1/f DNA Hydrogen-Bond Energy Noise

Nazarii Boichuk
Bioelectronics (ICS-8),
Forschungszentrum Jülich,
52425 Jülich, Germany
n.boichuk@fz-juelich.de

Yurii Kutovyi
Bioelectronics (ICS-8),
Forschungszentrum Jülich,
52425 Jülich, Germany
y.kutovyi@fz-juelich.de

Nicolas Lobato-Dauzier
LIMMS/CNRS-IIS,
The University of Tokyo,
Tokyo 153–8505, Japan
lobato@iis.u-tokyo.ac.jp

Anthony Genot
(LIMMS/CNRS-IIS),
The University of Tokyo,
Tokyo 153–8505, Japan
genot@iis.u-tokyo.ac.jp

Teruo Fujii
Institute of Industrial Science (IIS),
The University of Tokyo,
Tokyo 153–8505, Japan
tfujii@iis.u-tokyo.ac.jp

Andreas Offenhäusser
Bioelectronics (ICS-8),
Forschungszentrum Jülich,
52425 Jülich, Germany
a.offenhaeusser@fz-juelich.de

Svetlana Vitusevich
Bioelectronics (ICS-8),
Forschungszentrum Jülich,
52425 Jülich, Germany
s.vitusevich@fz-juelich.de

Nicolas Clément
LIMMS/CNRS-IIS,
The University of Tokyo,
Tokyo 153–8505, Japan
nclement@iis.u-tokyo.ac.jp

Abstract—**The power spectrum of the hydrogen-bond energy fluctuation of DNA was investigated by molecular dynamics simulation. A *1/f* frequency response is found, even for simple configurations of DNA composed only of thymine bases and with the presence of an equal number of complementary strands. This suggests that various relaxation processes are involved as a general trend. The noise amplitude strongly depends on the temperature. These results indicate that experimental measurements of the hydrogen-bond energy noise may provide additional degrees of freedom for a wide range of studies from DNA nanotechnologies to biosensors.**

Keywords—DNA, hydrogen-bond energy, 1/f noise, biosensors, DNA nanotechnology

I. INTRODUCTION

Hydrogen-bond (hb) interactions are ubiquitous in nature, and their dynamics is expected to play a key role in chemical reactions and biomolecular recognition [1, 2]. Recent experimental setups allowing the direct observation of single-molecule hydrogen-bond dynamics with single-molecule resolution for solvent/surface interaction open up new opportunities for the study of hb dynamics [2]. In particular, it has recently been shown that liquid water yields *1/f* noise in hb energy, whereas simple liquids such as liquid argon exhibit a near white spectrum [3]. This observation was related to network rearrangement dynamics. In DNA systems, hb interactions are typically studied from temperature ramps in order to assess a melting temperature T_m and are measured by fluorescence. The direct investigation of hb dynamics is extremely difficult at the molecular level as the noise in these experimental systems is typically too high to directly observe hb energy fluctuations, but the application of fluorescence correlation microscopy is a very promising approach for such studies [4]. Recent progress in molecular dynamics (MD) simulations means that experimental results are satisfactorily reproduced, in particular for DNA [5, 6]. Nonetheless, hydrogen-bonding dynamics was not revealed in these studies. By means of MD simulations, we investigate the dynamics of hb energy, and we explore the potential for using DNA hb fluctuations as an additional signal for studies in DNA nanotechnology and biosensors. Used methods, including MD, are described in Sec. II. The simulation results and the discussion are presented in Sec. III and conclusions are put forward in Sec. IV.

II. SIMULATION METHOD

Our work was carried out by means of an oxDNA code where the coarse-grained DNA model was introduced [7]. For simplicity, we examined an archetype system for DNA with a nucleic acid sequence of only 10 thymine bases (T_{10}) and with the presence of an equal number of complementary strands (A_{10}) (Fig. 1). 1, 10, and 100 double-stranded DNAs (dsDNA) were randomly confined in cubic boxes whose size corresponded to 133 µM dsDNA. The selected concentration is rather high when compared to typical experimental conditions, but the aim was to preserve the computational time for hb energy dynamics monitoring over a sufficiently long period to study low-frequency noise. A periodic boundary condition was considered to keep the concentration constant. Additionally, the system was studied at salt concentrations equivalent to 0.1 M of NaCl, which is typical experimentally, and which corresponds to a Debye screening length of approximately 1 nm.

Fig. 1. Representation of the investigated dsDNA. Red and white spheres show backbone repulsion sites, and cyan ellipsoids indicate bases.

The computation was performed in two steps. During the first step, dsDNAs were inserted into the box at a random position and the molecules were relaxed by Monte Carlo simulation. The trajectory and hb energy calculations were subsequently computed for the system using molecular dynamics simulation with a Langevin thermostat for at least 10^9 steps. Note that hb energy, E_{hb}, corresponds to the sum of all hb interaction energies.

The power spectral density of hb energy was estimated as

$$S_{Ehb}(f) = \frac{1}{t_{max} - t_{min}} \left| \int_{t_{min}}^{t_{max}} E_{hb}(t) e^{i2\pi ft} dt \right|^2 \quad (1)$$

where $E_{hb}(t)$ is the total hydrogen bond energy of the system at time t. To obtain quality curves, we introduced an averaging procedure for each spectrum.

In order to investigate the effect of temperature variations, we calculated the noise spectra for different temperatures from 10 °C to 80 °C.

III. SIMULATION RESULTS AND DISCUSSION

We first evaluated an hb energy averaged over time, $<E_{hb}>$, as a function of temperature to confirm that the system is in equilibrium. Typical time dependences of $E_{hb}(t)$ calculated for 1, 10 and 100 molecules are shown in Fig. 2(a-c) when T = 10 °C. As can be seen, the value of E_{hb} fluctuates around $<E_{hb}>$. The dependences of $<E_{hb}>$ on temperature for 1, 10 and 100 molecules are shown in Fig. 2(d-f). As shown in the figure, $<E_{hb}>$ displays a sigmoid shape. Such behavior of $<E_{hb}>$ can be obtained analytically by considering a two-state approximation for the system. The process of denaturation as a forward bimolecular reaction and the reverse reaction of hybridization is given by

$$AB \leftrightarrow A + B \quad (2)$$

where AB denotes the ordered state of ten-base dsDNA, and A and B stand for single strands, A_{10} and T_{10}, in the random coil state. Note that no intermediate states are considered in this case. The equilibrium constant for the reaction is given by the law of mass action (square brackets symbolize the concentration):

$$K = [A] \cdot [B] / [AB] \quad (3)$$

Therefore, by considering the concentration of A_{10} strands to be equal to the concentration of T_{10} strands ([A] = [B]) and taking into account the conservation of mass [A] + [AB] = [AB_{init}], with [AB_{init}] the initial concentration of dsDNAs, the equation for the fraction of paired strands, x = [AB]/[AB_{init}], can be derived from (3):

$$x = 1 + \frac{K}{2[AB_{init}]} - \sqrt{\left(1 + \frac{K}{2[AB_{init}]}\right)^2 - 1} \quad (4)$$

It should be noted that only the $0 \leqslant x \leqslant 1$ root of the solution was used to satisfy the physical meaning of the fraction of paired strands.

Importantly, there is a relationship between the Gibbs free energy change, ΔG, and the equilibrium constant at temperature, T, $K = C \cdot \exp(-\Delta G/RT)$, where R is the gas constant and C is a matching coefficient. The results of fitting with the relation $E_{hb}(T) = E_{max} \cdot x(T)$ are shown by dashed lines in Fig. 2(d-f). From the calculated fitting, the free energy change is in the order of 400-550 kJ/mol (Table I.). E_{max} represents the total energy of the fully hybridized dsDNA. Considering a typical enthalpy for the A-T bond around $\Delta H = 0.287$ eV per bond as a value for comparison [8], E_{max} extracted from fittings using the sigmoid function acquires the values that are of the same

order as ΔH for 1 (2.87 eV), 10 (28.7 eV) and 100 dsDNAs (287 eV), which proves the correctness of the simulations.

The melting temperature, T_m, of the duplex formation is defined as the temperature at which half of the available strands are in the double-stranded state and half of the strands are in the random coil state. From the curves in Fig. 2(d-f), we can extract the melting temperature by solving (4) when $x(T_m) = 1/2$. The melting temperature calculated for different numbers of molecules is in the range of 51-53 °C, which is as expected for relatively large dsDNA concentrations.

TABLE I. PARAMETERS OBTAINED FROM SIGMOIDAL SHAPE FITTING FOR DIFFERENT NUMBERS OF DSDNA

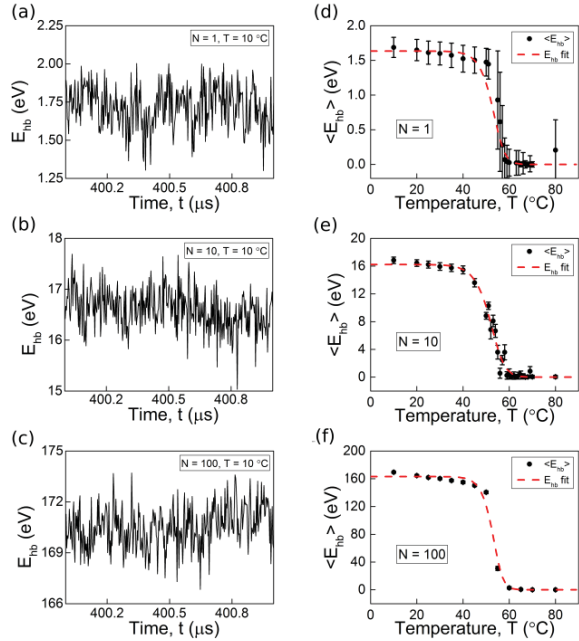| Parameter	1 dsDNA	10 dsDNAs	100 dsDNAs
E_{max}, eV	1.63	16.22	163.14
T_m, °C	52.7	51.7	52.8
ΔG, kJ/mol	470	398	550

Fig. 2. (a-c) The total hb energy time dependence in the system with 1, 10 and 100 dsDNAs at 10 °C. (d-f) Hydrogen bond energy as a function of temperature for 1, 10 and 100 dsDNAs in 133 μM dsDNA solution. Error bars are standard deviations for the corresponding energy dependence. The melting temperatures are 52.7 °C, 51.7 °C and 52.8 °C obtained from fitting curves in Fig. 3d, e and f respectively.

The power spectrum of the hb energy fluctuation S_{hb} (1) for 100 dsDNA is shown in Fig. 3a. We find a $1/f^\gamma$ frequency response. Moreover, the amplitude of S_{hb} strongly depends on the temperature (Fig. 3b). More quantitatively, a maximum is observed at $T = T_m$. The hb energy dependence (simulated data from Fig. 2f) is also depicted for comparison. Thus, the following power proportionality between noise at 3 MHz and the energy level can be obtained: $S_{hb}(3 \text{ MHz}) \sim E_{hb}^{0.84}$.

The power density spectra of 1, 10 and 100 dsDNAs molecules are shown in Fig. 4a. It should be emphasized that
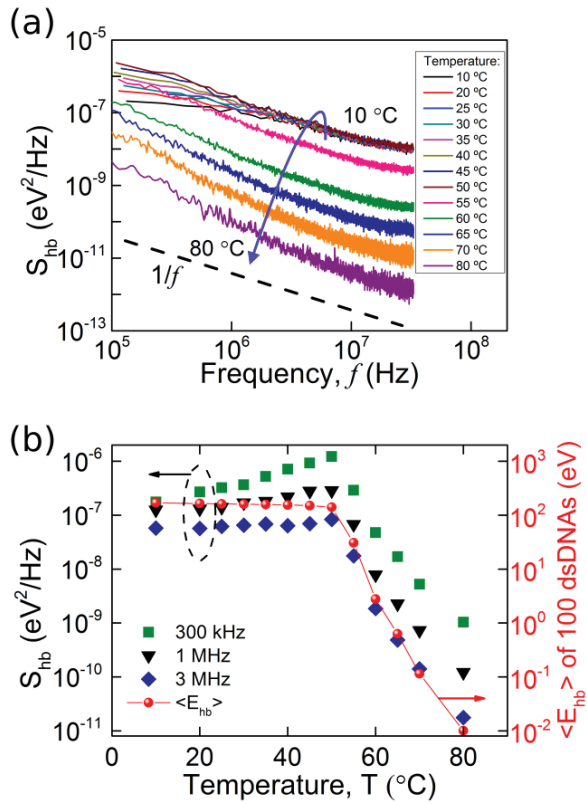
Fig. 3. (a) The power spectra of hb energy in the 100 dsDNAs system. The system was investigated at different temperatures. Averaging was implemented for 100 spectral curves for each temperature. A dashed line indicates $1/f$ behavior. The line with an arrow at the end shows the temperature increase. (b) Temperature dependence of noise level at different frequencies for 100 dsDNAs system compared with hb energy. Data was taken from Fig. 3a at 300 kHz, 1 MHz, and 3 MHz.
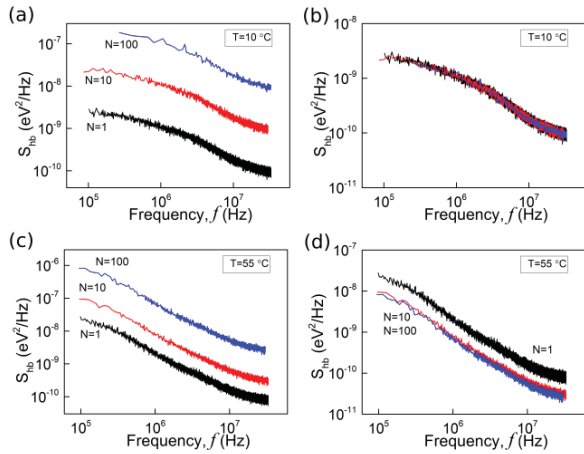

Fig. 4. Power spectra density for different numbers of molecules calculated at 10 °C (a) and 55 °C (c). Spectra normalized per number of molecules are shown in (b) and (d).

similar $1/f$ behavior in the frequency range 0.1 MHz - 33 MHz was observed for different numbers of molecules. More precisely, at low temperature, when all molecules are hybridized, the noise level is directly proportional to the number of molecules (Fig. 4b). This is also the case when $T = T_m$ (Fig. 4(c-d)), with a slight deviation observed when the number of molecules is small.

These results suggest that π-π intermolecular interactions [9] between neighboring bases at the single-molecule level may play a greater role than the statistical hybridization fluctuations relative to the number of molecules.

Another interesting feature is that the slope (γ) of the flicker noise ($1/f^\gamma$) shows a strong dependence on temperature, as depicted in Fig. 5. In a temperature range from 10 °C to $T_m \approx 52$ °C, parameter γ yields a linear dependence on temperature with a slope of 0.008 °C^{-1}. However, when the system reaches melting point, the slope of gamma becomes almost three times as high as at the lower temperatures. This leads to the suggestion that T_m is a cross-over stage for noise behavior, which requires further investigation.
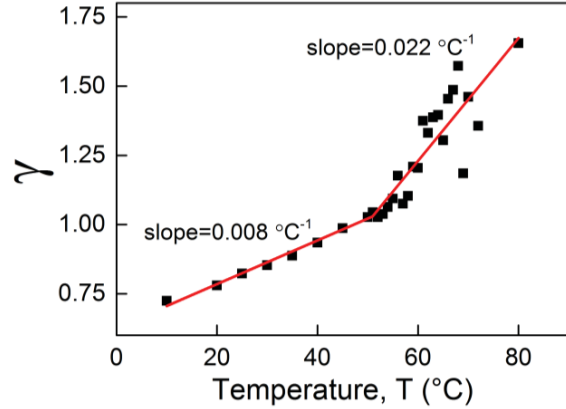

Fig. 5. Dependence of gamma parameter of flicker noise for the 10 dsDNAs system on temperature. Cross-over point corresponds to the melting temperature.

IV. CONCLUSIONS

We analyzed the power spectra of the hydrogen bond energy fluctuation in DNA by coarse-grained molecular dynamics and found near $1/f$ noise behavior. We suggest that these results may be related to multiple relaxation processes induced by the fluctuation of π-π molecular interactions as well as possible partial hybridization and a statistical distribution of these relaxation processes in the case of multiple molecules. The temperature dependence of the noise also demonstrates that noise could be a powerful approach providing supplementary information in addition to the ensemble and average measurements depicted by the usual sigmoid response. For example, it appears that the melting temperature is a crossover for the $1/f^\gamma$ noise slope. We suggest that further investigation of DNA sequence, length, concentration and ionic strength may provide useful information for future experiments. An analytical model for hb noise is under development.

REFERENCES

[1] D. Granata, L. Ponzoni, C. Micheletti, and V. Carnevale, "Patterns of coevolving amino acids unveil structural and dynamical domains," PNAS, vol. 114, 2017, pp. E10612–E10621.

[2] C. Zhou et al. "Direct observation of single-molecule hydrogen-bond dynamics with single-bond resolution." Nat. Commun., vol. 9, 2018, pp 807.

[3] M. Sasai, I. Ohmine, and R. Ramaswamy, "Long time fluctuation of liquid water: 1/f spectrum of energy fluctuation in hydrogen bond network rearrangement dynamics," J. Chem. Phys., vol 96, 1992, pp 3045–3053.

[4] M. J. Shon and A. E. Cohen, "Mass Action at the Single-Molecule Level," J. Am. Chem. Soc., vol. 134, 2012, pp 14618–14623.

[5] T. E. Ouldridge, A. A. Louis, and J. P. K. Doye, "DNA Nanotweezers Studied with a Coarse-Grained Model of DNA," Phys. Rev. Lett., vol 104, 2010, pp 178101.

[6] J. Y. Lee et al., "Base triplet stepping by the Rad51/RecA family of recombinases", Science, vol. 359, 2015, pp 977–981.

[7] B. E. K. Snodin et al., "Introducing improved structural properties and salt dependence into a coarse-grained model of DNA," J. Chem. Phys., vol. 142, 2015, pp 234901.

[8] D. F. V. Lewis, "Hydrogen Bonding in Human P450-Substrate Interactions: A Major Contribution to Binding Affinity," The Scientific World Journal, vol. 4, 2004, pp. 1074–1082.

[9] J. Trasobares et al., "Estimation of π-π electronics couplings from current measurements", Nanolett., vol. 17, 2017, pp 3215–3224.