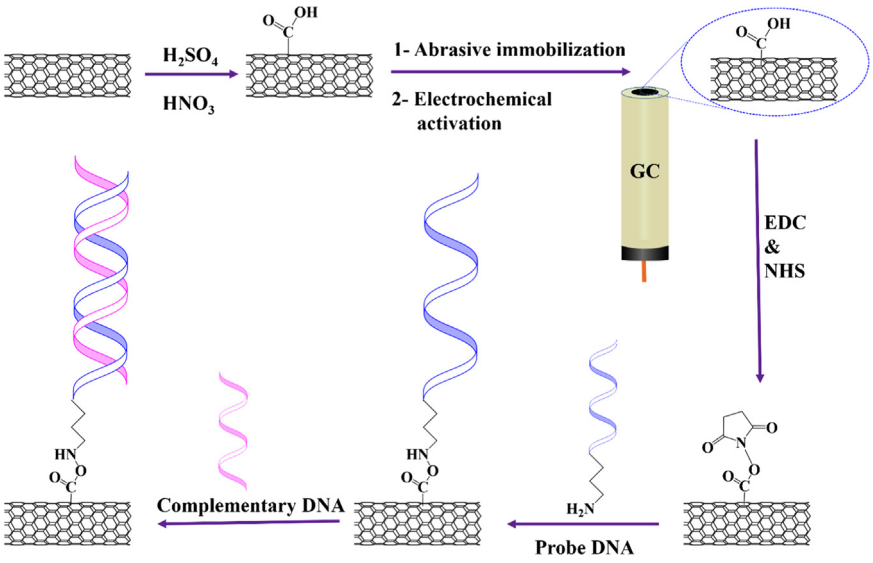
### 3.1. Characterization of the electrode modification

As schematically presented in Scheme 2 and explained in details in the experimental section (see SI, Experimental Section), we modified a GC electrode with COOH-functionalized CNTs to provide a suitable substrate for amino-terminated DNA immobilization. After hybridization of the DNA probes with the corresponding complementary sequences, we studied the interactions of three different biogenic polyamines with dsDNA sequences of varying base composition.

We used CV and EIS techniques as well as scanning electron microscopy imaging to characterize the electrode in each modification step as detailed in the SI, characterization of the electrode modification section (Fig. S1).

### 3.2. Electrochemical behavior of polyamines at DNA modified electrode

As indicated before, we have simultaneously followed two goals in this study; the first goal was fabrication of a biosensor for quantification of polyamines, and the second goal was exploring the modes of binding that are involved in the interaction of polyamines with DNA. To better realize the type of functional groups that are involved in the interaction of polyamines with DNA, which make the DNA a suitable recognition element for polyamine's biosensing, we first tried to unravel the most influencing parameters that are involved in DNA-polyamine interaction. knowing that helps us to have a better understanding of the principle of the biorecognition reactions, and selection of the best DNA sequence, based on nucleobase composition, as a recognition element. Thus, after preparation of the modified electrode and covalent immobilization of the DNA probes, and subsequent hybridization of the probes with the corresponding complementary sequences (as detailed in SI, Procedure Section), the interaction of




**Scheme 2.** Electrode preparation. Stepwise procedure for modification of the electrode.

polyamines with dsDNA sequences were studied. Polyamines are protonated at physiological pH with two, three and four positive charges for PUT, SPD and SPM respectively, which enables them to interact with anionic molecules such as DNA. Previous studies have shown that binding of RuHex to DNA is a pure electrostatic interaction, because RuHex lacks planar organic groups that can intercalate into the DNA π-stack (Ahmed et al., 2013). Tarlov et al. (Steel et al., 1999) have reported the binding constant of RuHex to calf thymus dsDNA, immobilized on an electrode surface (in an electrolyte containing 100 mM $Na^+$), as $4.1 \times 10^4\ M^{-1}$. Thus, biogenic polyamines with a high affinity to DNA can replace RuHex on the electrode surface. Occupation of DNA binding sites renders RuHex from binding to DNA thus, its redox peak current decreases in the presence of polyamines. Fig. 1A shows the CVs of the interaction of PUT with mixed probe DNA in different concentrations of PUT from 10 nM to 100 μM. Both the reduction and oxidation peak currents of RuHex decreased with increasing PUT concentration and leveled off at about 10 μM of PUT. The interactions of other polyamines, SPM and SPD, were also investigated in the same manner (Fig. 1B and C).

It is assumed that DNA and ligand only produce a single complex, $DNA(Ligand)_m$.

$$DNA + m\ Ligand \leftrightarrows DNA(Ligand)m \quad (1)$$

The values of binding constants for the interaction of polyamines with DNA were determined using Eq. (2) (Wang et al. 2006):

$$Log\frac{I_{DNA(Ligand)m}}{I_{DNA} - I_{DNA(Ligand)m}} = -Log k_b + mLog\frac{1}{[Ligand]} \quad (2)$$

where $k_b$ is the apparent binding constant, $I_{DNA}$ is the signal of the probe in zero molar concentration of the probe, i.e. dsDNA immobilized electrode, $I_{DNA(Ligand)m}$ is the signal of the redox probe on a DNA modified electrode in the presence of polyamines, and $m$ is number of bounded ligands per DNA. Assuming that DNA and ligand form a single complex, the plot of $Log(I_{DNA(Ligand)m})/(I_{DNA} - I_{DNA(Ligand)m})$ vs. $Log(1/[Ligand])$ is linear with a slope $m$ and intercept of $-\log k_b$ (Fig. 1D–F).

The values of the binding constants determined by this technique were $5.25 \times 10^5$, $4.17 \times 10^5$ and $1.46 \times 10^5\ M^{-1}$, for DNA-SPM, DNA-SPD and DNA-PUT respectively. The binding constant obtained for the interaction of SPD with DNA is consistent with the previously reported constant of $4.08 \times 10^5\ M^{-1}$, calculated electrochemically for the interaction of SPD with calf thymus DNA sequences, which has a higher AT/GC ratio (Ghanbari et al., 2008). The slight differences in the reported values of the binding constant might be due to the differences in solution conditions. In addition the higher length of the calf thymus DNA, which makes it more flexible, could also have a role in the observed small difference. From the slope of the trendlines showed in Fig. 1D–F, which are close to unity (0.879, 0.959, and 0.948 for PUT, SPM and SPD), a binding stoichiometry of one ligand per mixed dsDNA probe can be deduced.

We also investigated the effects of the number of $NH_2$-group of polyamines on their interaction with DNA, and their preferential binding modes. A more detailed description of the DNA-polyamine binding modes is presented in SI file (DNA-polyamine binding modes section). As previously mentioned, we calculated the $k_b$ values of the interaction of a mixed DNA sequence (80% AT) with SPM, SPD and PUT as $5.24 \times 10^5$, $4.17 \times 10^5$, $1.46 \times 10^5\ M^{-1}$ respectively. It shows that when the number of amine group increases the binding constant increases as well, which can be attributed to the electrostatic interaction between polyamines and DNA. While the number of amino group increases, the positive charge of polyamines increases and hence, it could be attracted more intensely with dsDNA.

### 3.3. Interaction of SPD with $Oligo(dA.dT)_{15}$ and $Oligo(dG.dC)_{15}$

To explore the contribution of base composition on such an interaction, the interactions of SPD, as a model compound, with three different DNA sequences (GC, AT and mixed DNA sequences) were examined and the binding constants were compared (see SI, Fig. S2A and B). The results showed a decrease in the peak current of RuHex with increasing SPD concentration. The reduction peak current of RuHex changed linearly with increasing SPD concentration. The $k_b$ values were calculated as $2.36 \times 10^5$ and $1.56 \times 10^5\ M^{-1}$ for the interaction of SPD with AT and GC sequences, respectively (see SI, Fig. S2C and D, and Table 1).The $k_b$ values, obtained for the interaction of SPD with AT and GC sequences indicate that the polyamines have a higher affinity for binding to an AT sequences compared to a GC sequences. However, the $k_b$ value for the interaction of SPD with the mixed DNA sequence ($4.17 \times 10^5\ M^{-1}$) is even higher than the two other sequences. The higher $k_b$ values of polyamines with a mixed DNA

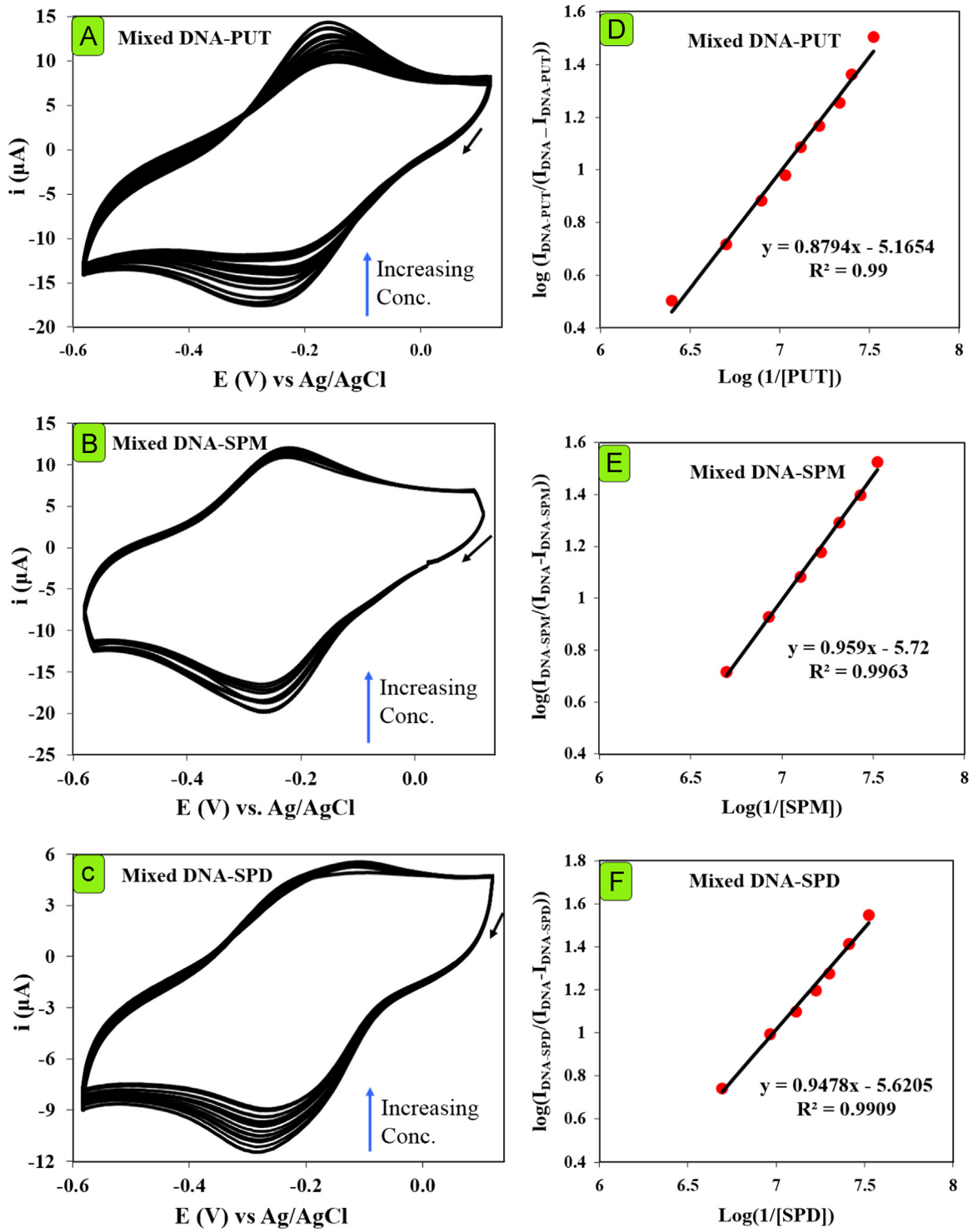



**Fig. 1.** DNA-polyamine interaction. CVs of the mixed dsDNA/CNT/GC electrodes in the presence of different concentrations of (A) PUT, (B) SPM, and (C) SPD. Plot of Log ($I_{DNA-PA}/I_{DNA}-I_{DNA-PA}$) vs. Log (1/[PA]) for the determination of binding constants of (D) PUT, (E) SPM, and (F) SPM with mixed dsDNA sequence. Note: RuHex concentration is 0.5 mM and the scan rate is 50 $mVs^{-1}$; PA stands for polyamine.

**Table 1**
Analytical results of interaction between DNA and polyamines.

| DNA sequence | Polyamine | $K_b$ ($M^{-1}$) | Dynamic range (μM) | $R^2$ |
|---|---|---|---|---|
| Mixed DNA | PUT | $1.46 \times 10^{-5}$ | 0.08–100 | 0.989 |
| Mixed DNA | SPM | $5.24 \times 10^{-5}$ | 0.04–100 | 0.990 |
| Mixed DNA | SPD | $4.17 \times 10^{-5}$ | 0.01–24 | 0.993 |
| 100%AT | SPD | 2.36 × 10-5 | 0.4–16 | 0.992 |
| 100%GC | SPD | $1.56 \times 10^{-5}$ | 0.9–24 | 0.990 |

sequence compared with that of homopolymeric AT and GC sequences indicate that the type and sequence of the bases play a distinct role. Thus combinations of different modes of interactions are probably involved. For better understand the basis of how polyamines interact with DNA molecules, the distance between functional groups of both DNA and polyamines, and the dimensions of the major and minor grooves in different sequences should be considered. We took the correlation between the distances of different functional groups of DNA and polyamines into

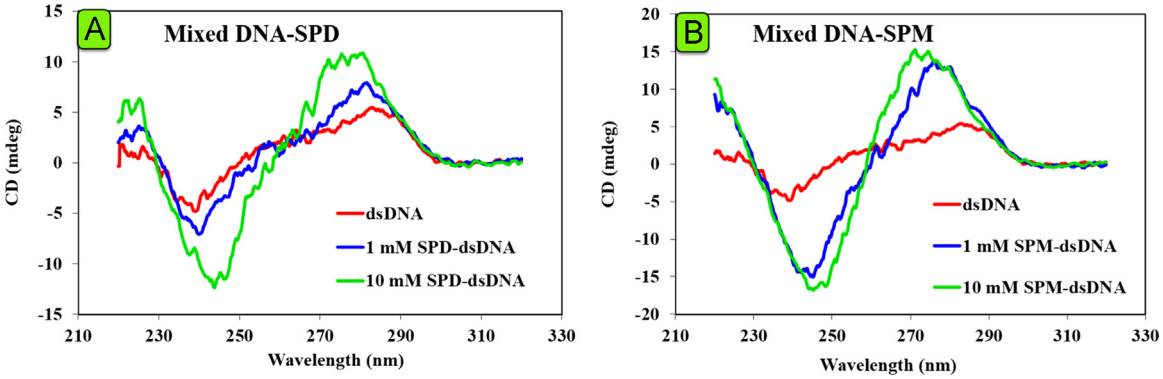



**Fig. 2.** Circular Dichroism study. CD spectra of the mixed DNA sequence in absence (Red), and presence of two different concentrations (1.0 mM (Blue), and 10.0 mM (Green)) of SPD (A), and SPM (B) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

consideration and discussed our experimentally obtained $k_b$ values with molecular modeling methods with the results that are consistent with the previously reported data (Ouameur and Tajmir-Riahi, 2004). For a more detailed description of the molecular modeling see SI, molecular modeling section, Fig. S3-S8.

### 3.4. CD analysis of SPD–DNA interaction

For following the structural changes of the oligonucleotides after their interaction with polyamines, CD spectra of the samples were recorded. Polyamines by themselves are optically inactive and do not show any CD spectra; whereas, B-form dsDNA shows a characteristic large positive CD band at about 270–280 nm and a negative band at about 248 nm. Thus, any changes in the CD spectra of the DNA after its interaction with polyamines can be solely attributed to the changes in conformation of the oligonucleotides (Bathaie et al., 2007; Hoshyar et al., 2012).

Fig. 2 shows the CD spectra of the mixed DNA sequence in the presence of SPD and SPM, at pH 7.4. The CD spectra of the mixed DNA sequences in the solution showed two CD bands. There was a positive band in 282 nm and a negative band in 248 nm. These CD bands are originated from the stacking interaction between the base pairs and the helical DNA structure that provides an asymmetric environment for the bases. In the presence of SPD the spectra of the mixed sequence showed a decrease in the intensity of negative band at 248 nm and an increase in the intensity of positive band at 282 nm (Fig. 2A). SPM also interacted similarly with the mixed DNA sequence (Fig. 2B).

The two panels show a similar trend, as a result SPM and SPD interact similarly with a mixed DNA sequence. However, the differences in the intensities indicate that the interaction is more intense with SPM and less with SPD which correlates with the increasing number of amino groups of the two polyamines. The decrease in the intensity of the negative band indicates the formation of H-bind between the polyamines and DNA. The increase in the ellipticity of the positive band confers the conformational changes in the DNA which agrees with the previously reported results (Kabir et al., 2013; Kabir and Suresh Kumar, 2013; Ouameur and Tajmir-Riahi, 2004). The overall CD results indicate that polyamines induce some conformational changes in the DNA sequences.

### 3.5. Interaction of SPD with mixed dsDNA in presence of histone H1

We previously showed that some small molecules can weaken DNA-histone H1 complex *in vitro* (Ashrafi et al., 2005; Rahmanpour and Bathaie, 2011). Here, we have investigated the possibility of the interaction of SPD with DNA in the presence of histone H1 to explore the possible impact of polyamines on DNA structure in a cell and the possible competition between polyamines and histone H1 for binding to DNA. The importance of DNA-histone H1 interaction and the role of histone H1 in a cell is presented in SI file.

Fig. S9 shows the interaction of SPD with the mixed dsDNA in the presence of histone H1. As is obvious, after interaction of DNA with histone H1, the reduction peak current of RuHex has decreased which indicates a good affinity of histone H1 for binding to DNA. After immersing the histone H1-conjugated electrode in SPD solution, the reduction peak current of RuHex remained almost unchanged which reveals that SPD could not interact with DNA in the presence of histone H1. It means that the histone H1-DNA complex is strong enough that is not separated by SPD. Since histone H1-DNA interaction is dominantly electrostatic and the number of positive charges on histone H1 is more than SPD, the result indicates that other strong bindings (rather than electrostatic one) are not solely involved in the interaction of SPD with DNA, i.e. electrostatic interaction also plays a role.

### 3.6. Analytical application

The levels of polyamines in body fluids of normal individuals are low, whereas their levels rise remarkably in patients with neoplastic diseases (Boffi et al., 2015). In general, the in vivo levels of SPM and SPD are in mM concentration range, whereas PUT level is slightly lower. Herein, we present an electrochemical biosensor for quantification of nanomolar to micromolar concentration range of the biogenic polyamines by using a DNA probe as a recognition element. The DNA sequence that we used for biosensing of polyamines was a mixed DNA sequence, since our study showed that a mixed DNA sequence exhibits a higher binding constant with biogenic polyamines. The reduction peak current of RuHex was followed as a marker of the polyamines concentration. Fig. 3 shows the calibration curves for quantification of polyamines with the constructed biosensor. The biosensor responded linearly to SPM, SPD and PUT in the range of 0.04–100 μM, 0.01–24 μM, and 0.08–100 μM, respectively, with detection limits of a few nM. The relative standard deviation of the three repetitive measurements was less than 5%. The characteristics of the presented method based on dynamic range and detection limit have been compared in Table S2 with previously published papers on polyamines quantification. As can be seen, the proposed approach shows a better characteristics compared to most of the previous studies while holding the simplicity, cost-effectiveness, and potential miniaturizability of electrochemical detection approaches. However, further studies are required to quantify polyamines individually in a mixed solution. This proof-of-principle study, demonstrates the potential applicability of the biosensor for monitoring of polyamines as a disease marker for future detection of cancers or monitoring of the therapy effectiveness.

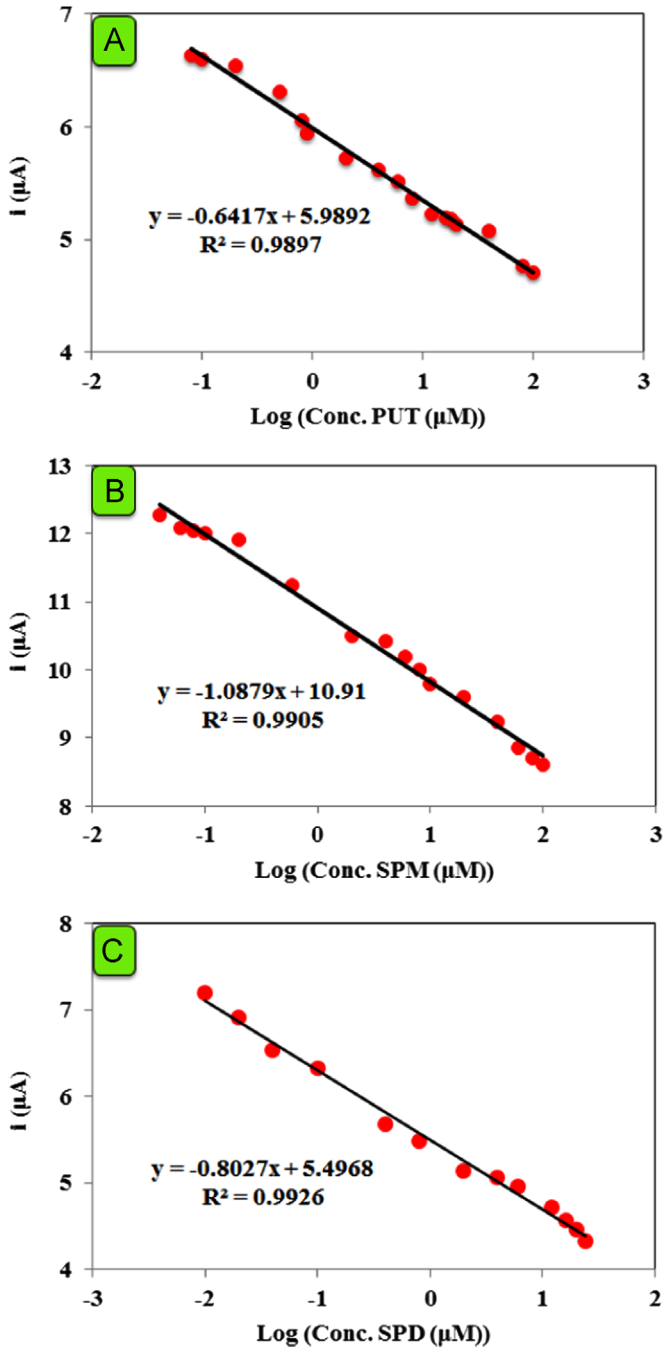



**Fig. 3.** Calibration curve. Quantification of (A) PUT, (B) SPM, and (C) SPD with the fabricated biosensor. The corresponding equations are presented in each graph.

## 4. Conclusion

The multiwalled carbon nanotube-modified glassy carbon electrode was employed as a good nanostructured platform for the immobilization of DNA sequences. We fabricated a sensitive electrochemical nanobiosensor for quantification of polyamines with relatively broad dynamic ranges and low detection limits. We also quantitatively analyzed the interaction of 80% AT as well as homopolymeric AT and GC DNA sequences with three of the most important biogenic polyamines. The modes of binding have also been deduced using the electrochemical and CD studies. Some functional groups of DNA that possibly are involved in interaction with polyamines, and the intramolecular distances that match with that of polyamines are evaluated. We also demonstrate the impotency of SPD for replacing histone H1 in a cell. Although still in the proof-of-concept stage, the proposed method could potentially promote the design and development of a more sophisticated protocol for detection of individual polyamines along with cancer-therapy follow up.

## Author contribution

Z.B. and A.N. contributed equally to this work.

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## Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bios.2015.10.025.

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