Remarks on Discrete and Continuous Large-Scale Models of DNA Dynamics

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Abstract

We present a comparison of the continuous versus discrete models of large-scale DNA conformation, focusing on issues of relevance to molecular dynamics. Starting from conventional expressions for the elastic potential energy we derive elastic dynamic equations in terms of cartesian coordinates of the helical axis curve together with a twist function representing the helical or excess twist. It is noted that the conventional potential energies for the two models are not consistent. In addition we derive expressions for random Brownian forcing for the nonlinear elastic dynamics and discuss the nature of such forces in a continuous system.

1 Introduction

There is growing experimental evidence that the large-scale conformation and dynamics of DNA is essential to its biological functionality. Laboratory study of this subject is rapidly becoming more feasible (Finzi and Gelles, 1995, Yin et al., 1995, Yokota et al., 1995, Smith et al., 1996, Fritzsche et al., 1996, Larson et al., 1997, Schwartz and Samad, 1997) and so mathematical modelling of DNA conformation and dynamics is becoming increasingly important. A number of approaches of varying degrees of accuracy and, inversely, feasibility are possible, ranging from quantum mechanics and molecular mechanics to the crude "elastic" chain and rod models that are the subject of this paper. Use of less accurate but simpler models becomes necessary for simulation of long (in space or time) stretches of DNA.

Discrete modelling of DNA was first discussed by Schellman (1974, 1980). The so called "link model" for DNA treats each basepair as a virtual bond. The local energy for bending

and torsion of the chain (helical) axis were considered, while the twist around the axis was neglected. These early works only dealt with thermodynamical aspects of the model. The twist was explicitly introduced to the link model first for isotropic bending (Wilcoxon and Schurr 1983) and later for anisotropic bending (Schurr, 1985). Anisotropic bending contributes to the twist equilibrium when there is large deflection (Schurr, 1985, Landau and Lifshitz, 1986). Hagerman and Zimm (1981) studied the dynamics of DNA based on a discrete model consisting of overlapping beads with the goal of understanding rotation of the whole DNA molecule (not internal dynamics). Later, Allison and McCammon (1984) used Brownian dynamics to simulate internal DNA motion. For an overview, see Malhotra et al., 1993. More recently bead models have included versions of twist dynamics (Chirico and Langowski, 1994; Heath, Gebe, Allison, and Schurr, 1996).

The link model was originally developed to deal with the DNA molecule on intermediate length scales between those modelled by rigid rods and Gaussian chains ($\sim$ 1000-2000Å). The motivation was modelling of macroscopic properties of DNA in terms of its structural parameters employed in molecular conformational analysis; this still seems to be an important reason for utilizing discrete models today. The continuous, wormlike chain model on the other hand has a long history in polymer physics. Of particular relevance is the seminal paper by Harris and Hearst (1966) which developed a constrained dynamic model including bending dynamics. The constraint in their model is on the total length of the chain rather than local inextensibility. This difference leads to different dynamical equations (see below). More recently, continuous elastic rod models of DNA have become popular, mostly for static equilibrium calculations (see Schlick 1995 for a recent review). Some dynamical modeling has been done as well (Schlick, Li, and Olson, 1994; Ramachandran and Schlick, 1995) and several authors have considered related issues in elastic dynamics (Coleman, Lembo, and Tobias 1996, Dichmann and Maddocks 1996, Klapper 1996, Goriely and Tabor 1997).

In this paper we compare discrete chain (or link-and-bead) models of DNA, where each vertex of the chain represents a base-pair, to continuous curve (or rod) models, where lengths of DNA are smeared into a smooth curve. Ultimately, since the discrete models share the parameters for DNA with other high resolution structural studies, a comparison of discrete and continuous models may help provide a connection between the atomic scale energetics of DNA and its large scale dynamics. Both models assume an elastic potential energy functional that is quadratic in bending and twisting displacements from equilibrium, the so-called linear elasticity approximation. The mechanics and dynamics of large-scale motion is nonetheless nonlinear due to the nonlinear kinematics in the elasticity. Despite their apparent similarity, the standard energy functionals are not consistent with each other, as will be discussed. In particular, due to the imposed concentration of bending and twisting at the vertices of the discrete model as opposed to the smooth spread in the continuous model, even in the limit of the discretization length approaching zero the two models may very well result in different dynamics. Thus while it would be hoped that on very large scales the two approaches would give the same results, it is possible that this may in fact not be the case. If in fact the two sets of dynamics are different in a physically significant way, then some thought needs to be applied to the physical relevance of each. However, as will be noted, it is possible to "fix"

the discrete energy in such a way so that it is consistent with the continuous.

This inconsistency aside, the principle difference between the two approaches is that the smooth continuous rod can be used with minimum resources to resolve structure on the bending persistence length scale ($\sim$ 150 bp) or longer (twist persistence length is about the same, $\sim$ 600Å or 180 bp according to Wilcoxon and Schurr, 1983) whereas the chain model resolves lengths as short as a few base-pairs. Arguing conservatively, a continuous model can thus handle a length of DNA about 10 times longer (again in space or time) than the discrete model. In the case of dynamical simulations this may be a considerable underestimate as the time step can be expected to increase with the spatial discretization. Of course if resolution below the bending persistence length is desired or required then this advantage is lost and it would seemingly not be sensible to smooth a discrete system (namely DNA itself) over the base-pair scale only afterwards to re-discretize it again for the purposes of numerical computation. The degrees of freedom of a DNA molecule that play an important role in large scale structure seem to be the so-called tilt, roll, and twist angles between base-pairs. As there is no natural separation of length and time scales for the random motion, in order for a model to include entropic effects in a coherent manner via Brownian dynamics, it would apparently be necessary to resolve DNA at the base-pair level.

2 The Basic Models and Examples

We begin by presenting two models of large-scale DNA conformation, the discrete and continuous models. The continuous model description consists of a piece of double-stranded DNA described as a curve $\mathbf{x}(s,t)$, representing the helical axis, together with a scalar twist function $\omega(s,t)$, where s is contour arclength and t is time, respectively. The function ω is the rate of twist of the two DNA strands around the central curve $\mathbf{x}$ and is in fact the only internal structural information that is kept; the DNA dynamics are to be described by the motion in time of a twistable space curve. The idea is to retain only the minimal structural information essential for large-scale conformation. We note that other coordinate representations of the curve-twist pair $(\mathbf{x},\omega)$ are possible (e.g., Euler angles or quaternions, see Shuster 1993). The mixed cartesian-intrinsic coordinate system $(\mathbf{x},\omega)$ seems most convenient for present purposes. The second model we consider, the discrete model with N base-pairs, is represented by the cartesian coordinates of the N base pairs $\mathbf{y}_k(t) = (x_k(t), y_k(t), z_k(t))$, $k = 1, 2, \ldots, N$ together with the twist between each base-pair $\omega_k(t)$, $k = 1, 2, \ldots, N-1$. The base-pair locations $\mathbf{y}_k$ thus form the vertices of a piecewise-linear chain. The numbers ω_k correspond to the twist degree of freedom between base-pairs. We define the 3N-vector $\mathbf{y}(t)$ to be made up of the 3N components of the vertices $\mathbf{y}_k$ and the (N-1)-vector $\boldsymbol{\omega}$ to be made up of the N-1 values ω_k.

Typical dynamical evolution equations for $\mathbf{y}$ (or $\mathbf{x}$) take the form

$$\mathbf{M}\mathbf{y}_{tt} = -\nabla U(\mathbf{y}, \boldsymbol{\omega}) - \mathbf{H}\mathbf{y}_t + \mathbf{f} \tag{1}$$

(Newton's law with damping and random forcing $\mathbf{f}(t)$ due to the surrounding solvent) or

$$\mathbf{H}\mathbf{y}_t = -\nabla U(\mathbf{y}, \boldsymbol{\omega}) + \mathbf{f} \tag{2}$$

(overdamped system with random forcing) where $U(\mathbf{y}, \omega)$ is a potential energy functional. $\mathbf{M}$ is the mass matrix for the system and $\mathbf{H}$ is the so-called hydrodynamic interaction matrix (the Oseen tensor, Doi and Edwards, 1986). Evolution according to the Newtonian law (1) is sometimes called Langevin dynamics while evolution according to the overdamped system (2) is sometimes called Brownian dynamics. In this paper we consider the overdamped case although remarks made generally apply to both. Additional accompanying equations for $\boldsymbol{\omega}$ are necessary – these will be discussed later. The nature of the random forcing term $\mathbf{f}$ will also be considered.

Typical quadratic potential energy functionals take the form

$$U(\mathbf{x}, \omega) = \int_0^L \left[C_\kappa(s)(\boldsymbol{\kappa} - \hat{\boldsymbol{\kappa}}(s))^2 + C_\omega(s)(\omega - \hat{\omega}(s))^2 \right] ds + \int_0^L C_T(\sigma)(\partial s/\partial \sigma - 1)^2 d\sigma \quad (3)$$

for the continuous model (where s is arclength along the curve $\mathbf{x}$ and σ is a parametrization that stretches with the curve) while for the discrete model

$$U(\mathbf{y}, \boldsymbol{\omega}) = \sum_{k=1}^{N-1} \left[C_\theta(k)(\theta_k - \hat{\theta}_k)^2 + C_\phi(k)(\phi_k - \hat{\phi}_k)^2 + C_\omega(k)(\omega_k - \hat{\omega}_k)^2 \right]. \quad (4)$$

(In equation (3) and throughout we use the notation $\mathbf{v}^2$ to denote $\mathbf{v} \cdot \mathbf{v}$.) In both cases we have included only local forces, neglecting for instance long-range electrostatic interactions. The vector $\boldsymbol{\kappa}(s, t)$ in equation (3) is the curvature vector $\boldsymbol{\kappa} = \partial^2 \mathbf{x}/\partial s^2$ of the curve $\mathbf{x}$. The numbers θ_k and ϕ_k in equation (4) are the tilt and roll angles between base-pairs. The elastic constants $C_\kappa, C_\omega, \ldots$ may be expected to be functions of position. The functions $\hat{\boldsymbol{\kappa}}(s)$ and $\hat{\omega}(s)$ in (3) are the intrinsic bend and twist of the rod, and $\hat{\theta}_k$, $\hat{\phi}_k$ and $\hat{\omega}_k$ in (4) are equilibrium values of the tilt, roll, and twist angles. The last term in (3) is a stretching energy which measures the contraction or dilation of the curve $\mathbf{x}$. The material parameter σ stretches or contracts with the curve; at equilibrium $\sigma = s$, the arclength. It is often assumed that $\mathbf{x}$ is inextensible in which case the stretching term is absent and instead a constraint on the forcing appears. Likewise the discrete system is typically assumed inextensible but may be allowed to be extensible in which case a stretching potential would appear in (4). The fact that equation (3) has only two angular terms while equation (4) contains three is because it is generally assumed that, because it is an average of a relatively long length of DNA, the continuous rod is isotropically flexible. This restriction can be easily relaxed. We shall also remark that it can be argued that due to DNA asymmetry (anisotropic bending and helical symmetry), the discrete energy functional should also have a cross-term linking twist and bend (Schurr, 1985; Marko and Siggia, 1994). It is believed that this cross-term is averaged out on long scales and hence will not appear in the continuous energy (Kehrbaum and Maddocks, 1997).

To illustrate the relation between the two types of models, we begin with a simple example, namely a one dimensional elastic rubber band $x(\sigma)$ with unit length, $0 \leq \sigma \leq 1$. By one dimensional it is meant that the rubber band does not bend or twist, just stretch, i.e., $x : [0, 1] \to R$. We start with the continuous, linear potential energy functional for x with

an elasticity constant A independent of the spatial variable σ:

$$U = \frac{A}{2}\int_0^1 (x'(\sigma,t)-1)^2 d\sigma. \tag{5}$$

In order to compare with the discrete model we discretize the continuous model using discretization points y_0, y_1, ..., y_N for the continuous values $x(0)$, $x(1/N)$, ..., $x(1)$. This discrete approximation has potential energy

$$U = \frac{A}{2}\sum_{k=1}^{N}\frac{1}{N}\left(\frac{y_k - y_{k-1}}{1/N} - 1\right)^2 \tag{6}$$

which can be rewritten as

$$U = \frac{\alpha}{2}\sum_{k=1}^{N}(y_k - y_{k-1} - 1/N)^2 \tag{7}$$

where α is the elastic constant for a discrete elastic model. We see that if $\alpha = NA$ then in the limit $N \to \infty$, (7) approaches (5). This factor of N also arises in the mass and frictional coefficient of the deterministic evolution equations (cf. Eqs. 1 and 2). For stochastic dynamics, however, it effectively reduces the amplitude of the random term $\mathbf{f}$ by $(1/N)^{1/2}$ as the discretization becomes finer (see below). This is in fact a requirement in order to maintain finite energy (Kloeden and Platen, 1992).

For simplicity suppose the above discrete system obeys periodic boundary conditions. Set $Y_k = (y_k - k/N) - (y_{k-1} - (k-1)/N) = y_k - y_{k-1} - 1/N$, the nonequilibrium displacement between particles $k-1$ and k (known as the *strain* in continuous mechanics). Then combining (2) and (7)

$$\frac{d}{dt}Y_k = (\alpha/\zeta)(Y_{k+1} - 2Y_k + Y_{k-1}) + \zeta^{-1}f_k(t) \tag{8}$$

identifying Y_{N+1} with Y_1. ζ is the frictional coefficient for each discrete segment. Equation (8) can be solved by decomposing into normal modes (see, e.g., Doi and Edwards, 1986). Substituting $Y_k^\ell = \exp(2\pi i k\ell/N)\xi_\ell^t$, $1 \le \ell \le N$, we find

$$\frac{d}{dt}Y_k^\ell = (2\alpha/\zeta)(\cos(2\pi\ell/N) - 1)Y_k^\ell + \zeta^{-1}f_k(t) \tag{9}$$

so that the N eigenvalues of the system are

$$\lambda_\ell = 2(\cos(2\pi\ell/N) - 1), \qquad 0 \le \ell \le N-1, \tag{10}$$

with corresponding orthogonal eigenvectors $\mathbf{v}_{\ell,k} = \exp(2\pi i k\ell/N)$, $k = 1, 2, \ldots, N$, $\mathbf{v}_\ell \cdot \mathbf{v}_m = N\delta_{\ell m}$. Now expanding Y_k in terms of the normal modes:

$$Y_k = \sum_{\ell=0}^{N-1}\xi_\ell^t \mathbf{v}_{\ell,k}, \qquad k = 1, 2, ..., N$$

and using the orthogonality of $\mathbf{v}_\ell$, the ξ_ℓ^t's satisfy the evolution equations

$$\frac{d}{dt}\xi_\ell^t = (\alpha/\zeta)\lambda_\ell \xi_\ell + (N\zeta)^{-1}\hat{f}_\ell(t) \tag{11}$$

where $\hat{f}_\ell(t) = \sum_k \exp(2\pi i k\ell/N) f_k(t)$ is the wavenumber ℓ component of the discrete Fourier transform of the noise. The solution to this equation is the stochastic process

$$\xi_\ell^t = \xi_\ell^0 e^{(\alpha/\zeta)\lambda_\ell t} + (N\zeta)^{-1}\int_0^t e^{(\alpha/\zeta)\lambda_\ell(t-s)}\hat{f}_\ell(s)ds$$

where ξ_ℓ^0 is the initial condition. Note that if $\langle f_k(t)\rangle = 0$ (the $\langle\cdot\rangle$ here refers to an ensemble average) and ξ_ℓ^0 is assumed to be random with $\langle\xi_\ell^0\rangle = 0$ then $\langle\xi_\ell^t\rangle = 0$, i.e., the stochastic process is stationary. If not then stationarity will be asymptotic since $\lambda_\ell < 0$. If we require in addition that the f_k be uncorrelated in time and space, i.e., $\langle f_k(t) f_h(s)\rangle = \sigma^2\delta_{kh}\delta(t-s)$, then,

$$\begin{aligned}
\langle|\xi_\ell^t|^2\rangle &= e^{2(\alpha/\zeta)\lambda_\ell t}\langle(\xi_\ell^0)^2\rangle + (N\zeta)^{-2}\int_0^t\int_0^t e^{(\alpha/\zeta)\lambda_\ell(t-s+t-s')}\langle\hat{f}_\ell(s)\hat{f}_\ell(s')\rangle ds ds' \\
&= e^{2(\alpha/\zeta)\lambda_\ell t}\langle(\xi_\ell^0)^2\rangle + \frac{\sigma^2}{N\zeta^2}\int_0^t\int_0^t e^{(\alpha/\zeta)\lambda_\ell(t-s+t-s')}\delta(s-s')ds ds' \\
&= e^{2(\alpha/\zeta)\lambda_\ell t}\langle(\xi_\ell^0)^2\rangle + \frac{\sigma^2}{2N\zeta\alpha\lambda_\ell}\left(e^{2(\alpha/\zeta)\lambda_\ell t} - 1\right)
\end{aligned}$$

so

$$\lim_{t\to\infty}\langle|\xi_\ell^t|^2\rangle = \frac{\sigma^2}{2N\zeta\alpha|\lambda_\ell|}$$

where $\lambda_\ell < 0$. σ^2 can then be determined if we assume that the system relaxes to the Boltzmann equilibrium distribution. Since the eigenvectors $\mathbf{v}_\ell$ are orthogonal, the Boltzmann distribution is

$$P(\mathbf{Y}) = C\exp\left(-\frac{U(\mathbf{Y})}{k_B T}\right) = C\exp\left(-\frac{N\alpha}{2k_B T}\sum_{\ell=0}^{N-1}|\lambda_\ell|(\xi_\ell^\infty)^2\right). \tag{12}$$

where k_B is the Boltzmann constant and T is the equilibrium temperature. Hence $\sigma^2 = 2N\zeta\alpha|\lambda_\ell|\lim_{t\to\infty}\langle(\xi_\ell^t)^2\rangle = 2k_B T\zeta$.

Compare now to the continuous periodic system

$$\frac{\partial}{\partial t}X = (A/\zeta)\frac{\partial^2}{\partial s^2}X + \zeta^{-1}f(s,t)$$

with eigenvalues

$$\lambda_\ell = -4\pi^2\ell^2$$

and eigenfunctions $\exp(2\pi i\ell s)$. Setting

$$X(s,t) = \sum_{\ell=0}^{\infty}\xi_\ell^t\exp(2\pi i\ell s)$$

then

$$P(X) = C \exp\left(-\frac{A}{2k_BT}\sum_{j=0}^{\infty}|\lambda_j|\xi_j^2\right) = C\exp\left(-\frac{\alpha}{2Nk_BT}\sum_{j=0}^{\infty}|\lambda_j|\xi_j^2\right) \tag{13}$$

Note that

$$N^2\lambda_{\ell,discrete} = -4\pi^2\ell^2 + O(\ell^4/N^2) = \lambda_{\ell,continuous} + O(\ell^4/N^2), \quad 0 \le \ell \le N-1$$

so that the 2 distributions (12) and (13) will be close if N is large enough compared to k_BT so that the the ℓ-modes close to N are insignificant, i.e., $\ell_{max}^2/T \approx N^2/T$ is small. Thus $N \sim T^{1/2}$ which seems to agree with our intuition.

More generally if we consider periodic systems of the form

$$\frac{\partial}{\partial t}X = (1/\zeta)\frac{\partial}{\partial s}\left(p(s)\frac{\partial}{\partial s}X\right) + (1/\zeta)q(s)X + (1/\zeta)f(s,t) \tag{14}$$

then the eigenvalue problem is a Sturm-Liouville system (Courant and Hilbert, 1953). Under the appropriate change of variables the eigenvalue problem for (14) takes the form

$$u''(s) - r(s)u(s) = -\lambda u(s).$$

This problem has a countable set of simple eigenvalues $\lambda_0 < \lambda_1 < \lambda_2 < \ldots$ with $\lim_{n\to\infty}\lambda_n = \infty$. On the other hand, a discrete version of this system, say

$$\frac{d}{dt}Y_k = (Y_{k+1} - 2Y_k + Y_{k-1}) + r_kY_k + F_k(t),$$

has eigenvalues bounded by $C\max|r_k|$.

The requirement that random force behaves as a white noise, i.e., $\langle f_k(t)f_k(s)\rangle = \sigma^2\delta(t-s)$ is a mathematical convenience and is in principle unphysical. Strictly speaking Langevin trajectories are not related to actual trajectories; only the distribution of all Langevin trajectories has physical meaning. At least for discrete systems since there is an upper bound on the eigenvalues corresponding to the fastest relaxation time, the random force can be interpreted to be white noise if the solvent dynamics, which constitute the random force, are faster. Such an argument, however, is not valid for a continuous system where there is no upper bound on the eigenvalues and hence no lower bound on the normal frequencies. There is in fact a connection between fast temporal and short spatial scales in a continuous system. We will return to more discussion on this in Section 4.

3 The Potential Energy Gradient

3.1 Continuous model

In analogy to a finite degree of freedom system, the elastic force acting on a rod (see equation (2)) is obtained from the functional gradient of the potential energy. (Since we only consider

overdamped dynamics, the kinetic energy wil be neglected.) In this section we derive the functional gradient of the quadratic elastic potential energy for the continuous model

$$U = \frac{1}{2}\int_0^L (C_\kappa \kappa^2 + C_\omega \omega^2) ds$$

where s is arclength. We assume (for simplicity only) that the intrinsic curvature $\hat{\boldsymbol{\kappa}}$ and intrinsic twisting $\hat{\omega}$ are zero. Effects of non-zero intrinsic curvature and twist can be included without significant difficulty, but the added computation distracts from the main points to be considered here. We begin with the curvature portion of U, namely

$$U_\kappa = \frac{1}{2}\int_0^L C_\kappa \kappa^2 ds = \frac{1}{2}\int_0^L C_\kappa \left(\frac{\partial^2 \mathbf{x}}{\partial s^2}\cdot\frac{\partial^2 \mathbf{x}}{\partial s^2}\right) ds$$

The functional gradient is obtained by varying the curve $\mathbf{x}(s)$, $0 \le s \le L$, in the direction of an arbitrary but smooth function $\mathbf{h}(s)$, $0 \le s \le L$. Choosing an arclength parametrization s, the curvature potential energy carried by $\mathbf{x}(s)$ between s and $s + \Delta s$ is

$$\frac{1}{2}\int_{s_0}^{s_0+\Delta} C_\kappa \left(\frac{\partial^2 \mathbf{x}}{\partial s^2}\right)^2 ds = \frac{\Delta}{2} C_\kappa \left(\frac{\partial^2 \mathbf{x}}{\partial s^2}\right)^2_{s=s_0} + O(\Delta^2)$$

Note however s in general no longer parametrizes the varied curve $(\mathbf{x}+\epsilon\mathbf{h})(s)$ by arclength. Instead let r be the arclength parametrization variable for the new curve and set $A = ds/dr$. Then the potential energy carried by the curve $(\mathbf{x}+\epsilon\mathbf{h})(r)$ between r_0 and $r_0 + \Delta$ is

$$\begin{aligned}
\frac{1}{2}\int_{r_0}^{r_0+\Delta} C_\kappa \left(\frac{\partial^2 \mathbf{x}}{\partial r^2} + \epsilon\frac{\partial^2 \mathbf{h}}{\partial r^2}\right)^2 dr &= \frac{1}{2}\int_{s_0}^{s_0+A^{-1}\Delta} C_\kappa A^4 \left(\frac{\partial^2 \mathbf{x}}{\partial s^2} + \epsilon\frac{\partial^2 \mathbf{h}}{\partial s^2}\right)^2 A^{-1} ds + O(\Delta^2) \\
&= \frac{\Delta}{2} C_\kappa \left(\frac{\partial^2 \mathbf{x}}{\partial s^2} + \epsilon\frac{\partial^2 \mathbf{h}}{\partial s^2}\right)^2 A^2 + O(\Delta^2) \\
&= \frac{1}{2}\int_{s_0}^{s_0+\Delta} C_\kappa \left(\frac{\partial^2 \mathbf{x}}{\partial s^2} + \epsilon\frac{\partial^2 \mathbf{h}}{\partial s^2}\right)^2 A^2 ds + O(\Delta^2)
\end{aligned}$$

where s_0 is chosen so that s_0 and r_0 correspond to the same points on the curve $(\mathbf{x}+\epsilon\mathbf{h})$. Noting that

$$A = \frac{ds}{dr} = \sqrt{\left(\mathbf{t} + \epsilon\frac{d\mathbf{h}}{ds}\right)^{-2}},$$

where $\mathbf{t} = \partial\mathbf{x}/\partial s$ is the unit tangent vector to the curve $\mathbf{x}$, then

$$\begin{aligned}
U_\kappa(\mathbf{x}+\epsilon\mathbf{h}) &= \frac{1}{2}\int_0^L C_\kappa \left(\frac{\partial^2 \mathbf{x}}{\partial s^2}\right)^2 ds \\
&\quad + \frac{\epsilon}{2}\int_0^L C_\kappa \left[-2\left(\frac{\partial^2 \mathbf{x}}{\partial s^2}\right)^2 \frac{\partial \mathbf{x}}{\partial s}\cdot\frac{\partial \mathbf{h}}{\partial s} + 2\frac{\partial^2 \mathbf{x}}{\partial s^2}\cdot\frac{\partial^2 \mathbf{h}}{\partial s^2}\right] ds + O(\epsilon^2).
\end{aligned}$$

The first $O(\epsilon)$ term on the right-hand side arises from the component of variation in the $\partial\mathbf{x}/\partial s = \mathbf{t}$ direction and reflects the change of energy due to a coupling between bending and stretching $\mathbf{x}$ for large deformations. More importantly, even if the curve is inextensible, this stretching force term does not disappear but in fact still acts like a tension, resulting in non-tangential motion. This contribution is notably absent from the discrete energy gradient.

Returning to the calculation, after integrating by parts we obtain

$$\begin{aligned}\lim_{\epsilon\to 0}\frac{U_\kappa(\mathbf{x}+\epsilon\mathbf{h})-U_\kappa(\mathbf{x})}{\epsilon} &= \int_0^L C_\kappa\left[\frac{\partial}{\partial s}(\kappa^2\mathbf{t})+\frac{\partial^2}{\partial s^2}(\kappa\mathbf{n})\right]\cdot\mathbf{h}\,ds \\ &\quad -C_\kappa\kappa^2\mathbf{t}\cdot\mathbf{h}\big|_0^L + C_\kappa\kappa\mathbf{n}\cdot\frac{\partial\mathbf{h}}{\partial s}\bigg|_0^L - C_\kappa\frac{\partial}{\partial s}(\kappa\mathbf{n})\cdot\mathbf{h}\,\big|_0^L \qquad (15)\end{aligned}$$

where $\kappa\mathbf{n} = \partial\mathbf{t}/\partial s$ and $\mathbf{n}$ is the unit normal vector to the curve $\mathbf{x}$. The boundary terms are zero if, for example, $\kappa = \partial\kappa/\partial s = 0$ at both ends. These conditions correspond to free ends. Restricted ends force in turn restrictions on $\mathbf{h}(0)$ and $\mathbf{h}(L)$ and result in different boundary conditions. Relation (15) is the directional derivative of U_κ in the $\mathbf{h}$ direction and thus as $\mathbf{h}$ was arbitrary we obtain the deterministic dynamical equation for $\mathbf{x}(t,s)$

$$\begin{aligned}\zeta\frac{\partial\mathbf{x}}{\partial t} &= -\nabla U_\kappa \qquad (16)\\ &= -C_\kappa\frac{\partial}{\partial s}(\kappa^2\mathbf{t}) - C_\kappa\frac{\partial^2}{\partial s^2}(\kappa\mathbf{n}) \\ &= -C_\kappa\mathbf{x}'''' - C_\kappa[(\mathbf{x}''\cdot\mathbf{x}'')\mathbf{x}']' \qquad (17)\end{aligned}$$

with, in the case of free ends, boundary conditions $\mathbf{x}''(0) = \mathbf{x}''(L) = \mathbf{x}'''(0) = \mathbf{x}'''(L) = 0$ and initial conditions $\mathbf{x}(s,0) = \mathbf{f}_0(s)$, $(\partial/\partial t)\mathbf{x}(s,0) = \mathbf{g}_0(s)$. The coefficient ζ is a dissipation constant; in principle ζ may be a matrix (the Oseen tensor).

The time-independent solutions of Equation (17) are the equilibria for pure bending of an elastic rod with circular cross-section. Integrating we obtain

$$-C_\kappa\mathbf{x}''' - C_\kappa(\mathbf{x}''\cdot\mathbf{x}'')\mathbf{x}' = \mathbf{F}$$

where $\mathbf{F}$, a constant vector, is the equilibrium internal stress (from bending energy only). Hence

$$C_\kappa\mathbf{x}'\times\mathbf{x}''' = \mathbf{F}\times\mathbf{x}'$$

which is well known (Landau and Lifshitz, 1986).

Calculation of the gradient of the twist energy is somewhat more involved than for the curvature energy. In preparation we first study the kinematics of twist evolution under an imposed motion of the the axis curve $\mathbf{x}(s,t)$. The twist itself represents the rotation rate in s of a unit vector $\boldsymbol{\xi}(s)$ around the curve $\mathbf{x}(s)$. That is, the curves $\mathbf{x}$ and $\mathbf{x}+\epsilon\boldsymbol{\xi}$ constitute the edges of a ribbon which twists at rate ω (more specifically $(\boldsymbol{\xi}\times(\partial/\partial s)\boldsymbol{\xi})\cdot\mathbf{t} = \omega$). We

assume that $\boldsymbol{\xi}$ is perpendicular to $\mathbf{x}$, i.e., $\boldsymbol{\xi} \cdot \partial\mathbf{x}/\partial s = 0$, for all s and t. Thus, since $\boldsymbol{\xi}$ is a unit vector,

$$\frac{\partial \boldsymbol{\xi}}{\partial s} = \boldsymbol{\Lambda} \times \boldsymbol{\xi} = \left[\omega \mathbf{t} + \mathbf{t} \times \frac{\partial \mathbf{t}}{\partial s}\right] \times \boldsymbol{\xi} \tag{18}$$

where, again, $\mathbf{t}$ is the unit tangent vector to $\mathbf{x}$. ($\boldsymbol{\Lambda}$ is the infinitesimal rotation vector of the *body-fixed frame* along the central curve $\mathbf{x}$). Likewise in order that $\boldsymbol{\xi}$ remain a unit vector perpendicular to $\mathbf{x}$,

$$\frac{\partial \boldsymbol{\xi}}{\partial t} = \boldsymbol{\Omega} \times \boldsymbol{\xi} = \left[\alpha \mathbf{t} + \mathbf{t} \times \frac{\partial \mathbf{t}}{\partial t}\right] \times \boldsymbol{\xi} \tag{19}$$

for some function $\alpha(s,t)$ which we will call the *spin*. ($\boldsymbol{\Omega}$ is the infinitesimal rotation vector of the body-fixed frame in time.) We assume temporarily that $\alpha(s,t)$ and $\mathbf{x}(s,t)$ (and hence $\mathbf{t}(s,t) = \partial\mathbf{x}/\partial s$) are known functions. Also we assume that the curve $\mathbf{x}$ is inextensible, i.e., that $\partial\mathbf{x}/\partial s$ is a unit vector for all s and t (see Longcope and Klapper (1997) for the extension of the argument to extensibility). The motion of $\mathbf{x}$ and the spin of the ribbon around $\mathbf{x}$ results in a change of $\boldsymbol{\xi}(s,t)$ according to (19), which in turn specifies the evolution of $\omega(s,t)$ through (18). Taking the partial derivative of (18) with respect to time and the partial derivative of (19) with respect to space, and then dotting by $\mathbf{t} \times \boldsymbol{\xi}$, we obtain

$$\frac{\partial \omega}{\partial t} = \frac{\partial \alpha}{\partial s} + \left(\frac{\partial \mathbf{t}}{\partial s} \times \frac{\partial \mathbf{t}}{\partial t}\right) \cdot \mathbf{t} \tag{20}$$

(see for example Dill, 1992). The first contribution on the right hand side is independent of the motion of $\mathbf{x}$ and, in the case of an inertial elastic system, is associated with torsional waves. The second contribution,

$$\left(\frac{\partial \mathbf{t}}{\partial s} \times \frac{\partial \mathbf{t}}{\partial t}\right) \cdot \mathbf{t} = \kappa \mathbf{b} \cdot \frac{\partial \mathbf{t}}{\partial t}$$

(where $\mathbf{b} = \mathbf{t} \times \mathbf{n}$ is the *binormal* vector) measures the twist to writhe conversion rate $\kappa\mathbf{b} \cdot \partial\mathbf{t}/\partial t =$ the rate of out-of-plane rotation of $\mathbf{x}$ times the curvature, i.e., the "local helical change" of $\mathbf{x}$.

We now proceed to take the functional derivative of the twist potential energy

$$U_\omega(\mathbf{x}, \boldsymbol{\xi}) = \frac{1}{2}\int_0^L C_\omega \omega^2 ds = \frac{1}{2}\int_0^L C_\omega \left[\left(\boldsymbol{\xi} \times \frac{\partial \boldsymbol{\xi}}{\partial s}\right) \cdot \frac{\partial \mathbf{x}}{\partial s}\right]^2 ds$$

in the direction $(\mathbf{h}, \boldsymbol{\gamma})$ with the restriction $\boldsymbol{\gamma} \cdot \mathbf{t} = \boldsymbol{\gamma} \cdot \boldsymbol{\xi} = 0$. Expanding as before we obtain

$$\begin{aligned} U_\omega(\mathbf{x} + \epsilon\mathbf{h}, \boldsymbol{\xi} + \epsilon\boldsymbol{\gamma}) \;=\; & \frac{1}{2}\int_0^L C_\omega \left[\left(\boldsymbol{\xi} \times \frac{\partial \boldsymbol{\xi}}{\partial s}\right) \cdot \frac{\partial \mathbf{x}}{\partial s}\right]^2 ds \\ & + \epsilon \int_0^L C_\omega \left(\boldsymbol{\gamma} \times \frac{\partial \boldsymbol{\xi}}{\partial s}\right) \cdot \frac{\partial \mathbf{x}}{\partial s} \left(\boldsymbol{\xi} \times \frac{\partial \boldsymbol{\xi}}{\partial s}\right) \cdot \frac{\partial \mathbf{x}}{\partial s} ds \end{aligned}$$

$$
\begin{aligned}
&+\epsilon\int_0^L C_\omega\left(\boldsymbol{\xi}\times\frac{\partial\boldsymbol{\gamma}}{\partial s}\right)\cdot\frac{\partial\mathbf{x}}{\partial s}\left(\boldsymbol{\xi}\times\frac{\partial\boldsymbol{\xi}}{\partial s}\right)\cdot\frac{\partial\mathbf{x}}{\partial s}ds\\
&+\epsilon\int_0^L C_\omega\left(\boldsymbol{\xi}\times\frac{\partial\boldsymbol{\xi}}{\partial s}\right)\cdot\frac{\partial\mathbf{h}}{\partial s}\left(\boldsymbol{\xi}\times\frac{\partial\boldsymbol{\xi}}{\partial s}\right)\cdot\frac{\partial\mathbf{x}}{\partial s}ds\\
&-\epsilon\int_0^L C_\omega\left(\left(\boldsymbol{\xi}\times\frac{\partial\boldsymbol{\xi}}{\partial s}\right)\cdot\frac{\partial\mathbf{x}}{\partial s}\right)^2\frac{\partial\mathbf{x}}{\partial s}\cdot\frac{\partial\mathbf{h}}{\partial s}ds+O(\epsilon^2).
\end{aligned}
$$

Again, integrating by parts,

$$
\begin{aligned}
\lim_{\epsilon\to0}\frac{U_\omega(\mathbf{x}+\epsilon\mathbf{h},\boldsymbol{\xi}+\epsilon\boldsymbol{\gamma})-U_\omega(\mathbf{x},\boldsymbol{\xi})}{\epsilon} &= \int_0^L C_\omega\left[-\frac{\partial\omega}{\partial s}(\mathbf{t}\times\boldsymbol{\xi})\cdot\boldsymbol{\gamma}-\frac{\partial}{\partial s}(\omega\kappa\mathbf{b})\cdot\mathbf{h}\right]ds\\
&+ C_\omega\omega^2\mathbf{t}\cdot\mathbf{h}\big|_0^L+C_\omega\omega(\boldsymbol{\xi}\times\mathbf{t})\cdot\boldsymbol{\gamma}\,\big|_0^L+C_\omega\,\omega\left(\boldsymbol{\xi}\times\frac{\partial\boldsymbol{\xi}}{\partial s}\right)\cdot\mathbf{h}\Big|_0^L
\end{aligned}
$$

The boundary terms are 0 if, for example, $\omega(0)=\omega(L)=0$ (free boundaries). Thus considering $-\nabla U_\omega$ with $\boldsymbol{\xi}$ fixed (i.e., $\boldsymbol{\gamma}=0$)

$$
\zeta\frac{\partial\mathbf{x}}{\partial t}=C_\omega\frac{\partial}{\partial s}\left(\omega\frac{\partial\mathbf{x}}{\partial s}\times\frac{\partial^2\mathbf{x}}{\partial s^2}\right)=C_\omega\left(\omega\frac{\partial\mathbf{x}}{\partial s}\times\frac{\partial^3\mathbf{x}}{\partial s^3}+\frac{\partial\omega}{\partial s}\frac{\partial\mathbf{x}}{\partial s}\times\frac{\partial^2\mathbf{x}}{\partial s^2}\right). \tag{21}
$$

Boundary conditions are determined by requiring for example $\dot\omega(0)=\dot\omega(L)=0$ (see equation (22)). The right-hand side of Equation (21) is the force arising from the twist energy gradient (e.g. Heath et al., 1996, Eqn. A33, A34). Similarly considering $-\nabla U_\omega$ with $\mathbf{x}$ fixed (i.e., $\mathbf{h}=0$)

$$
\hat\zeta\frac{\partial\boldsymbol{\xi}}{\partial t}=C_\omega\frac{\partial\omega}{\partial s}\mathbf{t}\times\boldsymbol{\xi}.
$$

where $\hat\zeta$ is a torsional dissipation constant. In principle $\hat\zeta$ may be a matrix. As $\mathbf{x}$ is assumed fixed for this last calculation, (19) implies that

$$
\hat\zeta\alpha=C_\omega\frac{\partial\omega}{\partial s}
$$

and so, using (20),

$$
\frac{\partial\omega}{\partial t}=\frac{C_\omega}{\hat\zeta}\frac{\partial^2\omega}{\partial s^2}+\left(\frac{\partial\mathbf{t}}{\partial s}\times\frac{\partial\mathbf{t}}{\partial t}\right)\cdot\mathbf{t} \tag{22}
$$

with $\omega(0)=\omega(L)=0$.

Finally, in addition to the curvature and twist contributions to the potential energy, there is also a tension contribution (the last term, $U_\mathcal{T}$ in (3)). Proceeding with a functional gradient calculation as above, we obtain

$$
\lim_{\epsilon\to0}\frac{U_\mathcal{T}(\mathbf{x}+\epsilon\mathbf{h},\boldsymbol{\xi}+\epsilon\boldsymbol{\gamma})-U_\mathcal{T}(\mathbf{x},\boldsymbol{\xi})}{\epsilon}=\frac{\partial}{\partial s}(\mathcal{T}\mathbf{t})+\mathcal{T}\mathbf{t}\cdot\mathbf{h}\big|_0^L
$$

where the tension $\mathcal{T} = (\partial s/\partial\sigma - 1)$. Here σ is a parametrization that stretches with $\mathbf{x}$ and s again is arclength. Alternatively it is possible to enforce inextensibility for $\mathbf{x}$, i.e. $\partial s/\partial\sigma = 1$. In this case $\mathcal{T}$ is defined in a different manner (see e.g., Klapper 1996). If $\mathcal{T}(0) = \mathcal{T}(L) = 0$ then

$$\zeta \frac{\partial \mathbf{x}}{\partial t} = -E \frac{\partial}{\partial s}(\mathcal{T}\mathbf{t}) \tag{23}$$

where E is the elastic Young's module for extension. Combining (17), (21), and (23) we obtain finally the deterministic forces on $\mathbf{x}$. Equation (22) describes the deterministic evolution of ω.

The time-independent mechanical equilibrium for an isotropic inextensible elastic rod with bending, twist and tension is

$$-C_\kappa[\mathbf{x}'''' + ((\mathbf{x}'' \cdot \mathbf{x}'')\mathbf{x}')'] + C_\omega \omega \mathbf{x}' \times \mathbf{x}''' + E(\mathcal{T}\mathbf{x}')' = 0 \tag{24}$$

noting that $\omega' = 0$ at equilbrium. Equation (24), the starting point for analyzing rod equilibrium and buckling, has first integral

$$-C_\kappa[\mathbf{x}''' + (\mathbf{x}'' \cdot \mathbf{x}'')\mathbf{x}'] + C_\omega \omega \mathbf{x}' \times \mathbf{x}'' + E\mathcal{T}\mathbf{x}' = \mathbf{C}$$

3.2 Discrete case

We move from continuous systems to discrete ones where the discrete coordinates form the vertices of a piecewise linear chain, assumed to be inextensible, i.e., each link of the chain has constant (in time) length. For simplicity we assume each link has length 1 and that the intrinsic bending and twisting angles are 0. Let $\mathbf{x}_i(t)$, $0 \le i \le N$ be the locations of the vertices of the chain and let $\mathbf{t}_i = \mathbf{x}_i - \mathbf{x}_{i-1}$ be the unit vector pointing along the ith link. Define θ_j, $1 \le j \le N-1$ to be the angle between $\mathbf{t}_{j+1}$ and $\mathbf{t}_j$. We suppose that the potential energy of the chain is a function of the θ_j's, i.e., $U_b = U_b(\boldsymbol{\theta})$. Using as in the continuous case the linear approximation to U_b, we obtain

$$U_b(\boldsymbol{\theta}) = \frac{1}{2} \sum_{j=1}^{N-1} C_j \theta_j^2 \tag{25}$$

for some constants C_j.

In addition to the potential energy, we have constraints $g^j(\mathbf{x}) = (\mathbf{x}_j - \mathbf{x}_{j-1})^2 - 1 = 0$, $1 \le j \le N$ to satisfy. Taking a time derivative, we obtain

$$\dot{\mathbf{x}} \cdot \nabla g^j = \mathbf{t}_j \cdot \dot{\mathbf{t}}_j = 0 \tag{26}$$

and thus the vertex velocities must be perpendicular to the gradients of the constraints.

We then arrive at the evolution equations

$$\zeta \frac{d}{dt}\mathbf{x} = -\frac{1}{2}\nabla_{\mathbf{x}} \sum_{j=1}^{N-1} A_j \theta_j^2(\mathbf{x}) - \sum_{j=1}^{N} T_j \nabla g^j + \mathbf{f}(t)$$

where the discretized tensions T_j are defined so that (26) are satisfied. Note that we are required to take derivatives of the θ's with respect to cartesian coordinates $\mathbf{x}$. This is a awkward computation that can be avoided, however, by observing that

$$\begin{aligned}(\mathbf{t}_{i+1}-\mathbf{t}_i)^2 &= 2-2\mathbf{t}_{i+1}\cdot\mathbf{t}_i \\ &= 2-2\cos\theta_i \\ &= \theta_i^2+O(\theta_i^4).\end{aligned}$$

Since (25) is a approximation of U_b only valid through $O(\theta^2)$ terms anyways, then the approximation

$$\begin{aligned}U_b(\mathbf{x}) &= \frac{1}{2}\sum_{j=1}^{N-1} C_j(\mathbf{t}_{j+1}-\mathbf{t}_j)^2 \\ &= \frac{1}{2}\sum_{j=1}^{N-1} C_j(\mathbf{x}_{j+1}-2\mathbf{x}_j+\mathbf{x}_{j-1})^2\end{aligned} \tag{27}$$

is equally valid. Using the new potential energy we get the evolution equations

$$\zeta\frac{d}{dt}\mathbf{x} = -\frac{1}{2}\nabla_{\mathbf{x}}\sum_{j=1}^{N-1} A_j^2(\mathbf{t}_{j+1}-\mathbf{t}_j)^2 - \sum_{j=1}^{N} T_j\nabla g^j + \mathbf{f}(t). \tag{28}$$

Note that $-(1/2)\nabla_{\mathbf{x}i}(\mathbf{t}_{j+1}-\mathbf{t}_j)^2 = -\mathbf{x}_{i+2}+4\mathbf{x}_{i+1}-6\mathbf{x}_i+4\mathbf{x}_{i-1}-\mathbf{x}_{i-2}$, the centered difference approximation to the first term on the right-hand side of (17), $-(d^4/ds^4)\mathbf{x}$. However, the gradient of the discretized bending energy U_b is not an exact discretized version of the gradient of the continuous version of U_κ. In particular the term $\partial/\partial s(\kappa^2\mathbf{t})$ appears only in the continuous case. (The reason for this is that in the discrete energy the curvature is concentrated entirely at the vertices whereas the term $\partial/\partial s(\kappa^2\mathbf{t})$ represents a sort of "curvature spreading" effect.) Thus the continous and discrete bending energies are not consistent, i.e., in the limit of the discretization length going to zero, one does not obtain the continuous equations. The difference is subtle but possibly important. A similar phenomenon occurs in the comparison of the twist potential energies. In addition we remark that (28) is identical to the linear equation obtained by Harris and Hearst (1966) except for the nonlinear tension terms. Harris and Hearst assume inextensibility as well so in principle their system should include these nonlinear tension terms.

We can make the discrete and continuous energies consistent by altering (27) to

$$\begin{aligned}U_b(\mathbf{x}) &= \frac{1}{2h^2}\sum_{j=1}^{N-1} C_j(\mathbf{t}_{j+1}-\mathbf{t}_j)^2 \\ &= \frac{1}{2}\sum_{j=1}^{N-1} C_j h^{-2}(\mathbf{t}_{j+1}-\mathbf{t}_j)^2 \\ &= \frac{1}{2}\sum_{j=1}^{N-1} C_j\frac{(\mathbf{t}_{j+1}-\mathbf{t}_j)^2}{(\mathbf{x}_{j+1}-\mathbf{x}_j)^2}\end{aligned} \tag{29}$$

(where h is the distance between vertices) so that the discrete energy depends not only on the vertex angles but also on the distances between vertices. Since h is assumed constant it is natural to apply the gradient only to the $(\mathbf{t}_{j+1} - \mathbf{t}_j)^2$ terms. Note however that applying the gradient to (29) will result in an extra term (namely a discretized version of $\partial/\partial s(\kappa^2 \mathbf{t})$). The constraint $h =$ constant is enforced afterwards by the tension terms referred to earlier. If on the other hand the energy is truly angle dependent as is commonly the case in discrete systems, then the energy probably should not depend on h. In this case the discrete and continuous energies are inconsistent.

Twist potential energy contributes in a similar manner. Defining a ribbon of width ϵ with unit vectors $\boldsymbol{\xi}_k$, then $[\boldsymbol{\xi}_k \times (\boldsymbol{\xi}_{k+1} - \boldsymbol{\xi}_k)] \cdot \mathbf{t}_k = (\boldsymbol{\xi}_k \times \boldsymbol{\xi}_{k+1}) \cdot \mathbf{t}_k = \omega_k + O(\omega_k^3) + O(\epsilon^2(\theta^2 + \omega^2))$ so that we can write

$$U_t = \frac{1}{2} \sum_{j=1}^{N-1} C_\omega [(\boldsymbol{\xi}_k \times \boldsymbol{\xi}_{k+1}) \cdot \mathbf{t}_k]^2.$$

Varying the $\boldsymbol{\xi}_k$'s as well as $\mathbf{x}$ (as in the previous section) we obtain the contributions of ∇U_t to the ω and $\mathbf{x}$ evolution equations. As in the continuous version, the $\boldsymbol{\xi}_k$'s are used only to derive the evolution equations but do not appear in those equations themselves. Again, the result is a discretization of the results of the continuous model except for a discrepancy than can be removed by including $h_j^2 = (\mathbf{x}_{j+1} - \mathbf{x}_j)^2$ in the discrete energy, i.e.,

$$U_t = \frac{1}{2} \sum_{j=1}^{N-1} C_\omega \frac{[(\boldsymbol{\xi}_k \times \boldsymbol{\xi}_{k+1}) \cdot \mathbf{t}_k]^2}{(\mathbf{x}_{j+1} - \mathbf{x}_j)^2}.$$

The original (and standard) discrete twist potential energy $\sum C_\omega \omega_k^2$ again is inconsistent with the continuous twist potential energy due to the fact the discrete version constrains twist to be concentrated at discrete points even in the limit of the discretization going to 0.

4 The Random Forcing

We now turn our attention to the random forcing term. Typically the dynamics of a macromolecular conformation $\mathbf{x}$ in a viscous solvent is modeled using a set of evolution equations of the form

$$\mathbf{H} \frac{d\mathbf{x}}{dt} = -\nabla U(\mathbf{x}) + \boldsymbol{\Sigma} \dot{\mathbf{w}}, \quad \mathbf{x}(0) = \mathbf{x}_0 \tag{30}$$

where $\mathbf{H}$, the "hydrodynamic interaction" matrix, is assumed to be a symmetric positive-definite function of $\mathbf{x}$. We note that the equation for twist evolution should also have a random forcing term and in fact the theory to be re-derived in this section covers twisting noise as well. $\boldsymbol{\Sigma}\boldsymbol{\Sigma}^T$ is a covariance matrix, and $\mathbf{w}$ is a noise vector satisfying $\langle dw_i \rangle = 0$, $\langle dw_i dw_j \rangle = \delta_{ij} dt$. We imagine integrating (30) on the time interval $t \in [0, \hat{t}]$ for some finite $\hat{t}$ over many realizations of the noise in order to develop a transition probability density $P(\mathbf{x}, t | \mathbf{x}_0, 0)$ that our system is in state $\mathbf{x}$ at time t given that it started in state $\mathbf{x}_0$ at time 0. Equation (30) defines a diffusion process $\mathbf{x}(t)$. To use (30) to derive an equation for the

probability density of states $\mathbf{x}$, note that

$$\begin{aligned} P(\mathbf{x}, t+s) &= \int P(\mathbf{x}(t+s), t+s \mid \mathbf{x}(t) = \mathbf{x}', t) P(\mathbf{x}', t) d\mathbf{x}' \\ &= \int \Big[P(\mathbf{x}(t), t|\mathbf{x}', t) + \frac{\partial}{\partial x_i} P(\mathbf{x}(t), t|\mathbf{x}', t)(\mathbf{x}(t+s) - \mathbf{x}(t))_i \\ &\quad + \frac{1}{2} \frac{\partial^2}{\partial x_i \partial x_j} P(\mathbf{x}(t), t|\mathbf{x}', t)(\mathbf{x}(t+s) - \mathbf{x}(t))_i (\mathbf{x}(t+s) - \mathbf{x}(t))_j \\ &\quad + O((\mathbf{x}(t+s) - \mathbf{x}(t))^3) \Big] P(\mathbf{x}', t) d\mathbf{x}'. \end{aligned}$$

On the right-hand side we have Taylor-expanded in the Langevin trajectories that arrive at location $\mathbf{x}$ at time $t+s$. Note that $P(\mathbf{x}(t), t|\mathbf{x}', t) = \delta(\mathbf{x}(t) - \mathbf{x}')$. Then to first order in s, we see that $\mathbf{x}(t+s) - \mathbf{x}(t) = \Delta\mathbf{x} = -s\mathbf{H}^{-1}\nabla U + \mathbf{H}^{-1}\boldsymbol{\Sigma}\Delta\mathbf{w}$ so that

$$\begin{aligned} P(\mathbf{x}(t+s), t+s) - P(\mathbf{x}(t), t) &= \int [-s\nabla P(\mathbf{x}(t), t|\mathbf{x}', t)\mathbf{H}^{-1}\nabla U \\ &+ \frac{s}{2}\nabla^2 P(\mathbf{x}(t), t|\mathbf{x}', t)\mathbf{H}^{-1}\boldsymbol{\Sigma}\boldsymbol{\Sigma}^T\mathbf{H}^{-T} \\ &+ O((\mathbf{x}(t+s) - \mathbf{x}(t))^3)] P(\mathbf{x}', t) d\mathbf{x}'. \end{aligned}$$

using $\langle \Delta w_i \rangle = 0$ and $\langle \Delta w_i \Delta w_j \rangle = s\delta_{ij}$. Taking the limit $s \to 0$ and integrating by parts we find that P satisfies

$$\frac{\partial P}{\partial t} = \nabla \cdot (P\mathbf{H}^{-1}\nabla U) + \frac{1}{2}\sum_{i,j} \frac{\partial^2}{\partial x_i \partial x_j} \left((\mathbf{H}^{-1}\boldsymbol{\Sigma}\boldsymbol{\Sigma}^T\mathbf{H}^{-T})_{ij} P \right), \quad P(\mathbf{x}, 0) = \delta(\mathbf{x} - \mathbf{x}_0) \tag{31}$$

the Fokker-Planck equation for P.

We now assume that the system we wish to study is in thermal equilibrium. An equilibrium entails stationarity and the principle of *detailed balance*, namely that $P_{AB}P_{eq}(A) = P_{BA}P_{eq}(B)$ where A and B are any 2 possible events, $P_{eq}(A)$ and $P_{eq}(B)$ are the respective equililbrium probabilities of those 2 events, and P_{ij} is the transition probability of our system going from event i to event j. This assumption can be shown to be equivalent to the reversibility of the stationary diffusion process (Qian et al., 1991). If we assume that the transition probability should tend to the stationary Boltzmann distribution as $t \to \infty$, i.e., $P(\mathbf{x}, t|\mathbf{x}_0) \to P_{eq}(\mathbf{x}) = C\exp(-U(\mathbf{x})/k_BT)$, then we are led to a selection principle for $\boldsymbol{\Sigma}$ called the fluctuation-dissipation theorem (Fox, 1978) as follows. The differential form of the principle of detailed balance is (Fukushima, 1980; Qian et al., 1991)

$$\int (Lf(\mathbf{x}))g(\mathbf{x})P_{eq}(\mathbf{x})d\mathbf{x} = \int f(\mathbf{x})(Lg(\mathbf{x}))P_{eq}(\mathbf{x})d\mathbf{x} \tag{32}$$

for any smooth functions f and g, where L is the differential "transition probability" operator in Equation (31):

$$Lf = \nabla \cdot (fH^{-1}\nabla U) + \frac{1}{2}\sum_{i,j}\frac{\partial}{\partial x_i}\left((H^{-1}\boldsymbol{\Sigma}\boldsymbol{\Sigma}^T H^{-T})_{ij}\frac{\partial f}{\partial x_j}\right)$$

A short calculation shows (32) to be true if $P_{eq} \sim \exp(-U/k_BT)$, the Boltzmann distribution, and

$$\int (g\nabla f - f\nabla g)\left[\frac{\mathbf{H}^{-1}\boldsymbol{\Sigma}\boldsymbol{\Sigma}^T\mathbf{H}^{-T}}{2k_BT} - \mathbf{H}^{-1}\right]\cdot\nabla U\exp(-U/k_BT)d\mathbf{x} = 0,$$

e.g., $\boldsymbol{\Sigma} = \sqrt{2k_BT\,\mathbf{H}}$. If $\mathbf{H}$ is diagonal, then the noise is independent for each degree of freedom, with each amplitude determined by the corresponding frictional coefficient using the Einstein relation. More generally $\boldsymbol{\Sigma} = \sqrt{k_BT\mathbf{H}}\mathbf{Q}$ for any orthogonal matrix $\mathbf{Q}$. This freedom reflects the fact that an isotropic Brownian motion is invariant under rigid rotations.

If $\nabla U(\mathbf{x}) = \mathbf{E}\mathbf{x}$ is linear with some symmetric matrix $\mathbf{E}$ then (30) can be diagonalized. The generalized eigenvalue problem $\mathbf{E}\mathbf{v} = \lambda\mathbf{H}\mathbf{v}$ has a full set of eigenvalues and eigenvectors, i.e., there is a basis of eigenvectors. If $\mathbf{B}$ is a matrix with columns made up of these eigenvectors then $\mathbf{E}\mathbf{B} = \mathbf{H}\mathbf{B}\boldsymbol{\Lambda}$ where $\boldsymbol{\Lambda}$ is a diagonal matrix with the eigenvalues of $\mathbf{E}\mathbf{v} = \lambda\mathbf{H}\mathbf{v}$ as diagonal elements. Setting $\mathbf{B}\mathbf{y} = \mathbf{x}$, (30) becomes

$$\begin{aligned}\mathbf{H}\mathbf{B}\frac{d\mathbf{y}}{dt} &= -\mathbf{E}\mathbf{B}\mathbf{y} + \boldsymbol{\Sigma}\dot{\mathbf{w}} \\ &= -\mathbf{H}\mathbf{B}\boldsymbol{\Lambda}\mathbf{y} + \boldsymbol{\Sigma}\dot{\mathbf{w}}\end{aligned}$$

and hence

$$\frac{d\mathbf{y}}{dt} = -\boldsymbol{\Lambda}\mathbf{y} + (\mathbf{H}\mathbf{B})^{-1}\boldsymbol{\Sigma}\dot{\mathbf{w}}.$$

If $\mathbf{H} = \zeta\mathbf{I}$ where $\mathbf{I}$ is the identity matrix, then $\mathbf{B}^{-1}$ is orthogonal and can be absorbed in $\boldsymbol{\Sigma}$. The stationary solution for this separable linear stochastic differential equation is

$$\begin{aligned}P_{eq}(\mathbf{y}) &= C\exp\left(-\mathbf{y}(\boldsymbol{\Sigma}^{-1}\mathbf{H}\mathbf{B})^T(\boldsymbol{\Sigma}^{-1}\mathbf{H}\mathbf{B})\boldsymbol{\Lambda}\mathbf{y}\right) \\ &= C\exp\left(-(\mathbf{B}\mathbf{y})\mathbf{H}^T\boldsymbol{\Sigma}^{-T}\boldsymbol{\Sigma}^{-1}\mathbf{E}(\mathbf{B}\mathbf{y})\right)\end{aligned}$$

where C is a normalization factor. We therefore have

$$P_{eq}(\mathbf{x}) = C\exp\left(-\frac{\mathbf{x}\mathbf{E}\mathbf{x}}{2k_BT}\right)$$

since $\mathbf{B}\mathbf{y} = \mathbf{x}$ and $\boldsymbol{\Sigma}\boldsymbol{\Sigma}^T = 2k_BT\mathbf{H} = 2\zeta k_BT\mathbf{I}$. This is the well known result of Onsager for linear relaxation (Fox, 1978; Doi and Edwards, 1986). However, as indicated above a fluctuation-dissipation relation holds for more general systems than linear.

Returning to a continuous model, consider a dynamics equation of the general form

$$\frac{\partial\mathbf{x}(t,s)}{\partial t} = D_s[\mathbf{x}(t,s)] + g(t,s) \tag{33}$$

where D_s is a nonlinear differential operator and $g(t,s)$ is a random forcing with some spatial correlation. More specifically, g is a stationary process with zero mean and

$$\int_0^\infty \langle g(t,s)g(t+\tau,s+\nu)\rangle d\nu = \delta(\tau)C(\nu)$$

where $C(\nu)$ provides the spatial characteristics of the random force. To relate the continuous forcing to that of the discrete model, we discretize the spatial variable $\mathbf{x}$ by introducing

$$\mathbf{x}_n(t) = \frac{1}{\Delta}\int_{n\Delta}^{(n+1)\Delta} \mathbf{x}(t,s)ds.$$

Therefore

$$\frac{d\mathbf{x}_n(t)}{dt} = \frac{1}{\Delta}\int_{n\Delta}^{(n+1)\Delta} \frac{\partial \mathbf{x}(t,s)}{\partial t}ds = \frac{1}{\Delta}\int_{n\Delta}^{(n+1)\Delta} D_s[\mathbf{x}(t,s)]ds + g_n(t)$$

where

$$g_n(t) = \frac{1}{\Delta}\int_{n\Delta}^{(n+1)\Delta} g(t,s)ds$$

is a random process with zero mean and

$$\begin{aligned}\langle g_n(t)g_m(t+\tau)\rangle &= \frac{1}{\Delta^2}\int_{n\Delta}^{(n+1)\Delta}\int_{m\Delta}^{(m+1)\Delta}\langle g(t,s)g(t+\tau,s')\rangle ds ds' \\ &= \frac{2\delta(\tau)}{\Delta}\int_0^\Delta C((n-m)\Delta+\nu)\left(1-\frac{\nu}{\Delta}\right)d\nu \qquad (34)\end{aligned}$$

If the correlation length of $C(\nu)$ is chosen to be sufficiently smaller than Δ, for example $C(\nu) \propto \delta(\nu)$, then a δ_{mn} term arises since

$$\int_0^\Delta C((n-m)\Delta+\nu)\left(1-\frac{\nu}{\Delta}\right)d\nu = \delta_{mn}\int_0^\Delta C(\nu)\left(1-\frac{\nu}{\Delta}\right)d\nu$$

In this case, the discrete and continuous models are equivalent within a scaling factor $N = L/\Delta$, and the variance of g_n is inversely proportional to the discretization length Δ. It is important to note that with decreasing Δ, eventually $C(\nu)$ can no longer be treated as a Dirac δ-function, and its integral becomes proportional to Δ. This indicates that a truly self-consistent continuous model has to include a finite correlation length. On the other hand, however, we see that if one is only interested in the large-scale dynamics of a polymer, one can introduce white noise with appropriate amplitude. This is equivalent to introducing white noise into the continuous system by either discretizing the system or by studying its normal modes. In order to resolve the noise however any discretization of a continuous system should resolve length scales of $O(\Delta)$. If a normal mode approach is used then modes with wavelength shorter than $O(\Delta)$ should be damped. On the other hand, however, the main utility of a continuous approximation to a discrete system is the use of smoothed length scales much large than $O(\Delta)$. Both of these requirements contradict that advantage. This should not be seen as a surprise since any approximation has limitations. If a continuous system is used nevertheless then (34) suggests that the noise amplitude (i.e., $\sqrt{T}$) on the long smoothed length scale L should be scaled by a factor L/Δ.

5 Discussion

This paper is intended as a comparison of mathematical aspects of two large-scale models of DNA conformation. The most significant results are, one, the observation that their respective potential energy functionals are not consistent with each other, and, two, an analysis of the most appropriate random forcing for the two models. At the present time, we are not able to quantitatively assess the importance of the difference in energy functionals but believe that it should not be ignored. It is possible to state without question that there is a physical basis to the difference in energy functionals – continuous curvature and twist, even in discretized form, is fundamentally different from discrete bending and twisting. The discrete bending energy cares only about the angle between base-pairs and not their separation. The continuous curvature energy smooths those angles and results in an extra tension-like force due to the fact that energy can be reduced by spreading the curvature around. (A similar remark holds for twisting energy.) In the continuous case, the further apart base-pairs are, the lower the energy, because extra separation allows a smoother, lower curvature connection. Hence the curvature based energy has a dependence on arclength that the angle based energy does not, resulting in an extra term in the dynamics. It is important to note that this difference is entirely independent of true tension forces arising from the extensional energy; there are other mutually consistent contributions to the two different dynamics that contain those effects of extension or contraction.

In addition to differences arising from the two energy functionals we have also discussed the use of random forcing to simulate the effects of solution on the DNA molecule or fragment. As noted noise can be used in order to explore the equilibrium distribution in an artificial way; it may not necessarily result in true physical trajectories in phase space. The use of Brownian or Langevin dynamics to study time correlations in particular should be attempted with caution. We re-derived the appropriate form of the random forcing for the discrete model. For the continuous model we have discussed the nature of random forcing where degrees of freedom are smoothed together, with the aim of providing a coherent scheme for approximating entropic effects while computing with a continuous model.

The relative applicability of the two models probably depends on the context. For very large-scale modeling where effects on the base-pair scale are hoped to be small, the continuous model would seem to be preferable. For problems where base-pair scale (but not smaller) effects are significant, it may be more appropriate to use a discrete model that can include entropic effects more accurately and can treat connections between base-pairs as true angles, avoiding the introduction of smoothing artifacts. For example, while the continuous model could be appropriate for the large scale dynamics of interphase DNA (Yokota et al., 1995), the discrete model might be a better one for studying DNA looping induced by repressor proteins (Finzi and Gelles, 1995). On an even smaller scale, generally all-atom models would be required, for example, to study the dynamic interaction between proteins and DNA.

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7 References

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