Text explanations for the presentation "Numerical realization of helicoidal DNA model"

Maria **OSTRIK** [1], Victor **LAKHNO** [2]

[1] Leonov University of Technology, Korolev, 141074, Russia

[2] The Institute of Mathematical Problems of Biology RAS, Pushchino, 142290, Russia

The numerical realization of the helicoidal mechanical model of the DNA molecule by the Runge-Kutta method of the fifth order of accuracy with an automatically selectable variable step in time is proposed. The model is a further development of the well-known helicoidal DNA model developed by M. Barbi et al.

Molecular dynamic modeling of DNA denaturation was carried out on the basis of the proposed model. Agreement of the calculated temperature of denaturation with its experimental values is obtained.

DNA molecules can be used as structural elements of promising electronic devices. Electronic nanobiochips have a number of advantages over modern silicon chips (miniature, high-speed performance and accuracy). It is also possible to use DNA molecules in memory and logic devices. The success of the use of DNA in electronics depends on the possibility of ensuring its conductivity, which is largely determined by the properties of open states. The formation of open states (denaturation bubbles) and their propagation can be numerically modeled based on various mechanical models. Interest in description of the physical and mechanical behavior of DNA molecules began with work [3] and increased in part of mathematical modeling of this behavior after work. A fairly general dynamic helicoidal model for describing the mechanical behavior of a DNA molecule was developed in the works of M. Barbi et al. This work is devoted to the further development and numerical realization of the M. Barbi model.

Slide 1 (MECHANICAL DNA MODEL). The stages of transitioning from the actual helical geometry of a DNA molecule to a helicoidal DNA model are shown here. In it, each pair of nitrogenous bases rotates in a relatively rigid backbone of the molecule and its configuration is given by two generalized coordinates (n = 1,..., N; N is the number of base pairs in DNA): r_n is a radial variable associated with the break of hydrogen bonds and Φ_n is the rotation angle of each of the base pairs (the combination of these angles sets the current helical structure of DNA; the initial twist of the molecule is given by the constant difference between the angles of rotation of adjacent pairs θ). In this case, the bases themselves are considered as indivisible and non-deformable objects (point masses).

Summing the energy over all bases and interactions, we get from the dimensionless Lagrange function for the considered mechanical system ($1/a$ is the length scale; D is energy scale; $\sqrt{m/D/a^2}$ is time scale). This Lagrange function is presented at the bottom of the slide. The dynamic behavior with The Parameters of the homogeneous DNA molecule from A-T bases pairs are presented in Table.

Slide 2 (LAGRANGE EQUATIONS). According to the obtained dimensionless Lagrange function, we find a system of $2N$ equations of bases motion. Each of the ordinary differential equations of the system has a second order and to obtain a single solution to this system, it is necessary to set the $4N$ of initial conditions ($2N$ initial values of generalized coordinates and $2N$ initial values of generalized velocities). The system of nonlinear equations with initial conditions is written in the form of a system of 4N equations of the first order and is integrated numerically by the Runge-Kutta method of the fifth order of accuracy with variable and automatically selectable time steps. The time step is selected from the conditions providing stability and the required accuracy.

Slide 3 (DYNAMICS OF SINGLE DISTURBANCE). The dynamic behavior of a homogeneous DNA molecule of N = 128 base A-T pairs under a single perturbation was previously modeled

numerically. The purpose of the simulation was to test the connection between radial and rotational forms of DNA molecule motion. The equilibrium radial state was perturbed, that led to the development of torsional vibrations. The upper part of the slide shows distributions of radial and angular generalized coordinates of DNA base pairs for t = 8, 40, 72 ps at radial disturbance of five pairs on each side of the DNA center n = N/2 by setting initial conditions as:

$$y_n(0) = \varphi_n(0) = \overset{*}{\varphi}_n(0) = 0, \quad \overset{*}{y}_n(0) = \begin{cases} v_{y\,max} cos^2\left(\left(n - N/2\right)\pi/10\right), & \left|n - N/2\right| \le 5 \\ 0\,, & \left|n - N/2\right| > 5. \end{cases}$$

It can be seen that the twist of the molecule develops in different directions from its center. When the amplitude of the initial perturbation is doubled (from v_{max}=1,1 Å/ps to v_{max}=2,2 Å/ps), the characteristic amplitude of the swirling of pairs by the time t = 72 ps changes 5 times (from 0.2 radians to 1.0 radians), which indicates a fundamentally non-linear non-stationary behavior of the molecule.

The lower part of the slide shows the results of similar calculations with random uniformly distributed radial perturbation of all DNA pairs. Initial conditions were set as (ξ_n is random variable, $\xi_n \in$ (0, 1])

$$y_n(0) = \varphi_n(0) = \overset{*}{\varphi}_n(0) = 0, \; \overset{*}{y}_n(0) = v_{y\,max} \times \xi_n.$$

In this case, non-linear behavior of the DNA molecule is also observed, but the twist angles of the base pairs turn out to be much large. Despite setting the initial conditions randomly, that makes them oscillating (non-smooth), the numerical model retains its stability and accuracy (the total energy in the system is preserved with high accuracy).

Slide 4 (RANDOM DISTRIBUTIONS GENERATORS TESTING). For further study of DNA denaturation by molecular dynamics method, generators of pseudorandom values distributed evenly over a given interval or according to a normal law are required. The accuracy of the simulation depends on the quality of these generators. Therefore, such generators need testing. The results of such testing are visually presented on this slide. Pseudo-random numbers distributed according to the normal law are obtained from uniformly distributed numbers through the Box-Muller transformation.

Slide 5 (MOLECULAR DYNAMICS). To study the statistical properties of DNA and its denaturation, the method of direct molecular dynamics modeling (DMDM) was used. The study was carried out for a microcanonical ensemble, i.e. a set of microstates of the DNA molecule was statistically averaged at constant external thermodynamic parameters (the number of particles, its total energy and volume (no external work under the molecule)). The setting of each DMDM microstate was generated by setting the initial radial velocities of the pairs randomly according to a normal distribution with a mathematical expectation of μ=0 and a standard deviation σ.

$$y_n = 0, \quad \overset{*}{y}_n = \zeta_n, \quad \varphi_n = 0, \quad \overset{*}{\varphi}_n = 0, \quad \zeta \sim G\left(\mu = 0, \sigma\right).$$

Performing a statistically representative series of calculations, we obtain the average values of the total E and kinetic E_{kin} energy of the system of interacting base pairs. To establish a microstate (redistribution between potential and kinetic energies) according to the equations of motion (6), (7) at a given mean square deviation of the σ and averaging over the number of draws in the series, it was necessary to perform at least 10^4 implementations of random DNA states obtained by numerical integration with a dimensionless time step $\Delta t \le 0.02$ up to t=10^5.

Temperature is determined by the average kinetic energy of the system. Each base pair has two degrees of freedom and, according to the equipartition theorem of kinetic energy over degrees of freedom, it corresponds to the energy in dimensionless variables $2 \times k_B T/2/D$ (k_B is the Boltzmann constant), from

where (division by D is preserved in equations to use dimensionless values obtained in the calculation) $\mathrm{k_B}T / D = E_{kin} / N / D$. The total dimensionless energy per freedom degree is $e = E / (2N) / D.$ Having carried out the above series of calculations of DMDM for various σ, we obtain the dependence of temperature on energy $T = T$ (e) in parametric form (value σ plays the role of a parameter): $\mathrm{k_B}T / D = f(\sigma)$, $e = \psi(\sigma)$, where f, ψ are functions defined from DMDM.

DMDM results are presented in this slide. A solid line shows the work data by M. Barbi et al., crosses are the values obtained in our work. There is agreement on the results, but in the denaturation zone (horizontal line on the graph $T = T_{\mathrm{D}}$ = const) the temperature values in the case of our DMDM do not remain strictly constant.

The results show that during denaturation, the temperature is almost constant $\left(\mathrm{k_B}T_D / D\right)_{num} \approx 0,2$, and like the phase transition of the first order, this T_{D} temperature can be taken as one of the main characteristics of the formation of open states in a DNA molecule. Then we have $\left(\mathrm{k_B}T_D / D\right)_{num} \approx 0,2 \Rightarrow T_D \approx 0,2D / \mathrm{k_B} \approx 350K \approx 77^O C.$ Experimental data give close values of $\left(T_D\right)_{exp} = 75\ldots85^O\mathrm{C}$. The value of entropy change in denaturation is also consistent with theoretical data by M. Barbi et al.

Slide 6 (CONCLUSIONS). The conclusions of the work are presented on this slide. The main conclusion is that the model is workable and its further development is required to more adequately describe the real DNA molecule, which is fundamentally heterogeneous and contains a significantly larger number of base pairs than was assumed in the calculations of the present work.

REFERENCES

[1] V. Lakhno, A. Vinnikov Molecular devices based on DNA, Preprint IPM named after M.V. Keldysh RAS, Num. 137, 2018.

[2] D. Goldhaber-Gordon, M. Montemerlo, J. Love, et al. Overview of nanoelectronic devices, IEEE, 1997, V. 85, Num. 4, 521-540.

[3] E. Schrödinger What is Life? The Physical Aspect of the Living Cell. Cambridge at the University Press, 1944.

[4] M Frank-KamenetskiI Unraveling DNA: The Most Important Molecule Of Life, VCH Publishers (UK) Ltd., Cambridge, 1993.

[5] M. Peyrard, A.R. Bishop Statistical Mechanics of a Nonlinear Model for DNA Denaturation, Phys. Rev. Letters 62, 2755, 1989.

[6] T. Dauxois, M. Peyrard Entropy-driven transition in a one-dimensional system, Phys. Rev. E 51,1995, 4027.

[7] M. Barbi, C. Cocco, M. Peyrard Helicoidal model for DNA opening, Phys. Lett. A Vol. 253, Issues 5–6, 1999, 358-369.

[8] M. Barbi, C. Cocco, M. Peyrard, et al. A Twist Opening Model for DNA. Journal of Biological Physics 24, 1999, 97–114.

[9] M. Barbi, S. Lepri, M. Peyrard, et al. Thermal denaturation of a helicoidal DNA model, Phys. Rev. E 68, 2003, 061909.

[10] Calladine C and Drew H. Understanding DNA, Academic Press, London, 1992.

[11] E. Hairer, S. P. Nшrsett, G. Wanner Solving Ordinary Differential Equations I: Nonstiff Problems, New York: Springer, 1987.