A computational study of dsDNA pairs and vibrational resonance in separating water

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Abstract This article investigates the relationship between molecular sequence and dependent interacting behavior of molecular segment pairs and secondly, sequence dependent, vibrational resonance in surrounding normal saline, protein-free water. The development of a molecular model to explore these systems phenomena, the results of several nanoscale molecular dynamics simulations, and analysis of behavior of interacting ΦX174 double-stranded DNA segment pair models in various configurations are presented. Fourier analysis revealed intriguing vibration frequencies within the solvent plane between the segments, while subsequent frequency domain transformation of the time domain waveforms revealed statistically significant resonating harmonic signals in the THz range.

Keywords DNA · Resonance · Segregation · Homologous pairing · Molecular vibration

Introduction

Homologous chromosome pairing involving DNA recognition, highly coordinated spatial movement, and synchronized timing

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is an explanatory challenge that spans decades (Sybenga 1999). To varying degrees for a given interaction, successful pairing rests in part on organism and cycle phase phenomenon (Sybenga 1999), “bouquet” clustering of telomeres at the nuclear envelope (Bass et al. 2000), sustained and rapid chromosomal movement (Brown et al. 2011), chromosomal pairing centers (Tsai and McKee 2011), genes (Joyce et al. 2012) proteins (Lukaszewicz et al. 2010; Nimonkar et al. 2012; Trelles-Sticken et al. 2005), and the synaptonemal complex (Hayashi et al. 2010). Contrasting with protein-mediated Watson–Crick single-stranded DNA (ssDNA) and ssDNA or double-stranded (dsDNA) pairing, protein-free “recombination-independent” pairings fundamentals remain mysterious (Danilowicz et al. 2009). Engineering a synthetic biological understanding of this process would support future research into DNA replication, cell division, and molecular oscillators, and would begin to answer one of the ‘grand challenges of synthetic life’ identified by Porcar et al. (2011): having enough information to use models to go back to cell design.

For protein-free pairings, Kornyshev et al. (2007) identified various electrostatic theories, van der Waals forces, and hydration forces that contribute to an understanding of the structure and interactions of dsDNA helices. Sequence dependencies of the backbone might also result in sequence homology recognition without unzipping the double helix. Baldwin et al. (2008) examined, in a protein free environment, sequence dependent behavior of homologous dsDNA segments taken from ΦX174 bacteriophage. Specifically, after a 2 week equilibration in sealed microscopy slides at room temperature (20 °C), they reported uniform Maltese cross optical textures for four molecular segments each with identical nucleotides $^{469}_{176}$ DNA. The observed 1–3 nm of water that separated the surfaces of the nearly parallel nearest neighbor DNAs in equilibrium was consistent with 25 Angstrom (Å) theoretical helix main axis

separation under those conditions reported by Kornyshev et al. (2007). At that distance “the interaction becomes repulsive due to the contribution of image forces and possible hard-core clashes between residues on opposing molecules”. Kornyshev et al. (2007) also reported the same uniformity with four molecular segments with sequence $^{699}_{406}$ DNA. Contrasting with the aforementioned homologous pairs, 1:1 non-homologous mixtures of two molecular segments with sequence $^{469}_{176}$ DNA with two molecular segments with sequence $^{699}_{406}$ DNA showed disrupted textures, indicating the possible results of sequence-dependent effects on the molecular interaction. From these sequence dependent behaviors, Baldwin et al. (2008), inferred recognition of mutual homology based on helix electrostatics in a protein-free environment.

Subsequent to Baldwin et al. (2008), Danilowicz et al. (2009) demonstrated, *in vitro* with parallel single molecules, in physiologically similar temperature, and monovalent salt conditions, free homology recognition and homologous pairing in minutes/hours in the absence of proteins, divalent metal ions, crowding agents, or free DNA ends. Stable pairing of homologous molecules at low DNA concentration in monovalent salt solutions revealed deficiencies in the electrostatic theory (Cortini et al. 2011). Danilowicz et al. (2009) indicated hydration effects in the water surrounding the molecules may also play a role in homology-dependent dsDNA/dsDNA interaction as a common underlying physical basis. At first glance, Danilowicz et al. (2009) and the theory put forth by Kornyshev et al. (2007) investigated by Baldwin et al. (2008) appear to be inconsistent; however, experimental purposes and therefore experimental conditions differed. Both the experimental results from Danilowicz et al. (2009) and the theory from Kornyshev et al. (2007), indicated increased likelihood of pairings at higher temperature and salt levels. Kornyshev et al. (2007) attributes pairings to reduced electrostatic repulsion caused by increased salt and temperature levels. Danilowicz et al. (2009) indicated hydration effects in the water surrounding the molecules may also play a role in homology-dependent dsDNA/dsDNA interaction as a common underlying physical basis. They encouraged future studies to assess the physical basis for such homology-dependent recognition and the relevance to, and rules for, DNA/DNA-mediate homologous pairing *in vivo*. Among the many follow on studies, the role of electrostatics and protein-induced bridging (Cherstvy and Teif 2013) and macromolecular crowding (Hancock 2012) have been insightful.

Methods

In silico investigation enables exploration of the physical basis for homology-dependent molecular behavior in

smaller time increments than the often weeks, hours or even minutes long *in vivo* experiments. Further, *In silico* investigation enables observation and analysis of low-frequency vibrations in surrounding water (Buranachai et al. 2006; Chou 1984) as well as harmonic and anharmonic dynamics occurring at picosecond fluctuations in molecular segments (Meinhold et al. 2007; Smith et al. 1996). We investigate the hypothesis that sequence-dependent molecular vibrational energy may be a contributor to picosecond fluctuations in interacting molecular segment pairs and that homology-dependent harmonized and resonating low-frequency vibrations may be an additional mechanisms contributing to interaction behavior.

Our *in silico* experiment approach is based on the *in vitro* Baldwin et al. (2008) experiment. Similarities and differences between the *in silico* and the *in vitro* outcomes are reported.

Nano-scale Molecular Dynamics (NAMD) with Chemistry at HARvard Molecular Mechanics (CHARMM) force field (Brooks et al. 2009) and Visual Molecular Dynamics (VMD) modeling (Phillips et al. 2005) are the primary tools we used to conduct the research as recommended by Guvench and MacKerell (2008).

Based on Baldwin et al. (2008), we constructed four different configurations of Φ X174 molecular systems each consisting of two segments with sequence 176–469 DNA ($^{469}_{176}$ DNA) with two segments with sequence 406–699 DNA ($^{699}_{406}$ DNA).

For the experiment focused on behavior of molecular pairs, four Φ X174 DNA segments were generated using an automated version of the nucleic acid builder subroutine from the Amber Suite of bio-molecular simulation programs and placed in water boxes with 20 Å of separation between DNA segments and solvated 15 Å beyond the DNA. The solvent was ionized to a level similar to that in a natural cellular environment and set at $T = 310$ K. The system underwent three required process simulations necessary to place it in a naturalized state ready for regular molecular dynamic simulation. The simulations were run in sequential segments, all with an equal number of 2 fs steps for consistency. A total of 2,400,000 fs or 2.4 ns (ns) of simulation time were simulated. While 2.4 ns is not the 2 weeks taken in Baldwin et al. (2008), the objective of this portion of the work was simply to observe if similar distortion occurred in the molecular segments and if so to determine direction of molecular movement.

For the vibrational resonance experiment, four molecular systems were initially constructed with simple 10-mer configurations using two macromolecules: end-to-end, parallel, perpendicular tee, and skew. The circular geometric configuration was not considered. The four systems were carefully constructed to be symmetrical along the

z-axis with a similar thickness slab of water between the DNA. The four systems were each run for a total of 2 ns of simulation run-time using the same routine as Φ X174 DNA except the special profiling feature of NAMD was utilized to output individual pressures for each system slab. Using this feature all but Ewald sums are computed during the normal simulation run. Because the simulations are run using the Particle Mesh Ewald method (PME), the Ewald contributions had to be calculated with a secondary calculation-only run (no MD was performed) based on the first run trajectories. The Ewald data was then added back into the pressure data from the original run providing the complete pressure profile for each system. The Fourier Transform of system pressures could be examined for the existence of frequency components. Any component with a signal to noise ratio above that present in water in its natural state and that is statistically significant may be considered evidence of vibrational resonance. The calculations were performed again with the popular MINITAB 16.1.0 and Chi Square with a p value without Yates' correction. The MATLAB[®] crosstab function returned the same.

Experimental objectives and variables

Behavior of molecular segment pairs is of interest as it is the defining characteristic of homologous recognition. The visual variable chosen for analysis of segment pair behavior was distortion of the molecules as seen in Baldwin et al. (2008). Change in the geometric distance between DNA molecular segments indicates segment movement. To determine movement the simulation trajectory files were loaded into VMD and the center of mass was calculated for each helix on the first frame of the trajectory and the very last frame of the trajectory. Using the 3D coordinates for the centers of mass an Excel spreadsheet was used to then calculate the initial distance and the final distance between each molecule using the standard Cartesian three-dimensional displacement calculation.

The initial distance was subtracted from the final distance to obtain the relative movement in Å of each molecule with respect to each of the other three. A positive value indicates movement away from each other and a negative value represents closure. The results were tabulated and superimposed on a graphical representation of the virtual system as positive and negative vectors that correspond to separation/closure.

Our expectation is that the unique structure of the DNA double helix may broadcast by vibrational resonance a frequency and magnitude that are dependent only on the nucleotide base pair sequence. If valid, sequence dependent

vibrational resonance might exhibit a magnitude far greater than typical normal mode vibrations most likely at a lower frequency. The intrinsic structural characteristic of each helix strand may determine the frequency, magnitude, and other harmonics similar to how organ pipes determine notes in an organ. The intrinsic property of the structure might cause normally random thermal vibration to synchronize within the hydrophobic region of the double helix causing segments of the DNA to emit longitudinal pressure waves out into the surrounding water environment. These waves may simply be transverse compressions and rarefactions of the water molecule bonds surrounding the double helix. If a second DNA molecule of similar sequence within close physical proximity were to be exposed to these waves moving through the solvent, interaction at a higher level may occur causing further concentration or superposition of vibrational energy into fewer and lower frequencies. This concentration of energy could effectively amplify certain pressure variation frequencies at the expense of others maintaining conservation of energy.

Recent research indicates that low-frequency vibrational modes of nucleotides occur from two primary sources: the structural flexibility of the molecules themselves (Nikolaenko et al. 2011), and the occurrence of weak CH $\cdots$ O/N H-bonds between the molecules (Brovarets' et al. 2013; Yurenko et al. 2011). That these vibrational modes and relaxed force constants vary per nucleotide, and even per conformation, further strengthens prior sequence-dependent DNA mechanics research (Miyamoto et al. 2005; Rief et al. 1999; Ten et al. 2009). We are now adding the idea that the specific frequencies and their spectral magnitudes are directly related to the nucleotide sequence, as proposed by Miyamoto et al. (2005) and Ten et al. (2009). The sequence hypothesis may be adequately tested if we could establish a relationship between the DNA molecule base pair sequence and the observed frequency content.

The intent of the vibrational resonance experiment that we analyzed was to identify a relationship between spectral content and nucleotide sequence potentially substantiating the new sequence hypothesis. To explore that relationship, we selected on unique system from the vibrational resonance experiment geometric configurations to test for sequence change. We used the system with the most pronounced frequency characteristics to best highlight system-to-system differences. We reasoned that changing the nucleotide sequence and re-running the system with the most statistically significant coefficients would exhibit the most observable change in coefficients if sequence were actually a factor. With that in mind, the two simplest methods of selecting the best system to re-run were a) the system with the greatest number of significant coefficients as a percentage of total coefficients or b) the system with

Fig. 1 Relative movement during 2 ns simulation time

the greatest ratio of power in significant coefficients to total power.

Results

The conformational changes that occurred over the course of the 2 ns are shown in Fig. 1.

Euclidian movement of the molecular segments is depicted in Fig. 1. Segments N1, N2, N3 and N4 correspond to sequence ⁴⁶⁹₁₇₆DNA. Segments N5, N6, N7 and N8 correspond to sequence ⁶⁹⁹₄₀₆DNA.

Molecular distortion at the end of the simulation run is visually obvious and consistent with that observed in figure 1C page 1061 (Baldwin et al. 2008). All positive values indicate that during 2 ns of MD simulation time the molecules moved away from the 20 Å initial separation and consistent with theory and toward equilibrium at approximately 29 Å.

Experiments on vibrational resonance

To determine which system was most energetic for the purposes of searching for vibrational resonance, four molecular systems were constructed with simple configurations using two macromolecules: end-to-end, parallel, perpendicular tee, and skew. We applied the Fourier

Table 1 Statistical uniqueness of observed frequencies

System	Chi square	Yates' Chi square	Yates' <i>p</i> value
End-to-end	719.95	718.30	<0.0001
Parallel	528.20	526.64	<0.0001
Perpendicular T	592.93	591.34	<0.0001
Skew	672.86	671.23	<0.0001

Table 2 Percentage comparison of 4 systems

System	% Power in significant coefficients	% of Significant coefficients
End-to-end	22.77	1.95
Parallel	20.47	1.56
Perpendicular T	19.93	1.69
Skew	21.55	1.86

Transform to simulated pressures generated by MM algorithms. The result of the transform will be a frequency “spectrum” of the real-time pressure data observed in the water separating the molecules. The spectrum observed had frequency content from DC to approximately 50 THz, however, the most energetic spectra (i.e. the spectra with highest amplitude) were predominantly in the 1–100 GHz range.

The statistical uniqueness of the frequencies observed are summarized below:

In every case the low *p* value indicates the association between rows (System) and columns (coefficients significant or insignificant) indicate frequencies observed are statistically significant (Table 1).

General observations regarding these data

There are several notable points to be made about the spectral data obtained thus far. First is the extreme variability between systems of all major indicators. The DC component, frequency values and frequency magnitudes all differ as widely as the distribution of power as seen in Table 2.

The most powerful single frequency in the Parallel configuration is about four times larger than the most powerful frequency in the Skew configuration.

Selection of contrasting system and sequence

A quick look at the data suggested that re-running the end-to-end system, as originally intended, would provide the greatest contrast of sequence related variation.

Before an antithetical end-to-end system could be constructed an appropriate ‘dissimilar’ sequence had to be selected. Two factors needed to remain constant between systems in order to maintain the same system electronic charge, the total number of nucleotides and the total of each type of nucleotide. Beyond that, the ‘dissimilar’ sequence should be totally random. The MATLAB® ‘randsample’ command was employed to provide 20 random samples of a pool of nucleotides that composed the energetic sequence ‘tataaacgcctataaacgcc’. This was done ‘without replacement’ meaning each time a nucleotide type is chosen it is removed from the available pool thereby eliminating the possibility of changing the overall quantity of each nucleotide. The result was a new sequence consisting of the same number of each nucleotide chosen completely at random. A ‘dissimilar’ end-to-end system was re-constructed, solvated and ionized with two (2) randomly generated sequences and put through the exact same MD regime as the original end-to-end system. The Ewald pressure calculation run was completed and the entire post simulation data parsing routine was completed.

Discussion

There are, of course, many new questions about the data. Is the observed periodicity an artifact of the models or characteristic behavior of the molecules as we suspect? If the periodicity is characteristic behavior of the molecules then of which molecules is this behavior a characteristic? Are the specific frequencies and amplitudes of the harmonized resonance a direct function of DNA nucleotide sequence, run-length, or both?

In light of the periodic behavior found in simulated intermolecular pressures it is relevant to determine if the pressure variation is related to DNA sequence. There were 28 statistically significant frequencies that appeared in the frequency spectrum of all four systems that contained the energetic sequence. Of the 28, 21 frequencies showed up as significant in the end-to-end system with random molecular sequence. This means that seven specific frequencies present in all four energetic sequences were absent from the random molecular sequence. At the same time, 14 new frequencies became significant in the random sequence macromolecule. Previous work in this area suggests that each nucleic acid base has a relatively unique spectra (Santamaria et al. 1999); regardless, without further research it cannot be determined if the seven missing and 14 new frequency values are directly related to a specific nucleotide sequence, related to systemic variables or are simple indications of a random change in the power distribution.

One possibly confounding influence to this analysis is that the configurable parameter in the molecular dynamics simulators known as “Periodic Boundary Conditions” (PBCs) acts in a similar fashion to a bathtub inasmuch as it serves to contain the water within the system during molecular dynamics. Wassenaar and Mark (2006) report that molecular pressure propagating through the boundary could “reflect” back into the system or enter the system from a periodic image much like waves slosh around in a bathtub. Therefore, it is possible that waves may “reflect” off of the DNA molecules themselves further complicating the already “choppy water” wave system, however such effects were found to be small (no more than 10 %), though statistically significant nonetheless (Wassenaar and Mark 2006).

Conclusions

Our Fourier analysis of the simulation outcomes revealed a rich selection of periodic pressure variations occurring in the water solvent environment between simulated dsDNA/dsDNA molecules. The unique and statistically significant pressure forces observed appear sufficient to drive solvent from between the homologous molecules thus facilitating the potential for pair alignment to the point of electromagnetic repulsion theorized by Kornyshev et al. (2007). Our thesis is that atomic-level resonating molecular vibrations synchronized by specific molecular sequences produce a harmonized collective force, strong enough in aggregate to move molecules in a water environment to facilitate alignment of homologous dsDNA/dsDNA molecular pairs. At a more basic level, we theorize the molecular sequence driven harmonized resonance may represent a previously un-investigated molecular movement mechanism whose computational basis has yet to be validated through correlated observable experimentation. Understanding this mechanism would be one of many building blocks required to achieve the ideal scenario of understanding individual causal mechanisms for biological processes and understanding the significance of “patterned noise” as identified by Porcar et al. (2011) Until a greatly expanded experimental design involving additional and larger molecules over larger time frames, greater separation between molecules, greater separation between molecules and boundary, and accompanied with mirroring “hard cell” research which are run and analyzed, there are simply too many alternative explanations for our data to safely conclude that there is DNA sequence related interaction. Nonetheless, if the idea is validated, we expect this research idea will advance the understanding of molecular oscillators. The ultimate goal of this line of research is to identify healthy and unhealthy biology through vibrational signature, which would be useful when diagnosing cellular

models during the engineering and testing of more complex systems.

In an expanded research, we wish to address the question how DNA can operate as a low frequency oscillator in its own right as well as transmit dynamic information throughout a bio-macromolecule while adding to the verification and validation of the NAMD computational models that underlie our hypotheses. Gathering spectral data has previously been performed by Shishkin et al. (2000a, b), examining the features of the lower-frequency vibrational modes of 2'-deoxyribonucleosides. In this context, our idea for further research is to conduct verification and validation of the computational modeling by conducting larger scale matching computational and observable experiments. This investigatory approach to our research idea will consist of "soft cell" and "hard cell" parallel efforts with outcomes to be analyzed for similarity of frequency content and molecular movements by an interdisciplinary team of experts in Modeling and Simulation, Molecular Biology, and Physics. The "soft cell" computational experimentation idea will greatly extend the physical and time dimensions of our existing computational research to dimensions that are observable in "hard cell" experimentation. The combination of molecular dynamic simulation and biochemical and micro-spectroscopy techniques make it possible to investigate the concept of DNA-driven harmonics in "hard cell" experimentation. Our notion for "hard cell" experimentation consists of two steps. In the first step we will amplify through polymerase chain reaction (PCR) double-stranded human genomic DNA. The purified amplicon will be precipitated with alcohol and dissolved in the appropriate buffer in an appropriate volume for the instrumental analysis. The second step in the hard cell analysis will consist of low-frequency light scattering spectroscopy of the DNA assemblies and DNA-water interactions. Analysis of the frequencies observed in the computational "soft cell" experimentation will be validated against frequencies observed in the parallel "hard cell" experimentation.

A first phase of this expanded research is currently being undertaken to, through simulation, better understand the relationship between DNA's sequence and the vibrational motion it undergoes in solvent. Our hypotheses that vibrational motion is sequence-dependent and that it is sufficiently unique to form a sort of identifying signature will be tested using similar methods to this research, but through multiple runs in a more classical experimental design in the hopes of finding any sequence-dependent effects that may exist. This research has been encouraged by the results reported by Rief et al. (1999), and Miyamoto et al. (2005).

Conflict of interest The authors declare that they have no conflict of interest.

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