

Looping probabilities of elastic chains: A path integral approach

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We consider an elastic chain at thermodynamic equilibrium with a heat bath, and derive an approximation to the probability density function, or pdf, governing the relative location and orientation of the two ends of the chain. Our motivation is to exploit continuum mechanics models for the computation of DNA looping probabilities, but here we focus on explaining the novel analytical aspects in the derivation of our approximation formula. Accordingly, and for simplicity, the current presentation is limited to the illustrative case of planar configurations. A path integral formalism is adopted, and, in the standard way, the first approximation to the looping pdf is obtained from a minimal energy configuration satisfying prescribed end conditions. Then we compute an additional factor in the pdf which encompasses the contributions of quadratic fluctuations about the minimum energy configuration along with a simultaneous evaluation of the partition function. The original aspects of our analysis are twofold. First, the quadratic Lagrangian describing the fluctuations has cross-terms that are linear in first derivatives. This, seemingly small, deviation from the structure of standard path integral examples complicates the necessary analysis significantly. Nevertheless, after a nonlinear change of variable of Riccati type, we show that the correction factor to the pdf can still be evaluated in terms of the solution to an initial value problem for the linear system of Jacobi ordinary differential equations associated with the second variation. The second novel aspect of our analysis is that we show that the Hamiltonian form of these linear Jacobi equations still provides the appropriate correction term in the inextensible, unsharable limit that is commonly adopted in polymer physics models of, e.g. DNA. Prior analyses of the inextensible case have had to introduce nonlinear and nonlocal integral constraints to express conditions on the relative displacement of the end points. Our approximation formula for the looping pdf is of quite general applicability as, in contrast to most prior approaches, no assumption is made of either uniformity of the elastic chain, nor of a straight intrinsic shape. If the chain is uniform the Jacobi system evaluated at certain minimum energy configurations has constant coefficients. In such cases our approximate pdf can be evaluated in an entirely explicit, closed form. We illustrate our analysis with a planar example of this type and compute an approximate probability of cyclization, i.e., of forming a closed loop, from a uniform elastic chain whose intrinsic shape is an open circular arc.

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I. INTRODUCTION

In vivo, DNA looping is important in many cellular processes—such as transcriptional regulation, recombination and replication—because it allows for two distant sites on the DNA to come in close proximity [1–5]. The likelihood of a loop being formed depends on the mechanical properties of the intervening DNA, as determined by both the number and specific sequence of bases between the two sites of interest. In particular DNA need not be intrinsically straight; for instance A-tracts form one specific sequence motif that is believed to have a significant intrinsic curvature. And such sequence-dependent effects can strongly affect the efficiency of looping. Accordingly, a quantitative understanding of the effects of sequence-dependent shape and stiffness on DNA looping probabilities is crucial for the analysis of the available experimental data.

The length scales of interest here vary from a few tens to a few hundreds of base pairs. At such length scales a fully

atomistic description is already too complicated for analysis, and (currently) prohibitively intensive for long numerical simulations. Therefore a suitable coarse-grain description must be adopted. For our current purpose, the two most pertinent choices for coarse graining are those in which the DNA is approximated as a chain of interacting rigid base pairs, or the continuum limit of that model where the DNA is described as an elastic rod (or wormlike chain). We mention in particular the work of Zhang and Crothers [6], which was first used to model cyclization experiments and later generalized to consider other looping problems [33]. They compute a “semiclassical approximation” to the looping probability density function, or pdf, from an assumed Boltzmann distribution of chain configurations; in other words they compute a minimum energy configuration between prescribed configurations of first and last base pairs (which they achieve using an iterative numerical approach), and then include effects of harmonic fluctuations in a quadratic well about each minimum energy configuration via the approximate evaluation of certain Gaussian integrals. They adopt a constrained model in which the translational degrees of freedom at each base-pair junction are held fixed; in the language of DNA shift, slide and rise are frozen. As a consequence the relative translational displacement of the two ends is a highly nonlinear and nonlocal function of the an-

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gular deformations at each base-pair junction, and as a consequence the necessary Gaussian integrals are only evaluated approximately after passing to Fourier space.

Our objective is to develop the analogous semiclassical theory, but working entirely within the computationally efficient context of sequence-dependent elastic rod models. Elastic rod models, in which DNA is pictured as a framed curve in space encompassing bend and twist, have been introduced and used with considerable success in the determination of minimal energy configurations of DNA oligomers since the late nineteen seventies [7–13]. For example, the iterative algorithms applied in [6] to find minimum energy shapes in their rigid base-pair description can both be computationally more expensive, and also manifest convergence problems when compared to methods based on symmetry breaking and parameter continuation applied to a continuum rod description [9]. On the other hand, the challenge for continuum descriptions is to include in a tractable way the effect of quadratic fluctuations about minimum energy configurations; to that end an appropriate theory of path integrals must be introduced.

Starting from an assumed Boltzmann distribution on rod configurations, it is widely understood that a looping pdf can be expressed as the ratio of the Boltzmann weighted integral over all paths satisfying the desired looping condition, to the analogous weighted path integral over all admissible configurations. In turn these path integrals can be explicitly evaluated if they can be transformed to be quadratic in appropriate variables, or if they are approximated by a quadratic “semiclassical” expansion about a minimum energy configuration. This is the computational approach that we here make explicit in the specific context of planar rod models. Our final approximation of a planar looping probability density function is detailed in Eq. (69), and is of the general form

$$e^{-\beta \bar{E}_l} \sqrt{\det \frac{2\pi}{\beta} \mathbf{J}}, \quad (1)$$

where β is the inverse temperature scale (set by the solvent heat bath), \bar{E}_l is the energy of a minimizer satisfying the desired looping boundary conditions, and \mathbf{J} is a matrix that can be computed from the solution of an initial value problem for the Jacobi system of linear ordinary differential equations at the energy minimizer. Expressions with the same functional form as expression (1) are quite familiar in the theory of semiclassical path integrals. However, as detailed below, our result is not standard for two reasons. First, in order that looping can be expressed simply as boundary conditions on the configuration variables we work with a rod model that includes degrees of freedom associated with shear and extension. (In the language of DNA we allow shift, slide, and rise to fluctuate.) In that model the second variation at energy minimizers inevitably has certain cross-terms, which places evaluation of the associated quadratic path integral outside the simple standard cases. To handle these cross-terms our result relies on an elegant algebraic argument stated originally for a quantum mechanical system in [14], followed by the construction of a nonlinear change of vari-

ables to arrive finally at an expression in terms of solutions of the classic linear system of Jacobi equations. Second, we show that in the limit of an inextensible and unshearable rod, which is analogous to the standard models of polymer physics, our expression (1) remains valid provided that the matrix \mathbf{J} is evaluated as a solution of an initial value problem for specifically the *Hamiltonian* form of the Jacobi equations. This Hamiltonian form of the Jacobi equations is related to the definition of conjugate points for isoperimetrically constrained calculus of variations problems [10], where, in the context of inextensible, unshearable models of DNA, the isoperimetric constraints reflect the nonlinear, nonlocal conditions fixing the relative Cartesian coordinates of the end points of the oligomer.

The formula (1) is robust in the sense that it remains valid for all of the standard cases arising in DNA modeling, including sequence-dependent stiffness and intrinsic shape. The formula is also highly amenable to a straightforward numerical evaluation even in the general case. On the other hand, in some special cases of interest, the formula can even be evaluated in a completely closed form, and we give an example of this type.

It is worth noting that the crucial assumption used when adopting the semiclassical approximation of a path integral via consideration of only quadratic fluctuations around a minimal energy configuration is that the energy required to deform the system is large with respect to $K_B T = 1/\beta$. This physically means that we should either consider short enough fragments of DNA, or the temperature should be low enough. The approximation of quadratic fluctuations is presumably a reasonable one if we intend to describe the mechanics of DNA at the length scale of a few persistence lengths or less. This in turn is a length scale of great relevance in biology as DNA is known to often be tightly bent at length scales at and below the persistence length [4,5].

For the quantitative modelling of most DNA looping experiments, the three-dimensional version of formula (1) is necessary, as is a realistic set of input parameters for a sequence-dependent energy describing DNA. We do not consider these aspects here. Rather we here focus on the analytical derivation of the expression (1), and therefore follow [15–17], in choosing to present our approach in the simpler context of two-dimensional or planar problems, where the details of parametrizing the three-dimensional rotation group $SO(3)$ do not obfuscate the central ideas of our analysis. Moreover, as already observed in [15], the confinement of DNA to a given surface is growing in relevance as an experimental method (see, for instance, [18]), so that a planar model of such two-dimensional (2D) data are also of intrinsic interest. We note that in the planar case the configuration of an inextensible, unshearable rod is completely specified by a single scalar angle function $\phi(s)$. Nevertheless in our theory for this case, the matrix \mathbf{J} appearing in formula (1) is of size 3×3 , and must be computed from a six dimensional Hamiltonian system of ordinary differential equations.

The structure of the paper is as follows. In Sec. II, we introduce a planar version of the special Cosserat theory of rods, including the strain energy density for the shearable, extensible case. Section III develops our path integral method approach in seven subsections. In Sec. III A, we state

the precise question to be addressed. In Sec. III B, we introduce the minimal energy approximation, and in Sec. III C we define the path integrals of interest via a discretization in arc-length followed by a limiting procedure. Sec. III D and III E are devoted to the explicit computation of the approximate probability density function by means of the approach proposed in [14]. In Sec. III F we establish the connection to a basis of solutions to the Jacobi equations. In Sec. III G, we extend our method to the constrained case of inextensible, unshearable rods. In Sec. IV, we consider the example of a uniform, but intrinsically curved rod, and we compute analytically the approximate pdf (1) for cyclization, i.e. for the formation of a closed loop, from a rod whose intrinsic shape is an open circular arc. In Sec. V, we present a brief and preliminary comparison between our semiclassical pdf and direct Monte Carlo simulations, as well as discussing its parameter dependence. Conclusions and future directions are discussed in Sec. VI.

A considerable prior literature is available on the computation of looping probabilities, including both analytical and numerical approaches in both discrete and continuum models of DNA, for instance [6,9–13,15–17,19–39]. Accordingly we close this introduction with a brief review of these results.

For a homogeneous chain, the exact statistical mechanical theory of both the wormlike chain, where no twist is considered [23,24], and the helical wormlike chain [23] has been derived. In particular in [27] a uniform, isotropic, intrinsically straight and helical wormlike chain twisting at a constant rate is considered. The chain orientation Green's function, which gives the probability that a chain with known initial orientation will have a given end orientation, is expressed in terms of a complete set of eigenfunctions (Wigner functions) whereas the full Green's function, giving the probability that the end is fixed in location and orientation, is computed via an average with respect to the chain orientation Green's function. In Fourier space, the Taylor expansion of the Fourier-space Green's function gives an infinite sum of moments of the end-to-end distribution function with fixed end orientations. The results of [23] for the wormlike chain, have then been generalized to include deviations from linear elasticity: in [28] kinks are allowed and the DNA described by such a kinking-worm-like chain is assumed to rapidly become very soft to bending beyond a critical stress. In [29] a toy model, the sub-elastic-chain model, where the effective bending energy density is a convex but otherwise arbitrary function of curvature, is discussed. Both of the exact theories presented in (28) and (29) are for uniform, isotropic, and untwistable chains. A clear advantage of the approach exploited in [23,24,27] is that the theory is valid for any given chain length and persistence length. In [19] the ring-closure probabilities for a uniform helical wormlike chain, at small length scales was obtained by replacing the continuous chain by an equivalent discrete chain and then by expanding the energy about the minimal energy configuration, whereas for large length scales its evaluation was performed by means of the Daniels approximation and the weighting function method. Homogeneous models and a semiclassical approximation of the partition function have also been considered in [30,31] to discuss the force-extension relation for DNA molecules bearing sliding loops and deflection defects, and in

[32] to discuss the effects of thermal fluctuations in the non-linear buckling regime. The semiclassical approach for discrete base-pair models that was originally presented in [6] has been further developed to include effects of binding proteins, sequence effects and disorder and spontaneous curvature in [33–39].

II. PLANAR ELASTIC ROD

In this section we introduce the planar version of the special Cosserat rod theory of continuum mechanics [40]. A systematic and comprehensive overview of elastic rods can be found in [41], whereas more details on the variational formulation can be found in, for instance [42,43], and references therein.

A planar Cosserat rod is a framed curve restricted to lie in a plane (Fig. 1). To be consistent with three-dimensional (3D) nomenclature we assume this plane to be spanned by the usual Cartesian basis vectors ($\mathbf{e}_2, \mathbf{e}_3$). Accordingly, the centerline $\mathbf{r}(s)$ of the rod has no component along the \mathbf{e}_1 axis so that

$$\mathbf{r}(s) : [0, L] \rightarrow \mathbb{R}^2 \quad (2)$$

has Cartesian coordinates

$$\mathbf{r}(s) = [y(s), z(s)]. \quad (3)$$

In the Cosserat theory there is an orthonormal director frame $\{\mathbf{d}_i(s)\}$, which may be interpreted as specifying the orientation of the material cross-section (or base-pair) of the rod at each s . In the planar theory we assume that

$$\mathbf{d}_1(s) = \mathbf{e}_1, \quad (4)$$

and

$$\mathbf{d}_2 = \cos\phi(s) \mathbf{e}_2 + \sin\phi(s) \mathbf{e}_3,$$

$$\mathbf{d}_3 = -\sin\phi(s) \mathbf{e}_2 + \cos\phi(s) \mathbf{e}_3. \quad (5)$$

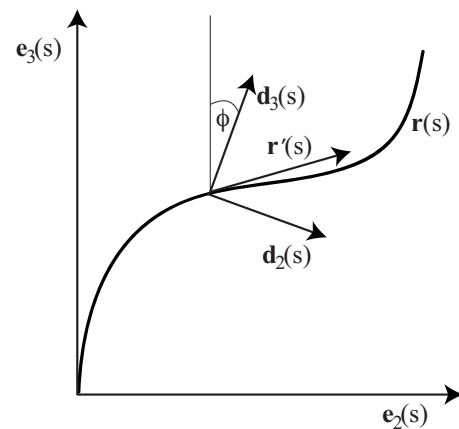


FIG. 1. A Cosserat rod confined to the ($\mathbf{e}_2, \mathbf{e}_3$) plane. The orthonormal director frame $\{\mathbf{d}_2, \mathbf{d}_3\}$ is a rotation about the normal to the plane $\mathbf{e}_1 \equiv \mathbf{d}_1$ through an angle $\phi(s)$ (positive counterclockwise). The derivative of the angle of rotation $\phi' =: u_1$ is the bending strain. The components of the tangent vector \mathbf{r}' on the director basis $\{\mathbf{d}_2, \mathbf{d}_3\}$ are, respectively, the strains of shear and extension v_2 and v_3 .

Positive ϕ corresponds to a counter clockwise rotation of the directors in the $(\mathbf{e}_2, \mathbf{e}_3)$ plane. It is the fact that a single scalar function $\phi(s)$ serves to parameterize the director frame which makes the treatment of the planar case simpler, and a more convenient context in which to illustrate the novel analytic aspects of our approach.

In the planar case, the configuration of the rod is therefore given by

$$\mathbf{q}(s) : [0, L] \rightarrow \mathbb{R}^2 \times \mathbb{R}, \quad (6)$$

with

$$\mathbf{q}(s) := (y(s), z(s), \phi(s)), \quad (7)$$

where $y(s)$, and $z(s)$ are the Cartesian coordinates of the centerline with respect to the fixed frame, and the angle $\phi(s)$ may take values in the whole of \mathbb{R} .

The tangent vector \mathbf{v} to the rod centerline is by definition

$$\mathbf{v}(s) := \mathbf{r}'(s) \quad (8)$$

and its components with respect to $(\mathbf{d}_2, \mathbf{d}_3)$ are referred to as the strains associated with shear and stretch (or compression) of the rod. By (3), (5), and (8), we obtain the following expressions for the strains v_2 and v_3 :

$$\begin{aligned} v_2(s) &:= \mathbf{v} \cdot \mathbf{d}_2 = \cos\phi y' + \sin\phi z', \\ v_3(s) &:= \mathbf{v} \cdot \mathbf{d}_3 = -\sin\phi y' + \cos\phi z'. \end{aligned} \quad (9)$$

Any parameter dependent orthonormal frame has a Darboux vector \mathbf{u} (analogous to an angular velocity) which in our planar context is orthogonal to the $(\mathbf{e}_2, \mathbf{e}_3)$ plane, and which therefore has the special and simple form $\mathbf{u}(s) \equiv u_1 \mathbf{d}_1$. Furthermore with the choice expressed in Eq. (5) it can be verified that

$$u_1 = \phi'(s). \quad (10)$$

Physically u_1 is the strain associated with bending of the rod.

The reference configuration of the rod, typically a minimal energy configuration in which there are no stresses, may be neither straight nor uniform, and so is characterized by certain prescribed intrinsic strain functions $\hat{v}_{2,3}(s)$ and $\hat{u}_1(s)$. There is no loss of generality in assuming that in the unstressed reference configuration the parameter s is arc-length, with $\hat{v}_2 \equiv 0$ and $\hat{v}_3 \equiv 1$.

To complete our model we introduce the form that we assume for the internal or potential energy of the rod. We assume a linear constitutive relation between stresses and strains, which in our planar case is equivalent to assuming an energy of the form

$$E = \frac{1}{2} \int_0^L [v_2(v_3 - 1)(u_1 - \hat{u}_1)] \mathbf{P} \begin{bmatrix} v_2 \\ (v_3 - 1) \\ (u_1 - \hat{u}_1) \end{bmatrix} ds, \quad (11)$$

where v_2 , v_3 , and u_1 are defined in Eqs. (9) and (10); $\hat{v}_2 \equiv 0$, $\hat{v}_3 \equiv 1$, and \hat{u}_1 are the intrinsic strains; \mathbf{P} is a stiffness matrix, that is a (3×3) positive definite, symmetric matrix, which we partition in the form

$$\mathbf{P} = \begin{pmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{B}^T & K \end{pmatrix}, \quad (12)$$

where

$$\mathbf{A} = \begin{bmatrix} A_2 & A_{23} \\ A_{23} & A_3 \end{bmatrix}, \quad \mathbf{B} = \begin{bmatrix} B_{11} \\ B_{21} \end{bmatrix}, \quad (13)$$

\mathbf{B}^T is the transpose of \mathbf{B} , and K is a positive scalar. Thus, the model allows coupling between the deformations of shear, extension, and bend.

The energy (11) satisfies the necessary frame indifference properties because the integrand is a function of only the strains, which are expressed as components of vectors in the director frame. The entries of the matrix \mathbf{P} express the material properties of the polymer, and can be (prescribed) functions of the parameter s . In the context of DNA for example, the nonuniformity of $\mathbf{P}(s)$ would model sequence-dependent variations in stiffness, while $\hat{u}_1(s)$ would model sequence dependent intrinsic curvature.

We remark that while the expression (11) is a quadratic function of the strains, it is a nonquadratic function of the configuration variable (7) (and its derivatives) because we have made no linearization approximation in the nonlinear geometry expressed in Eq. (9).

The above energy (or Hamiltonian in statistical mechanics language) is notably more complex than the usual one assumed in polymer physics, namely, that for the wormlike chain

$$E_{\text{WLC}} = \frac{1}{2} \int_0^L K(u_1 - \hat{u}_1)^2 ds, \quad (14)$$

which corresponds to the inextensible and unsharable limit of the energy (11). Specifically, for an inextensible and unsharable planar rod, the constraints

$$v_2(s) \equiv v_3(s) - 1 \equiv 0, \quad (15)$$

hold in any configuration, not just in the reference configuration. Thus, in any configuration the tangent vector $\mathbf{r}'(s)$ coincides with the unit vector \mathbf{d}_3 and the parameter s is arc-length. The constraints (15) suppress two degrees of freedom and the elastic energy becomes a function purely of the strain $u_1(s)$ and the corresponding intrinsic strain $\hat{u}_1(s)$ as in definition (14).

Because the energy (11) is frame indifferent, we may, with no loss of generality, eliminate rigid body motions of the rod by imposition of the Dirichlet boundary conditions,

$$\mathbf{q}(0) = \mathbf{q}_0 = (0, 0, 0). \quad (16)$$

In this paper we will provide a method to approximate the probability density function for the location and orientation of the other end of the rod, i.e., a way to compute the probability density function (on \mathbb{R}^3) that at $s=L$

$$\mathbf{q}(L) = \mathbf{q}_L = (y_L, z_L, \phi_L). \quad (17)$$

Our starting point will be the assumption that due to the thermal motion induced by the rod's interaction with a solvent heat bath, the energy (11) induces an ensemble of admissible configurations $\mathbf{q}(s)$ satisfying boundary condition

(16) that is governed by a Boltzmann distribution of the form

$$\frac{e^{-\beta E[\mathbf{q}(s)]}}{Z}, \quad (18)$$

where Z is the partition function and β an inverse temperature scale. Given the distribution (18), the problem is to determine the implied conditional probability density function on the end point $\mathbf{q}(L)$. In the continuum context the precise sense of the distribution (18) depends upon the theory of path integrals.

III. A PATH INTEGRAL APPROACH

A. Precise formulation of the problem of looping

Assuming a Boltzmann distribution on configurations $\mathbf{q}(s)$, and given the parameter and coefficient functions appearing in the energy (11), namely, the undeformed length of the rod L , the stiffness matrix $\mathbf{P}(s)$ and intrinsic curvature $\hat{u}_1(s)$, what is the probability for the rod to form a given loop? Because of frame indifference, we need only consider configurations that satisfy the initial boundary condition (16), and we seek the probability density function that at $s=L$, the final boundary conditions (17) are satisfied. We stress that it is key that at this stage the model is an extensible, shearable rod; otherwise looping could not be expressed as simple boundary conditions at $s=0$ and $s=L$.

In mathematical terms, we aim to compute the conditional probability density function

$$\rho[\mathbf{q}_0, \mathbf{q}_L; 0, L] := \frac{\int e^{-\beta E[\mathbf{q}(s)]} \mathcal{D}[\mathbf{q}(s)]_{\Gamma_0}}{\int e^{-\beta E[\mathbf{q}(s)]} \mathcal{D}[\mathbf{q}(s)]}, \quad (19)$$

where $\beta = 1/K_B T$, with K_B the Boltzmann constant and T the temperature of the solvent heat bath. Here $\mathcal{D}[\mathbf{q}(s)]$ is a measure on configurations (7) satisfying only the boundary conditions (16) while $\mathcal{D}[\mathbf{q}(s)]_{\Gamma_0}$ is the measure on configurations (7) satisfying both of the boundary conditions (16) and (17). Thus expression (19) may be viewed as the ratio of the Boltzmann partition functions for the ensemble satisfying both boundary conditions (16) and (17), and the ensemble satisfying only boundary condition (16).

The integrals appearing in expression (19) are path integrals or functional integrals. Mathematically path integrals are an extension or generalization to infinite-dimensional spaces of the familiar concept of integral in finite dimensions [44–47]. It is a delicate matter to define the appropriate path differential rigorously: one way is called “time slicing,” or in our case “parameter slicing,” which is to replace the infinite-dimensional integral with the limit for $n \rightarrow \infty$ of n iterated finite-dimensional integrals. In this case the path integral is defined via a limiting procedure, as was done originally by Feynman [44]. We follow this procedure and show that while neither the numerator nor denominator in Eq. (19) has a finite limit, the ratio does converge, in an entirely standard sense. Although we do not pause to discuss the matter in detail, within our modeling context the parameter slicing ap-

proach even has the physical interpretation that the discretized version of Eq. (19) corresponds to a certain rigid base-pair model of DNA with n base pairs, so that the continuum limit may be interpreted as a good approximation to a finite dimensional system of n base pairs with n large. Before passing to a detailed description of our technique for the evaluation of the path integrals, we first introduce a further simplifying approximation.

B. Expansion about a minimal energy configuration

In the literature it is well known that, under specific hypotheses, it is possible to approximate expressions of the form of both the numerator and denominator in Eq. (19) by means of an expansion around a minimal energy configuration [14,45–48]. In our context that means determining a solution to the Euler-Lagrange equations of the energy (11) that is a strict local minimum and which for the numerator satisfies both sets of Dirichlet boundary conditions (16) and (17), while for the denominator satisfies the Dirichlet boundary conditions (16) and the appropriate natural boundary conditions at $s=L$. In fact the global minimizer for the denominator is provided by the known unstressed reference configuration $\bar{\mathbf{q}}(s)$, while the determination of a local minimizer $\bar{\mathbf{q}}(s)$ for the numerator will for most boundary data in condition (17) involve a nontrivial computation, perhaps numerical as for example in [9]. In any case we assume in the following that such a local minimizer $\bar{\mathbf{q}}(s)$ has been determined.

In an expansion around a local minimal energy configuration we have

$$\mathbf{q}(s) = \bar{\mathbf{q}}(s) + \mathbf{h}(s), \quad (20)$$

where $\bar{\mathbf{q}}(s)$ is the minimal energy configuration and $\mathbf{h}(s)$ is the variation field describing fluctuations about it. In our planar case

$$\mathbf{h}(s) \equiv (\delta y(s), \delta z(s), \delta \phi(s)), \quad (21)$$

and for our analysis of the numerator $\mathbf{h}(s)$ satisfies the linearized version of the original boundary conditions (16) and (17),

$$\mathbf{h}(0) = \mathbf{0} = \mathbf{h}(L). \quad (22)$$

We may then approximate the energy (11) by

$$E[\mathbf{q}(s)] \simeq E[\bar{\mathbf{q}}(s)] + \delta^2 E[\bar{\mathbf{q}}(s), \mathbf{h}(s)], \quad (23)$$

where the second variation $\delta^2 E[\bar{\mathbf{q}}, \mathbf{h}]$ is a quadratic functional of the perturbation field \mathbf{h} and depends on the minimal energy configuration in that the coefficient matrices are to be evaluated at $\bar{\mathbf{q}}$, and, by definition,

$$\delta E[\bar{\mathbf{q}}, \mathbf{h}] = 0 \quad (24)$$

for all admissible \mathbf{h} .

The expression for the second variation of the energy functional (11) can be computed straightforwardly

$$\delta^2 E = \frac{1}{2} \int_0^L [\mathbf{h}'^T \mathbf{P}(s) \mathbf{h}' + 2\mathbf{h}'^T \mathbf{C}(s) \mathbf{h} + \mathbf{h}^T \mathbf{Q}(s) \mathbf{h}] ds \quad (25)$$

where now we write the variations in the director frame,

$$\mathbf{h} = \begin{bmatrix} \cos \phi & \sin \phi & 0 \\ -\sin \phi & \cos \phi & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} \delta y \\ \delta z \\ \delta \phi \end{bmatrix}, \quad (26)$$

\mathbf{P} is given in Eq. (12) and

$$\mathbf{Q}(s) = \begin{bmatrix} u_1^2 A_3 & -u_1^2 A_{23} & u_1 \alpha_3 \\ -u_1^2 A_{23} & u_1^2 A_2 & -u_1 \alpha_2 \\ -u_1 \alpha_3 & -u_1 \alpha_2 & \alpha_1 \end{bmatrix}, \quad (27)$$

$$\mathbf{C}(s) = \begin{bmatrix} u_1 A_{23} & -u_1 A_2 & \alpha_2 \\ u_1 A_3 & -u_1 A_{23} & \alpha_3 \\ u_1 B_{31} & -u_1 B_{21} & 0 \end{bmatrix}, \quad (28)$$

with

$$\begin{aligned} \alpha_1 &= (A_2 - A_3)(v_3^2 - v_2^2) - 2A_{23}v_2v_3 + A_3v_3 + A_{23}v_2 \\ &\quad - (u_1 - \hat{u}_1)[B_{21}v_3 + B_{11}v_2], \\ \alpha_2 &= (A_2 - A_3)v_3 - 2A_{23}v_2 + A_3 - B_{21}(u_1 - \hat{u}_1), \\ \alpha_3 &= (A_2 - A_3)v_2 + 2A_{23}v_3 - A_{23} + B_{11}(u_1 - \hat{u}_1). \end{aligned} \quad (29)$$

We remark that even for an arbitrary rod equilibrium in three dimensions and for nonquadratic energy, relatively simple closed form expressions for the coefficient matrices in the second variation (25) as a function of the strains, forces and moment can be found, see [49] or [50]. We also remark that the coefficient matrix (28) of the cross terms in the second variation need not be symmetric, so that these terms cannot be integrated away. Indeed we know of no significant cases where the matrix (28) is symmetric. As we shall see below, this asymmetry complicates the necessary analysis substantially.

After the expansion (23) is performed, the probability density (19) is approximated as

$$\rho[\mathbf{q}_0, \mathbf{q}_L; 0, L] \simeq \frac{e^{-\beta E[\bar{\mathbf{q}}]} \int e^{-\beta \delta^2 E[\bar{\mathbf{q}}, \mathbf{h}]} D[\mathbf{h}(s)]}{\int e^{-\beta E[\mathbf{q}]} D[\mathbf{q}(s)]}. \quad (30)$$

It can be expected that this approximation is reasonable when the temperature scale β is sufficiently large. However, the assumption that $\bar{\mathbf{q}}$ is a strict local minimizer is important, for otherwise the second variation will have a zero eigenvalue.

C. Discretizing the path integrals

We next carry out the parameter-slicing limit procedure by partitioning the arc-length interval $[0, L]$ into n subintervals, each of size $\epsilon = L/n$,

$$0 = s_0 < s_1 < \dots < s_j < \dots < s_n = L, \quad (31)$$

so that $s_j = j\epsilon$, $\forall j=0 \dots n$. And we replace the configuration $\mathbf{q}(s)$ with a discrete configuration, built up from a sequence of linear segments the coordinates of which are given by the values of the configurations at each subinterval of the partition. In the following, the subscript j will indicate that the corresponding quantity is evaluated at s_j .

The approximate conditional probability density (30) can thus be discretized as

$$\begin{aligned} \rho[\mathbf{q}_0, \mathbf{q}_L; 0, L] &\simeq \frac{e^{-\beta E[\bar{\mathbf{q}}]} \int e^{-\beta \delta^2 E[\bar{\mathbf{q}}, \mathbf{h}]} D[\mathbf{h}(s)]}{\int e^{-\beta E[\mathbf{q}]} D[\mathbf{q}(s)]} \\ &\equiv \lim_{n \rightarrow \infty} e^{-\beta E[\bar{\mathbf{q}}]} \\ &\quad \times \frac{\int \dots \int \dots \int e^{-\beta \epsilon \sum_{j=0}^{n-1} \delta^2 E[\bar{\mathbf{q}}, \mathbf{h}_j]} \prod_{j=1}^{n-1} d\mathbf{h}_j}{\int \dots \int \dots \int e^{-\beta \epsilon \sum_{j=0}^{n-1} E[\mathbf{q}_j]} \prod_{j=1}^n d\mathbf{q}_j}, \end{aligned} \quad (32)$$

where the boundary conditions on the configurations imply that no integration on \mathbf{q}_0 in the denominator, nor on either \mathbf{h}_0 or \mathbf{h}_n in the numerator is needed. Here $d\mathbf{q}_j$ is the appropriate measure in the discretized approximation to the configuration space of the system, and $d\mathbf{h}_j$ is the appropriate measure in the discretized approximation of the variations in the configuration space of the system.

The objective is now to compute explicitly the limit on the right hand side of Eq. (32).

D. Evaluation of the denominator

We first compute the limiting asymptotic behavior of the denominator

$$\int \dots \int \dots \int e^{-\beta \epsilon \sum_{j=0}^{n-1} E[\mathbf{q}_j]} \prod_{j=1}^n d\mathbf{q}_j, \quad (33)$$

as $\epsilon = L/n \rightarrow 0$. The appropriate measure in the discretized approximation to the configuration space is just

$$d\mathbf{q}_j = dy_j dz_j d\phi_j. \quad (34)$$

However, the integrand in (11) is quadratic in the shifted strains so that

$$\epsilon \sum_{j=0}^n E[\mathbf{q}_j] = \frac{\epsilon}{2} \sum_{j=0}^{n-1} \mathbf{w}_j^T \mathbf{P}_j \mathbf{w}_j, \quad (35)$$

where

$$\mathbf{w}_j = [v_{2,j}(v_{3,j} - 1)(u_{1,j} - \hat{u}_{1,j})]^T, \quad (36)$$

and

$$\begin{bmatrix} v_{2,j} \\ v_{3,j} \\ u_{1,j} \end{bmatrix} = \frac{1}{\epsilon} \begin{bmatrix} \cos\phi_j & \sin\phi_j & 0 \\ -\sin\phi_j & \cos\phi_j & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} y_{j+1} - y_j \\ z_{j+1} - z_j \\ \phi_{j+1} - \phi_j \end{bmatrix}, \quad (37)$$

are from definitions (9) and (10) finite difference approximations to the strains. Here we use the notation that for components of a vector \mathbf{a} : $a_{k,j} := a_k(s_j)$. We regard $\hat{u}_{1,j}$ as being prescribed at each j .

We now use Eq. (37) as an invertible nonlinear change of variable, which is possible because there are no boundary conditions on (y_n, z_n, ϕ_n) , and we note that the range of integration of each of the old and new variables is the whole of \mathbb{R} . Thus, we need to insert the Jacobian of the transformation from the discretized strains $\{(v_{2,j}, v_{3,j}, u_{1,j})\}$ to the discretized variables $\{(y_j, z_j, \phi_j)\}$ where the index j now runs from $j=0$ to $j=(n-1)$. From definitions (9) and (10) we easily see that the components v_2, v_3 of \mathbf{v} depend on both the centerline and the angle ϕ , whereas u_1 depends solely on the angle. The $(3n \times 3n)$ Jacobian matrix \mathcal{J} will then be an upper triangular block matrix, of the form

$$\mathcal{J} = \begin{pmatrix} \mathcal{J}_1((v_{2,j}, v_{3,j}), (y_j, z_j))_{2n \times 2n} & \mathcal{J}_*((v_{2,j}, v_{3,j}), \phi_j)_{2n \times n} \\ \mathbf{0}_{n \times 2n} & \mathcal{J}_2(u_{1,j}, \phi_j)_{n \times n} \end{pmatrix} \quad (38)$$

so that the determinant of Eq. (38) is given by

$$|\mathcal{J}| = \frac{1}{\epsilon^{3n}}. \quad (39)$$

In conclusion, we are able to compute expression (33), as

$$\int \cdots \int \cdots \int e^{-(\beta\epsilon/2)\sum_{j=0}^{n-1} \mathbf{w}_j^T \mathbf{P}_j \mathbf{w}_j} \prod_{j=0}^{n-1} \epsilon^3 dv_{2,j} dv_{3,j} du_{1,j}, \quad (40)$$

where \mathbf{w}_j was defined in Eq. (36). The multiple integral (40) now factors into the product of n Gaussian integrals each over the whole of \mathbb{R}^3 and which can therefore be evaluated to yield

$$\prod_{j=0}^{(n-1)} \sqrt{\det\left(\frac{2\pi\epsilon}{\beta} \mathbf{P}_j^{-1}\right)}. \quad (41)$$

Formula (41) provides the necessary asymptotics of the denominator.

E. Approximate probability density function

Substitution of the expression (41) for the denominator in the ratio (32), implies that we are left with the computation of the limit $\epsilon \rightarrow 0$ of

$$\int \cdots \int \cdots \int \prod_{j=0}^{(n-1)} \sqrt{\det\left(\frac{\beta \mathbf{P}_j}{2\pi\epsilon}\right)} e^{-\beta\epsilon \sum_{j=0}^{n-1} \delta^2 E[\bar{\mathbf{q}}_j, \mathbf{h}_j]} \prod_{j=1}^{n-1} d\mathbf{h}_j, \quad (42)$$

where $d\mathbf{h}_j$ is given by

$$d\mathbf{h}_j = d\delta y_j d\delta z_j d\delta\phi_j, \quad (43)$$

and the discretized version of the second variation (25) reads

$$\epsilon \sum_{j=0}^n \delta^2 E[\bar{\mathbf{q}}_j, \mathbf{h}_j] = \frac{1}{2\epsilon} \sum_{j=1}^{n-1} (\mathbf{h}_j^T \mathcal{A}_j \mathbf{h}_j - \mathbf{h}_{j+1}^T \mathbf{L}_j \mathbf{h}_j - \mathbf{h}_j^T \mathbf{L}_j^T \mathbf{h}_{j+1}), \quad (44)$$

where a midpoint prescription [46] has been used;

$$\mathcal{A}_j = \mathbf{P}_{j-1} + \mathbf{P}_j + \epsilon^2 \mathbf{Q}_j, \quad (45)$$

$$\mathbf{L}_j = \left[\mathbf{P}_j + \frac{\epsilon}{2} (\mathbf{C}_{j+1}^T - \mathbf{C}_j) \right], \quad (46)$$

and we have used the boundary conditions (22). In fact Eq. (44) can be written as

$$\frac{1}{2\epsilon} \mathbf{h}_{n-1}^T \mathbf{M}_{n-1} \mathbf{h}_{n-1}, \quad (47)$$

where \mathbf{h}_{n-1} is a $3(n-1) \times 1$ vector of the form

$$\mathbf{h}_{n-1} = [\mathbf{h}_1^T \ \mathbf{h}_2^T \ \mathbf{h}_3^T \ \cdots \ \mathbf{h}_{n-1}^T]^T, \quad (48)$$

and \mathbf{M}_{n-1} is a $3(n-1) \times 3(n-1)$ block tridiagonal matrix of the form

$$\mathbf{M}_{n-1} = \begin{bmatrix} \mathcal{A}_1 & -\mathbf{L}_1^T & \mathbf{0} & \cdots & \mathbf{0} \\ -\mathbf{L}_1 & \mathcal{A}_2 & -\mathbf{L}_2^T & \cdots & \mathbf{0} \\ \mathbf{0} & -\mathbf{L}_2 & \mathcal{A}_3 & \cdots & \mathbf{0} \\ \vdots & \vdots & \vdots & \ddots & -\mathbf{L}_{n-1}^T \\ \mathbf{0} & \cdots & \cdots & -\mathbf{L}_{n-1} & \mathcal{A}_{n-1} \end{bmatrix}. \quad (49)$$

Expression (42) thus becomes

$$\int_{\mathbf{R}^{3(n-1)}} \prod_{j=0}^{(n-1)} \sqrt{\det\left(\frac{\beta \mathbf{P}_j}{2\pi\epsilon}\right)} e^{-\beta/2 \mathbf{e} \mathbf{h}_{n-1}^T \mathbf{M}_{n-1} \mathbf{h}_{n-1}} d\mathbf{h}_{n-1} \quad (50)$$

and the multidimensional Gaussian integral is easily computed in terms of the inverse square root of the determinant of \mathbf{M}_{n-1} . We note that the change of variable used in the evaluation of the denominator cannot be used here because of the additional boundary conditions. And we must obtain an expression for the determinant of the matrix \mathbf{M}_{n-1} in the limit as its dimension tends to infinity.

We follow an approach described in [14]. Defining the recursion

$$\mathbf{A}_1 = \mathcal{A}_1 = \mathbf{P}_0 + \mathbf{P}_1 + \epsilon^2 \mathbf{Q}_1, \quad (51)$$

$$\mathbf{A}_{j+1} = \mathcal{A}_{j+1} - \mathbf{L}_j \mathbf{A}_j^{-1} \mathbf{L}_j^T \quad j \geq 1, \quad (52)$$

and assuming that at each step \mathbf{A}_j is an invertible matrix, by row operations one may transform the matrix (49) into an upper triangular block matrix, whose determinant is just given by the product of the block diagonal matrices \mathbf{A}_j . Then, after extensive use of the properties of determinants, the expression (42) can be written in the form

$$\rho[(\mathbf{q}_0, \mathbf{q}_L; 0, L)] \approx e^{-\beta \bar{E}} \lim_{n \rightarrow \infty} \sqrt{\det \frac{\beta}{2\pi} \mathbf{D}_{n-1}^{-1}}, \quad (53)$$

where $\mathbf{D}_{n-1} = \epsilon(\prod_{k=1}^{n-1} \mathbf{A}_k \mathbf{P}_k^{-1})^T \mathbf{P}_0^{-1}$.

Finally, following the argument presented in [14], it can be shown [14,50] that the above definition for \mathbf{D}_{n-1} combined with the recurrence relation (52) for \mathbf{A}_j leads, in the limit $n \rightarrow \infty$, to the following nonlinear matrix differential equation [14],

$$\begin{aligned} [\mathbf{P}\mathbf{D}'']' + \mathbf{C}^s \mathbf{D} - [\mathbf{Q} + \mathbf{C}^a \mathbf{P}^{-1} \mathbf{C}^a] \mathbf{D} \\ = -\mathbf{C}^a \mathbf{D}' + \mathbf{P}\mathbf{D}' \mathbf{D}^{-1} \mathbf{P}^{-1} \mathbf{C}^a \mathbf{D}, \end{aligned} \quad (54)$$

where the matrices $\mathbf{P}, \mathbf{Q}, \mathbf{C}$ are defined, respectively, in Eqs. (12), (27), and (28); \mathbf{C}^s and \mathbf{C}^a are the symmetric and anti-symmetric parts of \mathbf{C} ; \mathbf{D} is a 3×3 matrix and $'$ denotes differentiation with respect to the arc-length parameter s . We remark that the system of differential equations (54) is in fact the transpose of that derived in [14], according to the definition for \mathbf{D}_{n-1} : we refer to Eq. (54) as the Papadopoulos equations. When $\mathbf{D}(s)$ is the solution of the ordinary differential equations (54) that satisfies the specific initial conditions

$$\mathbf{D}(0) = \mathbf{0}, \quad \mathbf{D}'(0) = \mathbf{P}(0)^{-1}, \quad (55)$$

then $\lim_{n \rightarrow \infty} \mathbf{D}_{n-1} = \mathbf{D}(L)$ [14,50].

Thus, the same algebraic arguments exploited in [14] to treat a quantum mechanical system, implies that the approximate looping probability density function (30) can be evaluated as

$$\rho[(\mathbf{q}_0, \mathbf{q}_L; 0, L)] \approx e^{-\beta \bar{E}} \sqrt{\det \frac{2\pi}{\beta} \mathbf{D}(L)}, \quad (56)$$

where \mathbf{D} satisfies the Papadopoulos equations (54), with initial conditions (55). We note that Eq. (54) is a nonlinear system of ordinary differential equations when the matrix \mathbf{C} is not symmetric.

F. Connections with Jacobi fields

We now show that one can go beyond the Papadopoulos equations to prove that the limit on the right hand side of Eq. (53) can also be evaluated as the inverse square root of the determinant of a matrix of solutions to the linear system of Jacobi ordinary differential equations associated with the second variation (25) that satisfy simple prescribed initial conditions. As they are linear the Jacobi equations are not only much easier to solve in special cases than Eq. (54), but they are also intrinsically related to the variational problem of finding minimal energy configurations for the energy (11). In particular it is known that the absence of a conjugate point of the Jacobi fields in $(0, L]$, i.e., the vanishing of the determinant to be introduced below, is a necessary condition for a solution $\bar{\mathbf{q}}(s)$ of the Euler-Lagrange equations to be a local minimizer.

We derive the new expression via a nonlinear change of variable [50]

$$\mathbf{J}' \mathbf{J}^{-1} = \mathbf{D}' \mathbf{D}^{-1} - \mathbf{P}^{-1} \mathbf{C}^a \quad (57)$$

such that \mathbf{D} will satisfy Eq. (54), if and only if \mathbf{J} satisfies

$$[\mathbf{P}\mathbf{J}' + \mathbf{C}\mathbf{J}]' - \mathbf{C}^T \mathbf{J}' = \mathbf{Q}\mathbf{J}, \quad (58)$$

i.e., the Jacobi equation for the functional (25). Moreover the following two important points can be proven: (i) if the matrix \mathbf{J} is constructed via Eq. (57), and if \mathbf{D} satisfies the initial conditions (55), then \mathbf{J} must also satisfy the same initial conditions, and (ii) $\det \mathbf{D}(s) = \det \mathbf{J}(s)$, $\forall s$.

We first comment on the change of variable (57) and the way it was constructed. The matrix equation in Eq. (54) is in fact associated to a Riccati matrix equation [50]: if we define

$$\mathbf{W} = \mathbf{P}\mathbf{D}' \mathbf{D}^{-1} + \mathbf{C}_s, \quad (59)$$

where \mathbf{D} is a solution to Eq. (54), then \mathbf{W} will satisfy the following symmetric Riccati matrix equation:

$$\mathbf{W}' + \mathbf{W}\mathbf{P}^{-1}\mathbf{W} = [\mathbf{Q} - \mathbf{C}^T \mathbf{P}^{-1} \mathbf{C}] + \mathbf{C}^T \mathbf{P}^{-1} \mathbf{W} + \mathbf{W}\mathbf{P}^{-1} \mathbf{C} \quad (60)$$

and vice versa. Moreover if \mathbf{W} satisfies Eq. (60), the inverse matrix

$$\mathbf{Z} = \mathbf{W}^{-1} = [\mathbf{1} + \mathbf{D}[\mathbf{D}']^{-1} \mathbf{P}^{-1} \mathbf{C}_s]^{-1} \mathbf{D}[\mathbf{D}']^{-1} \mathbf{P}^{-1} \quad (61)$$

itself satisfies the symmetric Riccati matrix equation

$$\mathbf{Z}' + \mathbf{Z}[\mathbf{Q} - \mathbf{C}^T \mathbf{P}^{-1} \mathbf{C}]\mathbf{Z} = \mathbf{P}^{-1} - \mathbf{Z}\mathbf{C}^T \mathbf{P}^{-1} - \mathbf{P}^{-1} \mathbf{C}\mathbf{Z}, \quad (62)$$

where now, given initial conditions Eq. (55), the initial condition for \mathbf{Z} is $\mathbf{Z}(0) = \mathbf{0}$. And it is known from the Radon lemma [51–53] that any initial value problem for a matrix Riccati equation corresponds, or is locally equivalent, to an initial value problem for a specific linear system of equations. In the case of the matrix equation (62), the associated linear system is

$$\begin{bmatrix} \mathbf{J} \\ \mathbf{M} \end{bmatrix}' = \mathbf{U} \begin{bmatrix} \mathbf{J} \\ \mathbf{M} \end{bmatrix}, \quad (63)$$

where $\mathbf{M} = \mathbf{P}\mathbf{J}' + \mathbf{C}\mathbf{J}$ and

$$\begin{aligned} \mathbf{U} &= \begin{bmatrix} -\mathbf{P}^{-1} \mathbf{C} & \mathbf{P}^{-1} \\ \mathbf{Q} - \mathbf{C}^T \mathbf{P}^{-1} \mathbf{C} & \mathbf{C}^T \mathbf{P}^{-1} \end{bmatrix} \\ &= \begin{bmatrix} \mathbf{0} & \mathbf{1} \\ -\mathbf{1} & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{C}^T \mathbf{P}^{-1} \mathbf{C} - \mathbf{Q} & -\mathbf{C}^T \mathbf{P}^{-1} \\ -\mathbf{P}^{-1} \mathbf{C} & \mathbf{P}^{-1} \end{bmatrix}, \end{aligned} \quad (64)$$

with the initial conditions

$$\begin{bmatrix} \mathbf{J} \\ \mathbf{M} \end{bmatrix}(0) = \begin{bmatrix} \mathbf{0} \\ \mathbf{1} \end{bmatrix}. \quad (65)$$

We recognize Eq. (63) as a matrix version of the Hamiltonian form of the linear system of Jacobi equations (58) for energy functional (25), \mathbf{M} being the matrix version of the variable conjugate to \mathbf{J} . In particular, the association between Eqs. (62) and (63), implies $\mathbf{W}\mathbf{J} = [\mathbf{P}\mathbf{J}' + \mathbf{C}\mathbf{J}]$ which in turn, given Eq. (59), provides the correspondence (57) between the matrix \mathbf{D} satisfying the Papadopoulos equation (54) with initial condition (55), and the matrix \mathbf{J} of solutions to the Jacobi equation (58) satisfying identical initial conditions

$$\mathbf{J}(0) = \mathbf{0}, \quad \mathbf{J}'(0) = \mathbf{P}(0)^{-1}. \quad (66)$$

We now prove the second important point: that when \mathbf{D} and \mathbf{J} are related by Eq. (57) then their determinant is the same at

each s . We first simply take the trace of both sides of Eq. (57) to obtain

$$\text{tr}[\mathbf{D}'\mathbf{D}^{-1}] = \text{tr}[\mathbf{J}'\mathbf{J}^{-1}], \quad (67)$$

because $\text{tr}[\mathbf{P}^{-1}\mathbf{C}^a] = 0$ from the symmetry of \mathbf{P} and the asymmetry of \mathbf{C}^a .

From Eq. (67), and using the well known formula for $\text{tr}[\mathbf{A}'\mathbf{A}^{-1}]$ for a nonsingular matrix \mathbf{A} , we obtain

$$\frac{1}{\det \mathbf{D}} (\det \mathbf{D})' = \frac{1}{\det \mathbf{J}} (\det \mathbf{J})', \quad (68)$$

which implies $\det \mathbf{J}(s) = c \det \mathbf{D}(s)$ where c is some constant. However, $\lim_{s \rightarrow 0} \det[\mathbf{J}(s)\mathbf{D}^{-1}(s)] = 1$, as is evident from the Taylor expansions of the matrices \mathbf{D} and \mathbf{J} around $s=0$, and taking into account the initial values (55) and (66). Thus, $c=1$.

Finally, we can conclude that the expression (56) for the conditional probability density function can be re-expressed as

$$\rho[(0,0,0), (y_L, z_L, \phi_L); 0, L] \approx e^{-\beta \bar{E}} / \sqrt{\det \frac{2\pi}{\beta} \mathbf{J}(L)} \quad (69)$$

where \mathbf{J} satisfies the Jacobi equations (58) with the initial conditions (66). Formula (69) is our main result. Alternatively \mathbf{J} can be computed from the Hamiltonian form (63) with the initial conditions (65).

G. Constrained systems

In the standard models of polymer physics, effects of shear and extension are typically not included. We have done so because then the looping problem can be formulated purely in terms of boundary conditions, rather than nonlocal and nonlinear integral side conditions, and as a consequence we were able to derive the expression (69) for the looping probability. We next demonstrate that this simple expression remains valid in the limit of an inextensible, shearable rod.

We wish to consider a slightly extensible and shearable rod and to investigate the limit as the shear and extension degrees of freedom become negligible. This limit corresponds to the stiffness matrix (12) being of the form

$$\mathbf{P} = \begin{pmatrix} \mathbf{A}/\omega^2 & \mathbf{B}/\omega \\ \mathbf{B}^T/\omega & K \end{pmatrix} \quad (70)$$

with ω being a small parameter.

In the limit $\omega \rightarrow 0$ some of the entries in this stiffness matrix will diverge, whereas in the same limit the inverse stiffness matrix remains well defined. Specifically

$$\lim_{\omega \rightarrow 0} \mathbf{P}^{-1} = \begin{pmatrix} \mathbf{0}_{2 \times 2} & \mathbf{0}_{2 \times 1} \\ \mathbf{0}_{1 \times 2} & (K - \mathbf{B}^T \mathbf{A}^{-1} \mathbf{B})^{-1} \end{pmatrix}. \quad (71)$$

Note that the stiffness matrix \mathbf{P} in Eq. (70) is positive definite if and only if the matrix \mathbf{A} and its (in this case scalar) Schur complement $(K - \mathbf{B}^T \mathbf{A}^{-1} \mathbf{B})$ are also positive definite.

Our observation is that in the linear Hamiltonian system of Eqs. (63) only \mathbf{P}^{-1} , and not \mathbf{P} itself appear in the coeffi-

cients. Moreover the initial values (65) are only on the variables \mathbf{J} and \mathbf{M} . Thus the Hamiltonian IVP is well defined in the limit $\omega \rightarrow 0$, and we conclude that the formula (69) remains valid.

Finally we observe that the limiting form of the Hamiltonian Jacobi system can be recognized [50] as the Hamiltonian form of the Bolza Jacobi system for isoperimetrically constrained calculus of variations problems that is discussed in [10].

IV. UNIFORM CIRCULAR LOOP

We next present a concrete example to illustrate our theory. In order to be able to carry out all of the necessary computations explicitly and without resort to numerics, we now restrict ourselves to consider a *uniform* linearly elastic rod. The energy associated to the rod still reads as in formula (11), but now the stiffness matrix and the intrinsic strains are constant functions with no explicit dependence on s present.

A. Shearable extensible rods

To simplify further the necessary computations in our example we additionally assume that there is no coupling between the strains of shear, extension and bend, so that the stiffness matrix (12) takes the particular diagonal form

$$\mathbf{P} = \begin{pmatrix} A_2 & 0 & 0 \\ 0 & A_3 & 0 \\ 0 & 0 & K \end{pmatrix}, \quad (72)$$

where A_2 , A_3 , and K are three constants representing, respectively, the shear, stretch and bend stiffness. Then for a linearly elastic, extensible, shearable, uniform, planar rod with diagonal stiffness matrix (72), the energy becomes

$$E = \frac{1}{2} \int_0^L [A_2 v_2^2 + A_3 (v_3 - 1)^2 + K (u_1 - \hat{u}_1)^2] ds \quad (73)$$

and \hat{u}_1 is a prescribed constant of either sign in the intrinsically curved case, or zero in the intrinsically straight case.

For a closed loop, the boundary conditions to be considered are

$$\mathbf{r}(0) = \mathbf{r}(L) = \mathbf{0},$$

$$\mathbf{d}_i(0) = \mathbf{d}_i(L) = \mathbf{e}_i, \quad i = 2, 3. \quad (74)$$

For uniform rods it is straightforward to verify that among the equilibria satisfying boundary conditions (74) there are configurations with circular centerlines and vanishing shear and extension. (There are also equilibria with figure eight centerlines.)

For a right-handed circular equilibrium (closed in the counterclockwise direction) the centerline, expressed in the fixed frame, is

$$\mathbf{r}(s) = \frac{1}{\alpha} (\cos \alpha s - 1, \sin \alpha s)^T, \quad (75)$$

where $\alpha = 2\pi/L$, while the angular function implying the director framing via Eq. (5) is now

$$\phi(s) = \alpha s = (2\pi/L)s, \tag{76}$$

with $s \in [0, L]$. This equilibrium satisfies the boundary conditions,

$$\begin{aligned} y(0) = y(L) &= 0, \\ z(0) = z(L) &= 0, \\ \phi(0) = 0, \quad \phi(L) &= 2\pi. \end{aligned} \tag{77}$$

In the following we will denote the probability density function for this boundary value problem as

$$\rho_c(L) := \rho[(0,0,0), (0,0,2\pi); 0, L]. \tag{78}$$

We now evaluate the semiclassical approximation (69) to $\rho_c(L)$ on the right-handed circular equilibrium. At this equilibrium, the second variation of the energy functional (73) reads as in Eq. (25) where now we have the following explicit expressions for the three coefficient matrices: the stiffness matrix \mathbf{P} is given in Eq. (72), while

$$\mathbf{C} = \begin{pmatrix} 0 & -\alpha A_2 & A_2 \\ \alpha A_3 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \mathbf{Q} = \begin{pmatrix} \alpha^2 A_3 & 0 & 0 \\ 0 & \alpha^2 A_2 & -\alpha A_2 \\ 0 & -\alpha A_2 & A_2 \end{pmatrix}, \tag{79}$$

where $\alpha = 2\pi/L$ as before. In particular all three coefficient matrices are constant, independent of s .

The Hamiltonian form of the Jacobi system (63) is now constant coefficient with the 6×6 coefficient matrix (64) taking the explicit form

$$\mathbf{U} = \begin{pmatrix} 0 & \alpha & -1 & \frac{1}{A_2} & 0 & 0 \\ -\alpha & 0 & 0 & 0 & \frac{1}{A_3} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{K} \\ 0 & 0 & 0 & 0 & \alpha & 0 \\ 0 & 0 & 0 & -\alpha & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \end{pmatrix}. \tag{80}$$

This matrix has eigenvalues $0, \pm i\alpha$ each of algebraic multiplicity two and geometric multiplicity one. The associated eigenvectors and generalized eigenvectors allow the explicit construction of the solution to Eq. (63) with coefficient matrix (80) and initial conditions (65). Introducing the dimensionless parameter

$$W := \left[1 + \left(\frac{2\pi}{L} \right)^2 K \left(\frac{1}{A_2} + \frac{1}{A_3} \right) \right], \tag{81}$$

the three columns of the 3×3 matrix \mathbf{J} then read

$$\begin{aligned} \mathbf{h}_1(s) &= \left[\frac{A_2 W (\alpha s \cos \alpha s - \sin \alpha s) + 2\alpha^2 K \sin \alpha s}{2A_2 \alpha^3 K}, \frac{2(1 - \cos \alpha s) - W \alpha s \sin \alpha s}{2\alpha^3 K}, \frac{1 - \cos \alpha s}{\alpha^2 K} \right]^T, \\ \mathbf{h}_2(s) &= \left[\frac{2(\cos \alpha s - 1) + W \alpha s \sin \alpha s}{2\alpha^3 K}, \frac{\alpha s (2 + W \cos \alpha s) - \left(3 + \alpha^2 K \frac{A_3 - A_2}{A_2 A_3} \right) \sin \alpha s}{2\alpha^3 K}, \frac{\alpha s - \sin \alpha s}{\alpha^2 K} \right]^T, \\ \mathbf{h}_3(s) &= \left[\frac{\cos \alpha s - 1}{\alpha^2 K}, \frac{\alpha s - \sin \alpha s}{\alpha^2 K}, \frac{s}{K} \right]^T. \end{aligned} \tag{82}$$

Accordingly the determinant of $\mathbf{J}(L)$, which appears in expression (69), can be computed to be

$$\det[\mathbf{J}(L)] = \frac{W^2 L^7}{4(2\pi)^4 K_1^3}, \tag{83}$$

and the semiclassical probability density function (69) reduces to

$$\rho_c(L) \simeq e^{-\beta L K / 2(2\pi/L - \hat{u}_1)^2} \frac{2\sqrt{2\pi}}{W} \sqrt{\frac{(\beta K)^3}{L^7}}. \tag{84}$$

It is a special feature of planar uniform rods that the intrinsic shape \hat{u}_1 enters only in the energy prefactor and not in the

semiclassical determinant (83). Similarly the shear and stretch stiffnesses enter only through the nondimensional quantity W introduced in definition (81). Before discussing the features of this expression in more detail we consider an inextensible, unshearable limit.

B. Unshearable, inextensible case

As discussed in the previous section, we can consider the unshearable, inextensible case as the limit of a slightly shearable and extensible rod. Accordingly we scale the stiffness matrix (72) by a positive scalar ω as in Eq. (70), so that

$$\lim_{\omega \rightarrow 0} \mathbf{P}^{-1} = \mathbf{P}_{\text{in}}^{-1} = \begin{pmatrix} \mathbf{0}_{2 \times 2} & \mathbf{0}_{2 \times 1} \\ \mathbf{0}_{1 \times 2} & K^{-1} \end{pmatrix}. \quad (85)$$

As in the shearable, extensible case, the boundary conditions satisfied by a right-handed circular equilibrium are Eq. (77). We will compute the semiclassical pdf at such an equilibrium in the inextensible, unshearable limit $\omega \rightarrow 0$. In fact the analysis is particularly simple because the equilibrium configuration (75) and (76) is independent of the value of ω , because there is neither a shear nor stretch deformation.

After taking the limit $\omega \rightarrow 0$ we may proceed as before and compute the solution to Eq. (63) subject to initial conditions (65) where the limit form of the coefficient matrix is

$$\mathbf{U}^{\text{in}} = \begin{pmatrix} 0 & \alpha & -1 & 0 & 0 & 0 \\ -\alpha & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{K} \\ 0 & 0 & 0 & 0 & \alpha & 0 \\ 0 & 0 & 0 & -\alpha & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \end{pmatrix}. \quad (86)$$

Both of the matrices (80) and (86) are upper block triangular with equal diagonal blocks, so we see that their eigenvalues are the same, and the necessary computations to construct the full solution directly parallels that of the extensible, shearable case. The conclusions that are finally reached are that the semiclassical determinant and pdf in the unshearable, inextensible case coincide with the case $W=1$ of the analogous quantities (83) and (84) valid in the shearable, extensible case. This observation is compatible with (but not proven by) the observation that with the scaling (70) we have

$$W(\omega) := \left[1 + \left(\frac{2\pi\omega}{L} \right)^2 K \left(\frac{1}{A_2} + \frac{1}{A_3} \right) \right]. \quad (87)$$

and $\lim_{\omega \rightarrow 0} W(\omega) = 1$.

V. DISCUSSION

In the previous sections we have derived a semiclassical approximation to the probability density function for the formation of a circular loop. It is then of interest to pose the question: how accurate is this semiclassical approximation? We know of no general error estimate, but comparison to numerical simulations can be made in specific cases. To that end we first nondimensionalize our semiclassical pdf (84) for the planar cyclization problem. We introduce the length scale $L_p = \beta K$, where L_p is the classic persistence length of a polymer in 3D (approximately 150 base pairs for duplex DNA). We then introduce nondimensional variables ℓ , a_2 , a_3 , and \hat{u} via

$$L = \ell L_p, \quad A_2 = \frac{a_2}{\omega^2 \beta L_p}, \quad A_3 = \frac{a_3}{\omega^2 \beta L_p}, \quad \hat{u}_1 = \hat{u} \frac{2\pi}{L_p}, \quad (88)$$

where ω is a nondimensional parameter indicating the degree of shearability and extensibility of the polymer compared to

its bending rigidity. In this particular problem it is convenient to set the scale of ω by imposing the condition

$$4\pi^2 \left(\frac{1}{a_2} + \frac{1}{a_3} \right) = 1. \quad (89)$$

Expressed in these nondimensional variables the pdf (84) becomes

$$\rho_c(\ell) = \frac{1}{L_p^2} \frac{2\sqrt{2\pi} e^{-2\pi^2/\ell(1-\ell\hat{u})^2}}{W(\ell) \ell^{7/2}}, \quad (90)$$

where now

$$W(\ell) := \left[1 + \left(\frac{\omega}{\ell} \right)^2 \right]. \quad (91)$$

We remark that the expression (90) has dimensions inverse length squared, as it must. This is because a pdf will yield a nondimensional probability when integrated, or used in a quadrature rule, over a volume in configuration space. And for the planar rod looping problem the end point configuration space is (x_L, y_L, ϕ_L) , so that the appropriate volume has dimensions length squared. If we pick the simplest one-point quadrature rule, namely multiplying the volume by the pdf evaluated at the centre of the domain, then the probability of falling within the volume will be expression (90) multiplied by volume measured in units of L_p^2 .

In Fig. 2, the solid line is a plot of expression (90) scaled by L_p^2 versus nondimensional length ℓ for the inextensible, unshearable case $\omega=0$, and for vanishing intrinsic curvature $\hat{u}=0$. The dots are data generated from Monte Carlo simulations in the following way. An ensemble of rod configurations were generated using a discretized version of the probability distribution (18) (in fact 100 linear segments were used, although the conclusions are not sensitive to this choice). Then the number of trajectories for which (x_L, y_L, ϕ_L) fell within a prescribed volume, actually a box, centered on $(0, 0, 2\pi)$ were counted. A probability was obtained by dividing by the total number of trajectories, and the pdf ρ_c was approximated by dividing this probability by the volume of the box. The error in the approximation of the pdf using the one-point quadrature rule is decreased by choosing smaller boxes, while the statistics of the number of hits in the Monte Carlo simulation is improved by increasing the size of the volume. The error bars indicated are a standard deviation obtained by repeating this process for 27 different choices of increasingly small volumes. The data suggest that the circular equilibrium semiclassical pdf is a rather good approximation up to three or even four persistence lengths. For longer lengths the Monte Carlo estimates of the pdf are consistently above the semiclassical result, although both methods suggest a peak at approximately six persistence lengths. We remark that the Monte Carlo simulations and the semiclassical analysis are complementary in the sense that the semiclassical pdf is increasingly inaccurate at longer lengths where the circular equilibrium is ‘‘floppier’’ and where it is easier to obtain good statistics with Monte Carlo. At the shorter scales where the equilibrium is ‘‘stiffer’’ the semiclassical pdf is

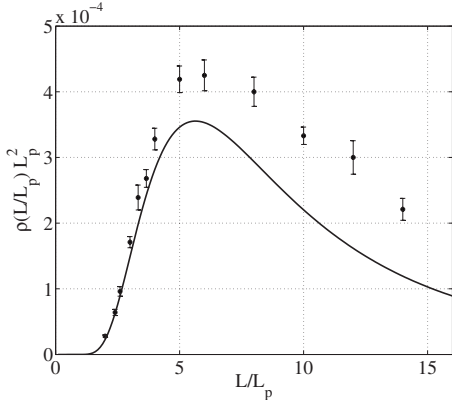


FIG. 2. Comparison of cyclization probability densities as a function of nondimensional length $\ell=L/L_p$. The solid line is the semiclassical approximation (90) scaled by L_p^2 in the specific case of an intrinsically straight inextensible, unshearable rod, while the dots are estimates of the full pdf (along with standard deviation error bars) based on Monte Carlo random sampling. The fit is rather good up to three persistence lengths.

more accurate, but it is considerably more computationally intensive to obtain good Monte Carlo statistics because the event is much rarer.

Plots 3–5 illustrate how the pdf (90) varies with the parameters \hat{u} and ω . In Fig. 3, the five solid lines are the semiclassical approximation (90) scaled by L_p^2 in the specific cases (bottom to top) $\hat{u}=-0.02, -0.01, 0, 0.01, 0.02$ and for an inextensible, unshearable rod with $\omega=0$. With our nondimensionalization an intrinsic curvature $\hat{u}=0.02$ corresponds to a radius of curvature of $8L_p$, i.e., rather small. Alternatively it corresponds to a difference in angle between tangents of 7 degrees per persistence length L_p . The conclusion

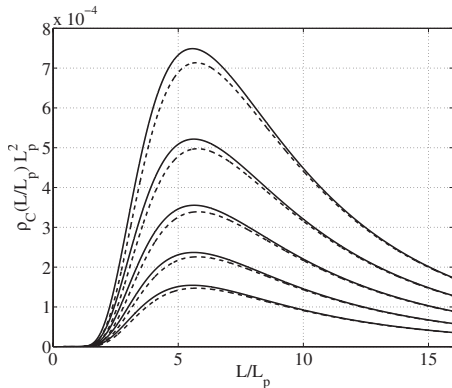


FIG. 3. Comparison of cyclization probability densities as a function of nondimensional length $\ell=L/L_p$. The solid lines are the semiclassical approximation (90) scaled by L_p^2 in the specific cases (from bottom to top) $\hat{u}=-0.02, -0.01, 0, 0.01, 0.02$ and for an inextensible, unshearable rod with $\omega=0$. (The case $\hat{u}=0$ also appears in Fig. 2) Dashed curves are the same range of values of \hat{u} , but in the slightly extensible, shearable case corresponding to $\omega=4\pi/10 \approx 1.26$. Changing the intrinsic curvature \hat{u} has a strong effect on the pdf, either increasing or decreasing according to sign, while the addition of effects of extension and shear systematically lowers the pdf.

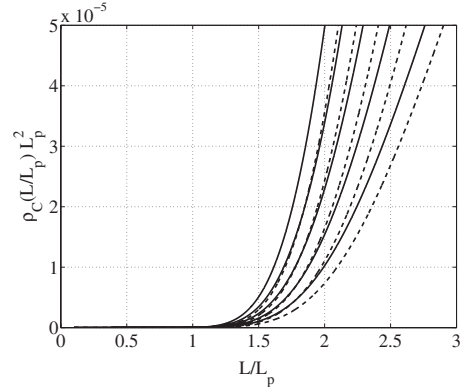


FIG. 4. A magnification of Fig. 3 (note different scales particularly in the ordinate). Here the five solid and five dashed lines can be observed to start to cross, indicating a shift of the relative importance of effects of intrinsic curvature and of extension and shear at shorter length scales.

is that small changes in intrinsic curvature can lead to significant changes in the cyclization pdf. Our right-handed circular equilibrium is closing against a negative intrinsic curvature \hat{u} so that the pdf is reduced, while positive \hat{u} enhances the pdf.

The five dashed lines are the semiclassical approximation (90) scaled by L_p^2 with the same range of intrinsic curvatures, but now for the parameter value $\omega=4\pi/10$ corresponding to a polymer that allows extension and shear. Changing ω can be interpreted as changing the physical composition of the polymer, and the issue of whether ω is large or small is harder to quantify. For us the scale of ω is set by the condition (89). For nonvanishing ω the pdf is systematically shifted downward, with the shift being smaller at larger ℓ , as can be seen from the form of W (91). However the range of ℓ for which the difference starts to decrease is already beyond the 3–4 persistence lengths where the semiclassical pdf gives good agreement with Monte Carlo simulations.

Figures 4 and 5 show magnifications of Fig. 3 at shorter lengths. Here, the effect of changing to a shearable, extensible model increasingly dominates the effect of changing intrinsic curvature. This behavior follows from an examina-

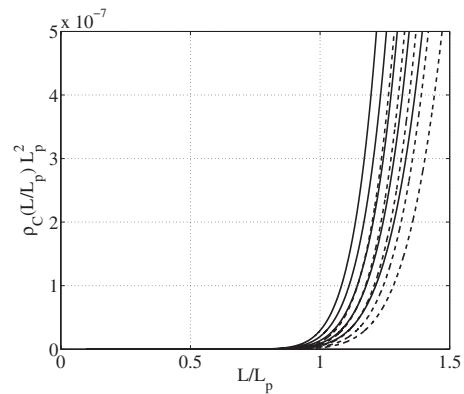


FIG. 5. A further magnification of Fig. 4 (note different scales particularly in the ordinate). Now effects of variations in ω start to dominate those of changes in \hat{u} .

tion of Eq. (90) where the leading order behavior of the denominator for $\omega \neq 0$ is $\ell^{5/2}$, while it is $\ell^{7/2}$ for $\omega=0$.

VI. CONCLUSIONS

Working within the context of continuum rod models we have exploited a path integral approach to derive a solution formula for the approximate evaluation of the conditional probability density of the relative displacement and orientation of two ends of an elastic chain at thermodynamic equilibrium with a heat bath. The presentation focused on the planar case for the sake of simplicity of exposition.

The derivation relies on the assumption that, at equilibrium, the collection of the configurations available to the system follows a Boltzmann distribution, and on the assumption that there exists a locally isolated minimal energy configuration around which quadratic fluctuations can be considered. We use an algebraic argument first introduced in [14] to evaluate contributions to the probability density due to quadratic fluctuations. We then show that the associated Papadopoulos equations, whose nonlinearity arises from the presence of a cross-term in the second variation of the energy functional, can be related via Riccati equations to the classic linear Jacobi equations of the system. This last result is immediate when the coefficient matrix of the cross-term is symmetric, as then the nonlinear Papadopoulos equations immediately collapse to the linear Jacobi equations. But other than this case the nonlinearity is unavoidable [54], making the connection to the Jacobi field unclear. As the presence of nonsymmetric cross-terms in the second variation for elastic rod models of DNA seems to be generic, our change of variables seems to be both necessary and nontrivial in that context. Our final conclusion is that our approximate, or semiclassical, formula for the looping probability density function can be evaluated according to Eq. (69) in terms of an assumed local energy minimizer satisfying prescribed end-point conditions, and the solution of an initial value problem for the Hamiltonian form of the associated linear Jacobi differential equations independent of whether or not the rod is inextensible and unshearable.

For the case of complex Feynman path integrals the connection between the Van-Hove-Morette determinant and the Jacobi matrix is well known: it is the Van-Hove-Morette determinant which appears in the semiclassical approximation to Feynman's propagator (corresponding to the transition amplitude of a position-position transition). It is also the negative inverse of a $(2n \times 2n)$ Jacobi matrix [46,48,55,57]. In [46], a direct proof, by using the Gelfand-Yaglom method [56], is given for a one-dimensional system whose Lagrangian does not contain cross terms. In the handbook of Feynman path integrals [57] one does indeed find the semiclassical approximation to the Feynman kernel for a general quadratic Lagrangian with cross-terms expressed as a function of the Jacobi solutions, but no reference is made to the Papadopoulos equations and the Papadopoulos matrix.

We remark that although analytical continuation to negative imaginary time or space, may be useful to compare and make analogies between our real valued, or Wiener, path integrals, and complex valued, or Feynman, path integrals,

complex cross terms are not mapped to real cross-terms. In fact, for $t \rightarrow \tilde{t} = -i\beta\hbar$,

$$\begin{aligned} & \frac{i}{\hbar} \int [\dot{\mathbf{x}}'^T \mathbf{A} \dot{\mathbf{x}}' - \mathbf{x}'^T \mathbf{B} \mathbf{x}' + \mathbf{x}'^T \mathbf{C} \mathbf{x}'] dt \\ & \qquad \qquad \qquad \Downarrow \\ & -\beta \int [\dot{\tilde{\mathbf{x}}}^T \tilde{\mathbf{A}} \dot{\tilde{\mathbf{x}}} + \tilde{\mathbf{x}}^T \tilde{\mathbf{B}} \tilde{\mathbf{x}} - i \tilde{\mathbf{x}}^T \tilde{\mathbf{C}} \tilde{\mathbf{x}}] d\tilde{t} \end{aligned} \quad (92)$$

where $\dot{\tilde{\mathbf{x}}} := \frac{d}{d\tilde{t}}$ and $\tilde{\mathbf{M}} = \mathbf{M}(\tilde{t})$ for each coefficient matrix, so that a direct application of the formula provided in [57] to the problem of computing Eqs. (19) and (30) for a general quadratic energy function is not straightforward. Thus we believe that our analysis implying a connection between the second order quadratic approximation to conditional path integrals and the Jacobi fields, without being a surprise, is nevertheless original in the presence of nontrivial cross terms.

In both the classic discrete models of polymer physics and in the rod theory of continuum mechanics, in particular in models of DNA, it is common to assume a constrained theory in which the chain or rod is both inextensible and unshearable. The second part of our development demonstrated that our semiclassical path integral formulation extends to this constrained problem merely by dint of taking the appropriate inextensible, unshearable limit in the Hamiltonian form of the associated Jacobi equations. Moreover this limit coincides with the appropriate system of isoperimetric Jacobi equations for the constrained case that is derived in [10].

Thus, the evaluation of the effects of harmonic fluctuations about a minimizer always involves only the numerical solution of a matrix, linear, ordinary differential equation with appropriate initial value conditions. For this reason, the major benefits of the semiclassical formulas developed here is that they are highly amenable to numerics. The numerical computation of the energy minimizer itself involves the solution of the Euler-Lagrange equations, i.e., a nonlinear two-point boundary value problem. This is a nontrivial numerical task, but various methods involving symmetry breaking and parameter continuation have been sufficiently developed [9,11,12] that it can now be regarded as routine in the context of DNA looping equilibria. In any case, computation of the equilibrium shape is an unavoidable part of any simulation, and in the approach presented here, once the minimal energy shape is found, the correction term can be handled with standard methods for numerically solving linear ODE.

When the rod happens to be uniform the Jacobi system may have constant coefficients on some equilibria, in which case the expression (69) can be evaluated analytically in closed form. As an example of this type, we treated the particular case of cyclization of a planar uniform rod to form a circular configuration to arrive at the expression (84), where the strong effect of the intrinsic curvature \hat{u}_1 is manifested in the exponential prefactor of the energy of the equilibrium.

The main theoretical concerns which have not been discussed here are related to the existence of multiple, but isolated local minima, to conjugate points, and the possibility of nonisolated minima. Throughout the derivation we have as-

sumed the existence of a locally unique minimizer of the energy for the given boundary data. However it is known that the boundary value problems for elastic rods modeling DNA frequently do exhibit multiple minima. In the case of multiple isolated minimizers the analysis presented here can just be applied at each minimum, and consequently, a second order correction as expressed in the formulas above may be computed. The total probability density of forming a loop with boundary conditions which admit distinct isolated minimizers, will thus be given by the sum of each individual probability density as computed around the respective minimizers. For instance, in the cyclization example of Sec. IV, closed loops could be formed with both left and right handed circular equilibria (because the director framing allows a distinction between these two cases), and in our analysis the two circles are distinct minimizers. The sign of any nonzero intrinsic curvature \hat{u}_1 will favor one circular equilibrium over the other, while in the case $\hat{u}_1=0$ by symmetry the total probability density of any circular loop forming would be twice that predicted by the semiclassical computation at one of the circles.

The absence of conjugate points, that is points \bar{s} , $0 < \bar{s} < L$ where a non trivial solution to the Jacobi IVP vanishes, is a completely natural restriction in the theory described here. As a conjugate point is approached the semiclassical probability density will diverge. In fact at that specific \bar{s} , the matrix of Jacobi fields will have linearly dependent columns, and the matrix itself will be singular with vanishing determinant. If the conjugate point occurs within the interval considered, the whole algebraic argument used to derive the Papadopoulos equations fails [14], as well as the nonlinear change of variables, which relies on the nonsingularity of the matrices $\mathbf{D}(s)$ and $\mathbf{J}(s)$, $\forall s \neq 0$. That this is the case is completely natural, as absence of a conjugate point is intrinsically associated with the stability properties of equilibrium configurations. For unconstrained problems it is well known that the absence of any conjugate point is a necessary condition for a given equilibrium configuration to actually be a local minimizer for the energy. Analogous results have been proven for isoperimetrically constrained systems, including the case of inextensible, unsharable rods that is of interest here [10,58]. In other words, the semiclassical theory should break down if a conjugate point is present, as the configuration around which perturbations are being considered is not a local minimizer of the associated energy.

We remark that in the quantum mechanics literature for the case of imaginary path integrals, the effect of conjugate points is a much more delicate issue. In the context of semi-

classical quantum mechanics, the singularities of the Van-Hove-Morette determinant have been discussed for the first time by Choquard [57]. In this context there are results such as the Gutzwiller formula [59], which provides a correction to the semiclassical kernel through a phase factor related to the Maslov-Morse index, which in turn quantifies the dimension of the space over which the second variation is negative.

In the case of real path integrals and the application to looping of DNA, one context where the presence of conjugate points at $\bar{s}=L$ is to be expected, and should be treated, is that of isotropic boundary value problems, where the equilibria are local minima, but are nonisolated because of a continuous symmetry that generates a family of local minima. In that case it can be anticipated that an appropriate semiclassical expression can be obtained by appropriately integrating over the orbit of nonisolated minimizers, rather than summing over a finite number of local minimizers.

To conclude, the semiclassical probability density function formulas that we have obtained are of quite general applicability, especially as, in contrast to prior theories for predicting looping, no assumption is made on uniformity of the chain, or on isotropy, or on the presence or absence of the integral constraints that arise in inextensible, unsharable models for DNA. Thus, we believe that the theory derived here to be rather robust and to have the potential to describe a variety of different situations which are of relevance to understanding DNA looping in vivo, and in analyzing ongoing in vitro experiments aimed at understanding sequence-dependent effects in the mechanical properties of DNA. Of course the generalization to three dimensional theory will be required, where issues of the parametrization of the rotation group $SO(3)$ need to be addressed. However the bulk of the analysis presented here, which involves the derivation of the Papadopoulos equations, and the transformation to the Jacobi system, in both the unconstrained and constrained contexts are largely unaffected.

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- [1] R. Schleif, *Science* **240**, 127 (1988); *Annu. Rev. Biochem.* **61**, 199 (1992); K. S. Matthews, *Microbiol. Rev.* **56**, 123 (1992).
 [2] L. Saiz and J. M. G. Vilar, *Curr. Opin. Struct. Biol.* **16**, 344 (2006); J. M. G. Vilar and S. Leibler, *J. Mol. Biol.* **331**, 981 (2003).
 [3] S. Jun and J. Bechhoefer, *Phys. Can.* **59**, 85 (2003).
 [4] R. Metzler *et al.*, *J. Comput. Theor. Nanosci.* **4**, 1 (2007).
 [5] H. Garcia *et al.*, *Biopolymers* **85**, 115 (2007).
 [6] Y. Zhang and D. M. Crothers, *Biophys. J.* **84**, 136 (2003).
 [7] C. J. Benham, *Biopolymers* **18**, 609 (1979).
 [8] C. J. Benham, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 2397 (1977).
 [9] R. S. Manning, J. H. Maddocks, and J. D. Kahn, *J. Chem. Phys.* **105**, 5626 (1996).
 [10] R. S. Manning, K. A. Rogers, and J. H. Maddocks, *Proc. R.*

- Soc. London, Ser. A **454**, 3047 (1998).
- [11] R. S. Manning and J. H. Maddocks, *Comput. Methods Appl. Mech. Eng.* **170**, 313 (1999).
- [12] P. B. Furrer, R. S. Manning, and J. H. Maddocks, *Biophys. J.* **79**, 116 (2000).
- [13] B. D. Coleman, W. K. Olson, and D. Swigon, *J. Chem. Phys.* **118**, 7127 (2003).
- [14] G. J. Papadopoulos, *Phys. Rev. D* **11**, 2870 (1975).
- [15] A. Prasad, Y. Hori, and J. Kondev, *Phys. Rev. E* **72**, 041918 (2005).
- [16] P. K. Purohit and P. C. Nelson, *Phys. Rev. E* **74**, 061907 (2006).
- [17] N. J. Agrawal, R. Radhakrishnan, and P. K. Prashant, *Biophys. J.* **94**, 3150 (2008).
- [18] G. Witz, K. Rechendorff, J. Adamcik, G. Dietler, *Phys. Rev. Lett.* **101**, 148103 (2008).
- [19] J. Shimada and H. Yamakawa, *Macromolecules* **17**, 689 (1984).
- [20] H. Yamakawa and W. H. Stockmayer, *J. Chem. Phys.* **57**, 2843 (1972).
- [21] H. Jacobson and W. H. Stockmayer, *J. Chem. Phys.* **18**, 1600 (1950).
- [22] J. Yan and J. F. Marko, *Phys. Rev. Lett.* **93**, 108108 (2004).
- [23] A. J. Spakowitz and Z. G. Wang, *Macromolecules* **37**, 5814 (2004).
- [24] S. Stepanow, *Eur. Phys. J. B* **39**, 499 (2004).
- [25] E. Villa, A. Balaeff, and K. Schulten, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 6783 (2005).
- [26] L. Czaplá, D. Swigon, and W. K. Olson, *J. Chem. Theory Comput.* **2**, 685 (2006).
- [27] A. J. Spakowitz, *EPL* **73**, 684 (2006).
- [28] P. A. Wiggins, R. Phillips, and P. C. Nelson, *Phys. Rev. E* **71**, 021909 (2005).
- [29] P. A. Wiggins and P. C. Nelson, *Phys. Rev. E* **73**, 031906 (2006).
- [30] I. M. Kulić, H. Mohrbach, V. Lobaskin, R. Thaokar, and H. Schiessel, *Phys. Rev. E* **72**, 041905 (2005).
- [31] I. M. Kulić, H. Mohrbach, R. Thaokar, and H. Schiessel, *Phys. Rev. E* **75**, 011913 (2007).
- [32] M. Emanuel, H. Mohrbach, M. Sayar, H. Schiessel, and I. M. Kulić, *Phys. Rev. E* **76**, 061907 (2007).
- [33] Y. Zhang *et al.*, *Biophys. J.* **90**, 1903 (2006).
- [34] D. Swigon, B. D. Coleman, and W. K. Olson, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 9879 (2006).
- [35] C. Vaillant *et al.*, *Eur. Phys. J. E* **19**, 263 (2006).
- [36] S. Rappaport and Y. Rabin, *Macromolecules* **37**, 7847 (2004).
- [37] C. Vaillant, B. Audit, and A. Arnéodo, *Phys. Rev. Lett.* **95**, 068101 (2005).
- [38] Y. O. Popov and A. V. Tkachenko, *Phys. Rev. E* **76**, 021901 (2007).
- [39] T. D. Lillian *et al.*, *Biophys. J.* **95**, 5832 (2008).
- [40] E. Cosserat and F. Cosserat, *Théorie des Corps Déformables* (Hermann, Paris, 1909).
- [41] S. S. Antman, *Nonlinear Problems of Elasticity* (Springer-Verlag, New York, 1995).
- [42] D. J. Dichmann, Y. Li, and J. H. Maddocks, in *IMA Volumes in Mathematics and its Applications*, edited by J. P. Mesirov, K. Schulten, and D. Sumners (Springer-Verlag, Berlin, 1996), pp. 85, 71–113.
- [43] Y. Li and J. H. Maddocks (unpublished).
- [44] R. P. Feynman and A. R. Hibbs, *Quantum Mechanics and Path Integrals* (McGraw-Hill, New York, 1965).
- [45] M. Chaichian and A. Demichev, *Path Integrals in Physics. Volume I: Stochastic Processes and Quantum Mechanics* (IOP, London, 2001).
- [46] L. S. Schulman, *Techniques and Applications of Path Integration* (Wiley, New York, 1981).
- [47] F. W. Wiegand, *Introduction to Path Integral Methods in Physics and Polymer Science* (World Scientific, Singapore, 1986).
- [48] C. DeWitt-Morette, *Ann. Phys.* **97**, 367 (1976).
- [49] N. Chouaieb, Ph.D. thesis 2717, École Polytechnique Fédérale de Lausanne, 2003.
- [50] L. Cotta-Ramusino, Ph.D. thesis 4017, École Polytechnique Fédérale de Lausanne, 2008.
- [51] W. T. Reid, *Riccati Differential Equations* (Academic, New York, 1972).
- [52] R. W. R. Darling, *SIAM Rev.* **39**, 508 (1997).
- [53] G. Freiling, *Linear Algebra Appl.* **351-352**, 243 (2002).
- [54] G. J. Papadopoulos (private communication).
- [55] Ph. Choquard and F. Steiner, *Helv. Phys. Acta* **69**, 636 (1996).
- [56] I. M. Gelfand and A. M. Yaglom, *J. Math. Phys.* **1**, 48 (1960).
- [57] C. Grosche and F. Steiner, *Handbook of Feynman Path Integrals* (Springer, New York, 1998).
- [58] K. A. Rogers, Ph.D. dissertation, University of Maryland, 1997.
- [59] M. C. Gutzwiller, *Chaos in Classical and Quantum Mechanics* (Springer-Verlag, Berlin, 1980).