Fokker-Planck equations for an equilibrium model of chromatin folding

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Abstract

We analyze the effects of random local linker length variability on the global morphology of a very long, linear, homogeneous chromatin fiber that is modelled as a diffusion process that is parametrized by arclength under a suitable spatial re-scaling. We obtain Fokker-Planck equation for the process whose solution, a probability density function describes the folding.

1 Introduction

In this work, we study the large-scale physical space structure of an equilibrium chromatin folding model that was first proposed by Woodcock *et al* in [10] which incorporates natural linker length variability. The model is in equilibrium, or static, in the sense that time is not a parameter in the problem, and the folded chromatin fiber is constructed as a realization of a continuous Markov process which is parametrized by discrete nucleosome-linker units. Linkers are assumed to be straight lines, not space-filling; and nucleosomes are reduced to contact points between consecutive linkers. For very small linker length average values – relative to the length of the entire fiber – we show that the limit of Markov process is a homogeneous diffusion process that is parametrized by arclength. We find that for specific choices of entry-exit angles at the nucleosomes, and twisting angle distributions between consecutive nucleosome-linker units, this limiting diffusion process resembles the Frenet system of ordinary differential equations for a helix in space plus a lower order noise term. From the diffusion process, we derive a corresponding Fokker-Planck equation which describes its probability density function. The density function provides probabilistic information about the location of one endpoint of the fiber given a fixed arclength and the geometry of the other endpoint.

The paper is organized as follows: Section 2 introduces the chromatin folding problem, the equilibrium model and its equivalent Markovian scheme which we shall be considering. In Sections 3 and 4, we discuss the limiting process of the Markovian scheme, a diffusion process, which yields a Fokker-Planck equation and its corresponding probability density function. Diffusion processes corresponding to special cases of entry-exit and twisting angle distributions is considered here. Appendix A contains detailed computations for the drift and diffusion (covariance) coefficients of the diffusion process for general and special cases.

2 An equilibrium model of DNA folding

In eukaryotic cells, the genomic double-helix deoxyribonucleic acid (DNA) strand is complexed with histone proteins to form *chromatin* – with the negatively-charged DNA wrapping around cores of positively-charged histones [2]. Histones confer upon the chromatin regular, repeating structures which look like beads on a string called *nucleosomes*. Each "bead" is approximately 11 nm in diameter and the "string" between the beads, called *linker DNA*, is 2 nm in diameter and has variable length on the order of 58 to 76 base pairs (bp) of DNA with 1 bp ≈ 0.33 nm [10]. Uncoiled, a DNA strand has total length from 1.7 to 8.5 cm, and a problem of significant interest in cell biology concerns how this huge amount of genetic material is packed into the relatively small volume inside a cell nucleus whose diameter is on the order of 10^{-3} cm. The architecture of the individual nucleosome ("beads") is generally well understood. On the other hand, while it is known that the chromatin fiber (approximately 30 nm in diameter, hence often called *30-nm chromatin fiber* in the cell biology literature) is formed from packed nucleosomes, the arrangement of the nucleosomes in the 30-nm fiber is uncertain [4]. Specifically, the structural principles that come into play during transition from a loose chain of nucleosomes to a compact 30-nm fiber has not been established [3], and it has not been possible to resolve the DNA path between nucleosomes using direct microscopic observations.

Furthermore, it is known that the ionic strength of the medium in which the chromatin sits affects its compaction [10].

In [10], Woodcock *et al.* considered the structure of chromatin fiber in terms of two separate components:

- DNA *folding* that is derived from the intrinsic properties of the nucleosome-linker unit.
- Chromatin *compaction* as determined by the local concentration of ions and other charged molecules.

In particular, they discussed how folding may be affected by the variations in linker length that occur naturally between consecutive nucleosomes and that will give rise to changes in the relative twisting angle between nucleosome-linker units, and how these *local* foldings in turn influence the *global* morphology of the resulting fiber. To this end, the authors proposed a model for chromatin folding in which the linker lengths are variable – averaging at 76 bp – while assuming these linkers between the nucleosomes to be essentially straight homogeneous (base pairs are not distinguished) "sticks" with a fixed rotational position at the nucleosome "beads". The model is *static*, in the sense that starting with two connected nucleosome-linker units in an arbirary orientation in $\mathbb{R}^3$, an already compacted or folded fiber is constructed according to a set of rules which involve the entry-exit linker angle (fixed at α) at each nucleosome and the relative twisting angle (β_i) between consecutive linker-nucleosome units indexed by $i \in \mathbb{N}$. The twisting angle between consecutive nucleosome-linker pairs is a linear modulo 10 bp function of its linker length, l_i. It is known that each base pair in the linker DNA leads to an additional 36° angular twist [5], [10]. The resulting structural model does not change in time and the authors investigated how it was affected by the choice of α and l_i distributions (hence β_i). Computer simulations using the model produced three dimensional, irregular zig-zag "beads-and-sticks" curves which conform very well to the general appearance of nucleosomes and linker DNA as observed *in vitro* using X-ray scattering and electron tomography techniques [3], [1].

Ehrlich *et al.* [5] and Jian *et al.* [11] have since proposed *dynamic* models of chromatin folding which take into account the bending, stretching and twisting forces of the DNA and the electrostatic interaction between linkers. Such effects are spatially long-range and subsequently, the fiber model evolves in time to minimize the respective elastic and electrostatic energies. The dynamic models share identical stochastic (Langevin) differential equations that specify the position of each nucleosome for all time. The model in [5] is based upon the static model in [10], with elastic-electrostatic properties added.

Here, we explore the dependence of the large-scale spatial structure of the equilibrium chromatin folding model as proposed by Woodcock *et al.* [10] upon the entry-exit angle α and twist β_i as for very small average linker lengths. This limit is of interest since linker lengths ($\sim 10^{-8}$ m) are by nature microscopic compared with the macroscopic length of the entire chromatin fiber ($\sim 10^{-2}$ m). In our analysis, the nucleosome "beads" are assumed to have zero diameter and are reduced to contact points between consecutive linker DNAs. The linker lengths are normalized so that the only source of randomness are the independent twisting angles β_i which are drawn from a common prescribed probability distribution. Note especially that in this regard, it is valid to regard the model as being that of a very long chromatin fiber comprising of relatively microscopic nucleosome-linker units – the *normalized* linkers *do not* affect the twisting angles. We derive a numerical scheme that is a nine-dimensional Markov process parametrized by $i \in \mathbb{N}$ which indexes the nucleosome-linker units for the model, and study its behavior for very small linker lengths averages. The formal limit of this Markov process is a stochastic ordinary differential equation, namely a diffusion process, that is parametrized by arclength s (as opposed to time, t). We show that for special choices of entry-exit and twisting angle distributions, this diffusion process is the Frenet equation for a helix with a lower order noise (formal Brownian derivative) term. We then derive a corresponding Fokker-Planck equation for the diffusion process that describes its probability density function. The Fokker-Planck equation associated with the diffusion process is a natural object to consider for the problem since its solution indicates – given an arclength $s > 0$ and the geometry and location $X(0)$ of one endpoint in $\mathbb{R}^3$ – the probability of the other endpoint $X(s)$ being in a certain subset of positions or locations in $\mathbb{R}^3$.

It is reasonable to conjecture that when long-range elastic-electrostatic interactions are incorporated into this static model, mimicking the dynamic setup in [5] and [11], the limiting process for very small linker lengths averages will be a stochastic partial differential equation system in both arclength and time. Obvious limitations in this current model, apart from its static and homogeneous (we do not distinguish between base pair combinations) nature, is that the fiber is not modelled as a space-filling curve and linkers are straight lines.

2.1 Model specifications and construction

Let $\{v_i : i \in \{0, 1, \cdots\}\} \subset \mathbb{R}^3$ represent linker DNA units of the chromatin fiber configured in such a way that the head of v_i is joined to the tail of v_{i+1} – refer to Figure 11. We use the notation $\langle u, v\rangle$ and $u \times v$ to mean the dot and cross products respectively for vectors u and v in $\mathbb{R}^3$. Let $\|u\|^2 \doteq \langle u, u\rangle$ be the squared Euclidean length of u, and $l_i \doteq \|v_i\| > 0$ be the length of the i-th linker piece. Following the construction in [10], we denote the angle between any two consecutive vectors, v_i and v_{i+1} by $\pi - \alpha_i$, with $0 < \alpha_i < \pi$ and $\alpha_i = \alpha$ for $i \in \{0, 1, \cdots\}$. The initial data for this process are the first two linker pieces v_0 and v_1. Recall that the nucleosome between consecutive linkers v_i and v_{i+1} is assumed to have zero diameter and is reduced to the contact points between the linkers. In order to construct v_{i+1} given v_{i-1} and v_i, we follow the two steps below:

Step 1 (*Magnitude*) The length of v_{i+1}, denoted by l_{i+1}, is a random variable of some specified distribution.

Step 2 (*Direction*) Let v'_{i+1} be a vector of length l_{i+1} lying in the plane spanned by v_{i-1} and v_i, making an angle $\pi - \alpha_i$ with v_i, and with $v_i \times v'_{i+1}$ pointing in the same direction as $v_{i-1} \times v_i$. A positive rotation of v'_{i+1} about v_i by an angle β_i will produce v_{i+1}. Let β_i is a linear function of l_i, i.e., the torsion of the $(i + 1)$-th linker out of the plane spanned by v_{i-1} and v_i is a linear function of the i-th linker length, l_i.

Note that with no loss in generality, we may assume that β_i is a linear function of l_i – not linear modulo 10 bp as in [10] originally – since in the upcoming calculations we shall normalize the linker lengths so that the only source of variability in the model are the β_is. In the next sub-section, we present detailed computations for the steps outlined above with the goal of obtaining a Markovian algorithm for the numerical implementation of the model.

2.2 Calculating $v_{i+1} = F(v_i, v_{i-1}, \alpha_i, \beta_i)$

By **Step 1**, v_{i-1} and v_i are not co-linear. We want to express v_{i+1} as a linear combination of v_{i-1}, v_i and $(v_{i-1} \times v_i)$. Without loss of generality, we may assume that all v_k are unit vectors – see (2.8). We will compute v'_{i+1} first. Clearly, $v'_{i+1} = Av_i + Bv_{i-1}$ for scalars A and B. Since we know that the angle between v_{i+1} and v_i to be $\pi - \alpha_i$,

$$\begin{array}{lcl} \langle v'_{i+1}, v_i \rangle & = & \cos(\pi - \alpha_i) \\ \langle A v_i + B v_{i-1}, v_i \rangle & = & -\cos\alpha_i \\ A + B\langle v_{i-1}, v_i \rangle & = & -\cos\alpha_i \\ A - B\cos\alpha_{i-1} & = & -\cos\alpha_i \ . \end{array} \tag{2.1}$$

The length of v'_{i+1} being one implies that,

$$\begin{array}{lcl} \langle v'_{i+1}, v'_{i+1} \rangle & = & 1 \\ \langle A v_i + B v_{i-1}, A v_i + B v_{i-1} \rangle & = & 1 \\ A^2 + 2AB\langle v_{i-1}, v_i \rangle + B^2 \rangle & = & 1 \\ A^2 - 2AB\cos\alpha_{i-1} + B^2 & = & 1 \ . \end{array} \tag{2.2}$$

Henceforth as in [10], we will suppose that $\alpha_k = \alpha$, for all $k \in \{0, 1, \cdots\}$. Solving for A, B from (2.1) and (2.2) produces two sets of solutions,

$$\{A = 0, \ \ B = 1\} \ , \qquad\qquad \{A = -2\cos\alpha, \ \ B = -1\} \ , \tag{2.3}$$

and we pick the solution set with $A \neq 0$, therefore,

$$v'_{i+1} \ = \ A v_i + B v_{i-1} \ = \ -\cos\alpha \, v_i - \ v_{i-1} \ .$$

Recall from **Step 2** that v_{i+1} is obtained by a positive rotation of v'_{i+1} about v_i by angle β_i. Denote this rotation by $\mathsf{R}_{v_i}^{\beta_i}(\cdot)$, in which case it is easy to see that,

$$v_{i+1} \ = \ \mathsf{R}_{v_i}^{\beta_i}\left(v'_{i+1}\right) \ = \ \mathsf{R}_{v_i}^{\beta_i}\left(A v_i + B v_{i-1}\right) \ = \ A v_i + B \, \mathsf{R}_{v_i}^{\beta_i}\left(v_{i-1}\right)$$

Since v_{i-1} and v_i are not co-linear, we may write $\mathsf{R}_{v_i}^{\beta_i}\left(v_{i-1}\right) = C v_i + D v_{i-1} + E v_{i-1} \times v_i$, where C, D and E are real constants, and $BE \geq 0$. The angle between $\mathsf{R}_{v_i}^{\beta_i}\left(v_{i-1}\right)$ and v_i is obviously unchanged at $(\pi - \alpha)$ so that,

$$\begin{array}{lcl} \left\langle \mathsf{R}_{v_i}^{\beta_i}\left(v_{i-1}\right), v_i \right\rangle & = & \cos(\pi - \alpha) \\ \langle C v_i + D v_{i-1} + E v_{i-1} \times v_i, v_i \rangle & = & -\cos\alpha \\ C + D\langle v_{i-1}, v_i \rangle + 0 & = & -\cos\alpha \\ C - D\cos\alpha & = & -\cos\alpha \end{array} \tag{2.4}$$

Let θ be the angle between $\mathsf{R}_{v_i}^{\beta_i}\left(v_{i-1}\right)$ and v_{i-1}. An elementary calculation shows that $\cos\theta = \cos^2\alpha + \sin^2\alpha\cos\beta_i$ – therefore,

$$\begin{array}{lcl} \left\langle \mathsf{R}_{v_i}^{\beta_i}\left(v_{i-1}\right), v_{i-1} \right\rangle & = & \cos\theta \\ \langle C v_i + D v_{i-1} + E v_{i-1} \times v_i, v_{i-1} \rangle & = & \left(\cos^2\alpha + \sin^2\alpha\cos\beta_i\right) \\ C\langle v_i, v_{i-1} \rangle + D + 0 & = & \left(\cos^2\alpha + \sin^2\alpha\cos\beta_i\right) \\ -C\cos\alpha + D & = & \left(\cos^2\alpha + \sin^2\alpha\cos\beta_i\right) \end{array} \tag{2.5}$$

Solving for C and D from (2.4) and (2.5) leads to,

$$\{C = \cos\alpha(\cos\beta_i - 1),\ \ D = \cos\beta_i\}\ . \tag{2.6}$$

With these C, D and the fact that the length of $\mathsf{R}_{v_i}^{\beta_i}(v_{i-1})$ is l_{i-1}, we have,

$$\begin{array}{lcl} \left\langle \mathsf{R}_{v_i}^{\beta_i}(v_{i-1}), \mathsf{R}_{v_i}^{\beta_i}(v_{i-1}) \right\rangle & = & 1 \\ \langle Cv_i + Dv_{i-1} + Ev_{i-1}\times v_i, Cv_i + Dv_{i-1} + Ev_{i-1}\times v_i\rangle & = & 1 \\ C^2 + 2\,CD\langle v_{i-1}, v_i\rangle + D^2 + E^2\|v_{i-1}\times v_i\|^2 & = & 1 \\ C^2 - 2\,CD\cos\alpha + D^2 + E^2\sin^2\alpha & = & 1 \end{array} \tag{2.7}$$

Solving for E, we have that $E = \pm\sin\beta_i$. Finally, E is picked so that $BE > 0$ since we are interested in a positive rotation β_i,

$$\begin{array}{rcl} v_{i+1} & = & Av_i + B\,\mathsf{R}_{v_i}^{\beta_i}(v_{i-1}) \\ & = & Av_i + B\ (C\,v_i + D\,v_{i-1} + E\,v_{i-1}\times v_i) \\ & = & (A+BC)\,v_i + BD\,v_{i-1} + BE\,v_{i-1}\times v_i \\ & = & (-\cos\alpha(\cos\beta_i+1))\ v_i + (-\cos\beta_i)\ v_{i-1} + (\sin\beta_i)\ v_{i-1}\times v_i\ . \end{array}$$

In general, when v_k are not unit vectors it can be similarly shown that,

$$\begin{array}{rcl} \dfrac{v_{i+1}}{l_{i+1}} & = & \underbrace{(-\cos\alpha(\cos\beta_i+1))}_{G}\ \dfrac{v_i}{l_i}\ +\ \underbrace{(-\cos\beta_i)}_{H}\ \dfrac{v_{i-1}}{l_{i-1}} \\ & & \qquad\qquad +\ \underbrace{(\sin\beta_i)}_{J}\ \dfrac{v_{i-1}}{l_{i-1}}\times\dfrac{v_i}{l_i}\ . \end{array} \tag{2.8}$$

Clearly the scheme (2.8) is not properly Markovian because the $(i+1)$-th iteration depends upon two of its preceding steps: i and $(i-1)$.

We will next reformulate scheme (2.8) into a Markov process. Define the unit vectors,

$$T_i\ \doteq\ \frac{v_i}{l_i}\,, \qquad N_i\ \doteq\ \frac{T_i - T_{i-1}}{\sqrt{2(1+\cos\alpha)}}\,, \qquad B_i\ \doteq\ \frac{T_{i-1}\times T_i}{\sin\alpha}\ .$$

Note that B_i is equivalently $\frac{T_i\times N_i}{\|T_i\times N_i\|}$, $\langle T_i, N_i\rangle = \frac{\sqrt{2(1+\cos\alpha)}}{2}$, and $\langle T_i, B_i\rangle = \langle N_i, B_i\rangle = 0$. Under this change of variables, equation (2.8) becomes,

$$T_{i+1}\ =\ G\,T_i + H\,T_{i-1} + J\ (T_{i-1}\times T_i)\ . \tag{2.9}$$

Recall that linker lengths l_k are positive, independent and identically - distributed random variables with a prescribed distribution, and that β_k is a linear function of l_k. We are interested in the limiting process of (2.9) when the mean of linker lengths is very small ($\ll 1$) relative to the length of the entire fiber. By definition, each T_k is a unit vector and in equation (2.9) the effect of linker length variability manifests itself through corresponding variations in β_k in the coefficient terms G, H and J. Thus,

$$
\begin{aligned}
T_{i+1} &= G\,T_i + H\,T_{i-1} + J\ (T_{i-1} \times T_n) \\
&= G\,T_i + H\,T_i + H\,T_{i-1} - H\,T_i + J\ (T_{i-1} \times T_n) \\
&= (G+H)\,T_i - \sqrt{2(1+\cos\alpha)}\ H\ N_i + \sin\alpha\ J\ B_i\ , \\[2ex]
N_{i+1} &= \tfrac{T_{i+1}-T_i}{\sqrt{2(1+\cos\alpha)}} \\
&= \tfrac{(G+H-1)}{\sqrt{2(1+\cos\alpha)}}\,T_i - H\ N_i + \tfrac{\sin\alpha}{\sqrt{2(1+\cos\alpha)}}\ J\ B_i\ , \\[2ex]
B_{i+1} &= \tfrac{T_i \times T_{i+1}}{\sin\alpha} \\
&= \tfrac{T_i \times (G\,T_i + H\,T_{i-1} + J\,T_{i-1} \times T_i)}{\sin\alpha} \quad = \quad -H\ B_i + J\ \tfrac{T_i \times\ (T_{i-1} \times T_i)}{\sin\alpha} \\
&= -H\ B_i - \tfrac{J\,\sqrt{2(1+\cos\alpha)}}{\sin\alpha}\ N_i + \tfrac{J\ (1+\cos\alpha)}{\sin\alpha}\ T_i\ .
\end{aligned}
\tag{2.10}
$$

Observe that in order to obtain the expression for B_{i+1}, we had used the vector identity $a \times (b \times c) = \langle a, c\rangle\, b - \langle a, b\rangle\, c$, to get,

$$
\begin{aligned}
T_i \times (T_{i-1} \times T_i) &= \langle T_i, T_i\rangle\, T_{i-1} - \langle T_i, T_{i-1}\rangle\, T_i \\
&= T_{i-1} + (\cos\alpha)\, T_i \\
&= T_{i-1} - T_i + T_i + (\cos\alpha)\, T_i \\
&= -\sqrt{2(1+\cos\alpha)}\ N_i + (1+\cos\alpha)\, T_i\ .
\end{aligned}
$$

Motivated by the idea of a Frenet frame [6] which characterizes curves in $\mathbb{R}^3$ uniquely up to Euclidean transformations, we rewrite (2.9) using the T_i, N_i and B_i definitions to obtain a continuous Markov process that is indexed (parametrized) by $i \in \{0, 1, \cdots\}$,

$$
\begin{pmatrix} T_{i+1} \\ N_{i+1} \\ B_{i+1} \end{pmatrix} = \begin{pmatrix} G+H & -H\sqrt{2(1+\cos\alpha)} & J\sin\alpha \\ \frac{G+H-1}{\sqrt{2(1+\cos\alpha)}} & -H & \frac{J\sin\alpha}{\sqrt{2(1+\cos\alpha)}} \\ \frac{J(1+\cos\alpha)}{\sin\alpha} & -\frac{J\sqrt{2(1+\cos\alpha)}}{\sin\alpha} & -H \end{pmatrix} \begin{pmatrix} T_i \\ N_i \\ B_i \end{pmatrix}\ , \tag{2.11}
$$

where (T_i, N_i, B_i) is a (3×3) matrix with rows T_i, N_i and B_i. The process is homogeneous with respect to its index (parameter) i, i.e., $\mathsf{P}(Y_j \in B | Y_i = x) = \mathsf{P}(Y_{j-i} \in B | Y_0 = x)$ for $0 \le i \le j$, for a Borel set $B \subset \mathbb{R}^9$ and the underlying probability space is $(\Omega, \mathcal{F}, \mathsf{P})$. Abbreviating by $\Delta Y_{k+1} \doteq Y_{k+1} - Y_k$ leads to,

$$\begin{pmatrix} \Delta T_{i+1} \\ \Delta N_{i+1} \\ \Delta B_{i+1} \end{pmatrix} = \underbrace{\begin{pmatrix} G+H-1 & -H\sqrt{2(1+\cos\alpha)} & J\sin\alpha \\ \frac{G+H-1}{\sqrt{2(1+\cos\alpha)}} & -H-1 & \frac{J\sin\alpha}{\sqrt{2(1+\cos\alpha)}} \\ \frac{J(1+\cos\alpha)}{\sin\alpha} & -\frac{J\sqrt{2(1+\cos\alpha)}}{\sin\alpha} & -H-1 \end{pmatrix}}_{Q_i} \begin{pmatrix} T_i \\ N_i \\ B_i \end{pmatrix}, \tag{2.12}$$

where

$$Q_i = \begin{pmatrix} -(\cos\alpha+1)(\cos\beta_i+1) & \cos\beta_i\sqrt{2(1+\cos\alpha)} & \sin\beta_i\sin\alpha \\ -\frac{(\cos\alpha+1)(\cos\beta_i+1)}{\sqrt{2(1+\cos\alpha)}} & \cos\beta_i - 1 & \frac{\sin\beta_i\sin\alpha}{\sqrt{2(1+\cos\alpha)}} \\ \frac{\sin\beta_i(1+\cos\alpha)}{\sin\alpha} & -\frac{\sin\beta_i\sqrt{2(1+\cos\alpha)}}{\sin\alpha} & \cos\beta_i - 1 \end{pmatrix},$$

and the only source of randomness are the twist angles β_i. Equation (2.12) is not the form of the problem which we will be using for the subsequent asymptotic analysis in Section 3. Instead, we will rewrite (2.12) into an equivalent nine-dimensional system. First, we define the column vector $Y_i \in \mathbb{R}^9$ as,

$$\begin{aligned} Y_i &\doteq \begin{pmatrix} \mathbf{y^1}_i \\ \mathbf{y^2}_i \\ \mathbf{y^3}_i \end{pmatrix}, \qquad \mathbf{y^j}_i \doteq \begin{pmatrix} T_i^j \\ N_i^j \\ B_i^j \end{pmatrix}, \qquad j = 1,2,3\,, \\ \mathbf{y^j}_i \otimes \mathbf{y^k}_i &\doteq \mathbf{y^j}_i \left(\mathbf{y^k}_i\right)^t = \begin{pmatrix} T_i^j T_i^k & T_i^j N_i^k & T_i^j B_i^k \\ N_i^j T_i^k & N_i^j N_i^k & N_i^j B_i^k \\ B_i^j T_i^k & B_i^j N_i^k & B_i^j B_i^k \end{pmatrix}. \end{aligned} \tag{2.13}$$

Note that the $\otimes$ operation is not commutative. Under this new definition, (2.12) will now appear as a vector-valued continuous Markov process parametrized by $i \in \mathbb{N}$,

$$\Delta Y_i = \underbrace{\begin{pmatrix} Q_i & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & Q_i & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & Q_i \end{pmatrix}}_{\mathbf{Q}_i} Y_i\,, \qquad \mathbf{0} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}. \tag{2.14}$$

3 Asymptotic analysis

In this section, we shall investigate the asymptotic limit of (2.14) as the average of the linker DNA lengths becomes very small ($\ll 1$). This limit is considered since linker lengths are naturally on the order of 10^{-8} m – microscopic, compared with the total macroscopic length of a chromatin fiber which is on the order of 10^{-2} m. As remarked in Section 2, since the linkers have been normalized in our analysis and the only source of randomness is the twisting angles β_i, one may consider this model as being that of a very long chromatin fiber made up of relatively microscopic nuclesome-linker units. The system (2.14) essentially describes the discretization of a space curve that is parametrized by *arclength* since $\|T_i\| = 1$. We will denote this parameter by $s \doteq n\delta$ where $\delta > 0$ is the mean of linker DNA lengths and $n \in \{0, 1, \cdots\}$ is a linker index. We are interested in the behavior of this system for $\delta \ll 1$. Following the Markov chain approximating techniques for stochastic differential equations in [7], the limit of (2.14) will be a system of nine stochastic ordinary differential equations (Ito diffusions, c.f. Section 4),

$$dY_s = b(Y_s)\, ds + \sigma(Y_s)\, d\vec{W}_s\,, \qquad \vec{W}_s = (W_s, \cdots, W_s) \in \mathbb{R}^9\,, \tag{3.1}$$

where W_s is a Brownian motion parametrized by s and is generated by the random twists β_i in (2.12), (2.14). In this context, Y_s is the continuum version of Y_i as defined in (2.13) when $\delta \ll 1$. Following [7], the drift $b(Y_s)$ and covariance $A(Y_s) \doteq \sigma(Y_s)\sigma^t(Y_s)$ matrix terms are related to the original Markov process (2.11) via,

$$\begin{aligned} b(Y)\,\delta \;&=\; \mathsf{E}\left(\Delta Y_i \mid Y_i = Y\right) \;+\; O(\delta^2)\,, \qquad\qquad \delta \ll 1\,, \\ A(Y)\,\delta \;&=\; \mathsf{E}\left((\Delta Y_i - \mathsf{E}\Delta Y_i)(\Delta Y_i - \mathsf{E}\Delta Y_i)^t \mid Y_i = Y\right) \;+\; O(\delta^2)\,. \end{aligned} \tag{3.2}$$

The position vector of the curve (a realization of the chromatin model) in space, call it $X(s)$ is then,

$$X(s) \;=\; \int_0^s T(\rho)\, d\rho \;+\; X(0)\,, \tag{3.3}$$

and without loss of generality, we set $X(0) = \vec{0}$.

3.1 General drift matrix term

From equation (3.2), $\mathsf{E}\left(\Delta Y_i \mid Y_i = Y\right) \;=\; \mathsf{E}\left(\mathbf{Q}_i Y_i \mid Y_i = Y\right) \;=\; (\mathsf{E}\mathbf{Q}_i)Y$. A moment's reflection tells us that it suffices to consider the expectation of the diagonal (3×3) sub-matrix Q_i which makes up $\mathbf{Q}_i$, c.f. (2.14),

$$\mathsf{E}Q_i = \begin{pmatrix} -(\cos\alpha + 1)(\mathsf{E}\cos\beta_i + 1) & \mathsf{E}\cos\beta_i\sqrt{2(1+\cos\alpha)} & \mathsf{E}\sin\beta_i\sin\alpha \\ -\frac{\sqrt{2(\cos\alpha+1)}(\mathsf{E}\cos\beta_i+1)}{2} & \mathsf{E}\cos\beta_i - 1 & \frac{\mathsf{E}\sin\beta_i\sin\alpha}{\sqrt{2(1+\cos\alpha)}} \\ \frac{\mathsf{E}\sin\beta_i(1+\cos\alpha)}{\sin\alpha} & -\frac{\mathsf{E}\sin\beta_i\sqrt{2(1+\cos\alpha)}}{\sin\alpha} & \mathsf{E}\cos\beta_i - 1 \end{pmatrix}. \tag{3.4}$$

Therefore from (3.2), $b(Y_s)\,\delta \;=\; \mathsf{E}\mathbf{Q}_i\,Y_s \;+\; O(\delta^2)$, and $\|b(Y) - b(\tilde{Y})\| \leq K_1\|Y - \tilde{Y}\|$ for some constant $K_1 > 0$, where $\|b(Y)\|^2 = \sum_{i,j=1}^{9} \|\mathbf{Q}_i^{jk} Y^k\|^2$.

3.2 General covariance and diffusion matrix term

For the covariance matrix $A(Y)$, it is easy to see that $(\Delta Y_i - \mathsf{E}\Delta Y_i) = (\mathbf{Q}_i - \mathsf{E}\mathbf{Q}_i)\,Y_i$ and therefore, $\mathsf{E}\left((\Delta Y_i - \mathsf{E}\Delta Y_i)(\Delta Y_i - \mathsf{E}\Delta Y_i)^t | Y_i = Y\right)$

$$\begin{aligned} &= \mathsf{E}\left(((\mathbf{Q}_i - \mathsf{E}\mathbf{Q}_i)Y_i)((\mathbf{Q}_i - \mathsf{E}\mathbf{Q}_i)Y_i)^t | Y_i = Y\right) \\ &= \mathsf{E}\left(\,(\mathbf{Q}_i - \mathsf{E}\mathbf{Q}_i)\,(Y\,Y^t)\,(\mathbf{Q}_i - \mathsf{E}\mathbf{Q}_i)^t\,\right) \\ &= \mathsf{E}\left(\,\bar{\mathbf{Q}}_i\,Y\,Y^t\,\bar{\mathbf{Q}}_i^t\,\right)\;, \end{aligned}$$

where $\mathbf{Q}_i - \mathsf{E}\mathbf{Q}_i$ has been abbreviated by $\bar{\mathbf{Q}}_i$ in which each diagonal sub-matrix (3×3) matrix of $\bar{\mathbf{Q}}_i$, call it $\bar{Q}_i$, has the form,

$$\bar{Q}_i = \begin{pmatrix} -(\cos\alpha + 1)(\cos\beta_i - \mathsf{E}\cos\beta_i) & (\cos\beta_i - \mathsf{E}\cos\beta_i)\sqrt{2(1+\cos\alpha)} & (\sin\beta_i - \mathsf{E}\sin\beta_i)\sin\alpha \\ -\frac{(\cos\alpha+1)(\cos\beta_i - \mathsf{E}\cos\beta_i)}{\sqrt{2(1+\cos\alpha)}} & \cos\beta_i - \mathsf{E}\cos\beta_i & \frac{(\sin\beta_i - \mathsf{E}\sin\beta_i)\sin\alpha}{\sqrt{2(1+\cos\alpha)}} \\ \frac{(\sin\beta_i - \mathsf{E}\sin\beta_i)(1+\cos\alpha)}{\sin\alpha} & -\frac{(\sin\beta_i - \mathsf{E}\sin\beta_i)\sqrt{2(1+\cos\alpha)}}{\sin\alpha} & \cos\beta_i - \mathsf{E}\cos\beta_i \end{pmatrix}.$$

The matrix $\bar{\mathbf{Q}}_i\,Y\,Y^t\,\bar{\mathbf{Q}}_i^t$ is symmetric and non-negative definite of the form,

$$\begin{pmatrix} \mathcal{M}_{11} & \mathcal{M}_{12} & \mathcal{M}_{13} \\ \mathcal{M}_{21} & \mathcal{M}_{22} & \mathcal{M}_{23} \\ \mathcal{M}_{31} & \mathcal{M}_{32} & \mathcal{M}_{33} \end{pmatrix}\,, \qquad \begin{aligned} \mathcal{M}_{jk} &\doteq Q_i\mathbf{y^j}_i \otimes \mathbf{y^k}_i Q_i^t\,, \\ j,k &= 1,2,3\,. \end{aligned}$$

In order to compute the mean value of $\bar{\mathbf{Q}}_i Y Y^t \bar{\mathbf{Q}}_i^t$, it is necessary to consider only one of the six unique jk-th (3×3) matrices $\mathcal{M}_{jk} = Q\mathbf{y^j}\otimes\mathbf{y^k}Q^t$, where the sub-index i for nucleosome-linker units has been eliminated for clarity. The nine entries of $\mathcal{M}_{jk}$ are (noting certain symmetries: $\mathcal{M}_{jk}^{1,2} \sim \mathcal{M}_{jk}^{2,1}$, $\mathcal{M}_{jk}^{1,3} \sim \mathcal{M}_{jk}^{3,1}$, $\mathcal{M}_{jk}^{2,3} \sim \mathcal{M}_{jk}^{3,2}$),

$$
\begin{aligned}
\mathcal{M}^{1,1}_{jk} &= (1+\cos\alpha)^2\,\tilde{C}\,T^jT^k - \tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{2}\,\tilde{C}\,T^jN^k - (1+\cos\alpha)\sin\alpha\,\tilde{M}\,T^jB^k \\
&\quad -\tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{2}\,\tilde{C}\,N^jT^k + 2(1-\cos\alpha)\,\tilde{C}\,N^jN^k + \sin\alpha\sqrt{2(1+\cos\alpha)}\,\tilde{M}\,N^jB^k \\
&\quad -(1+\cos\alpha)\sin\alpha\,\tilde{M}\,B^jT^k + \sin\alpha\sqrt{2(1+\cos\alpha)}\,\tilde{M}\,B^jN^k + \sin^2\alpha\,\tilde{S}\,B^jB^k, \\
\mathcal{M}^{1,2}_{jk} &= \tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{4}\,\tilde{C}\,T^jT^k - (1+\cos\alpha)\,\tilde{C}\,T^jN^k - \tfrac{\sin\alpha\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{M}\,T^jB^k \\
&\quad -(1+\cos\alpha)\,\tilde{C}\,N^jT^k + \sqrt{2(1+\cos\alpha)}\,\tilde{C}\,N^jN^k + \sin\alpha\,\tilde{M}\,N^jB^k \\
&\quad -\tfrac{\sin\alpha\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{M}\,B^jT^k + \sin\alpha\,\tilde{M}\,B^jN^k + \tfrac{\sin^2\alpha}{\sqrt{2(1+\cos\alpha)}}\,\tilde{S}\,B^jB^k, \\
\mathcal{M}^{1,3}_{jk} &= -\tfrac{(1+\cos\alpha)^2}{\sin\alpha}\,C\,T^jT^k + \tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{2\sin\alpha}\,\tilde{M}\,T^jN^k - (1+\cos\alpha)\,\tilde{C}\,T^jB^k \\
&\quad +\tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{2\sin\alpha}\,\tilde{M}\,N^jT^k - \tfrac{2(1+\cos\alpha)}{\sin\alpha}\,\tilde{M}\,N^jN^k + \sqrt{2(1+\cos\alpha)}\,\tilde{C}\,N^jB^k \\
&\quad +(1+\cos\alpha)\,\tilde{S}\,B^jT^k - \sqrt{2(1+\cos\alpha)}\,\tilde{S}\,B^jN^k + \sin\alpha\,\tilde{M}\,B^jN^k,
\end{aligned}
$$

$$
\begin{aligned}
\mathcal{M}^{2,1}_{jk} &= \tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{4}\,\tilde{C}\,T^jT^k - (1+\cos\alpha)\,\tilde{C}\,T^jN^k - \tfrac{\sin\alpha\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{M}\,T^jB^k \\
&\quad -(1+\cos\alpha)\,\tilde{C}\,N^jT^k + \sqrt{2(1+\cos\alpha)}\,\tilde{C}\,N^jN^k + \sin\alpha\,\tilde{M}\,N^jB^k \\
&\quad -\tfrac{\sin\alpha\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{M}\,B^jT^k + \sin\alpha\,\tilde{M}\,B^jN^k + \tfrac{\sin^2\alpha}{\sqrt{2(1+\cos\alpha)}}\,\tilde{S}\,B^jB^k, \\
\mathcal{M}^{2,2}_{jk} &= \tfrac{(1+\cos\alpha)}{2}\,\tilde{C}\,T^jT^k - \tfrac{\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{C}\,T^jN^k - \tfrac{\sin\alpha}{2}\,\tilde{M}\,T^jB^k \\
&\quad -\tfrac{\sqrt{2(1+\cos\alpha)}}{2}\,N^jT^k + \,\tilde{C}\,N^jN^k + \tfrac{\sin\alpha}{\sqrt{2(1+\cos\alpha)}}\,\tilde{M}\,N^jB^k \\
&\quad -\tfrac{\sin\alpha}{2}\,\tilde{M}\,B^jT^k + \tfrac{\sin\alpha}{\sqrt{2(1+\cos\alpha)}}\,\tilde{M}\,B^jN^k + \tfrac{(1-\cos\alpha)}{2}\,\tilde{S}\,B^jB^k, \\
\mathcal{M}^{2,3}_{jk} &= -\tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{4\sin\alpha}\,\tilde{M}\,T^jT^k + \tfrac{(1+\cos\alpha)}{\sin\alpha}\,\tilde{M}\,T^jN^k - \tfrac{\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{C}\,T^jB^k \\
&\quad +\tfrac{(1+\cos\alpha)}{\sin\alpha}\,\tilde{M}\,N^jT^k - \tfrac{\sqrt{2(1+\cos\alpha)}}{\sin\alpha}\,\tilde{M}\,N^jN^k + A\,N^jB^k \\
&\quad +\tfrac{\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{S}\,B^jT^k - B\,B^jN^k + \tfrac{\sin\alpha}{\sqrt{2(1+\cos\alpha)}}\,\tilde{M}\,B^jB^k,
\end{aligned}
\tag{3.5}
$$

$$
\begin{aligned}
\mathcal{M}_{jk}^{3,1} &= -\tfrac{(1+\cos\alpha)^2}{\sin\alpha}\,\tilde{M}\,T^jT^k + \tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{2\sin\alpha}\,\tilde{M}\,T^jN^k + (1+\cos\alpha)\,\tilde{S}\,T^jB^k \\
&\quad + \tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{2\sin\alpha}\,\tilde{M}\,N^jT^k - \tfrac{2(1+\cos\alpha)}{\sin\alpha}\,\tilde{M}\,N^jN^k - \sqrt{2(1+\cos\alpha)}\,\tilde{S}\,N^jB^k \\
&\quad -(1+\cos\alpha)\,\tilde{C}\,B^jT^k + \sqrt{2(1+\cos\alpha)}\,\tilde{C}\,B^jN^k + \sin\alpha\,\tilde{M}\,B^jN^k, \\
\mathcal{M}_{jk}^{3,2} &= -\tfrac{(2(1+\cos\alpha))^{\frac{3}{2}}}{4\sin\alpha}\,\tilde{M}\,T^jT^k + \tfrac{(1+\cos\alpha)}{\sin\alpha}\,\tilde{M}\,T^jN^k + \tfrac{\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{S}\,T^jB^k \\
&\quad + \tfrac{(1+\cos\alpha)}{\sin\alpha}\,\tilde{M}\,N^jT^k - \tfrac{\sqrt{2(1+\cos\alpha)}}{\sin\alpha}\,\tilde{M}\,N^jN^k - B\,N^jB^k \\
&\quad - \tfrac{\sqrt{2(1+\cos\alpha)}}{2}\,\tilde{C}\,B^jT^k + A\,B^jN^k + \tfrac{\sin\alpha}{\sqrt{2(1+\cos\alpha)}}\,\tilde{M}\,B^jB^k, \\
\mathcal{M}_{jk}^{3,3} &= \tfrac{1+\cos\alpha}{1-\cos\alpha}\,\tilde{S}\,T^jT^k - \tfrac{\sqrt{2(1+\cos\alpha)}}{(1-\cos\alpha)}\,\tilde{S}\,T^jN^k + \tfrac{(1+\cos\alpha)}{\sin\alpha}\,\tilde{M}\,T^jB^k \\
&\quad - \tfrac{\sqrt{2(1+\cos\alpha)}}{(1-\cos\alpha)}\,\tilde{S}\,N^jT^k + \tfrac{2}{1-\cos\alpha}\,\tilde{S}\,N^jN^k - \tfrac{\sqrt{2(1+\cos\alpha)}}{\sin\alpha}\,\tilde{M}\,N^jB^k \\
&\quad + \tfrac{(1+\cos\alpha)}{\sin\alpha}\,\tilde{M}\,B^jT^k - \tfrac{\sqrt{2(1+\cos\alpha)}}{\sin\alpha}\,\tilde{M}\,B^jN^k + \tilde{C}\,B^jB^k,
\end{aligned}
$$

where,

$$
\begin{aligned}
\tilde{C} &\doteq (\cos\beta_i - \mathsf{E}\cos\beta_i)^2, \qquad \tilde{M} \doteq (\cos\beta_i - \mathsf{E}\cos\beta_i)(\sin\beta_i - \mathsf{E}\sin\beta_i), \\
\tilde{S} &\doteq (\sin\beta_i - \mathsf{E}\sin\beta_i)^2.
\end{aligned}
$$

Detailed calculations for $A(Y) \approx \delta^{-1}\mathsf{E}\left(\bar{\mathbf{Q}}_i\,Y\,Y^t\,\bar{\mathbf{Q}}_i^t\right)$, the covariance term are found in Appendix A. Since the matrix $\mathsf{E}\left(\bar{\mathbf{Q}}_i\,Y\,Y^t\,\bar{\mathbf{Q}}_i^t\right)$ is symmetric and non-negative definite, it has a Cholesky or "square root" decomposition [9], i.e., there exists a (3×3) matrix D such that $\mathsf{E}\left(\bar{\mathbf{Q}}_i\,Y\,Y^t\,\bar{\mathbf{Q}}_i^t\right) = D\,D^t$. From (3.2), the diffusion coefficient term for (3.1) satistifies,

$$
\begin{aligned}
A(Y_s)\,\delta &= \sigma(Y_s)\,\sigma^t(Y_s)\,\delta = D\,D^t + O(\delta^2)\,, \\
A(Y_s) &= \begin{pmatrix} \mathsf{E}\mathcal{M}_{11} & \mathsf{E}\mathcal{M}_{12} & \mathsf{E}\mathcal{M}_{13} \\ \mathsf{E}\mathcal{M}_{21} & \mathsf{E}\mathcal{M}_{22} & \mathsf{E}\mathcal{M}_{23} \\ \mathsf{E}\mathcal{M}_{31} & \mathsf{E}\mathcal{M}_{32} & \mathsf{E}\mathcal{M}_{33} \end{pmatrix}, \qquad A_{jk}(Y_s) \doteq \mathsf{E}\mathcal{M}_{jk}\,.
\end{aligned}
$$

Furthermore – recalling that $2ab \le a^2 + b^2$ for $a, b \in \mathbb{R}$ – it can be easily shown that $|A(Y) - A(\tilde{Y})|^2 \le K_2\|Y - \tilde{Y}\|^2$ and thus $|\sigma(Y) - \sigma(\tilde{Y})| \le K_2\|Y - \tilde{Y}\|$, for some constant $K_2 > 0$, where the L^2-matrix norm $|\sigma|^2 = \sum_{i,j=1}^{9} |\sigma^{ij}|^2$.

3.3 Asymptotic limit equations for special cases

For illustration purposes, we shall write down the drift term b of the stochastic ordinary differential equations (3.1) explicitly for three special cases. Recall that $A(y) = \sigma(y)\sigma^t(y)$. Let A_{jk} denote the jk-th $(3{\times}3)$ sub-matrix of A. and β_i are independent and uniformly-distributed on a closed, real interval $[B,\ C]$ where $B, C \in \mathbb{R}$. Refer to Appendix A for detailed calculations.

Case I: $[B,\ C] = [-\tau\delta,\ \tau\delta], \quad \alpha = \pi - \kappa\,\delta$

$$
\begin{aligned}
dY_s \;&=\; \begin{pmatrix} \mathsf{E}Q_i & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathsf{E}Q_i & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathsf{E}Q_i \end{pmatrix} Y_s\, ds \;+\; \sigma(Y_s)\, d\vec{W}_s \;+\; O(\delta)\,, \\
\mathsf{E}Q_i \;&=\; \begin{pmatrix} 0 & \kappa & 0 \\ -\kappa & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \qquad A_{jk}(Y_s) \;=\; \begin{pmatrix} 0 & 0 & 0 \\ 0 & B^jB^k & -B^jN^k \\ 0 & -N^jB^k & N^jN^k \end{pmatrix} \tfrac{\tau\sqrt{\delta}}{\sqrt{3}}\,.
\end{aligned}
\tag{3.6}
$$

Case II: $[B,\ C] = [0,\ \tau\delta], \quad \alpha = \pi - \kappa\,\delta$

$$
\begin{aligned}
dY_s \;&=\; \begin{pmatrix} \mathsf{E}Q_i & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathsf{E}Q_i & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathsf{E}Q_i \end{pmatrix} Y_s\, ds \;+\; \sigma(Y_s)\, d\vec{W}_s \;+\; O(\delta) \\
\mathsf{E}Q_i \;&=\; \begin{pmatrix} 0 & \kappa & 0 \\ -\kappa & 0 & \frac{\tau}{2} \\ 0 & -\frac{\tau}{2} & 0 \end{pmatrix}, \qquad A_{jk}(Y_s) \;=\; \begin{pmatrix} 0 & 0 & 0 \\ 0 & B^jB^k & -B^jN^k \\ 0 & -N^jB^k & N^jN^k \end{pmatrix} \tfrac{\tau\sqrt{\delta}}{\sqrt{12}}\,.
\end{aligned}
\tag{3.7}
$$

Case III: $[B,\ C] = [0,\ 2\pi], \quad \alpha \in (0, \pi)$ a constant

$$
\begin{aligned}
dY_s \;&=\; \delta^{-1} \begin{pmatrix} \mathsf{E}Q_i & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathsf{E}Q_i & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathsf{E}Q_i \end{pmatrix} Y_s\, ds \;+\; \sigma(Y_s)\, d\vec{W}_s \;+\; O(1)\,, \\
\mathsf{E}Q_i \;&=\; \begin{pmatrix} -(\cos\alpha + 1) & 0 & 0 \\ -\frac{\sqrt{2(\cos\alpha+1)}}{2} & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix}, \qquad \sigma(Y_s) \;=\; O(\delta^{-\frac{1}{2}})\,.
\end{aligned}
\tag{3.8}
$$

Note that in cases **I** and **II**, the stochastic term vanishes as $\delta \downarrow 0$, and one obtains a system of deterministic ordinary differential equations – in case **II**, one finds the familiar Frenet system for a helix in $\mathbb{R}^3$ with curvature

κ and torsion $\frac{\tau}{2}$. The equation in case **III** may be rescaled in arclength $Y^\delta(s) = Y(\delta s)$ – recall that the formal derivative of Brownian motion scales in the sense of distributions as $\dot{W}(\gamma s) = \gamma^{-\frac{1}{2}}\dot{W}(s)$ – and leads to,

$$
\begin{aligned}
dY_s^\delta \;&=\; \begin{pmatrix} \mathsf{E}Q_i & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathsf{E}Q_i & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathsf{E}Q_i \end{pmatrix} Y_s^\delta\, ds \;+\; \sigma(Y_s)\, d\vec{W}_s \;+\; O(\delta^{\frac{1}{2}})\,, \\
\mathsf{E}Q_i \;&=\; \begin{pmatrix} -(\cos\alpha+1) & 0 & 0 \\ -\frac{\sqrt{2(\cos\alpha+1)}}{2} & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix}, \qquad \sigma(Y_s) \;=\; O\left((ds)^0\right)\,.
\end{aligned}
$$

We refer to Appendix A for details of the entries of case **III**'s covariance matrix.

4 Associated Fokker-Planck equations

Let $Y_s(\omega) = (Y_s^1(\omega), Y_s^2(\omega), \cdots, Y_s^d(\omega)) : [0,\,\infty] \times \Omega \to \mathbb{R}^d$ be a stochastic process defined on a probability space $(\Omega, \mathcal{F}, \mathsf{P})$. The target space is $(\mathbb{R}^d, \mathcal{L}, \lambda)$ where λ is the d-dimensional Lebesgue measure and $\mathcal{L}$ its corresponding σ-field. From [8], we recall that an (s-homogeneous) *Ito diffusion* is a stochastic process $Y_s(\omega)$ satisfying a stochastic differential equation of the form,

$$
dY_s \;=\; b(Y_s)\, ds \;+\; \sigma(Y_s)\, dW_s\,, \quad s_0 \le s\,, \quad Y_{s_0} = y\,, \tag{4.1}
$$

where W_s is a d-dimensional Brownian motion and the drift $b : \mathbb{R}^d \to \mathbb{R}^d$ and diffusion $\sigma : \mathbb{R}^d \to \mathbb{R}^{d\times d}$ coefficients satisfy,

$$
\|b(Y) - b(\tilde{Y})\| \;+\; |\sigma(Y) - \sigma(\tilde{Y})| \;\le\; K\,\|Y - \tilde{Y}\|\,, \tag{4.2}
$$

where again $\|b\|^2 = \sum_{j=1}^d \|b^j\|^2$ and $|\sigma|^2 = \sum_{j,k=1}^d |\sigma^{jk}|^2$. It is well-known that the stochastic differential equation (4.1) determines a strong Markov process [12]. Define the transition probabilities of this d-dimensional process by,

$$
\mathsf{P}(r, x; s, B) \;=\; \mathsf{P}(Y_s \in B | Y_r = x)\,, \qquad s_0 \le r < s\,, \quad B \in \mathcal{L}\,. \tag{4.3}
$$

The probability density functions corresponding to these transition probabilities are denoted $p(r, x; s, \cdot)$ and for any Borel set B,

$$\mathsf{P}(r, x; s, B) \;=\; \int_{B\subset\mathbb{R}^d} p(r, x; s, y)\, d\lambda(y)\,. \tag{4.4}$$

From [12], for fixed r and x, $p(s, y) = p(r, x; s, y)$ satisfy the Fokker-Planck equation,

$$\frac{\partial}{\partial s}p + \sum_{i=1}^{d} \frac{\partial}{\partial y^i}\left(b^i(y)\, p\right) - \frac{1}{2}\sum_{i,j=1}^{d} \frac{\partial^2}{\partial y^i \partial y^j}\left((A(y))^{ij}\, p\right) \;=\; 0\,, \tag{4.5}$$

with $A(y) = \sigma(y)\, \sigma^t(y)$ and the initial condition,

$$\lim_{s\downarrow r} p(r, x, s, y) \;=\; \delta(x - y),$$

where $\delta(\cdot)$ here indicates a Dirac measure on $\mathbb{R}^d$. Thus the density of (4.3) is a fundamental solution of the parabolic partial differential equation (4.5).

In the case of the limiting stochastic differential equation for chromatin folding that is considered here: The state space of the diffusion process is $\mathbb{R}^9$, c.f. (3.1), and both the drift coefficient $b(Y_s)$, c.f. (3.4), and covariance matrix $A(Y_s)$, c.f. (3.5), satisfy the required growth conditions. For the choice of α and β_i considered in Section 3.3, the limiting diffusion processes have corresponding Fokker-Planck equations (not necessarily second-order elliptic):

<u>**Case I**</u>:

$$\frac{\partial}{\partial s}p \;-\; \frac{2\,\tau\sqrt{\delta}}{\sqrt{3}} \sum_{i=1}^{3} \frac{\partial^2}{\partial N^i \partial B^i}p \;=\; 0\,.$$

<u>**Case II**</u>:

$$\frac{\partial}{\partial s}p \;-\; \frac{2\,\tau\sqrt{\delta}}{\sqrt{12}} \sum_{i=1}^{3} \frac{\partial^2}{\partial N^i \partial B^i}p \;=\; 0\,.$$

The equation for case **III** is complicated and will not be written out explicitly here. In order to obtain a corresponding Fokker-Planck equation which incorporates the position vector $X = X(s) \in \mathbb{R}^3$ of the chromatin in space, c.f. (3.3), we augment the stochastic differential equation system (3.1) from nine to twelve dimensions by the system $dX_s = T(s)\,ds$ and define $Z_s \doteq (X_s,\, Y_s)$ to produce,

$$
\begin{gathered}
dZ_s = \tilde{b}(Z_s)\,ds + \tilde{\sigma}(Z_s)\,d\vec{W}_s\,, \\
Z_s = \begin{pmatrix} X_s \\ Y_s \end{pmatrix} \in \mathbb{R}^{12}\,, \qquad\qquad \vec{W}_s = \begin{pmatrix} W_s \\ \vdots \\ W_s \end{pmatrix} \in \mathbb{R}^{12}\,,
\end{gathered}
\tag{4.6}
$$

where referring to (2.13), (3.4) and (3.5) we have,

$$
\tilde{b}(Z_s) = \begin{pmatrix} \mathbf{0} & I^{11} & I^{22} & I^{33} \\ \mathbf{0} & \mathsf{E}Q_i & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathsf{E}Q_i & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathsf{E}Q_i \end{pmatrix} Z_s\,, \qquad \tilde{\sigma}(Z_s) = \begin{pmatrix} \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & & & \\ \mathbf{0} & & \sigma(Y_s) & \\ \mathbf{0} & & & \end{pmatrix}\,,
$$

with,

$$
I^{11} \doteq \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}\,, \quad I^{22} \doteq \begin{pmatrix} 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{pmatrix}\,, \quad I^{33} \doteq \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}\,.
$$

The Fokker-Planck equation associated with the diffusion process (4.6) is a natural object to consider for the problem since its solution p indicates, given s and an initial position $X(s_0)$ where $s_0 \leq s$, the probability of $X(s)$ being in a subset of positions or locations in $\mathbb{R}^3$ within a distance s from $X(s_0)$. In particular when $s_0 = 0$ and given a specific arclength s, the coordinates $X(0)$ and geometry of one endpoint of the chromatin fiber, the density function p contains probabilistic information about the location $X(s)$ of the other endpoint of the fiber.

Appendix A Covariance, diffusion calculations

As noted in Section 3, the jk-th (3×3) sub-matrix of $\bar{\mathbf{Q}}YY^t\bar{\mathbf{Q}}^t$ has the form $\mathcal{M}_{jk} \doteq Q\mathbf{y^j}\otimes\mathbf{y^k}Q^t$ with the nine entries as displayed in (3.5). We have eliminated the nucleomsome-linker index i for clarity and concentrate on calculating the mean value for a typical (3×3) sub-matrix $\mathcal{M}_{jk}$ of $\bar{\mathbf{Q}}_iYY^t\bar{\mathbf{Q}}_i^t$. Recall that β_i are independent and uniformly-distributed random variables on a closed, real interval $[B,\, C]$ where $B, C \in \mathbb{R}$. The entry-exit angle α is a deterministic parameter. We examine three special choices of α and β_i as outlined in Section 3.3: **Case I** denotes when $[B,\, C] = [-\lambda,\, \lambda]$, $\lambda = \tau\delta$, $\alpha = \pi - \kappa\,\delta$ and its formal Taylor expansion about $\delta = 0$. **Case II** is when $[B,\, C] = [0,\, \lambda]$, $\lambda = \tau\delta$, $\alpha = \pi - \kappa\,\delta$ and its formal Taylor expansion about $\delta = 0$. **Case III** denotes when $[B,\, C] = [0,\, 2\pi]$ and $\alpha \in (0, \pi)$ is a constant. Since the twist angle β_i is the only random component in these entries it suffices to consider the means of three different combinations of β_i.

Combination 1: $\mathsf{E}(\cos\beta - \mathsf{E}\cos\beta)$

$$\begin{aligned}
\mathsf{E}(\cos\beta - \mathsf{E}\cos\beta)^2 &= \mathsf{E}\cos^2\beta - (\mathsf{E}\cos\beta)^2 \\
\textbf{(I)} &= \tfrac{1}{2}\left(1 + \tfrac{\sin 2\lambda}{2\lambda}\right) - \left(\tfrac{\sin\lambda}{\lambda}\right)^2 = \tfrac{\lambda^4}{45} + O(\lambda^6), \\
\textbf{(II)} &= \tfrac{1}{2}\left(1 + \tfrac{\sin 2\lambda}{2\lambda}\right) - \left(\tfrac{\sin\lambda}{\lambda}\right)^2 = \tfrac{\lambda^4}{45} + O(\lambda^6), \\
\textbf{(III)} &= \tfrac{1}{2}.
\end{aligned}$$

Combination 2: $\mathsf{E}(\sin\beta - \mathsf{E}\sin\beta)$

$$\begin{aligned}
\mathsf{E}(\sin\beta - \mathsf{E}\sin\beta)^2 &= \mathsf{E}\sin^2\beta - (\mathsf{E}\sin\beta)^2 \\
\textbf{(I)} &= \tfrac{1}{2}\left(1 - \tfrac{\sin 2\lambda}{2\lambda}\right) = \tfrac{\lambda^2}{3} - \tfrac{\lambda^4}{15} + O(\lambda^6), \\
\textbf{(II)} &= \tfrac{1}{2}\left(1 - \tfrac{\sin 2\lambda}{2\lambda}\right) - \left(\tfrac{1-\cos\lambda}{\lambda}\right)^2 = \tfrac{\lambda^2}{12} - \tfrac{\lambda^4}{40} + O(\lambda^6), \\
\textbf{(III)} &= \tfrac{1}{2}.
\end{aligned}$$

Combination 3: $\mathsf{E}(\cos\beta - \mathsf{E}\cos\beta)(\sin\beta - \mathsf{E}\sin\beta)$

$$\mathsf{E}(\cos\beta - \mathsf{E}\cos\beta)(\sin\beta - \mathsf{E}\sin\beta) = \mathsf{E}(\cos\beta\sin\beta) - \mathsf{E}\cos\beta\,\mathsf{E}\sin\beta$$

$$\begin{aligned}
\textbf{(I)} &= 0, \\
\textbf{(II)} &= \tfrac{\sin^2\lambda}{2\,\lambda} - \left(\tfrac{\sin\lambda}{\lambda}\right)\left(\tfrac{1-\cos\lambda}{\lambda}\right) = -\tfrac{\lambda^3}{24} + \tfrac{7\lambda^5}{720} + O(\lambda^6), \\
\textbf{(III)} &= 0.
\end{aligned}$$

We define the following symbols,

$$\tilde{C} \doteq (\cos\beta - \mathsf{E}\cos\beta)^2, \qquad \tilde{M} \doteq (\cos\beta - \mathsf{E}\cos\beta)(\sin\beta - \mathsf{E}\sin\beta),$$
$$\tilde{S} \doteq (\sin\beta - \mathsf{E}\sin\beta)^2.$$

A.1 Drift and diffusion terms for special cases

Case I: $[B,\, C] = [-\tau\delta,\, \tau\delta], \quad \alpha = \pi - \kappa\,\delta$

Let $\lambda = \tau\delta$.

$$\begin{aligned}
\mathsf{E}Q &= \begin{pmatrix} -(\cos\alpha+1)(\frac{\sin\lambda}{\lambda}+1) & \frac{\sin\lambda}{\lambda}\sqrt{2(1+\cos\alpha)} & 0 \\ -\frac{\sqrt{2(\cos\alpha+1)(\frac{\sin\lambda}{\lambda}+1)}}{2} & \frac{\sin\lambda}{\lambda}-1 & 0 \\ 0 & 0 & \frac{\sin\lambda}{\lambda}-1 \end{pmatrix} \\
&= \begin{pmatrix} -\kappa^2\delta & \kappa & 0 \\ -\kappa & -\frac{\tau^2\delta}{6} & 0 \\ 0 & 0 & -\frac{\tau^2\delta}{6} \end{pmatrix} \delta \;+\; O(\delta^3)
\end{aligned}$$

$$\begin{aligned}
\mathsf{E}\mathcal{M}^{1,1}_{jk} &= \tfrac{\kappa^4\tau^4\delta^8}{180}\,T^jT^k \;-\; \tfrac{\kappa^3\tau^4\delta^7}{90}\,T^jN^k \;+\; 0\,T^jB^k \\
&\quad - \tfrac{\kappa^3\tau^4\delta^7}{90}\,N^jT^k \;+\; \tfrac{4\tau^4\delta^4}{45}\,N^jN^k \;+\; 0\,N^jB^k \\
&\quad + 0\,B^jT^k \;+\; 0\,B^jN^k \;+\; \tfrac{\kappa^2\tau^2\delta^4}{3}\,B^jB^k \\
\mathsf{E}\mathcal{M}^{1,2}_{jk} &= \tfrac{\kappa^3\tau^4\delta^7}{180}\,T^jT^k \;-\; \tfrac{\kappa^2\tau^4\delta^6}{90}\,T^jN^k \;+\; 0\,T^jB^k \\
&\quad - \tfrac{\kappa^2\tau^4\delta^6}{90}\,N^jT^k \;+\; \tfrac{\kappa\tau^4\delta^5}{45}\,N^jN^k \;+\; 0\,N^jB^k \\
&\quad + 0\,B^jT^k \;+\; 0\,B^jN^k \;+\; \tfrac{\kappa\tau^2\delta^4}{3}\,B^jB^k \\
\mathsf{E}\mathcal{M}^{1,3}_{jk} &= 0\,T^jT^k \;+\; 0\,T^jN^k \;-\; \tfrac{\kappa^2\tau^4\delta^6}{90}\,T^jB^k \\
&\quad + 0\,N^jT^k \;+\; 0\,N^jN^k \;+\; \tfrac{\kappa\tau^4\delta^5}{45}\,N^jB^k \\
&\quad + \tfrac{\kappa^2\tau^2\delta^4}{6}\,B^jT^k \;-\; \tfrac{\kappa\tau^2\delta^3}{3}\,B^jN^k \;+\; 0\,B^jB^k \\
\mathsf{E}\mathcal{M}^{2,1}_{jk} &= \tfrac{\kappa^3\tau^4\delta^7}{180}\,T^jT^k \;-\; \tfrac{\kappa^2\tau^4\delta^6}{90}\,T^jN^k \;+\; 0\,T^jB^k \\
&\quad - \tfrac{\kappa^2\tau^4\delta^6}{90}\,N^jT^k \;+\; \tfrac{\kappa\tau^4\delta^5}{45}\,N^jN^k \;+\; 0\,N^jB^k \\
&\quad + 0\,B^jT^k \;+\; 0\,B^jN^k \;+\; \tfrac{\kappa\tau^2\delta^4}{3}\,B^jB^k \\
\mathsf{E}\mathcal{M}^{2,2}_{jk} &= \tfrac{\kappa^2\tau^4\delta^6}{180}\,T^jT^k \;-\; \tfrac{\kappa\tau^4\delta^5}{90}\,T^jN^k \;+\; 0\,T^jB^k \\
&\quad - \tfrac{\kappa\tau^4\delta^5}{45}\,N^jT^k \;+\; \tfrac{\tau^4\delta^4}{45}\,N^jN^k \;+\; 0\,N^jB^k \\
&\quad + 0\,B^jT^k \;+\; 0\,B^jN^k \;+\; \tfrac{\tau^2\delta^2}{3}\,B^jB^k \\
\mathsf{E}\mathcal{M}^{2,3}_{jk} &= 0\,T^jT^k \;+\; 0\,T^jN^k \;-\; \tfrac{\kappa\tau^4\delta^5}{90}\,T^jB^k \\
&\quad + 0\,N^jT^k \;+\; 0\,N^jN^k \;+\; \tfrac{\tau^4\delta^4}{45}\,N^jB^k \\
&\quad + \tfrac{\kappa\tau^2\delta^3}{6}\,B^jT^k \;-\; \tfrac{\tau^2\delta^2}{3}\,B^jN^k \;+\; 0\,B^jB^k
\end{aligned}$$

$$
\begin{aligned}
\mathsf{E}\mathcal{M}^{3,1}_{jk} &= 0\,T^jT^k \;+\; 0\,T^jN^k \;+\; \tfrac{\kappa^2\tau^2\delta^4}{6}\,T^jB^k \\
&\quad + 0\,N^jT^k \;+\; 0\,N^jN^k \;-\; \tfrac{\kappa\tau^2\delta^3}{3}\,N^jB^k \\
&\quad - \tfrac{\kappa^2\tau^4}{90}\,B^jT^k \;+\; \tfrac{\kappa\tau^4\delta^5}{45}\,B^jN^k \;+\; 0\,B^jB^k \\
\mathsf{E}\mathcal{M}^{3,2}_{jk} &= 0\,T^jT^k \;+\; 0\,T^jN^k \;+\; \tfrac{\kappa\tau^2\delta^3}{6}\,T^jB^k \\
&\quad + 0\,N^jT^k \;+\; 0\,N^jN^k \;-\; \tfrac{\tau^2\delta^2}{3}\,N^jB^k \\
&\quad - \tfrac{\kappa\tau^4\delta^5}{90}\,B^jT^k \;+\; \tfrac{\tau^4\delta^4}{45}\,B^jN^k \;+\; 0\,B^jB^k \\
\mathsf{E}\mathcal{M}^{3,3}_{jk} &= \tfrac{\kappa^2\tau^2\delta^4}{12}\,T^jT^k \;-\; \tfrac{\kappa\tau^2\delta^3}{6}\,T^jN^k \;+\; 0\,T^jB^k \\
&\quad - \tfrac{\kappa\tau^2\delta^3}{6}\,N^jT^k \;+\; \tfrac{\tau^2\delta^2}{3}\,N^jN^k \;+\; 0\,N^jB^k \\
&\quad + 0\,B^jT^k \;+\; 0\,B^jN^k \;+\; \tfrac{\tau^4\delta^4}{45}\,B^jB^k
\end{aligned}
$$

$$
\delta\, A_{jk}(Y_s) \;=\; \mathsf{E}\mathcal{M}_{jk} \;=\; \begin{pmatrix} 0 & 0 & 0 \\ 0 & B^jB^k & -B^jN^k \\ 0 & -N^jB^k & N^jN^k \end{pmatrix} \frac{\tau^2\delta^2}{3} + O(\delta^3)\,.
$$

The matrix $\bar{\mathbf{Q}}\, Y\, Y^t\, \bar{\mathbf{Q}}^t$, being symmetric and non-negative definite, has a Cholesky decomposition [9], i.e., there exists a (3×3) matrix D such that $D\,D^t = \mathsf{E}\mathcal{M}$, and clearly $D \;=\; O(\delta)$.

Case II: $[B,\, C] = [0,\, \tau\delta], \quad \alpha = \pi - \kappa\,\delta$

Let $\lambda = \tau\delta$.

$$
\begin{aligned}
\mathsf{E}Q &= \begin{pmatrix} -(\cos\alpha+1)(\frac{\sin\lambda}{\lambda}+1) & \frac{\sin\lambda}{\lambda}\sqrt{2(1+\cos\alpha)} & \frac{(1-\cos\lambda)}{\lambda}\sin\alpha \\ -\frac{\sqrt{2(\cos\alpha+1)}(\frac{\sin\lambda}{\lambda}+1)}{2} & \frac{\sin\lambda}{\lambda}-1 & \frac{(1-\cos\lambda)\sin\alpha}{\lambda\sqrt{2(1+\cos\alpha)}} \\ \frac{(1-\cos\lambda)(1+\cos\alpha)}{\lambda\,\sin\alpha} & -\frac{(1-\cos\lambda)\sqrt{2(1+\cos\alpha)}}{\lambda\,\sin\alpha} & \frac{\sin\lambda}{\lambda}-1 \end{pmatrix} \\
&= \begin{pmatrix} -\kappa^2\delta & \kappa & \frac{\kappa\tau\delta}{2} \\ -\kappa & -\frac{\tau^2\delta}{6} & \frac{\tau}{2} \\ \frac{\kappa\tau\delta}{4} & -\frac{\tau}{2} & -\frac{\tau^2\delta}{6} \end{pmatrix} \delta \;+\; O(\delta^3)
\end{aligned}
$$

$$
\begin{aligned}
\mathsf{E}\mathcal{M}^{1,1}_{jk} &= \tfrac{\kappa^4\tau^4\delta^8}{180}\, T^jT^k \;-\; \tfrac{\kappa^3\tau^4\delta^7}{90}\, T^jN^k \;+\; \tfrac{\kappa^3\tau^3\delta^6}{48}\, T^jB^k \\
&\quad -\; \tfrac{\kappa^3\tau^4\delta^7}{90}\, N^jT^k \;+\; \tfrac{4\tau^4\delta^4}{45}\, N^jN^k \;-\; \tfrac{\kappa^2\tau^3\delta^5}{24}\, N^jB^k \\
&\quad +\; \tfrac{\kappa^3\tau^3\delta^6}{48}\, B^jT^k \;-\; \tfrac{\kappa^2\tau^3\delta^5}{24}\, B^jN^k \;+\; \tfrac{\kappa^2\tau^2\delta^4}{12}\, B^jB^k \\
\mathsf{E}\mathcal{M}^{1,2}_{jk} &= \tfrac{\kappa^3\tau^4\delta^7}{180}\, T^jT^k \;-\; \tfrac{\kappa^2\tau^4\delta^6}{90}\, T^jN^k \;+\; \tfrac{\kappa^2\tau^3\delta^5}{48}\, T^jB^k \\
&\quad -\; \tfrac{\kappa^2\tau^4\delta^6}{90}\, N^jT^k \;+\; \tfrac{\kappa\tau^4\delta^5}{45}\, N^jN^k \;-\; \tfrac{\kappa\tau^3\delta^4}{24}\, N^jB^k \\
&\quad +\; \tfrac{\kappa^2\tau^3\delta^5}{48}\, B^jT^k \;-\; \tfrac{\kappa\tau^3\delta^4}{24}\, B^jN^k \;+\; \tfrac{\kappa\tau^2\delta^3}{12}\, B^jB^k \\
\mathsf{E}\mathcal{M}^{1,3}_{jk} &= \tfrac{\kappa^3\tau^3\delta^6}{96}\, T^jT^k \;-\; \tfrac{\kappa^2\tau^3\delta^5}{48}\, T^jN^k \;-\; \tfrac{\kappa^2\tau^4\delta^6}{90}\, T^jB^k \\
&\quad -\; \tfrac{\kappa^2\tau^3\delta^5}{48}\, N^jT^k \;+\; \tfrac{\kappa\tau^3\delta^4}{24}\, N^jN^k \;+\; \tfrac{\kappa\tau^4\delta^5}{45}\, N^jB^k \\
&\quad +\; \tfrac{\kappa^2\tau^2\delta^4}{24}\, B^jT^k \;-\; \tfrac{\kappa\tau^2\delta^3}{12}\, B^jN^k \;-\; \tfrac{\kappa\tau^3\delta^4}{24}\, B^jB^k \\
\mathsf{E}\mathcal{M}^{2,1}_{jk} &= \tfrac{\kappa^3\tau^4\delta^7}{180}\, T^jT^k \;-\; \tfrac{\kappa^2\tau^4\delta^6}{90}\, T^jN^k \;+\; \tfrac{\kappa^2\tau^3\delta^5}{48}\, T^jB^k \\
&\quad -\; \tfrac{\kappa^2\tau^4\delta^6}{90}\, N^jT^k \;+\; \tfrac{\kappa\tau^4\delta^5}{45}\, N^jN^k \;-\; \tfrac{\kappa\tau^3\delta^4}{24}\, N^jB^k \\
&\quad +\; \tfrac{\kappa^2\tau^3\delta^5}{48}\, B^jT^k \;-\; \tfrac{\kappa\tau^3\delta^4}{24}\, B^jN^k \;+\; \tfrac{\kappa\tau^2\delta^3}{12}\, B^jB^k \\
\mathsf{E}\mathcal{M}^{2,2}_{jk} &= \tfrac{\kappa^2\tau^4\delta^6}{180}\, T^jT^k \;-\; \tfrac{\kappa\tau^4\delta^5}{90}\, T^jN^k \;+\; \tfrac{\kappa\tau^3\delta^4}{48}\, T^jB^k \\
&\quad -\; \tfrac{\kappa\tau^4\delta^5}{90}\, N^jT^k \;+\; \tfrac{\tau^4\delta^4}{45}\, N^jN^k \;-\; \tfrac{\tau^3\delta^3}{24}\, N^jB^k \\
&\quad +\; \tfrac{\kappa\tau^3\delta^4}{48}\, B^jT^k \;-\; \tfrac{\tau^3\delta^3}{24}\, B^jN^k \;+\; \tfrac{\tau^2\delta^2}{12}\, B^jB^k \\
\mathsf{E}\mathcal{M}^{2,3}_{jk} &= \tfrac{\kappa^2\tau^3\delta^5}{96}\, T^jT^k \;-\; \tfrac{\kappa\tau^3\delta^4}{48}\, T^jN^k \;-\; \tfrac{\kappa\tau^4\delta^5}{90}\, T^jB^k \\
&\quad -\; \tfrac{\kappa\tau^3\delta^4}{48}\, N^jT^k \;+\; \tfrac{\tau^3\delta^3}{24}\, N^jN^k \;+\; \tfrac{\tau^4\delta^4}{45}\, N^jB^k \\
&\quad +\; \tfrac{\kappa\tau^2\delta^3}{24}\, B^jT^k \;-\; \tfrac{\tau^2\delta^2}{12}\, B^jN^k \;-\; \tfrac{\tau^3\delta^3}{24}\, B^jB^k \\
\mathsf{E}\mathcal{M}^{3,1}_{jk} &= \tfrac{\kappa^3\tau^3\delta^6}{96}\, T^jT^k \;-\; \tfrac{\kappa^2\tau^3\delta^5}{48}\, T^jN^k \;+\; \tfrac{\kappa^2\tau^2\delta^4}{24}\, T^jB^k \\
&\quad -\; \tfrac{\kappa^2\tau^3\delta^5}{48}\, N^jT^k \;+\; \tfrac{\kappa\tau^3\delta^4}{24}\, N^jN^k \;-\; \tfrac{\kappa\tau^2\delta^3}{12}\, N^jB^k \\
&\quad -\; \tfrac{\kappa^2\tau^4\delta^6}{90}\, B^jT^k \;+\; \tfrac{\kappa\tau^4\delta^5}{45}\, B^jN^k \;-\; \tfrac{\kappa\tau^3\delta^4}{24}\, B^jB^k \\
\mathsf{E}\mathcal{M}^{3,2}_{jk} &= \tfrac{\kappa^2\tau^3\delta^5}{96}\, T^jT^k \;-\; \tfrac{\kappa\tau^3\delta^4}{48}\, T^jN^k \;+\; \tfrac{\kappa\tau^2\delta^3}{24}\, T^jB^k \\
&\quad -\; \tfrac{\kappa\tau^3\delta^4}{48}\, N^jT^k \;+\; \tfrac{\tau^3\delta^3}{24}\, N^jN^k \;-\; \tfrac{\tau^2\delta^2}{12}\, N^jB^k \\
&\quad -\; \tfrac{\kappa\tau^4\delta^5}{90}\, B^jT^k \;+\; \tfrac{\tau^4\delta^4}{45}\, B^jN^k \;-\; \tfrac{\tau^3\delta^3}{24}\, B^jB^k \\
\mathsf{E}\mathcal{M}^{3,3}_{jk} &= \tfrac{\kappa^2\tau^2\delta^4}{48}\, T^jT^k \;-\; \tfrac{\kappa\tau^2\delta^3}{24}\, T^jN^k \;-\; \tfrac{\kappa\tau^3\delta^4}{48}\, T^jB^k \\
&\quad -\; \tfrac{\kappa\tau^2\delta^3}{24}\, N^jT^k \;+\; \tfrac{\tau^2\delta^2}{12}\, N^jN^k \;+\; \tfrac{\tau^3\delta^3}{24}\, N^jB^k \\
&\quad -\; \tfrac{\kappa\tau^3\delta^4}{48}\, B^jT^k \;+\; \tfrac{\tau^3\delta^3}{24}\, B^jN^k \;+\; \tfrac{\tau^4\delta^4}{45}\, B^jB^k
\end{aligned}
$$

$$
\delta\, A_{jk}(Y_s) \;=\; \mathsf{E}\mathcal{M}_{jk} \;=\; \begin{pmatrix} 0 & 0 & 0 \\ 0 & B^jB^k & -B^jN^k \\ 0 & -N^jB^k & N^jN^k \end{pmatrix} \frac{\tau^2\delta^2}{12} + O(\delta^3)\,.
$$

The matrix $\bar{\mathbf{Q}}\, Y\, Y^t\, \bar{\mathbf{Q}}^t$, being symmetric and non-negative definite, has a Cholesky decomposition [9], i.e., there exists a (3×3) matrix D such that $D\,D^t = \mathsf{E}\mathcal{M}$, and clearly $D \;=\; O(\delta)$.

<u>**Case III**: $[B,\ C] = [0,\ 2\pi], \quad \alpha \in (0,\pi)$ a constant</u>

$$\mathsf{E}Q_i \;=\; \begin{pmatrix} -(\cos\alpha + 1) & 0 & 0 \\ -\frac{\sqrt{2(\cos\alpha+1)}}{2} & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix},$$

The expected value of the entries of the jk-th (3×3) sub-blocks of $\bar{\mathbf{Q}}YY^t\bar{\mathbf{Q}}^t$, $\mathcal{M}_{jk}$, are essentially (3.5) with $\mathsf{E}\tilde{C} = \mathsf{E}\tilde{S} = \frac{1}{2}$ and $\mathsf{E}\tilde{M} = 0$. And again, the matrix $\bar{\mathbf{Q}}\ Y\ Y^t\ \bar{\mathbf{Q}}^t$, being symmetric and non-negative definite, has a Cholesky decomposition [9], i.e., there exists a (3×3) matrix D such that $D\,D^t = \mathsf{E}\mathcal{M}$, and clearly $D\ =\ O(\delta^{-\frac{1}{2}})$.

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