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Influence of AC electric field on the charge generation in albumin solution in a flow-based AFM fishing system

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Abstract. In the present paper, the influence of AC electric field on charge accumulation in the measuring cell of a flow-based system for atomic force microscope (AFM) based fishing is considered. As a flow-based system, a device for AFM-based fishing of low-abundant proteins has been employed. The charge is generated in a femtomolar albumin solution during its flowing through an injector of this system. We have demonstrated that application of sinusoidal electric field (100 V, 50 Hz frequency) stimulates charge accumulation in the measuring cell upon the input of protein solution at 38°C. Taking this effect into account is of importance for the development of novel highly sensitive flow-based proteomic and diagnostic systems employing AFM-based fishing, for modeling the influence of electric field on hemodynamics, and also for the development of specified theoretical models describing physicochemical properties of water and aqueous solutions.

1. Introduction

The urgency of studying the influence of AC electric fields on the physicochemical properties of water and aqueous solutions is conditioned by the fact that account for this influence can be well used for increasing the sensitivity of biosensor devices. In this way, in our previous paper [1] the stimulating influence of AC electromagnetic field on the efficiency of protein capturing in atomic force microscope (AFM) based fishing system at femtomolar (10⁻¹⁵ M) and subfemtomolar concentrations was demonstrated. In the same paper [1], with the example of the detection of albumin, we demonstrated that AC electric fields applied to AFM chips can be well used for the sensitivity enhancement of a proteomic AFM-based fishing system. This allowed us to increase the detection sensitivity, reaching the detection limits of 10⁻¹⁸ to 10⁻¹⁷ M. As noted therein [1], the efficiency of fishing albumin protein correlated with the generation of charge occurring upon the input of the analysed solution into the measuring cell. The correlation between increasing the efficiency of protein fishing and efficiency of charge generation upon the input of analytic solution into a measuring cell through the injector of an AFM-based fishing system was also discussed. In Refs. [2-4], the efficiency of charge generation in an injector of an AFM-based fishing system in water and protein solutions upon their input with a peristaltic pump with preliminary neutralization of the charge after the pump has been considered. Earlier, the effect of spontaneous generation of charge in water due to a triboelectric effect in the absence of electric field was discussed in the paper by Choi et al. [5].
In our present paper, an injection part of a fishing system (which employs an AFM as a molecular detector) has been used to study the influence of external electromagnetic field on charge generation in flowing water and femtomolar albumin solution at 38°C upon their pumping through an injector (a pipette tip) without preliminary neutralization of charge of solution into a measuring cell containing an AFM chip. The protein molecules captured onto the chip surface in the course of fishing are to be detected on the chip surface by AFM. This scheme of solution input through an injector was employed by us earlier in AFM-based fishing biosensor measurements; it is also used in other analytical biosensor systems for their testing. As an electromagnetic field, sinusoidal AC electric field (of 50 Hz frequency, which occurs during the use of industrial electric devices) was used. As an object to be studied herein, bovine serum albumin has been selected, as it is a well-studied protein highly homologous to human serum albumin. Since analytical systems for studying biochemical processes in near-physiological conditions are operating in the temperature range near 38°C, our experiments have been performed at this temperature.

Herein, a stimulating influence of external electromagnetic field on charge generation in deionized water and albumin solution flowing through an injection part of a system, employing an AFM as a detector, has been observed.

Taking into account that charge state of protein solutions, which are injected through pipes or capillaries into the sensitive area of an AFM-based detector of fishing diagnostic systems (and also other highly sensitive systems, such as nanowire sensors), can have a significant influence on their sensitivity, the results obtained can be well used in analysis of operation efficiency of these systems. Moreover, the data obtained in the present study can be useful in the development of models describing physicochemical properties of protein solutions and hemodynamics in human body in normal and pathological states.

2. Methods
Deionized water (18 MΩ·cm resistivity) was obtained with a Millipore Simplicity UV system (Millipore, France). Fatty acid-free BSA (Sigma, cat. No. A6003) was dissolved in deionized water at 10⁻⁴M concentration. 10⁻¹⁵M BSA solution was prepared by sequential dilutions. Electric charge measurements were performed with an electrometer combined with the flow-based sample delivery system for AFM-based fishing [6].

Principal units of the sample delivery system included a peristaltic pump, a pipe with a tip for liquid delivery, and a measuring cell. Upon the measurements, water or protein solution (10⁻¹⁵M) was continuously pumped with an Ismatec ISM 597D peristaltic pump (IDEX Corp., Lake Forest, IL, USA) from a 50-mL polypropylene tube with a grounding stem inside, into the measuring cell. A sterile silicone pipe (40 cm length, 2.0 mm i.d.) with a standard disposable pipette tip (Eppendorf type, 1 to 10 µL nominal capacity, 0.4 mm i.d., Eppendorf AG, Hamburg, Germany) was used for the delivery of either water or protein solution. Flow rate (~15 µL/s) was set so that drops (~15 µL) were formed on the tip nozzle.

Stainless steel inner cylinder represents a measuring cell in the charge measurement system, connected to the electrometer. Charge registration accuracy was 0.1 nC.

The effect of a pulsed electric field on the liquids was produced with a sinusoidal voltage generator developed in IBMC. For this purpose, the tip of the liquid-supplying pipe was placed between two parallel metal plates; an AC sinusoidal voltage (100 V amplitude, 50 Hz frequency) from the generator was applied to the plates. The temperature of the analysed liquid (water or protein solution) was maintained using a Thermomixer Comfort thermoshaker (Eppendorf AG, Hamburg, Germany), into which the liquid-containing tube was placed. The experiments were carried out at 38°C.

3. Results
Figure 1 displays typical time dependencies of the value of charge accumulated in the measuring cell (∆q(t) dependencies) upon the input of water in the presence and in the absence of external sinusoidal electric field at 38°C.
Figure 1. $\Delta q(t)$ dependencies obtained upon pumping of water through the tip in the flow-based system in the absence (curves 1-4) and in the presence (curves 5-8) of sinusoidal electric field at 38°C and 15 µL/s flow rate.

As seen from Figure 1, for water in the absence of sinusoidal electric field (curves 1-4), a generation of charge and its accumulation in the measuring cell with a rate $\Delta q/\Delta t = 45\pm6$ nC/7 min is observed, and the $\Delta q(t)$ dependence is linear.

In the presence of the electric field (curves 5-8), an increase in the level of charge accumulation rate is observed, $\Delta q/\Delta t = 80\pm6$ nC/7 min. Thus, a stimulating influence of sinusoidal electric field on charge accumulation in the measuring cell by 78% at 38°C is observed.

Figure 2 displays typical $\Delta q(t)$ dependencies upon pumping of BSA solution in the presence and in the absence of external sinusoidal electric field at 38°C.

As seen from Figure 2, at 38°C, in the absence of external sinusoidal electric field (curves 1-4), a generation of charge in the protein solution and accumulation of this charge in the measuring cell with a rate $\Delta q/\Delta t = 49\pm1$ nC/7 min is observed.
In the presence of the electric field (curves 5-8), an increase in the level of charge arrived into the measuring cell with the protein solution and accumulated in the cell is observed, \(\Delta q/\Delta t = 82\pm4 \text{nC/7 min}\). Thus, a stimulating influence of sinusoidal electric field on charge accumulation in the measuring cell by 67% at 38°C is observed.

4. Discussion
As noted above, a charge generation occurs upon flow of a liquid through polymer pipes of the AFM-based fishing system [5]. In the same study, a linear character of time dependence of accumulation of charge induced in water was demonstrated.

The data obtained in our present study describe the effect of a 50 Hz sinusoidal AC electric field on charge generation in the course of flowing water and protein solution.

Let us consider summarized data obtained in our experiments. In this way, for water at 38°C, an increase in the value of charge accumulated in the measuring cell in 7 min from 45 nC (in the absence of electric field) to 80 nC (in the presence of electric field) – i.e., by 35 nC (by ~78%) has been demonstrated. For protein solution at 38°C, a stimulation of charge accumulation in the cell from 49 nC (in the absence of electric field) to 82 nC (in the presence of electric field) – i.e. by 33 nC (by ~67%) in 7 min has been observed. That is, the effect of electric field in the cases of water and protein solution is approximately equal.

Physical nature of the stimulation of accumulation of induced charge in water, flowing through a polymer pipe, can be described in the following way. As was discussed by Choi et al. [5], upon pipetting water through a pipette tip, a positive charge is generated at the expense of a triboelectric effect. Pershin et al. [7] reported about a phenomenon of excitation of a conversion of ortho-para isomers in the complex structure of water, representing a mixture of ice-like and liquid phases (para- and ortho-states of water); these states were characterized by different physicochemical properties (surface tension, viscosity etc.). Upon electrical excitation in AC electric field, similar increased conversion of the para-state of water to the ortho-state can occur. The possibility of such transitions in electromagnetic fields of several Hz frequency was reported by Pershin [7].

Thus, we have observed an increase in charge generation rate in water and in protein solution in the presence of a sinusoidal AC electric field. The change in the fraction of ice-like water structures in the presence of AC electric field can be one of the causes of the observed stimulation of charge generation.

It is known that 50 Hz sinusoidal electric fields have an effect on human organism. The effect observed in our study can determine the impact of these fields on hemodynamics in the body, as different phases of water have different physicochemical properties.

It is to be noted that the observed phenomenon can be useful for the development of models describing physicochemical properties of water and aqueous solutions.

5. Conclusion
An effect of a stimulating influence of sinusoidal AC electric field on charge generation in water and protein solution flowing through an injector of a fishing system for the detection of low-abundant proteins (which employs AFM as a molecular detector) without preliminary neutralization of the charge of the liquid after its pumping with a peristaltic pump has been measured.

Account for the discovered effect is important for the development of models describing physicochemical properties of water and aqueous solutions, as well as those describing the influence of sinusoidal electric field on the processes connected with circulatory system (including hemodynamics). It also will be useful in the development of novel highly sensitive diagnostic systems operating in the range of femtomolar concentrations.

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