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Numerical Investigation of Nucleotides' Interaction Considering Changes Caused by Liquid Influences

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Abstract: This work is devoted to the interaction of nucleotides. The goal of this study is to learn or try to learn how the interaction between nucleotides with exposure to a liquid takes place. Will the interacting forces of the nucleotides be sufficient to approach the incision? A numerical imitation of the interaction is conducted using the discrete element method and a Gears predictor–corrector as part of the integrated scheme. In this work, the results reflect the dynamics of nucleotides: velocity, displacement, and force graphs are presented with and without the effect of the liquid. During changes caused by the influence of a liquid, the nucleotide interaction transforms and passes three stages: a full stop, one similar to viscous damping, and one similar to non-dissipative behaviors. The main contribution of this work is a better understanding of the behavior of infinitely small objects that would be difficult to observe in vivo. The changing influence of a liquid can transform into certain effects. As a result, a model is provided, which can be based on the results of well-known physical experiments (DNA unzipping) for modeling nucleotide interactions.

Keywords: interaction; telomeres; nucleotide; mechanics

MSC: 34K60; 68U20; 70G60; 70K40; 70L05; 74A25; 92C10; 92D20

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1. Introduction

Telomerase nucleotide adding: One of the most important enzymes adding nucleotides at the ends of DNA chromosomes is telomerase. A review of the specialized mechanism of telomeric DNA synthesis by telomerase was conducted by Blackburn [1]. What makes telomerase processive and how important it is was presented by Lue [2]. He mentioned that a complex network of protein–RNA, protein–DNA, RNA–DNA, and protein–nucleotide interactions is apparently necessary to maintain the unique processive property of telomerase. Functional evidence for an RNA template in telomerase was presented by Shippen-Lentz and Blackburn [3]. Their data gives a direct demonstration of the template function for RNA telomerase and distinguish between the external boundaries of the telomeric template.

Nucleotide structure: A structure-independent nucleotide sequence analysis was conducted by Mills and Kramer [4]. They mentioned that the replacement of inosine should improve the resolution of all sequencing methods, which include the synthesis and electrophoretic separation of RNA or DNA fragments. A review of RNA nucleotide methylation was performed by Motorin and Helm [5]. They mentioned that modifications in the new species of RNA would establish ties with various cellular regulatory mechanisms, including the transcription modulation of gene expressions, gene silencing, and reactions to stress. Transcription-coupled nucleotide excision repairs and the transcriptional response to UV-induced DNA damage were presented by Nieto Moreno et al. [6]. They summarized the current understanding of these repair mechanisms, specifically focusing on the roles of stalled RNA polymerase II, Cockayne syndrome protein B (CSB), CSA, and UV-stimulated scaffold protein A (UVSSA) in TC-NER. The direction of nucleotides associated with transcriptions and the transcription reaction to damage to DNA from UV were presented by

Nieto Moreno et al. [6]. They analyzed these recovery mechanisms, particularly by considering the roles of stalled RNA polymerase II, CSA, and UV-stimulated scaffold protein A in TC-NER and Cocayne syndrome protein B.

Surroundings: The internal variability of the nucleotide sequence surrounding the origin of replications in the human mitochondrial DNA was studied by Greenberg et al. [7]. They mentioned that they cloned the main noncoding area of the mitochondrial DNA of a person from a certain number of human placentas. The level of DNA an individual transfers to untouched items in their immediate surroundings was investigated by Puliatti et al. [8]. They mentioned that the results of their study show that a person can deposit DNA in the areas that they were present, even if the objects and/or surfaces were not directly contacted and even after one day. The effects of molecular surroundings were investigated by considering Véry et al.'s [9] theory. They mentioned that the electronic characteristics of low-lying triplet states in water, acetonitrile, and DNA were investigated to decipher the environmental influence on the luminescent behavior of this class of molecules.

Observed phenomena: Strong doublet preferences in nucleotide sequences and DNA geometry were observed by Nussinov [10]. She mentioned that the tight packaging of DNA in the nucleosomes, in general, is a type of steric repulsion.

A comparative study on single nucleotide transport phenomena in carbon nanotubes was conducted by Wang et al. [11]. They demonstrated that individual nucleotides can be statistically identified in accordance with their current pulses, which indicates the potential use of sensors based on carbon nanotubes to identify nucleotides. Nergadze et al. [12] mentioned that CpG-island promoters drive the transcription of human telomeres. They also mentioned that the existence of subtelmeric promoters, involving the control of the transcription of the telomeric repeat-containing RNA transcriptions from independent ends of the chromosome, supports the idea that TERRA performs fundamental functions. The nucleotide distance affects the co-methylation between nearby CpG sites, as investigated by Affinito et al. [13]. They suggested that the establishment of a specific methylation scheme follows a universal rule that the synergistic and dynamic interaction of these two main factors should take into account: an intrinsic susceptibility to the methylation of a specific CpG and the nucleotide distance between two CpG sites.

Modelling of DNA: The molecular modeling (mechanics) of Pt/DNA and Pt/nucleotide interactions were investigated by Hambley and Jones [14]. They discussed the difficulties associated with modeling the Pt moieties and their interactions with biomolecules. Geant4-DNA modeling using complex DNA geometries obtained using the DnaFabric tool was studied by Meylan et al. [15]. They presented DnaFabric as a new tool aimed at promoting the visualization, edition, and creation of complex DNA geometries. Changes of the supercoils in closed round DNA by binding antibiotics and drugs evidence molecular models, including the intercalation examined by Waring [16].

Molecular modeling: The amino acid–nucleotide interaction database (AANT) was presented by Hoffman et al. [17]. They mentioned that this database classifies all amino acid and nucleotide interactions from experimentally determined protein and nucleic acid structures and provides users with a graphical interface to visualize these interactions in aggregate. Nucleotide-dependent lateral and longitudinal interactions in microtubules were investigated by Grafmüller et al. [18]. Their results suggest a consistent picture of a possible molecular mechanism by which nucleotide states cause changes in the H1 and S2 loop and more stable longitudinal bonds. An investigation of the interaction between DNA nucleotides and biocompatible liquids, a COSMO-RS study involving molecular modeling, was carried out by Gonfa et al. [19]. In their work, they investigated the interaction between DNA nucleotides and a biobased ionic liquid to understand the impact of ionic liquid structural changes on the formation of ionic liquids and DNA complexes. In order to better understand the interaction, when electrons interact with low energy consumption and DNA nucleotides in an aqueous solution was investigated by McAllister et al. [20]. Their modeling shows that the hydrogen bond and protoning of nucleotides with water can have a significant effect on barriers to ruptures of a strand.

Forces: The direct measurement of hydrogen bonds in DNA nucleotide bases by atomic force microscopy was carried out by Boland and Ratner [21]. They presented nondirectional van der Waals forces. The sequence-dependent mechanics of single DNA molecules were given by Rief et al. [22]. They mentioned that unzipping directly revealed the base-pair unbinding forces for A-T to be 9 $\pm$ 3 pN and for G-C to be 20 $\pm$ 3 pN. The mechanical stability of the molecules of a single DNA was determined by Clausen-Schaumann [23]. They presented information about the individual DNA double strands and mentioned, that due to a mechanical overstretch, the double helix melts into separate strands, which, depending on the attachment of two strands to mechanical actuators and on the number of ruptures of individual chains in the molecule, can be recombined into a double-helical conformation when relaxing the molecule. A comparative analysis of nucleotide translocations through protein nanopores using molecular adaptive displacements and controlled molecular dynamics was performed by Martin et al. [24]. They conducted a thorough comparison of constant velocity–steered molecular dynamics (cv–SMD) with an adaptive biasing force (ABF). A study of the effects of the atomic ratio of chitosan and the type of drug on the mechanical properties of nanocomposites of silica aerogel/chitosan using the approach of molecular dynamics was conducted by the Alasvandian et al. [25]. They emphasized the importance of using molecular dynamics.

Future important insights and directions of investigation: The role of telomeres and telomerase in cancer and aging was investigated by Saretzki [26]. She reviewed target papers in this field and made some insights. The structural information on the processing of nucleobase-modified nucleotides using DNA polymerases was determined by Hottin and Marx [27]. They mentioned that the adoption of unnatural substrates depends not only on the nature of its position in the complex and modifications but also on the DNA polymerase. A review of nucleotide excision repairs was conducted by Kamileri et al. [28]. They mentioned that defects in nucleotide excision repairs lead, in addition to aging and cancer, to anomalies of development, whose various severity and clinical heterogeneity cannot be explained by a deficiency of DNA repairs.

This work focuses on the numerical study of the effects of liquids on nucleotides. The objective is to look at nucleotide interactions under different fluid exposures. This study aims to demonstrate the different possible behaviors of nucleotides, including both oscillations and stopping. There are many tools for numerical modeling [29–31]. One of the tools for modeling small objects is the use of molecular dynamics. Modeling using molecular dynamics takes into account interatomic potentials/potential energy/potential function from which the acting forces are calculated. In this work, the discrete element method is considered, where the velocity and displacement are calculated, taking into account the integration of the equations of the acting forces in time. Due to this, the equations of acting forces are initially described and considered.

2. Problem Formulation

This study is one in a sequence of research studies, wherein a future study will focus on the transfer of nucleotide chains. Nevertheless, the beginning of these studies requires an analysis of individual nucleotides, which is performed in this work. The initial studies by Jasevičius [32,33] were developed to form a model that would allow for a numerical description of the mechanical interaction of nucleotides. The next step aims at further clarifying the interaction of individual nucleotides and concentrates more on the effect of the liquid, choosing the corresponding forces acting on the nucleotide (molecule) of the fluid. The essence of this work is to identify the effects of a fluid on nucleotides by considering the different influences of it.

Telomeres were selected as the object of numerical research, but some information about them must also be mentioned. Telomere length shortens as a person ages. Progressive telomere shortening leads to somatic cell senescence, apoptosis, or oncogenic transformation, affecting an individual's health and lifespan. Shorter telomeres are associated with an increased risk of various diseases, as well as a worsening of a person's quality of life, as his

chance of survival gradually decreases. The complexity of this study is based on the fact that most of the physical processes taking place within DNA molecules are known, but a mathematical study and description of the processes in terms of dynamics (when the mass of the molecule is also evaluated during movement) is not observed in the known literature. Moreover, relating the theoretical model to known physical experiments remains important. Therefore, the goal itself is also associated with the possibility of its implementation, in order to describe the behavior associated with DNA nucleotides, as well as the equations of the acting nonlinear forces. Later, by integrating the forces over time, it will be possible to study the dynamics of nucleotides. It is hoped that the obtained results will enable the numerical realization of the possibility of DNA sequence additions. With this in mind, the problems are formulated with a more forced description and numerical testing to construct a plausible model of nucleotide interactions. Although several publications on this topic have already been published, such as the studies by Jasevičius [32,33], writing them was a great challenge, allowing us to approach the modeling of extremely complex biological processes.

Various known physical tests could provide knowledge about the values of the forces acting on DNA. However, the intermolecular interaction that takes place in the DNA chain remains unclear in terms of mechanical science (the movement of molecules at each moment of time could be described by learning the velocities and displacements occurring during this picosecond time scale process). Considering this, the problem itself is new. Such a study would allow for a deeper examination of the processes taking place with extremely small objects. The theoretical mechanical behavior of DNA is described with the theoretically characteristic forces acting on the DNA molecule. The value of the acting force will be taken from known physical experiments. When performing a numerical experiment, studying the interaction of nucleotides is desired. For example, nucleotide crosslinking involves the process by which telomerase adds the required base pair at the end of the telomeres. The aim is to investigate this process of base-pair addition in relation to base-pair interactions in the telomere region of the chromosome. This work focuses on the interaction of the following base pairs: adenine (A) with thymine (T)—this interaction has two hydrogen bonds—and cytosine (C) with guanine (G)—this interaction involves three hydrogen bonds. The aim is to investigate the interaction forces acting between these base pairs. In this study, the interacting nucleotides are considered as the corresponding nano-sized molecular object. The interaction between DNA nucleotides is described in terms of the Lennard–Jones potential equation. This equation will be presented as a force-displacement equation, which will describe the interaction between molecules and include the intermolecular attraction and repulsion processes that occur during the interaction. The theoretical model of the interaction will also help to evaluate the possible mechanism of energy dissipation, when the fluctuations of molecules that occur during the interaction have a damping effect. Viscous damping and fluid drag forces are evaluated.

The aim of this work is to numerically investigate the behavior of nucleotides associated with DNA mechanics by evaluating the effects of interaction forces characteristic of it in a liquid. In this work, the mechanics of the interaction of nucleotides are investigated. The dynamics of the science of classical mechanics is aimed at adapting the study of DNA mechanics.

Numeric modeling is used, which can be applied to the discrete element method (DEM). The program was written on the basis of the Fortran software (version 95, IBM, 1 Orchard Road, Armonk, New York, NY, USA). Nucleotide interactions can be related to the attaching of nucleotides of a telomerase in the telomere region, as well as nucleotide excision repairs.

In this work, it is assumed and idealized that during two nucleotide interactions, one interacting nucleotide does not move. Initially, the other nucleotide moves towards the stationary nucleotide, in the liquid, obtaining liquid resistance. During this research, different liquid resistances are considered. The influence of the fluid is reduced gradually until the motion of the nucleotide closely approaches the case where it moves with the

fluid without its resistance. Also, this work takes into account known physical experiments describing the forces acting between nucleotides by applying the unzipping test of DNA chains—the achieved force between DNA chains is on the scale of piconewtons. In the simulation, the desired outcomes include processes relevant to the science of gerontology. The complex processes taking place in the cell are simplified, taking into account the specific case where, thanks to telomerase, the necessary nucleotides are added to the telomere region located at the ends of the chromosomes. The described theoretical force equations are based on the Lennar–Jones potential. This paper presents a comparison of the adenine/thymine (A/T) and guanine/cytosine (G/C) interactions of different nucleotide nucleobases. The contribution of this work is the ability to use the known discrete element method to numerically analyze such a task.

The task of this research is to investigate how the interaction of nucleotides takes place under the influence of a liquid and to analyze whether the attractive forces of nucleotides will be enough to overcome it. As mentioned, the numerical simulation of the interaction will be performed using the discrete element method and a predictor–corrector scheme for the time integration of nonlinear forces. The results of this work reflect the dynamics of nucleotides: velocity, displacement, and force graphs are presented. These graphs represent the behavior of infinitesimal objects that are difficult to observe in vivo. As mentioned, the applied theoretical model can be based on the research results of well-known physical experiments (DNA disassembly). Previous studies using the established energy dissipation mechanism, as well as viscous damping and fluid drag forces, are also evaluated. A theoretical model is created that will help to evaluate the oscillations of molecules during the interaction. The mentioned oscillation process can have a fading effect. The proposed study provides an opportunity to check the calculations and test the original program written in the Fortran programming language using the discrete element method It should be mentioned that previous studies using the discrete element method have not yet been applied to DNA studies by other authors, because the mass of nucleotides is extremely small. In this case, in order to describe the behavior of small objects on the picosecond scale, the time step is also very small.

In the work under consideration, the fluid is the cytoplasm, but when the drag force is applied, the changing (decreasing) influence of this drag force is chosen. This is performed because the applied theoretical model of the drag force (the force considers fluid resistance) does not give the expected effect, i.e., after assessing the full influence of the liquid, the nucleotides stop but do not vibrate. But when its influence decreases, the molecules begin to vibrate. This shows that there must be a different approach to modeling nucleotides. To achieve this, this article introduces the coefficient n_{fluid}, which takes into account not only the reduction in the influence of the liquid but also the effects of molecular vibrations/oscillations. Moreover, introducing this coefficient n_{fluid} allows for different variations in nucleotide vibrations, so it is also interesting from a fundamental point of view, where the simulation can include different nucleotide behaviors.

3. Methodology

A one-dimensional motion of an arbitrary nucleotide i in time t during normal contact is characterized by global parameters: positions $\boldsymbol{x}_i$, velocities $\dot{\boldsymbol{x}}_i$, and accelerations $\ddot{\boldsymbol{x}}_i$ of the center of mass and a force $\boldsymbol{F}_i$ applied to it. The global parameters are defined in Cartesian coordinates. Translational motion is described by the Newton's second law, which is applied to each nucleotide i:

$$m_i \ddot{\boldsymbol{x}}_i(t) = \sum_j \boldsymbol{F}_i(t) \tag{1}$$

where m_i and the vector $\ddot{\boldsymbol{x}}_i$ are the mass and acceleration of the i-th nucleotide, and the vector $\boldsymbol{F_i}$ corresponds to the resultants of forces added to the nucleotide i during the

interaction. If the normal orientation of contact will be defined by the unit vector $\boldsymbol{N}$, the force vector $\boldsymbol{F}_i(t)$ may be described by the time-dependent scalar variable $F_i(t)$:

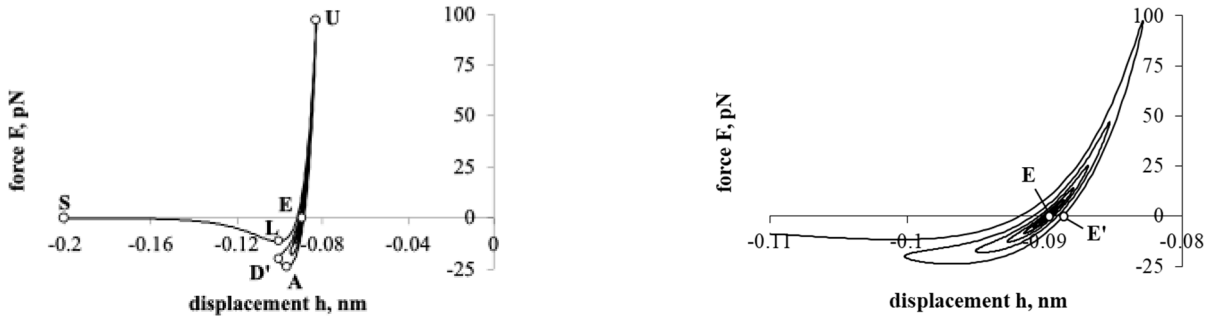
$$\boldsymbol{F}_i(t) = \boldsymbol{N}F_i(t) \tag{2}$$

The acting force described by Equations (1) and (2) is integrated with the 5th Gears predictor–corrector scheme of Jasevičius [32,33]. This Gears predictor–corrector scheme represents a two-step procedure, as Jasevičius and Kruggel-Emden [34] note. In this scheme, the time-dependent variables are denoted as the position $x(t)$, velocity $v(t) = dx/dt$, and acceleration $a(t) = d^2x/dt^2$ as well as the higher time derivatives, $b_3(t) = d^3x/dt^3$, $b_4(t) = d^4x/dt^4$, and $b_5(t) = d^5x/dt^5$, of the nucleotide by vector $y = \{x, v, a, b_3, b_4, b_5\}^T$. The new value variables at time increment $t + \Delta t$ are predicted by a simple series expansion up to a desired order of accuracy $y^p(t + \Delta t) = y(t) + y^p(\Delta t)$. Here, the incremental vector $\Delta y^p(\Delta t)$ presents the required terms of the expanded series. Then, according to the new positions and velocities, the particle forces and accelerations are corrected, and the acceleration increment Δa is updated. Finally, the vector of the particle variables is corrected as follows $y^c(t + \Delta t) = y^p(t + \Delta t) + \Delta y^c(c_j, \Delta t, \Delta a)$. Here, the correction vector Δy^c is calculated by using the given integration constants c_j. For this simulation, the bacterium motion is limited to the normal direction, and the position $x(t)$ is presented here as the displacement $h(t)$.

The values of the forces acting between nucleotides can be taken from physical experiments. Such a force–distance equation for the interaction can be described as follows (Jasevičius [29,30]):

$$F(t) = k\frac{\sigma|F_L|}{|h(t)|}\left[\left(\frac{\sigma}{|h(t)|}\right)^{12} - \frac{1}{2}\left(\frac{\sigma}{|h(t)|}\right)^{6}\right] + F_{drag} \tag{3}$$

where F_L is the extreme value of the attractive force, which acts between nucleotides (Figure 1, point L) during the approach; F_{drag} is the drag force; k is the fitting coefficient; and h is the distance between nucleotide surfaces. The fitting coefficient in this equation is considered as $k \approx 20.03$, according to Jasevičius [32,33].



(**a**) (**b**)

Figure 1. Nucleotide interaction model: force versus displacement. (**a**) The interaction is described by taking into account points of interaction in the prescribed manner of S-L-U-A-D′-E; (**b**) an enlargement of (**a**) and a consideration of points E and E′, as per Jasevičius [32,33].

The molecule is considered as a small object, and the Stokes' drag force (Gutiérrez-Varela and Santamaria [35]) is applied to the influence of the hydrodynamic force:

$$F_{drag}(t) = 6 \cdot n_{fluid} \cdot \pi \cdot \eta \cdot R_H \cdot v_{relative}(t) \tag{4}$$

where n_{fluid} is a fluid influence controlling the coefficient, which varies in this research $0 \leq n_{fluid} \leq 1$; η is the viscosity of the fluid; R_H is the hydrodynamic radius of the nucleotide; and, when $R_H = R_i$, $v_{relative}$ is the relative velocity in the normal direction:

$$v_{relative}(t) = v_i(t) - v_{blood}(t) \tag{5}$$

where v_i is the cell velocity in the normal direction, and v_{blood} is the blood velocity in the normal direction.

During approach, the nucleotide reaches an extreme value of the repulsion force at point U at a distance h_U. In simplified form, this can be written as $h_U \approx \sigma$, and the maximum repulsive force F_U can be achieved.

$$F_U \approx 24\frac{\varepsilon_{LJ}}{\sigma} \text{ or } F_U \approx \frac{1}{2}kF_L \tag{6}$$

Based on the Lennard–Jones potential, the general force–displacement curve is shown in Figure 1. Following the direction, the presented curve crosses the S-L-E-U points during approach and U-E-L-S during detachment. The extreme value of the attraction force F_L can be calculated at a distance h_L, using a known expression:

$$h_L = \sqrt[6]{\frac{26}{7}}\sigma \approx 1.2445\sigma \tag{7}$$

During the interaction, the force curve can reach zero force $F_E = 0$ at a certain point E. This point can be reached when, due to energy dissipation, the movement/oscillation of the nucleotide stops on that corresponding point E or in the case where the interaction of nucleotides occurs without taking energy dissipation into account. In this situation, during the oscillations of the nucleotide, the force–displacement curve will cross this point E, and the nucleotide will remain in motion. In both mentioned cases, point E will be reached at a distance h_E and can also be calculated with a known expression:

$$h_E = 2^{1/6}\sigma \approx 1.1225\sigma \tag{8}$$

As further studies show, the certain point E (when $F_E = 0$ and position is h_E) is already reached during the first nucleotide separation, but this happens, as mentioned, in two cases. Considering Equation (4), in the first case, the full fluid effect/influence is considered ($n_{fluid} = 1$), and in the second case, the fluid effect is not applied to the interaction of the nucleotide ($n_{fluid} = 0$). Given the fact that the molecules are constantly oscillating, the third case becomes interesting when the partial effect of the liquid is taken into account. It becomes important to answer the question of whether it is possible to have an effect of the drag force, as well as, at the same time, to have oscillations characteristic of molecules. In the third case, the first separation does not pass the force–displacement curve at the mentioned point E but is located at the corresponding distance from it, at point E′ (Figure 1b). Depending on the effect of the fluid, various shifts of position E′ from point E are possible during separation.

The third case becomes interesting with the following questions. When a decrease in the effect of the fluid is taken into account, with a decrease in the effect of liquid, how will the molecules' oscillation change, and how will the position E′ change in relation to point E? In order to get closer to these questions, additional calculations will be presented, where the percentage ratio ξ is considered for point E:

$$\xi\left(n_{fluid}\right) = 100\left(1 - \frac{h_{E'}\left(n_{fluid}\right)}{h_E}\right) \tag{9}$$

where h_E is the nucleotide position at point E, $h_{E'}$ is the nucleotide position at point E′, and n_{fluid} is a fluid influence-controlling coefficient. The following section shows the initial data.

4. Initial Data

The main data for nucleotide interactions are presented in Jasevičus [32,33]. The average weight of a DNA base pair (sodium salt) = 650 daltons, where 1 dalton equals the mass of a single hydrogen atom, or 1.66057×10^{-27} kg (see Williams et al. [36]). For the interaction of one nucleotide, we consider 325 daltons (Tseytlin [37]) of the base-pair average mass to be $325 \times 1.6605 \times 10^{-27} = 5.397 \times 10^{-25}$ kg. The diameter of the DNA double helix is 2.0 nm. DNA has a Young's modulus of the order of 0.3–1.0 GPa, which is similar to hard plastic (see Bloom [38]). Here, the force acting between nucleotides is based on an unzipping force AFM (atomic force microscopy) measurement, given by Rief et al. [22]. They mentioned that a 10 pN force acts on a poly-A/T (adenine/thymine) oligonucleotide duplex, while a 20 pN force acts on a poly-G/C (guanine/cytosine) duplex. The present study uses these values of force, although it is possible that there may be other values of force. The base pairs/nucleotides are precisely held by hydrogen bonding, with an energy of 1 to 5 kcal/mol (4 to 21 kJ/mol) or, considering Joules (1 kJ/mol = $1 \times 10^{23}/6.022 \times 10^{23}$ J), from 6.6423×10^{-21} to 34.872×10^{-21} J. This is considered to be 20×10^{-21} J, as per Jasevičius [32,33].

The initial velocity is set as zero $v_0 = 0$. The nucleotides are in the interaction zone, where the influence of attraction is enough to bring nucleotides on a surface. For the numerical simulation, the initial distance between two nucleotide surfaces is considered to be $h_0 = 0.2$ nm. The needed parameter σ is the finite distance at which the inter-nucleotide potential is zero and is considered as $\sigma = 0.08$ nm. Also, the initial data are presented in Table 1.

Table 1. Initial data for nucleotide interactions.

Parameters	Values	References
Initial velocity, v_0	0	Jasevičius [32,33]
Initial interaction distance, h_S	0.2 nm	Jasevičius [32,33]
Mass, m_i,	325 daltons or5.397×10^{-25} kg	Tseytlin [37]
Length of single base, l_{base}	≈0.676 nm	Chi et al. [39]
Length of single nucleotide, l_i	≈0.330 nm	Mandelkern et al. [40]
Young's modulus, $E_{ym,i}$	0.3–1.0 GPa	Bloom [38]
The adhesion force for A/T (adenine/thymine) oligonucleotide duplex (at point A)	10 pN	Rief et al. [22]
The adhesion force for G/C (guanine/cytosine) oligonucleotide duplex (at point A)	20 pN	Rief et al. [22]
Adhesive dissipative energy, $W_{adh,diss}$	20×10^{-21} J	Jasevičius [32,33]
Relative coefficient of energy dissipation, k	20.03	Jasevičius [32,33]
Finite distance at which the inter-nucleotide potential is zero, σ	0.08 nm	Jasevičius [32,33]
Damping coefficient, α_d (viscous damping is not considered in this work)	0.2	Jasevičius [32,33]
Dynamic viscosity of cytoplasm, η	0.00089 Pa·s	

Since cytoplasm is composed mainly of water, the dynamic viscosity of water must be taken into consideration, which is 8.90×10^{-4} Pa·s or 8.90×10^{-3} dyn·s/cm^2 or 0.890 cP at about 25 °C.

The influence of the fluid corresponds to the constrained movement of the nucleotide when its movement is essentially determined by the movement of the fluid. This work assumes that the liquid does not move, so the influence of the liquid, even under the influence of significant attractive forces, is decisive when it comes to interactions between nucleotides. The goal is to look at the interaction and to try to look at the small, molecular-level world, in which, in order for molecules to move and necessary reactions to take place, mechanisms should somehow be formed, otherwise there would be no interaction. In this work, we want to get closer to these complex processes, and at the same time, further research is needed for a deeper analysis. Also, it is important to get closer to the ingenious processes of evolution involving the movement of molecules and, judging by the diversity of different molecules, to look at the processes that take place many times in every human cell continuously.

5. Results

In this work, the effect of the fluid is studied by reducing its influence at appropriate times. The coefficient n_{fluid} applied in Equation (9) is used to control the effect of the fluid. The coefficient in this work was selected to be n_{fluid} = 1; 0.1; and 0.01, respectively. The coefficient n_{fluid} = 1 corresponds to the case where the influence of the fluid is not suppressed. When n_{fluid} = 0.1, the influence is decreased ten times, and when n_{fluid} = 0.01, it is decreased a hundred times, respectively. These three values of the coefficient n_{fluid} divide this study into three parts, where, in each case, the behavior of the nucleotides under the influence of the fluid is examined. It should be noted that as n_{fluid} decreases, the damping effect and the amount of energy dissipated decrease.

Now, the first case will be discussed when the interaction of the nucleotides is fully affected by the effect of the liquid, or when the coefficient is n_{fluid} = 1. This study aims to show that when the full influence of the liquid is considered, it becomes difficult for the nucleotides to approach each other. It also aims to show that in order for nucleotides to come closer, other mechanisms are needed to allow nucleotides to bond. One such helper is a ribonucleoprotein called telomerase, which seems to be always near or attached to the DNA strand. Also, after considering the full effect of the fluid, the question remains as to how the resistance of the fluid is overcome to allow the appropriate reactions specific to the DNA strand to occur. How are nucleotides attached mechanically? Also, how do not only nucleotides but various other known molecules, considering their extremely small mass, interact with the DNA strand?

In this work, the focus is on the interactions of the pairs of these bases: adenine (A) with thymine (T)—such an interaction has two hydrogen bonds (in Figures 2–4, it is presented with a red line)—cytosine (C) with guanine (G)—this interaction has three hydrogen bonds (in Figures 2–4, it is presented with a blue line). Considering the full effect of the fluid, the results are presented in Figure 2. The first graph in Figure 2a shows the dependence of force–displacement. Here, it is observed that no fluctuations in the interaction between nucleotides occurred and simply that the nucleotides stopped at the corresponding point, which corresponds to point E (Figure 1b, Equation (8)). Because different nucleotide pairs had different amounts of hydrogen bonds, different forces were achieved. The pair guanine/cytosine (G/C), which had the largest amount of hydrogen bonds (three), achieved a higher force during the interaction. This same trend is reflected in Figure 2b, which shows the time history, but although the pair reached the extreme force value, its interaction time was the shortest, while the interaction time of the nucleotide pair adenine/thymine (A/T) was the longest. Referring to Figure 2c, as mentioned earlier, both nucleotide pairs A/T and G/C stopped at the same point, so the value of the displacement remains constant in the corresponding time interval. This is achieved under the influence of the fluid, which, if not moving, the nucleotide remains in a stationary state. Additional graphs revealing

the interaction of the nucleotides with the weakening of the fluid influences will also be presented. As for the velocity change (Figure 2d), an increase in the velocity of nucleotides due to the effect of attraction is observed, followed by a sharp drop until a zero-rate value is reached. For additional illustrations, graphs of the velocity dependence on the force and displacement are presented (Figure 2e,f). This results in Figure 2g, which is an enlarged version of Figure 2a, showing a more detailed variation of forces versus displacements.

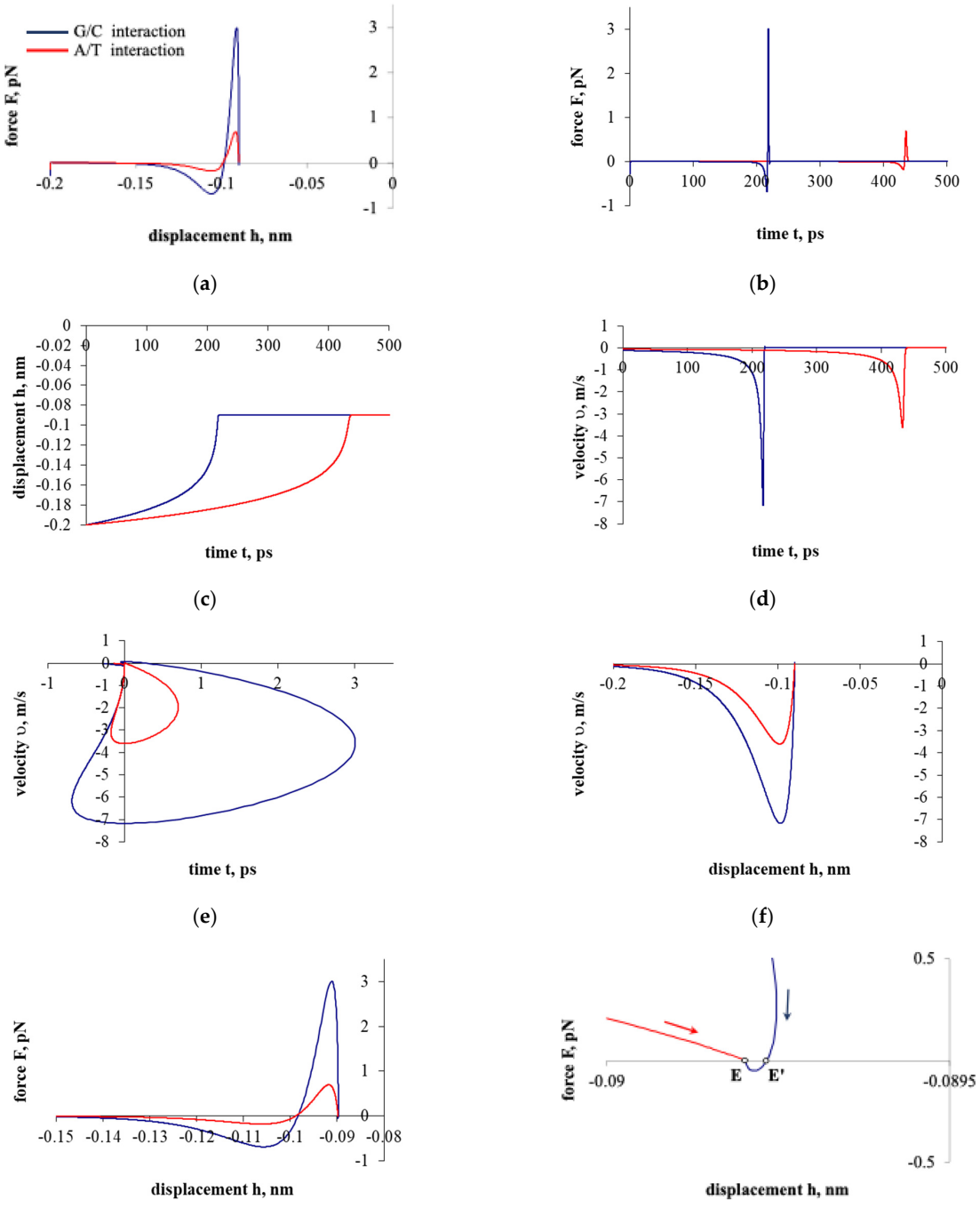


Figure 2. Nucleotide interaction when the full influence of the drag force is considered, $n_{fluid} = 1$. (**a**) Force versus displacement, (**b**) force, (**c**) displacement, (**d**) velocity history, (**e**) velocity versus force, and (**f**) displacement; (**g**,**h**) enlargement of force versus displacement (**a**); (**h**) reaching of point E. The nucleotides' guanine/cytosine (G/C) interaction is marked by a blue line, while the nucleotide pairs' adenine/thymine (A/T) interaction is marked by a red line.

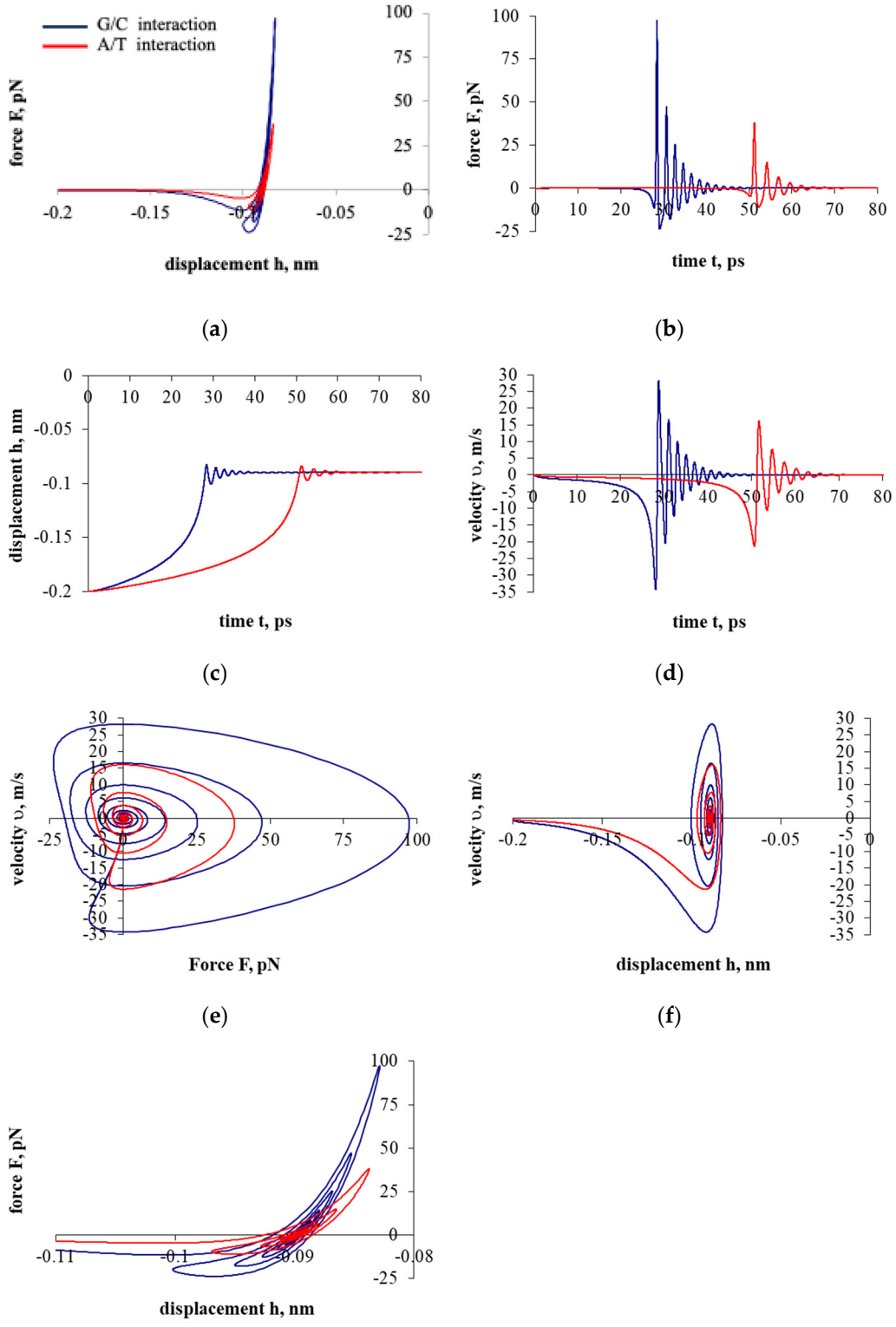


Figure 3. Nucleotide interaction when the full influence of the drag force is considered, $n_{fluid} = 0.1$. (**a**) Force–displacement, (**b**) force, (**c**) displacement, (**d**) velocity history, (**e**) velocity versus force, and (**f**) displacement; enlargement of force–displacement (**g**). The nucleotides' guanine/cytosine (G/C) interaction is marked by a blue line, while the nucleotide pairs' adenine/thymine (A/T) interaction is marked by a red line.

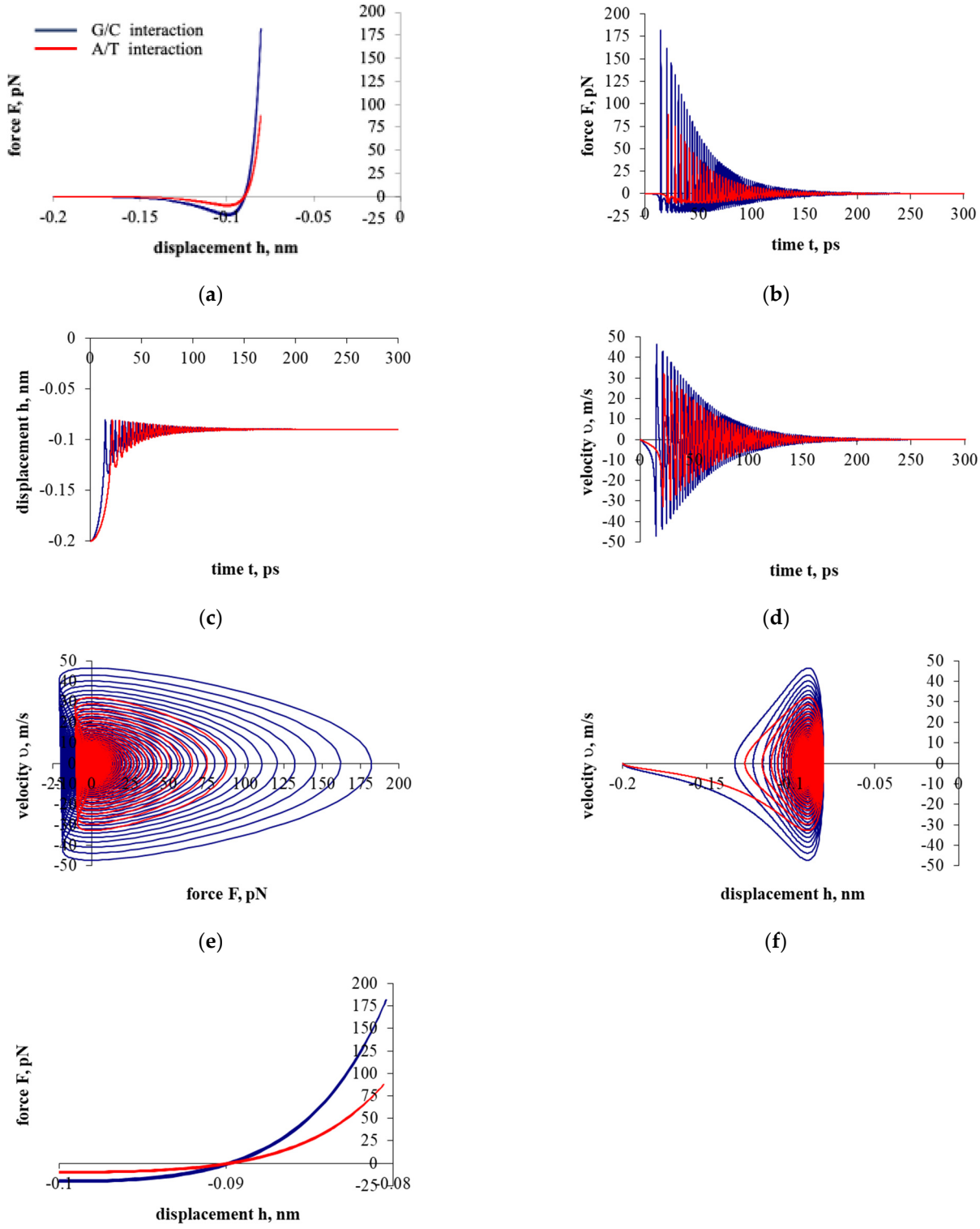


Figure 4. Nucleotide interaction when the full influence of the drag force is considered, $n_{fluid} = 0.01$. (**a**) Force–displacement, (**b**) force, (**c**) displacement, (**d**) velocity history, (**e**) velocity versus force, and (**f**) displacement; (**g**) enlargement of force–displacement. The nucleotides' guanine/cytosine (G/C) interaction is marked by a blue line, while the nucleotide pairs' adenine/thymine (A/T) interaction is marked by a red line.

Now, the second case will be discussed, wherein the interaction of nucleotides is partially affected by the influence of the liquid, whereby the coefficient is n_{fluid} = 0.1, which corresponds to the influence of a liquid decreased ten times. Figure 3 is presented below. These graphs are illustrative in nature and show that when the effect of the liquid is weakened, the DNA nucleotides begin to oscillate. Oscillations can also be obtained using viscous damping forces, according to Jasevičius [33]. However, this oscillation effect is achieved by considering the influence of the fluid. The movement of molecules causes not only oscillations but also a dissipation effect of the movement. Moreover, as the following graphs show, when the dissipation effect decreases, the molecules' motion will be close to the motion without the fluid, and such behavior (without the influence of a fluid) was examined earlier by Jasevičius [32].

Referring to Figure 3a, a pronounced force–displacement hysteresis is observed. As in the previous case (Figure 2), although the nucleotides will oscillate, they will still stop at the same point, which, as mentioned, corresponds to point E (Figure 1b, Equation (8)) when the force value at this point is zero. Since the amount of hydrogen bonds is different, the maximum repulsion force achieved is also different. But the achieved force values are much higher than in Figure 2, which is caused by the weakened influence of the liquid. An interesting phenomenon can be observed in Figure 3b; when the nucleotide (G/C) interaction (marked by the blue line) is suppressed, the nucleotide pair (A/T) with two nucleotide bonds (marked by the red line) begins to oscillate more strongly. When some oscillations are suppressed, others begin, and oscillations occur at different moments of time in such a way that a balance is created by the interaction of nucleotides with each other, creating conditions for the formation of a stable structure. It should be noted that one can only predict that different numbers of hydrogen bonds should promote less oscillations of the DNA strand (more stability) by connecting the corresponding number of nucleotides, as in, for example, when telomerase (a reverse transcriptase enzyme) adds the required number of base pairs (six base-pair repeat sequences, TTAGGG) at the end of the telomere. Additional studies will be needed in the future to address this issue.

The same pattern (oscillation and stop) is reflected in Figure 3c, where, when the oscillations are suppressed, as in the previous case, the nucleotides stop at the corresponding displacement value h_E (Equation (8)), which is the same for the different interacting pairs of nucleotides. This is also reflected in terms of velocity fluctuations in Figure 3d. The velocity decays, and after a corresponding time interval, the zero value of the nucleotide velocity is reached.

For illustrative purposes, additional graphs are provided in Figure 3e,f, which show the dependence of the velocity on the force and displacement, respectively. Additionally, Figure 3g shows an enlargement of the graph in Figure 3a. In it, the fluctuations of forces with respect to displacement are more noticeable.

Now, the third case will be discussed (the last example), wherein the interaction of nucleotides is small and is affected by the influence of the liquid when the coefficient is n_{fluid} = 0.01, which corresponds to a 100-fold reduction in the influence of the fluid. After reducing the effect of the liquid by a hundred times, the behavior of the nucleotides gets close to the interaction without the effect of the liquid, according to Jasevičius [32]. It can also be said that a small fluid influence could correspond to the case where the nucleotide has, similar to free motion, no resistance. This can also come close to free oscillations of the molecule. This is already noticeable in Figure 4a, where the force–displacement dependence is similar to a single line, and the hysteresis becomes more difficult to notice. In any case, fluctuations occur (Figure 4b), and their amount is much higher, but the dissipation effect remains. After a corresponding period of time, the nucleotide stops at point E, where the force value is equal to zero. Displacement oscillations (Figure 4c) also decrease, and after certain period of time, the oscillations disappear, as in the previously examined cases (Figures 2 and 3), and nucleotides stop at the same point h_E, the value of which remains the same in all three cases. This value, as mentioned before, can be calculated analytically by applying Equation (8). As for the graph displaying the variation of the

nucleotide velocity (Figure 4d), fluctuations are also observed, where after a certain time, the fluctuations disappear at a velocity value of 0. Unlike the previous case (Figure 3), the observed tendency is that when one pair of nucleotides stops oscillating (G/C), another one (A/T) starts to oscillate. Oscillations occur simultaneously but with different amplitudes of the oscillations. The amplitude of the oscillation of the nucleotide pair with a higher amount of hydrogen bonds (G/C) is higher. For further illustration, Figure 4e,f shows the dependence of the velocity on the force and displacement. For an additional illustration, see Figure 4g, which shows an enlarged view of Figure 4a, where the displacement dependence of the force variation is more noticeable.

Furthermore, Figure 5 presents the dependence of the various values of the considered fluid influence controlling the coefficient n_{fluid} on the deviation of point E, represented as the displacement difference in the percentages representing the coefficient $\xi\left(n_{fluid}\right)$, as per Equation (9). This graph is intended to show how the value of the displacement $h_{E'}$ changes in comparison with the value of the displacement h_E (Equation (8)). It should be noted that at the end of the interaction, considering different nucleotide interactions and different fluid effects, the numerical experiment and the one calculated according to Equation (8) coincide/are equal, i.e., $h_{E,numerical} = h_E$. Point E′ is obtained during the first unloading (Figure 1b), when the force value reaches zero. Meanwhile, point E is obtained when the nucleotide stops, as mentioned earlier, and at this point, the force value is also zero (Figure 1b).

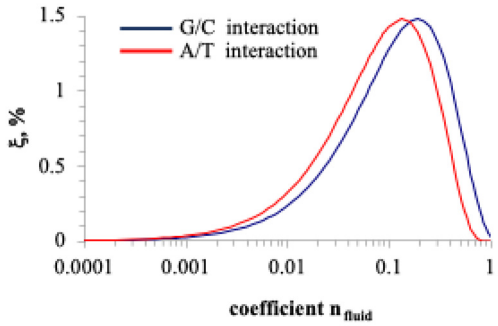


Figure 5. Displacement differences in the percentages representing the coefficient ξ depending on the fluid's influence-controlling coefficient n_{fluid}. The percentage expression of the difference in displacements h_E and $h_{E'}$ (considering the coefficient ξ from Equation (9)) at different influences of the fluid (considering the fluid influence-controlling coefficient n_{fluid}, which varies from 0.0001 to 1). The nucleotides' guanine/cytosine (G/C) interaction is marked by a blue line, while the nucleotide pairs' adenine/thymine (A/T) interaction is marked by a red line.

It should also be noted that each point of the curve is the result of a separate interaction of a pair of nucleotides, including the described cases with n_{fluid} = 1; 0.1; and 0.01 (Figures 2–4). To get a complete picture of the behavior of nucleotides when the influence of the liquid changes, more different n_{fluid} coefficients are taken.

In Figure 5, the results show that the force–displacement hysteresis as n_{fluid}, decreases and begins to widen, and the percentage expression of the distance E and E′ reaches up to 1.5% and then narrows and, as a result (when the influence of the fluid is small), is similar to the curve without force–displacement hysteresis.

It is also worth noting that with a higher attraction effect (Figure 5, blue line), after considering the full effect of the fluid at $n_{fluid} = 1$, the blue curve does not reach the h_E value immediately during unloading like the red curve (Figure 2h), since the blue curve has an additional loop.

A general analysis of Figure 5 shows that as the influence of the fluid changes from the case where it is not assessed to the case where it is fully assessed, the oscillations around point E involve different stages. When the influence of the liquid is not assessed ($n_{fluid} = 0$), oscillations around point E (displacement along the h axis, when the resultants

of forces are F = 0) are not observed; there is no hysteresis; and the oscillations do not dissipate, which corresponds to the behavior exhibited when the influence of the fluid is not considered, according to Jasevičius [29]. In the case of a small or partial influence of the liquid ($0 < n_{fluid} < 1$), the molecules begin to oscillate around point E (on the displacement axis h, when the resultants of forces are F = 0); hysteresis appears; and the oscillations dissipate; this behavior is similar to the case where viscous damping is considered, according to Jasevičius [33]. After fully taking into account the influence of the liquid ($n_{fluid} = 1$), the nucleotide stops at point E (when the resultants of forces are F = 0), and no repeated oscillations around point E (displacement along the h axis) are observed.

A correlation of the results with a known physical experiment should also be noted. As mentioned earlier, in this work, forces (from known physical experiments) between nucleotides were selected according to Rief et al. [22]. A 10 pN force acts on a poly-A/T (adenine/thymine) oligonucleotide duplex, while a 20 pN force acts on a poly-G/C (guanine/cytosine) duplex. These are precisely the values of the attractive forces that were achieved during the interaction of the numerical experiment, and they were also observed in previous studies by Jasevičius [32]. Integrating the nonlinear resultants of forces by Equation (3) over time with a 5th Gears predictor–corrector scheme using Newton's second law leads to values of velocities and displacements that are consistent with this force value. That is, if the molecule was affected by these forces, the corresponding behavior and values of the molecule would be achieved.

Future research requires additional analyses to find the different influences or different relationships of nucleotide behavior considering the following two cases: first, when a partial influence of the drag force is taken into account and second, when the viscous damping force is taken into account. Also, the behavior of nucleotides when both mentioned forces act together at the same time should be investigated.

6. Conclusions

This work investigated the influence of a liquid on the interaction of nucleotides. As a main result, it was observed that under different fluid influences, nucleotide interactions involve three relatively different behaviors. In the first case, when the influence of the liquid is fully evaluated ($n_{fluid} = 1$), the nucleotide stops, and fluctuations of the nucleotides are not observed during the interaction. When the influence of the liquid is partially evaluated ($n_{fluid} = 0.1$), decreasing oscillations of the nucleotide occur, which have a dissipation effect. This behavior is similar to the case where the viscous damping mechanism is evaluated, according to Jasevičius [32]. And in the third case, where the influence of the liquid is small ($n_{fluid} = 0.01$), the interaction could be close to the case where the free oscillation of nucleotides takes place in the absence of energy dissipation, according to Jasevičius [33].

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Nomenclature

Roman alphabets	
A	Adenine
AFM	Atomic force microscopy
b_3, b_4, b_5	Higher time derivatives
C	Cytosine
DEM	Discrete element method
DNA	Deoxyribonucleic acid
E	Point of interaction where zero force is reached (with the displacement of h_E, Equation (8))
E′	Interaction point where resultant force is 0 during detachment

F	Resultants of forces [pN]
F_i	Resultants of forces added to nucleotide i during the interaction [pN]
F_{LJ}	Lennard–Jones force [pN]
G	Guanine
h	Distance between nucleotide surfaces [nm]
k	Fitting coefficient
L	Point of interaction where maximum force of attraction is reached when approaching
LJ	Lennard–Jones
m_i	Mass of nucleotide [kg]
S	Initial point at which the interaction calculation begins
T	Thymine
U	Point of interaction where the maximum force of repulsion is reached when approaching
y	Time-dependent variables representing vectors
t	Time [ps]
Δt	Time step [s]
y^p	Incremental prediction vector
y^c	Incremental correction vector
Greek alphabets	
ε_{LJ}	Depth of potential well [kJ/mol]
η	Viscosity of fluid [Pa·s]
ξ	Displacement difference in percentages representing coefficient [%]
σ	Inter-nucleotide distance at which the potential is zero [nm]
v	Velocity of nucleotide [m/s]

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