

Des moteurs de jeux à la physique des chromosomes

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Modélisation Multi-échelle de la Matière Vivante

1. Directeur du laboratoire de Physique Théorique de la Matière Condensée : Pascal Viot
2. Équipe M3V :
 - ▶ Chef d'équipe : Jean-Marc Victor (Directeur de recherche au CNRS)
 - ▶ Annick Lesne (Directeur de recherche au CNRS)
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 - ▶ Julien Mozziconacci (Maitre de conférences à l'UPMC)
 - ▶ Laurence Signon (Chargé de recherche au CNRS et stagiaire au LPTMC)
 - ▶ Axel Cournac (Post-doctorant)
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 - ▶ Fabien Paillusson
 - ▶ Hua Wong
 - ▶ Eli Ben-Haim

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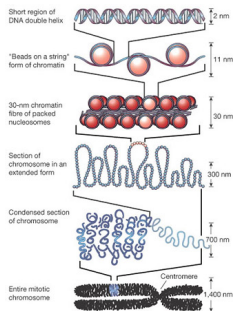
Comment compacter l'ADN ?

Pincés magnétiques et fibre de chromatine

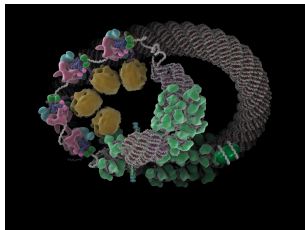
Nucleosome

Conclusion et perspectives

ADN nu sous pinces magnétiques : contexte biologique



(a)



(b) Wong & al, BIOESSAYS. 2009 Oct 29;31(12) :1357-1366

ADN nu sous pinces magnétiques : montage expérimental

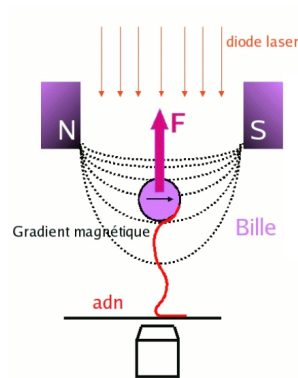


FIGURE: Vue schématique d'une expérience de pinces magnétiques.

Direct Mechanical Measurements of the Elasticity of Single DNA Molecules by Using Magnetic Beads

Steven B. Smith, Laura Finzi,* Carlos Bustamante†

Single DNA molecules were chemically attached by one end to a glass surface and by their other end to a magnetic bead. Equilibrium positions of the beads were observed in an optical microscope while the beads were acted on by known magnetic and hydrodynamic forces. Extension versus force curves were obtained for individual DNA molecules at three different salt concentrations with forces between 10^{-14} and 10^{-11} newtons. Deviations from the force curves predicted by the freely jointed chain model suggest that DNA has significant local curvature in solution. Ethidium bromide and 4',6-diamidino-2-phenylindole had little effect on the elastic response of the molecules, but their extent of intercalation was directly measured. Conversely, the effect of bend-inducing *cis*-diamminedichloroplatinum (II) was large and supports the hypothesis of natural curvature in DNA.

Propriété de courbure de l'ADN : persistance en courbure $p = 50$ nm
Cette expérience ne mesure pas la capacité de l'ADN à se tordre : persistance en twist t

Méthode du Pivot et du Krankshaft pour la simulation d'ADN

DNA Extension under the Action of an External Force

Alexander Vologodskii¹

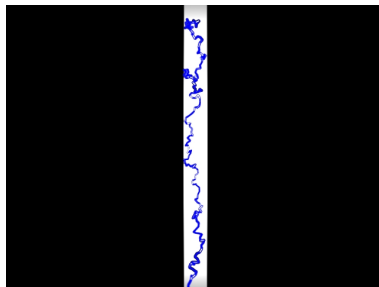
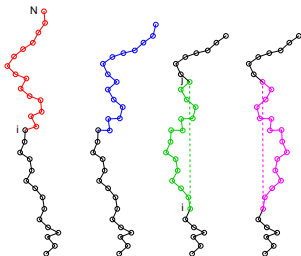
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*Received March 23, 1994; Revised Manuscript Received July 11, 1994**

ABSTRACT: We computed the extension-force dependence for the wormlike model of a polymer chain. The dependence that we obtained differs essentially from the corresponding well-known dependence for the freely jointed chain when the extension exceeds half of the chain contour length. We used the computed results to analyze the measurements of extension of individual DNA molecules under the action of force made recently (Smith, S. B.; Finzi, L.; Bustamante, C. *Science* 1992, 258, 1122). We took into account the electrostatic interaction between DNA segments for a very low salt concentration. The theoretical dependences obtained are in very good agreement with the experimental data.

(a) Vologodskii, *Macromolecules* **1994**, 27, 5623-5625

Pivot Rotation $R_p(\theta)(i \rightarrow N)$ Krankshaft Rotation $R_k(\theta)(i \rightarrow j)$



(b) Vue schématique des méthodes du Pivot (de rouge à bleu) et du Krankshaft (de vert à magenta) + algorithme de Metropolis

(c) Vue schématique d'un polymère greffé dans un tube

A Brownian Dynamics Program for the Simulation of Linear and Circular DNA and Other Wormlike Chain Polyelectrolytes

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Division Biophysics of Macromolecules, German Cancer Research Center, D-69120 Heidelberg, Germany

ABSTRACT For the interpretation of solution structural and dynamic data of linear and circular DNA molecules in the kb range, and for the prediction of the effect of local structural changes on the global conformation of such DNAs, we have developed an efficient and easy way to set up a program based on a second-order explicit Brownian dynamics algorithm. The DNA is modeled by a chain of rigid segments interacting through harmonic spring potentials for bending, torsion, and stretching. The electrostatics are handled using precalculated energy tables for the interactions between DNA segments as a function of relative orientation and distance. Hydrodynamic interactions are treated using the Rotne-Prager tensor. While maintaining acceptable precision, the simulation can be accelerated by recalculating this tensor only once in a certain number of steps.

Modèle du "Bead spring" (2)

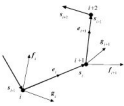


FIGURE 1 Chain geometry with the segment vectors $r_{i,j}$ and the segment center system (f, g, e) that define the relative orientation between consecutive segments.

The total energy of a given chain conformation is given as the sum of the stretching, bending, twist, and electrostatic energies.

The stretching energy is defined for each segment i :

$$\frac{E_i^s}{k_B T} = \frac{1}{2} \frac{C}{l_i^2} (l_i - l_i^0)^2 \quad (1)$$

Here k_B is the Boltzmann constant, T the temperature, l_i the segment equilibrium length, and C the stiffness parameter, so that $(l_i^0)^2$ is approximately equal to the variance of the segment length distribution.

The bending energy is defined for each chain joint. We call a joint *soft* if it connects segments that form a straight line at equilibrium, and *hard* if the angle $\theta_{i,j}^0$ between the segments at equilibrium is nonzero. To each bent joint i we attach an auxiliary unit vector b_i that is fixed in the coordinate system (f, g, e) , its polar coordinates being (θ_i^0, ϕ_i^0) . Note that this formalism is different from our first implementation (Chiriac and Langewald, 1996) where a heuristic "link potential" was used that was given in terms of the Euler angles for rotating one segment into the next. Here the bending energy of the i th joint is:

$$\frac{E_i^b}{k_B T} = \alpha_i \beta_i^2 \quad (2)$$

where β_i is the angle between e_{i-1} and e_i for a *soft* joint, or between e_{i-1} and b_i for a *hard* joint, α_i is the bending rigidity parameter chosen in such a way that the Kuhn length is equal to:

$$\tilde{L} = l_i \frac{1 + \langle \cos \beta \rangle}{1 - \langle \cos \beta \rangle} \quad (3)$$

where

$$\langle \cos \beta \rangle = \frac{\int_0^\pi \cos \beta \sin \beta \exp(-\alpha_i \beta^2) d\beta}{\int_0^\pi \sin \beta \exp(-\alpha_i \beta^2) d\beta}$$

The twist energy is defined for each adjacent segment pair:

$$\frac{E_{i,j}^t}{k_B T} = \frac{1}{2} \frac{C}{l_i l_j} \tau_{i,j}^2 \quad (4)$$

where C is the torsional rigidity constant and $\tau_{i,j}$ is the twist angle between the $(i-1)$ th and i th segments.

The twist angle $\tau_{i,j}$ is calculated by defining a vector $p_i = v_{i-1} \times v_i$, which is normal both to v_{i-1} and v_i . Now, we can easily calculate the angles α_i between f_{i-1} and p_i , and p_i and v_i between p_i and f_i . Then, $\tau_{i,j} = \alpha_i - \gamma_i$ (Fig. 2). During the BD simulation we assume that at time t , $\tau(t, t - \Delta t) = \pi \ll \tau(t) \approx \tau(t - \Delta t) + \pi$, where $\tau(t - \Delta t)$ is the twist angle one simulation step ago (Δt is chosen such that the probability that the twist angle changes by more than $\pm \pi$ becomes negligible).

The starting point for the electrostatic energy is the expression for the energy of interaction between two uniformly charged nonadipole segments (i, j) in a 1:1 salt solution in the Debye-Hückel approximation:

$$\frac{E_{i,j}^e}{k_B T} = \frac{q^2}{k_B T D} \int d\mathbf{r}_i \int d\mathbf{r}_j \frac{\exp(-\kappa r_{ij})}{r_{ij}} \quad (5)$$

The integration is done along the two segments: λ_i and λ_j are the distances from the segment beginnings, r_{ij} is the distance between the current positions at the segments to which the integration parameters λ_i and λ_j correspond, κ is the inverse of the Debye length, so that $\kappa^{-1} = \sqrt{\epsilon^2 / 4\pi \lambda_B T D}$, J is the ionic strength, e the proton charge, D the dielectric constant of water, ϵ the linear charge density which for DNA is equal to $\nu_{DNA} \lambda_B = -2e\lambda_B$, where $\lambda_B = 0.34$ nm is the distance between basepairs.

There are two problems to be solved for the Eq. 5: 1) the linear density ν should be renormalized from that of DNA to a smaller value in order to ensure the correct excluded volume effects; 2) the integration should be approximated by a more simple procedure to save computation time.

The renormalization of the linear density was done as in Singer (1977). As pointed out in Schellman and Singer (1977), the Gouy layer of immobile counterions reduces the effective charge density by a factor of $q = 0.73$ for NaCl concentrations between 1 and 500 mM. Next, the Debye-Hückel approximation is a linearization of the Poisson-Boltzmann equation and valid only for a very small electric potential: $\varphi \ll k_B T/e$. We choose the renormalized charge

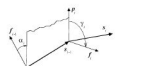


FIGURE 2 Definition of the twist angle $\tau_{i,j} = \alpha_i - \gamma_i$. p_i is perpendicular to v_{i-1} and v_i , α_i is measured between f_{i-1} and p_i , γ_i between p_i and f_i .

(a)

density ν^* in such a way that the known solution of the Debye-Hückel equation for a straight thin line with charge density ν^* coincides with the solution of the Poisson-Boltzmann equation for a cylinder of the DNA radius r_{DNA} and the charge density ν_{DNA} in the regime where $\varphi \ll k_B T/e$ (Fig. 3).

In order to save computation time, a tabulation of the double integral (Eq. 5) was used. For simplicity we assume that each segment has the same length l . For each segment pair (i, j) we can define a vector R_{ij} connecting the middle points of the two segments. Then the mutual position of the segments can be defined by the following four dimensionless parameters:

$$p_{ij} = |R_{ij}| \quad (6a)$$

center-to-center distance in L_i units, $(6a)$

$$p_{ij} \geq 0$$

$$\gamma_{ij} = (1/p_{ij}) \cdot R_{ij} \cdot e_{ij} \quad (6b)$$

nit angle cosine for the i th segment, $(6b)$

$$-1 \leq \gamma_{ij} \leq 1$$

$$\gamma_{ij} = -(1/p_{ij}) \cdot R_{ij} \cdot e_{ij} \quad (6c)$$

nit angle cosine for the j th segment, $(6c)$

$$-1 \leq \gamma_{ij} \leq 1$$

$$\sigma_{ij} = \frac{(e_i \times R_{ij}) \cdot (e_j \times R_{ij})}{|e_i \times R_{ij}| |e_j \times R_{ij}|}$$

twist angle cosine, $-1 \leq \sigma_{ij} \leq 1$ $(6d)$

Equation 5 can be rewritten in the form:

$$\frac{E_{i,j}^e}{k_B T} = \alpha_{ij} \int_{-l/2}^{l/2} \int_{-l/2}^{l/2} d\lambda_i \int_{-l/2}^{l/2} d\lambda_j \frac{\exp(-\kappa R_{ij})}{R_{ij}} \quad (7)$$

where $\alpha_{ij} = \nu_i^* \nu_j^* l_i l_j D$ and

$$f(p_{ij}, \gamma_{ij}, \sigma_{ij}) = \int_{-l/2}^{l/2} \int_{-l/2}^{l/2} d\lambda_i \int_{-l/2}^{l/2} d\lambda_j \frac{\exp(-\kappa R_{ij})}{R_{ij}} \quad (8)$$

$$R = p_{ij} v_i - x_i v_i + x_j v_j \quad (9)$$

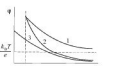


FIGURE 3 Electrostatic potential for the interaction between DNA segments. A Debye-Hückel potential (1) was renormalized (3) such as to coincide at large distances with the nonlinear Poisson-Boltzmann equation (2).

where v_i, v_j , and v_k are unit vectors oriented in such a way that $v_i v_j = v_j \cdot v_i = \gamma_{ij}$ and $(v_i \times v_j) \cdot (v_k \times v_l) = (v_i \times v_l) \cdot (v_j \times v_k) = \sigma_{ij}$.

In the following we used the partial derivatives of Eq. 8. At first, a four-dimensional table for the values of the integral (Eq. 8) and each of its partial derivatives was constructed numerically. Then, during the simulation, a linear interpolation was used to obtain the values of $f(p, \gamma, \sigma)$, $(\partial f / \partial p)$, $(\partial f / \partial \gamma)$, $(\partial f / \partial \sigma)$ at particular points of the (p, γ, σ) space. The table size was chosen such that the values of p , $\arccos \gamma$, and $\arccos \sigma$ had constant increments. The tabulation range for γ , v_i , and σ is $[-1, 1]$. The range of p [p_{min}, p_{max}], and the table size for each segment are parameters of the approximation, which we chose by the following criteria. For the minimum distance, p_{min} , all possible values of the electrostatic energy should be large enough (e.g., $>10 k_B T$), so that this distance is practically unresolvable during the simulation. For distances $> p_{max}$, all possible energy values should be negligible ($\approx \gamma, \ll 0.01 k_B T$). The mutual displacement of segments corresponding to one μ -step should not exceed the Debye length, and the same restriction is applied to the displacement of segment ends, corresponding to one step in the γ_i , γ_j , and σ dimensions. These criteria are rather "soft" in order to keep the total table size within reasonable limits (the minimum table size is $l_i = 10$ nm and $l_j = 1$ M is 14 MB of memory, including all partial derivatives of Eq. 8). We should note, however, that even crude hard-core potentials for electrostatic repulsion in DNA can be applied in many cases to predict statistical properties of DNA to good precision (Vologodski and Cozzarelli, 1995), therefore, the representation of the electrostatic potential according to Eqs. 7 and 8 is probably a good approximation.

So far, we neglected the fact that the segment length is only approximately equal to l_i . That means that the "sharp" segment does not coincide exactly with the "geometrical" segment. This seems to be a good approximation for the excluded volume effects, since the chain is supposed to be stiff with respect to stretching ($\delta \ll 1$). One can be careful, however, to avoid that during the simulation parts of the chain cross each other through discontinuities between adjacent charged segments, if the length of their phantom geometrical counterparts is greater than l_i . In order to exclude this possibility we define the R_{ij} vector for two segments (i, j) of arbitrary length in the following way:

$$R_{ij} = \frac{1}{L_i} (r_{ij}^{(m)} - r_{ij}^{(n)}) \quad (10)$$

where $r_{ij}^{(m)}$ is a "slufted" middle point of the segment:

$$r_{ij}^{(m)} = r_{i-1} + (l_i/2)v_i, \quad \text{if } |r_{ij}^{(m)} - r_{ij}^{(n)}| = |r_{ij}^{(m)} - r_{i-1}|; \quad (a)$$

$$r_{ij}^{(m)} = r_{i-1} + (l_i/2)v_i, \quad \text{else.} \quad (b)$$

$$r_{ij}^{(n)} = (r_j + r_{j+1})/2 \quad \text{is the actual middle point of the segment. This means that the geometrical segment that is used to calculate the excluded volume interaction is shifted$$

(b)

with it end toward the segment joint that is closest to the other segment in the interaction. Thereby, any gaps that might appear at the joint due to stretching are automatically closed and the chains cannot cross.

Since forces and torques are the partial derivatives of the energy over the system coordinates, the latter should be specified formally. For each segment i we chose the following four coordinates: the three space coordinates r_i of the segment beginning and the angle, ϕ_i , of rotation of the local vector basis (f_i, g_i, e_i) around the e_i axis. For the angle coordinate the zero position is not defined. Therefore, an addition, we need to specify here to keep the e_i coordinates unchanged while a displacement of the r_i coordinates takes place. The following rule was used to derive forces and torques and to perform moves in the simulation procedure. If, as a result of r_i displacement, the e_i vector has a new value e_i' and A_i is a rotation matrix, so that $e_i' = A_i e_i$, then the new values of the f_i vector are $f_i' = A_i f_i$.

In a linear chain three additional degrees of freedom r_{ij} are required for the last segment. Here are the expressions for the forces and torques for the i th segment obtained by differentiating Eq. 1, 2, 4, and 7.

Stretching force

The stretching force acting on the i th vertex from the $(i+1)$ th one is parallel to the h segment:

$$\mathbf{F}_{i,i+1}^{\text{stretch}} = \frac{r_i - L_i}{(L_i)^2} \mathbf{e}_i \quad (12)$$

The total stretching force for the i th vertex is therefore

$$\mathbf{F}_i^{\text{stretch}} = -\mathbf{F}_{i,i-1}^{\text{stretch}} + \mathbf{F}_{i,i+1}^{\text{stretch}} \quad (13)$$

Bending force

The contribution of the energy stored in the bending angle β_i to the bending force acting on the i th vertex from the $(i+1)$ th one is perpendicular to the h segment and lies in the bend plane:

$$\mathbf{F}_{i,i+1}^{\text{bend}} = \frac{2\alpha_b \beta_i}{z_i \sin \beta_i} \mathbf{e}_i \times \mathbf{e}_{i+1} \quad (14a)$$

for an unbound joint, and

$$\mathbf{F}_{i,i+1}^{\text{bend}} = \frac{2\alpha_b \beta_i}{z_i \sin \beta_i} (\mathbf{e}_{i+1} \times \mathbf{b}_i) \times \mathbf{e}_i \quad (14b)$$

for a bent joint. Here $\mathbf{b}_i = \mathbf{p}_i \mathbf{p}_i / |\mathbf{p}_i|^2$, $\mathbf{e}_i = \mathbf{e}_i \times \mathbf{e}_{i+1}$, so that $\mathbf{b}_i = \mathbf{e}_{i+1} \times \mathbf{e}_i / |\mathbf{p}_i|^2 \sin^2 \beta_i$ where β_i^* is the angle between \mathbf{e}_{i+1} and \mathbf{e}_i (for an unbound joint, $\beta_i^* = \beta_i$).

The analogous contribution to the bending force acting on the i th vertex from the $(i-1)$ th one is perpendicular to the

$(i-1)$ th segment and also lies in the bend plane:

$$\mathbf{F}_{i,i-1}^{\text{bend}} = \frac{2\alpha_b \beta_i}{z_{i-1}} \mathbf{e}_{i-1} \times \mathbf{e}_i \quad (15a)$$

for an unbound joint, and

$$\mathbf{F}_{i,i-1}^{\text{bend}} = \frac{2\alpha_b \beta_i}{z_{i-1} \sin \beta_i} [\mathbf{b}_{i-1} - (\mathbf{e}_{i-1} \cdot \mathbf{b}_{i-1}) \mathbf{e}_{i-1}] \quad (15b)$$

for a bent joint.

Note that Eqs. 14a and 15a for an unbound joint are symmetric with respect to renumbering the vertices in opposite order (one force can be obtained from the other by substituting $a \leftrightarrow -a$, $i \leftrightarrow i+1$, $\mathbf{e}_i \leftrightarrow -\mathbf{e}_i$, $\mathbf{b}_i \leftrightarrow -\mathbf{b}_i$). Obviously, there is no such symmetry for a bent joint because the \mathbf{b}_i vectors are not defined in a symmetrical way. We note also that the expressions for a bent joint (14b, 15b) become those for the unbound joint upon substituting $\mathbf{b}_i \leftrightarrow \mathbf{e}_i$.

The total bending force for the i th vertex is:

$$\mathbf{F}_i^{\text{bend}} = -\mathbf{F}_{i,i-1}^{\text{bend}} + \mathbf{F}_{i,i+1}^{\text{bend}} - \mathbf{F}_{i,i+1}^{\text{bend}} \quad (16)$$

Bending torque

The torque on segment i induced by bending is for a bent joint:

$$\mathbf{T}_i^{\text{bend}} = \frac{2\alpha_b \beta_i}{k_b T} \mathbf{e}_i \times (\mathbf{e}_i \times \mathbf{b}_i) \quad (17)$$

For an unbound joint, this torque is equal to zero.

Twisting force

The force on the i th vertex from the $(i+1)$ th one induced by mutual twisting of the $(i-1)$ th and i th segments by an angle τ_i is perpendicular to the plane of the h bend:

$$\mathbf{F}_{i,i+1}^{\text{twist}} = \frac{C}{k_t T} \frac{\tau_i}{\beta_i} (1 - \mathbf{e}_i \cdot \mathbf{e}_{i+1}) \mathbf{e}_i \quad (18)$$

The symmetric expression for the twisting force acting on the i th vertex from the $(i-1)$ th one is:

$$\mathbf{F}_{i,i-1}^{\text{twist}} = \frac{C}{k_t T} \frac{\tau_i}{\beta_i} (1 - \mathbf{e}_{i-1} \cdot \mathbf{e}_i) \mathbf{e}_i \quad (19)$$

The total twisting force for the i th vertex is then

$$\mathbf{F}_i^{\text{twist}} = -\mathbf{F}_{i,i-1}^{\text{twist}} + \mathbf{F}_{i,i+1}^{\text{twist}} - \mathbf{F}_{i,i+1}^{\text{twist}} \quad (20)$$

Twisting torque

The torque on the i th segment induced by twisting of the $(i+1)$ th segment by an angle τ_i with respect to the h one is

$$\mathbf{T}_i^{\text{twist}} = \frac{C}{k_t T} \frac{\tau_i}{\beta_i} \mathbf{T}_i \quad (21)$$

The total twisting torque for the i th segment is then

$$\mathbf{T}_i^{\text{twist}} = -\mathbf{T}_{i,i-1}^{\text{twist}} + \mathbf{T}_{i,i+1}^{\text{twist}} \quad (22)$$

Electrostatic force

The contribution of the electrostatic interaction between segments i and j to the force acting on the i th vertex is

$$\begin{aligned} \mathbf{F}_{i,j}^{\text{el}} &= \frac{1}{k_B T} - \frac{1}{k_B T} \frac{\partial^2 U}{\partial \mathbf{r}_i \partial \mathbf{r}_j} \\ &= \alpha_{ij} \left(\frac{\partial f_i}{\partial \mathbf{r}_i} \frac{\partial \mathbf{r}_j}{\partial \mathbf{r}_i} + \frac{\partial f_j}{\partial \mathbf{r}_i} \frac{\partial \mathbf{r}_i}{\partial \mathbf{r}_j} + \frac{\partial f_i}{\partial \mathbf{r}_j} \frac{\partial \mathbf{r}_j}{\partial \mathbf{r}_i} + \frac{\partial f_j}{\partial \mathbf{r}_j} \frac{\partial \mathbf{r}_i}{\partial \mathbf{r}_j} \right) \end{aligned}$$

where $f_i = f(\rho_i, \gamma_i, \sigma_i)$. An analogous relationship is valid for the force $\mathbf{F}_{i,j}^{\text{el}}$ acting on the $(j+1)$ th vertex from segment j . We assume that $\mathbf{F}_{i,i}^{\text{el}} = \mathbf{F}_{i,i}^{\text{twist}} = 0$ when $i = j$ or $i = j \pm 1$. The partial derivatives of Eq. (8) are tabulated as described above. The expressions for the derivatives of $\rho_i, \gamma_i, \sigma_i$ and σ_j with respect to r_i and r_{i+1} are given below, where the following auxiliary notations are used: $\mathbf{R}_i = \mathbf{R}_i / |\mathbf{R}_i|$ is a unit vector in the \mathbf{R}_i direction, α_{ij} and β_{ij} are the coefficients in the expression for the "shaded" middle-point of a segment:

$$r_{ij}^0 = \alpha_{ij} r_i + \beta_{ij} r_{i+1}$$

so that (see Eq. 11):

$$\alpha_{ij} = (1/2)(1 + (1 - L_j)/L_i)$$

$$\beta_{ij} = (1/2)(1 - (1 - L_j)/L_i)$$

The upper variant corresponds to the condition (a) in Eq. 11, the lower variant corresponds to the condition (b).

The partial derivatives are then:

$$\frac{\partial \rho_i}{\partial r_i} = \frac{1}{L_i} \alpha_{ij} \mathbf{R}_i = \frac{1}{2} \frac{\gamma_i}{z_i} \quad (23)$$

$$\frac{\partial \rho_{i+1}}{\partial r_{i+1}} = \frac{1}{L_i} \beta_{ij} \mathbf{R}_i = \frac{1}{2} \frac{\gamma_i}{z_i} \quad (24)$$

$$\frac{\partial \gamma_i}{\partial r_i} = \frac{1}{z_i} (\gamma_i \mathbf{e}_i - \mathbf{R}_i) - \frac{1}{\rho_i} \left[\frac{1}{2L_i} + \gamma_i \frac{\partial \rho_i}{\partial r_i} \right] \quad (25)$$

$$\frac{\partial \gamma_{i+1}}{\partial r_{i+1}} = \frac{1}{z_i} (\gamma_i \mathbf{e}_i - \mathbf{R}_i) - \frac{1}{\rho_i} \left[\frac{1}{2L_i} + \gamma_i \frac{\partial \rho_i}{\partial r_{i+1}} \right] \quad (26)$$

$$\frac{\partial \sigma_i}{\partial r_i} = \frac{1}{L_i} \left[\frac{1}{2} \alpha_{ij} \frac{(\mathbf{e}_i \cdot \mathbf{e}_j)}{z_i} - \gamma_i \frac{\partial \rho_i}{\partial r_i} \right] \quad (27)$$

$$\frac{\partial \sigma_{i+1}}{\partial r_{i+1}} = \frac{1}{L_i} \left[\frac{1}{2} \beta_{ij} \frac{(\mathbf{e}_i \cdot \mathbf{e}_j)}{z_i} - \gamma_i \frac{\partial \rho_i}{\partial r_{i+1}} \right] \quad (28)$$

$$\begin{aligned} \frac{\partial \sigma_j}{\partial r_i} &= \sqrt{1 - \sigma_j^2} \left(\frac{5\gamma_j}{|\mathbf{R}_j \times \mathbf{e}_j| \rho_j} \left[\frac{1}{2} \mathbf{T}_{ij}^{\text{twist}} (\mathbf{R}_j \times \mathbf{e}_j) \right] \right. \\ &\quad \left. + \frac{1}{2} \frac{(\mathbf{R}_j \times \mathbf{e}_j) \times \mathbf{e}_i}{z_i} \frac{1}{\rho_j} - \frac{\mathbf{R}_j \times \mathbf{e}_i}{|\mathbf{R}_j \times \mathbf{e}_i|} \left(1 - \frac{\alpha_{ij} z_i \gamma_j}{L_j \rho_j} \right) \right); \quad (29) \end{aligned}$$

$$\begin{aligned} \frac{\partial \sigma_{j+1}}{\partial r_{i+1}} &= \sqrt{1 - \sigma_j^2} \left(\frac{5\gamma_j}{|\mathbf{R}_j \times \mathbf{e}_j| \rho_j} \left[\frac{1}{2} \mathbf{T}_{ij}^{\text{twist}} (\mathbf{R}_j \times \mathbf{e}_j) \right] \right. \\ &\quad \left. + \frac{1}{2} \frac{(\mathbf{R}_j \times \mathbf{e}_j) \times \mathbf{e}_i}{z_i} \frac{1}{\rho_j} + \frac{1}{|\mathbf{R}_j \times \mathbf{e}_i|} \left(1 + \frac{\beta_{ij} z_i \gamma_j}{L_j \rho_j} \right) \right); \quad (30) \end{aligned}$$

In Eqs. 29 and 30 the positive values of the square root $\sqrt{1 - \sigma_j^2}$ is taken when $\mathbf{R}_j \cdot (\mathbf{e}_i \times \mathbf{e}_j) > 0$, and its negative value otherwise.

The total electrostatic force acting on the i th vertex is

$$\mathbf{F}_i^{\text{el}} = \sum_{j=0}^{N-1} (\mathbf{F}_{i,j}^{\text{el}} + \mathbf{F}_{i,j+1}^{\text{el}}) \quad (31)$$

The boundary conditions for the force expressions, Eqs. 12-31, are different for linear and circular chains. For a linear chain all parameters with indexes out of range do not exist and can be formally set to zero. The allowed ranges are: $0 \leq i \leq N-1$ for $\mathbf{F}_i^{\text{stretch}}$, $\mathbf{F}_i^{\text{bend}}$, $\mathbf{F}_i^{\text{twist}}$, \mathbf{F}_i^{el} , $\mathbf{F}_{i,i+1}^{\text{stretch}}$, $\mathbf{F}_{i,i+1}^{\text{bend}}$, $0 \leq i \leq N-1$, $0 \leq j \leq N-1$ for $\mathbf{F}_{i,j}^{\text{el}}$, $\mathbf{F}_{i,j+1}^{\text{el}}$. For a closed circular chain circular boundary conditions are in effect, such that all indices have to be taken modulo N .

Hydrodynamic interactions

In order to model hydrodynamic interactions defined between spherical objects, a bead with radius a was attached to each chain vertex. With $N' = N + 1$ beads for a linear and $N' = N$ beads for a circular chain, we describe the hydrodynamic interaction between beads i and j by a 3×3 Rosen-Prager tensor:

$$D_{ij} = D_0 \frac{3a^3}{4} \left[I + \frac{\eta_i \otimes \eta_j}{r_{ij}} + \frac{2a^2}{3r_{ij}^3} \left(I - 3 \frac{\eta_i \otimes \eta_j}{r_{ij}^2} \right) \right]$$

$$\text{if } r_{ij} \geq 2a, \quad i \neq j, \quad (32a)$$

$$D_{ij} = D_0 \left[\left(1 - \frac{9a^3}{32r_{ij}^3} \right) I + \frac{3}{32} \frac{\eta_i \otimes \eta_j}{r_{ij}} \right]$$

$$\text{if } r_{ij} \leq 2a, \quad i \neq j, \quad (32b)$$

$$D_{ij} = D_0 I \quad (32c)$$

where $\eta_i = \mathbf{r}_i - \mathbf{r}_j$, $r_{ij} = |\mathbf{r}_i - \mathbf{r}_j|$, $D_0 = k_B T / 6\pi \eta a$, η is the water viscosity, I is a unit 3×3 matrix, and $r \otimes r$ denotes a matrix with the components $(r_i r_j)$, $\alpha, \beta = x, y, z$.

The bead radius a is connected with the DNA hydrodynamic radius r_{HD} in the following way. Let us consider two

(a)

(b)

SHAKE

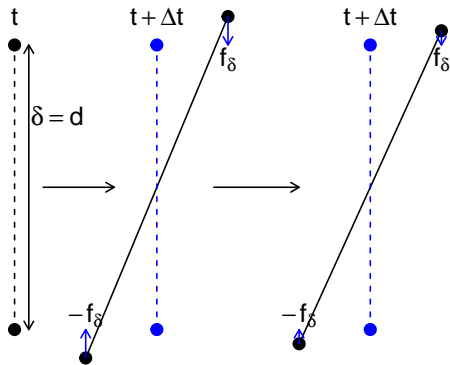


FIGURE: Vue schématique d'un algorithme type SHAKE.

Edberg & *al*, J. Chem. Phys. **84** (12), 15 June 1986

Forester & *al*, Journal of Computational Chemistry, Vol. 19, No. 1, 102-111 (1998)

Hess & *al*, Journal of Computational Chemistry, Vol. 18, No. 12, 1463-1472 (1997)

Ryckaert & *al*, Journal of Computational Physics **23**, 321-341 (1977)

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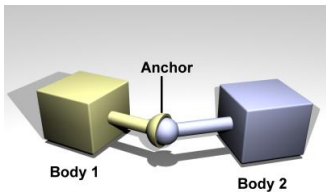
(a) Starcraft 2



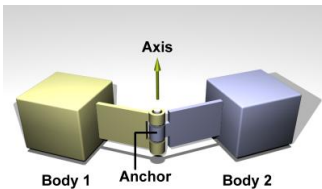
(b) Crysis 3

Joints mécaniques

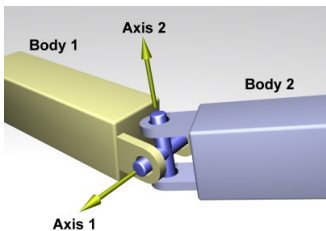
ODE is Copyright 2001-2004 Russell L. Smith. All rights reserved.



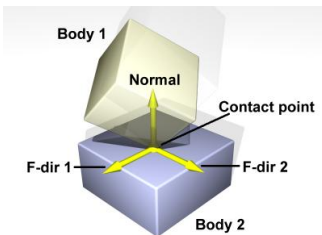
(a) Vue schématique d'un joint "Ball-in-Socket"



(b) Vue schématique d'un joint "Hinge"



(c) Vue schématique d'un joint de Cardan



(d) Vue schématique d'un joint de contact

Jointes mécaniques : formulation mathématique

- ▶ Équation de la dynamique d'un système de corps rigides

$$\begin{aligned}\mathcal{S} &= \{\mathbf{r}_1, \mathbf{q}_1 \dots \mathbf{r}_N, \mathbf{q}_N\}^T \\ \mathcal{V} &= \{\mathbf{v}_1, \boldsymbol{\omega}_1 \dots \mathbf{v}_N, \boldsymbol{\omega}_N\}^T \\ \mathcal{F}_e &= \{\mathbf{f}_1, \boldsymbol{\Gamma}_1 \dots \mathbf{f}_N, \boldsymbol{\Gamma}_N\}^T \\ \mathcal{M} &= \{\mathbf{m}_1, \mathcal{I}_1 \dots \mathbf{m}_N, \mathcal{I}_N\} \\ \dot{\mathcal{L}} &= \mathcal{F}_e \quad \text{avec} \quad \mathcal{L} = \mathcal{M}\mathcal{V}\end{aligned}$$

- ▶ Contrainte holonomique : $\delta(\mathcal{S}, t) = \mathbf{0}$ (jointes mécaniques)
- ▶ Contrainte cinématique : $\dot{\delta} = \mathcal{J}\mathcal{V} = 0$
- ▶ Torseur dynamique des contraintes $\mathcal{F}_c = \mathcal{J}^T \boldsymbol{\lambda}$, avec $\boldsymbol{\lambda}$ à calculer !
- ▶ Le torseur des contraintes ne travaille pas $\mathcal{F}_c^T \mathcal{V} = 0$!
- ▶ $\left[\mathcal{J}\mathcal{M}^{-1}\mathcal{J}^T + \frac{k_{\text{cfm}}}{\Delta t} \right] \boldsymbol{\lambda} = -\frac{k_{\text{erp}}}{\Delta t^2} \delta - \mathcal{J} \left[\frac{\mathcal{V}}{\Delta t} + \mathcal{M}^{-1} (\mathcal{F}_e - \dot{\mathcal{M}}\mathcal{V}) \right]$
- ▶ k_{erp} et k_{cfm} servent à contrôler la stabilité du système

Les différentes étapes de simulation

1. N cylindres de longueur $l = 3.34$ nm et de rayon effectif $r_{\text{eff}} = r_c + l_D$ (r_c représente le rayon cristallographique de l'ADN et l_D la longueur de Debye de la solution en sel) connectés par des joints "Ball-in-Socket"
2. Couples de courbure et de twist $\Gamma_{b+t} = g_b \mathbf{t}_1 \times \mathbf{t}_2 + \frac{g_t \phi}{1 + \cos \theta} (\mathbf{t}_1 + \mathbf{t}_2)$

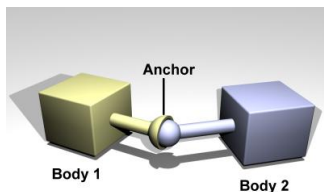


FIGURE: Vue schématique d'un joint "Ball-in-Socket"

3. Dynamique de Langevin-Euler locale de corps rigides $\mathcal{G} = -\Sigma \mathcal{L} + \Xi \dot{\mathcal{W}}$
4. ODE calcule les contraintes λ
5. Le système évolue du temps t au temps $t + \Delta t$ avec une intégration semi-implicite

Dynamique de Langevin-Euler avec un thermostat global (1)

Berendsen & al, J. Chem. Phys. 81 (8), 15 October 1984

Bussi & al, The Journal of Chemical Physics 126, 014101 (2007)

Bussi & al, Computer Physics Communications 179 (2008) 2629

- ▶ Thermostat global versus thermostat local
- ▶ Hamiltonien du système : $H(\mathbf{S}, \mathbf{V}) = T(\mathbf{v}) + R(\boldsymbol{\omega}) + U(\mathbf{S})$
- ▶ Distribution dans l'ensemble canonique : $P(\mathbf{S}, \mathcal{L}) d\mathbf{S}d\mathcal{L} \propto e^{-\beta H(\mathbf{S}, bsmcV)}$
- ▶ Vitesse de thermalisation de l'énergie cinétique :

$$\begin{aligned}dH &= \sum_{i=1}^{6N} \left[\left(\frac{\Sigma_{ii}^*}{\beta} - \frac{\Sigma_{ii}^*}{\mathcal{M}_{ii}^*} \mathcal{L}_i^{*2} \right) dt + \sqrt{\frac{2\Sigma_{ii}^* \mathcal{L}_i^{*2}}{\beta \mathcal{M}_{ii}^*}} d\mathcal{W}_i \right] \\ &= (\langle E \rangle - 2T) \Sigma_T^* dt + (\langle E \rangle - 2R) \Sigma_R^* dt + 2\sqrt{\frac{\Sigma_T^* T + \Sigma_R^* R}{\beta}} d\mathcal{W}\end{aligned}$$

- ▶ "Disturbance" $(\dot{\mathbf{L}} - \mathcal{F}_e)^T \mathcal{M}^{-1} (\dot{\mathbf{L}} - \mathcal{F}_e) = \mathbf{g}^T \mathcal{M}^{-1} \mathbf{g}$
- ▶ Dynamique de Langevin-Euler globale : $\tilde{\mathbf{g}} = \left[\Sigma^* \left[\frac{\langle E \rangle}{E} \left(1 - \frac{1}{2\beta \langle E \rangle} \right) - 1 \right] + \sqrt{\frac{\Sigma^*}{\beta E}} \dot{\mathcal{W}} \right] \mathcal{L}$
- ▶ $\tilde{\mathbf{g}}$ n'intervient pas dans le calcul du torseur des contraintes \mathcal{F}_c

Dynamique de Langevin-Euler avec un thermostat global (2)

Diffusion de la distance bout à bout d'une molécule d'ADN de longueur L :

$$\langle (\mathbf{R}(t + \tau) - \mathbf{R}(t))^2 \rangle = \langle \mathbf{R}^2(t + \tau) \rangle - 2 \langle \mathbf{R}^T(t + \tau) \mathbf{R}(t) \rangle + \langle \mathbf{R}^2(t) \rangle \quad (1)$$

Cas limite $\tau \gg \tau_{\text{deccorelation}}(\mathbf{R})$:

$$\langle (\mathbf{R}(t + \tau) - \mathbf{R}(t))^2 \rangle \simeq \langle \mathbf{R}^2(t + \tau) \rangle + \langle \mathbf{R}^2(t) \rangle = 4Lp \quad (2)$$

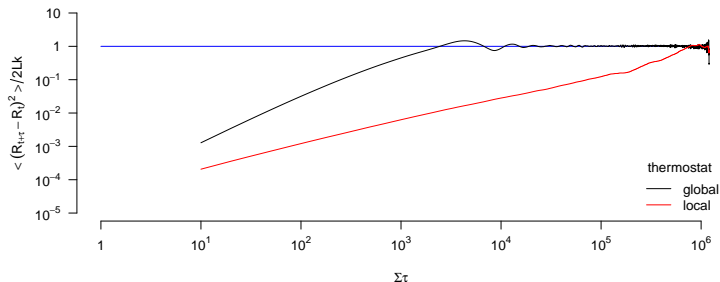


FIGURE: Diffusion de la distance bout à bout normalisée de la molécule d'ADN (en ordonnée) en fonction du temps adimensionné de simulation (en abscisse).

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Calibration de la longueur de persistance en courbure (1)

Corrélation tangentielle le long de la molécule d'ADN et validation des moyennes angulaires. Paramètres de la simulation $\rho = 50$ nm, $t = 95$ nm, et $L_{ADN} = 1$ μ m.

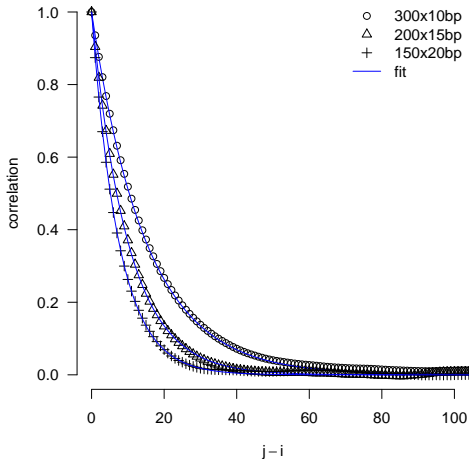


FIGURE: Corrélation tangentielle $\mathbf{t}_i^T \mathbf{t}_j = \exp -|j - i|/\rho$ (en ordonnée) le long de la molécule d'ADN (en abscisse).

Calibration de la longueur de persistance en courbure (2)

Molécule d'ADN sous force de traction. Paramètres de la simulation $p = 50$ nm, $t = 95$ nm, et $L_{ADN} = 1$ μ m.

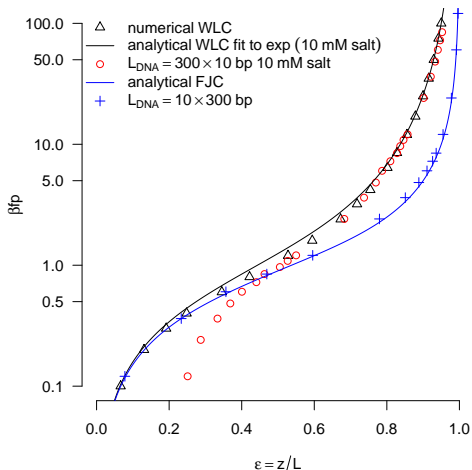


FIGURE: L'extension relative de la molécule d'ADN (en abscisse) est montrée en fonction de la force de traction adimensionnée (en ordonnée). Les résultats de simulations sont confrontés aux résultats expérimentaux de Bustamante 1992, Siggia 1995.

Vue schématique de plectonèmes à nombre de tours fixés obtenu avec ODE

Paramètres de la simulation $p = 50$ nm, $t = 95$ nm, $L_{ADN} = 1$ μ m, avec une force de traction $f = 0.74$ pN et un nombre de tour de bille magnétique $n = 15$.

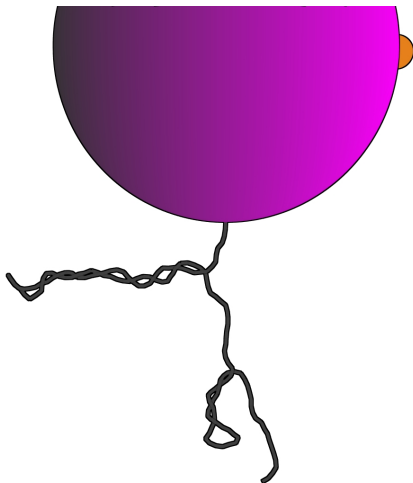


FIGURE: Vue schématique de plectonèmes à nombres de tours fixés (vidéo).

Calibration de la persistance en twist : simulation à nombre de tours fixé

Extension relative de la molécule d'ADN à nombre de tours de bille magnétique fixé. Paramètres des simulations $\rho = 50$ nm, $t = 95$ nm, $r_{\text{eff}} \simeq 2$ nm et $L_{\text{ADN}} = 1$ μm .

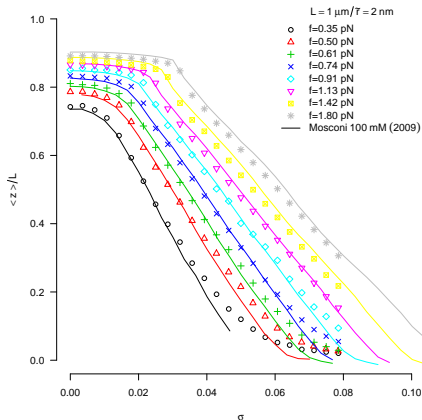


FIGURE: L'extension relative de la molécule d'ADN (en ordonnée) est montrée en fonction du nombre de tours de bille magnétique (en abscisse) pour une différentes forces de traction. Les symboles représentent les résultats de simulations et les lignes pleines représentent les résultats expérimentaux (Mosconi & al, PRL **102**, 078301 (2009) solution de 100 mM de sel).

Vue schématique de plectonèmes à couple fixé obtenu avec ODE

Paramètres de la simulation $p = 50$ nm, $t = 95$ nm, $L_{ADN} = 1$ μm , avec une force de traction $f = 0.74$ pN et un couple sur la bille magnétique $\Gamma_n = 15$ pN \cdot nm.

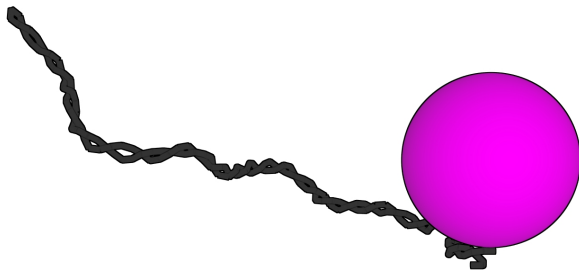
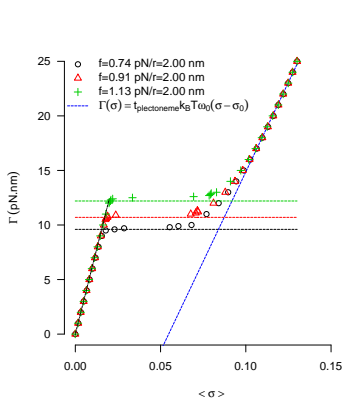


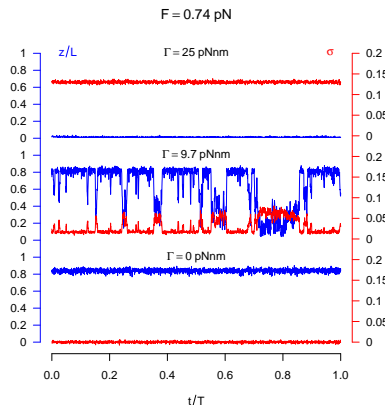
FIGURE: Vue schématique de plectonèmes à couple fixé (vidéo).

Calibration de la persistance en twist : simulation à couple fixé

Nombre de tours de la bille magnétique en fonction du couple appliqué. Paramètres des simulations $\rho = 50$ nm, $t = 95$ nm, $r_{\text{eff}} \simeq 2$ nm et $L_{\text{ADN}} = 1$ μm .



(a) L'overtwist (en abscisse) est montré en fonction du couple appliqué sur la bille magnétique. Les lignes en pointillées sont des estimations analytiques des couples de flambage (Mosconi & al PRL **102**, 078301 (2009)). Le couple est déduit des expériences à nombre de tours fixés (Zhang & al, PRE **77**, 031916 (2008)).



(b) L'overtwist (en rouge) et l'extension relative (en bleu) de la molécule d'ADN sont montrés (en ordonnée) en fonction du temps de simulation (en abscisse) et ce pour trois couples $\Gamma = 0, 9.7, 25$ pN \cdot nm et une force de traction $f = 0.74$ pN.

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(a) Configuration d'une molécule d'ADN



(b) Configuration d'une molécule d'ADN surenroulée



(c) 7 tétrasomes



(d) 4 nucléosomes

FIGURE: Vue schématique des deux différents mécanismes de compaction d'une molécule d'ADN de 900 bp.

Structural plasticity of single chromatin fibers revealed by torsional manipulation

Aurélien Bancaud¹, Natalia Conde e Silva², Maria Barbi³, Gaudeline Wagner¹, Jean-François Allemand⁴, Julien Mozziconacci³, Christophe Lavelle^{2,3}, Vincent Croquette⁴, Jean-Marc Victor³, Ariel Prunell² & Jean-Louis Viovy¹

Nucleosome Chiral Transition under Positive Torsional Stress in Single Chromatin Fibers

Aurélien Bancaud,^{1,7,8} Gaudeline Wagner,^{1,7} Natalia Conde e Silva,² Christophe Lavelle,^{2,3,4} Hua Wong,³ Julien Mozziconacci,³ Maria Barbi,³ Andrei Sivolob,⁵ Eric Le Cam,⁴ Liliane Mouawad,⁶ Jean-Louis Viovy,¹ Jean-Marc Victor,^{3,*} and Ariel Prunell^{2,*}

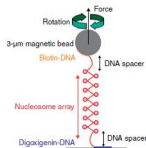
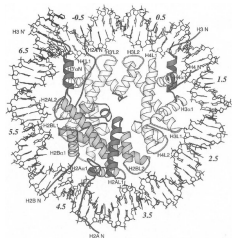


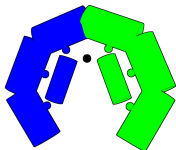
Figure 1 Schematic of the experiment. A single nucleosome array (~7.5 kbp), sandwiched between two naked DNA spacers (~600 bp each), is linked to a coated surface and to a magnetic bead. A pair of magnets placed above this molecule exerts controlled torsional and extensional constraints⁹.

Modèle gros-grain de nucléosome

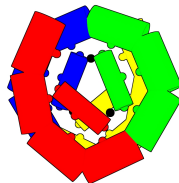
Analyse des modes normaux (J. Mozziconacci) et structuration mécanique (P. Carrivain et H. Wong)



(a) Nucléosome cristallographique Luger & *al*, Current Opinion in Structural Biology 1998, 8 :33-40



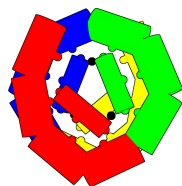
(b) Tétrosome



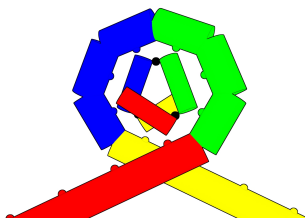
(c) Nucléosome

FIGURE: Vue schématique du modèle gros-grain de nucléosome construit à partir de la structure cristallographique. L'ADN nucléosomal est enroulé à gauche. Les dimères H2A-H2B sont représentés en rouge et jaune tandis que les dimères H3-H4 sont représentés en bleu et vert. Les sphères noires représentent les "Four-Helix-Bundle".

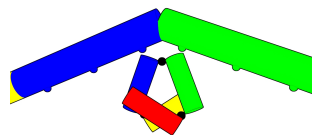
Nucléosome en traction



(a) Nucléosome fermé



(b) Nucléosome un tour de dégrafé



(c) Nucléosome deux tours de dégrafés

FIGURE: Vue schématique des trois états du nucléosome sous force de traction, modèle communément admis dans la littérature.

- ▶ Kruithof & *al*, Biophysical Journal Volume 96 May 2009 37083715
- ▶ Ettig & *al*, Biophysical Journal Volume 101 October 2011 19992008
- ▶ ...

Nucléosome en traction : données d'E. Praly

Avec D. Bensimon, V. Croquette, F. Ding, J. Mozziconacci, E. Praly et J-M. Victor

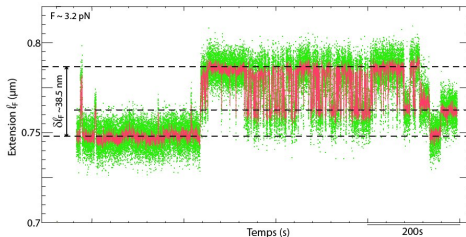


FIGURE 14.5 – Suivi de l'extension d'un substrat mononucléosomal insensible à la torsion, à force constante $\sim 3.2 \text{ pN}$, en fonction du temps. Les données brutes correspondent aux points verts ; un moyennage de ces données, sur 0.25 s, est donné en rouge.

FIGURE: Figure tirée de la thèse d'É. Praly (Étude du mécanisme d'action des facteurs de remodelage de la chromatine, à l'échelle de la molécule unique). Nous pouvons distinguer trois états d'extension associés à deux sauts de 12 nm puis 24 nm.

Nucléosome en traction : dégraissage symétrique de l'ADN

Avec D. Bensimon, V. Croquette, F. Ding, J. Mozziconacci, E. Praly et J-M. Victor

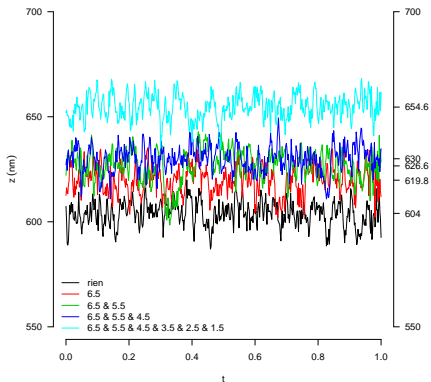


FIGURE: Schéma de dégraissage symétrique de l'ADN

Nucléosome en traction : dégraissage asymétrique de l'octamère (1)

Avec D. Bensimon, V. Croquette, F. Ding, J. Mozziconacci, E. Praly et J-M. Victor

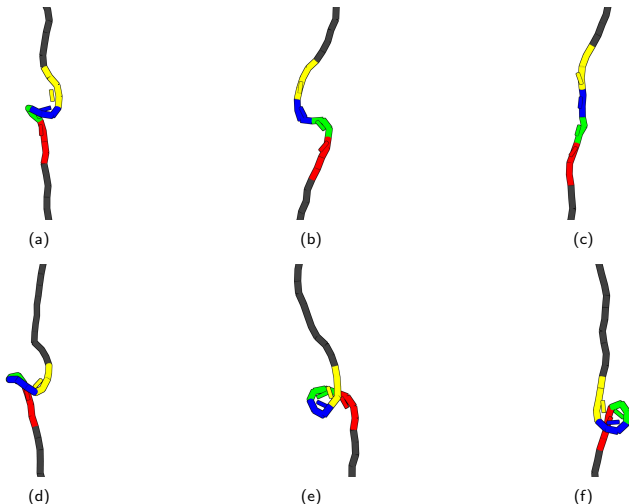


FIGURE: Ces images illustrent les différentes conformations accessibles au nucléosome pour un dégraissage asymétrique de l'octamère. La simulation est réalisée pour une force de traction de 3.2 pN et un couple nul $\Gamma = 0$.

Nucléosome en traction : dégraissage assymétrique de l'octamère (2)

Avec D. Bensimon, V. Croquette, F. Ding, J. Mozziconacci, E. Praly et J-M. Victor

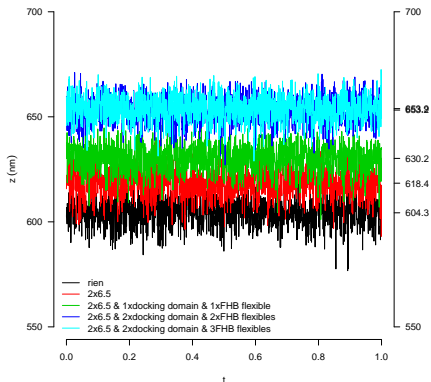


FIGURE: Schéma de dégraissage assymétrique de l'octamère. Deux sauts en extension de 12 nm et 23 nm.

Nucléosome en traction : modélisation dynamique

Avec D. Bensimon, V. Croquette, F. Ding, J. Mozziconacci, E. Praly et J-M. Victor

Modélisation des interactions avec des potentiels de Morse

Nucléosome sous une force de traction $f = 3.2$ pN et un couple de $\Gamma = 0$ pN · nm

Calcul de structure pour obtenir les interactions au sein du nucléosome

SHLs	D ($k_B T$)	a (nm^{-1})	r_e (nm)
± 6.5	2	3.46	0.20
± 5.5	10	0.80	0.87
± 4.5	15	0.51	1.35
± 3.5	20	0.78	0.89
± 2.5	15	0.85	0.81
± 1.5	15	0.62	1.12
± 0.5	20	0.85	0.81

(a) Paramètres pour les SHLs.

Interaction dimère-dimère	D ($k_B T$)	a (nm^{-1})	r_e (nm)
Docking Domain	5	0.69	1.00
Docking Domain	5	0.69	1.00
Four-Helix-Bundle	15	0.39	1.76
Four-Helix-Bundle	20	0.40	1.70
Four-Helix-Bundle	15	0.39	1.76

(b) Paramètres pour les DDs et FHBs.

FIGURE: Tableau récapitulatif des paramètres des potentiels de Morse utilisés pour reproduire les SHL, FHB et DD.

Nucléosome en traction et torsion

Avec D. Bensimon, V. Croquette, F. Ding, J. Mozziconacci, E. Praly et J-M. Victor

Réversible : nucléosome sous une force de traction $f = 3.2 \text{ pN}$ et un couple de $\Gamma = 25 \text{ pN} \cdot \text{nm}$

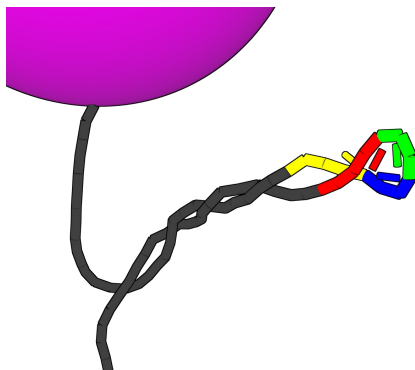
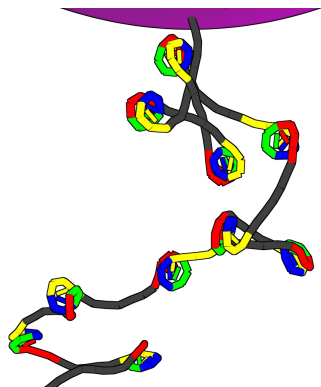


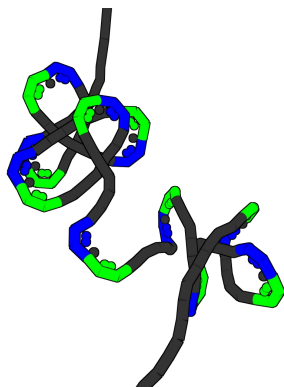
FIGURE: Vue schématique d'un réversible au milieu de plectonèmes : nucléosome sous une force de traction $f = 1 \text{ pN}$ et un couple de $\Gamma = 10 \text{ pN} \cdot \text{nm}$.

Réversible à l'intérieur d'une fibre de chromatine

Assemblages de nucléosomes et tétrasomes sous une force de traction de $f = 1$ pN et un couple $\Gamma = 10$ pN · nm

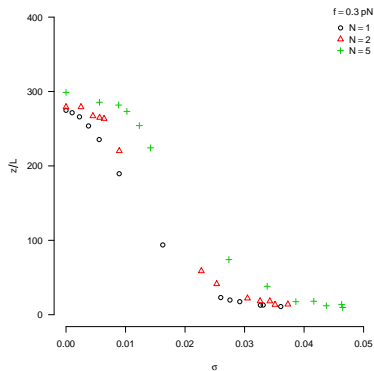


(a) Réversible à l'intérieur d'une fibre de chromatine

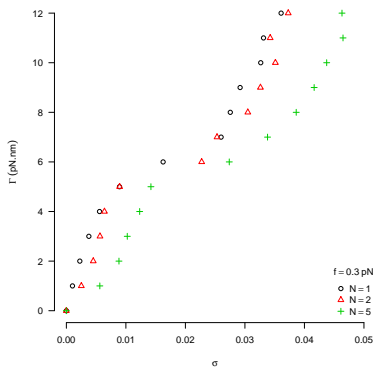


(b) Réversible à l'intérieur d'une "fibre" d'Archaea

Fibre de chromatine sous force de traction et couple appliqué sur la bille magnétique



(a) L'extension de la fibre de chromatine (avec 1, 2, 5 nucléosomes) est montrée en fonction du nombre de tours pour une force de traction $f = 0.3$ pN.



(b) Le couple appliqué sur la bille magnétique est montré en fonction du nombre de tours de la bille magnétique. Le couple de flambage est de l'ordre de $\Gamma_p = 6$ pN · nm

FIGURE:

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Comment compacter l'ADN ?

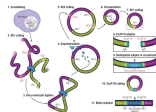
Pincettes magnétiques et fibre de chromatine

Nucleosome

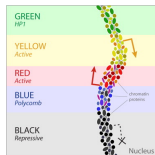
Conclusion et perspectives

Conclusion et perspectives

1. Nouvel outil pour la simulation de macromolécules : moteurs de jeux
2. Images des structures complexes telles que les fibres de chromatine sous contraintes
3. Finir le calcul de structure du nucléosome
4. Mesures de la diffusion des plectonèmes
5. Simulation du “crosslink” des expériences de HiC (Avec A. Cournac, J. Mozziconacci et J-M. Victor)



6. Simulation de fibre de chromatine inhomogène : les cinq couleurs de la chromatine chez la drosophile (Avec G. Cavalli et C. Vaillant)



7. Simulation des complexes de protéines “polycomb” et du noyau de drosophile (Avec G. Cavalli et C. Vaillant)