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Hypothetical physicochemical mechanisms of some intracellular processes: The hydrate hypothesis of mitosis and DNA replication

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Abstract

A DNA replication, mitosis, and binary fission hydrate hypothesis (MRH hypothesis) allowing non-trivial explanations for the physicochemical mechanisms of some intracellular processes is proposed. The hypothesis has a thermodynamic basis and is initiated by original experimental calorimetric and kinetic studies of the behavior of functional organic polymer and monomer substances in highly concentrated aqueous solutions. Experimental data demonstrating the occurrence of a short-range ordering in concentrated aqueous solutions of such substances are included. Hypothetical simple non-enzymatic unified mechanisms for the natural processes of DNA local unwinding preceding the start of duplication, DNA replication, formation and disappearance of the protein bonds between sister chromatids in the centromere region of eukaryotic DNA and in the centromere-like region of prokaryotic DNA, moving of daughter chromosomes apart to the opposite sides of cells in late anaphase, and formation of the nuclear envelopes in telophase and intracellular membranes between the newly formed nuclei in cytokinesis are formulated. The nature of a number of other intracellular phenomena is discussed.
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1. Introduction

In this paper, we try to reveal the central common natural physicochemical phenomenon underlying division of prokaryotic and somatic eukaryotic cells. Following Oparin [1], we consider living organisms as systems not differing fundamentally from the lifeless matter, i.e., we hold that the intracellular processes are controlled by the universal physical and chemical laws. We proceed from the assumption that eukaryotic mitosis [2 (Ch. 4), 3 (Ch. 13)] and prokaryotic binary fission [2 (Ch. 4), 3 (Ch. 12)] are connected with the same definite fundamental natural physicochemical phenomenon that has them "in tow". In other words, the same physicochemical phenomenon is the prime cause of the eukaryotic mitosis and prokaryotic binary fission. Otherwise, we should evidently take it that the first prokaryotes and the first eukaryotes had originated in nature independently and their subsequent metabolism and evolution were controlled by different physical and chemical regularities. In this case, these two branches of living matter most likely should be incompatible in their vital functions. Meanwhile, living organisms belonging to numerous species characterized by the anatomies and physiologies that are intermediate between those inherent in typical prokaryotes and eukaryotes are common in nature. This reasoning gives an indirect confirmation for our assumption on the similarity of the prime physicochemical causes underlying the mitosis and binary fission. We see additional confirmation for this assumption in the following fundamental common features of the anatomies and metabolisms of prokaryotes and eukaryotes. First, prokaryotes and eukaryotes transmit their principal hereditary characters from generation to generation through DNA molecules, which are similar in their chemical composition and molecular structure. Second, the eukaryotic mitosis and prokaryotic binary fission are principally similar in their results. Namely, either of them results in separation of genome into two identical halves and in subsequent cytokinesis leading to division of the cytoplasm and cell membrane into two identical new cells. Third, both the eukaryotic mitosis and prokaryotic binary fission are preceded by the DNA replication processes similar in their principal results. The hypothesis developed in this paper contains the supposition that

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formation of new nuclear envelopes and of cell membranes between two newly formed cells in the processes of mitosis and cytokinesis is provided by precipitation of complex organo-mineral substances from oversaturated solutions. However, the central phenomenon providing the existence of living matter is not mitosis as such, but transmission of duplicated genomic information from parental genomes to daughter ones, i.e., the DNA replication. We suppose that DNA replication is initiated by the neutralization of the amide–amide interactions in DNA double helixes by water dipoles. Thus, two familiar and commonly known natural phenomena (precipitation from oversaturated solutions and neutralization of the DNA–DNA dipole interactions by water dipoles) summarized with the phenomenon of continuous diffusion of water and organics into living cells from the outside represent the basis for the phenomenological content of living-matter reproduction.

However, each of these three phenomena proceeds monotonously in time and, therefore, the last statement as such is only a declaration that does not clarify metabolic processes. This paper represents an attempt to reveal the mechanisms of transformation of these monotonous processes into the cyclic ones providing development of living matter, including mitosis and DNA replication. We try to show that the so-called genetic code is nothing but manifestation of the universal physical and chemical laws guiding the chemical transformations in aqueous media containing organo-mineral substances of definite chemical compositions. We by no means consider all factors influencing the processes under consideration but try to reveal the core phenomena controlling the directions of these processes. Finishing the introduction to this paper, we would like to say that the occurrence of individual organelles inside living cells is not necessarily caused by the usefulness of all these niceties for the metabolic processes. The occurrence of some of them might be caused by the natural processes of precipitation of one or another organic crystal structure from the saturated solution, and their disappearance in the course of mitosis or replication might be associated with swelling or dissolving caused by the concentration variations within the cell. The complexity of the structures of intracellular organelles and the repetition of the structures from cycle to cycle by no means contradict this opinion. Indeed, now that a lot of supramolecular crystals are synthesized artificially, we know well how daedal and fantastical the forms of precipitated crystal organics can be. Some organelles, such as chloroplasts and mitochondria [4] in eukaryotic plant and animal cells, have their own DNA and, evidently, use the intracellular medium just as the corresponding eukaryotic plant and animal cells use their environment.

2. Involved information

The external manifestations of the processes accompanying the DNA replication and mitosis in living organisms are studied comprehensively and described in detail in the scientific literature (e.g., [2,3,5]). However, when some phenomenon or thing is observed in any experiment, it is not always clear whether it represents a necessary or inactive component and a constituent or an attendant with respect to the process under study. For example,

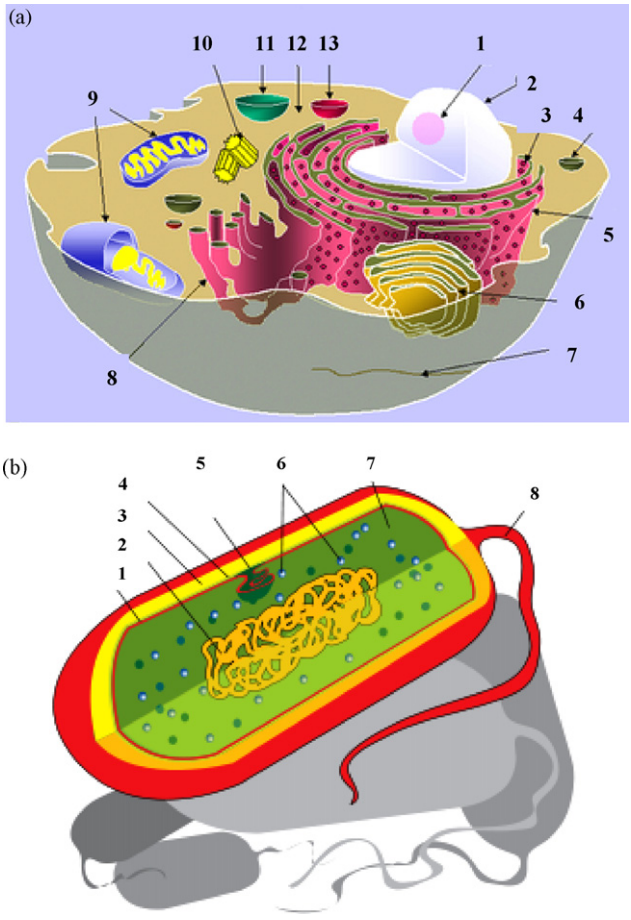

Fig. 1. Intracellular structures of: (a) eukaryotic cell: 1 – nucleolus, 2 – nucleus, 3 – ribosome, 4 – vesicle, 5 – rough endoplasmic reticulum (ER), 6 – Golgi apparatus, 7 – cytoskeleton, 8 – smooth ER, 9 – mitochondria, 10 – centrioles, 11 – vacuole, 12 – cytoplasm, 13 – lysosome; and (b) prokaryotic cell: 1 – plasma membrane; 2 – DNA (nucleoid), 3 – capsule, 4 – cell wall, 5 – mesosome, 6 – ribosomes, 7 – cytoplasm, 8 – bacterial flagellum (http://en.wikipedia.org/wiki/Cell (biology)).

it was recently stated that, in eukaryotic cells (Fig. 1), the centrosomes are not necessary for either mitosis or DNA replication [6]. Besides, the possibility of artifacts must not be ruled out in observations of so fine substance as living matter and its transformations. For example, the mesosomes (see Fig. 1) allegedly found in prokaryotic cells are, apparently, artifacts.

The eukaryotic cells are very complicated as compared to prokaryotic cells, and it is believed that almost all their elements and a multiplicity of enzymes participate in mitosis and DNA replication. The prevalent present notions on the eukaryotic-cell cycle set nature too many difficult problems for creation of all these elements and processes. Meanwhile, according to I. Newton (“Principia”), “... Nature is simple and does not luxuriate in excesses”. Most probably, by no means all the elements occurring in the eukaryotic cells are necessary for mitosis and replication. For example, in eukaryotes, the mitachondria and chloroplasts, besides the centrosomes mentioned above, are apparently unnecessary and are derived by Arhean eukaryotes from endosymbiotic bacteria as a result of evolution [7]. The functioning of some enzymes in the replication processes is

questionable. Thus, it is not clear how topoisomerase "finds out" when it should begin to affect the DNA double helix and why the molecules of other enzymes do not hinder each other from performance of their functions and "go away" at the right moment during the steps of replication. In prokaryotic communities, mitosis and DNA replication proceed in spite of the fact that the sets of structural elements and enzymes inherent in their cells are much poorer than those inherent in eukaryotic cells. Prokaryotes differ from eukaryotes very strongly, and, besides, the species with different intracellular structures and with different noticeable features of mitosis and replication occur among the former and the latter. Such a universal possibility of realization of mitosis and replication on the basis of very different intracellular structures and peculiarities of the processes underlying mitosis and replication gave us grounds for the supposition that a general intrinsic property defying direct observations but, nevertheless, providing these processes should exist in all living systems.

We develop the hypothesis according to which the intracellular processes are regulated by the well-known physical and chemical property of water to form hydrate structures (structures of the so-called gas-hydrates) in different water–substrate systems. The idea about water structuring inside living cells is not alien to the views, according to which cell water exists in a non-aqueous highly ordered state [8–10].

Let us introduce brief information on gas-hydrates [11–14], because we will repeatedly return below to this class of chemical substances. The term "gas hydrates" is used because the compounds of such a type were first identified as solids consisting of water and methane or one of noble gases; later, it was found that not only gases but also liquids (for example, tetrahydofurane, propylamine, etc.) are capable of forming such compounds. Hydrates of methane and noble gases are stable under corresponding pressures of the hydrate-forming gases, the equilibrium pressure being dependent on the temperature, nature of the hydrate-forming gas, and pressure of the so-called auxiliary gases, e.g., O_2, N_2, or H_2; hydrates of different organic substances are stable under the atmospheric pressure [12,13]. The well-known gas-hydrates represent honeycomb-like solid systems. Usually, gas-hydrates have the structure I or the structure II. Below, we will deal with the gas-hydrate structure II (Fig. 2). This structure is formed by host honeycomb-forming water molecules and some guest particles, which can be atoms, rather small polyatomic molecules, or functional groups of large molecules. The gas-hydrate structure II represents cubic crystal lattice build of unit cells with the lattice constant $a = 1.74$ nm. Each unit cell contains 136 waters forming 16 small and 8 large cavities. The guest particles are housed within large or small cavities (suitable for housing particles of size up to 0.69 or 0.48 nm, respectively) and are bound with the waters by weak van der Waals forces rather than by valence forces. As guests, particles of one type or two different types can be included into the large cavities and, in addition, particles of a third type can be included into the small cavities. The capability for hydrate formation is a fundamental property of water molecules. It is well-known that a number of multi-atomic organic substances are capable of hydrate formation under definite conditions. Sometimes,

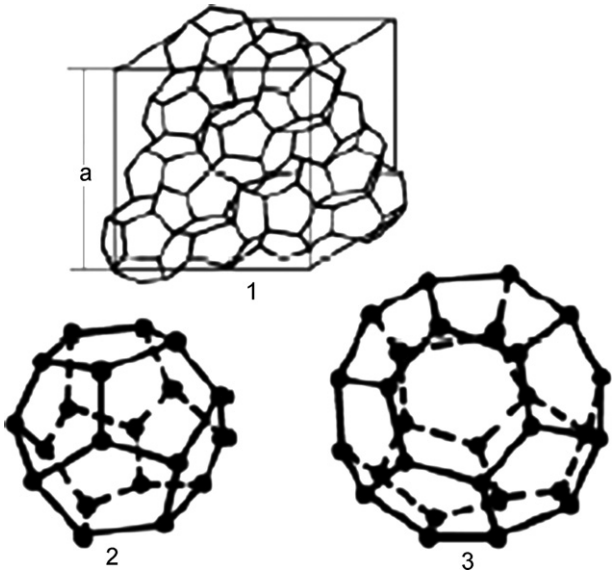

Fig. 2. Gas-hydrate crystal lattice of the structure II: (1) unit crystal-cell consisting of 136 waters forming 16 small and 8 large cavities; $a = 1.74$ nm; (2) small cavity, pentadodecahedron with $d = 0.48$ nm; (3) large cavity, hexadecahedron with $d = 0.69$ nm.

atoms of large-sized guest molecules partake in the formation of the "walls" of the cavities [15], for example, in the so-called semi-clathrate hydrates, such as hydrates of *n*-propylamine and other alkyl-amines. When each large cavity of the gas-hydrate structure II is filled with a guest particle, the water-to-guest stoichiometry n is equal to 17. If not all large cavities are filled with guest particles, this structure can exist up to n value equal to about 20. If the water content in the system increases, the hydrate structure destroys; however, the short-range ordering can keep. The decrease in the Gibbs free energy at structuring in the water (ice)–guest phase system is rather small and, therefore, the processes of hydrate formation are sensitive to the external conditions.

It was mentioned that the widely distributed gas-hydrates are solids. Meanwhile, the intracellular processes proceed in liquid, colloid, or gel media. The structuring in colloid or gel media reveals itself usually as the short-range ordering around order-forming molecules rather than the extended three-dimensional structure. Therefore, the processes of structuring in such media are difficult to study and are observable on the basis of only indirect measurements of different physical and chemical parameters, such as the inductivity, heat effects, kinetic effects, etc. One of the main difficulties of such studies is associated with the fact that the reversible order–disorder transformations in gas-hydrates are accompanied with rather small energy effects, and thus the energy fluctuations caused by convective processes, perturbations, and thermal motion of molecules in colloid or gel media at the temperatures at which solid hydrates are unstable can be sufficient for destroying the loosely coupled gas-hydrate structures. Therefore, studies of ordering in such systems require especial carefulness and are not easily reproducible. Meanwhile, the available data and generalizations allow the conclusion that the tendency to formation of structured hydrates inherent in solid water–substrate systems should be anticipated for gel-like highly

concentrated water media under conditions when the temperature is not too high. In rather extended systems, this tendency should reveal itself in formation of short-range ordering; however, it can be expected that, in small-size closed systems, such as biological cells, hydrate structures can occupy a significant portion of their volumes and influence significantly the chemical mechanisms.

Apparently, in the gas-hydrate structures, the water dipoles are neutralized to the highest degree; i.e., the water partial molar free energy in these structures is minimal. Just therefore, water tends to formation of such structures in different two- and three-component systems if the sizes of guest particles do not go beyond the sizes of the structure cavities. We think that the structures of the crystal monohydrates of thymine (Th), guanine (G), and cytosine (Cy) (Th·H_2O [16], G·H_2O [17], and Cy·H_2O [18,19]) represent the precursors of the corresponding highly wetted hydrate structures, which cannot be obtained in the crystal state, because water in them is bound very weakly and evaporates in the open air at a relative humidity below 100%.

Earlier, we developed a hypothesis according to which the water ability for hydrate formation underlies the natural origination of the simplest elements of living matter [20–24]. In Refs. [20,21], we proposed the basic principles for the hypothesis allowing explanation of the processes of mitosis and DNA replication on the basis of well-known physical and chemical notions, among which the notion on the formation–destruction of hydrate-like structures in the course of mitosis and replication is the central one.

This paper represents a subsequent development of the hydrate hypothesis of mitosis and DNA replication (hereafter the MRH hypothesis). The development of the MRH hypothesis is initiated by original experiments on water interaction with some substrates modeling DNA and other biological substances and by analyses of available literature data on interactions between DNA and water, mitosis, DNA replication, origin of life, and related subjects. Some of these experiments and some results of analyses of the available data are presented in Refs. [24–29] and [20,21,24], respectively.

It is well known that DNA molecules (Fig. 3a and b) [30] contain hydrophilic groups of three types: phosphate, desoxy-*d*-ribose, and nitrogen bases (N-bases). The functional groups of each type have a specific affinity to water. It is known that air-curing of dry solid phosphoric acid at 80–85% air humidity leads to its liquation, sugars become wet and caked at somewhat higher humidity, and N-bases absorb water with a noticeable rate only at 100% humidity. For understanding the mechanisms of DNA behavior in the course of mitosis and replication, water interaction with N-bases is of prime interest, because just such interactions are responsible for the DNA–DNA binding in the double helixes. The DNA–DNA bonds can be modeled by the bonds occurring between molecules of polyamides and amides. An idea of calorimetric studies of model substrate–water systems for clarification of the processes proceeding in protein-like systems was formulated, for example, in Ref. [31] and stimulated a number of studies directed to clarification of the behavior of amides in aqueous solutions.

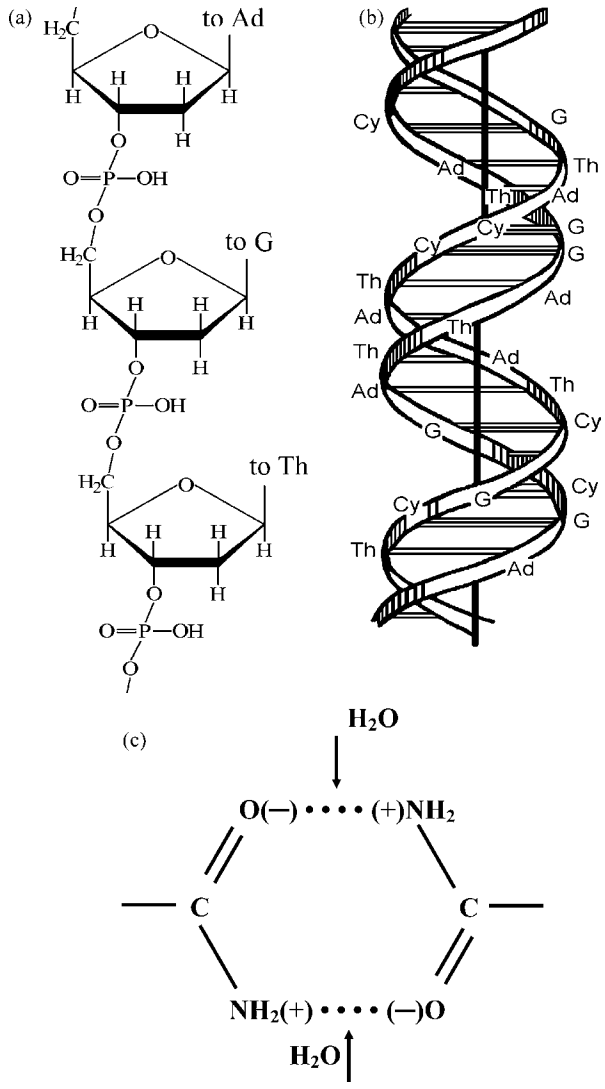

Fig. 3. Fragments of: (a) DNA helix and (b) DNA double helix; (c) hydrogen bonds between amido-groups of polyacrylamide molecules.

The amide–amide binding is shown in Fig. 3c. It is seen that each amide–amide binding is provided by two $NH_2\cdots O$ hydrogen bonds. The bonds of the same type make a major contribution to the DNA–DNA interactions (Fig. 4). In DNA–DNA double helixes, binding of cytosine–guanine and thymine–adenine pairs is provided by three $NH_2\cdots O$ bonds and two $NH\cdots N$ bonds. The energy of $NH\cdots N$ binding is significantly lower than the energy of $NH_2\cdots O$ binding, because the dipole moment of the $NH\cdots N$ bond is much smaller than that of the $NH_2\cdots O$ bond. Therefore, it is possible to consider approximately that the mean energy of purine–pyrimidine binding in the DNA double helix corresponds to the energy of two $NH_2\cdots O$ bonds, and thus the binding energies for any purine–pyrimidine pair in the DNA double helix and for any amide–amide pair are almost the same. When applying the data on the water–amide interactions for clarification of the DNA–DNA interactions in double helixes, we should keep in mind the following. The DNA–DNA and DNA–water interactions are much more similar to the

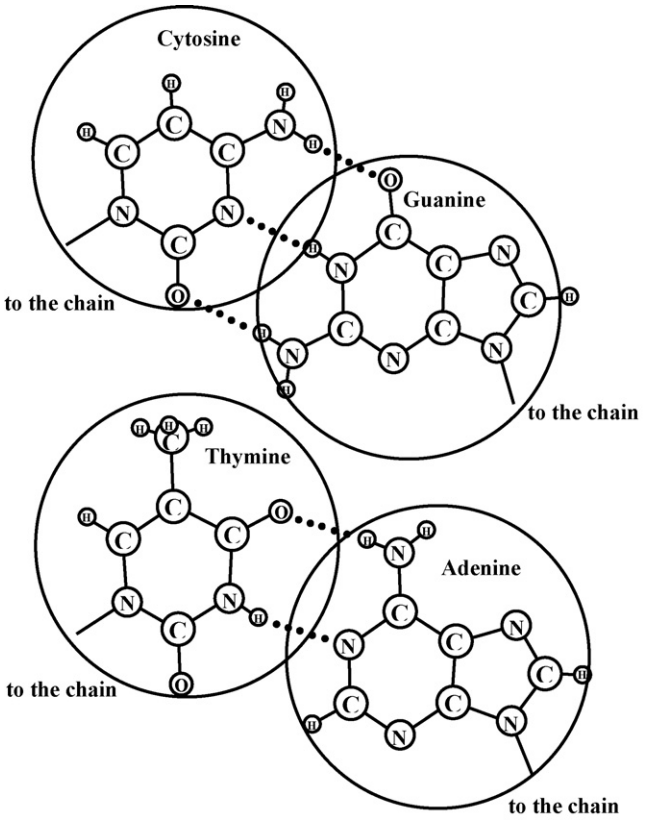

Fig. 4. Agreement between the sizes of N-bases belonging to a DNA double helix and of large cavities (large circles, $d = 0.69$ nm) of the hydrate structure II (the figure is given in proper scale).

polyacrylamide–polyacrilamide (PAA–PAA) and PAA–water interactions than to the acrylamide–acrylamide (AA–AA) and AA–water interactions. Indeed, the AA molecules are small in size and movable and, therefore, each of them can interact with more neighboring molecules than the PAA and DNA amido-groups, which are not movable and are joined to the polymer molecules; in addition, the PAA and DNA amido-groups are separated from each other in space and, therefore, they cannot interact with each other. Nevertheless, combined consideration of the data on the PAA–PAA and PAA–water interactions with the data on the AA–AA and AA–water interactions allows for revealing the peculiarities in the PAA behavior and, thus, for better understanding the DNA–DNA and DNA–water interactions.

The molar integral heats of dissolution of liquid formamide and solid acetamide [32–34], AA [35], and PAA [36,37] are negative and small in magnitude. The negativity of the molar integral heats of dissolution together with the data on the viscosity [38] and on the NMR spectra [39] for the PAA–water systems stimulated the idea about the tendency for hydration of amido-groups in aqueous solutions (see, e.g., Refs. [37–39]). The measurements of conductivity showed that in highly wetted, diluted PAA (and also AA)–water systems, each amido-group is seemingly bound to 5–6 water molecules [40]. The authors of paper [39] indicated that the hydrogen binding between the amido-groups is not extensive. In Ref. [37], it was concluded that amides and waters form discrete complexes. A similar conclusion was made in [38]. However, integral calorimetric measurements are low-informative for revealing the molecular mechanisms of physical and chemical processes. Apparently, we were the first to develop differential measurements of the heat effects of water–substrate interactions in combination with differential kinetic measurements and to explain the mentioned tendency by the general thermodynamically caused directedness of water systems to formation of short-range-ordered structures similar to the gas-hydrate structures (these views were initiated in Ref. [28] and were developed in Refs. [20–24,29]).

Below, we present some results that count in favor of the occurrence of short-range ordering in water systems containing biologically active substances. The pretreatment of the samples for water sorption and desorption and all measuring procedures are detailed in Ref. [29].

Fig. 5 contains the data on water-vapor sorption by pre-dried solid samples of PAA (Fig. 5b) and glycine and alanine (Fig. 5c) from air of 100% humidity at about 290 K. Fig. 5a illustrates the measurement procedure. Water sorption was measured through repeated weighing of the closed weight glasses with no agitation of their contents.

Fig. 6 presents the data on the calorimetric molar heats (Q) of sorption of small water-vapor portions by PAA (Fig. 6b) and on the probability (P) of desorption of any water molecule into vacuum from the PAA–water system per unit time (Fig. 6c) at about 290 K. The Q values were measured with a FOSKA

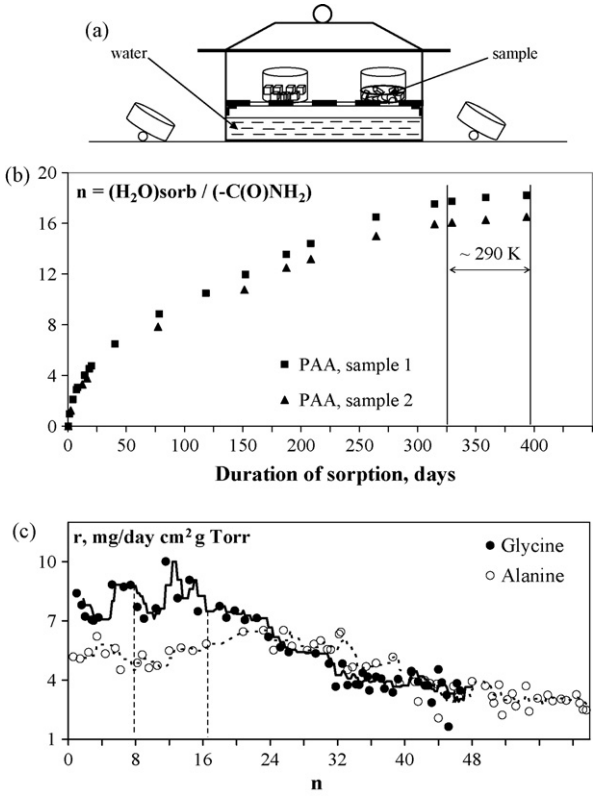

Fig. 5. Water-vapor sorption by different substrates from air of 100% humidity at about 290 K: (a) illustration of the experiments; (b) degree of wetting of polyacrylamide vs. duration of sorption; and (c) rate of sorption by glycine and alanine vs. degree of wetting.

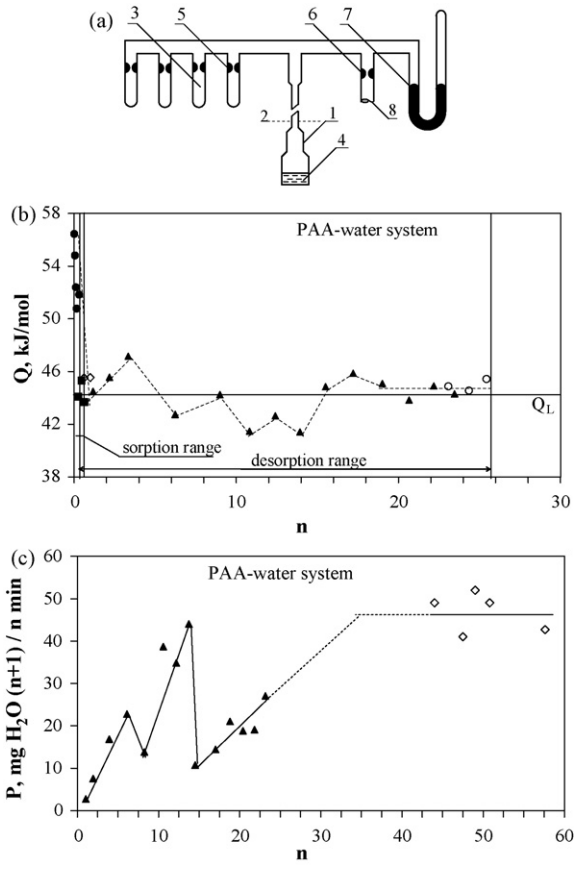

Fig. 6. Portion-by-portion desorption and sorption in the deaired polyacrylamide–water system: (a) illustration of the desorption experiments: (1) calorimetric ampoule, (2) top of the calorimeter, (3) test-tube, (4) sample for wetting, (5) neck, (6) neck, (7) mercury manometer, and (8) tube to vacuum setup; (b) calorimetric molar heats of water-vapor sorption: sorption by sample 8 (●) at 292 K and desorption from samples 7 (■), 9 (▲), 10 (◊), and 11 (○) at 292, 288, 297, and 291 K, respectively (samples 7, 9, 10, and 11 are aged before the experiments for 14, 9, 6, and 16 days, respectively); and (c) probability of desorption of any water molecule into vacuum from the PAA–water system per unit time: samples 9 and 10, 290 K; the level Q_L corresponds to the heat effect of water-vapor condensation at the liquid pure-water surface at 290 K.

microcalorimeter [41,42] in experiments on water-vapor sorption or desorption. The calorimetric measurements of water desorption were performed with samples of the PAA–water system in an isolated deaired portable glass apparatus (Fig. 6a). The heat effects were measured in series of repeated experiments on portion-by-portion desorption of small water amounts. Each experiment consisted of short-term cooling of one of the test-tubes (3) at 77 K, its sealing off under vacuum, measuring of the heat effect, and weighing of the desorbed water. The calorimetric measurements of water-vapor sorption were performed with samples of pre-dried PAA in a similar deaired apparatus, in which each test-tube is supplied additionally with a magnetic breaker and a small thin-walled hermetically sealed glass sphere filled with a water weight. Each series of the experiments consisted in successive breakings of the glass spheres and measuring of the heat effects of water-vapor sorption. The P values were calculated for each desorption experiment on the basis of the desorbed water mass, duration of desorption, and current degree of PAA wetting. The stronger the water–substrate bond, the lower the probability of desorption. Therefore, the P–n dependence shown in Fig. 6c indirectly characterizes the n-dependence of the strength of water binding in the sample. For systems, where there are no specific substrate–water interactions at any degree of wetting, it is reasonable to expect a monotonous P–n dependence at low degrees of wetting and a constant P value at high degrees of wetting.

The experimental errors were considered in detail in Refs. [29,41]. The random error in the mass of sorbed or desorbed water was 0.5% and that in the molar heat effects was 0.7%; the mean absolute error in the differential molar heat effects was 0.30–0.35 kJ/mol. The absolute error in the n values is within 0.05 ± 0.05. The error in the probability of desorption is within 10%. Meanwhile, one source of the uncertainty at least cannot be estimated quantitatively. The point is that the "motive force" for the process of hydrate formation from liquid water and solid PAA is not great and, in this connection, this process proceeds slowly. Bearing this factor in mind, we "aged" each sample for about 1 week or more before measurements and performed the experiments with time intervals. However, we had no possibility for controlling the establishing of the equilibrium before experiments in the systems under study.

Fig. 5b shows that water-vapor sorption terminates when the water-to-guest stoichiometry $n = (H_2O)_{sorb}/(–C(O)NH_2)$ is about 17 in two experiments. Fig. 5c shows that the rate (r) of water-vapor sorption by glycine and alanine begins to decrease when the n value is 17–20. From Fig. 6b, it is obvious that the differential heats of sorption have no trend for $n \geq 18$; the constant heat effect is equal to 44.71 ± 0.49 kJ/mol and differs from the heat of water condensation at the surface of liquid water (44.33 kJ/mol at 290 K) almost not at all. We believe that the heats of water sorption observed at $n < 18$ should be understood as follows. The molecules of solid PAA are bound to each other by the amide–amide bonds shown in Fig. 3c; however, a portion of amido-groups are not paired, because the equilibrium during the PAA solidification was not achieved. The initial portions of waters are concentrated predominantly around unpaired amido-groups with a rather high heat effect. Sorption of subsequent waters is accompanied with an endothermic effect of weakening of the amide–amide interactions, and, therefore, the observed heat effects are lower than those observed at n values differing from zero only slightly. Up to $n \approx 18$, a state responding to short-range ordering similar to the gas-hydrate structure II is being formed. This process proceeds step by step, and the entropy changes at different steps are not the same. The critical state responds approximately to formation of water surrounding around each amido-group; therewith, $n \approx 17$ similarly to that occurring in the gas-hydrate structure II. In this state, all amide–amide interactions are neutralized, waters are most strongly bound with the amido-groups, and the heat effect of desorption is maximum in magnitude. The subsequent water sorption leads to formation of a water continuum much similar to that occurring in liquid water. The polymer molecules move apart, waters of the PAA surrounding interact with the water continuum, their binding to PAA is being weakened, and the usual solution is being formed. The data presented in Fig. 6c show

that a minimum P value, i.e., the maximum strength of water binding, occurs at about $n = 15$ and that the P value is constant at high n values. Taking into account the above remark relating to the possible experimental uncertainty, we conclude that the data of Fig. 6c are in agreement with this concept.

An analysis performed by us in Refs. [20,21] on the basis of available works and the data presented above led us to the following views on the water state in living systems. The processes of water structuring and de-structuring in living cells play a decisive role in the processes of interactions of living cells with their environment. In definite periods of the cell cycle, water structuring within cells binds waters that diffuse into them and thus prevents excessive swelling and rupture of the cells. Namely, the intensity of water structuring is maximum when cells are "mature" and big and the danger for their rupturing is critical, while it is low when the cells are "young" and small and water diffusion from outside is not dangerous for their existence. The rate of cell swelling depends on the cell size, thickness and hydrostatic resistance of the semi-permeable membrane (plasma membrane or it together with cell wall), composition of the cell interior, transport of environmental substances and metabolites, and degree of hydrate formation (of water structuring). The values of the osmotic pressure and of the Donnan effect are the external attendant integral manifestations of the exchange by water, mineral and organic substances, and ions between living cells and their environment; the significance of artificial regulations of metabolism through variations of these effects is of common knowledge. The intracellular water content varies depending on the phase of the cell cycle, and, at every instant, different cells are in different phases of the cell cycle. For ribose, phosphate groups, unpaired N-bases, and paired N-bases belonging to DNA, the in-vivo integral molar strength of water binding, excessive in comparison with the energy of water condensation at the liquid pure-water surface, is different and depends on the degree of wetting of the corresponding functional groups of DNA. The water content in a living cell at each phase of the cell cycle is strictly defined. Diffusion of excessive water into a cell leads to neutralization of the DNA–DNA interactions and moving apart of the paired DNA molecules. In water-deficient media, the DNA–DNA binding in double helixes is realized predominantly through amido-groups of nitrogen bases. Decreasing of the environmental water concentration below some critical value leads to depression of the intracellular activity and to gradual degradation of the cells.

One of the phenomena that have stimulated the hypothesis considered in this paper is the following one. The sizes of each of the N-bases entering the DNA and RNA molecules are equal to the free size of the large cavities. This coincidence is shown in Fig. 4 given in proper scale, where the diameter of the big circles responds to the size of the large cavity. In addition, the sizes of phosphate group and riboses allow their housing in the small and large cavities, respectively [22]. In other words, the sizes of the gas-hydrate structure II agree well with the sizes of all the components of DNA and RNA molecules. It is seldom that such agreements in nature are causeless. Looks like nature has a tea-set with "baking cups" ranged for each of the DNA and RNA components.

3. The hydrate hypothesis for the cell-cycle processes

The present generally accepted notion on the DNA-replication and mitosis mechanisms is formulated, to a great extent, on the basis of the light micrographs corresponding to different phases of the cell cycle (see, e.g., [2,3]). The NMR method gives no possibility to determine the sizes of different minor details, the special benefits of the confocal laser scanning microscopes against the non-laser optical microscopes are not essential for size measurements, and methods requiring treatment of samples by vacuum, hard radiation, or freezing give no possibility for controlling the temporal variations in sizes of cell components in living matter. As for the light micrographs, they, on frequent occasions, cannot be explained unambiguously. The point is that the maximum degree of magnification of light microscopes is limited by light diffraction, and the resolution of the best classic optical microscopes is no more than 0.2 μm (2000 Å). This means that an object of 2×10^3 Å in diameter is seen under microscopes as a point, which can be detailed by no photographic or PC means. Meanwhile, the C–C bond is about 1.5 Å; i.e., the carbon chain consisting of 1300 atoms or a graphite plane consisting of about 1.7×10^6 atoms is seen as a point, and the attempts to use PC softwares for revealing the interior structures of such points are questionable. Moreover, the light microscopes give almost no information on the intracellular transformations proceeding in the interphase covering about 90% of the cell-cycle period. Thus, the micrographs give limited information for estimating the comparative variations in the form and density of chromosomes in the course of the observable portion of cell cycles; however, they give no grounds for description of chromosome details smaller than 1300 atoms in length or 1.7×10^6 atoms in plane. Meanwhile, the examples of excessive insubstantial detailing of the chromosome-transformation phases are available in literature and can lead to erroneous views on the degree of clarification of the real mechanisms of intracellular processes if these views are presented as results of analyses of micrographs rather than as authors' suppositions.

Below, we propose a hypothetical physicochemical explanation for some processes proceeding in the course of mitosis and DNA replication. Our MRH hypothesis relates to the maternal function of cells rather than to their function as a chemical factory producing organic materials. In this connection, we do not consider the cell-environment transport of organic substances and minerals and the chemism of intracellular reactions. We believe that a number of phenomena observable during mitosis and interphase can be explained on the basis of well-known physicochemical regularities inherent in the processes of continuous water diffusion into cells, formation and destruction of hydrate structures around N-bases belonging to the DNA molecules, and variations in the water concentration and precipitation and dissolution of organic substances in the cytoplasm.

In order for any chemical process to proceed in a fluid medium and to produce a desired product, the following conditions should be fulfilled: (1) the thermodynamics should allow proceeding of this process; (2) the concentrations of the reactants should be rather high; (3) the steric hindrances should not be insuperable; (4) the temperature should be rather high in order

for the molecular mobility to be provided; (5) the rate of formation of the desired product should be higher than the rate of its subsequent transformations if the last are possible; and (6) no one of the source reactants should be consumed in any side reaction before its action in the desired reaction.

As was mentioned above, DNA replication is the central phenomenon inherent in living matter. Generally speaking, cells can duplicate or not duplicate, but duplication of chromosomes is necessary for the existence of living matter and transmission of the hereditary features. Apparently, DNA replication could proceed under some conditions without mitosis. (Similar ideas were expressed earlier, e.g., in Refs. [43,44].) Therefore, we will consider the cycles of replication and of cell division separately. Let the replication cycle proceed from the moment of separation of sister chromatids in a mother cell and formation there of two daughter chromosomes of the first generation to the moment of separation of sister chromatids in a daughter cell and formation there of two daughter chromosomes of the second generation, and let the cell-division cycle proceed from the moment of division of the mother cell to the moment of division of the daughter cell. Thus, in our consideration, the replication cycle does not coincide with the cell-division cycle.

Water is necessary for the processes of mitosis (in the case of prokaryotes, of binary fission) and DNA replication. It diffuses (in parallel with organic and inorganic substances) into living cells continuously from the outside through the cell membrane, and, as noted above, the rate of water diffusion is time-dependent. The water structuring within cells stimulates continuous water flow into cells.

Bearing in mind six conditions formulated above and the involved data presented in Section 2, we give the hypothetical explanation for the binary fission and DNA replication processes inherent in prokaryotes and in eukaryotes and consider their common features and peculiarities.

First we apply the MRH hypothesis to prokaryotes.

Prokaryotes are the simplest cellular organisms, and analyses of their cell cycle can provide revealing the fundamental necessary and sufficient features of metabolism purified as much as possible of side processes and phenomena that are not necessary for metabolic processes. Meanwhile, the necessary and sufficient factors of metabolism of eukaryotes may be obscured by the occurrence of some intracellular organelles, the absence of which does not exclude the principal possibility of metabolism. It is known that each of the prokaryotic cells usually has one DNA double helix termed chromosome and consisting of two circular DNA mono-strands bound together through purine–pyrimidine hydrogen bonds. The prokaryotic cell cycle includes replication of this chromosome and binary fission of the cell.

Consider the hypothetical mechanisms of the prokaryotic replication cycle. Before separation of sister chromatids in two daughter chromosomes, water-dipole layers are formed along each of two coupled circular DNA double helixes. These double helixes repulse from each other by an electrostatic force, the nature of which will be explained somewhat below, and two daughter chromosomes (of the first generation) move apart to the opposite sides of the cell and take up positions in immediate proximity to the plasma membrane. Just this moment is taken by us as the onset of the replication cycle. According to the conclusions made in Section 2, waters should penetrate slowly into each double helix, envelope the N-bases, and house them into cavities similar to those existing in the gas-hydrate structure II. Just such a process is in progress after formation of the daughter chromosomes. It starts at several different locations of the chromosome at almost one time, because different locations have no preferences for water structuring (this statement will be confirmed below). The first step of this process is thermodynamically caused and is analogous to the process of water sorption by PAA (see Fig. 6b) under conditions when the n value is somewhat higher than unity but is significantly lower than 17. A similar process at 100% humidity goes spontaneously (Fig. 5b); i.e., it is characterized by a negative change in the Gibbs free energy. These experimental results give grounds to assert that the process of hydration of the amide–amide bonds is associated with a very small decrease in the Gibbs free energy and proceeds slowly and that formation of a water continuum and moving of amido-groups from each other should be thermodynamically caused when the water surrounding of the neighboring N-bases is sufficiently extended. Fig. 6b shows that the difference between the molar heat effects of water sorption and water condensation at the liquid pure-water surface is rather small in magnitude and can be positive or negative depending on the degree of wetting of the substrate, i.e., that water sorption proceeds as a result of the occurrence of entropy peculiarities. Each of the daughter chromosomes sorbs water intensively, and the water inflow to the cell from the outside becomes inadequate for covering their water demands. Therefore, the chromosomes sorb water stored in the intracellular cytoplasm. Within the cell, two opposite water flows directed from the central region of the cell to the daughter chromosomes arise. Because the water density exceeds the densities of organic liquids, the water outflows from the central region of the cell lead to a decrease in the fullness of this cell region and to a decrease in the density of the intracellular medium in it. In addition, water depletion of the central cell region results in its supersaturation by phospholipids and other polymers. These phenomena initiate formation of a cleavage furrow and precipitation of excessive lipids in the equatorial plane of the cell and result finally in cell division in two daughter cells, each containing one daughter chromosome of the first generation. Thus, the binary fission realizes. Below, we consider one of the daughter cells.

The young daughter cell is small and water-deficient. However, the “water requirement” of the daughter chromosome is already satisfied partially and, therefore, the rate of water structuring around N-bases of this chromosome is decreased. As a result, the water inflow through the plasma membrane leads to swelling of the cell. Meanwhile, the water inflow enriches the peripheral cytoplasmic layer by water, thus increasing its density, and weakens the chromosome-to-membrane cohesion. As a result, the chromosome moves into the cell central region, which is enriched (as compared to the peripheral region) with organic substances and, therefore, has a decreased density. The so-called nucleoid forms. By this, the process of water structuring around N-bases of the chromosome DNA double-strand is

yet not completed; however, in some chromosome locations, the DNA–DNA interactions are already neutralized by waters and the rate of water uptake by the chromosome is minimized. Such a situation initiates a new step of the DNA replication.

In this period, the process of construction of DNA-replicas on the basis of each mono-strand of the daughter chromosome starts. This process is stimulated by the appearance of chromosome regions where several neighboring DNA–DNA hydrogen bonds are neutralized, i.e., of minor primitive water-filled capillaries, and by the organic and mineral substances taken up by the cell together with the water inflow. Apparently, the process of DNA replication starts almost simultaneously in different DNA locations where the DNA–DNA hydrogen bonds are neutralized, because the circular-chromosome locations differ by nothing but the degree of hydration of the N-bases responsible for the hydrogen bonding of two DNA mono-strands. The data [45,47] showing that eukaryotic chromosomes begin to replicate in different chromosome locations simultaneously count in favor of the analogous phenomenon of multiplicity of start locations of DNA watering and subsequent replication in prokaryotes. To understand the mechanism of the replication process, the well-known peculiarities of water behavior in contact with microcapillaries or microslots (the so-called capillary condensation) and the above-given information about smallness of the difference between the energies of amide–amide, amide–water, and water–water interactions should be taken into consideration. It is well known that capillary condensation in solid–vapor systems starts at a relative humidity below 100% depending on the capillary diameter (more exactly, on the water-meniscus curvature). For the capillaries of a definite diameter, the start of capillary condensation is determined by the water concentration or, to be precise, by the water activity. In microcapillaries, when the capillary diameter and molecular interatomic distances are of the same order of magnitude, water capillary condensation can proceed in solutions with water activity significantly lower than unity. The process similar to the capillary condensation should proceed in living cells after the step of formation of water envelopes around N-bases, because this step leads to some separation of the DNA mono-strands from each other and to some unwinding of the DNA double helixes. The process of capillary condensation of water promotes formation of small water continuums in the volume between N-bases of the neighboring DNA mono-strands. Formation of these water continuums leads to reorientation of water dipoles forming envelopes around N-bases, to partial neutralization of their dipole moment by the water continuums, and, as a result, to weakening of the binding between the water envelopes and N-bases. Under such conditions, the hydrogen binding between the N-bases belonging to the DNA mono-strands and the nucleotides dissolved in the cytoplasm becomes more favorable thermodynamically than the hydrogen binding between these N-bases and their water envelopes. Therefore, the nucleotides “moor” to these DNA mono-strands and form hydrogen bonds with them, initiating formation of two sister chromatids of the second generation (as was said above, we do not consider the chemism and, therefore, do not consider the details of this chemical process). So long as the N-bases are not enveloped by water molecules, water sorption around them is thermodynamically caused. Therefore, the water continuum moves along the DNA mono-strand, enveloping gradually the pairs of N-bases; dissolved nucleotides move together with water, destroy water envelopes, and replace them. This process continues up to the confluence of the water continuums moving towards each other from the different starting locations of DNA replication. During the process of replication, the water dipoles, entering between the DNA mono-strands of the daughter chromosome of the first generation, orient along each of them in such a way that the poles of the same polarity are directed to each of the newly formed DNA double strands. Therefore, the outer facings of the water-dipole layers surrounding each sister chromatid of the second generation have the same polarity. Thus, these chromatids are affected by a repulsive electrostatic force, which unfolds them in a “double page” and pushes them apart as soon as the centromere-like region that has arisen between the sister chromatids of the second generation is replicated. The originated daughter chromosomes of the second generation move apart to the opposite walls of the cell. The replication cycle is finished.

The process of DNA replication proceeds for a rather long period, during which the segments consisting of two DNA double helixes and of one DNA double helix coexist along any one chromosome. In such a situation, there are no principal hindrances for simultaneous hydration of the segments of both types. Thus, replication of some segments of a newly forming chromosome can start before complete replication of its parental chromosome. Evidently, the parental chromosome is somewhere multilayer and is increased in its cross-section; just this phenomenon makes the chromosomes sufficiently thick to be visible under optical microscopes.

Thus, we described the hypothetical physicochemical mechanism of DNA replication and cell division for prokaryotes without notions on either enzymes or genetic code (therewith, we emphasize that we do not consider the chemism of these processes). Note in this connection that an opinion that nonenzymatic replication is conceivable in a wide range of synthetic chemical systems was expressed in a number of works, e.g., in Refs. [44,46].

Now we consider the principal peculiarities of the physicochemical mechanisms for the replication and cell-division cycles inherent in eukaryotic cells.

The distinctions between eukaryotes and prokaryotes are essential and manifold. However, as was mentioned above, we think that the fundamental physicochemical regulations controlling the DNA replication and cell division for prokaryotes and eukaryotes are the same.

Unlike the prokaryotic cells, the eukaryotic ones contain a chromosome family (from 8 chromosomes in the fruit fly cells up to 1200, 380, and 46 chromosomes in the fern, butterfly, and human cells, respectively) and each of the chromosomes has a linear (not circular) structure. Fig. 7 presents the scheme of the eukaryotic cycle of chromosome replication for one pair of daughter chromosomes of the first generation, AC and BD (Fig. 7c); the capital letters A, B, C, D, E, F, G, and H under each of the DNA mono-strands individualize them and allow observation of their history. In this figure, we consider the chromosome

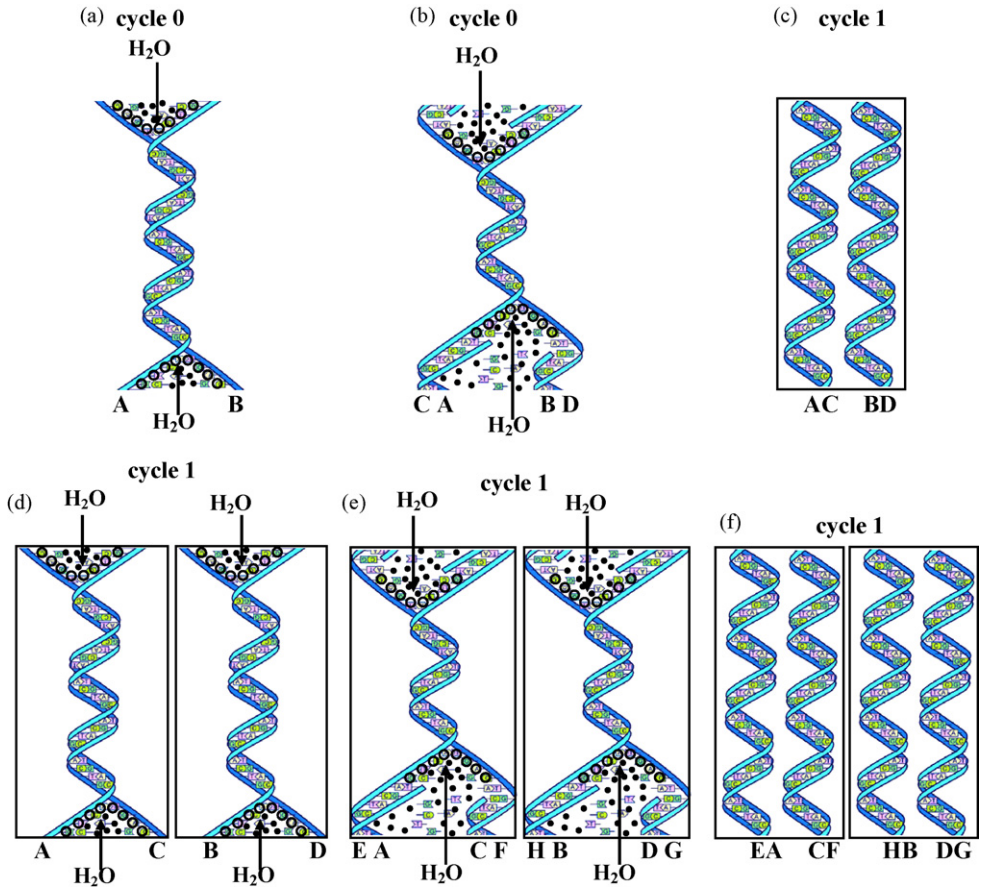

Fig. 7. Scheme of the DNA replication cycle in eukaryotic cells (in the centromere vicinity) (the capital letters A, B, C, D, E, F, G, and H under each of the DNA mono-strands individualize the DNA mono-strands): c–f: the replication cycle 1; c: start of replication cycle 1, late anaphase of cell cycle 1, just after chromosome dissociation along the centromere; d: replication cycle 1, just after cytokinesis of cell cycle 1; e: replication cycle 1, late prophase of cell cycle 2; f: finish of replication cycle 1, late anaphase of cell cycle 2; a: replication cycle 0, just after cytokinesis of cell cycle 0; b: replication cycle 0, late prophase of cell cycle 1; ● is water molecule, , , , and are different nucleotides; ◯ is the water envelope of an N-base.

region in the vicinity of the centromere. Fig. 7c and f correspond to the start of replication cycle 1 in a mother cell, which is symbolized by one rectangle, and to the finish of this cycle in two daughter cells, which are symbolized by two rectangles, respectively. Fig. 7a and b respond to the prehistory of these daughter chromosomes in the previous replication cycle 0. Fig. 7a and d and Fig. 7b and e correspond to the DNA states after cytokinesis and after prophase, respectively. The physicochemical mechanism of replication for any eukaryotic chromosome consists in the processes of enveloping of the N-bases joining together the mono-strands in the DNA double helix, some unwinding of the DNA double helix, entering of waters and dissolved nucleotides into the capillaries thus formed, formation of a water continuum, "mooring" of the nucleotides to the corresponding sites at each of two DNA mono-strands, extrusion of water by the nucleotides, movement of the water continuum and dissolved nucleotides along the DNA double strand, and gradual duplication of each DNA mono-strand. The start of these processes is thermodynamically caused by a rather high water activity (i.e., by a rather high its concentration) in the cytoplasm; it occurs simultaneously in different chromosome locations [45,47] including two ends of the chromosome and induces no additional strain in the DNA double helix. For example, in [47], the following confirmation of this phenomenon for human chromosomes is given: "An average-sized human chromosome contains a single linear DNA molecule of about 150 million nucleotide pairs. To replicate such a DNA molecule from end to end with a single replication fork moving at a rate of 50 nucleotides per second would require $0.02 \times 150 \times 10^6 = 3.0 \times 10^6$ s (about 800 h). As expected, therefore, the autoradiographic experiments ... reveal that many forks are moving simultaneously on each eukaryotic chromosome." According to our views, the hydration and start of unwinding of chromosomes should proceed spontaneously and are in no want of extraneous support. Therefore, such enzymes as helicase and topoisomerase seem to be "jobless".

We consider some eukaryotic peculiarities on the basis of Fig. 8 showing schematically (not in proper scale) the chromosome sections II and III adjoining to one of the ends of the centromere I. Let A and B be the mono-strands of the chromosome under consideration. Waters and nucleotides enter at the end of this chromosome between the DNA mono-strands (at the bottom of Fig. 8) and steadily move along them (in the upward direction in Fig. 8), unwinding the DNA double helix and duplicating each of the DNA mono-strands (in Fig. 8, the duplication of each of the mono-strands approaches to the boundary between

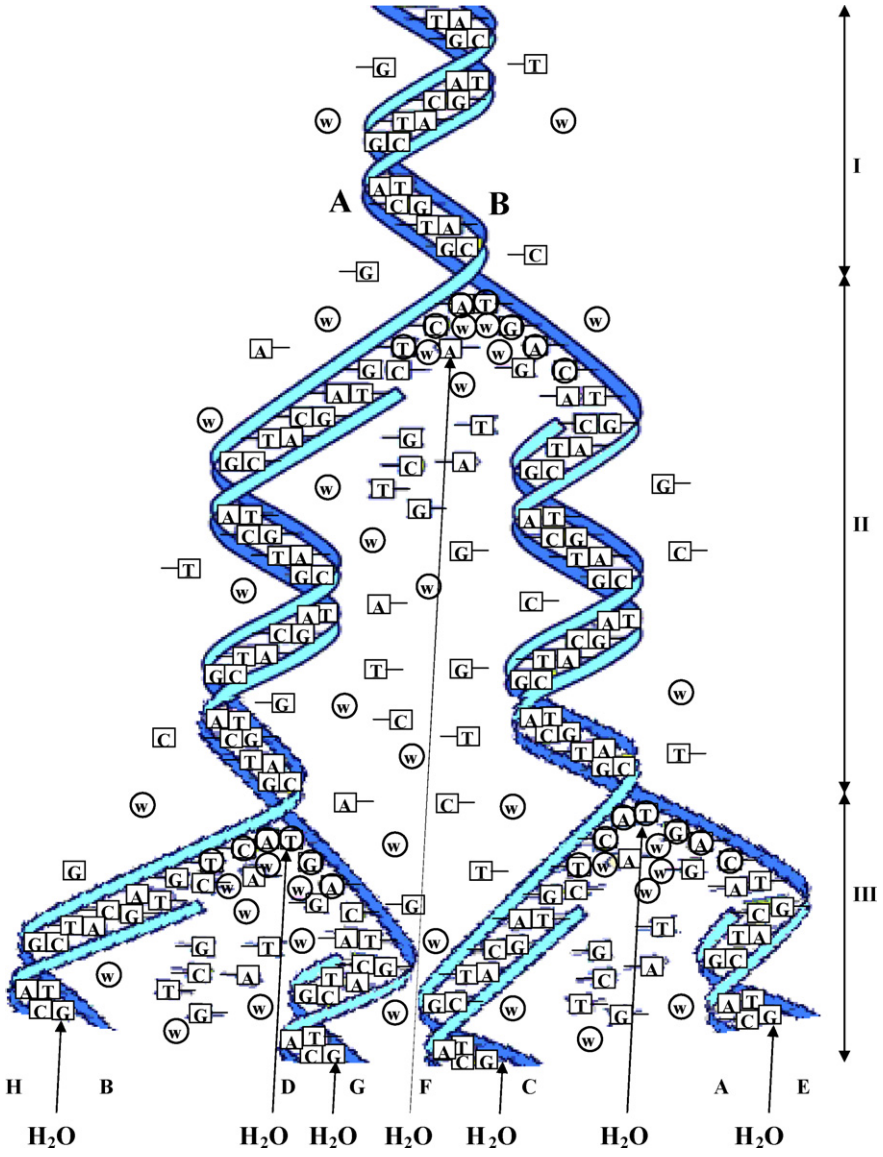

Fig. 8. Scheme of the "branchy" chromosome sections adjoining to one of the ends of the centromere: ⓦ is water molecule; other denotations the same as in Fig. 7.

the regions I and II). In the course of this process, nothing prevents duplication of the AC and BD double strands just formed; therefore, we believe that formation of new branches HB, DG, FC, and AE should begin. Later, two DNA double helixes begin to form on the basis of each of these double strands. A similar pattern occurs at the other end of the chromosome under consideration. Thus, we are of opinion that each of the DNA double helixes in vivo has a "branchy" structure with a rather long bare (not branchy) "stem", the central region of which is the centromere, and with branchings located at either end of this stem. We are of opinion that just such a branchy structure of the DNA double helixes and water structuring around each of their elements increase the cross-sections of chromosomes in vivo and make them visible under light microscopes. Two opposite fronts of DNA double-helix duplication move steadily to the centromere and shorten the section that binds the sister chromatids. This process proceeds for so long that the central section of the centromere have time to be covered with an organic protein-like layer hampering the final separation of the sister chromatids. However, the protein-like layer eventually dissolves; the moment of dissolution terminates the replication cycle.

It was mentioned that, according to the available data, the DNA replication begins at its different locations simultaneously. Therefore, it may seem strange that the centromere region is located in the vicinity of the central section of the chromosome. The MRH hypothesis allows the following explanation of this phenomenon. The available light micrographs of living cells in early anaphase of mitosis show that the central regions of chromosomes before their movement to the cell poles are located closely to each other, contrary to the end segments of these chromosomes, which are similar to two fans open widely on either side of the so-called mitotic spindle [48]. Therefore, water and nucleotide diffusion to the central segments is hampered and their replication starts significantly later than replication of the peripheral segments of the chromosomes. Thus, it becomes clear

why replication of the central segments terminates later than replication of the end segments.

Consider now the eukaryotic cell-division cycle, including mitosis. We consider the cell-division cycle as the time period between the moment right after cytokinesis in a cell cycle 0 (Fig. 7a) and the moment of cytokinesis in the following cell cycle 1 (Fig. 7d). The eukaryotic cell-division cycle differs fundamentally from the prokaryotic binary fission by the occurrence of a chromosome family instead of one chromosome, of a specific cell-cycle phase called interphase, and of a specific chromosome-family state termed chromatin and also by the formation of an envelope housing all newly formed chromosomes within each newly formed cell (the so-called nuclear envelope). Below, we describe the mechanism of the cell-division cycle, basing on the MRH hypothesis.

By the beginning of prophase, the cytoplasm is enriched with organic substances and the chromosomes are concentrated within the nuclear envelope, their end segments being duplicated. During prophase, the chromosomes sorb water and organic substances and become thicker as a result of formation of the hydrate-like structure inside double helixes, progressive duplication of their end segments, and branching. Active sorption of water by the chromosomes intensifies water diffusion into the cell from the outside, the water concentration in the cell increases, the cell and its nucleus grow, and the nuclear envelope begins to dissolve as a result of dilution of the cytoplasm by water.

The disappearance of the nuclear envelope and formation of the so-called mitotic plate can be explained as follows. During prometaphase and metaphase, the chromosomes continue to duplicate, the water concentration in the cell continues to increase, the nuclear envelope dissolves, the nucleus organics spill into the cell, the cytoplasm density in the equatorial plane of the cell decreases, and the chromosomes convene themselves in the zone of decreased density, forming the mitotic plate.

During anaphase, water continues to diffuse into the cell, the cytoplasm viscosity minimizes, chromosome replication along the centromere terminates, and each pair of sister chromatids dissociates into two daughter chromosomes moving apart to the opposite walls of the cell. Thus, two families of the newly formed chromosomes arise. As was said above, the chromosomes are separated as a result of action of the electrostatic force induced by the water-dipole layers surrounding each daughter chromosome. A number of authors (e.g., [47]) hold the opinion that the daughter chromosomes move apart to the cell poles by the motors on microtubules; when a microtubule connects with the kinetochore, the motor activates, “crawls” up toward the centrosome, and the kinetochore provides separation of the sister chromatids. However, we think that this description is no more than one of the possible explanations of the observable phenomenon, because it is not clear how the microtubules learned to perform this complicated job. Besides, we refer to work [6], which claims that cells of different eukaryotic species can undergo mitosis (and interphase) without centrosomes (after their irradiation by laser); i.e., mitosis of eukaryotic cells can proceed normally without help of centrosomes. This work means that the cause-effect relation between the “motor” and movement of daughter chromosomes apart does not exist or it is opposite to the prevalent one. The prokaryotic binary fission proceeding with no developed organelles forces to be in earnest about this possibility. Apparently, the MRH hypothesis allows simple and natural explanations for the process of separation of sister chromatids and for moving of the daughter chromosomes to the opposite cell poles.

During telophase and cytokinesis, chromosomes of each of two families are localized in opposite sides of the cell, are not connected to each other, and each chromosome sorbs water and nucleotides with minimal steric hindrances. As a result, two nuclei arise and the cell divides in two. Thus the cell cycle is complete.

In the course of telophase and cytokinesis of eukaryotic cells, a rather complicated hydrodynamic situation arises. Each family of chromosomes sucks in water from the center of the cell and from the region of the other family; in addition, water diffuses into the cell from the outside, the flows being different near the chromosome families and in the central region of the cell, because each chromosome family functions as a pump and, the closer the pump, the stronger the water diffusion flow; besides, the water concentrations and cytoplasm compositions are different in different cells. Above, when considering the mechanism of the prokaryotic binary fission, we qualitatively explained the formation of the cleavage furrow and the subsequent cell division. However, it is known that three different situations are possible in living cells: (1) the above-described situation typical for prokaryotes; (2) the situation most abundant for eukaryotes, when cytokinesis and mitosis occur in conjunction, i.e., formation of two new nuclear envelopes and of the intracellular membrane separating two new nuclei proceeds almost simultaneously; and (3) the situation observable for a number of eukaryotes, when cytokinesis and mitosis occur separately and single cells with multiple nuclei exist for a rather long time.

Apparently, each of these situations can be clarified on the basis of consideration of a rather complicated hydrodynamic problem responding to cells filled with a semi-liquid substance, the density of which varies along the cell diameter. We think that formation of the nuclear envelopes and intracellular membranes should be explained by the same phenomena of sedimentation of organo-mineral substances from oversaturated aqueous solutions under conditions when chromosomes sorb water more rapidly than it diffuses into the cell from the outside. Analytical consideration of this problem is beyond this work; however, we think that all mentioned phenomena could be explained on the basis of such a physicochemical model. Evidently, the absence of nuclear envelopes in prokaryotic cells is caused by a rather high water concentration in the cytoplasm during mitosis and by the occurrence of only one parental chromosome in each cell. Namely, the rate of water sorption by each of the daughter prokaryotic chromosomes before binary fission is insufficient for formation of a region of oversaturated solution of organo-mineral substances around each of them. Meanwhile, the occurrence of nuclear envelopes in the cells of most species of eukaryotes is caused by a lower water concentration in the cytoplasm of dividing cells and by the occurrence of a family of chromosomes in each of them. Namely, the water flows directed to each

of the chromosome families in a dividing eukaryotic cell are so intensive that they promote formation of regions of oversaturated solutions and precipitation of nuclear envelopes around each of the newly formed chromosome families and subsequent formation of a similar region and precipitation of a membrane between the newly formed nuclear envelopes. Thus, the phenomena observable in prokaryotic and eukaryotic cells can be understood on the basis of hydrodynamic consideration of the processes proceeding in aqueous solutions of organo-mineral substances whose concentrations vary near the saturation conditions.

In this connection, we return to the idea that some organelles occurring in eukaryotic cells can be nothing but different organo-mineral crystals disappearing as a result of their swell and full dissolution or precipitating due to variations in the water concentration in the cytoplasm (see the last paragraph of Section 1). The occurrence of only primitive organelles in the cells of some prokaryotic species [49] or the absence of organelles in the cells of other prokaryotic species can be, apparently, explained by the poorness of the organic composition of the prokaryotic cytoplasm and by a high water concentration in it. As for such organelles as mitochondria and chloroplasts, which "live" inside eukaryotic cells and have their own DNA, their metabolism is evidently controlled by the regularities resembling those inherent in prokaryotic cells.

4. Conclusions

The hydrate hypothesis of mitosis and DNA replication (MRH hypothesis) allows non-trivial explanations for the physicochemical mechanisms of some intracellular processes. These explanations are based on the thermodynamic approach to the revealing of the nature of intracellular processes and on the experimental calorimetric and kinetic data demonstrating that, in concentrated aqueous solutions of substrates modeling biologically active substances, short-range structures similar to those occurring in solid gas-hydrates are possible. Our explanations of different stages of the processes of DNA replication and mitosis proceeding in prokaryotic and eukaryotic cells are based on the same notions and are basically similar. Consideration of this water property together with well-known regularities inherent in aqueous solutions allows simple non-enzymatic (this term is adopted from Ref. [46]) unified physicochemical descriptions for the natural processes of DNA local unwinding preceding the start of duplication, DNA replication, formation and disappearance of the protein bonds between sister chromatids in the centromere region of eukaryotic DNA and in the centromere-like region of prokaryotic DNA, moving of the daughter chromosomes apart to opposite sides of cells in late anaphase, and formation of the nuclear envelopes in telophase and of intracellular membranes between newly formed nuclei in cytokinesis. Besides, we make assumptions on the chromosome branching as the cause of the visualization of chromosomes under routine light microscopes and on the difference in the water concentration and variety of organic composition for the cytoplasm of prokaryotic and eukaryotic cells as the cause of their different population by the families of those organelles which do not have their own DNA.

DNA replication could proceed without cell division. This idea is not original; some examples of the laboratory syntheses of organic molecules by the replication mechanism are presented in Ref. [44]. In order for the replication to initiate the cell division, the concentration of organo-mineral substances in cytoplasm should be rather high and the chromosome family should be rather numerous. According to the hypothesis presented in [21,22,24], origination of the simplest elements of living matter (N-bases, riboses, and DNA- and RNA-like molecules) proceeded in systems of rather high water concentration and was not accompanied with cell formation; first cellular organisms originated after the medium was enriched with organic substances. For example, viruses traveling at present from cells to cells originated evidently as noncellular organisms as a result of DNA replication in the systems without cell division. As for the process of cell division, it can proceed only in association with the process of replication of DNA or DNA-like molecules.

Thermodynamically, the reacting components of every living cell located in a medium containing water and organic and mineral substances represent an open system. On the one hand, the intracellular medium continuously tends to an equilibrium state; on the other hand, the process of continuous diffusion of water and organic and mineral substances from the outside into the cell hampers the equilibrium and stimulates the continuity of the process of formation of some products and evolution of some side substances. These two tendencies combined with the oscillating rates of diffusion of source substances into the system and side products from the system lead to a cyclic process of formation of intracellular substances and to cell division. The reactions proceed with a decrease in the molar Gibbs free energy; i.e., the system evolves just those side products whose evolution provides the feasibility of these reactions. At each step of a normally proceeding cell cycle, nature converges to the equilibrium in the processes proceeding within the cell; however, each such a tendency intermits inevitably by a phenomenon maturing inside the reacting system under the influence of the interference of different intracellular processes stimulated by flows of the substances entering the system from the outside. We are of opinion that the intracellular transformations are controlled by no biological code other than nature's code that is under the complete control of the physicochemical regulations each of which is long ago revealed and analytically described but the combinations of which are not always describable by the available analytical methods.

Summing up, we would like to say that, apparently, the water capability of forming hydrate structures, more precisely, the phenomenon of formation–destruction of hydrate structures around nitrogen bases, represents the phenomenon that provides the processes of DNA replication and mitosis.

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