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Improvement of the fidelity of molecular DNA computations: control of DNA duplex melting using Raman spectroscopy

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Abstract

In this study it is demonstrated that use of laser Raman spectroscopy for monitoring biochemical reactions provides the detection and control of the processes of renaturation and denaturation of DNA strands, the determination of state of strands, and also the control of possible mutations in DNA molecules. The obtained results are very promising to improve the fidelity of DNA computations, i.e. to provide the greater convergence of the estimated and exact values.

Keywords: DNA strand, DNA duplex melting, molecular computations, nitrogenous bases, Raman spectroscopy

(Some figures may appear in colour only in the online journal)

1. Introduction

Although now molecular biology has not reached a level that allows the monitoring and control of a cell completely, distinct physical processes are fairly well understood and can be used for the elaboration of new devices [1–3]. The formation of weak bonds based on the Watson–Crick complementarity principle, DNA restriction and hybridization, and protein mechanical processes refer to such processes [1]. As a result of these discoveries, the natural means of data storage, and the processing and transfer of information in biological systems have become clear. In turn, progress in the field of the latest informational and molecular technologies has made it possible to install information in a biomolecular medium and to read it. This has promoted the elaboration of principles of molecular computations using biological objects and the development of biocomputers [4].

In living cells genetic information is encoded by the deoxyribonucleic acid (DNA) molecule. DNA provides storage, transfer from generation to generation, as well as the realization of the genetic program of evolution and the functioning of living organisms [5]. These unique properties of DNA are used in molecular computations. In DNA computations every DNA molecule corresponds to another molecule; the Watson–Crick complement [1]. The complement has an opposite direction in comparison with the original molecule and its bases, adenine (A), thymine (T), cytosine (C), guanine (G), are replaced with their paired bases [1]. As a result of the attraction of adenine to thymine and cytosine to guanine a double helix is formed, which provides the opportunity of doubling the number of DNA bases at cell division [6, 7].

The problem of doubling is solved using a special enzyme, polymerase. This enzyme moves along a DNA molecule and synthesizes on its base a new molecule, in which all of the bases are replaced by the corresponding paired bases (PCR, the polymerase chain reaction). The synthesis begins only in a case where a short segment of the complementary strand (primer) is attached to the initial DNA strand. This property is actively used in molecular biology and molecular computations. In fact, PCR is an implementation of the Turing machine [8]. It consists of two tapes and a programmable control desk. The control desk reads data from one tape, processes them according to a certain algorithm, and records them on another tape. The polymerase also consecutively reads an initial data from one tape (DNA) and forms on their base a new tape with the results of the computations (the Watson–Crick complement).

DNA molecules were used by Adleman for the first time for the solution of the computational problem of the existence of

the Hamiltonian path in the given directed graph with selected first and last vertexes, that is, the path that passes each vertex exactly once [9]. He suggested encoding the information about the vertexes and the edges of the graph using DNA strands and carrying out the process of searching for the Hamiltonian path by means of biochemical reactions. Adleman's 'computer' itself was a test-tube with a water solution of DNA strands. The solution of this problem took 7 d [9]. The synthesis of the initial data and the immediate carrying out of the biochemical reactions took several min, and the rest of time was taken by the extraction of already prepared result, the sequencing obtained DNA strands using gel-electrophoresis.

The suggested approach was developed further in the series of studies [10–19]. In [10] the possibility of using a DNA 'biocomputer' for the solution of the Boolean satisfiability problem was considered, and in [11] molecular computations were used for breaking one of the data encryption systems—DES (Data Encryption Standard System) with 256 different methods of data encryption. One should note that in this study only the principal opportunity of breaking the data encryption system was demonstrated in supposition of the absence of experimental errors during the realization of the algorithm.

Algorithms for the solution of various problems using DNA strands suggested by Adleman and Lipton [10–12] were developed in the studies of many scientific groups. The theoretical schemes of the solution of a wide class of optimization problems relating to graph theory were suggested and tested experimentally by the group of Watada. In [13, 14] the problem of scheduling was solved first for two elevators in a six-storey building, then for many elevators in multi-storey building. In [15] the algorithm for the solution of the cable trench problem (CTP) was elaborated. For the first time in the group of Watada, DNA computations were used for the development of the clustering technique [16]. The authors of [17] suggested the solution of the sufficiently important problem of the creation of a true random number generator using molecular computation. It was shown that as a result of biochemical reactions in solutions of long DNA strands occurring in special temperature conditions, one can create a random number generator. In [18] the further development of the algorithm of data encryption and decryption based on DNA computations was suggested. In [19] molecular computations were used for searching for structural errors in the Rule-Based Systems. The suggested algorithm allowed them to find all the basic errors in Rule-Based Systems: Redundancy, Incompleteness, Circularity, and Inconsistency.

In conversation about quantum and molecular computations the same problems are the subject of discussion: Integer factorization, searching for the paths in a graph with different parameters, and pattern recognition. It is still unclear if it can be explained by the small number elaborated for both paradigms' algorithms, or if some interior propinquity exists between these paradigms. It is obvious that quantum and molecular computations have many evident common characteristics distinguishing these approaches from conventional computations on silicon-based computers: For example, a very high degree of parallelism of the calculations, high energy efficiency, and high density of information in the unit of volume. However, quantum and molecular computations have many common problems, for example, fidelity of the computations. This problem is very complex and versatile.

The authors of many publications about the experimental approbation of the algorithms of DNA computations note a substantial dependence of the accuracy of the computations on the state and the concentration of biological molecules, the length of the DNA strands, the temperature and time regimes of the biochemical reactions, the type of buffer solution, and the pH values of the mixtures [20–23]. The authors of [21] have demonstrated that the accuracy of the DNA computations strongly depends on the temperature of the solutions and the duration of the reactions. On changing the temperature one can achieve an increase in the efficiency of the reactions between DNA molecules, and control of the processes of the denaturation and renaturation of the strands. The temperatures can vary from 0 up to 95 °C. Therefore, one should first track the moment of the DNA duplexes melting, i.e. control the state of the complementary strands at different moments of time and at different temperatures.

In the process of biochemical reactions the loss or damage of the DNA molecules during intermediate operations, an accidental mutation in the DNA strands, and a violation of the conditions of the reactions are possible. Meanwhile, the loss of even 1% of the initial mass of the DNA molecules during the computations leads to missing the correct solution of the problem. All this makes the problem of the control of errors during molecular computations very important. It is obvious that, first of all, the fidelity of the DNA computations depends on the control of the state and the concentration of the DNA molecules and on the selection of the optimal parameters of the reaction regime and their control throughout the time of the biochemical reaction. It is also obvious that the methods of this control must be non-invasive, express, and must work in real-time mode. That is why for the elaboration of these methods laser spectroscopy is used, and Raman spectroscopy in particular.

Laser Raman spectroscopy successfully and for a long time has been used for the study of the structure, state, and properties of DNA strands [24–32]. In the Raman spectra of DNA molecules the bands corresponding to the vibrations of the nitrogenous bases (adenine, guanine, thymine, cytosine) and the DNA backbone are identified [24–32], and the characteristic bands-markers of every base are determined [26]. There is information about the peculiarities of the behavior of several vibrational bands of DNA strands during melting duplexes [27–30]. In [31, 32] it was demonstrated that laser Raman spectroscopy provides the opportunity of determining a concentration of individual nitrogenous bases in their one-component solutions by a non-destructing method in real-time mode. For this the calibration dependencies of the intensities of the Raman markers on concentration were used; the total concentration of DNA in the solution was also determined.

This paper continues the series of publications regarding the successful application of Raman spectroscopy for increasing the accuracy of molecular DNA computations. In this study, the basics of the method of the control of the state of DNA molecules during the biochemical reactions, namely,

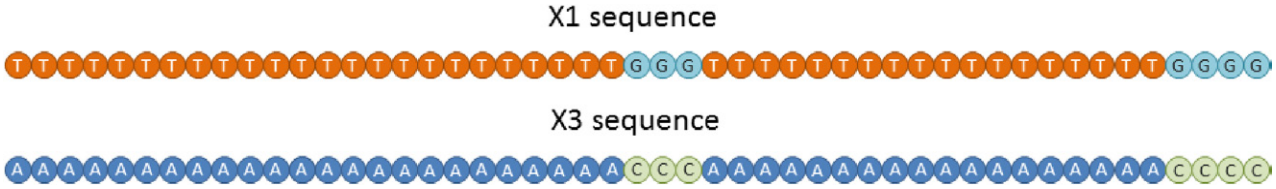

Figure 1. Nucleotide sequence of specially synthesized complementary DNA strands X1 and X3.

during the renaturation and denaturation of DNA strands, were elaborated using Raman spectroscopy. The elaborated method can be implemented in remote real-time mode.

2. Materials and methods

2.1. Objects of research

As mentioned in [31, 32], the question about the concentration of DNA molecules in the solution, 'working substance', is very important for molecular computations. According to the literature data, this concentration can vary in a rather wide range, from units [33] to tens [34] g l^{-1} depending on the concrete problem.

Since the main objective of the given study was to determine the state of DNA strands at the moment of duplex melting, the linear complementary DNA strands X1 and X3 were used as objects of research. These samples were synthesized specially for this experiment. Each X1 and X3 strand consisted of 54 specified in advance nucleotides (figure 1) in a saline-sodium citrate (SSC) buffer (20×).

The maximal concentration of each of the X1 and X3 strands in the SSC buffer (20×) was 11.8 g l^{-1}. As a result of the renaturation of the complementary X1 and X3 strands the DNA double helix was formed. The temperature dependence of the Raman spectra of the solution of the formed duplex was studied experimentally in order to reveal the peculiarities of the vibrational bands at the moment of duplex melting/denaturation.

2.2. Experiment

Due to the high concentration of DNA molecules in the samples it was possible to use macro-Raman spectroscopy, when the signal was collected from the bulk of the solution. This allowed us to control almost the whole volume of the 'working substance'. The Raman spectra were measured using a spectrometer consisting of an argon laser (wavelength 488 nm, incident laser power 250 mW) and a system of registration comprising a monochromator (Acton, focal length 500 mm, grades 900 and 1800 g mm^{-1}) and a CCD-camera (Horiba Jobin-Yvon, Synapse 1024 * 128 BIUV-SYN). The spectra were measured in 90° scattering geometry with a practical resolution of 1 cm^{-1} in the spectral range 200–4000 cm^{-1}. In order to suppress the signal of elastic scattering, an edge-filter (Semrock) was used.

To measure and maintain the temperature of the samples, a special thermostabilization system KRIO-VT-01 was used. It provided the samples' temperature setting and monitoring in a wide range from −30 °C up to +100 °C with an accuracy better than 0.1 °C.

The primary spectra processing consisted of a subtracting pedestal and normalization by the square of the water Raman valence band (in order to exclude the influence of the instability of the laser power on the measured spectra). Then the spectra were normalized by the intensity of band near 1090 cm^{-1}.

3. Results and discussion

3.1. Signs of changes in the state of the DNA strands during molecular computations

As a result of the renaturation of the complementary X1 and X3 strands with the concentrations 11.8 g l^{-1} in the SSC (20×) buffer at a temperature of 25 °C the DNA double helix was formed. In figure 2 the Raman spectra of the solutions of single DNA X1 and X3 strands and a double helix (X1 + X3) with an equal concentration of DNA molecules 11.8 g l^{-1} are presented.

As can be seen from figure 2, the spectra of the solutions both of the single DNA X1, X3 strands and the double helix (X1 + X3) contain many spectral bands corresponding to certain molecular groups of DNA molecules. As a result of the formation of the duplex the parameters of the spectral bands of the single-stranded DNA changed: Some bands disappeared, and some new bands caused by new interactions between the strands appeared in the Raman spectrum of the (X1 + X3) solution. This behavior of the bands provides an opportunity for the determination of the state of the DNA strands during the biochemical reactions. Analysis of the mechanisms of the formation of the Raman spectra of single-stranded DNA and the duplex was performed as a result of studying the process of DNA thermal denaturation.

To determine the state of the DNA strands in the solutions the experimental temperature dependence of the Raman spectra on the solution (X1 + X3) with concentration 11.8 g l^{-1} was obtained in the range from 25 °C to 93 °C with a temperature increment of 5–10 °C. In figure 3, one can see Raman spectra of the solution (X1 + X3) at different temperatures. Analysis of the obtained dependence demonstrated the existence of a series of spectral features of duplex melting (in our sample melting occurs near 60 °C) (figure 4). Exactly this variety of the found identification features turned out to be the basis of the express remote method of the determination of the state of the DNA strands during molecular computations. Let us consider the detected spectral features of DNA duplex melting.

The band with a maximum near 667 cm^{-1} in the spectrum of double strand (X1 + X3) is the thymine marker caused by

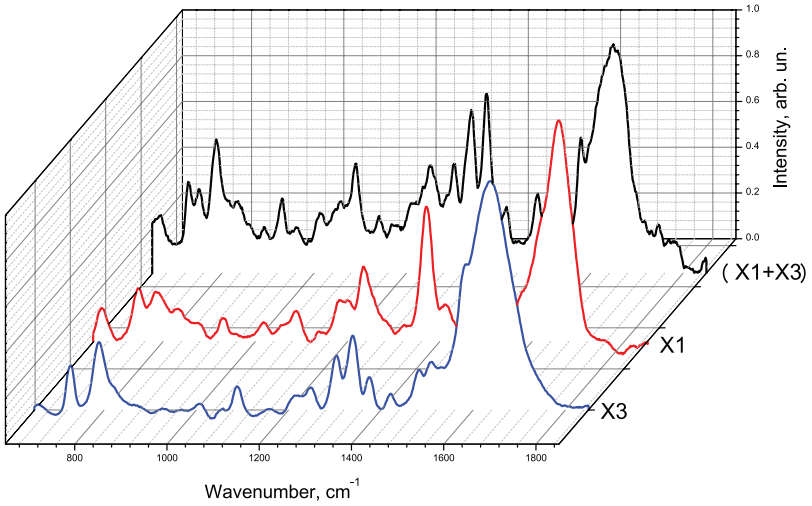

Figure 2. Raman spectra of single DNA X1 and X3 strands and a double helix (X1 + X3) with an equal concentration of DNA molecules 11.8 g l^{-1}.

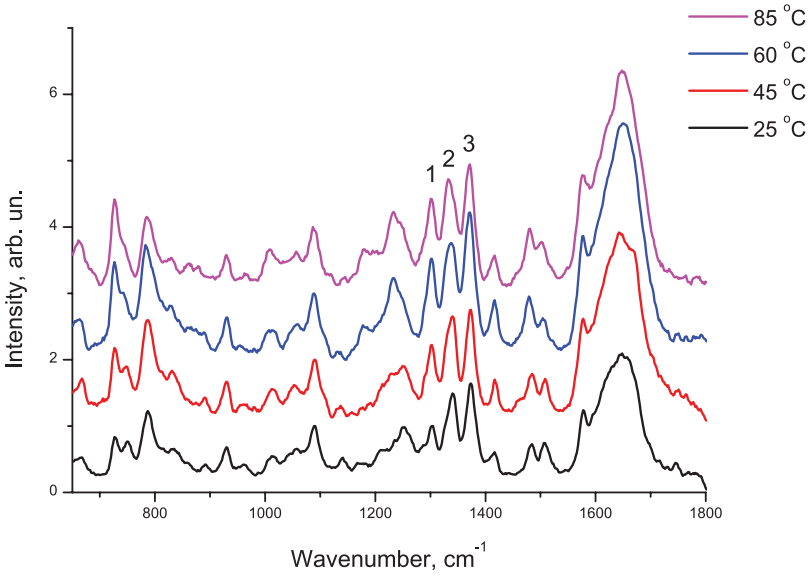

Figure 3. Raman spectra of the DNA solution (X1 + X3) with the concentration 11.8 g l^{-1} at different temperatures.

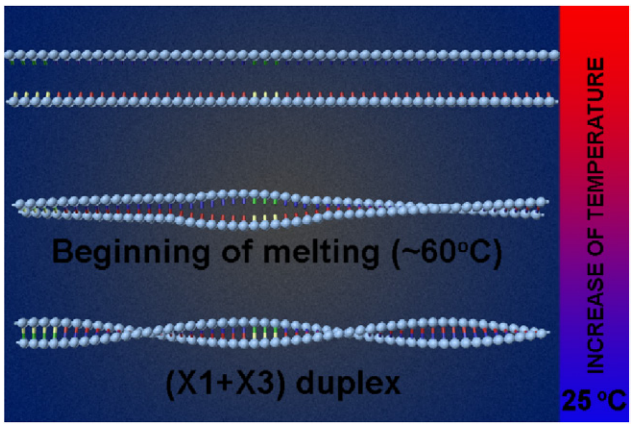

Figure 4. Melting DNA duplex at temperature 60 °C.

the 'windshield-wiper' motions of the C = O groups of the thymine ring [21]. With a temperature increase starting from the melting temperature 60 °C this band slightly shifts to lower frequencies (figures 3 and 5). This behavior is caused by an emergence of several conformers of thymine nucleoside, which induces the slight fading and shifting of the band.

The band centered near 728 cm^{-1} is the adenine marker. This is caused by the 'breathing' vibrations of the purine ring of adenine. During the DNA duplex melting the intensity of this band increases (figure 3), and the band slightly shifts to higher frequencies (figure 6). Similar changes of the DNA Raman band near 730 cm^{-1} were obtained in [29].

The band centered near 751 cm^{-1} is the thymine marker. This is caused by 'breathing' vibrations of pyrimidine ring of thymine. During the DNA duplex melting this band broadens and shifts to lower frequencies (figure 6). At temperatures above 60 °C (after melting) this band disappears, merging with the band near 728 cm^{-1} (figures 3 and 6). The behavior of this band is similar to the behavior of the thymine marker near 667 cm^{-1}. This can be explained by the emergence of other conformers of thymine nucleoside as the temperature increases (for example, the C2′-endo-anti conformer [28, 29]).

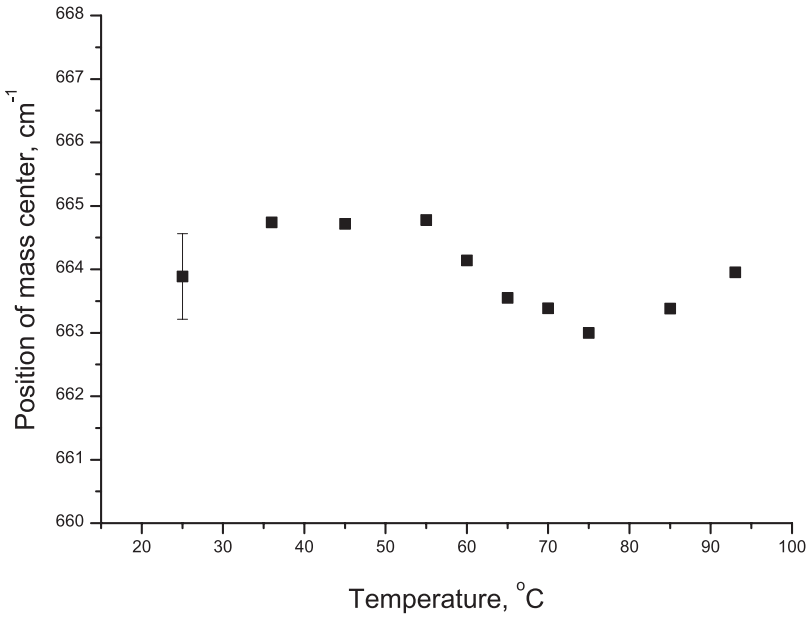

Figure 5. Dependence of the position of the mass center of the band with maximum 667 cm^{-1} (the guanine marker) in the Raman spectrum of the solution (X1 + X3) on the temperature of the solution.

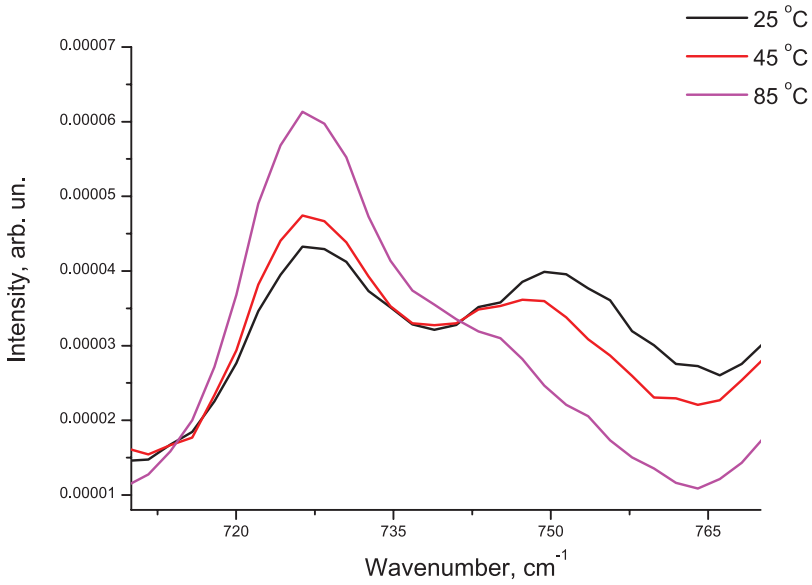

Figure 6. Changes of the bands near 728 cm^{-1} and 751 cm^{-1} in the Raman spectra of the solution (X1 + X3) with a temperature increase.

Thus, both thymine markers characterize the distribution of different conformers of thymine nucleoside [28].

The band near 787 cm^{-1} is caused by the 'breathing' vibrations of the pyrimidine ring of cytosine near 784 cm^{-1} and by the DNA backbone vibrations (O–P–O bond) near 792 cm^{-1}. The main contribution is brought by the backbone vibrations. During the DNA duplex melting the band shifts to lower frequencies (figures 3 and 7(b)).

The band centered near 1090 cm^{-1} is caused by the DNA backbone vibrations (symmetric valence vibrations of the PO_2^- groups). It is present both in the spectra of the single strands and the duplexes (figures 2 and 3). When the temperature changes the parameters of this band do not change. This is why this band can be used as an inner standard. The absence of changes in the intensity of this band is explained by the high localization of the vibrations of the PO_2^- groups [28].

The band centered near 1251 cm^{-1} is an indicator of the interactions of adenine with thymine. When the sample is heated to melting point, this band shifts significantly to lower frequencies, to 1238 cm^{-1} (figure 7(b). This shift can be explained by the abrupt weakening of the bonds between adenine and thymine when the temperature increases. A similar shift of the mentioned band under heating was found by the authors of [30].

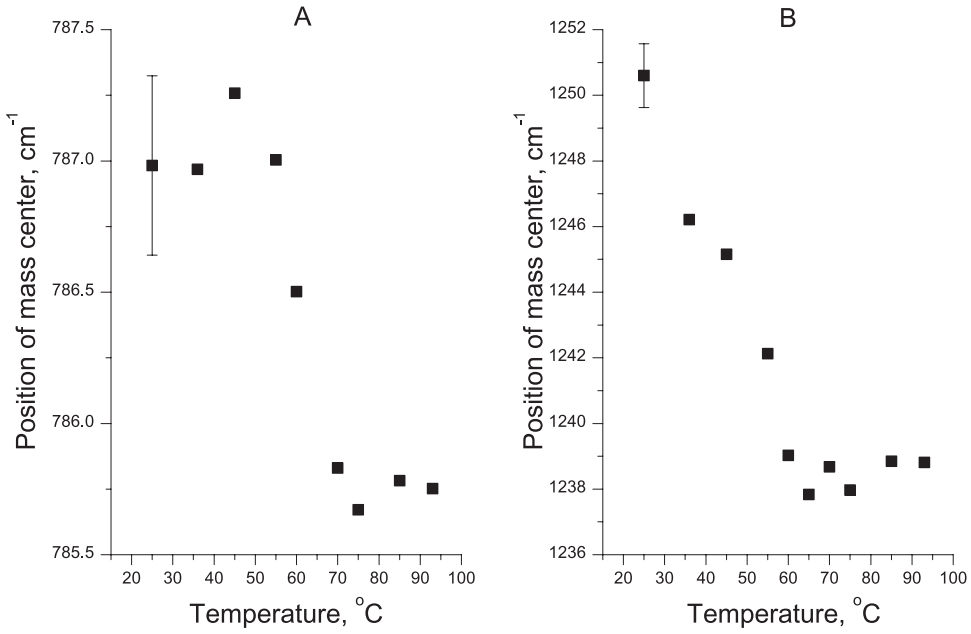

Figure 7. Dependencies of the position of the mass center of the bands centered near 787 cm^{-1} (A) 1251 cm^{-1} (B) in the Raman spectrum of the solution (X1 + X3) on the temperature of the solution.

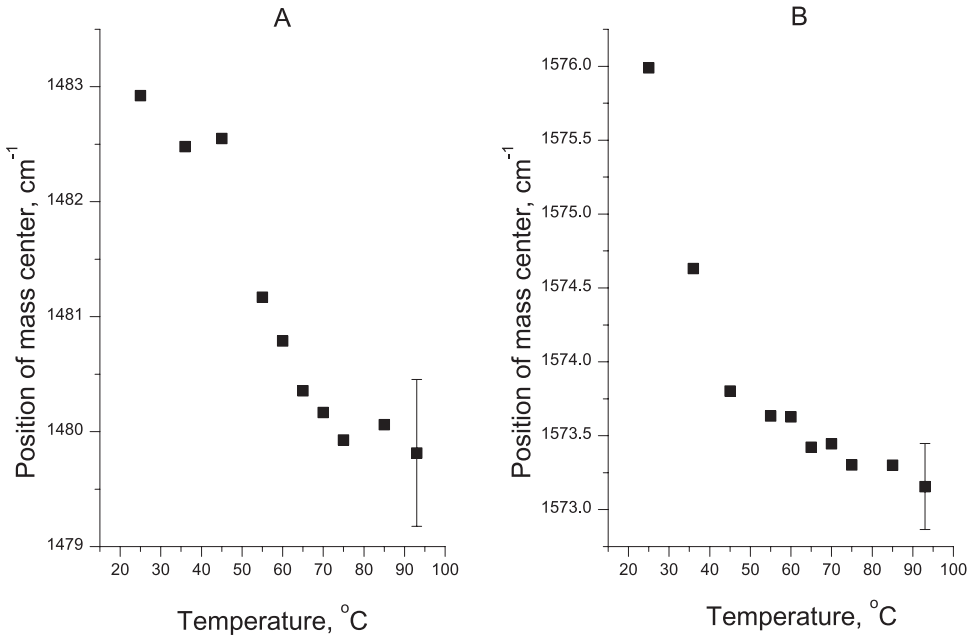

Figure 8. Dependencies of the position of the mass center of the bands centered near 1485 cm^{-1} (A), 1578 cm^{-1} (B) in the Raman spectrum of the (X1 + X3) solution on the temperature of the solution.

The bands centered near 1485 cm^{-1} and 1578 cm^{-1} are caused by the guanine and adenine vibrations (mainly by guanine). When the duplex solution temperature increases (during thermal denaturation) these bands behave similarly: They shift to lower frequencies (figure 8). This can be explained by the following: The hydrogen bonds between the nitrogenous bases in the DNA duplex are weaker in comparison with the hydrogen bonds between the water molecules and nitrogenous bases in the single strand.

As can be seen from figure 3, when the temperature of the solution increases, the position and ratio of the intensities of the three narrow bands centered near 1302 cm^{-1} (adenine band), 1340 cm^{-1} (adenine band), and 1373 cm^{-1} (thymine and adenine band) (figure 2) change. In figure 3 one can see these bands at different temperatures. For the quantitative characterization of the ratio of the intensities of the above-mentioned bands we introduced parameter η, which is equal to the ratio of maximal intensity of the middle peak to the

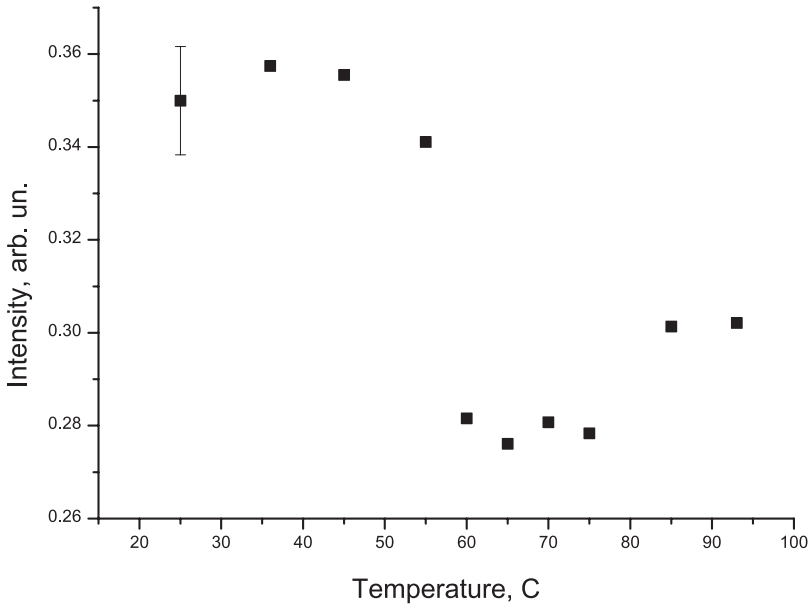

Figure 9. Dependence of parameter η on the temperature.

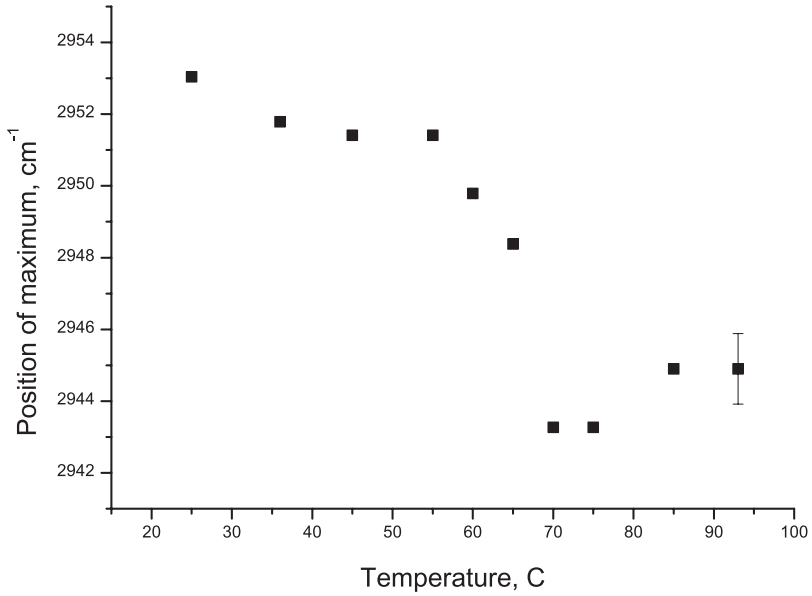

Figure 10. Dependence of the position of the maximum of the band near 2800–3000 cm^{-1} in the Raman spectrum of the (X1 + X3) solution on the temperature.

sum of the intensities of all three peaks: $\eta = I_2/(I_1 + I_2 + I_3)$ (figure 3). In figure 9 the dependence of the parameter η on the temperature is demonstrated. As is seen, parameter η abruptly decreases at the moment of duplex melting. This is also one of the indicators of the state of the DNA strands.

The bands near 2800–3000 cm^{-1} are caused by the valence vibrations of the CH groups of deoxyribose (figure 3 from [31]). It is known that these bands are very sensitive to changes in DNA conformation: In the B-conformation there are broad bands with the maximum at 2963 cm^{-1} and two more weak satellites at 3021 cm^{-1} and 2890 cm^{-1}; in the A-conformation the maximum of the main peak shifts to 2950 cm^{-1} and the small shoulder near 2971 cm^{-1} increases [35]. When the temperature increases to the melting temperature the position of the main peak abruptly shifts to lower frequencies (figure 10), and during further heating it does not return to the initial position. This shift of the band near 2950 cm^{-1} is a reliable criterion of the state of the DNA strands.

3.2. Monitoring of the state of DNA strands during molecular computations

Thus, as the result of the analysis of the changes in the characteristics of the spectral Raman bands of the DNA duplex solution during its melting, many potential signs of changes in the DNA strands state were revealed, namely, the signs of

Table 1. The revealed signs of changes in the states of the DNA strands during the biochemical reactions.

№	Band	Indicator	Signs of change in the state of the DNA	Conclusion about the state of the DNA
1	667 cm^{-1}	Thymine marker	Broadening and shifting of the band to lower frequencies	Start of duplex melting. Emergence of several conformers of thymine nucleoside
2	728 cm^{-1}	Adenine marker	Increase in the intensity and shifting of the band to higher frequencies	DNA duplex melting
3	751 cm^{-1}	Thymine marker	(a) Broadening and shifting of the band to lower frequencies	(a) DNA duplex melting. Emergence of several conformers of thymine nucleoside
			(b) Disappearing of the band	(b) DNA molecules are in the single-stranded state
4	787 cm^{-1}	Marker of the cytosine and backbone vibrations	Shift of the band to lower frequencies	DNA duplex melting
5	1090 cm^{-1}	Backbone vibrations	Change in the intensity or the position of the band	Change of the concentration of nucleotides in DNA solution
6	1251 cm^{-1}	Interaction between adenine and thymine	(a) Position of the maximum change and becomes equal to 1240 cm^{-1}	(a) DNA duplex melting completed
			(b) Position of the maximum does not change and is equal to 1240 cm^{-1}	(b) DNA molecules are in the single-stranded state
7	1485 cm^{-1} and 1578 cm^{-1}	Marker of guanine and thymine	Shift of the bands to lower frequencies	Probability of DNA duplex denaturation increases
8	1302, 1340, 1373 cm^{-1}	Parameter $\eta = I_2/(I_1 + I_2 + I_3)$	Abrupt decrease of parameter η	DNA duplex melting completed
9	2800–3000 cm^{-1}	Vibrations of CH groups of deoxyribose	(a) Position of the main peak	(a) 2963 cm^{-1}—B-conformation of DNA duplex; 2950 cm^{-1}—A-conformation of DNA duplex
			(b) Abrupt shift of the main peak to lower frequencies	(b) DNA duplex melting completed

changes in the nucleoside conformation, and the denaturation and renaturation of the DNA strands. The set of the revealed signs is presented in table 1.

Permanent monitoring of the behavior of the specified (table 1) bands-indicators of the state of the DNA molecules during the biochemical reactions, serves as a basis for this method to increase the accuracy of molecular DNA computations.

4. Conclusions

Experiments carried out in this study to reveal the peculiarities of the behavior of the Raman bands of DNA solutions during the melting/denaturation of the duplex have demonstrated the principal opportunity of the determination and control of the state of the DNA strands during molecular computations using Raman spectroscopy. As a result of the conducted analysis of changes in the characteristics of spectral bands of the DNA duplex during its melting, many signs of the change of the state of the DNA strands were revealed, namely, the signs of change of the conformation of the DNA double helix, changes in the conformation of nucleosides, signs of the processes of the renaturation and denaturation of the DNA strands.

By carrying out periodic (or continuous) laser sensing of a container where biochemical reactions occur, and obtaining sequentially a series of Raman spectra of the solutions of DNA molecules during these reactions, one can control the behavior of the specified bands-indicators of the state of the DNA strands. This control allows us to reveal possible changes in the DNA double helix conformation and changes in the conformation of the nucleosides. Besides that, this monitoring of the process of biochemical reactions provides the revelation of the processes of the renaturation and denaturation of the DNA strands, the determination of the state of the strands (single or twisted in a helix), and also control of possible mutations in the DNA molecules.

Thus, permanent control of the behavior of the detected bands-indicators of the state of the DNA molecules during biochemical reactions serves as a basis for the method of increasing the accuracy of molecular computations.

Acknowledgments

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