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The time duration for DNA thermal denaturation

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Abstract
Motivated by the thermal denaturation of DNA, we consider two interacting three-dimensional macromolecular chains, bound to each other, in a medium at thermal equilibrium from about room temperature up to about the melting one (T_m), at which they become unbound. We outline models for the non-equilibrium evolution of the double-stranded system, based upon the Smoluchowski equation, and allow for heterogeneities, excluded-volume effects and hydrodynamic interactions. A moment method leads us to approximate the Smoluchowski equation by a one-dimensional differential equation for the lowest order moment, containing a global effective potential between the two strands. We concentrate on the time duration (τ) required for thermal denaturation to occur, for long times and temperature $T \simeq T_m$. Here τ is approximated by the so-called mean first passage time (MFPT) for the relative separation of the centres of mass of the two chains. An approximate formula for the MFPT is obtained and employed for estimates. The consistency of the MFPT with experimental results is discussed for both Rouse and Zimm regimes.

1. Introduction

Denaturation of double-stranded DNA (dsDNA) is a very important phenomenon involving biological, chemical and physical features [1, 2]. Here, we shall treat one of its physical aspects, namely, thermal denaturation at temperature T_m, which has attracted extensive researches in the last decades [2–27]. Above thermal denaturation, three-dimensional dsDNA splits into two separate single three-dimensional chains (ssDNA). Although our main interest is dsDNA for temperature $T < T_m$, for a wider understanding, we shall also outline and refer to some properties of ssDNA below and above T_m. At thermal equilibrium, both dsDNA and ssDNA have known persistence lengths d_{ds} ($T < T_m$) [4, 9] and $d_{ss} < d_{ds}$ ($T > T_m$) [28–33], respectively, and they can be regarded as formed by certain effective monomers having lengths d_{ds} and d_{ss}. The dynamics of dsDNA and ssDNA inside a fluid (a 'solvent', at thermal equilibrium) and the influence of hydrodynamic interactions have been investigated experimentally [34, 35].

We shall focus on the time evolution of the double-stranded system, initially out of thermal equilibrium, inside a 'solvent' at thermal equilibrium at T, so as to analyse the characteristic time duration τ required for thermal denaturation of dsDNA (with total molecular weight M_{tot}) to occur at $T \simeq T_m$. Several models [36–41], with different interpretations, have yielded approximate expressions and/or estimates for τ displaying the behaviour: $\tau \propto M_{tot}^{\alpha}$, in terms of a constant exponent α (see Volkenshtein [2], section 7.5, for discussions and comments about various models). Early experiments aimed to measuring τ (also referred to as the characteristic time for unwinding or as the time required for strand separation), yielded values for α certainly smaller than the currently accepted value: $\alpha \simeq 2$. A comparative critical discussion about the former experiments on τ was presented by Spatz and Crothers [42]. A value $\alpha \simeq 2$ is quoted in [39]. Further experiments, measuring the time (τ) required for DNA to be converted to a state in which essentially complete unwinding occurs and the two strands become separated, have yielded successively $\alpha \simeq 2$ [43, 44] and α approximately 2 (specifically, compatible with $\alpha \simeq 2.3$) [42]. It is adequate to quote the following statements by Volkenshtein ([2], page 262) regarding the state of the subject by 1983: (1) 'Experiments show that τ is proportional to M_{tot}^2

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for a number of phage DNAs'. (2) '... the kinetics of the melting of DNA corresponds to an entire spectrum of times τ. The true theory of this phenomenon has not yet been worked out: serious difficulties are encountered in the investigation of the relation between the attainment of internal equilibrium and unwinding ...'. It seems adequate to revisit τ, to present an alternative approach to and a possible interpretation for it, different from those previously proposed [36–41], and to discuss possible relationships to the effective monomers in dsDNA and to the influence of hydrodynamic interactions on the dynamics of dsDNA and ssDNA, provided by the experiments mentioned above [34, 35]. We stress that τ refers to the melting of dsDNA as a whole, but not to that of specific sections of the double helix. We shall not treat the kinetics of different sections (several hundreds base pairs long) of dsDNA, which follow specific relaxation mechanisms with different relaxation times. They require procedures (specifically, equations typical of chemical kinetics, but not the Smolukowski equation) quite different from those to be employed here, and have been analysed thoroughly (see [45] and references therein).

This paper is organized as follows. Section 2 will summarize various features and simplifying assumptions for dsDNA and ssDNA. For large times, off-equilibrium dsDNA ($T < T_{\rm m}$) can also be regarded, by assumption, as formed by effective (statistically independent) monomers, similar to those for equilibrium. Section 3 outlines the off-equilibrium models in the discretized case. Section 4 describes the moment method and global effective potentials. In section 5, τ is approximated by some mean first passage time (MFPT) for the separation (y) of the centres of mass of the two strands, and presents approximate formulae and estimates for the MFPT. General studies on the MFPT are well documented [46–48]. By regarding y as a stochastic variable and for $T \simeq T_{\rm m}$, the MFPT is the average time elapsed until y leaves, for the first time, the domain for dsDNA towards the configuration of two separate ssDNAs at $T \simeq T_{\rm m}$. Section 6 contains the conclusions. Appendices A, B and C summarize justifications for sections 3 and 4.

2. Some general features and survey of approximations

2.1. Equilibrium: dsDNA ($T \leqslant T_m$)

We suppose that the region, inside which the strands move, is a sphere of very large radius R_0. In this section, we deal with three-dimensional dsDNA (say, B-DNA), at thermal equilibrium for T in an interval below and about $T_{\rm m}$. For B-DNA, $T_{\rm m} \simeq 360$ K. For $T < T_{\rm m}$ dsDNA is a bound system of two single three-dimensional ssDNAs. In turn, each ssDNA is formed by nucleotides, each of which includes a base, a sugar ring and a phosphate group [1, 2]. The masses of the four bases A, C, G and T differ from their average mass by less than 5, 13, 18 and 11%, respectively. We shall regard each ssDNA as a discretized chain formed by N ($\gg$1) nucleotides as basic units, all with equal mass M (the total mass of one single ssDNA being NM).

The most energetic degrees of freedom in ssDNA and dsDNA are the electronic ones. Next, there are the large covalent–bond interactions, with energies somewhat smaller than the (largest) electronic ones. Large covalent–bond interactions are responsible for the very existence of each ssDNA (either isolated or belonging to dsDNA) as a connected extended object, for a range of Ts appreciably (or much) larger than that from room temperature up to $T_{\rm m}$. The vibrations of individual nucleotides, subject to those large covalent–bond interaction, about their equilibrium positions along each ssDNA, yield essentially constant bond lengths d between successive nucleotides in each ssDNA [27]. We shall take $d \simeq 7.2$ Å, for each ssDNA in B-DNA. In the single (rth, $r = 1, 2$) strand, residual covalent–bond interactions $V_{\rm a}^{(r)}$, weaker than those yielding constant d, constrain rotational degrees of freedom and give rise to almost constant bond angles, the cosines of which are $\beta^{(0)}$ ($\simeq$0.8 for each ssDNA in B-DNA), consistently with the worm-like chain model. Constraints in macromolecules and the subsequent approximate simplification in their degrees of freedom play a crucial role, which continue to motivate active researches [49]. In this work, we shall treat $V_{\rm a}^{(r)}$ and other interactions (equation (3)) and the resulting statistical description of ssDNA and dsDNA through classical statistical mechanics. In each single ssDNA of dsDNA at thermal equilibrium, the $\beta^{(0)}$-constraining $V_{\rm a}^{(r)}$ lead to certain effective monomers (named e-monomers in this work), as natural molecular blocks on suitable medium and large length scales [27]. Each e-monomer is a single substrand of ssDNA formed by $n_{\rm e}$ nucleotides, and different e-monomers behave as statistically independent from one another, approximately. All e-monomers are assumed to have approximately the same effective length $d_{\rm e}$. Each ssDNA in dsDNA could be regarded as formed by $L(= (N-1)/n_{\rm e} \simeq N/n_{\rm e} \gg 1)$ e-monomers. We shall now discuss briefly $n_{\rm e}$ and $d_{\rm e}$, by following appendix D of [27]. Let $\mathbf{z}_l^{(r)}$ be the vector from the origin up to the end of the lth e-monomer, $l = 1, \ldots, L$: the components of $\mathbf{z}_l^{(r)}$ are $(\mathbf{z}_l^{(r)})_\alpha$, $\alpha = 1, 2, 3$. The statistical average of $\mathbf{z}_l^{(r)2}$ equals [50] $d_{\rm e}^2 + n_{\rm e} d^2 x_d$, with:

$$d_{\rm e} = d n_{\rm e}^{1/2} \left[\frac{1+\beta^{(0)}}{1-\beta^{(0)}}\right]^{1/2}, \tag{1}$$

$$x_d = -\frac{2\beta^{(0)}}{n_{\rm e}} \frac{1-\beta^{(0)n_{\rm e}}}{(1-\beta^{(0)})^2}. \tag{2}$$

Different e-monomers in the rth strand can be regarded approximately as statistically independent if $n_{\rm e} {\rm d}^2 x_d$ can be neglected compared to $d_{\rm e}^2$. We shall suppose that $d_{\rm e}^2$ is adequately larger than $n_{\rm e} d^2 x_d$, so that such statistical independence holds approximately. In such a case, the following standard property holds: the statistical average of the product $(\mathbf{z}_l^{(r)})_\alpha (\mathbf{z}_{l'}^{(r)})_{\alpha'}$ equals, approximately, $3^{-1} d_{\rm e}^2 \delta_{l,l'} \delta_{\alpha,\alpha'}$, the δs being the Kronecker ones. Then, for given $d = 0.72$ nm and $\beta^{(0)} \simeq 0.8$ for B-DNA, equations (1) and (2) and the assumption that $d_{\rm e}^2$ be adequately larger than $n_{\rm e} {\rm d}^2 x_d$ allow to assess reasonable ranges for both $n_{\rm e}$ and $d_{\rm e}$ for an e-monomer in each ssDNA of dsDNA. Lower limits of those ranges are about $n_{\rm e} = 20$, $d_{\rm e} \simeq 10$ nm. The upper limits of those ranges are relatively close (although, strictly, still exclude)

values corresponding to the persistence length $d_{\rm ds} \simeq 50$ nm (corresponding to 150 nucleotides) for dsDNA. In fact, $n_{\rm e} = 150$ and $d_{\rm e} \simeq 50$ nm do belong to the physically allowed ranges and are close to their upper limits, provided that $d = 0.72$ and $\beta^{(0)} \simeq 0.94$ (instead of $\beta^{(0)} \simeq 0.8$). In [27], $n_{\rm e}$ and $d_{\rm e}$ were chosen relatively close to the lower limits. In this work, we shall be less restrictive and allow for $n_{\rm e}$ and $d_{\rm e}$ to take on, in principle, any values in those ranges, even close to the upper limits (say, relatively close to $d_{\rm ds}$).

All e-monomers in dsDNA are subject to additional effective residual intra-chain and inter-chain interactions (weaker than all covalent ones). These additional interactions will be described by an effective potential V (equation (3)) among the e-monomers with length $d_{\rm e}$, in the domain of validity of Gaussian and long-distance approximations [27]. Typical potential energies of the A–T pair are appreciably smaller in absolute value than those of the C–G pair: such heterogeneities should be taken into account in the effective potential V among the e-monomers in dsDNA. The important role played by heterogeneities on the cooperative melting of DNA sections (several hundred base pairs long) has been demonstrated [45]. Heterogeneities played an important role in [20, 26]. In connection with that, see [51] for the relevance of disorder (without excluded-volume interactions). V includes three effective interactions [27]: (a) between all pairs of (complementary or mate) e-monomers at the same positions in the different chains (V_0), (b) between different e-monomers in the same chain ($\sum_{r=1}^{2} V_1^{(r)}$), self-interactions of one e-monomer with itself being also included, (c) between pairs of e-monomers at unequal or non-complementary positions in the different chains (V_2). (a), (b) and (c) should be repulsive for short distances. (b) and (c) take care of stacking interactions, which play a role in thermal denaturation [19]. (a) and, eventually, (c) give rise to attraction at intermediate and large distances. In the rth chain, $r = 1, 2$, $\mathbf{R}_l^{(r)}$ and $\mathbf{R}_{l+1}^{(r)}$ will represent the three-dimensional position vectors of the origin and the end of the lth e-monomer, $l = 1, \ldots, L$. We shall suppose that:

$$V = V_0 + \sum_{r=1}^{2} V_1^{(r)} + V_2, \tag{3}$$

$$V_0 = \sum_{l=1}^{L+1} v_{0,l}(|\mathbf{R}_l^{(1)} - \mathbf{R}_l^{(2)}|), \tag{4}$$

$$V_1^{(r)} = \sum_{l=1}^{L+1} \sum_{n=0}^{n_1} v_{1;l,n}(|\mathbf{R}_{l+n}^{(r)} - \mathbf{R}_l^{(r)}|), \tag{5}$$

$$V_2 = \sum_{l=1}^{L} \sum_{n=1}^{n_2} \Big[v_{2;12;l,n}(|\mathbf{R}_{l+n}^{(1)} - \mathbf{R}_l^{(2)}|) + v_{2;21;l,n}(|\mathbf{R}_{l+n}^{(2)} - \mathbf{R}_l^{(1)}|) \Big], \tag{6}$$

with integers n_1 and n_2 ($n_2 \ll L$), $v_{1;l,n} = 0$ if $l + n > L + 1$ while $v_{2;12;l,n} = 0$ and $v_{2;21;l,n} = 0$ if $l + n > L + 1$. All vs are positive for short distances ($\leqslant d_{\rm e}$). For instance, $v_{0,l}$ could be modelled by a Morse potential. The dependences of $v_{0,l}$, $v_{1;l,n}$, $v_{2;12;l,n}$ and $v_{2;21;l,n}$ on their corresponding subscripts account for the heterogeneities arising from the (A–T) versus (G–C) interactions. To describe those heterogeneities requires to have information on the sequences of nucleotides along dsDNA: to handle such information and to extract reliable consequences from it is not easy. It has been argued that excluded-volume effects in dsDNA could be disregarded in various ambient conditions (not only in 'θ' conditions): see section 4.1 in [9]. On the other hand, several aspects of excluded-volume effects in dsDNA have been investigated [52–57]. In this work, we shall allow for excluded-volume effects in V, mostly in $\sum_{r=1}^{2} V_1^{(r)}$ (as n_1 is not $\ll L$). Detailed information on heterogeneities and stacking in V will play no role in order to estimate roughly the dsDNA time duration τ, as we shall see. Electrical conductivity in DNA is another interesting phenomenon, actively investigated (see [58, 59] and references therein). The DNA models considered in this work will not include electrical conductivity effects.

Different choices for the e-monomers (and, hence, for $d_{\rm e}$) would yield somewhat different Vs. The model considered in this work makes sense in a range of Ts up to $T_{\rm m}$. The additional residual intra-chain and inter-chain interactions modelled by V lead to regard dsDNA also as formed by certain effective monomers (specifically referred to as ds-monomers), statistically independent of one another [4, 9]. A ds-monomer has persistence length $d_{\rm ds}$, is formed by two substrands of nucleotides and should not be confused with the single-strand e-monomers, with length $d_{\rm e}$. For B-DNA, a ds-monomer has $d_{\rm ds} \simeq 50$ nm (or, equivalently, a Kuhn length about 100 nm) and about 150 nucleotides [4, 9]: these are relatively close to the numerical values of the upper limits of the physically allowed ranges for $d_{\rm e}$ and $n_{\rm e}$ for e-monomers, as commented above.

The classical partition function Z_2 for the three-dimensional discretized dsDNA at thermal equilibrium in $T \leqslant T_{\rm m}$ reads, by including the CM contribution (and correcting some misprints) in [27]:

$$Z_2 = \left[\frac{K_{\rm B}T}{2\pi\hbar^2}\right]^{2(N-1)} \left[\frac{MNK_{\rm B}T}{4\pi\hbar^2}\frac{M_{\rm tot}K_{\rm B}T}{2\pi\hbar^2}\right]^{3/2} \times \frac{4\pi R_0^3 d^{4(N-1)} Z}{3(N/M^{N-1})^3} \prod_{r=1}^{2} Z_R^{(r)}, \tag{7}$$

where

$$Z = \left[\frac{4\pi R_0^3}{3}\right]^{-1} \int \left[\prod_{r=1}^{2}\prod_{l'=1}^{L+1} {\rm d}^3\mathbf{R}_{l'}^{(r)}\right] W_{\rm eq}, \tag{8}$$

$$W_{\rm eq} = \left[\prod_{r=1}^{2}\prod_{l=1}^{L} W_{\rm G}(\mathbf{R}_{l+1}^{(r)} - \mathbf{R}_l^{(r)}; 2d_{\rm e}^2)\right] \exp[-(K_{\rm B}T)^{-1}V], \tag{9}$$

$$W_{\rm G}(\mathbf{R}_{l+1}^{(r)} - \mathbf{R}_l^{(r)}; 2d_{\rm e}^2) = \left[\frac{3}{2\pi d_{\rm e}^2}\right]^{3/2} \times \exp[-3(\mathbf{R}_{l+1}^{(r)} - \mathbf{R}_l^{(r)})^2/(2d_{\rm e}^2)], \tag{10}$$

$K_{\rm B}$ is Boltzmann's constant and $M_{\rm tot} = 2MN$ is the total mass of dsDNA. $Z_R^{(r)}$, given by equations (C.4) and (C.2) in [27], are T-independent and will not be relevant here. $W_{\rm G}$ denotes the Gaussian distribution for the lth e-monomer in the rth strand.

2.2. Equilibrium: ssDNA ($T > T_m$)

Above denaturation ($T > T_{\rm m}$), the residual intra-chain and inter-chain interactions become negligible ($V \simeq 0$) and dsDNA becomes two separate ssDNAs. No covalent bonds in DNA (thermal) denaturation are broken (p 342 in [1]), provided that, as we assume here, T ($>T_{\rm m}$) be not too high. It seems natural that the electronic and the large covalent–bond interactions continue to be as effective in each separate ssDNA as in dsDNA, and yield the same constant bond lengths $d \simeq 7.2$ Å in each separate ssDNA (for B-DNA). The weaker residual covalent–bond interactions $V_{\rm a}^{(r)}$ also persist in each separate ssDNA and, so, give rise in them to constant bond angles, with cosines $\beta_{\rm ss}^{(0)}$, and to effective monomers (ss-monomers) with length $d_{\rm ss}$, statistically independent on one another. A physical question is whether such residual covalent–bond interactions in each separate ssDNA equal those in the ssDNAs bound in dsDNA, so that $\beta_{\rm ss}^{(0)}$ and $d_{\rm ss}$ for ssDNA equal, respectively, $\beta^{(0)}$ and $d_{\rm e}$ for dsDNA, or not. $d_{\rm ss}$ has been experimentally measured [28–33]. A value $d_{\rm ss} \simeq d \simeq 0.7$ nm has been reported [29], although other measurements yielded values in the range 1.5 nm $\leqslant d_{\rm ss} \leqslant$ 3 nm [28, 30–33]. We shall accept that $d_{\rm ss}$ is about 2 nm, as a reasonable choice between two extreme possibilities. Then, $d_{\rm ss} > d$ seems to confirm the existence of residual covalent interactions constraining bond angles $\beta_{\rm ss}^{(0)}$ in each separate ssDNA [1, 27]. However, $d_{\rm ss} < d_{\rm e}$ also appears to indicate that, in reality, those residual covalent interactions in each separate ssDNA differ somewhat from those in ssDNAs bound in dsDNA, as a consequence of the denaturation transition at $T_{\rm m}$. In [27], it was assumed that those residual covalent interactions were much the same in separate ssDNAs and in ssDNAs bound in dsDNA and, hence, that $d_{\rm ss} = d_{\rm e}$. Each ss-monomer is a single strand formed by $n_{\rm ss}$ nucleotides. Then, each separate ssDNA could be regarded as formed by $L_{\rm ss}(= (N-1)/n_{\rm ss} \simeq N/n_{\rm ss} \gg 1)$ ss-monomers. We shall discuss $n_{\rm ss}$ and $\beta_{\rm ss}^{(0)}$, by replacing, in equations (1) and (2), $d_{\rm e}$, $n_{\rm e}$ and $\beta^{(0)}$ by $d_{\rm ss}$, $n_{\rm ss}$ and $\beta_{\rm ss}^{(0)}$, respectively. For given $d \simeq 0.7$ nm and $d_{\rm ss} \simeq 2$ nm, we also use equations (1) and (2). Then, the criterion that different ss-monomers are statistically independent approximately ($d_{\rm ss}^2$ being adequately larger than $n_{\rm ss} d^2 x_d$) allow to assess reasonable ranges for both $n_{\rm ss}$ and $\beta_{\rm ss}^{(0)}$. One possible choice is $n_{\rm ss} = 3$, $\beta_{\rm ss}^{(0)} \simeq 0.7$. One would also expect some effective potential (including excluded-volume effects) for each separate ssDNA, qualitatively similar to one of the $V_1^{(r)}$s in equation (5): however, such effective potential for each separate ssDNA should be quantitatively different from the $V_1^{(r)}$s in ssDNAs bound in dsDNA, as a consequence of the denaturation transition at $T_{\rm m}$.

2.3. Non-equilibrium

As typical Brownian particles are usually larger and more massive than the molecules forming the liquid (the 'solvent') inside which the former evolve, the resulting approximate physical picture is understood [60–62]. That picture should also apply, plausibly, for macromolecules (having nucleotides as molecular subunits) in 'solvents', as we shall outline below. Leaving aside phosphate groups and sugar rings, the masses of A, C, G and T (in units of the hydrogen mass) are, roughly, 135, 111, 151 and 114, respectively, while the mass of a molecule of water (the 'solvent') is about 18. The motions of the macromolecular subunits are considered for temporal and spatial scales much larger than those characterizing the 'fast' microscopic motions of the 'solvent' molecules. Then, the 'solvent' would behave effectively as having relaxed to a state of approximate thermal equilibrium at absolute temperature T, much quicker than the macromolecular subunits (adiabatic approximation). On those scales, the 'solvent' behaves as an environment at thermal equilibrium producing friction on (and, possibly, mediating interactions in) the macromolecule. A typical macromolecular subunit would collide with many fluid molecules during temporal intervals in which the position of that subunit would not change appreciably. Then, the distributions of the momenta of those macromolecular subunits, due to their interactions with the 'solvent', would relax approximately to thermal equilibrium on suitable temporal and spatial scales more quickly than the distributions of their positions: those expectations would be in contrast with the behaviour of a dilute gas, where the momentum of a generic particle relaxes to equilibrium only by collisions with other particles in the gas.

Next, we turn to dsDNA as a non-equilibrium system, at T in an interval $\leqslant T_{\rm m}$, with the same internal interactions as at equilibrium, and immersed in a 'solvent'. Plausibly, in the time evolution and, at least for suitably large spatial scales and times, the two-chain system can also be regarded as formed by e-monomers of length $d_{\rm e}$, similar to those for equilibrium, which are also approximately statistically independent from one another, and subject to the same interactions (say, equation (3)). The remarks in the previous paragraph in this section also hold if those macromolecular subunits are the e-monomers. The 'solvent', at thermal equilibrium, should also produce friction on the individual momenta of the e-monomers with length $d_{\rm e}$ of each chain, and could mediate additional hydrodynamic interactions among e-monomers in each single strand. Thus, the accepted wisdom of the Rouse and Zimm models for one chain, as summarized in [63–65], will be extended directly to dsDNA in section 3.

3. Non-equilibrium Smoluchowski equations for dsDNA

Smoluchowski equations for single macromolecules, regarded as many-Brownian-particle systems, are well documented [60–66]. dsDNA, off-equilibrium at the initial time $t = 0$, evolves towards thermal equilibrium at $T \leqslant T_{\rm m}$, for long time t. Let $H_{l,l'}^{(r)}$ account for friction effects on the lth and the l'th e-monomers in the rth strand due to the 'solvent', and allow for hydrodynamic interactions between those e-monomers, mediated by the 'solvent'. The matrix formed by all $H_{l,l'}^{(r)}$, $l, l' = 1, \ldots, L+1$ ($L+1$ being included as $L \gg 1$), is assumed to be Hermitian and positive definite. Let $[\mathbf{R}]$ denote the set of all $\mathbf{R}_l^{(r)}$ ($r = 1, 2$ and $l = 1, \ldots, L+1$), and let $W = W([\mathbf{R}]; t)$ be the probability distribution for an arbitrary configuration of the effective e-monomers in dsDNA,

at $0 \leqslant t < +\infty$. By extending directly single-strand equations (for instance, equation (4.1) in [63]), using d_e as effective length for any e-monomer in ssDNAs and the same V as in equation (3), W fulfils the Smoluchowski equation for dsDNA ($T \leqslant T_m$):

$$\frac{\partial W}{\partial t} = SW, \tag{11}$$

$$SW = K_B T \sum_{r=1}^{2} \sum_{l,l'=1}^{L+1} \nabla_{\mathbf{R}_l^{(r)'}} H_{l,l'}^{(r)} \times \left\{ \nabla_{\mathbf{R}_{l'}^{(r)'}} W + W \nabla_{\mathbf{R}_{l'}^{(r)'}} \left[\frac{3}{2d_e^2} \sum_{s=1}^{2} \sum_{l''=1}^{L} \times (\mathbf{R}_{l''+1}^{(s)'} - \mathbf{R}_{l''}^{(s)'})^2 + \frac{V}{K_B T} \right] \right\}. \tag{12}$$

A justification of equations (11) and (12) is outlined in appendix A. In the rth chain, $r = 1, 2$, let $\mathbf{z}_l^{(r)} = \mathbf{R}_{l+1}^{(r)} - \mathbf{R}_l^{(r)}$ correspond to the lth effective e-monomer, $l = 1, \ldots, L$. $[\mathbf{z}]$ will denote the set of all $\mathbf{z}_l^{(r)}$. Also, let $\mathbf{R}_{CM}$ denote the centre of mass (CM) of both chains and let $\mathbf{y}$ be the relative position vector of the centres of mass of the two chains. $y = |\mathbf{y}|$ can be regarded, in the framework of chemical kinetics, as the 'reaction coordinate'. One has:

$$\mathbf{R}_l^{(r)} = \mathbf{R}_{CM} + (-1)^r \mathbf{y}/2 + \sum_{l'=1}^{L} \alpha_{l,l'}^{(r)} \mathbf{z}_{l'}^{(r)}. \tag{13}$$

For $l = 1, \ldots, L$, $\alpha_{l,l'}^{(r)} = L^{-1} l'$ and $-L^{-1}(L - l')$, for $l' = 1, \ldots, l-1$ and $l' = l, \ldots, L$, respectively. Also, $\alpha_{L+1,l'}^{(r)} = L^{-1} l'$, for $l' = 1, \ldots, L$. Upon replacing all $\mathbf{R}_l^{(r)}$s by $\mathbf{R}_{CM}$, $\mathbf{y}$ and $[\mathbf{z}]$ using equation (13), SW becomes:

$$SW = K_B T \frac{1}{4L^2} H_{hyd} \nabla_{\mathbf{R}_{CM}}^2 W + S_{in} W, \tag{14}$$

The constant $H_{hyd} = \sum_{r=1}^{2} \sum_{l,l'=1}^{L+1} H_{l,l'}^{(r)} (> 0)$ accounts for both friction and possible hydrodynamic interactions, due to the 'solvent', on the CM of the bound two-chain system and on $\mathbf{y}$, as equation (17) for $S_{in} W$ will display. We factor out the CM evolution: $W = W_{CM}(\mathbf{R}_{CM}; t) W_{in}$. Equation (14) yields:

$$\frac{\partial W_{CM}}{\partial t} = K_B T \frac{1}{4L^2} H_{hyd} \nabla_{\mathbf{R}_{CM}}^2 W_{CM}. \tag{15}$$

The equilibrium solution $W_{CM,eq}$ of equation (15) equals a constant. Equation (15) displays the relaxation of the CM of dsDNA towards thermal equilibrium (its solution W_{CM} approaches $W_{CM,eq}$ as $t \to +\infty$). Such a relaxation is similar to those in the Rouse and Zimm models for one single strand [63]. On the other hand, $W_{in} = W_{in}(\mathbf{y}, [\mathbf{z}]; t)$ and:

$$\frac{\partial W_{in}}{\partial t} = S_{in} W_{in}, \tag{16}$$

$$S_{in} W_{in} = K_B T \frac{1}{L^2} H_{hyd} \nabla_{\mathbf{y}} \left[\nabla_{\mathbf{y}} W_{in} + W_{in} \frac{1}{K_B T} \nabla_{\mathbf{y}} V \right] + K_B T \sum_{r=1}^{2} \sum_{l,l'=1}^{L+1} [\nabla_{\mathbf{z}_{l-1}^{(r)}} - \nabla_{\mathbf{z}_l^{(r)}}] H_{l,l'}^{(r)} \left[(\nabla_{\mathbf{z}_{l'-1}^{(r)}} - \nabla_{\mathbf{z}_{l'}^{(r)}}) W_{in} + W_{in} (\nabla_{\mathbf{z}_{l'-1}^{(r)}} - \nabla_{\mathbf{z}_{l'}^{(r)}}) \left(\frac{3}{2d_e^2} \sum_{s=1}^{2} \sum_{l''=1}^{L} (\mathbf{z}_{l''}^{(r)})^2 + \frac{V}{K_B T} \right) \right], \tag{17}$$

with $\nabla_{\mathbf{z}_0^{(r)}} \equiv 0$, $\nabla_{\mathbf{z}_{L+1}^{(r)}} \equiv 0$. V (equations (3)–(6)) is expressed in terms of $\mathbf{y}$ and $[\mathbf{z}]$. The equilibrium distribution for equations (16) and (17) is W_{eq}, given in equation (9) (recast in terms of $\mathbf{y}$ and $[\mathbf{z}]$). Equation (16) displays relaxation towards thermal equilibrium (its solution W_{in} approaches W_{eq} as $t \to +\infty$). A direct analysis of equation (16), in order to estimate the dsDNA time duration τ is rather difficult. In fact, the normal modes for each separate ssDNA (which would facilitate the analysis) are not easy to handle.

For both Rouse and Zimm regimes, we set: $(4L^2)^{-1} H_{hyd} = (2L\zeta_0)^{-1}$. The Rouse regime (inclusion of friction but neglect of hydrodynamic interactions) corresponds to $H_{l,l'}^{(r)} = \delta_{l,l'}/\zeta$, $\zeta (> 0)$ and $\delta_{l,l'}$ being the friction coefficient and the Kronecker symbol, respectively. The Stokes formula gives: $\zeta = 6\pi\eta\beta d_e$, η being the viscosity of the 'solvent'. The dimensionless quantity β depends on the models for the friction due to the 'solvent': we take $0.1 \leqslant \beta \leqslant 1$, to cover different models. For the Rouse model, one has $\zeta_0 = \zeta$. The Zimm regime includes both friction and hydrodynamic interactions [63–65]. Since both the CM and the $\mathbf{y}$ dependences refer to large scales, it may be not unreasonable to approximate $\frac{1}{4L^2} H_{hyd}$ for the Zimm model by its continuum approximation (this is, in practice, our only use of the continuum approximation: otherwise, we consider only discretized chains throughout this work). Moreover, for the Zimm model, we treat the hydrodynamic interaction among e-monomers in preaveraging approximation [63]. Under 'θ' conditions, $\zeta_0 = (3/8)(6\pi^3)^{1/2} \eta d_e L^{-1/2}$ [63], η being also the viscosity of the 'solvent'. For a 'good solvent', and including excluded-volume effects, $\zeta_0 = \eta d_e L^{\nu-1}$, $\nu (= 3/5)$ being the standard excluded-volume exponent.

For $T > T_m$, ssDNA has a different structure, as discussed in section 2.2. ssDNA off-equilibrium can be described through a standard single-chain Smoluchowski equation [60–66] with its characteristic d_{ss} (in principle, for either Rouse or Zimm regimes). That ssDNA Smoluchowski equation would include some effective potential, similar to (but not identical with) $V_1^{(r)}$ in equation (5), to account for excluded-volume effects, as commented at the end of section 2.2.

The relaxation dynamics of an elongated DNA molecule, with one of its end point fixed by optical tweezers and subject to a uniform flow, has been measured [34]. The results seemed more consistent with the Zimm model than with the Rouse one, but with an exponent of L indicating excluded-volume effects smaller than usual (attributed to electrostatic repulsion inside DNA [64]). On the other hand, in [35] the kinetics of random motion of suitable macromolecular subunits in dsDNA and ssDNA have been studied experimentally, and the results have been analysed in the framework of the continuum approximation. In particular, for dsDNA those subunits were the ds-monomers, characterized by the Kuhn length $2d_{ds} \simeq 100$ nm. It was found [35] that: 'While Zimm-type kinetics for ssDNA corresponds to the common view on polymer dynamics and, thus, could have been expected, the Rouse regime observed for dsDNA is puzzling. The fact that the hydrodynamic interactions are negligible over a wide range of monomer motion in dsDNA is apparently related to dsDNA semiflexibility. A large Kuhn length means that the distances

between segments are relatively large and, respectively, the hydrodynamic interactions between them are weak'. The relatively large separations among effective ds-monomers for dsDNA could be due to the repulsive phosphate interactions.

4. A moment method for the dsDNA Smolukowski equation

4.1. Global effective potentials for dsDNA ($T \leqslant T_m$)

Let $y = |\mathbf{y}|$. For homogeneous dsDNA at thermal equilibrium, a global effective y-dependent potential between the two strands has been introduced [27], by integrating over $[\mathbf{z}]$. Unexpectedly, the global effective potential idea (extended for heterogeneous dsDNA) will turn out to be certainly quite useful off-equilibrium, in order to approximate in equations (11) and (12) and to estimate the dsDNA time duration τ, as we shall see. Let $[\mathrm{d}\mathbf{z}] \equiv \prod_{r=1}^{2}(\prod_{l'=1}^{L} \mathrm{d}^3\mathbf{z}_{l'}^{(r)})$. With W_{eq} given in equation (9), one defines the exact global effective potential $V_{\mathrm{g}} = V_{\mathrm{g}}(y)$ for heterogeneous dsDNA as:

$$\int [\mathrm{d}\mathbf{z}] W_{\mathrm{eq}} = \exp[-(K_{\mathrm{B}}T)^{-1} V_{\mathrm{g}}(y)]. \tag{18}$$

Due to rotational invariance, $V_{\mathrm{g}}(y)$ is independent on the direction of $\mathbf{y}$. The dependence of $V_{\mathrm{g}}(y)$ on y is due to V_0 and V_2. For $y \to +\infty$, $V_{\mathrm{g}}(y)$ does not tend to zero but to some $V_{\mathrm{g}}(\infty) \neq 0$, due to the contribution of $\sum_{r=1}^{2} V_1^{(r)}$. $V_{\mathrm{g}}(y) - V_{\mathrm{g}}(\infty)$ can be expected: (i) to be positive for $y = 0$ and for small y up to some y_1, (ii) to be negative and large for an interval of intermediate values of y, from about y_1, up to some y_2, appreciably larger than d_{e}, (iii) to increase quite appreciably, being always negative, as y increases in $y_2 \leqslant y \leqslant y_3$ (y_3 being adequately or much larger than y_2), and (iv) to be entirely negligible for $y > y_3$. Then (leaving perhaps aside the transition region from small to intermediate y) the shape of $V_{\mathrm{g}}(y) - V_{\mathrm{g}}(\infty)$ appears to be, quite naturally and rather roughly, Morse-like. An upper bound $\langle V\rangle = \langle V\rangle(y)$ has been obtained for $V_{\mathrm{g}}(y)$ in appendix B. $\langle V\rangle$ is the global effective potential, which extends the one introduced in [27] for the actual heterogeneous dsDNA. We shall accept that $\langle V\rangle$ describes the global behaviour of $V_{\mathrm{g}}(y)$ for intermediate and large y, at least qualitatively: this will suffice in order to estimate the time duration, as we shall see in section 5,

Approximate bounds for $\langle V\rangle(y)$ for intermediate and large y read:

$$\sum_i \frac{v'_{i,-}}{L^{1/2}} \exp\left[-\frac{b_i y^2}{2Ld_{\mathrm{e}}^2}\right] \simeq \langle V\rangle - \sum_{r=1}^{2}\langle V_1^{(r)}\rangle \simeq \sum_i \frac{v'_{i,+}}{L^{1/2}} \exp\left[-\frac{b_i y^2}{2Ld_{\mathrm{e}}^2}\right], \tag{19}$$

$\sum_{r=1}^{2}\langle V_1^{(r)}\rangle$ (containing excluded-volume interactions) is constant. $\sum_i$ is a finite sum of about $n_2 + 1$ terms (the same n_2 as in equation (6)). b_i are positive numerical constants. $v'_{i,\pm}$ are constant. See appendix B. We suppose that $v'_{i,\pm} < 0$. Then, having accepted that $\langle V\rangle$ accounts for global features of $V_{\mathrm{g}}(y)$ for intermediate and large y, it follows that $V_{\mathrm{g}} - V_{\mathrm{g}}(\infty)$ is attractive (<0) for intermediate and large y. In the long-distance approximation $\langle V\rangle$ contains $L^{1/2}d_{\mathrm{e}}$ as a large length scale. For $y \gg L^{1/2}d_{\mathrm{e}}$, $\langle V\rangle - \sum_{r=1}^{2}\langle V_1^{(r)}\rangle \to 0$ and, hence, $V_{\mathrm{g}} - V_{\mathrm{g}}(\infty)$ is negligible as well. For $y \leqslant y_2$, equation (19) yields a small $\langle V\rangle$ and, hence, an attempt to use $\langle V\rangle$ in order to obtain qualitative information on V_{g} fails.

4.2. Moments and approximations for dsDNA ($T \leqslant T_m$)

The following moment method will enable to approximate equation (16) for W_{in} by a simpler distribution $f = f(y;t)$, depending only on y and t. In turn, $f = f(y;t)$ will yield an approximate approach towards the dsDNA time duration τ in section 5. The essentials of the moment method employed in this section are outlined in appendix C in a simpler context. Let $[n]$ denote a suitable set of non-negative integers (n being the sum of all them). Different sets $[n]$ correspond to the same n. We shall introduce the denumerably infinite set $W_{[n]}$ of all polynomials in $\mathbf{z}_{l'}^{(r)}$, which are orthonormalized with respect to the positive (weight) function W_{eq}, provided that one integrates over all $\mathbf{z}_{l'}^{(r)}$s but no integration over $\mathbf{y}$ be performed: $\int [\mathrm{d}\mathbf{z}] W_{\mathrm{eq}} W_{[n]} W_{[n']} = \delta_{[n],[n']}$. $\delta_{[n],[n']}$ denotes a product of Kronecker delta's. The order of the polynomials $W_{[n]}$ increases as n does. The $W_{[n]}$s also depend on $\mathbf{y}$ parametrically. We introduce the following t- and $\mathbf{y}$-dependent moments $\omega_{[n]} = \omega_{[n]}(\mathbf{y};t)$ of W_{in} and the associated moment expansion:

$$\omega_{[n]} = \int [\mathrm{d}\mathbf{z}] W_{\mathrm{in}} W_{[n]},\ W_{\mathrm{in}} = W_{\mathrm{eq}} \Sigma_{[n']} \omega_{[n']} W_{[n']}, \tag{20}$$

($\omega_{[n']} = 0$ if $n' < 0$). Like in appendix C, one gets an infinite recurrence relation for all moments $\omega_{[n]}$, for all $[n]$. In the simplest approximation, we retain only the equation in that recurrence for $n = 0$, and we keep in that equation only the contribution due to $\omega_{[0]}$. See appendix C. The resulting approximate equation for $\omega_{[0]}$ (the counterpart of equation (C.5)) reads for both Rouse and Zimm regimes:

$$\frac{\partial \omega_{[0]}}{\partial t} \simeq \frac{2K_{\mathrm{B}}T}{L\zeta_0} W_{[0]} \nabla_{\mathbf{y}} \left[\left(\int [\mathrm{d}\mathbf{z}] W_{\mathrm{eq}}\right) (\nabla_{\mathbf{y}}(\omega_{[0]} W_{[0]}))\right]. \tag{21}$$

From section 4.1, one has: $W_{[0]} = [\int [\mathrm{d}\mathbf{z}] W_{\mathrm{eq}}]^{-1/2} = \exp[(2K_{\mathrm{B}}T)^{-1} V_{\mathrm{g}}(y)]$. V_{g} is the exact global effective potential introduced in section 4.1. The equilibrium solution of equation (21) is $W_{[0]}^{-1}$. Then, equation (21) becomes:

$$-\frac{\partial \omega_{[0]}}{\partial t} \simeq \frac{2K_{\mathrm{B}}T}{L\zeta_0}[-\nabla_{\mathbf{y}}^2 + V_{\mathrm{g},1}]\omega_{[0]}, \tag{22}$$

$$V_{\mathrm{g},1} = V_{\mathrm{g},1}(y) = -\frac{\nabla_{\mathbf{y}}^2 V_{\mathrm{g}}}{2K_{\mathrm{B}}T} + \left(\frac{\nabla_{\mathbf{y}} V_{\mathrm{g}}}{2K_{\mathrm{B}}T}\right)^2, \tag{23}$$

$\mathbf{y}$ could be regarded as a 'slow' variable, compared to all $\mathbf{z}_{l'}^{(r)}$. Such a dominance of 'slow' variables is conceptually important. It constitutes an extension, to the double-stranded system, of related approximations (based upon different scales for time evolution) holding for many cases, like various cooperative systems (lasers, chemical reactions, fluids, ...) [67], the propagation of light in photorefractive materials [68] and others. Notice that $V_{\mathrm{g},1} \to 0$ for $y \to +\infty$.

The Hermitian operator $(K_B T/(2L\zeta_0))[-\nabla_{\mathbf{y}}^2 + V_{g,1}]$ in the three-dimensional equation (22) has no negative eigenvalues and it has only a continuous non-negative spectrum (sweeping the whole interval $(0, +\infty)$). This corresponds to the fact that '... the kinetics of the melting of DNA corresponds to an entire spectrum of times τ' ([2], p 262).

One can factorize directly radial (y) and angular dependences ($\mathbf{y}/y$) in $\omega_{[0]}$ in equation (22). For the long t analysis, it will suffice to restrict to $\omega_{[0]} = \omega_{[0]}(y; t)$, independent on $\mathbf{y}/y$. Equation (22) yields directly the following one-dimensional radial Smoluchowski equation for $f = f(y; t) = y^2 \omega_{[0]} \exp[-(2K_B T)^{-1} V_g]$:

$$\frac{\partial f}{\partial t} \simeq \frac{2K_B T}{L\zeta_0} \frac{\partial}{\partial y}\left[\frac{\partial f}{\partial y} + f\left(-\frac{2}{y} + \frac{1}{K_B T}\frac{\partial V_g}{\partial y}\right)\right]. \quad (24)$$

5. Mean first passage time for dsDNA ($T \simeq T_m$)

We shall estimate approximately the time duration τ for thermal denaturation of dsDNA (with total molecular weight $M_{tot} = 2MN$), at $T \simeq T_m$. As already commented before, efforts to provide an unambiguous and quantitative definition of τ meet conceptual difficulties. To illustrate the latter once more, notice that the one-dimensional operator $-(2K_B T/(L\zeta_0))(\partial/\partial y)[(\partial/\partial y) + (-(2/y) + (K_B T)^{-1}(\partial V_g/\partial y))]$ in equation (24): (i) has only a continuous non-negative infinite spectrum (its eigenvalues λ_c lie in $0 \leqslant \lambda_c < +\infty$, without negative eigenvalues) and, then, (ii) lacks discrete strictly positive eigenvalue (the inverse of the smallest one of which being a natural candidate for τ). This continuous spectrum is intimately connected to that quoted in [2] (p 262).

From the approximate study of V_g in section 4.1, for $T < T_m$ one expects that the probability for the bound double-stranded structure: (i) is small for $0 \leqslant y \leqslant y_1$, (ii) is concentrated in some interval $y_1 \leqslant y \leqslant y_2$, (iii) decreases as y increases in $y_2 \leqslant y \leqslant y_3$ (y_3 being appreciably larger than y_2), and (iv) is negligible for $y > y_3$. It seems natural to use $\langle V \rangle$ in order to infer the scales of V_g, for intermediate and large y: specifically, we shall suppose that (19) holds for $y \geqslant y_2$, and that $y_3 \simeq L^{1/2} d_e$. We shall try to give some meaning to τ as the average time required for y, regarded as a stochastic variable, to leave the region $y_1 \leqslant y \leqslant y_2$ towards $y \simeq y_3$ and $y \geqslant y_3$ for the first time, at $T \simeq T_m$. This expectation is qualitatively consistent with views expressed in section 2.8 in [8]. At $T \simeq T_m$, the double-stranded structure melts, with very small probability for becoming bound again (enzymes would act on each strand to initiate DNA replication, but the latter process is excluded from our analysis). Then, it may be not unreasonable to interpret τ as some mean first passage time (MFPT) for equation (24) with $T \simeq T_m$, with suitable boundary conditions. The MFPT is also closely connected to the theory of diffusion-controlled reactions [66]. In what follows, we shall suppose that $T \simeq T_m$. Based upon [46–48], a MFPT $\tau(y)$ is the solution of the so-called 'adjoint equation' corresponding to equation (24), namely, of:

$$\frac{2K_B T}{L\zeta_0}\left[\frac{\partial^2 \tau(y)}{\partial y^2} - \left(-\frac{2}{y} + \frac{1}{K_B T}\frac{\partial V_g}{\partial y}\right)\frac{\partial \tau(y)}{\partial y}\right] = -1, \quad (25)$$

in $y_0 \leqslant y \leqslant y_3$, with the ('absorbing') boundary condition $\tau(y_3) = 0$ and with another one, to which we now turn. It seems reasonable that $y_0 \simeq y_2$ and to avoid an 'absorbing' boundary condition at y_0. In fact, V_g is repulsive at short distances, and the physical reason for y to leave stochastically the region $y_1 \leqslant y \leqslant y_2$ is thermal denaturation towards large y_3 at $T \simeq T_m$. As a simple possibility, we impose the 'reflecting' boundary condition $\partial\tau(y)/\partial y = 0$ at $y = y_0$. We shall not need to specify y_0 in a more precise way. The solution of (25) with those boundary conditions is:

$$\tau(y) = \frac{L\zeta_0}{2K_B T}\int_y^{y_3} \frac{dy' \exp[(K_B T)^{-1} V_g(y')]}{y'^2} \times \left(\int_{y_0}^{y'} dy'' y''^2 \exp[-(K_B T)^{-1} V_g(y'')]\right), \quad (26)$$

[46, 47] give solutions of MFPT equations like (25) with: (i) reflecting and absorbing boundary conditions at y_3 and y_0, respectively, and, conversely, (ii) reflecting and absorbing boundary conditions at y_0 and y_3, respectively (with which (26) agrees). The solution with the boundary conditions (i) has been applied in [46] to determine the time for recombination of a diffusing molecule in the short-range Morse-like potential U of a fixed molecule. The Morse-like shape of U (figure 24 in [46]) is qualitatively similar to that for $V_g - V_g(\infty)$. For dsDNA at $T \simeq T_m$, we interpret the dsDNA time duration, approximately, as $\tau \simeq \tau(y)$, for y about or somewhat larger than $y_2 \simeq y_0$ (with $y < y_3$). Recall that (19) holds for $y \geqslant y_2$, and that we use $\langle V \rangle$ as a guide for qualitative behaviours and estimates of V_g for intermediate and large y. As a first and rough approximation, we neglect V_g in (26) for $T \simeq T_m$. Then, the dominant contribution to (26) is:

$$\tau \simeq \tau(y) \simeq \frac{L\zeta_0}{12K_B T} y_3^2 \simeq \left[\frac{M_{tot}}{2Mn_e}\right]^2 \frac{d_e^2 \zeta_0}{12K_B T_m}, \quad (27)$$

equation (27) can also be obtained by extending directly approximate techniques employed in the transition state theory [69] (related, in turn, to the so-called flux-over-population method [46]): for brevity, we shall omit the latter approximation procedure. Use has been made of $y_3 \simeq L^{1/2} d_e$ and $L \simeq M_{tot}/(2Mn_e)$ in (27). Notice that ζ_0 was given in section 3 for both Rouse and Zimm dynamics. For the Rouse regime, (27) becomes:

$$\tau \simeq \frac{\pi\beta}{2}\left[\frac{M_{tot}}{2Mn_e}\right]^2 \frac{d_e^3 \eta}{K_B T_m}. \quad (28)$$

For the Zimm model, with 'θ' conditions, (27) gives:

$$\tau \simeq \frac{(6\pi^3)^{1/2}}{32}\left[\frac{M_{tot}}{2Mn_e}\right]^{1.5} \frac{d_e^3 \eta}{K_B T_m}. \quad (29)$$

For the Zimm model, with 'good solvent', (27) yields:

$$\tau \simeq \left[\frac{M_{tot}}{2Mn_e}\right]^{1.6} \frac{d_e^3 \eta}{12K_B T_m}. \quad (30)$$

Experimental values for τ, for a number of phages, appear to follow a M_{tot}^2 behaviour (as summarized in [2], section 7.5),

which appears to be more consistent with (28) for the Rouse regime than with (29) and (30) for the Zimm dynamics. In [37], the behaviour $\tau \simeq c_0 M_{\rm tot}^{\alpha}$, with $\alpha = 5/2$, has been predicted. In [41], lower and upper bounds on the behaviour of τ were given: $\tau > c_l M_{\rm tot}^{3/2}$ and $\tau < c_u M_{\rm tot}^{3}$ (c_l and c_u being constants). The procedures employed in [37] and in [41] did not apply either the Smolukowski or moment methods or MFPTs and, so, were very different from those used in the present work.

For rough order of magnitude estimates, we take $M_{\rm tot}/2M = 4 \times 10^5$ ($M_{\rm tot}$ of order 10^8 times the hydrogen mass), η about the viscosity of water (10^{-2} poise) and $\beta \simeq 0.16$. Experimental values for τ (for instance, for *coli* DNA) are about 1 min: see [2] (section 7.5) and [41]. For $d_{\rm e} = 10$ nm and $n_{\rm e} = 20$, equation (28) (Rouse regime) gives $\tau \simeq 0.4$ min. On the other hand, equations (29) and (30) (Zimm model) yield τ between 10^{-1} and 10^{-2} min. A Rouse regime for dsDNA would seem not to agree with [34], but it would be consistent with [35]. For $d_{\rm e} = d_{\rm ds} = 50$ nm and $n_{\rm e} = 150$, equation (28) (Rouse model), with the same $M_{\rm tot}/2M$, η and similar values for β also gives τ about half a minute.

Even if a $M_{\rm tot}^2$ behaviour seems accepted [2], it may be adequate to comment the following. The experiments by Spatz and Crothers [42], although consistent with a $M_{\rm tot}^2$ behaviour, seemed to favour $M_{\rm tot}^{2.3}$, which would appear to amplify the disagreement with a Zimm behaviour. Possibly, (26) could yield results for τ approximately or numerically similar to a behaviour $M_{\rm tot}^{\alpha}$, with an exponent α a bit higher than 2, if the contributions of $V_{\rm g}$ were not neglected (so that one would keep $V_{\rm g}(y') - V_{\rm g}(y'')$). A proper numerical assessment of such corrections is not an easy task and lies outside our scope here.

A rate constant (or reaction rate) at $T \simeq T_{\rm m}$ could then be introduced as τ^{-1} [46, 47].

6. Conclusions and final comments

We shall summarize the main assumptions, techniques and approximations in our approach:

(1) At equilibrium with $T \leqslant T_{\rm m}$, each ssDNA in dsDNA can be regarded as formed by effective monomers (e-monomers) with size $d_{\rm e}$ (the same holds for ssDNA with $T > T_{\rm m}$, with other monomers).

(2) A Smoluchowski equation for dsDNA is assumed, in terms of the same e-monomers as for equilibrium, so as to describe approximately its irreversible long-time relaxation towards thermal equilibrium, from about room temperature up to $T \simeq T_{\rm m}$. The e-monomers interact through an effective potential V, which includes stacking, heterogeneities and excluded-volume effects.

(3) By integrating suitably the equilibrium distribution over all configurations of the e-monomers, but not over the relative position vector ($\mathbf{y}$) of the centres of mass of the two ssDNAs, an exact global effective potential $V_{\rm g}$ is introduced for $T \leqslant T_{\rm m}$. $V_{\rm g}$ includes heterogeneities, stacking and excluded-volume effects only in an average way and it depends only on $y = |\mathbf{y}|$. By extending [27], an approximation $\langle V \rangle$ for $V_{\rm g}$ is given and employed for qualitative estimates for intermediate and large distances.

(4) By integrating suitably over all configurations of the e-monomers, the Smoluchowski equation is replaced by an equivalent infinite recurrence relation for suitable moments, which depend on $\mathbf{y}$ and t. The recurrence is approximated by the single equation for the lowest moment $\omega_{[0]} = \omega_{[0]}(\mathbf{y}; t)$. The latter equation: (i) yields the correct irreversible long-time relaxation towards thermal equilibrium, (ii) is determined by $V_{\rm g}$. One restricts to $\omega_{[0]}$ depending only on $y = |\mathbf{y}|$ (assuming no angular dependences) and on t.

(5) The time duration τ for the complete separation of dsDNA into two ssDNA, for $T \simeq T_{\rm m}$, is approximated by some MFPT for y (regarded as a stochastic 'reaction coordinate'). In so doing, we apply concepts of reaction-rate theory [46–48]. The MFPT depends on $\omega_{[0]}$ and, so, on $V_{\rm g}$.

(6) An explicit formula for the MFPT (26) is given (assuming reflecting and absorbing boundary conditions).

(7) Expecting that the leading contributions to τ come from intermediate and large distances, the contribution of $V_{\rm g}$ is estimated qualitatively using $\langle V \rangle$ also for intermediate and large distances.

(8) By neglecting $V_{\rm g}$-dependent contributions, based upon (7), equation (26) gives a simple approximate formula for τ (equation (27)), for $T \simeq T_{\rm m}$. Equation (27) is influenced by $d_{\rm e}$ and possibly, through ζ_0, by hydrodynamic interactions and excluded-volume effects, but (due to the neglect of $V_{\rm g}$) not by either heterogeneities or stacking.

The above items (3) ($V_{\rm g}$ and $\langle V \rangle$), (4) (moments, recurrence relation and approximations thereof) and (5) (approximation of τ by some MFPT) are some main results of this work. To the best of our knowledge, previous approaches to τ [36–41] did not make use of either global effective potentials, or such moment methods or the MFPT's. Although previous experiments [34] would favour a Zimm behaviour for dsDNA, the Rouse regime for it seems supported by recent experimental results [35]. The approximate (28) for τ with Rouse regime (another result of this work) yields a $M_{\rm tot}^2$ behaviour and numerical estimates, which seem consistent with experimental results for a number of phages [2, 39, 42–44]. That approximate consistency should, however, be taken with caution and reservations, due to the various approximations made (in particular, those in items (7) and (8)) and to the negligibility (or magnitude) of hydrodynamic interactions and excluded-volume effects. Further experimental data on the latter and, even, on τ, and theoretical analysis would seem adequate for dsDNAs.

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Appendix A. Kramers versus Smoluchowski equations

In one spatial dimension x, let a particle of mass m and momentum p evolve, subject to: (i) a real potential $V = V(x)$, and (ii) friction effects and to an additional interaction, both due to a 'solvent' and represented by the real function $H(x) > 0$. Let the probability distribution $W = W(x, p; t)$ for the particle fulfil the irreversible Kramers equation [47, 48]:

$$\frac{\partial W}{\partial t} + \frac{p}{m}\frac{\partial W}{\partial x} - \frac{\partial V}{\partial x}\frac{\partial W}{\partial p} = \frac{\partial}{\partial p}\frac{1}{H(x)}\left[p + mK_{\rm B}T\frac{\partial}{\partial p}\right]W. \tag{A.1}$$

The equilibrium solution of equation (A.1) is: $W_{\rm eq} = \exp[-(K_{\rm B}T)^{-1}(p^2/(2m) + V)]$. We shall introduce the following moments $W_n = W_n(x; t)$ $(n = 0, 1, 2, \ldots)$ of W: $W_n = (\pi^{1/2}2^n n!)^{-1/2}\int_{-\infty}^{+\infty} {\rm d}p H_n(p/(2mK_{\rm B}T)^{1/2})W$ where $H_n(q)$ denotes the Hermite polynomial of order n. Equation (A.1) implies the following infinite three-term linear recurrence relation for all W_ns $(n = 0, 1, 2, \ldots)$:

$$\frac{\partial W_n}{\partial t} + \left[\frac{K_{\rm B}T}{2m}\right]^{1/2}\left[(2(n+1))^{1/2}\frac{\partial W_{n+1}}{\partial x} + (2n)^{1/2} \times \left(\frac{\partial W_{n-1}}{\partial x} + \frac{1}{K_{\rm B}T}\frac{\partial V}{\partial x}W_{n-1}\right)\right] = -\frac{n}{H(x)}W_n, \tag{A.2}$$

with $W_{-1} = 0$. If $W = W_{\rm eq}$, then $W_{{\rm eq},0}$ is proportional to $\exp[-(K_{\rm B}T)^{-1}V]$ and $W_{{\rm eq},n} = 0$, $n = 1, 2, \ldots$. We perform the long-time approximation in equation (A.2) for $n + 1$, by neglecting $\frac{\partial W_{n+1}}{\partial t}$ and $(2(n+2))^{1/2}(\partial W_{n+2}/\partial x)$, so that:

$$W_{n+1} \simeq -\frac{(2(n+1))^{1/2}H(x)}{(n+1)}\left[\frac{K_{\rm B}T}{2m}\right]^{1/2} \times \left[\frac{\partial W_n}{\partial x} + \frac{1}{K_{\rm B}T}\frac{\partial V}{\partial x}W_n\right]. \tag{A.3}$$

By replacing W_{n+1} from (A.3) into the exact equation (A.2) for n, we get:

$$\frac{\partial W_n}{\partial t} + \left[\frac{K_{\rm B}T}{2m}\right]^{1/2}\left[(2n)^{1/2}\left(\frac{\partial W_{n-1}}{\partial x} + \frac{1}{K_{\rm B}T}\frac{\partial V}{\partial x}W_{n-1}\right)\right] = -\left[\frac{n}{H(x)} - \frac{K_{\rm B}T}{m}\frac{\partial}{\partial x}H(x)\left(\frac{\partial}{\partial x} + \frac{1}{K_{\rm B}T}\frac{\partial V}{\partial x}\right)\right]W_n, \tag{A.4}$$

together with (A.2) for $n = 0, 1, \ldots, n-1$. Due to the damping term $-nH(x)^{-1}W_n$ in (A.4), all W_n, $n = 1, 2, \ldots$, relax faster than W_0, and W_n $(n > 0)$ relax the faster the larger n is. Equation (A.4) for $n = 0$ dominates the long t approach towards $W_{\rm eq}$.

Based upon the above one-dimensional model, we shall justify, in outline, equations (11) and (12). The roles played by x and p will be played by all e-monomer vectors $\mathbf{R}_l^{(r)}$, and by their canonically conjugate momenta $\mathbf{P}_l^{(r)}$. Let $[\mathbf{P}]$ denote the set of all $\mathbf{P}_l^{(r)}$. Let $W_{\rm K} = W_{\rm K}([\mathbf{R}], [\mathbf{P}]; t)$ be the probability distribution for a configuration of the double-stranded system, with given $[\mathbf{R}]$ and $[\mathbf{P}]$, at time t. By assumption, $W_{\rm K}$ evolves through a Kramers equation, which generalizes directly (A.1), with $V(x)$ replaced by $[\frac{3}{2d_{\rm e}^2}\sum_{s=1}^{2}\sum_{l''=1}^{L}(\mathbf{R}_{l''+1}^{(s)} - \mathbf{R}_{l''}^{(s)})^2 + \frac{V}{K_{\rm B}T})]$ and $(H(x))^{-1}$ by $[(H^{(r)})^{-1}]_{l,l'}$. $(H^{(r)})^{-1}$ is the inverse of the matrix formed by all $H_{l,l'}^{(r)}$, which appear in (12). We introduce moments for $W_{\rm K}$ regarding all $\mathbf{P}_l^{(r)}$, using suitable Hermite polynomials in the latter, by generalizing directly W_n. The actual moment of zeroth order, $(\pi^{-1/4})^{3(L+1)}\int[{\rm d}^3\mathbf{P}]W_{\rm K}$, will be identified with the distribution W in (11). The Kramers equation for $W_{\rm K}$ implies an infinite linear hierarchy for its moments, which generalizes (A.2). In the latter hierarchy, we perform a long-time approximation similar to that in (A.3): this implements the physical fact that the distributions of all e-monomer momenta $\mathbf{P}_l^{(r)}$ should relax towards thermal equilibrium faster than those for $\mathbf{R}_l^{(r)}$. The counterpart of (A.4) for the moment of zeroth order of $W_{\rm K}$ has the slowest relaxation and is just equation (11). The inverse powers of L in (15), (17) and (21) amount to amplify friction. They also support equations (11) and (12) as large-friction approximations for the Kramers equation for $W_{\rm K}$, consistently with [47].

Appendix B. Global effective potential

We recall that all $W_{\rm G}$s are concentrated in $|\mathbf{z}_l^{(r)}| \leqslant d_{\rm e}$. For $y = 0$ and for small y up to some y_1, $\int[{\rm d}\mathbf{z}]W_{\rm eq} = \int[{\rm d}\mathbf{z}][\prod_{r=1}^{2}\prod_{l=1}^{L}W_{\rm G}(\mathbf{z}_l^{(r)}; 2d_{\rm e}^2)]\exp[-(K_{\rm B}T)^{-1}V]$ could be expected to be dominated by the integration domains with $|\mathbf{z}_l^{(r)}| \leqslant d_{\rm e}$. On the other hand, the potentials $v_{0,l}$, $v_{1;l,n}$, $v_{2;12;l,n}$ and $v_{2;21;l,n}$ contributing to V can be reasonably expected to be positive (repulsive) and, possibly, large for short distances. Then, for $y = 0$ and for small y up to some y_1, $\int[{\rm d}\mathbf{z}]W_{\rm eq}$ could be expected to be small and, hence, $V_{\rm g}(y)$ would be positive. A similar qualitative argument would yield the positivity of $V_{\rm g}(y) - V_{\rm g}(\infty)$ for $y = 0$ and for small y up to some y_1.

We introduce the Gaussian averaging:

$$\langle A\rangle \equiv \int[{\rm d}\mathbf{z}]\left[\prod_{r=1}^{2}\prod_{l=1}^{L}W_{\rm G}(\mathbf{z}_l^{(r)}; 2d_{\rm e}^2)\right]A. \tag{B.1}$$

One has: $\int[{\rm d}\mathbf{z}]W_{\rm eq} = \exp[-(K_{\rm B}T)^{-1}V_{\rm g}(y)] \geqslant \exp[-(K_{\rm B}T)^{-1}\langle V\rangle(y)]$, with $\langle V\rangle \geqslant V_{\rm g}$. Then:

$$\langle V\rangle = \langle V_0\rangle + \sum_{r=1}^{2}\langle V_1^{(r)}\rangle + \langle V_2\rangle. \tag{B.2}$$

We shall be primarily interested on $\langle V\rangle$ for intermediate and large distances. Let us consider $\langle V_0\rangle$. We express $v_{0;l}$ in (4) in terms of its Fourier transform $\tilde{v}_{0;l}(\mathbf{q})$ (with wavevector $\mathbf{q}$) and employ (13). $\langle\exp{\rm i}\mathbf{q}(\mathbf{R}_l^{(1)} - \mathbf{R}_l^{(2)})\rangle$ is computed through Gaussian integrations. One gets:

$$\langle V_0\rangle = \sum_{l=1}^{L+1}\frac{1}{(2\pi)^3}\int{\rm d}^3\mathbf{q}\tilde{v}_{0;l}(\mathbf{q})\exp(-{\rm i}\mathbf{q}\mathbf{y})\exp(-\mathbf{q}^2 a_l), \tag{B.3}$$

$$a_l = \frac{d_{\rm e}^2}{18L}[6(l - 2^{-1}(L+1))^2 + 2^{-1}(L^2 - 1)]. \tag{B.4}$$

As L is large, small $|\mathbf{q}|$ values dominate (consistent with the regime of intermediate and large distances). Integrating

approximately over **q**:

$$\langle V_0\rangle \simeq \frac{1}{8\pi^{3/2}}\sum_{l=1}^{L+1}\frac{\tilde{v}_{0;l}(0)}{a_l^{3/2}}\exp[-(4a_l)^{-1}y^2]. \tag{B.5}$$

For homogeneous (*hom*) dsDNA formed only by complementary AT bases with attractive interaction: $\tilde{v}_{0;l}(0)\equiv\tilde{v}_{0;\mathrm{AT}}(0)<0$. Through a numerical study, (B.5) yields:

$$\langle V_0\rangle_{\mathrm{hom;AT}} \simeq \frac{27\tilde{v}_{0;\mathrm{AT}}(0)}{2\pi^{3/2}d_{\mathrm{e}}^3L^{1/2}}\exp[-(4Ld_{\mathrm{e}}^2)^{-1}27y^2] \tag{B.6}$$

and so on for GC. The Gaussian average of V_0 with two Gaussians (corresponding to both ssDNA in dsDNA) behaves, for large y, as a Gaussian. We now turn to heterogeneous dsDNA. Let both distributions of complementary AT and GC bases contain, respectively, N_{AT} and N_{GC} pairs occupying the N sites in an aperiodic way, so that $N_{\mathrm{AT}}+N_{\mathrm{GC}}=N$ and $N_{\mathrm{AT}}/N_{\mathrm{GC}}$ is neither very large nor very small. For the two lth e-monomers, $\tilde{v}_{0;l}(0)$ amounts to some averaging over the aperiodic distributions of complementary AT and GC bases in those e-monomers. The GC interaction is more attractive than the AT one. Then, that averaging indicates that $\langle V_0\rangle$ for heterogeneous dsDNA is larger (smaller) then that for homogeneous dsDNA formed only by GC (AT):

$$\langle V_0\rangle_{\mathrm{hom:GC}}\leqslant\langle V_0\rangle\leqslant\langle V_0\rangle_{\mathrm{hom:AT}}<0, \tag{B.7}$$

equation (B.7) provides bounds on $\langle V_0\rangle$ for intermediate and large y. $\sum_{r=1}^{2}\langle V_1^{(r)}\rangle$ is **y**-independent. Like for $\langle V_0\rangle$, each of the n_2 ($n_2\ll L$) contributions to $\langle V_2\rangle$ for heterogeneous dsDNA is subject, under analogous assumptions, to approximations similar to (B.5)–(B.7), but with slightly different numerical constants. This is easily checked for $n_2=1$. All that lead to b_i and $v'_{i;\pm}(<0)$ in (19).

Appendix C. Moments and recurrence relation

We shall illustrate the essentials of the moment method with the following Smoluchowski equation for the distribution $\tilde{W}=\tilde{W}(y,z;t)$ ($-\infty<y,z<+\infty$):

$$\frac{\partial\tilde{W}}{\partial t}=\sigma\frac{\partial}{\partial y}\left[\frac{\partial\tilde{W}}{\partial y}+\tilde{W}\frac{\partial\tilde{V}}{\partial y}\right]+\sigma\frac{\partial}{\partial z}\left[\frac{\partial\tilde{W}}{\partial z}+\tilde{W}\frac{\partial\tilde{V}}{\partial z}\right], \tag{C.1}$$

with constant $\sigma>0$. Equation (C.1), y, z, σ and $\tilde{V}$ are caricatures of equations (11) and (12), **y**, all $\mathbf{z}_{l'}^{(r)}$, H_{hyd} and $H_{l,l'}^{(r)}$ and V plus the Gaussian contribution in (12), respectively. $\tilde{V}=\tilde{V}(y,z)$ is a potential, which fulfils: (i) $\tilde{V}\to+\infty$ (as z^2 times a constant) if $|z|\to+\infty$, for fixed y, and (ii) $\tilde{V}\to\tilde{V}_0(z)$ if $|y|\to+\infty$, for fixed z. The equilibrium distribution for equation (C.1) is $\tilde{W}_{\mathrm{eq}}=\exp(-\tilde{V})$. We shall introduce the denumerably infinite set W_n, $n=0,1,2,\ldots$, of all polynomials in z, which are orthonormalized with respect to the positive (weight) function $\tilde{W}_{\mathrm{eq}}$, provided that one integrates in $-\infty<z<+\infty$ (but not over y). The order of the polynomials increases as n does. One has the orthonormality relation: $\int\mathrm{d}z\,\tilde{W}_{\mathrm{eq}}W_nW_{n'}=\delta_{n,n'}$, where $\delta_{n,n'}$ denotes the Kronecker delta. The coefficients in each polynomial W_n are y-dependent, in general, but they become y-independent for $|y|\to+\infty$. We introduce the moments $\omega_n=\omega_n(y;t)$ of $\tilde{W}$ and the associated moment expansion:

$$\omega_n=\int\mathrm{d}z\,\tilde{W}W_n,\ \tilde{W}=\tilde{W}_{\mathrm{eq}}\Sigma_{n'=0}^{+\infty}\omega_{n'}W_{n'}, \tag{C.2}$$

($\omega_{n'}=0$ if $n'<0$). We multiply equation (C.1) by W_n, integrate in $-\infty<z<+\infty$, leaving y unintegrated, and integrate by parts over z. We get the following infinite recurrence for all moments ω_n, $n=0,1,2,\ldots$, equivalent to equation (C.1):

$$\frac{\partial\omega_n}{\partial t}=-\sigma\Sigma_{n'=0}^{+\infty}\omega_{n'}\left[\int\mathrm{d}z\,\tilde{W}_{\mathrm{eq}}\frac{\partial W_n}{\partial z}\frac{\partial W_{n'}}{\partial z}\right]+\sigma\Sigma_{n'=0}^{+\infty}\left[\int\mathrm{d}z\,W_n\frac{\partial}{\partial y}\left(\tilde{W}_{\mathrm{eq}}\frac{\partial(W_{n'}\omega_{n'})}{\partial y}\right)\right]. \tag{C.3}$$

Equation (C.3) gives, for large $t>0$:

$$\frac{1}{2}\frac{\partial(\Sigma_{n'=0}^{+\infty}\int\mathrm{d}y\,\omega_n^2)}{\partial t}=-\sigma\int\mathrm{d}y\,\mathrm{d}z\,\tilde{W}_{\mathrm{eq}}\times\left[\left(\frac{\partial(\Sigma_{n'=0}^{+\infty}\omega_nW_n)}{\partial z}\right)^2+\left(\frac{\partial(\Sigma_{n'=0}^{+\infty}\omega_nW_n)}{\partial y}\right)^2\right]\leqslant0. \tag{C.4}$$

In equation (C.4) (expressing irreversibility), an additional term (arising from an integration by parts over y of the second term in equation (C.3)) has been neglected. In fact, the neglected term is the more negligible the larger t is, if $\tilde{W}$ is going to relax towards $\tilde{W}_{\mathrm{eq}}$. The use of $\tilde{W}_{\mathrm{eq}}$ (including the full $\tilde{V}$) in defining the W_ns and the ω_ns is crucial, in order to ensure the correct long-time relaxation of the moments towards equilibrium. In the simplest approximation, we consider only equation (C.3) for $n=0$ and, moreover, in its right-hand side, we keep only the contribution due to ω_0. Then, equation (C.3) is approximated by:

$$\frac{\partial\omega_0}{\partial t}\simeq\sigma\left[\int\mathrm{d}z\,W_0\frac{\partial}{\partial y}\left(\tilde{W}_{\mathrm{eq}}\frac{\partial(W_0\omega_0)}{\partial y}\right)\right], \tag{C.5}$$

W_0 being independent on z. The equilibrium solution of equation (C.5) is $\omega_{0,eq}=W_0^{-1}=(\int\mathrm{d}z\,\tilde{W}_{\mathrm{eq}})^{1/2}$. In spite of its crudeness, equation (C.5) yields a non-trivial time relaxation towards the equilibrium solution. In fact, equation (C.5) gives, for large $t>0$:

$$\frac{1}{2}\frac{\partial\left(\int\mathrm{d}y\,\omega_0^2\right)}{\partial t}=-\sigma\int\mathrm{d}y\,\mathrm{d}z\,\tilde{W}_{\mathrm{eq}}\left(\frac{\partial(\omega_0W_0)}{\partial y}\right)^2\leqslant0. \tag{C.6}$$

The additional contribution $-\sigma\int\mathrm{d}y\,\mathrm{d}z\,\tilde{W}_{\mathrm{eq}}(\frac{\partial(\Sigma_{n'=1}^{+\infty}\omega_nW_n)}{\partial z})^2$ in (C.4) suggest that the moments ω_n with $n>0$ would relax faster than ω_0. Since $\int\mathrm{d}z\,\tilde{W}_{\mathrm{eq}}W_0W_{n'}=0$ for $n'\neq0$, in equation (C.3) for $n=0$ the contribution due to $\omega_{n'}$s with $n'>0$ can be easily seen to contain the integral $\int\mathrm{d}z\,\tilde{W}_{\mathrm{eq}}(\partial W_{n'}/\partial y)$. The integrand of the latter integral is not positive, so that the magnitude of that integral could be small, due to cancellations. Then, for suitably large $t>0$, the neglect in equation (C.3) for $n=0$ of the contributions due to $\omega_{n'}$s with $n'>0$ does nor seem unreasonable. These arguments would support the validity of equation (C.5).

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