The Abdus Salam International Centre for Theoretical Physics

Conference on Atomistic Simulations of Biomolecules:
towards a Quantitative Understanding of Life Machinery
(6-10 March 2017)

Dynamics of ordered counterions in the ion-hydrate shell of DNA double helix

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06.03.2017

Outline

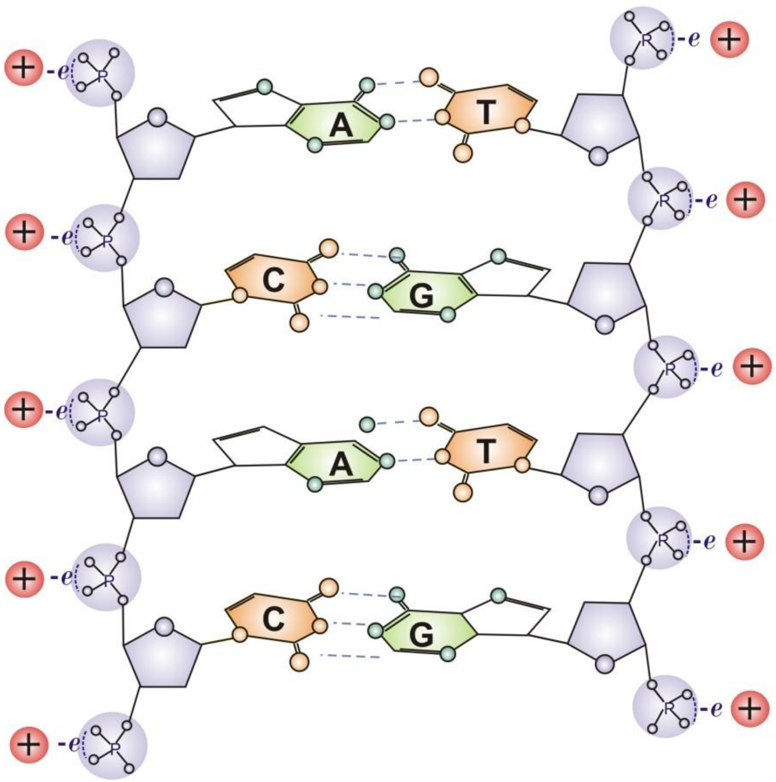
1. Ion-hydrate environment in the structure formation of DNA double helix.
   water molecules in the hydration shells of DNA double helix;
   counterion atmosphere around DNA macromolecule.
2. Counterion vibrations in the low-frequency spectra of DNA.
   model of conformational vibrations of DNA with counterions;
   manifestations of counterion dynamics in the low-frequency spectra.
3. MD simulations of counterion dynamics around DNA double helix.
   characteristic binding sites of Na^+, K^+, Cs^+ and Mg^{2+} with DNA;
   dynamics of counterions, tethered to DNA;
   dynamics of counterion dissociation;
4. Conclusions.

DNA double helix (1953)

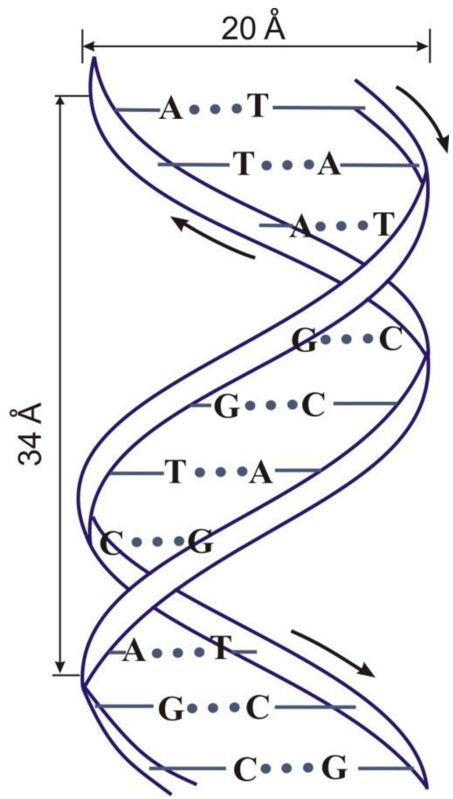
Maurice Wilkins
1916-2004

Rosalind
Franklin
1920 - 1958

Structure elements of DNA



DNA double helix



James Watson
1928

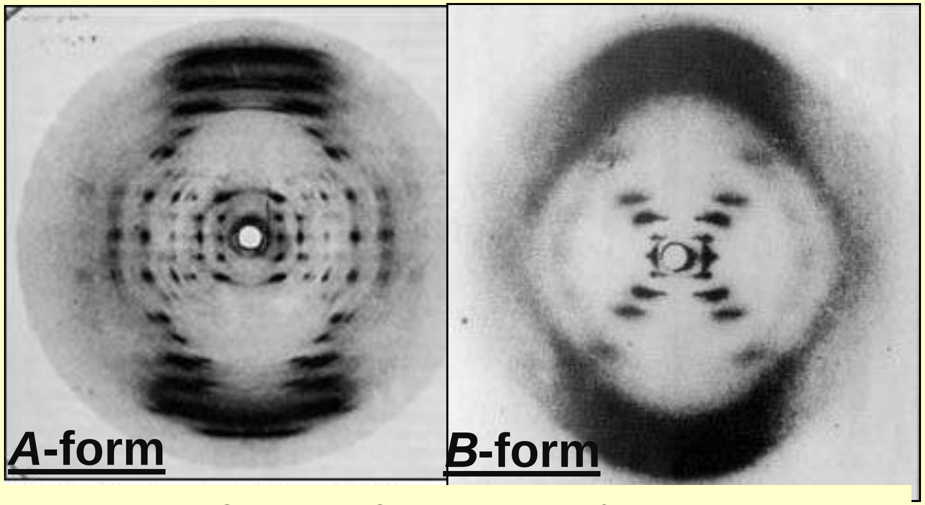
Francis Crick
1916 - 2004

Watson J.D., Crick F.H.C. A structure of deoxyribose nucleic acid. Nature. 171, 737-738 (1953).
Wilkins M.H.F., Stokes A.R., Wilson H.R. Molecular structure of deoxypentose nucleic acid. Nature. 171, 738-740 (1953).
Franklin R.E., Gosling R.G.,Molecular configuration in sodium thymonucleate. Nature. 171, 740-741 (1953).

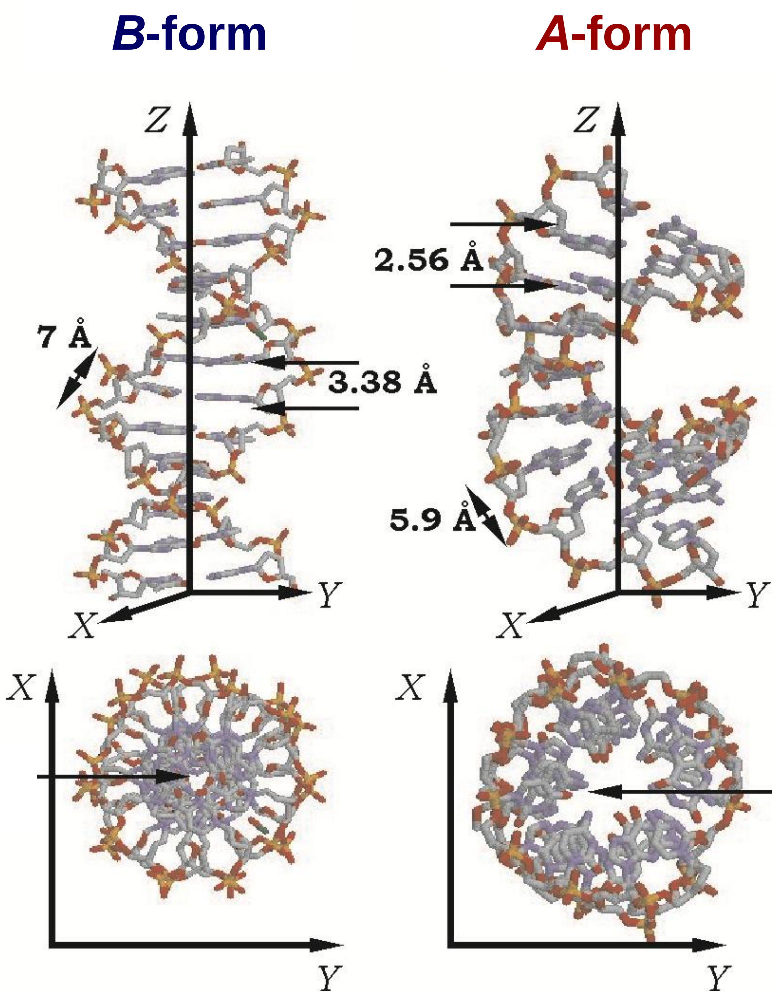
Different forms of DNA double helix

Rosalind Franklin (1920 – 1958)

X-ray diffraction images of DNA (Photo #51)



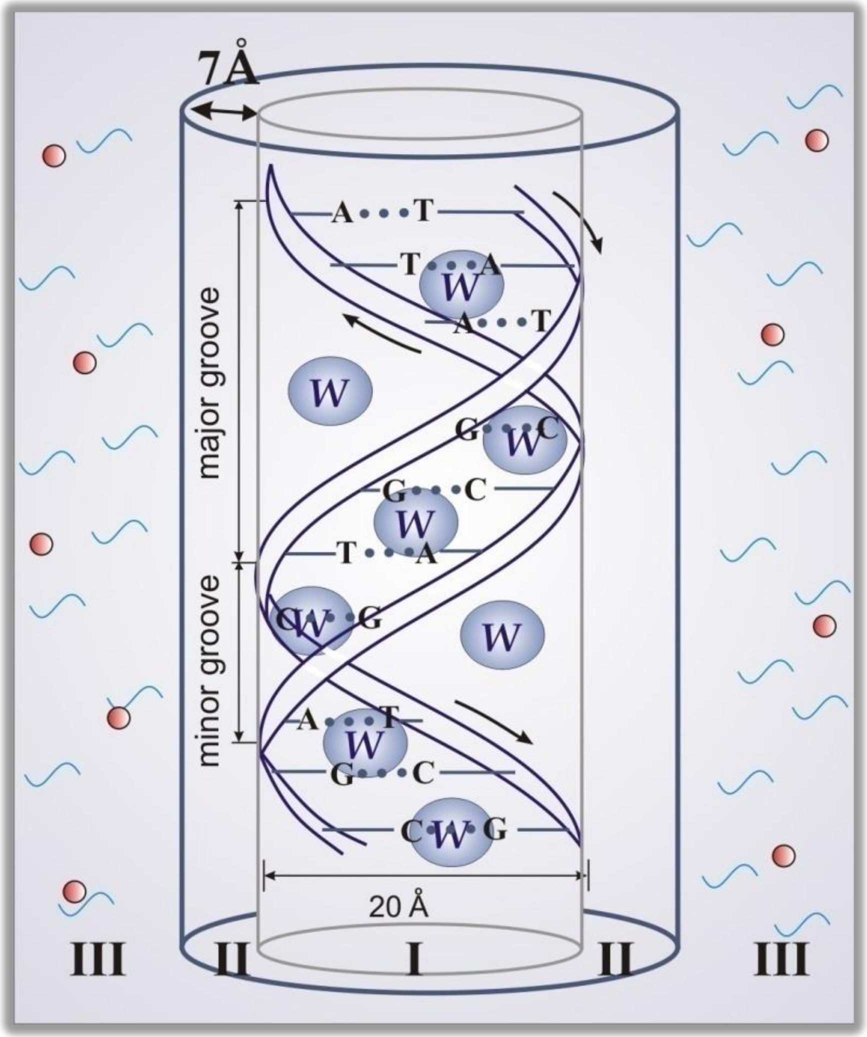
Franklin R.E., Gosling R.G.,Molecular configuration in sodium thymonucleate. Nature. **171**, 740-741 (1953).



NDB bd0007

Tereshko V., Minasov G., Egli M., *J.Am.Chem.Soc*. **121**, 470 (1999).

Structure of the ion-hydrate shell

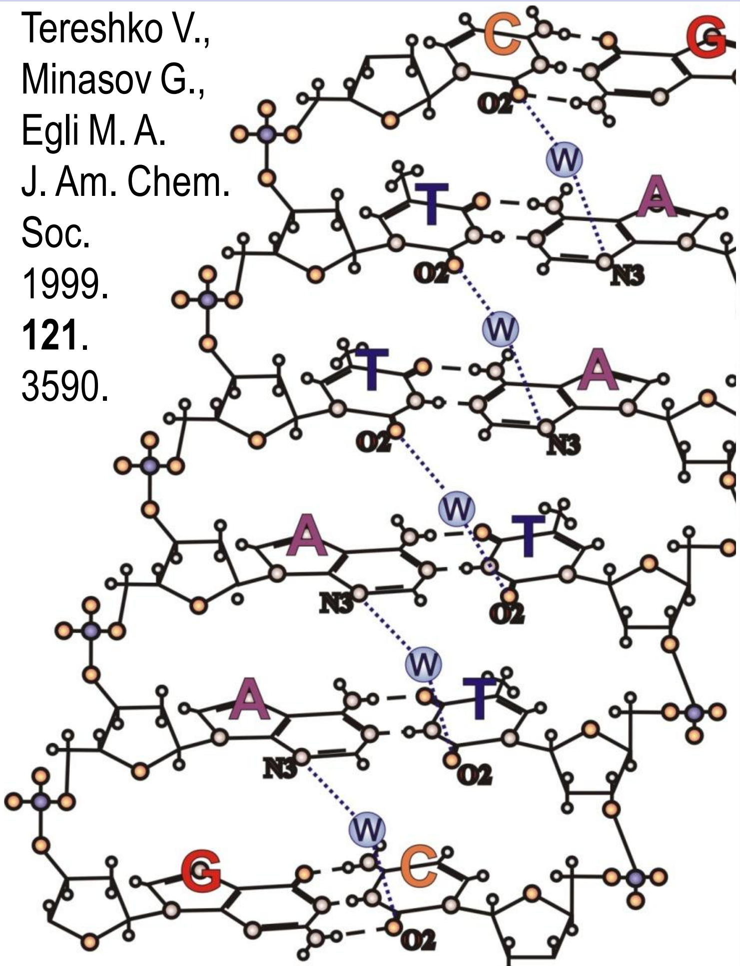


I – the first hydration shell (20w/bp);
II – the second hydration shell (30w/bp);
III – bulk water.

V.Ya. Maleev et al. *Biofizika*, 1993.

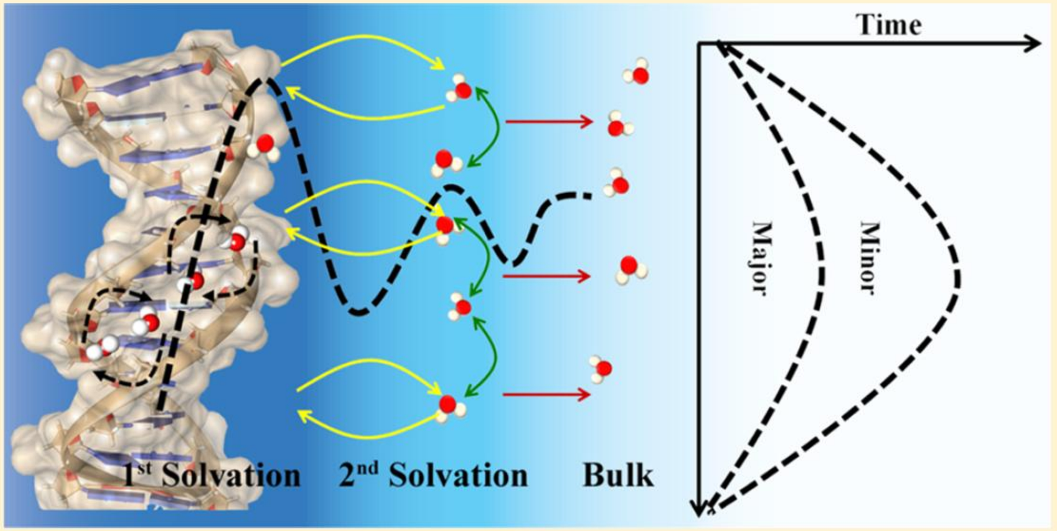
Hydration of DNA grooves

Tereshko V., Minasov G., Egli M. A. J. Am. Chem. Soc. 1999. **121**. 3590.

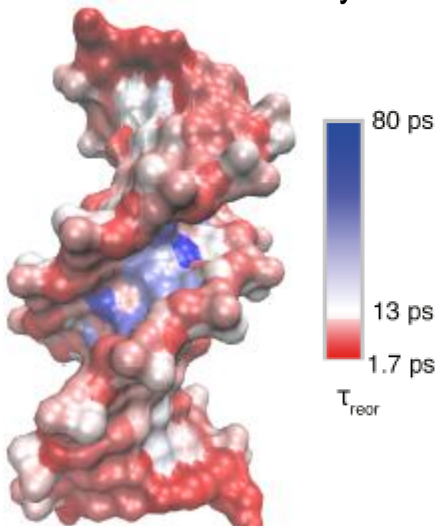


Drew H.R., Wing R.M., Takano T., Broka C., Takana S., Itakura K., Dickerson R.E., *Proc. Natl. Acad. Sci. USA*, **78**,2179,1981.

D. Saha, S. Supekar, A. Mukherjee. "Distribution of Residence Time of Water around DNA Base Pairs: Governing Factors and the Origin of Heterogeneity" J. Phys. Chem. B 2015, 119, 11371−11381



E. Duboué-Dijon, A.C. Fogarty, J.T. Hynes, D.Laage. "Dynamical disorder in the DNA hydration shell" *J Am Chem Soc* 2016.



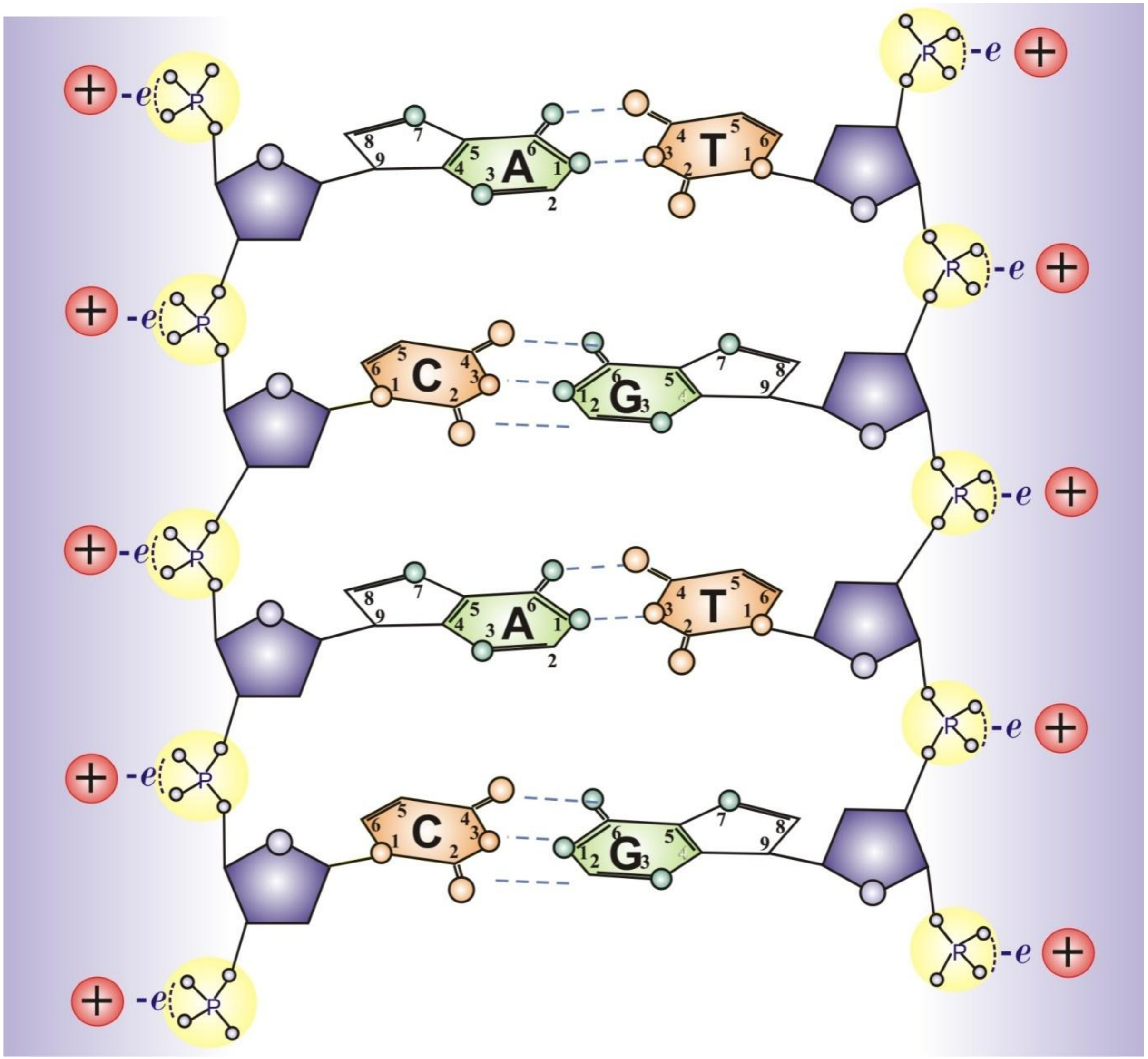
The assumption that hydration shell dynamics is much faster than DNA dynamics is thus not valid. Biomolecular conformational fluctuations are essential to facilitate the water motions and accelerate the hydration dynamics in confined groove sites.

Stabilization of the double helix by counterions

Under the natural conditions the phosphate groups are neutralized by metal counterions:

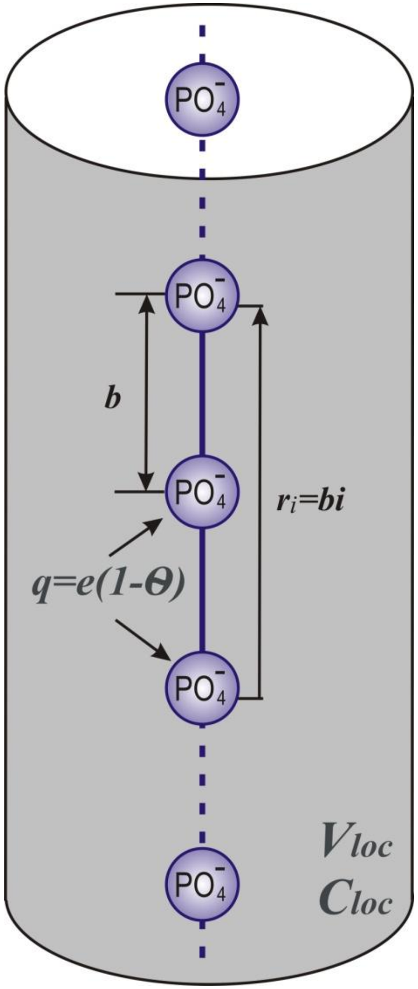
Na^+
K^+
Mg^{2+}
. . . .

Metals in a human body
Na^+
100 **(g/70 kg)**
K^+
140**(g/70 kg)**



Manning counterion condensation theory

Manning G.S.
Quant.Rev.Biophys.
11, 179 (1978).



Energy of the polyelectrolyte:

$$G = G_{rep} + G_{mix};$$

Electrostatic contribution:

$$G_{rep} = \frac{(1-\theta)^2 e^2}{4\pi\varepsilon\varepsilon_0}\sum_{ij}\frac{\exp(-r_{ij}/r_D)}{r_{ij}};$$

Entropy contribution:

$$G_{mix} = kTN\theta \ln\frac{C_{loc}}{C};$$

$$\frac{dg}{d\theta}=0, \qquad \frac{l_B}{b}(1-\theta)-1=0; \qquad \theta = 1-\frac{b}{l_B}. \qquad l_B = \frac{e^2}{4\pi\varepsilon\varepsilon_0 kT};$$

not charges correlated $b > l_b$

$b < l_B$ **Condensation of counterions**

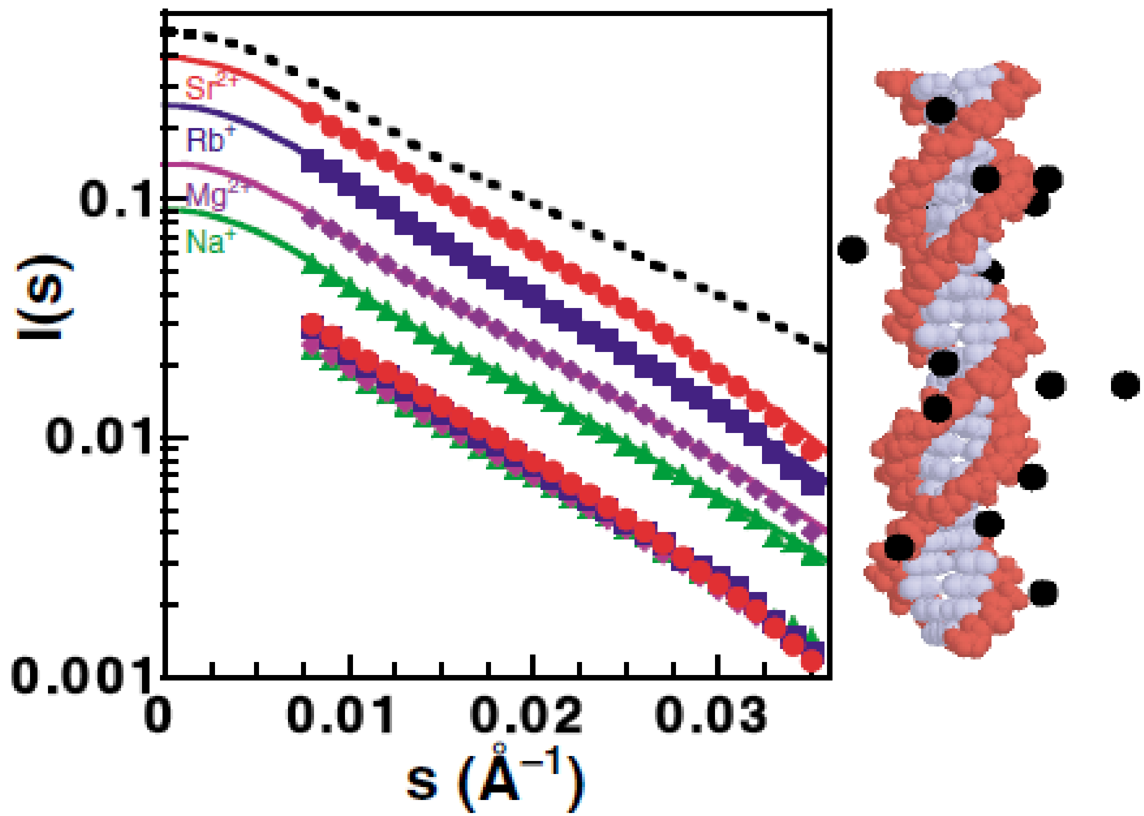
Form	l_b/b	C_{loc}(M)	L (Å)	θ
***B*-DNA**	4.2	1.18	7.4	0.76
***A*-DNA**	5.4	2.07	5.9	0.82

Localization of counterions around DNA: experiments

Counterion coating

Small angle X-ray scattering profiles for DNA in presence of different counterions (0.4M).

The experimental data show that the counterions form the cloud around the macromolecule. The data agree with the calculations of distributions of the ions within the framework of nonlinear PB equation.



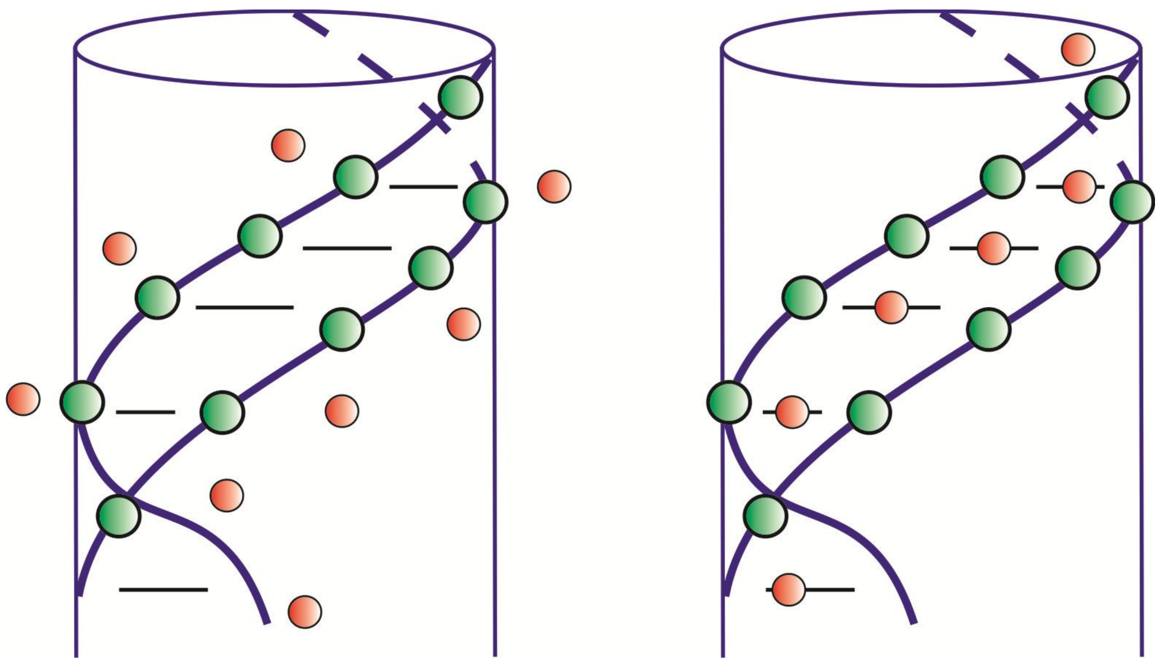
Actual curves (bottom) are shown, as well as offset curves (top), to aid visual comparison with calculations for DNA without modeled counterions (dashed line) and with NLPB ion atmospheres (solid lines).

Das R., et. al. *Phys.Rev.Lett.* **90**, 188103 (2003).

Ion-phosphate lattice of DNA

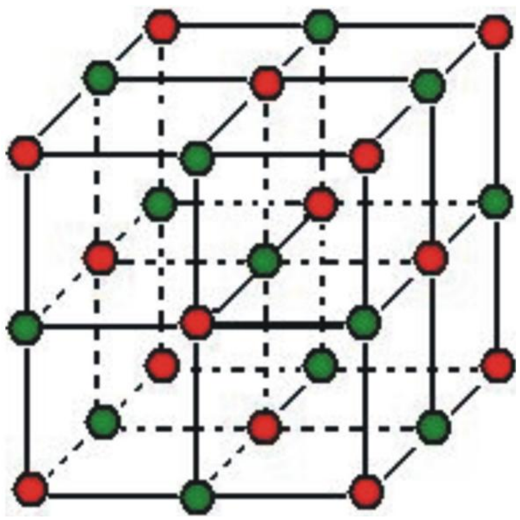
Single-stranded neutralization

Cross-stranded neutralization



Na⁺, K⁺, Rb⁺, Cs⁺, Mg²⁺

NaCl Crystal



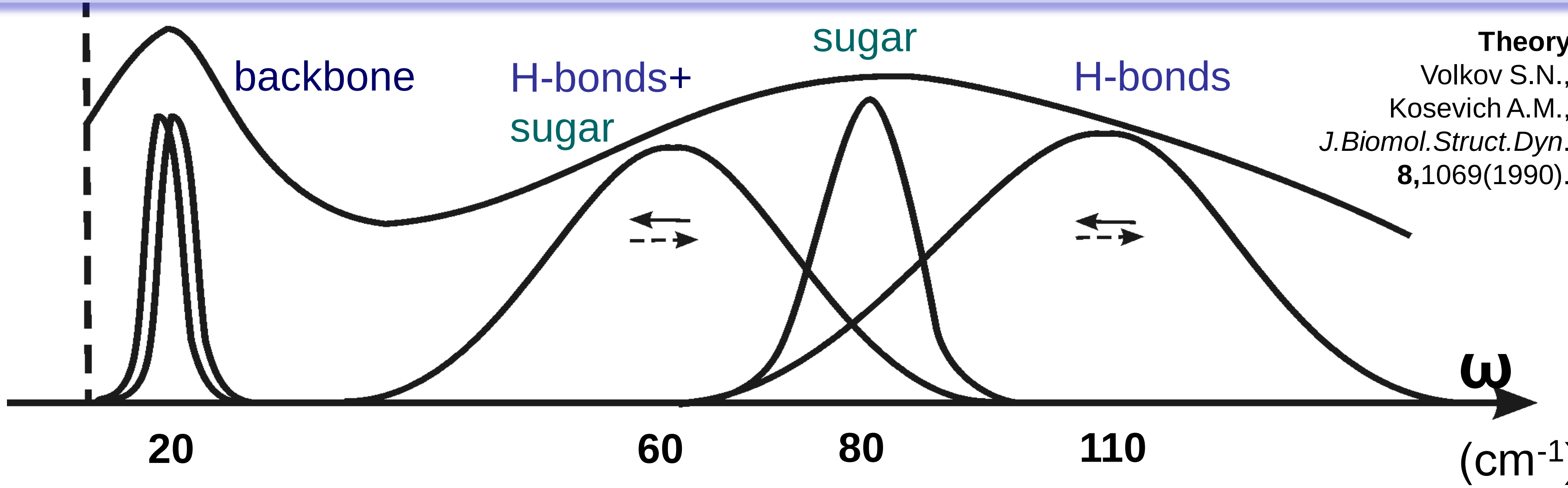
Vibrations in the ionic crystals <200 cm^{-1}.

C. Kittel *Intriduction to solid state physics* (1954).

S.M. Perepelytsya, S.N. Volkov,
Ukr. J. Phys. **49**, 1182 (2004).
Eur. Phys. J. E. **24**, 261 (2007).

The goal is to study the manifestations of ion-phosphate lattice vibrations in the low-frequency spectra of DNA double helix.

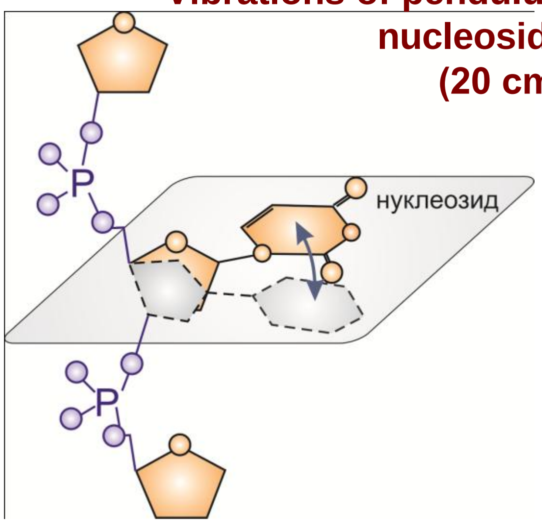
DNA low-frequency spectra



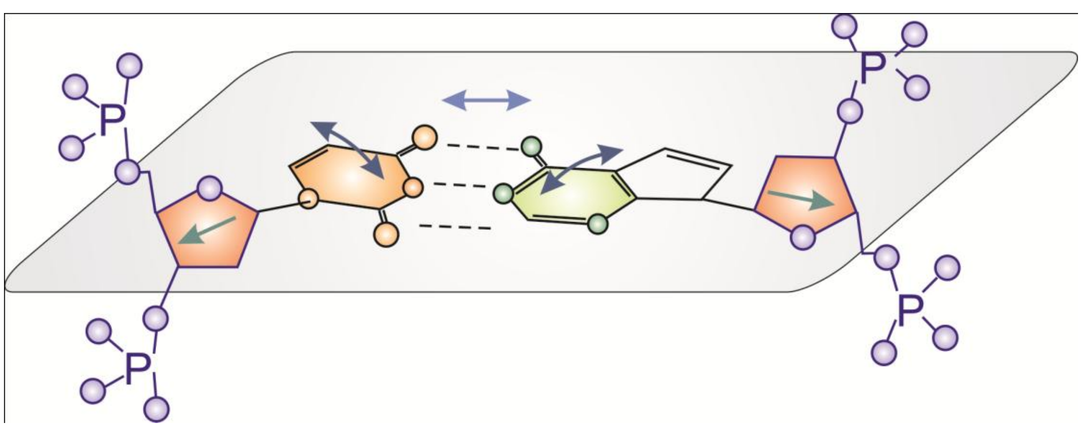
Theory
Volkov S.N.,
Kosevich A.M.,
J.Biomol.Struct.Dyn.
8,1069(1990).

Conformational vibrations of DNA double helix

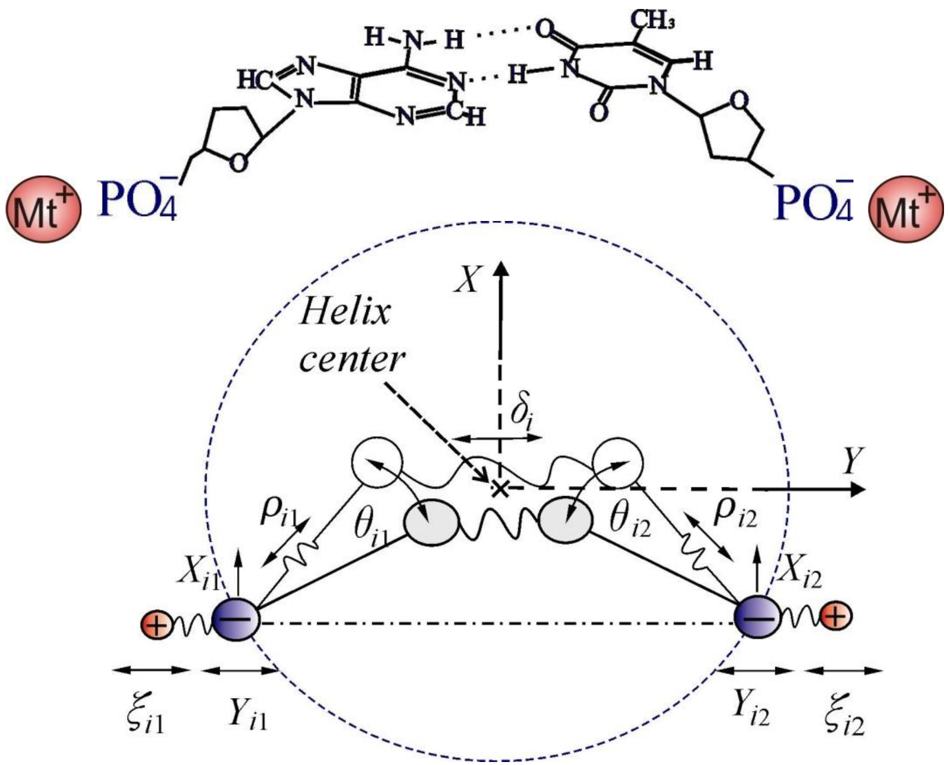
Vibrations of pendulum-nucleosides (20 cm^{-1})

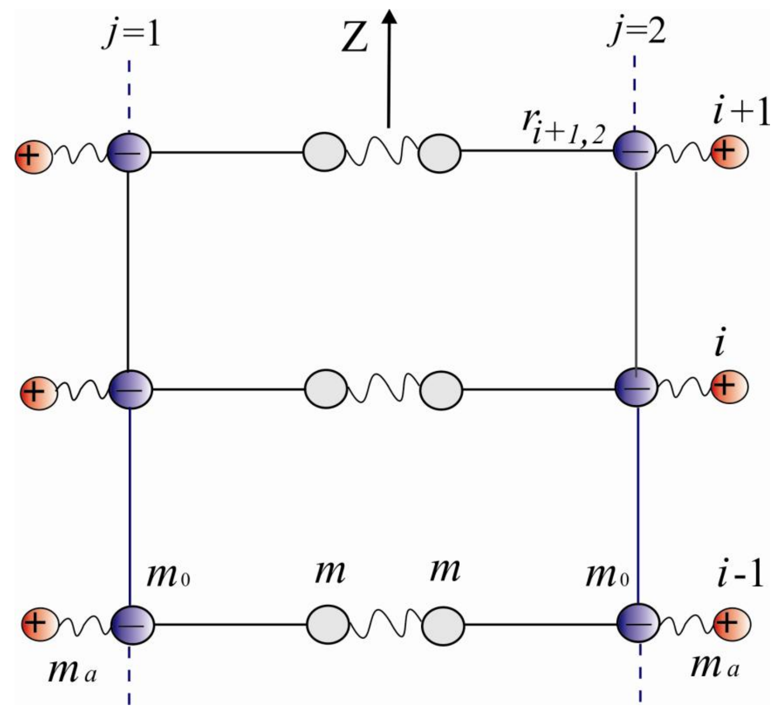


H-bond stretching vibrations (60, 80 and 110 cm^{-1})



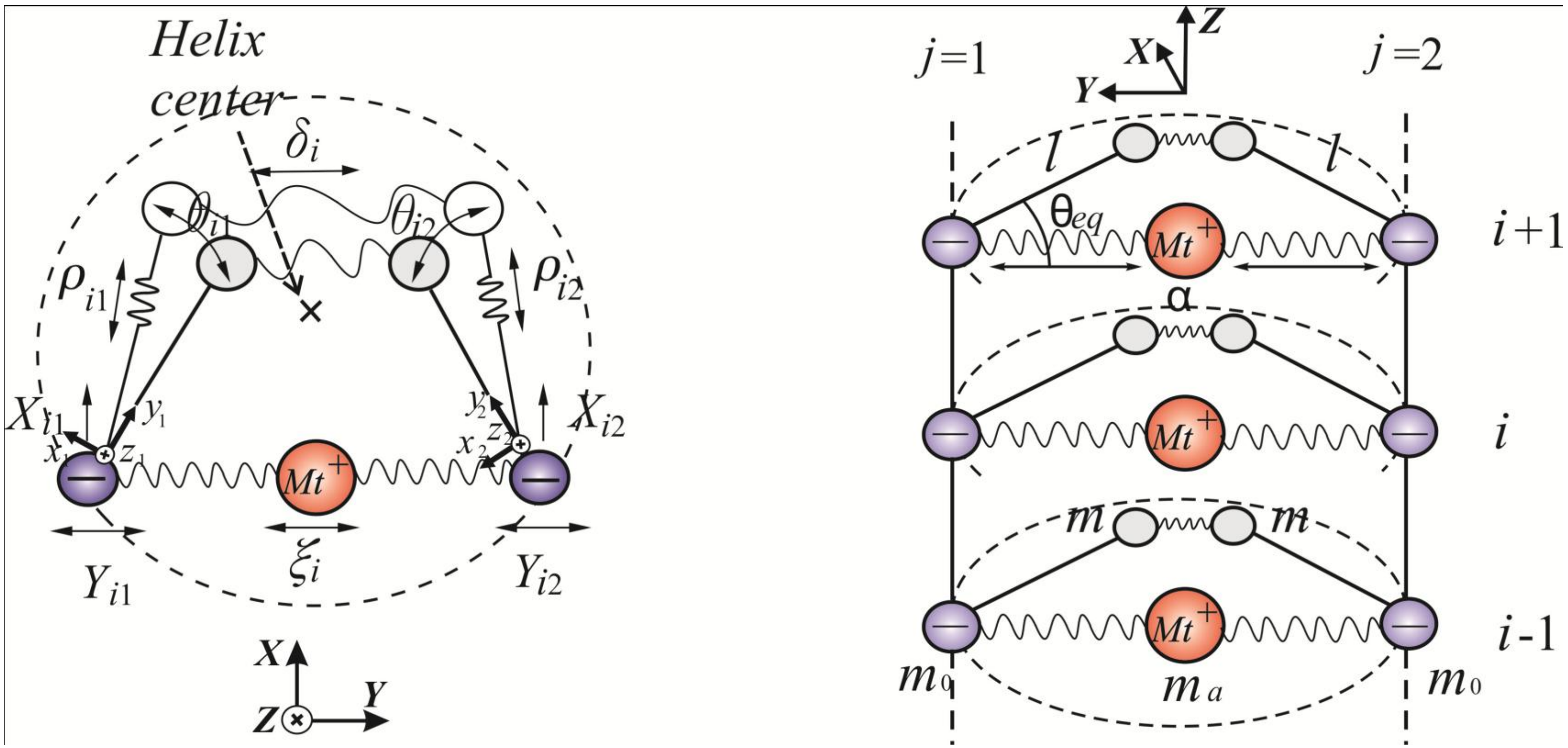
Model of DNA conformational vibrations





Perepelytsya S.M., Volkov S.N. *Ukr. J. Phys*., 49, 1072 (2004).
Перепелица С.Н., Волков С.Н. *Біофізичний вісник* (2005).
Perepelytsya S.M., Volkov S.N. *Eur. Phys. J. E.* (2007).

The model for counterion in the minor grove of the double helix



S.M. Perepelytsya, S.N. Volkov, *Ukr. J. Phys.* **55**, 1182-1188 (2010).
S.M. Perepelytsya S.N. Volkov, *J. Molec. Liq.* 5, 113-119 (2011).

Vibrational energy

$$E = \sum_i \left(E_i^h + E_i^c + E_{i,i+1}\right),$$

Energy of the monomer link:

$$E_i^h = \sum_{j=1}^{2} \left(K_{ij} + U_{ij}\right).$$

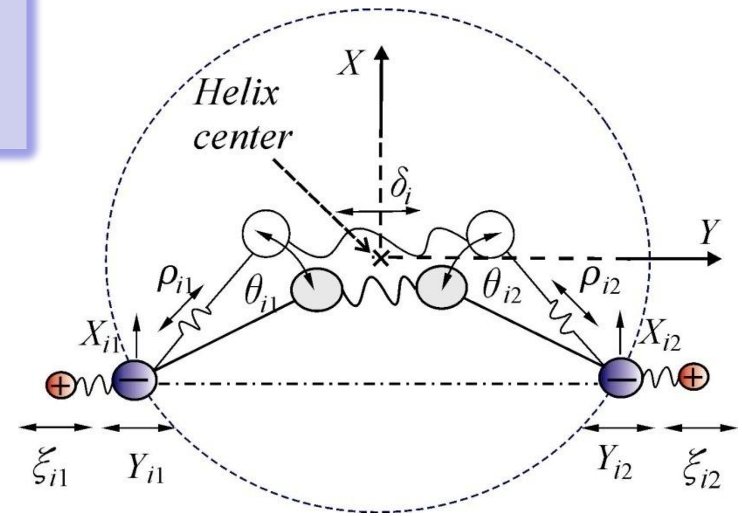
Kinetic energy of *i*-th link:

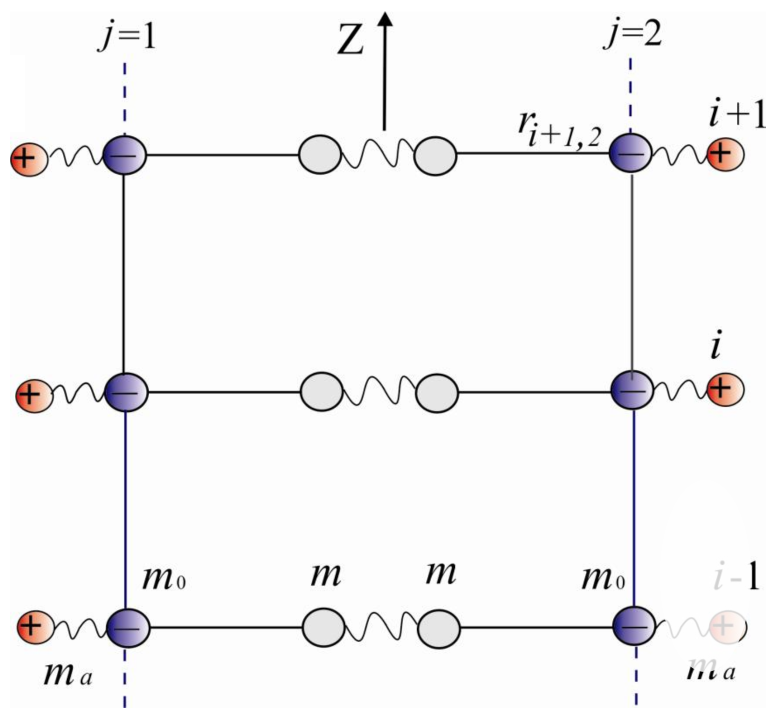
$$K_i = \frac{1}{2}\sum_{j=1}^{2}\Big[M\left(\dot X_{ij}^2 + \dot Y_{ij}^2\right) + m\big(\dot\rho_{ij}^2 + l^2\dot\theta_{ij}^2 +$$

$$2la\,\dot\theta_{ij}\dot Y_{ij} + 2b\dot\rho_{ij}\dot Y_{ij} - 2a\dot X_{ij}\dot\rho_{ij} + 2lb\dot X_{ij}\dot\theta_{ij}\big)\Big].$$

Potential energy:

$$U_i = \frac{1}{2}\alpha\delta_i^2 + \frac{1}{2}\sum_{j=1}^{2}\left(\sigma\rho_{ij}^2 + \beta\theta_{ij}^2\right).$$





Volkov S.N., Kosevich A.M., *J. Biomolec. Struct. Dyn*., **8,** 1069 (1991).

Energy of counterion vibrations

Single-stranded neutralization:

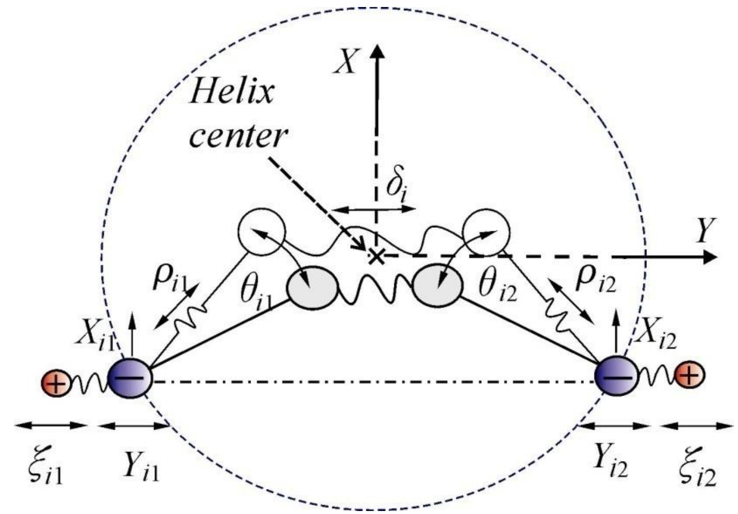
$$E_i^{\mathrm{sn}} = \frac{1}{2}\sum_{j=1}^{2}\left[m_a\left(\dot{\xi}_{ij} + \dot{Y}_{ij}\right)^2 + \gamma\xi_{ij}^2\right].$$

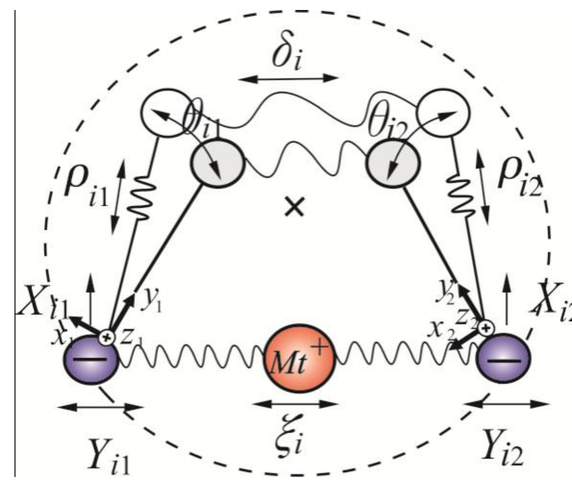
Cross-stranded neutralization:

$$E_i^{\mathrm{cn}} = \frac{1}{2}\sum_{j=1}^{2}\left[m_a\dot{\xi}^2 + \gamma\left(Y_{ij} + (-1)^j\xi_i\right)^2\right].$$

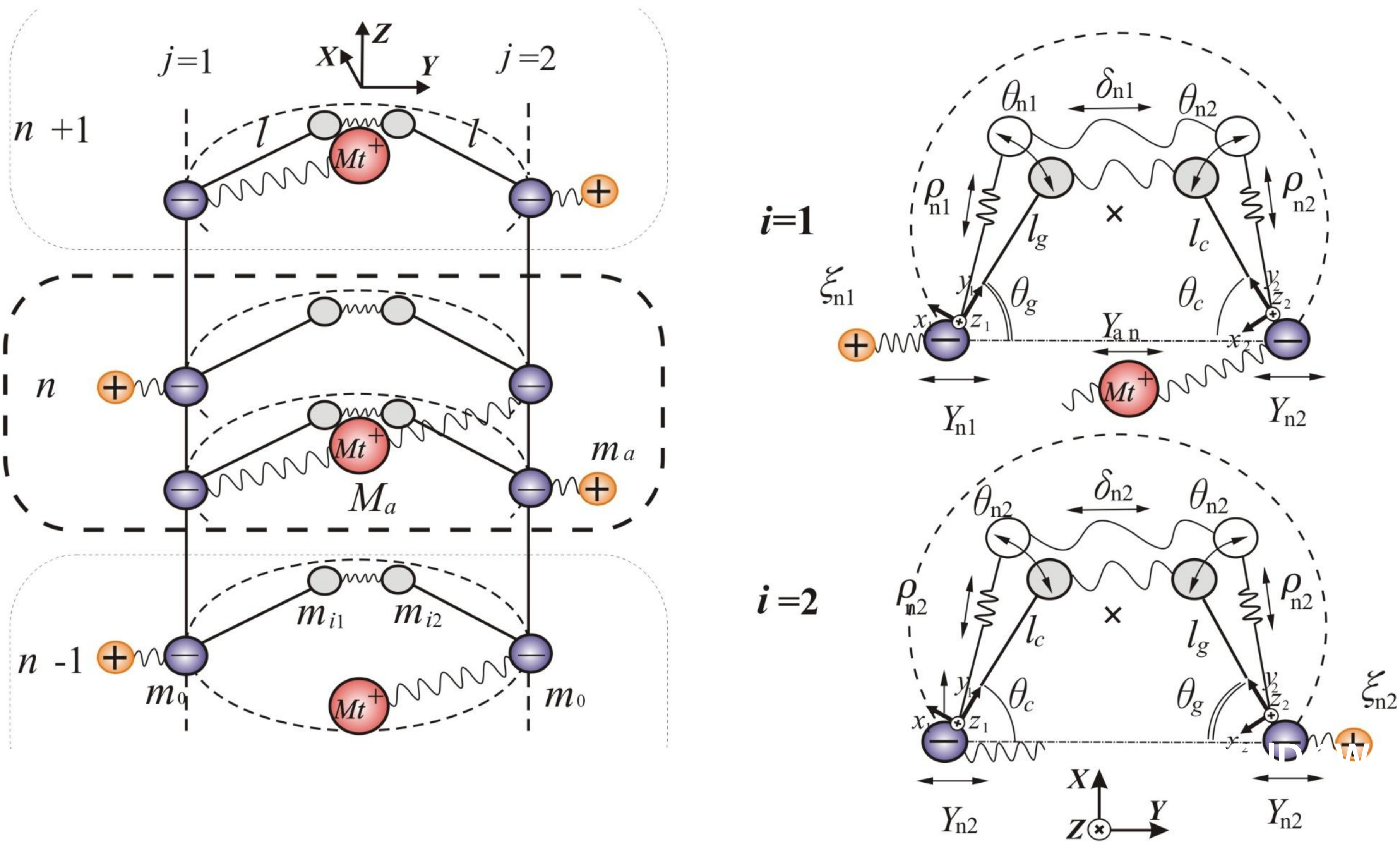
Interaction along the helix:

$$E_{i,i+1} = U\left(X',Y',\theta',\rho',\xi'\right).$$





Model for the left-handed Z-DNA



Vibrational energy for Z-DNA

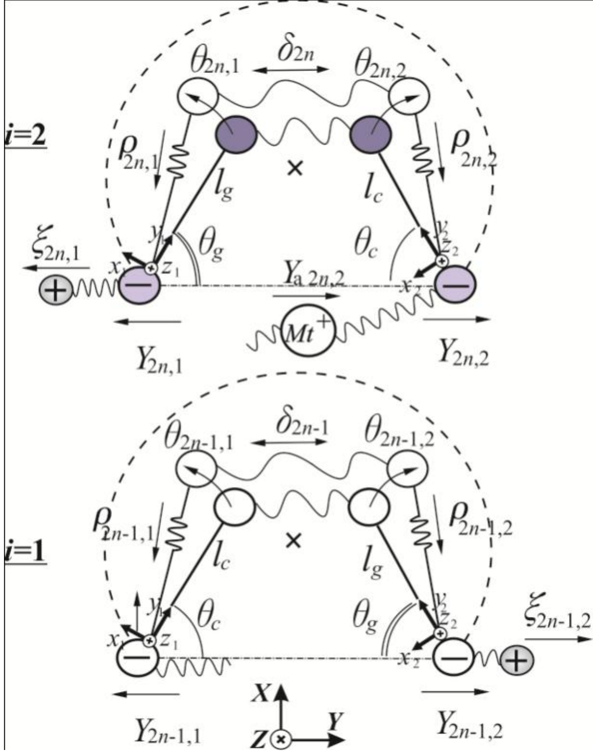
Kinetic energy

Potential energy

$$E = K + U;$$

$$K = \sum_n \left[\sum_{j=1}^{2} \left(K^h_{2n,j} + K^h_{2n-1,j} \right) + K^I_{2n} + K^I_{2n-1} \right];$$

$$U = \sum_n \left(U_{2n} + U_{2n-1} + U_{2n,2n-1} + U^{Ion}_{2n} + U^{Ion}_{2n-1} \right).$$



$$K^h_{2n,j} = \frac{1}{2}\left[M_{2nj}\dot{X}^2_{2nj} + + m_{2nj}\left(\dot{\rho}^2_{2nj} + l^2_{2nj}\dot{\theta}^2_{2nj} + 2b_{2nj}\dot{X}_{2nj}\dot{\rho}_{2nj} + 2l_{s2nj}\dot{X}_{2nj}\dot{\theta}_{2nj} \right) \right];$$

$$K^I_{2n} = M_a\dot{X}^2_{a2n} + m_a\left(\dot{X}_{2n1} + \dot{\xi}_{2n1} \right)^2; \qquad K^I_{2n-1} = m_a\left(\dot{X}_{2n-1,2} + \dot{\xi}_{2n-1,2} \right)^2.$$

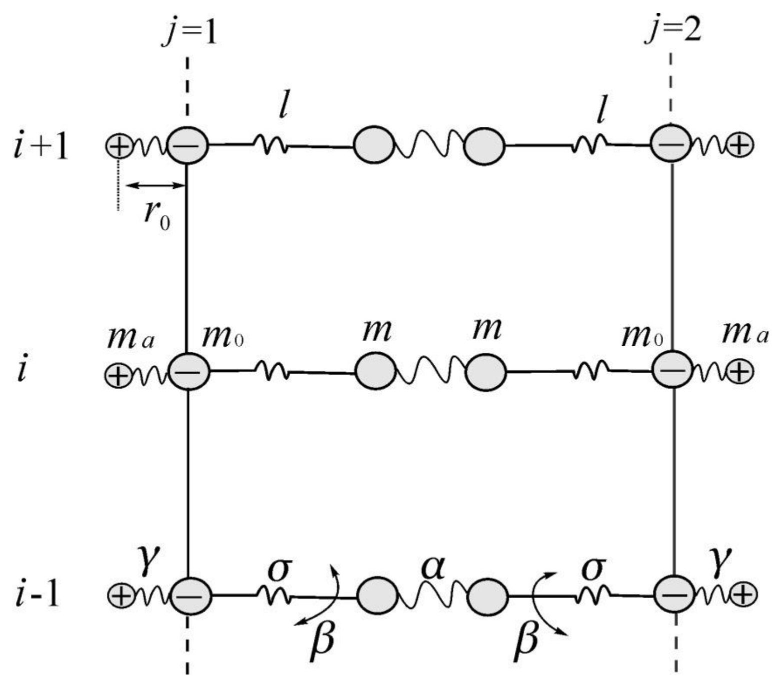
$$U_{2n} = \frac{1}{2}\left[\alpha\left(X_{2n1} + X_{2n2} + l_{s2n1}\theta_{2n1} + l_{s2n2}\theta_{2n2} + b_{2n1}\rho_{2n1} + b_{2n2}\rho_{2n2} \right)^2 + \sum_{j=1}^{2}\left(\beta_{2nj}\theta^2_{2nj} + \sigma_{2nj}\rho^2_{2nj} \right) \right];$$

$$U^I_n = \frac{\gamma_1}{2}\left[\left(X_{a2n} - X_{2n2} \right)^2 + \left(X_{a2n} + X_{2n-1,1} \right)^2 \right] + \frac{\gamma_2}{2}\left(\xi^2_{2n1} + \xi^2_{2n-1,2} \right).$$

Parameters of the models

Structure parameters

Nucleoside	*l* (Å)	θ_{eq} (º)	*m (а. о. м.)*
Adenosine	5,3	28	203
Thymidine	4,8	32	194
Guanosine	5,5	23	219
Cytosine	4,7	30	179
Average	4,9	27,5	199



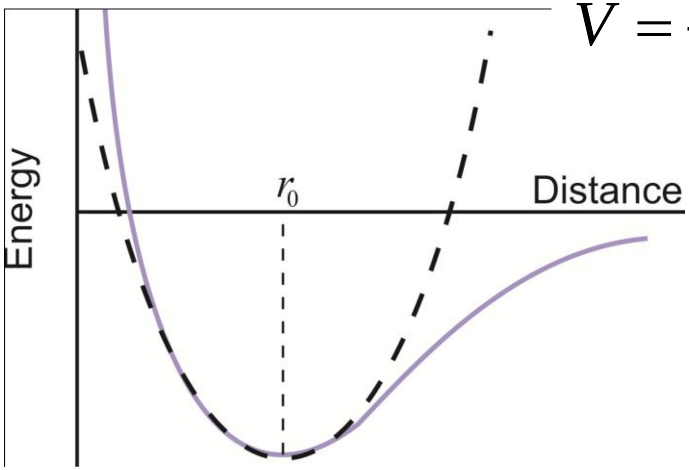
Force constants

DNA form	α (kcal/molÅ^2)	σ (kcal/molÅ^2)	β (kcal/molÅ^2)	γ (kcal/molÅ^2)
B-form	80 ±5	43 ±5	40 ±8	?
A-form	18	22	46	

Volkov S.N., Kosevich A.M., Wainreb G.E. Biopolimery i Kletka. 5, 32-39 (1989).
Volkov S.N., Kosevich A.M. *J. Biomolec. Struct. Dyn*., 8**,** 1069 (1990).

Constant of ion-phosphate vibrations

Potential with the Born-Mayer repulsion:



$$V = -\frac{M_\alpha \cdot e^2}{4\pi\varepsilon\varepsilon_0 r} + B \cdot \exp\left(-\frac{r}{g}\right);$$

$$\gamma = \frac{M_\alpha e^2}{4\pi\varepsilon\varepsilon_0 r_0^3}\left(\frac{r_0}{g} - 2\right).$$

The Madelung constant:

$$M_\alpha = r_0 \sum_{i,j}\left(\frac{1}{r_{ij}} - \frac{1}{d_{ij}}\right) + \frac{r_0}{d_{i1}}$$

Dielectric constant:

$$\varepsilon = n^2 \frac{M_\alpha (r_0/g - 2)}{M_\alpha (r_0/g - 2) - 8\pi r_0^3/V}.$$

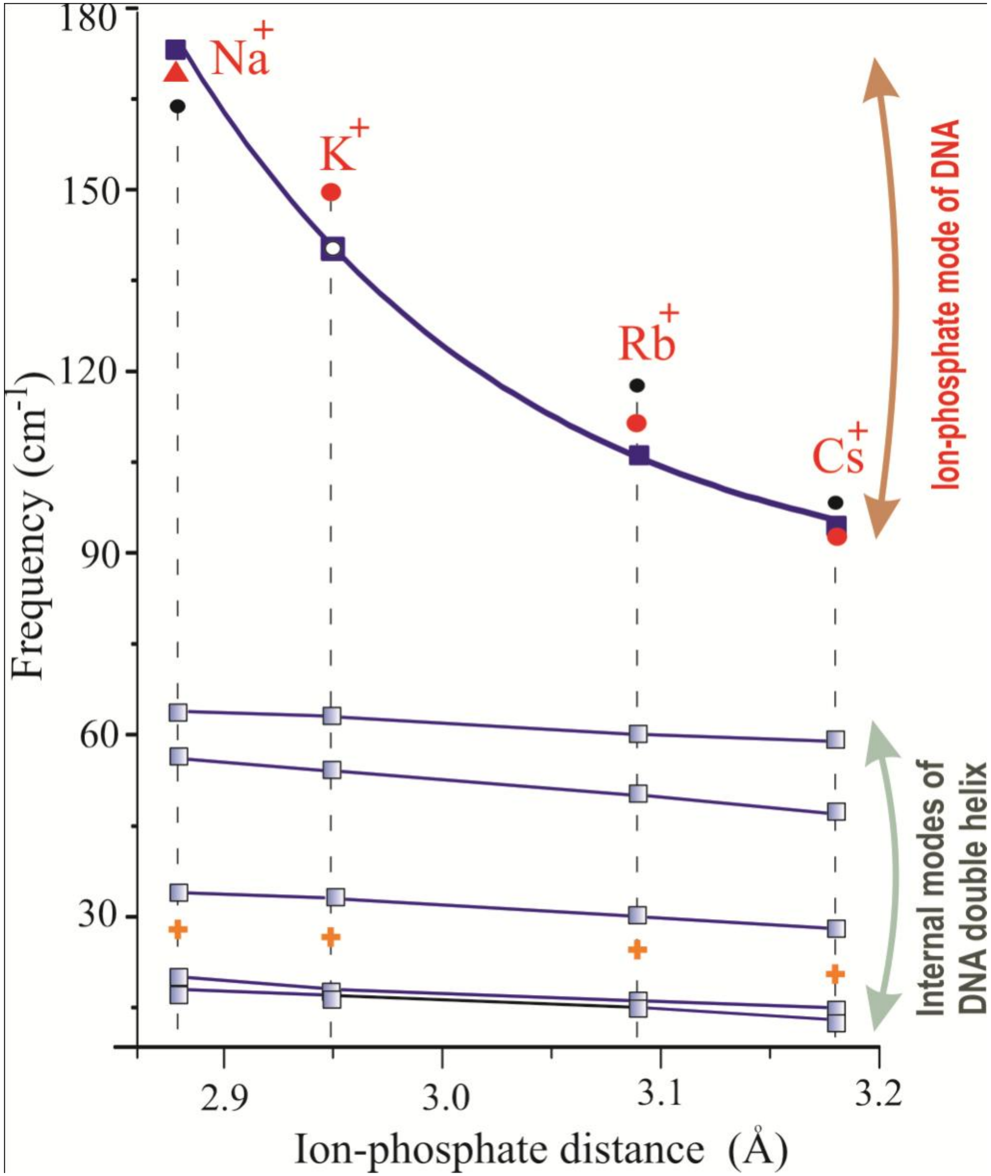
Values:

γ=30÷60 (kcal/molÅ^2)

M_α≈1÷1,3

ε=2.3÷2.6

Ion-phosphate vibrations in the low-frequency spectra of DNA



Atomic weight of metals (a.u.m.)

Na^+	K^+	Rb^+	Cs^+
23	39	86	133

Theory

Perepelytsya S.M., Volkov S.N.
Ukr. J. Phys., 49, 1072 (2004).
Eur. Phys. J. E. 24, 261 (2007).

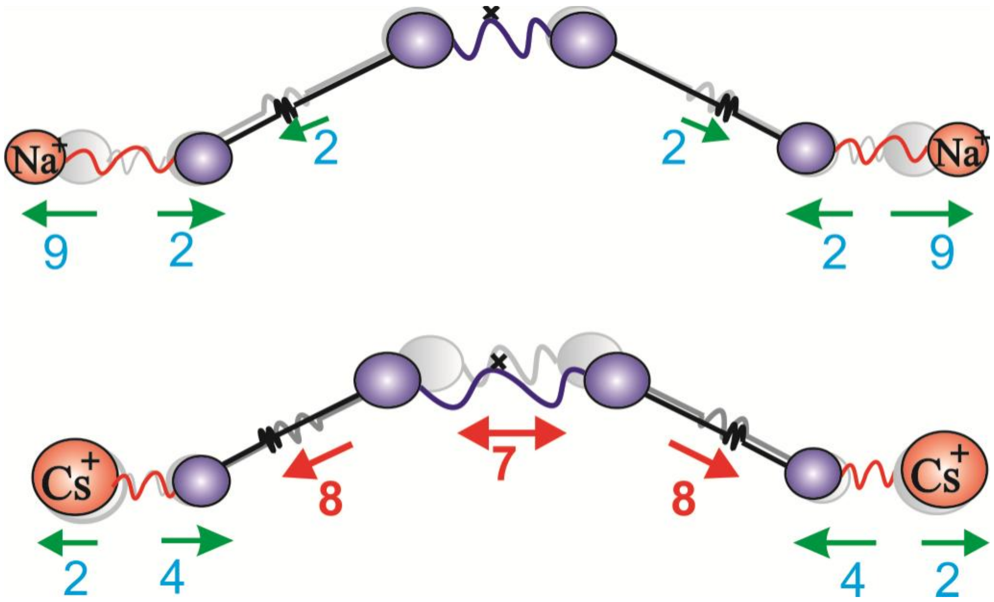
Experiment

Wittlin A. *et al. Phys. Rev. A*, **34**, 493 (1986).
Weidlich T. *et al*.
Biopolymers, **30**, 477 (1990).
Powell J. W. *et al.*
Phys. Rev. A, **35**, 3929 (1987).

In the IR low-frequency spectra of DNA the modes of ion-phosphate vibrations have been found.

Influence of heavy counterions

Scheme of structural motions in nucleotide pair (amplitudes in pm)



Na-DNA
182 cm^{-1}

Cs-DNA
118 cm^{-1}

Perepelytsya S.M., Volkov S.N. *Eur. Phys. J. E* (2007)

Intensities in the Raman low-frequency spectra of DNA

Semiclassical approach:
Volkenshtein M.V., Eliashevich M.A., Stepanov B.I., *Vibrations of Molecules. Volume 2.* (Moscow, 1949).

Semiclassical approach
+
Model of DNA conformational vibrations with counterions

$$J_n \approx \frac{3\kappa J_0(\nu_0-\nu_n)^4}{1-\exp\left(-h\nu_n/kT\right)}\left[\left(\sum_{j=1}^{2}A_j^n\right)^2+\left(\sum_{j=1}^{2}B_j^n\right)^2\right]$$

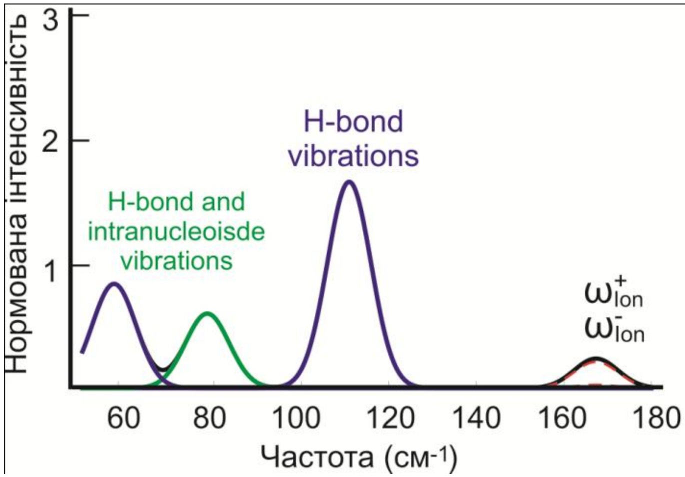
$$A_j^n=\left[\left(b_{jyy}-b_{jxx}\right)\sin 2\theta_{eq}+2(-1)^j b_{jxy}\cos 2\theta_{eq}\right]\cdot\left(\tilde{\theta}_j^n+\frac{\tilde{\rho}_j^n}{l}\right),$$

$$B_j^n=\left[\left(b_{jyy}-b_{jxx}\right)(-1)^j\cos 2\theta_{eq}-2b_{jxy}\sin 2\theta_{eq}\right]\cdot\left(\tilde{\theta}_j^n+\frac{\tilde{\rho}_j^n}{l}\right).$$

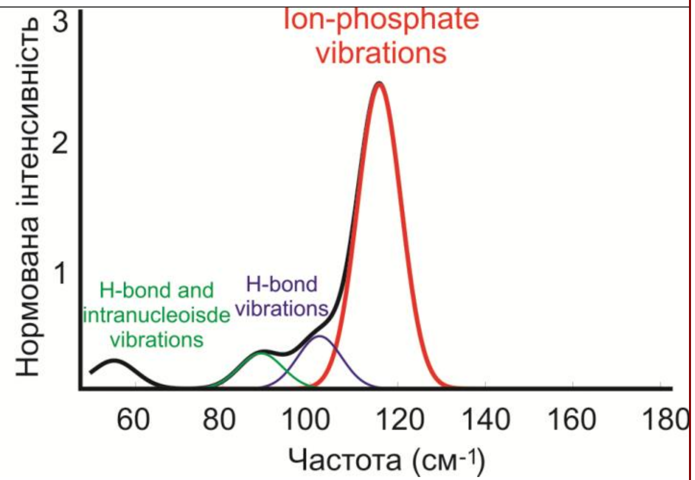
Perepelytsya S.M., Volkov S.N. *Biophys.Bull.* ***23(2)***, 5 (2009).
Perepelytsya S.M., Volkov S.N. *Eur. Phys. J. E.* **31**, 201 (2010).

Observation of DNA ion-phosphate vibrations

Na-DNA



Cs -DNA

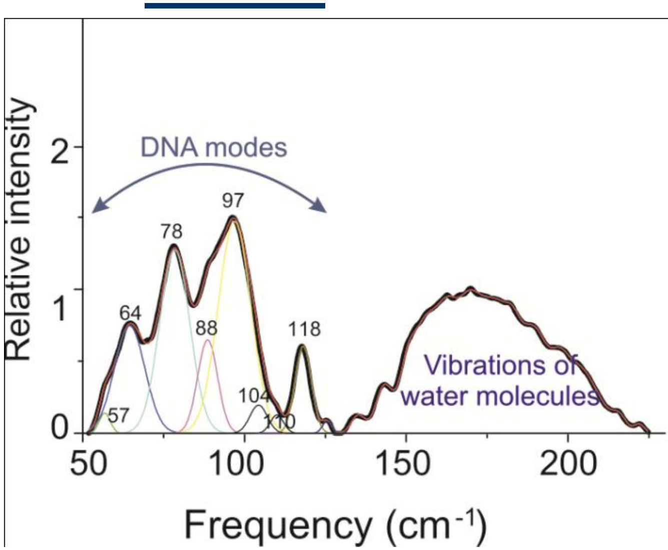


Theory

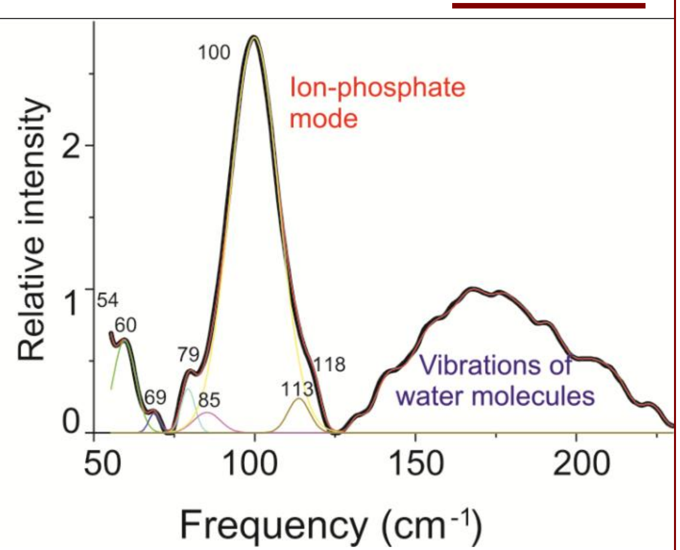
Approach for calculation of intensities in DNA low-frequency Raman spectra.

Perepelytsya S.M., Volkov S.N. Eur. Phys. J. E. **31**, 201 (2010). Biophys. Bull. (2009).

Na-DNA



Cs -DNA

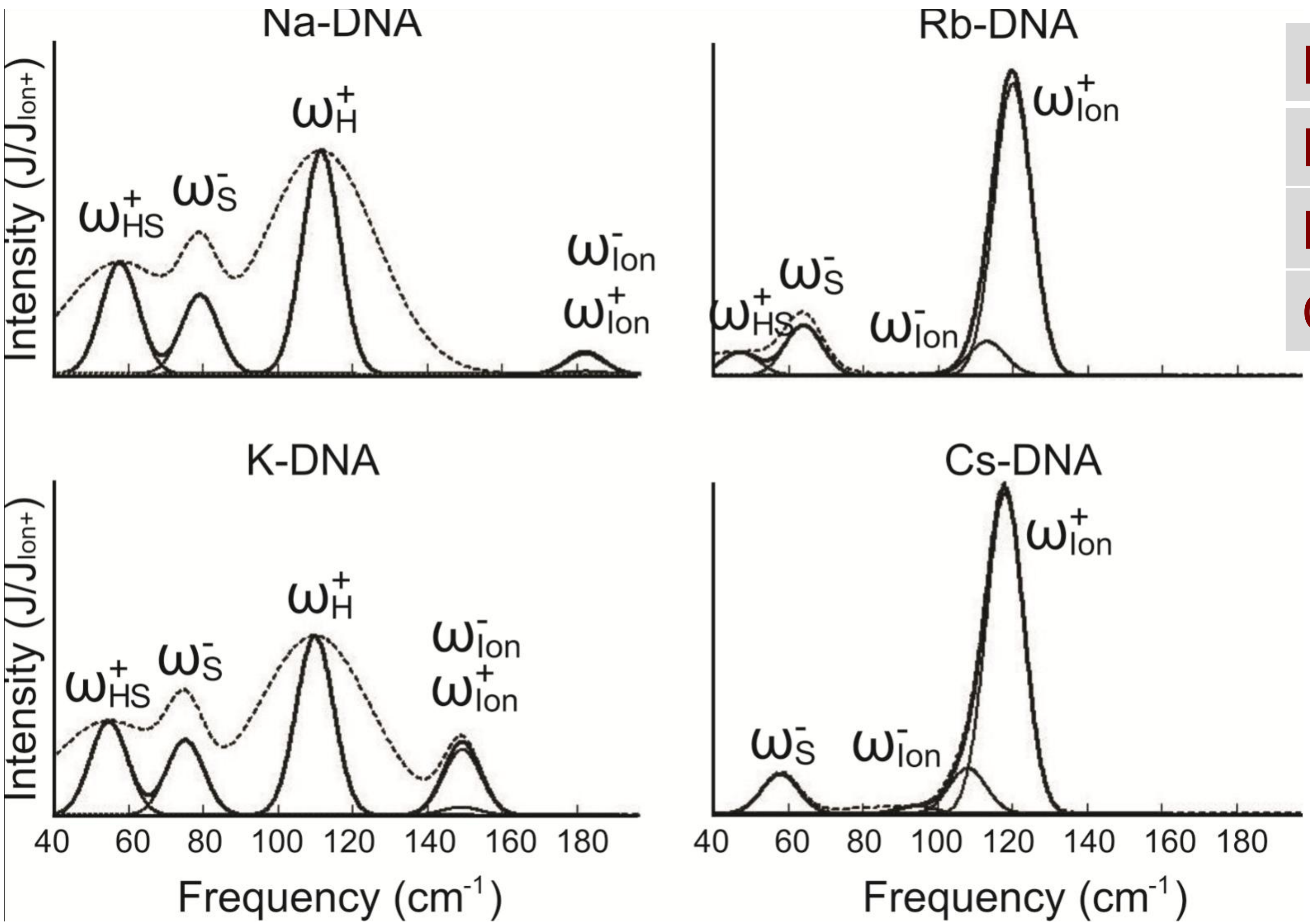


Experiment

Raman spectra of DNA water solutions with Na^+ and Cs^+ counterions

***Bulavin L.A.**, et al.* *Reports of NASU*, **9** (2007). arXiv:0805.0696v1

The calculated Raman spectra of *B*-DNA with alkali metal counterions



Na^+	23
K^+	39
Rb^+	86
Cs^+	133

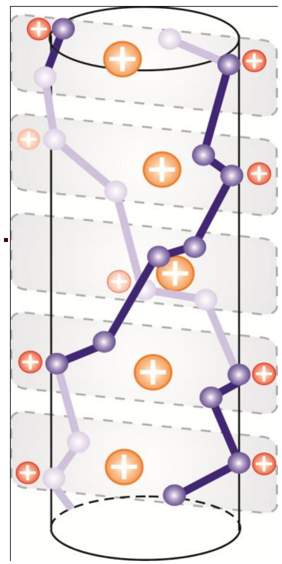
(a.u.m)

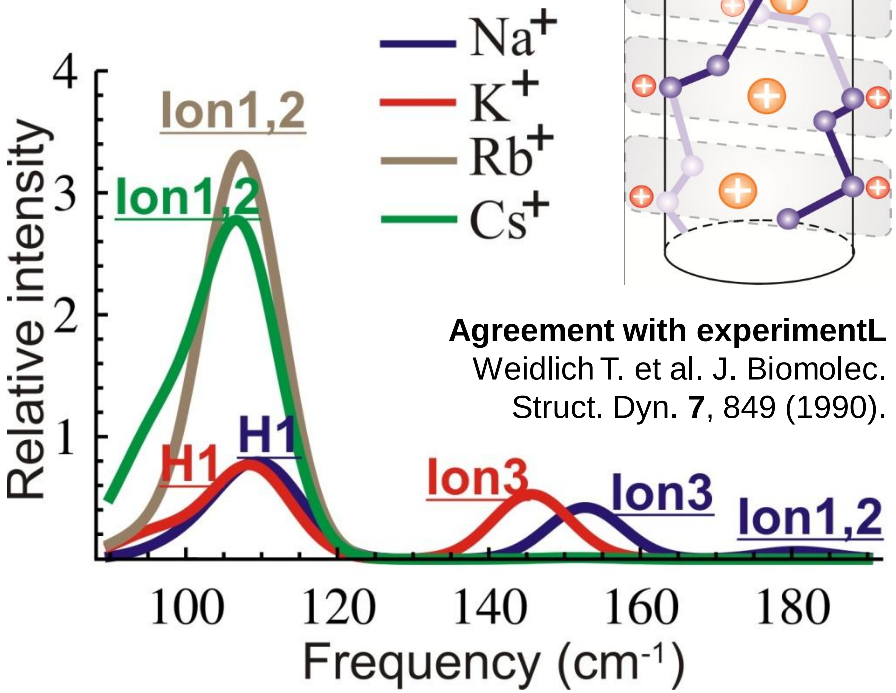
Perepelytsya S.M., Volkov S.N. *Eur. Phys. J. E.* **31**, 201 (2010).

Comparison of *Z*-and *B*-DNA low-frequency spectra

Z-DNA

S.M. Perepelytsya, S.N. Volkov,
Ukr. J. Phys. **58**, 554 (2013).
J. Phys.: C. Ser. **438**, 012013 (2013).

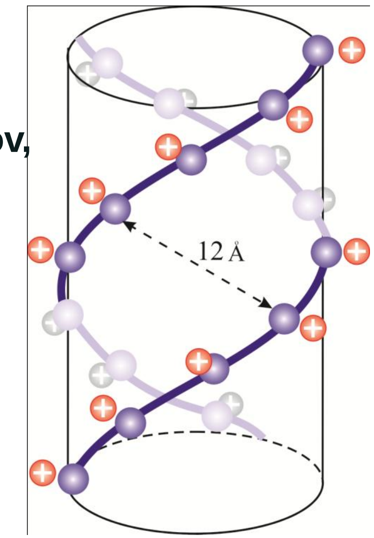


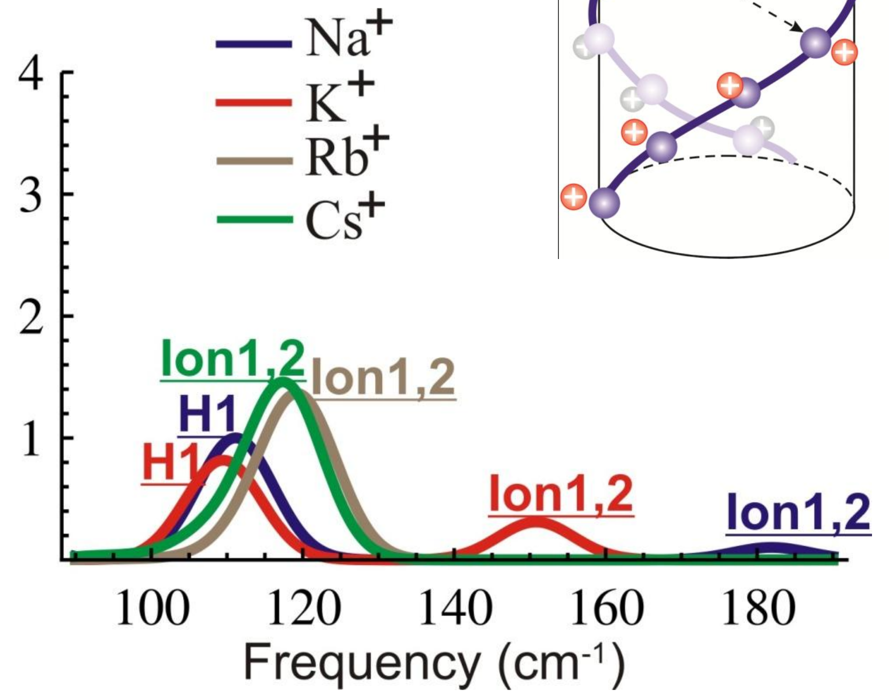


Agreement with experimentL
Weidlich T. et al. J. Biomolec. Struct. Dyn. **7**, 849 (1990).

B-DNA

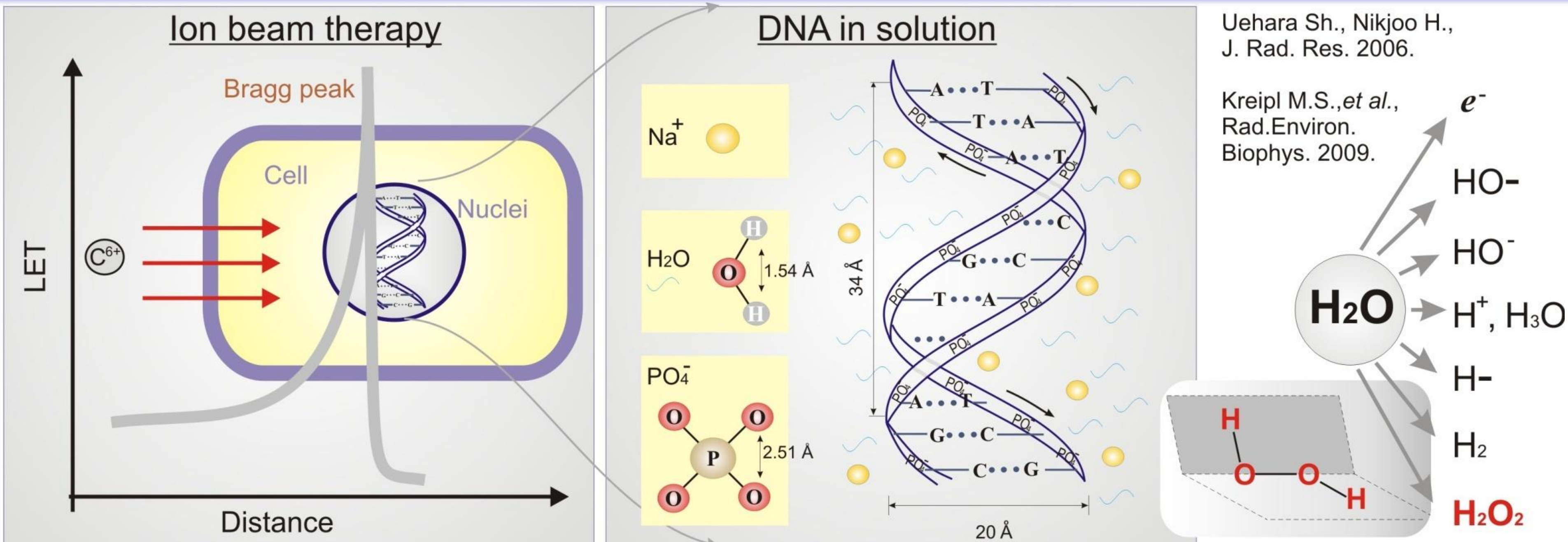
S.M. Perepelytsya, S.N. Volkov,
Eur. Phys. J. E. **31**, 201 (2010).
J. Molec. Liq. **5**, 113 (2011).





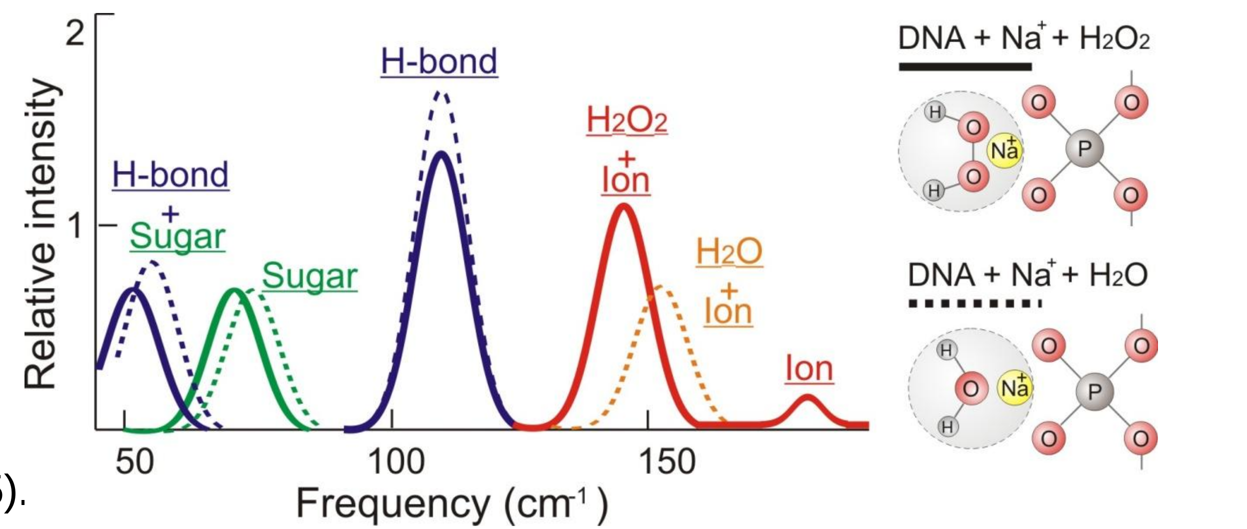
For the left-handed DNA (*Z*-form) the mode of ion-phosphate vibrations was found near 150 cm^{-1} that characterizes the vibrations of Mg^{2+} counterions with respect to the phosphate groups in the minor groove of the macromolecule.

Low-frequency spectra of DNA with H_2O_2



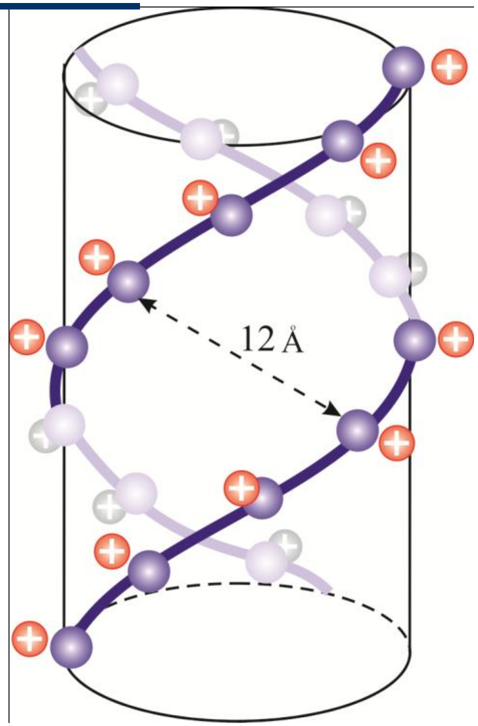
Low-frequency spectra of DNA with H_2O_2 and ions

D.V. Piatnytskyi,
O.O. Zdorevskkyi,
S.M. Perepelytsya,
S.N. Volkov,
Eur. Phys. J. D., **69**, 255 (2015).

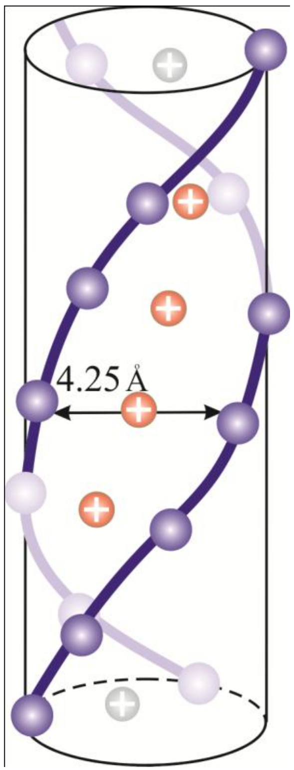


Spectroscopic manifestations of counterion ordering around DNA double helix

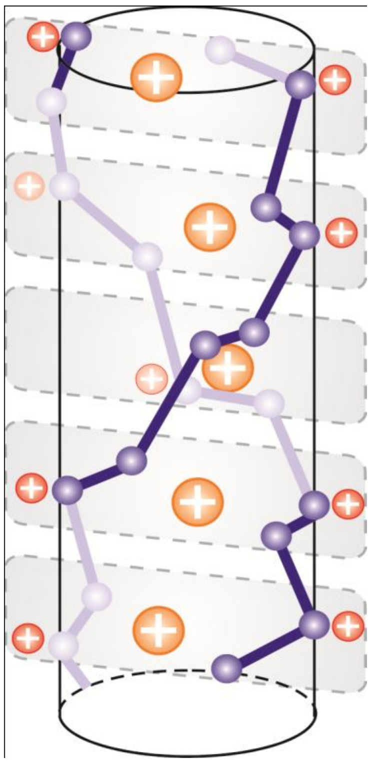
***B*-DNA**



***C*- and *D*-DNA**



Z-DNA



S.M. Perepelytsya, S.N. Volkov,
Eur. Phys. J. E. **24**, 261 (2007).
Eur. Phys. J. E. **31**, 201 (2010).

S.M. Perepelytsya, S.N. Volkov,
Ukr. J. Phys. **55**, 1182 (2010).
J. Molec. Liq. **5**, 113 (2011).

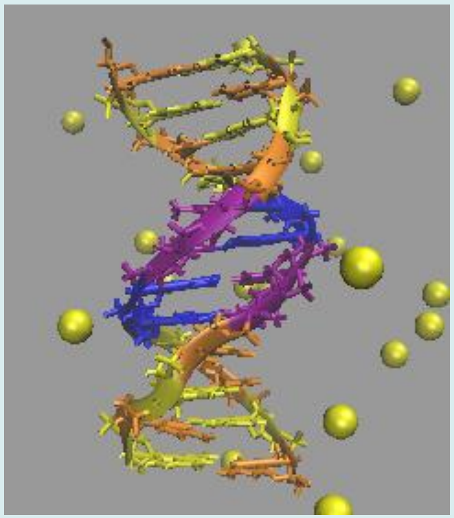
S.M. Perepelytsya, S.N. Volkov,
Ukr. J. Phys. **58**, 554 (2013).
J. Phys.: C. Ser. **438**, 012013 (2013).

Existence of lattice-like ordering of counterions is confirmed by observation of the ion-phosphate vibrations in DNA low-frequency spectra (200 cm^{-1}).

Modeling of DNA with counterions:

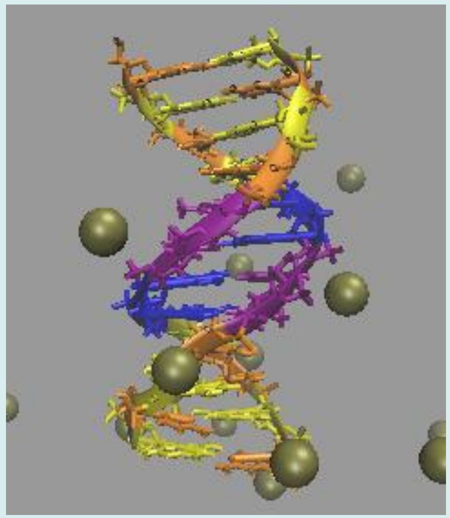
Classical MD simulations

Na-DNA



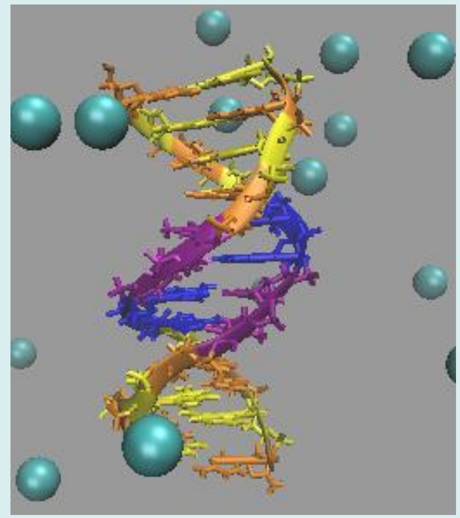
Sodium – 22
Water – 7912

K-DNA



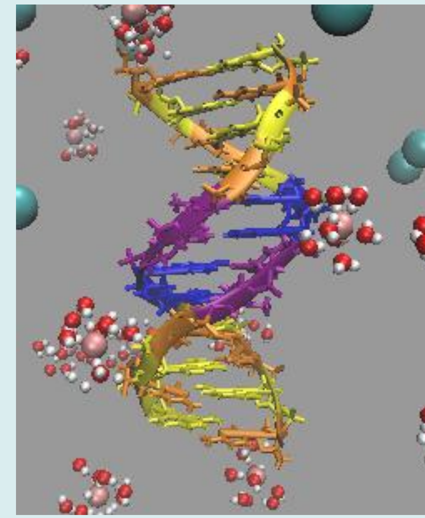
Potassium – 22
Water – 7912

Cs-DNA



Cesium – 22
Water – 7912

Mg-DNA



Magnesium – 18
Clorine – 14
Water – 7902

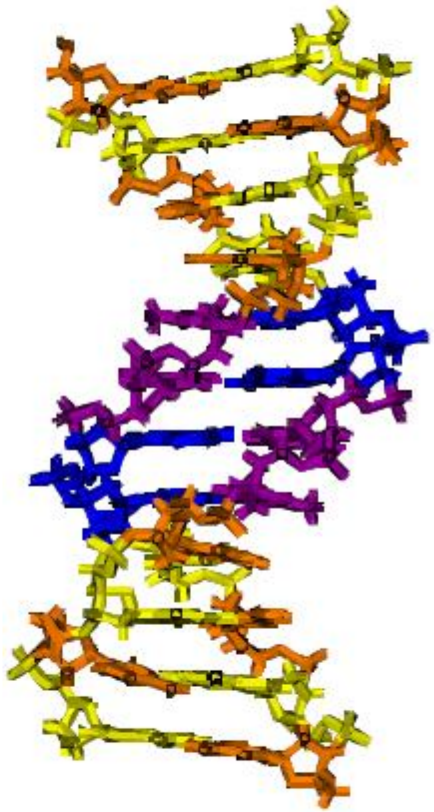
Box size 64x64x64 Å^3; simulation trajectory >100 ns.

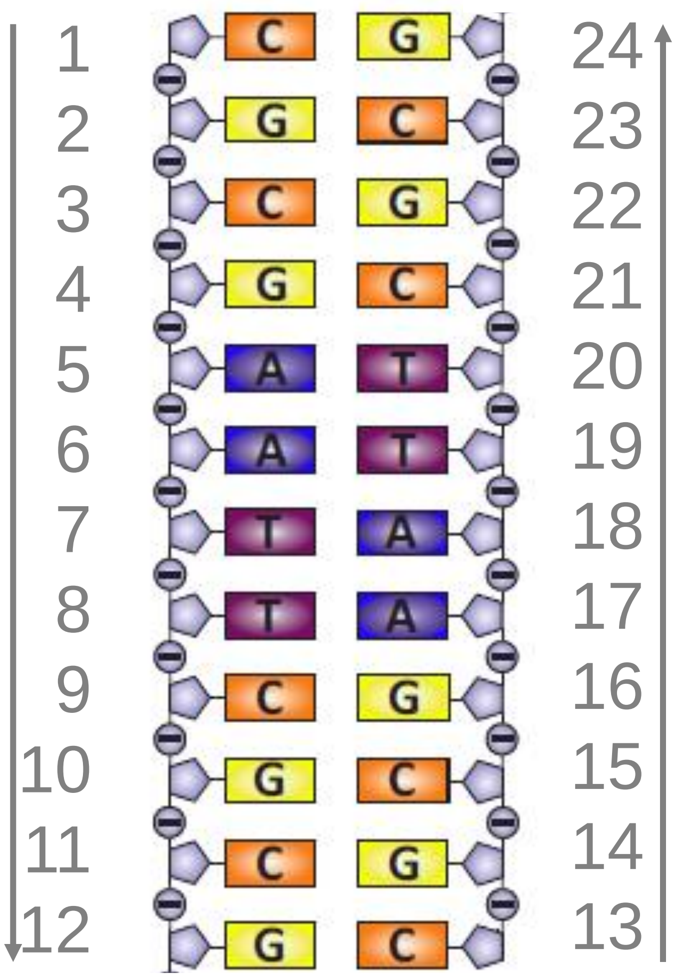
Software packages:
VMD NAMD
Force field: CHARMM27

Humphrey, W., Dalke, A. and Schulten, K., `VMD – Visual Molecular Dynamics', *J. Molec. Graphics* 1996, 14.1, 33-38.
Phillips J.C. *et al. J. Comp. Chem.* 26, 1781 (2005).

Drew-Dickerson dodecamer
(CGCGAATTCGCG)

X-ray structure 1BNA

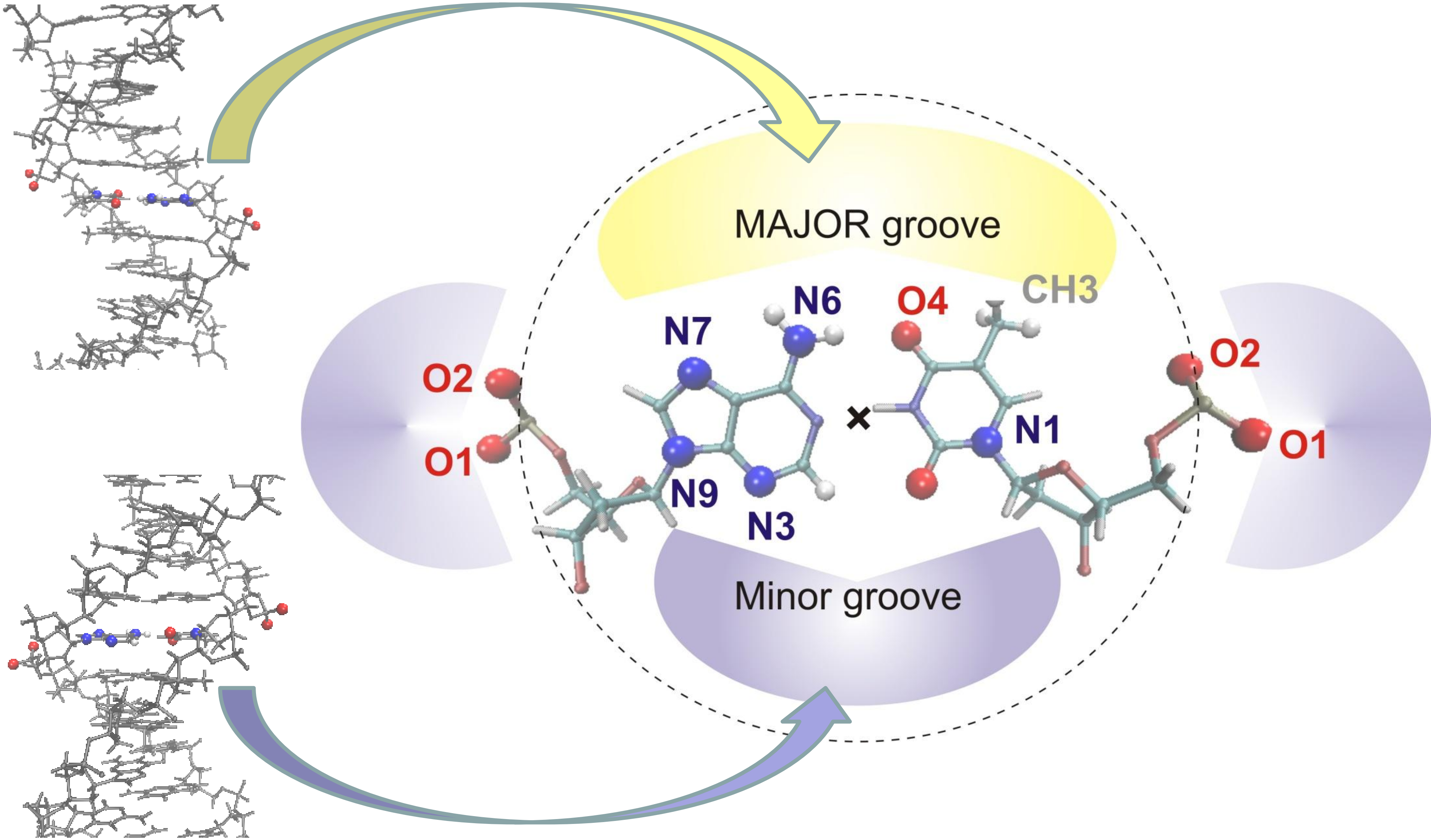




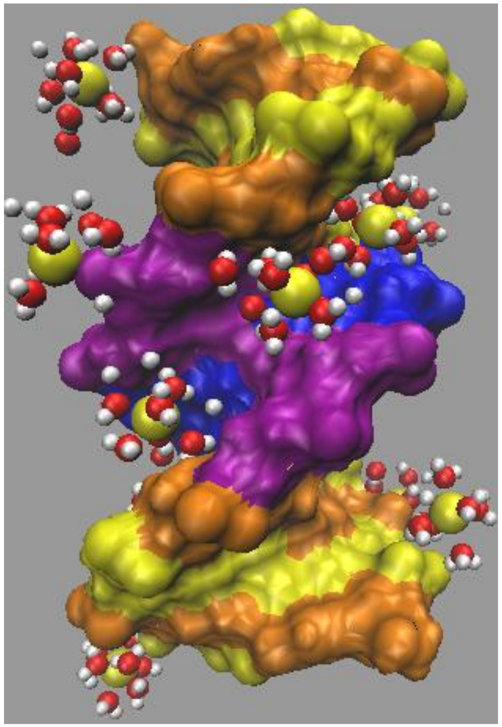
Schematic structure

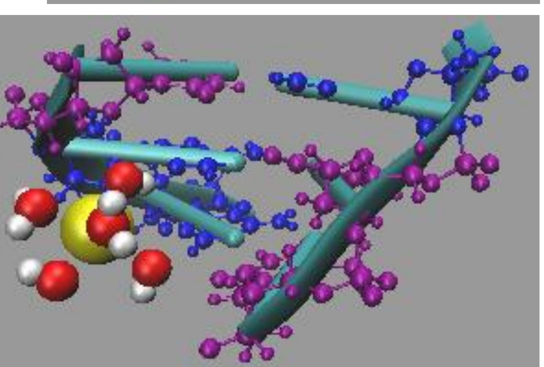
Drew H.R., Wing R.M., Takano T., Broka C., Takana S., Itakura K., Dickerson R.E., *Proc. Natl. Acad. Sci. USA*, **78**,2179-2183 (1981).

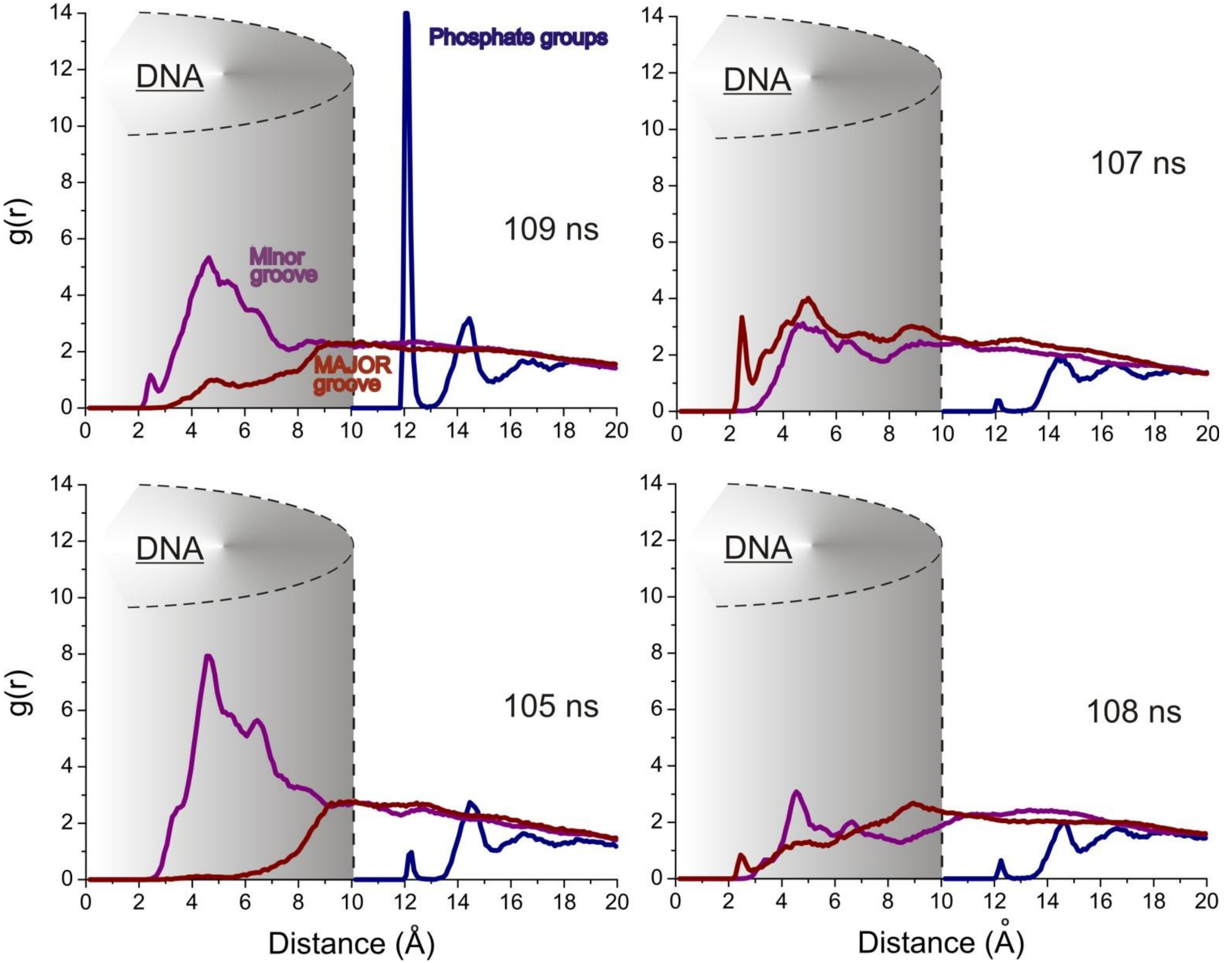
Radial distribution functions



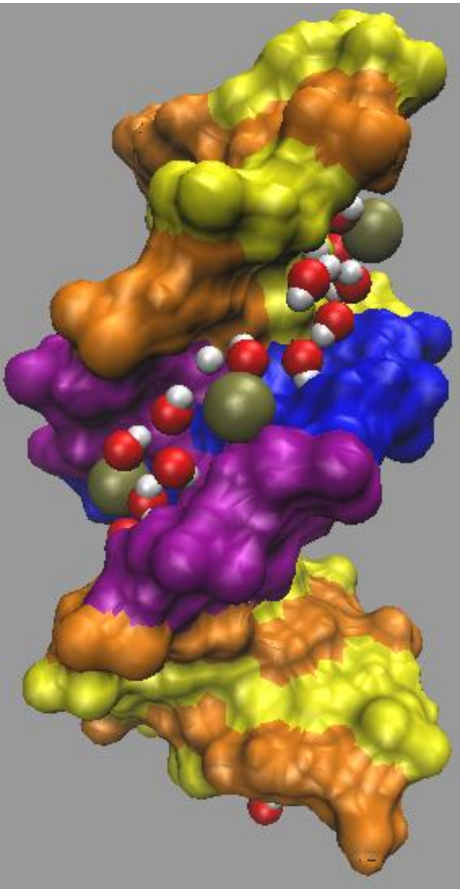
Distribution of ions in Na-DNA system

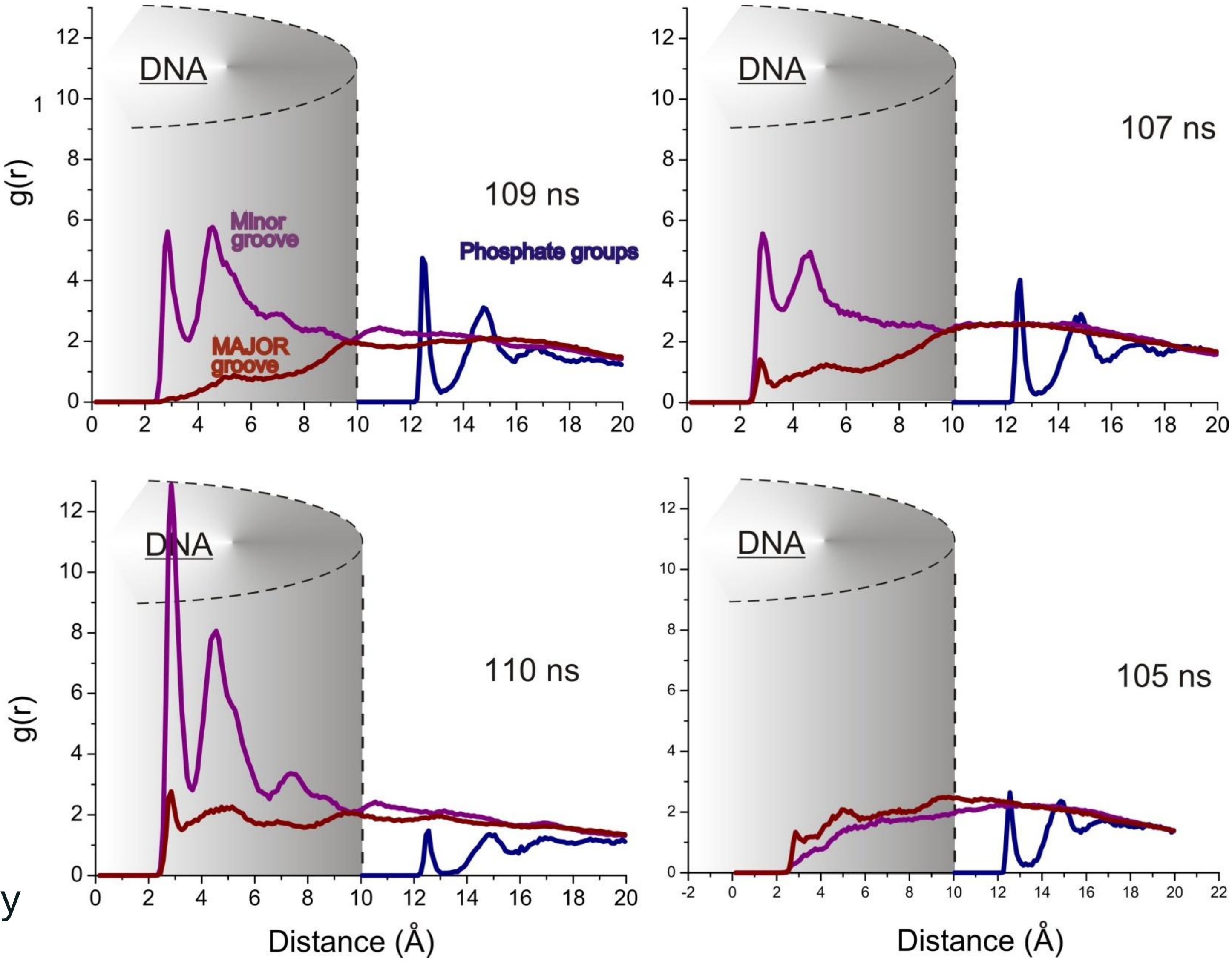






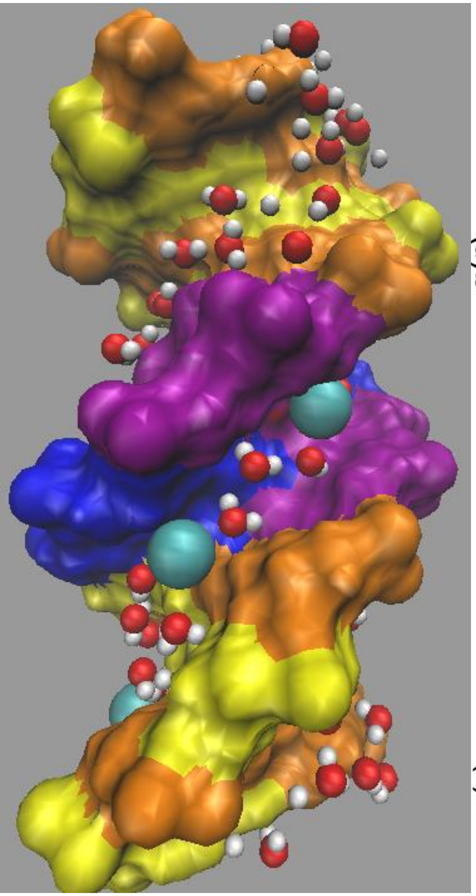
Distribution of ions in K-DNA system

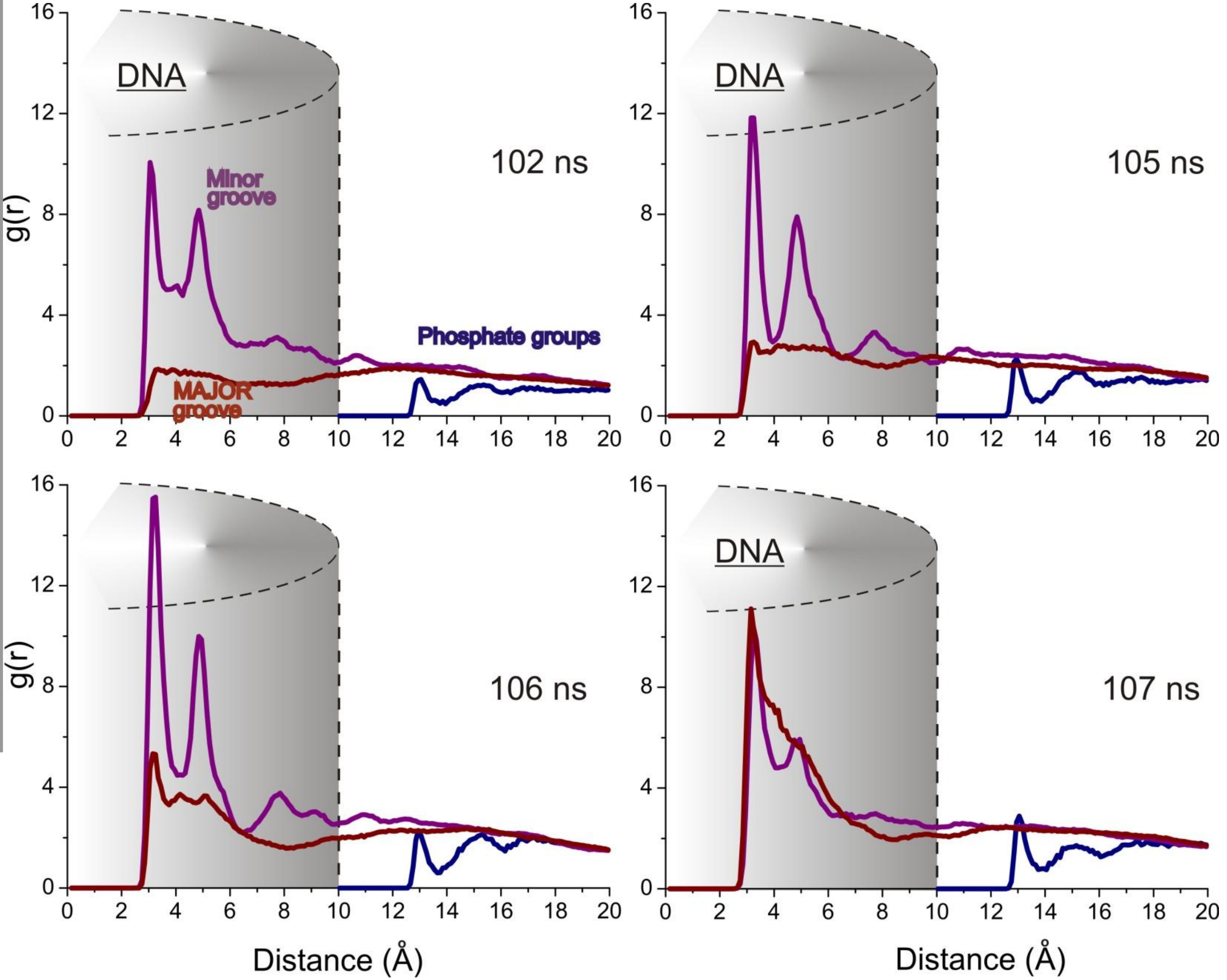




K+ in the minor groove. Localization inside the groove may reach about 0.3 ns.

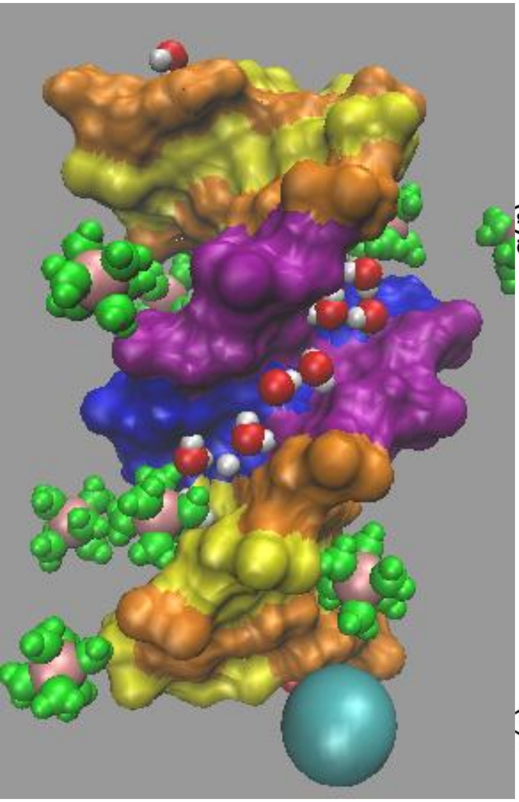
Distribution of ions in Cs-DNA system

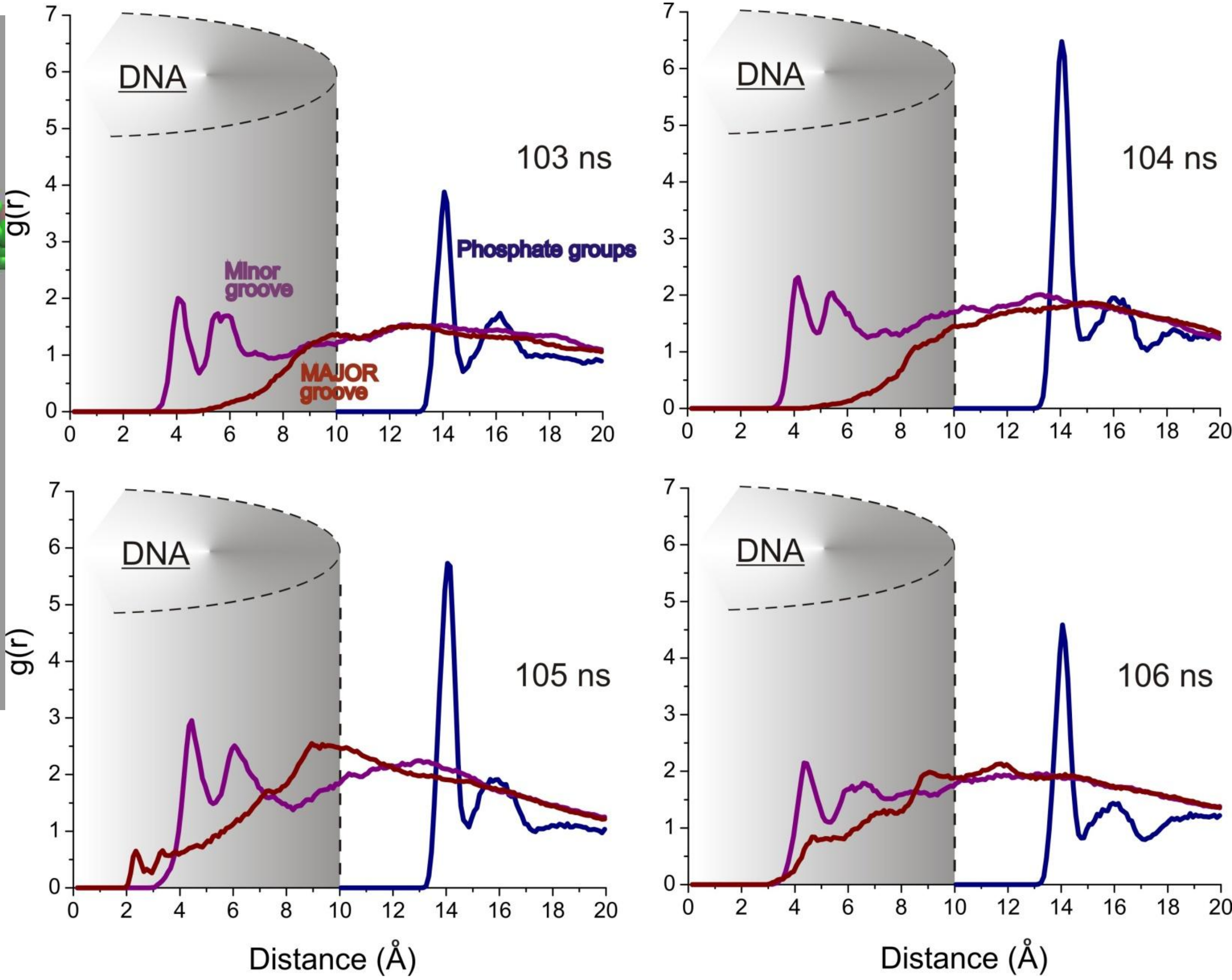




Cs+ in the minor groove. Localization inside the groove may reach > 1ns.

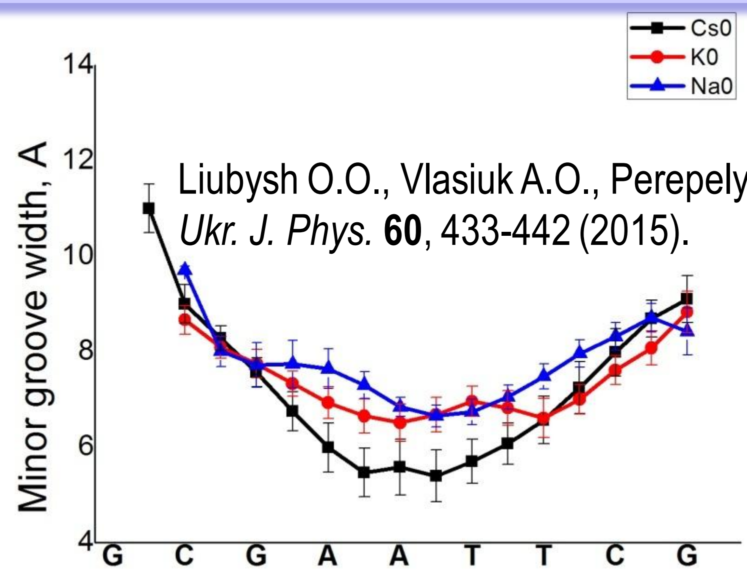
Distribution of ions in Mg-DNA system



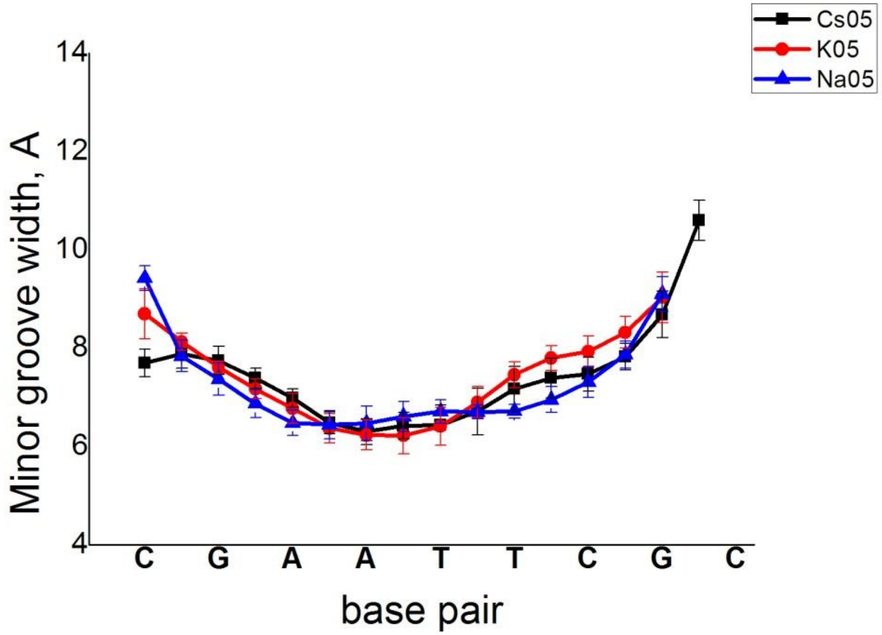


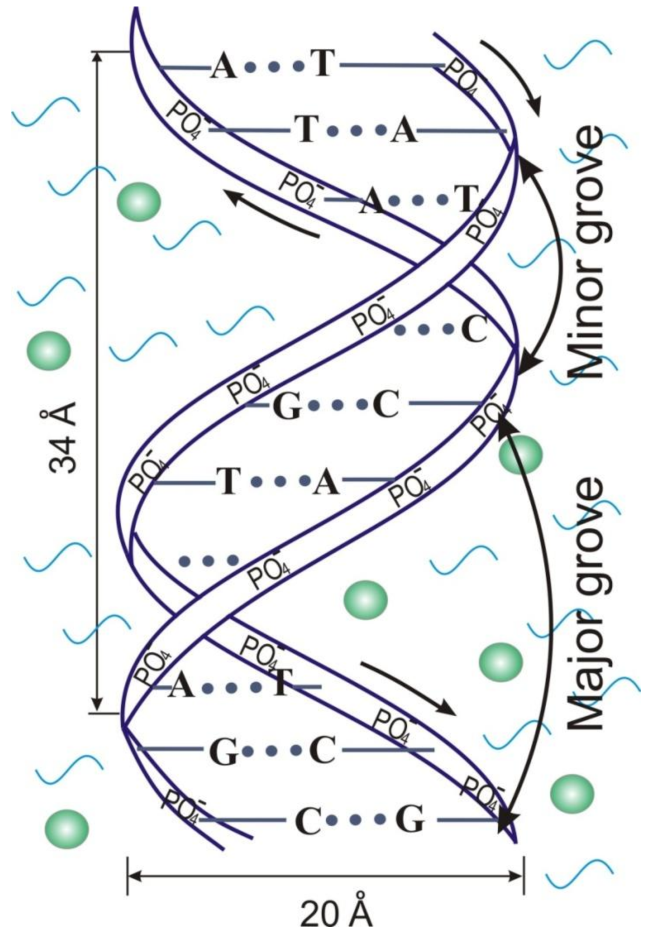
Hydrated Mg2+ ions are localized in the top edge of the minor groove and near the phosphates(t>1ns).

Width of DNA minor groove



Liubysh O.O., Vlasiuk A.O., Perepelytsya S.M.
Ukr. J. Phys. **60**, 433-442 (2015).

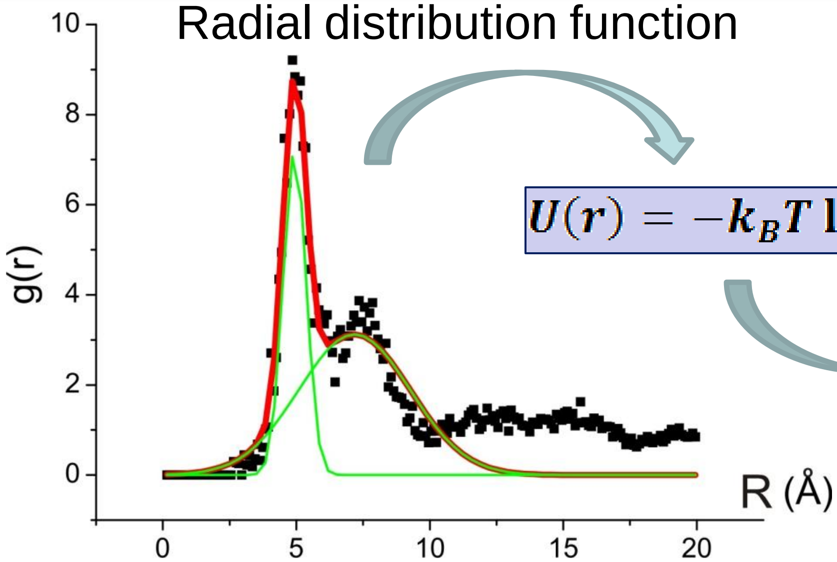




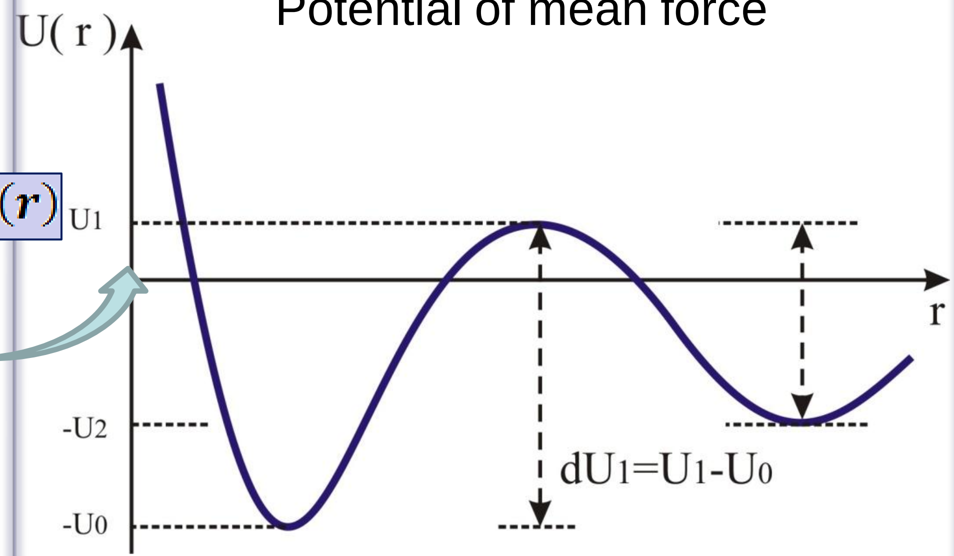
<u>Curves+</u>

Lavery R., Moakher M., Maddocks J.H., Petkeviciute D., Zakrzewska K., *Nucleic Acids Res.*, **37**, 5917-5929 (2009).

Estimation of the potential of mean force



$$U(r) = -k_B T \ln g(r)$$



Fitting of the RDF shape:

$$g(r) = g_0 + \frac{A_1}{w_1\sqrt{\frac{\pi}{2}}} e^{-\frac{2(r-r_{01})^2}{w_1^{\,2}}} + \cdots$$

$$U(r)|_{r_{01}} \approx U_1 + \frac{\gamma_1}{2}(r-r_{01})^2 =$$

$$-g_0 - \frac{A_1}{w_1\sqrt{\frac{\pi}{2}}} + \frac{2}{w_1^{\,2}}(r-r_{01})^2$$

$\frac{w}{2}$ is the standard deviation.

Estimation of average frequency of vibrations in the potential well:

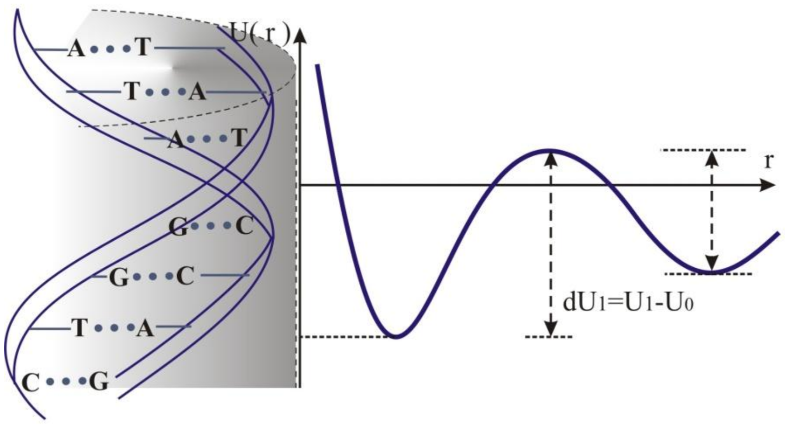
$$\nu_1 = \frac{1}{2\pi}\sqrt{\frac{\gamma_1}{m}} = \frac{1}{\pi w_1}$$

Estimation of average residence time of the ion in the potential well:

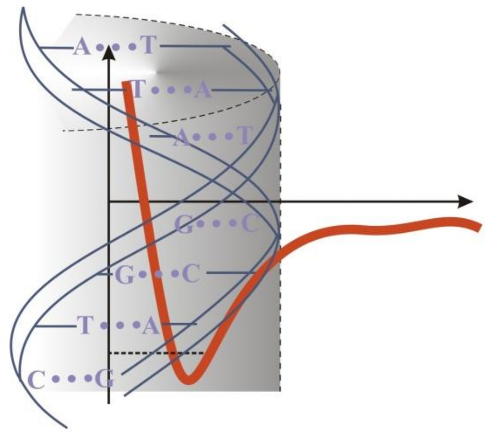
$$\tau = \tau_0 e^{\frac{\Delta U}{k_B T}}$$

Residence time of counterions and frequencies of vibrations

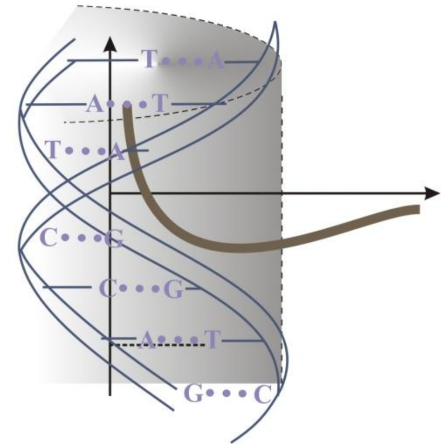
Phosphate groups



Minor groove



MAJOR groove



		Na-DNA	K-DNA	Cs-DNA	Mg-DNA
Phosphate group	**ω, THz**	5.5	3.7	1.7	1.4
	***τ*, ps**	122	15	32	400
Minor groove	**ω,THz**	0.94	2.8	1.5	0.8
	***τ*, ps**	429	142	2052	800
Well 1	**R_1, Å**	2.35	2.65	3.10	--
Well 2	**R_2, Å**	4.40	4.70	4.29	4.20

Conclusions

1. The counterions form a dynamical ordered structure around the DNA double helix that has a properties of the lattice of ionic crystal.
2. The manifestations of the counterion ordering are found in the DNA low-frequency spectra (<200 cm^{-1}) as the modes of ion-phosphate vibrations.
3. MD simulation data show:

- sodium counterions are localized from the outside of the double helix and at the top edge of the minor groove; the counterions interact with the atoms of the phosphate groups directly or via water molecules;
- potassium counterions may be localized at the both external or internal compartments of the double helix; the counterions interact with the atoms of the double helix directly or via water molecules;
- cesium counterions penetrate deeply inside the minor groove of the double helix and interact directly with the atoms of basses; the ions spend rather long time inside the minor groove (> 1ns) and may form a regular structure at this time scale;
- the ions in the major groove of the double helix are free to move;
- the frequencies of counterion vibrations corresponding to the potential wells characterizes the dynamics of the ions in bonded states; the estimated frequencies of vibrations of the counterions qualitatively agree with the previous calculations and experimental data.

Acknowledgments

Laboratory of Biophysics of Macromolecules

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Dr. D.V.Piatnytskyi

Ms. P.P.Kanevska

Prof. E.S.Kryachko

O.O.Zdorevskyi
(Ph.D. stud.)

UKRAINIAN NATIONAL GRID

Computational Facilities

Memorandum of Understanding between UW-CHTC and BCC

Grid computing cluster of the Bogolyubov Institute for Theoretical Physics

HTCondor
High Throughput Computing

Thank you for your attention!

Bogolyubov Institute for Theoretical Physics