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STRUCTURED BIOMOLECULAR FILMS FOR MICROELECTRONICS

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In order to develop the technology for dehydration of biomolecular films with specified parameters under an electrostatic field (EF), the structures of dehydrated films obtained from aqueous solutions of albumin molecules and deposited on solid glass substrates in the EF have been studied, dehydration conditions being varied. The resulting structures were examined under a microscope (with recording the micrographs) in the light passing through the films and in the one reflected from the substrates. An analysis of the micrographs made it possible to reveal characteristic inhomogeneities arising in the films and recognize their main types. The optimal regions of parameters in which the film production modes were predominantly realized were found. For the first time, a "bubble" model for interpretation of the spatially inhomogeneous structure of dehydrated biomolecular films was put forward. In the model, the processes conditioned by dissolved gases in the initial solutions were taken into account.

Keywords: self-organized structure, biomolecular film, microelectronics, biological molecule, electrochemistry, biosensor

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СТРУКТУРИРОВАННЫЕ БИОМОЛЕКУЛЯРНЫЕ ПЛЕНКИ ДЛЯ МИКРОЭЛЕКТРОНИКИ

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С целью разработки технологии дегидратации биомолекулярных пленок с заданными параметрами в электростатическом поле (ЭП), исследованы структуры дегидратированных пленок, полученных из водных растворов молекул альбумина и осажденных на твердых стеклянных подложках в ЭП; при этом варьировались условия дегидратации. Полученные структуры изучены под микроскопом (с регистрацией микрофотографий) в проходящем через пленки свете и отраженном от подложек. Анализ микрофотографий позволил выявить характерные неоднородности, возникающие в пленке, и выделить их основные типы. Определены оптимальные области параметров, в которых режимы получения пленок преимущественно реализуются. Впервые для интерпретации пространственно-неоднородной структуры дегидратированных биомолекулярных пленок предложена «пузырьковая» модель, в которой учитываются процессы, обусловленные растворенными газами в исходных растворах.

Ключевые слова: самоорганизованная структура, биомолекулярная пленка, микроэлектроника, биологическая молекула, электрохимия, биосенсор

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Introduction

Electronic devices incorporating organic layers on solid surfaces have rapidly gained importance in science and technology [1 – 13]. Studies and applications of polymer films (including protein, organic single-layer and multilayer) on solid substrates are diverse, combining physics, chemistry, materials science, biology, medicine, electronics, nanoscale engineering, etc. Biomolecular films are in demand for the protein production technologies, human genome sequencing, protein research, and in many other areas, ranging from food technologies to environmental problems [14 – 21].

Processes leading to chaotic or ordered inhomogeneities have been uncovered through implementations of technologies for synthesizing films on substrates [1 – 8]. For example, spatial inhomogeneities can evolve on the film surface, forming patterns of different size, order, morphology and complexity. Such patterns contain thin straight and curved lines dividing sections of the structure, ordered geometric shapes of bulges and depressions near the surface, as well as protrusions, grooves and cracks of varying depths, in particular those with long-range spatial order [4, 5]. Spiral, radial, circular cracks, etc., were observed in thin films. Some forms can be repetitive and stable; they are likely associated with some peculiar physicochemical properties observed in the films and their potential applications. For example, medical studies have established that the structure of patterns on dried samples of human blood, saliva, and tears can be used to diagnose diseases [6 – 8].

Isothermal dehydration can be an efficient and flexible method for incorporating biomolecular films in micro- and nanoelectronics; however, the nature of the inhomogeneities emerging and possible ways to eliminate them have not been fully understood yet [22 – 24].

The goal of the study consists in developing a technology for dehydration of biomolecular films with the given parameters at room and elevated temperatures under an applied electrostatic field, which are good candidates for microelectronics.

Isothermal dehydration method

The technology for removing water from a previously prepared solution (evaporation, dehydration, drying) is based on fundamental physical principles. Evaporation of atoms and molecules is described by the Clausius – Clapeyron reaction, essentially yielding a channel for loss of neutral particles:

$$n_a = bT^{1/2} \exp\left(-l_a / kT\right),$$

where n_a is the number of particles evaporating from a unit area per unit of time; l_a, J, is the work done during evaporation of a particle; T, K, is the temperature; k, J/K, is the Boltzmann constant; b, $K^{-1/2}$, is the thermal evaporation rate.

The mass transport of water from liquid surfaces is influenced by temperature, composition of the gas phase, activity of surface substances, bulk rheological properties and kinetics of vapor transport and heat flux through the surface, as well as the geometry of experimental conditions [25 – 27].

Film seems to have an optimal geometry for experiments developing the theory of evaporation from the surface, as it is characterized by small thickness in comparison with the other two dimensions. Isothermal processes in such objects make it possible to simplify their analysis. When self-organized structuring of the surface of a dehydrated biomolecular film on a substrate is caused by evaporation of the solvent at a constant temperature, stable patterns (including periodic ones) with widely varying morphologies appear on the film; the characteristic size of the patterns depends on the initial film thickness.

The heterogeneity of surface coatings arising through dehydration is caused by interfacial dynamic instability due to surface tension gradients, called the Marangoni instability [28, 29]. The main factors, namely the surface tension force and the viscous friction force, change along with varying temperature and amount of solvent.

As biological fluids have complex compositions, and there is a variety of physical, chemical, mechanical and other processes, the mechanisms behind the formation of different patterns induced by spontaneous evaporation are still poorly understood. The patterns observed are very intricate, so analytical formulas or a single model can hardly account for all the details of their formation [30]. The mechanism governing the growth of logarithmic spiral cracks is associated with a stress front propagating in a specific direction [31].

The pattern is affected by the structure of the substrate [32], temperature and humidity conditions, and the electric and magnetic fields applied to the objects during dehydration.

Ref. [33] reported on drying droplets of laponite gel (Laponite RD, a synthetic layered silicate) under an applied radial electric field. This created reproducible patterns that depended on the strength, direction and time of exposure to the electric field. As the electric field was applied, patterns on the film appeared after a certain amount of energy was dissipated.

Active electronic and physical properties of thin biomolecular films were discovered by impedance measurements and theoretical fluctuation studies [34, 35]. Such properties can be depend on the periodic structure of the films, which was revealed by optical measurements and methods of non-equilibrium thermodynamics [36, 37].

Correlations were found between the dynamics of protein film formation and the ionic component concentration in the initial solution, which made it possible to link the evolving processes with polarization of the sample's molecules (their electrical nature) [38, 39]. The effect of an electric field on protein (polypeptide) biomolecular films is a crucial problem for microelectronics; however, data on the subject are scarce in the literature.

It is known that biomolecular electrical conductivity is provided by different kinds of charge carriers, electrons and protons in molecules, playing a major role in the processes that govern the biological world; this type of conductivity can be implemented in electronic devices. Recent studies have substantiated the theoretical foundations of biomolecular electronics and ionics, proving that it can offer viable technologies [9, 10]. Remarkable strides have been made in producing biomolecular materials in the form of film metamaterials, which can maintain ion and electron currents over millemeter ranges in microelectronic devices. The structure of biomolecular metamaterials determines the electrical impedance over a wide frequency range, as well as the characteristics of electronic devices incorporating such materials.

We experimentally studied the spatial structure of dehydrated protein films obtained from an aqueous albumin solution on a dielectric substrate during isothermal drying at varying concentrations of the initial solutions, temperatures, and constant electric fields applied with the strengths ranging from zero to approximately 1 V/cm. We tested large molecules that can serve as good candidates for micro- and nanoelectronics during dehydration of solutions for the first time ever.

Method

Albumin protein (Human albumin) from Biotest Pharma GmHb (Dreieich, Germany) was used in the experiments. An aqueous solution with an initial concentration of 20% (200 g/L) was prepared from albumin. Working samples with a volume of 2 ml, each with concentrations of 2, 5, and 10%, were prepared from the primary solution for each experiment. The samples were placed in glass Petri dishes 20 mm in diameter.

Fig. 1 shows a schematic view of the experimental setup for studying the spatial structure of protein films dehydrated in a thermostat under an applied electric field. The setup contained a flat capacitor with fixed plate-shaped coatings (F. Pl.) made of stainless steel with the dimensions of 100 × 100 mm; the distance between the plates was 20 mm. Experimental solu-

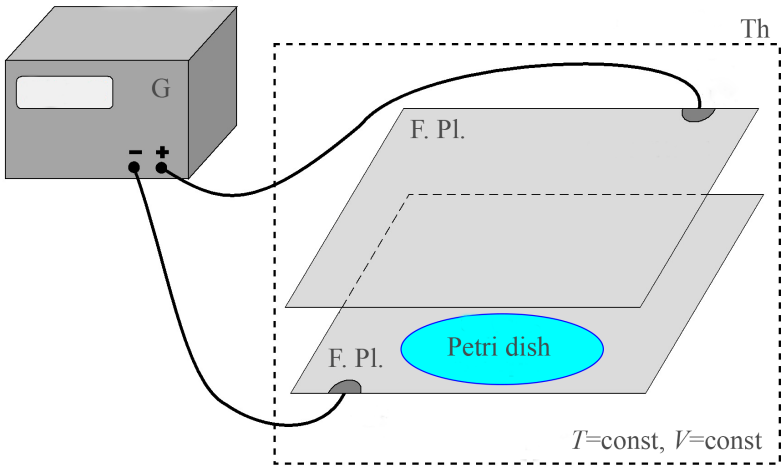

Fig. 1. Schematic representation of the experimental setup used for studies of the spatial structure of the protein film during its dehydration in an electric field: G – electric field generator; Th – thermostat; F. Pl. – fixed capacitor plates; Petri dish – Petri dish with aqueous solution

tion samples in a Petri dish were placed between the plates in an electric field (with a strength of 0; 0.5; 1.2; 5.0 V/cm) and put into a thermostat (Th) (at temperatures of 293, 298, 303, 308 and 313 K) for a dehydration period, which varied widely, from one hour or longer. A TC-1/80-SPU thermostat with forced air circulation was used to dry the films. The humidity in the thermostat chamber was 20 ± 1%.

Images of the films were recorded in transmitted light using an Olympus CX 43 optical microscope and a USB camera. We used an Altami UHCCD05000KPA camera with a resolution of 1280 × 980, a SONY ICX282AQ sensor, and a PlanC N microscope lens with a 40× magnification, an aperture of 0.10, and 24-bit depth. The spectral range was 380 – 650 nm.

All micrographs in this paper were recorded on a common scale. The average thickness of the obtained samples was 200 ± 10 μm with the measuring probe positioned on the sample in the center and at the edge of the cuvette.

Experimental results

Fig. 2 shows images of spatio-temporal structures in albumin protein films obtained at different strengths of the applied uniform electric field. Spatially periodic images were observed, containing thin dark straight lines delimiting individual regions, as well as transparent disks with circular or spiral boundaries.

After albumin films were dried, the typical sizes and densities of the disks and spirals changed with varying external conditions. The height h of disks and spirals was about 100 μm, corresponding to the film thickness H from $h << H$ to $h \approx H$. As the surface was quasi-periodically filled with such regions, the film acquired spatial ordering, exhibiting pronounced properties of a metamaterial. The main structural elements observed in Fig. 2 and below are represented by two types of patterns:

segments dividing straight and curved lines;

a network of disk granules.

All images in Fig. 2 have the same scale; a scale bar (300 μm) is given in the first image. The dividing segments are likely due to are caused by folds and higher density regions in the structure of the film obtained. Compact small-sized disk granules, transparent or bounded by circular and spiral dark walls are observed in the regions between straight lines (see Fig. 2). The spiral structures around the disks are similar to those described in the literature [40, 41]. A similar study

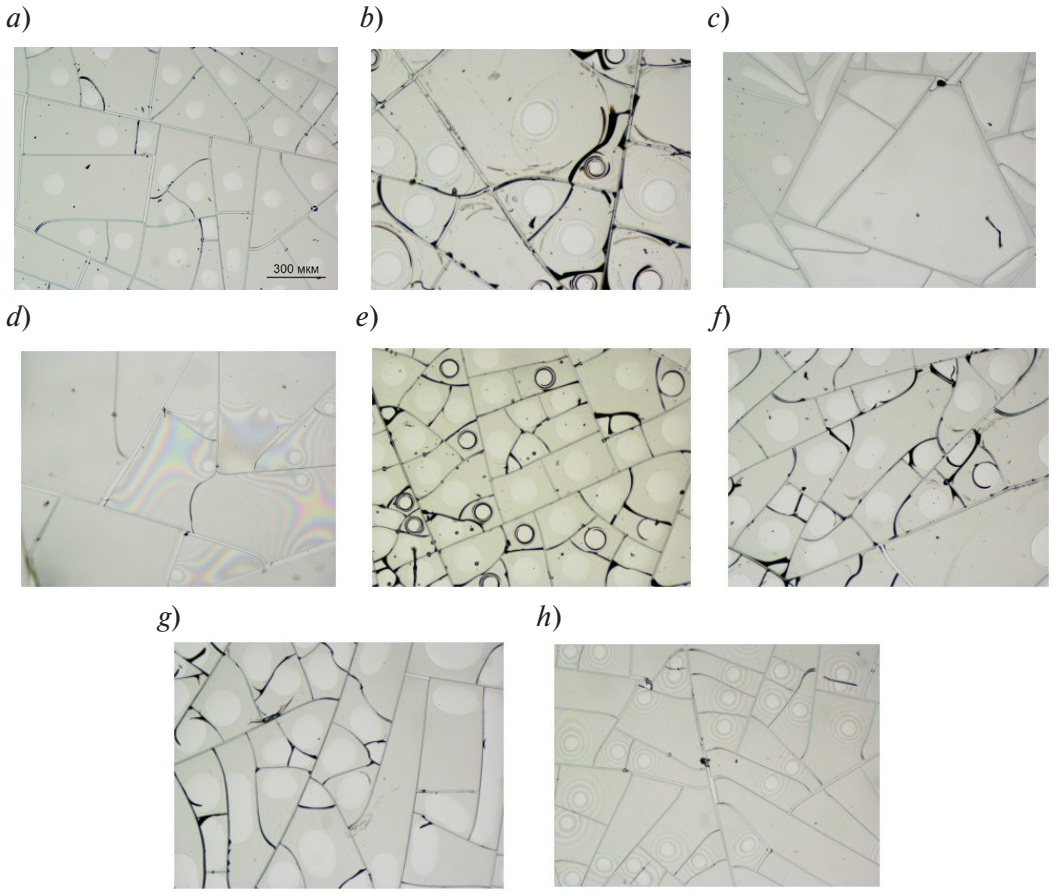

Fig. 2. Micrographs of protein films obtained at different albumin solution concentrations (2% ($a - d$) and 5% ($e - h$)) and electric field strengths, V/cm: 0.5 (a, e), 1, 0 (b, f), 2.0 (c, g), 5.0 (d, h); dehydration temperature $T = 310$ K

[41] obtained Newton's interference rings during sample drying. The authors attribute this to delamination of the film with an air gap growing between the sample and the glass substrate. Similar structures were also formed in our experiments. The same as in [41], they can be associated with diffraction of light by air bubbles and subsequent interference.

Spiral formation was linked to thermomechanical stresses, growth dynamics, and osmotic pressure in [40] and studies. To analyze the growth dynamics, we recorded the results of isothermal dehydration of protein films at different times, monitoring the film cracking process. Fig. 3 shows photographs (with a scale bar) of the inhomogeneities formed with a time step of 1 s. The finer details coincide in all images, which means that the processes are slow and fast changes are not observed.

Thermomechanical stresses and adhesion to the substrate depended on the mass of residual water, which was determined by weighing. The resulting dependence of the water mass on the protein concentration in the initial solution is shown in Fig. 4.

The dependence (Fig. 4) decreases smoothly as the initial concentration of albumin is increased to 15% (wt.%). The film was strongly bonded to the substrate in these conditions. The film became unstable with poor adhesion to the substrate at an initial albumin concentration of about 20% or higher. Comparing our results with the numerical data given in [42], we can analyze the dependence of free energy for dry film on the mass of residual water, as well as stability and adhesion of the films. However, such analysis is not given here as it would be beyond the scope of this study.

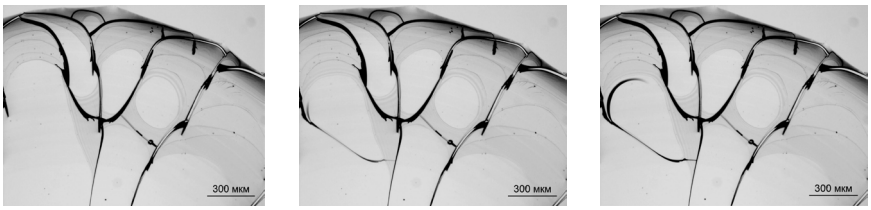

Fig. 3. Images of film inhomogeneities at different time moments with a step of 0.25 s.
The first image corresponds to 10 s after the object removal from the thermostat

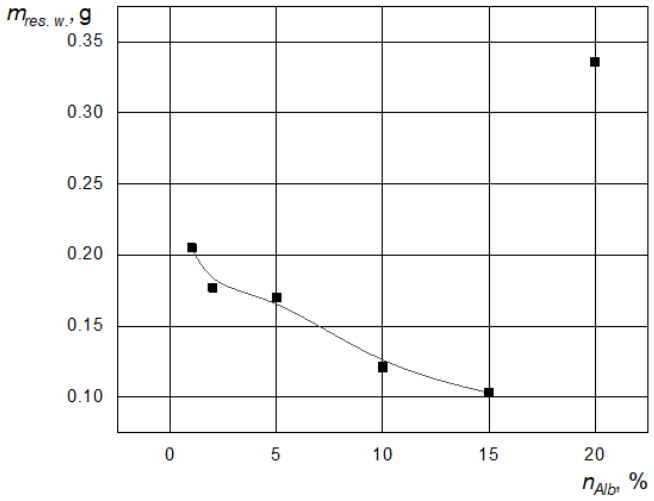

Fig. 4. Dependence of residual water mass in dehydrated albumin films
on albumin concentration in the initial solution

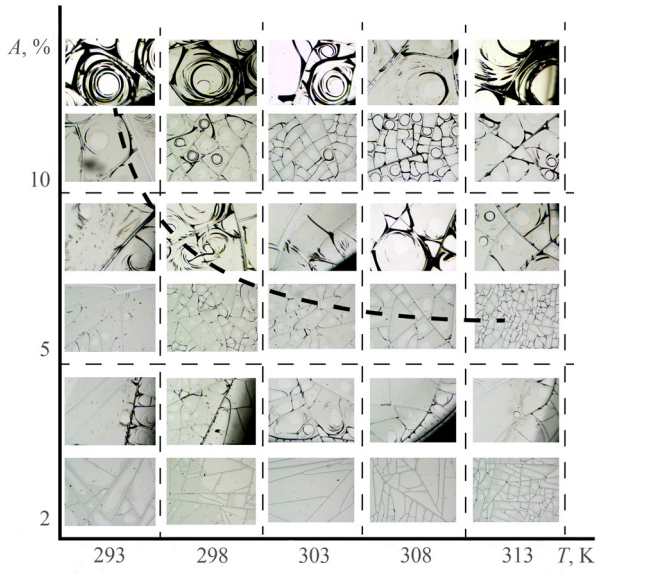

Fig. 5. Images of spatial structures in albumin protein films obtained
at different initial concentrations of albumin protein solution (determined by the mass
of components and plotted along the ordinate) and dehydration temperatures.
The dotted curve shows the approximate border of the regionb with increased
surface density of disk structures (the region lies above the curve)

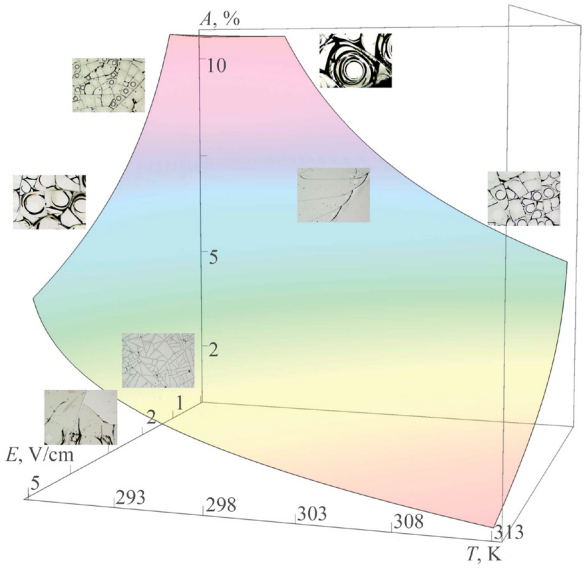

Fig. 6. Curved surface (obtained experimentally) separating the regions of increased and decreased concentrations of helical structures in dehydrated films of albumin protein as a function of initial solution concentration, dehydration temperature, and strength of the applied electric field

Fig. 5 shows the images of spatial structure for albumin protein films at different values dehydration temperatures and initial concentrations of albumin protein in the working sample.

Changes in temperature and concentration of albumin protein in the sample during dehydration had a joint effect on the disk granule structures evolving. Microscopic granules changed from transparent disks to those with circular or spiral boundaries under some conditions. The increase in the surface density and the total area of the spiral forms became more pronounced with higher concentrations of the initial solution in the working sample. More stable films and smoother lines dividing the surface regions were produced with higher dehydration temperatures. The dashed curve in Fig. 5 separates the region with increased surface density of disk structures, including circular and spiral forms (the latter lie mainly above the curve).

Fig. 6 shows an experimentally obtained curved surface separating regions with increased and decreased concentrations of disk (including circular and spiral) structures in dehydrated albumin films. This surface is given as a function of three parameters: the initial concentration of the solution, the dehydration temperature, and the strength of the applied external electric field. The spiral structures generally did not appear in the region lying below this surface. The quality of the films was assessed in this region by the observed division into regions with rectilinear or curved boundaries.

Increased concentrations of transparent disk granules, circular and spiral structures were observed in the films at sufficiently high initial concentrations of the solution, dehydration temperatures, and external electric field strengths. These results provide an insight into the nature of the physical processes occurring at the stage of film dehydration, making it possible to formulate the models explaining their evolution.

Discussion

The data given in Fig. 6 can serve as a basis for developing model representations of the physical processes occurring. We believe that the model propose should link the formation of spherical cavities (bubbles) with the reduced density of particles in solution films at the dehydration stage. It is likely that small volumes of air released from the solution act as such particles. Indeed, the phenomenon of bubble formation can be explained by taking into account the presence

of dissolved air in the initial working sample at atmospheric pressure. Outward signs indicate that this is similar to internal vaporization during liquid heating. However, quantitative analysis suggests more complex dependences on the parameters of the processes, which have not been sufficiently studied.

As water molecules evaporate, the boundaries of the film approach each other and the dissolved air is compressed, which leads to formation of gas bubbles. The bubbles appear as transparent disks in micrographs of the films (obtained in transmitted light). Due to high values of viscosity forces of the solution and surface tension, migration of bubbles is slow, and some of them remain bounded in the dehydrated film. As air escapes to the film surface, the protein mass may be stretched at the boundary of the channel in which the air bubble moves, with such stretching leading to a compacted a circular state.

The simple model we propose can qualitatively characterize the processes of formation of the observed structures by taking into account the presence of dissolved air in the film but requires a more complete quantitative description. In our opinion, this model is more adequate than those suggested earlier. It is proposed for the first time. A uniform bubble size distribution speaks in favor of our model. In addition, the model takes into account the physical processes of dissolution (absorption) and release of gases in liquids. The average bubble diameter is much smaller (by an order of magnitude or more) than the film thickness. Exfoliation of film sections from the substrate cannot be uniform in surface and shape, and, moreover, cannot be reproduced for different substrates in different measurement modes. Considering the processes associated with dissolved air turns out to be sufficient to interpret the results obtained, making it possible to ignore secondary physical effects.

Escape of air bubbles to the surface of the film can explain not only the disk shape of the patterns formed but also the spiral shapes evolving, which complements or even replaces the traditional thermomechanical model [43].

A spatially inhomogeneous film can form in an electric field under the action of nonstationary temperature and vapor-gas mechanical stresses, as well as external electrostatic pressure under lateral and spatial charge redistribution.

The measurement results (Fig. 6) indicate that the external electrostatic field has a pronounced effect. Indeed, the pressure of the electric field on the surface due to polarization of protein and water molecules is proportional to the square of the electric field strength E:

$$\frac{F}{S} = \varepsilon\varepsilon_0\sigma E^2,$$

where F, N, is the local value of the force acting on the region S (m^2); E, V/m, is the strength of the electrostatic field; ε is the relative dielectric constant of the film substance in the corresponding phase state; ε_0, F/m, is the dielectric constant ($\varepsilon_0 = 8.85 \cdot 10^{-12}$ F/m); σ, S/m, is the specific electrical conductivity.

The component of the electric field E normal to the film surface can induce a lateral charge redistribution in the volume of the liquid phase due to the appearance of a concentration gradient of ions and the potential they generate. The dielectric constant ε_0 produces a nonuniform disjoining pressure. In addition to thermomechanical effects, this pressure can increase the film deformation, leading to the formation of lines with higher density separating individual regions of the surface. Notably, however, the general effect of the electrostatic field is much more complex.

The polarizing electric field in an aqueous solution is proportional to the concentration of protein impurity ions, and the mobility of impurity ions is proportional to the process temperature. An increase in the impurity concentration and temperature lead to an increase in the ion current density and, accordingly, in the lateral and spatial charge redistribution. Lateral and spatial charge redistribution includes electrophoretic migration in the volume at the liquid phase stage, as well as induced surface charges at the transition stage to the solid phase.

Conclusion

We have considered the structure of dehy-

drated films obtained from aqueous solution of albumin molecules on a solid glass surface at an elevated temperature and under an applied external electrostatic field. Solutions of large molecules that appear to be suitable candidates for microelectronic technologies were tested for dehydration for the first time ever. The initial concentration of molecular solution, temperature conditions, and the strength of the electrostatic field applied were varied during dehydration. The method for studying the obtained films consisted in recording micrographs in the light transmitted through the film and reflected from the substrate. Analysis of the images revealed characteristic inhomogeneities of two main types in the films:

regions separated by thin lines,

microscopic disk-shaped granules (including those with pronounced circular or spiral boundaries), distributed over the surface.

As a result, we have found the parameter ranges for the conditions in which either the first or the second type of inhomogeneities evolves.

We have proposed a novel 'bubble' model for interpreting the spatially inhomogeneous structure of dehydrated biomolecular films accounting for the processes produced by dissolved gases in the initial solution.

The structure of the protein films synthesized apparently correlates with temperature conditions, the concentration of biomolecules in the initial solution and the applied electric field, which are characteristic for the studied dehydration processes. This provides insights into the thermomechanical and electrical nature of some of these processes.

The effects of dissolved gases and the bubble mechanism should also be taken into account in descriptions of the processes occurring in films prepared by other methods, for example, Langmuir – Blodgett or layer-by-layer deposition.

The proposed dehydration mechanism is at the stage of supercomputer and experimental verification. The data can be used to develop technologies for producing high-quality films with specific parameters, in particular, for microelectronics applications.

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