Supplementary Information: Analysis of single locus trajectories for extracting in vivo chromatin tethering interactions

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Supplementary Information

In this Supplementary Information, we detail the analysis, calculations and results presented in the main text.

Extracting the strength of a potential well for a Rouse polymer

A Rouse polymer which has one monomer interacting with a infinite potential well, can be described by the energy potential

$$\Phi(\boldsymbol{R}) = \frac{k}{2}\boldsymbol{R}_n^2 + \frac{\kappa}{2}\sum_{i=1}^{N-1}(\boldsymbol{R}_{i+1} - \boldsymbol{R}_i)^2. \tag{1}$$

where $\boldsymbol{R} = (\boldsymbol{R}_1, \boldsymbol{R}_2, ..., \boldsymbol{R}_N)$ is the collection of the monomers, connected by a spring constant $\kappa = dk_BT/b^2$, b is the standard-deviation of the distance between adjacent monomers [21], k_B the Boltzmann coefficient, T the temperature and d the dimensionality (dim 2 or 3), k is the strength of the external harmonic well acting on monomer n, located at the origin.
To extract the strength of the potential well applied on monomer n from the measured velocity of locus c ($n < c$), we will compute

$$\lim_{\Delta t \to 0} \mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t) - \boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{R}_c = \boldsymbol{x}\} = -D\int_\Omega d\boldsymbol{R}_1 .. \int_\Omega d\boldsymbol{R}_N(\nabla_{\boldsymbol{R}_c}\Phi)P(\boldsymbol{R}|\boldsymbol{R}_c = \boldsymbol{x}). \tag{2}$$

The force acting on monomer c, when its position is $\boldsymbol{x}$ is given by

$$\boldsymbol{F}^c_{\boldsymbol{R}_c=\boldsymbol{x}} = -\nabla_{\boldsymbol{R}_c}\Phi(\boldsymbol{R}_{c-1},\boldsymbol{R}_c,\boldsymbol{R}_{c+1})_{\boldsymbol{R}_c=\boldsymbol{x}} = -\kappa\left(\boldsymbol{x}-\boldsymbol{R}_{c-1}\right) - \kappa\left(\boldsymbol{x}-\boldsymbol{R}_{c+1}\right). \quad (3)$$

The equilibrium probability distribution function is the Boltzmann distribution, conditioned to $\boldsymbol{R}_c = \boldsymbol{x}$:

$$P(\boldsymbol{R}|\boldsymbol{R}_c=\boldsymbol{x}) = \mathcal{N}e^{-\Phi(\boldsymbol{R}_1,\ldots,\boldsymbol{R}_{c-1},\boldsymbol{x},\boldsymbol{R}_{c+1},..,\boldsymbol{R}_N)}, \quad (4)$$

with the normalization factor

$$\begin{aligned}
\mathcal{N}^{-1} &= \int_\Omega ..\int_\Omega d\boldsymbol{R}_1..d\boldsymbol{R}_{c-1}d\boldsymbol{R}_{c+1}..d\boldsymbol{R}_N P(\boldsymbol{R}|\boldsymbol{R}_c=\boldsymbol{x}) \\
&= \int \exp\left[-\kappa\boldsymbol{x}^2\right]\exp\left[-\frac{1}{2}\sum_{p,q=1;p,q\neq c}^{N} A_{p,q}R_pR_q + \sum_{p=1;p\neq c}^{N} B_pR_p\right] d\boldsymbol{R}_1..d\boldsymbol{R}_{c-1}...d\boldsymbol{R}_N \\
&= \left[\frac{(2\pi)^{N-1}}{\mathrm{detA}}\right]^{d/2} e^{-\kappa\boldsymbol{x}^2}e^{\frac{1}{2}\boldsymbol{B}^TA^{-1}\boldsymbol{B}}. \quad (5)
\end{aligned}$$

The matrix A is a matrix that can be decomposed into d blocks A^i, each of size $(N-1)\times(N-1)$. A^i is also a block matrix of

$$A^i = \begin{pmatrix} A^i_1 & 0 \\ 0 & A^i_2 \end{pmatrix} \quad (6)$$

with

$$A^i_1 = \begin{pmatrix}
\kappa & -\kappa & 0 & \cdots & 0 & 0 \\
-\kappa & 2\kappa & -\kappa & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
\vdots & 0 & -\kappa & 2\kappa+k & -\kappa & \vdots \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
\vdots & 0 & 0 & -\kappa & 2\kappa & -\kappa \\
\vdots & 0 & 0 & 0 & -\kappa & 2\kappa
\end{pmatrix}, \quad (7)$$

which is of size $(c-1)\times(c-1)$ and

$$A^i_2 = \begin{pmatrix}
2\kappa & -\kappa & 0 & \cdots & 0 & 0 \\
-\kappa & 2\kappa & -\kappa & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
\vdots & 0 & 0 & -\kappa & 2\kappa & -\kappa \\
\vdots & 0 & 0 & 0 & -\kappa & \kappa
\end{pmatrix}, \quad (8)$$

which is of size $(N-c)\times(N-c)$. The vector $\boldsymbol{B}$ is composed of d blocks, each given by

$$B^i = \begin{pmatrix} 0 \\ \vdots \\ \kappa x^i \\ \kappa x^i \\ 0 \\ \vdots \end{pmatrix}. \tag{9}$$

Since A^i is a tridiagonal matrix, we compute the determinant and its inverse using an algorithm proposed in [34]: first, the determinant of the matrix A^i is found by solving the recurrence relation

$$\begin{aligned} &\theta_l = b_l\theta_{l-1} - a_l c_{l-1}\theta_{l-2} \;\; l \geq 1, \\ &\theta_{-1} = 0, \\ &\theta_0 = 1, \end{aligned} \tag{10}$$

where b_j are the elements on the diagonal ($j = 1..N$), a_j are the elements bellow the diagonal ($j = 2..N$) and c_j are the elements above the diagonal ($j = 1..N-1$). For $l < n$ the recurrence relation is

$$\begin{aligned} &\theta_l = 2\kappa\theta_{l-1} - \kappa^2\theta_{l-2} \;\text{ for } n > l \geq 2, \\ &\theta_0 = 1, \\ &\theta_1 = \kappa. \end{aligned} \tag{11}$$

The characteristic polynomial of the relation is

$$P(t) = t^2 - 2\kappa t + \kappa^2, \tag{12}$$

which has one double root

$$r = \kappa. \tag{13}$$

Thus, the solution of the recurrence relation (11) is

$$\theta_l = k_1\kappa^l + k_2 l\kappa^l. \tag{14}$$

Substituting the initial conditions (eq.11), we find

$$\theta_l = \kappa^l \;\text{ for } l < n. \tag{15}$$

We next find the series solution at position n:

$$\theta_n = (2\kappa + k)\theta_{n-1} - \kappa^2\theta_{n-2} = \kappa^n + k\kappa^{n-1}, \tag{16}$$

while

$$\theta_{n+1} = 2\kappa\theta_n - \kappa^2\theta_{n-1} = \kappa^{n+1} + 2k\kappa^n. \tag{17}$$

We solve again the recurrence relation

$$
\begin{aligned}
&\theta_l = 2\kappa\theta_{l-1} - \kappa^2\theta_{l-2} \ \text{ for } l > n+1, \\
&\theta_n = \kappa^n + k\kappa^{n-1}, \\
&\theta_{n+1} = \kappa^{n+1} + 2k\kappa^n.
\end{aligned} \tag{18}
$$

Eq.(18) has the same characteristic polynomial (eq.12), thus

$$
\theta_l = k_1\kappa^l + k_2 l\kappa^l \tag{19}
$$

and with the new initial conditions (eq.18), we find

$$
\theta_l = \kappa^{n-1}\left(\kappa^{l-n+1} + (l-n+1)k\kappa^{l-n}\right), \quad \text{for } n \le l \le c-1. \tag{20}
$$

Thus, since $\det A_1^i = \theta_{c-1}$ [34]:

$$
\det A_1^i = \kappa^{n-1}\left(\kappa^{c-n-1+1} + (c-1-n+1)k\kappa^{c-1-n}\right) = \left(\kappa^{c-1} + (c-n)k\kappa^{c-2}\right) \tag{21}
$$

and using eq.(15) we find

$$
\det A_2^i = \kappa^{N-c}. \tag{22}
$$

The term in the exponential in eq.(5) is given by

$$
(B^i)^T[A^i]^{-1}B^i = (\kappa x^i)^2\left((A_1^i)^{-1}_{c-1,c-1} + (A_2^i)^{-1}_{1,1}\right). \tag{23}
$$

Since A_1^i is a tridiagonal matrix [34]

$$
(A_1^i)^{-1}_{c-1,c-1} = \frac{\theta_{c-2}}{\theta_{c-1}} = \frac{\kappa^{-1}\left(\kappa^{c-1} + (c-n-1)k\kappa^{c-2}\right)}{\left(\kappa^{c-1} + (c-n)k\kappa^{c-2}\right)} = \frac{\kappa + (c-n-1)k}{\kappa\left(\kappa + (c-n)k\right)}, \tag{24}
$$

while [34]

$$
(A_2^i)^{-1}_{1,1} = \frac{1}{\kappa}. \tag{25}
$$

Substituting (24) and (25) into (23) we find

$$
(B^i)^T[A^i]^{-1}B^i = (\kappa x^i)^2\left(\frac{\kappa + (c-n-1)k}{\kappa\left(\kappa + (c-n)k\right)} + \frac{1}{\kappa}\right) = (\kappa x^i)^2\left(\frac{2}{\kappa} - \frac{k}{\kappa\left(\kappa + (c-n)k\right)}\right). \tag{26}
$$

Substituting (26) into (5) we find

$$
\begin{aligned}
\mathcal{N}^{-1} &= \left[\frac{(2\pi)^{N-1}}{\left(\kappa + (c-n)k\right)\kappa^{N-2}}\right]^{3/2} e^{-\kappa \boldsymbol{x}^2} e^{\frac{1}{2}\boldsymbol{B}^T A^{-1}\boldsymbol{B}} \\
&= \left[\frac{(2\pi)^{N-1}}{\left(\kappa + (c-n)k\right)\kappa^{N-2}}\right]^{3/2} e^{-\frac{1}{2}\kappa \boldsymbol{x}^2} e^{-\dfrac{\boldsymbol{x}^2 k\kappa}{2\left(\kappa + (c-n)k\right)}}.
\end{aligned} \tag{27}
$$

We can now we calculate the conditional expectation of the measured velocity of monomer c (eq.2).

$$
\begin{aligned}
& \lim_{\Delta t \to 0} \mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t)-\boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{R}_c=\boldsymbol{x}\} = \\
& -\mathcal{N} D e^{-\kappa \boldsymbol{x}^2} \int \left(\kappa\left(\boldsymbol{x}-\boldsymbol{R}_{c-1}\right)-\kappa\left(\boldsymbol{R}_{c+1}-\boldsymbol{x}\right)\right) e^{-\frac{1}{2}\sum_{i,p,q} A^i_{p,q} R_p R_q + \sum_{i,p} B^i_p R^i_p} \prod_{i \neq c}^{N} d\boldsymbol{R}_i = \\
= \quad & -\mathcal{N} D \left[\frac{(2\pi)^{N-1}}{\det \mathrm{A}}\right]^{3/2} e^{-\kappa \boldsymbol{x}^2} e^{\frac{1}{2} B^T A^{-1} B} \kappa \left(2\boldsymbol{x} - \left(B_{c-1,c-1}(A^i_1)^{-1}_{c-1,c-1} + B_{c,c}(A^i_2)^{-1}_{1,1}\right)\right) = \\
& = -D\kappa \left(2\boldsymbol{x} - \kappa \boldsymbol{x}\left(\frac{2}{\kappa} - \frac{k}{\kappa\left(\kappa+(c-n)k\right)}\right)\right) = -D\frac{k\kappa \boldsymbol{x}}{\kappa+(c-n)k}. \qquad (28)
\end{aligned}
$$

Finally

$$
\lim_{\Delta t \to 0} \mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t)-\boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{R}_c=\boldsymbol{x}\} = -\boldsymbol{x} D k_{cn}, \qquad (29)
$$

where

$$
k_{cn} = \frac{k\kappa}{\kappa+(c-n)k}. \qquad (30)
$$

For a Rouse polymer the force depends only on the distance along the chain $|c-n|$. Interestingly, the restoring force decays inversely proportional to the distance along the chain.

0.1 The variance of monomer c position

We now compute the variance of a monomer position $\langle \boldsymbol{R}_c^2 \rangle$ with respect to its average position (mean zero)

$$
\begin{aligned}
\langle \boldsymbol{R}_c^2 \rangle &= \int .. \int \boldsymbol{R}_c^2 P(\boldsymbol{R}) \prod_{i=1}^{N} d\boldsymbol{R}_i = \mathcal{N} \int \boldsymbol{R}_c^2 e^{-\Phi(\boldsymbol{R})} \prod_{i=1}^{N} d\boldsymbol{R}_i \\
&= \mathcal{N} \int \boldsymbol{R}_c^2 \exp\left[-\frac{1}{2} \sum_{p,q=1;p,q\neq c}^{N} G_{p,q} R_p R_q\right] \prod_{i=1}^{N} d\boldsymbol{R}_i, \qquad (31)
\end{aligned}
$$

where the potential Φ is given by (1) and G is a matrix composed of d blocks (G^i), each of size $N \times N$:

$$G^i = \begin{pmatrix} \kappa & -\kappa & 0 & \cdots & 0 & 0 \\ -\kappa & 2\kappa & -\kappa & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \vdots & 0 & -\kappa & 2\kappa + k & -\kappa & \vdots \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \vdots & 0 & 0 & -\kappa & 2\kappa & -\kappa \\ \vdots & 0 & 0 & 0 & -\kappa & \kappa \end{pmatrix}. \tag{32}$$

Thus, rewriting eq.(31)

$$\begin{aligned} \langle \boldsymbol{R}_c^2 \rangle &= \mathcal{N} \int \boldsymbol{R}_c^2 \exp\left[-\frac{1}{2} \sum_{p,q=1;p,q\neq c}^{N} G_{p,q} R_p R_q \right] \prod_{i=1}^{N} d\boldsymbol{R}_i \\ &= \mathcal{N} \left[\frac{(2\pi)^{d(N-1)}}{\det G} \right]^{1/2} \sum_i (G^i)^{-1}_{cc} = \sum_i (G^i)^{-1}_{cc}, \end{aligned} \tag{33}$$

where [34]

$$(G^i)^{-1}_{cc} = \frac{\theta_{c-1}\phi_{c+1}}{\det G} \tag{34}$$

and

$$\begin{aligned} &\phi_l = b_l \theta_{l+1} - a_{l+1} c_l \theta_{l+2} \quad \text{for } n < l \leq N, \\ &\phi_{N+1} = 1, \\ &\phi_{N+2} = 0. \end{aligned} \tag{35}$$

Since $c > n$, solving the recurrence relation 35, we find

$$\phi_l = \kappa^{N-l+1} \quad \text{for} \quad \text{for } n < l \leq N, \tag{36}$$

Thus, using the value θ_{c-1} (eq.20)

$$\begin{aligned} \phi_{c+1} &= \kappa^{N-c} \\ \theta_{c-1} &= \kappa^{n-1} \left(\kappa^{c-n} + (c-n) k \kappa^{c-n-1} \right), \end{aligned} \tag{37}$$

while

$$\theta_{N-1} = \kappa^{n-1} \left(\kappa^{N-n} + (N-n) k \kappa^{N-n-1} \right) \tag{38}$$

Finally, the determinant is given by

$$\det G = \kappa\theta_{N-1} - \kappa^2\theta_{N-2} = k\kappa^{N-1} \tag{39}$$

and the inverse element

$$(G^i)^{-1}_{cc} = \frac{\theta_{c-1}\phi_{c+1}}{\det G} = \frac{\kappa + (c-n)k}{k\kappa} \tag{40}$$

Finally, substituting (40) into eq.(33), we find the variance for the position to be

$$\langle \boldsymbol{R}_c^2 \rangle = \sum_i \frac{\kappa + (c-n)k}{k\kappa} = \frac{d}{k_{cn}}, \tag{41}$$

where we use the definition 30 for k_{cn}.

0.2 Extracting the strength of a potential well for a β-polymer

We now derive an expression for the measured velocity of a monomer c when monomer n further away along the chain interacts with an harmonic potential well for the β-polymer model [24]. We recall that for the β-model, the polymer potential is given

$$\tilde{\phi}(\boldsymbol{R}_1, ..., \boldsymbol{R}_N) = \frac{1}{2}\sum_{l,m} \boldsymbol{R}_n \boldsymbol{R}_m A_{n,m} = \frac{k}{2}\sum_{pq=0}^{N-1} \alpha_p^n \alpha_q^n \boldsymbol{u}_p \boldsymbol{u}_q, \tag{42}$$

where

$$A_{l,m} = 4\kappa \frac{2}{N}\sum_{p=0}^{N-1} \sin^\beta\left(\frac{p\pi}{2N}\right)\cos\left(\left(l-\frac{1}{2}\right)\frac{p\pi}{N}\right)\cos\left(\left(m-\frac{1}{2}\right)\frac{p\pi}{N}\right). \tag{43}$$

When a localized interaction acts on monomer n, the polymer energy becomes

$$\tilde{\phi}(\boldsymbol{R}_1, ..., \boldsymbol{R}_N) = \frac{1}{2}\sum_{l,m} \boldsymbol{R}_l \boldsymbol{R}_m A_{l,m} + \frac{1}{2}k\boldsymbol{R}_n^2, \tag{44}$$

which can be represented as

$$\tilde{\phi}(\boldsymbol{R}_1, ..., \boldsymbol{R}_N) = \frac{1}{2}\sum_{l,m} \boldsymbol{R}_l \boldsymbol{R}_m C_{l,m}, \tag{45}$$

where

$$C_{l,m} = \begin{cases} A_{n,n} + k, & \\ A_{l,m}, & \text{else.} \end{cases} \tag{46}$$

The probability distribution function is the Boltzmann distribution

$$P(\boldsymbol{R}) = \mathcal{N} e^{-\tilde{\phi}(\boldsymbol{R})}, \tag{47}$$

while the conditional probability distribution function is

$$P(\boldsymbol{R}|\boldsymbol{R}_c = \boldsymbol{x}) = \mathcal{N} e^{-\tilde{\phi}(\boldsymbol{R}_n,...,\boldsymbol{R}_{c-1},\boldsymbol{x},\boldsymbol{R}_{c+1})}. \tag{48}$$

The normalization factor $\mathcal{N}$ is given by

$$\begin{aligned}
\mathcal{N}^{-1} &= \int P(\boldsymbol{R}|\boldsymbol{R}_c = \boldsymbol{x}) \prod_{k\neq c} d\boldsymbol{R}_k = \int e^{-\tilde{\phi}(...,\boldsymbol{R}_{c-1},\boldsymbol{x},\boldsymbol{R}_{c+1},...)} \prod_{k\neq c} d\boldsymbol{R}_k \\
&= \\
&= \int e^{-\frac{1}{2}C_{c,c}\boldsymbol{x}^2} \exp\left[-\frac{1}{2}\left(\sum_{l,m\neq c} C_{l,m}\boldsymbol{R}_l\boldsymbol{R}_m + 2\sum_{l\neq c} C_{l,c}\boldsymbol{R}_l\boldsymbol{x}\right)\right] \\
&= \int e^{-\frac{1}{2}C_{c,c}\boldsymbol{x}^2} \exp\left[-\frac{1}{2}\sum_{l,m} \tilde{C}_{l,m}\boldsymbol{R}_l\boldsymbol{R}_m + \sum_{l} F_l\boldsymbol{R}_l\right] \\
&= \left[\frac{(2\pi)^{N-1}}{\det\tilde{\mathrm{C}}}\right]^{3/2} e^{-\frac{1}{2}B_{c,c}\boldsymbol{x}^2} e^{\frac{1}{2}\boldsymbol{F}^T\tilde{C}^{-1}\boldsymbol{F}},
\end{aligned} \tag{49}$$

The matrix $\tilde{C}$ is the reduced matrix C (eq.46) when the row and column c is removed. It is a block matrix with d blocks each of size $(N-1)\times(N-1)$, where each block i given by

$$\tilde{C}^i = \begin{pmatrix}
A_{1,1} & \cdots & \cdots & \cdots & & \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
\vdots & A_{n,n}+k & \vdots & \vdots & \vdots & \\
\vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
\vdots & \vdots & A_{c-1,c-1} & A_{c-1,c+1} & A_{c-1,c+2} & \vdots \\
\vdots & \vdots & A_{c+1,c-1} & A_{c+1,c+1} & A_{c+1,c+2} & \vdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots
\end{pmatrix}, \tag{50}$$

and the vector $\boldsymbol{F}$ is compose of d blocks, each of size $(N-1)$:

$$F^i = \begin{pmatrix}
-A_{1,c}x^i \\
\vdots \\
-A_{c-1,c}x^i \\
-A_{c+1,c}x^i \\
\vdots \\
-A_{N,c}x^i
\end{pmatrix}. \tag{51}$$

The force acting on monomer c is given by

$$-\nabla_{\boldsymbol{R}_c}\tilde{\phi}(\boldsymbol{R}_1,...,\boldsymbol{R}_N) = -A_{c,c}\boldsymbol{R}_c - \sum_{l\neq c} A_{l,c}\boldsymbol{R}_l. \tag{52}$$

The conditional expectation of the velocity of monomer c at small time steps is

$$\lim_{\Delta t \to 0} \mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t)-\boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{R}_c=\boldsymbol{x}\} = D\int \left[-\nabla_{\boldsymbol{R}_c}\tilde{\phi}(\boldsymbol{R}_1,...,\boldsymbol{R}_N)\right]_{\boldsymbol{R}_c=\boldsymbol{x}}$$
$$P(\boldsymbol{R}|\boldsymbol{R}_c=\boldsymbol{x})\prod_{i\neq c} d\boldsymbol{R}_i, \tag{53}$$

where the conditional force is given by (52) and the conditional probability by (48) and (49). Thus

$$\lim_{\Delta t \to 0} \mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t)-\boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{R}_c=\boldsymbol{x}\} = D\int \left[-\nabla_{\boldsymbol{R}_c}\tilde{\phi}(\boldsymbol{R}_{c-1},\boldsymbol{R}_c,\boldsymbol{R}_{c+1})\right]_{\boldsymbol{R}_c=\boldsymbol{x}}$$
$$P(\boldsymbol{R}_{c-1},\boldsymbol{R}_c,\boldsymbol{R}_{c+1}|\boldsymbol{R}_c=\boldsymbol{x})\prod_{i\neq c} d\boldsymbol{R}_i =$$
$$-\mathcal{N}De^{-\frac{1}{2}C_{c,c}\boldsymbol{x}^2}\int(A_{c,c}\boldsymbol{x}+\sum_{l\neq c}A_{l,c}\boldsymbol{R}_l)\exp\left[-\frac{1}{2}\sum_{l,m}\tilde{C}_{l,m}\boldsymbol{R}_l\boldsymbol{R}_m+\sum_l \boldsymbol{F}_l\boldsymbol{R}_l\right]\prod_{i\neq c} d\boldsymbol{R}_i =$$
$$-A_{c,c}D\boldsymbol{x}-\mathcal{N}De^{-\frac{1}{2}C_{c,c}\boldsymbol{x}^2}\int\sum_{l\neq c}A_{l,c}\boldsymbol{R}_l\exp\left[-\frac{1}{2}\sum_{l,m}\tilde{C}_{l,m}\boldsymbol{R}_l\boldsymbol{R}_m+\sum_l \boldsymbol{F}_l\boldsymbol{R}_l\right]\prod_{i\neq c} d\boldsymbol{R}_i =$$
$$-A_{c,c}D\boldsymbol{x}-\mathcal{N}De^{-\frac{1}{2}C_{c,c}\boldsymbol{x}^2}\left[\frac{(2\pi)^{n-1}}{\det\tilde{\mathrm{C}}}\right]^{3/2}\sum_{i,l\neq c}A_{l,c}\frac{\partial}{\partial F_l^i}e^{\frac{1}{2}\boldsymbol{F}^T\tilde{C}^{-1}\boldsymbol{F}} =$$
$$-A_{c,c}D\boldsymbol{x}-De^{-\frac{1}{2}\boldsymbol{F}^T\tilde{C}^{-1}\boldsymbol{F}}\sum_{i,l\neq c}A_{l,c}\frac{\partial}{\partial F_l^i}e^{\frac{1}{2}\boldsymbol{F}_l\tilde{C}^{-1}_{l,m}\boldsymbol{F}_m} =$$
$$-A_{c,c}D\boldsymbol{x}-D\sum_{l\neq c}A_{l,c}\sum_{m\neq c}\tilde{C}^{-1}_{l,m}\boldsymbol{F}_m = -A_{c,c}D\boldsymbol{x}-D\sum_{l\neq c}A_{l,c}\sum_{m\neq c}\tilde{C}^{-1}_{l,m}(-A_{m,c}\boldsymbol{x}) =$$
$$-\boldsymbol{x}D\left(A_{c,c}-\sum_{l,m\neq c}A_{l,c}A_{m,c}\tilde{C}^{-1}_{l,k}\right). \tag{54}$$

We conclude that

$$\lim_{\Delta t \to 0} \mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t)-\boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{R}_c=\boldsymbol{x}\} = -\boldsymbol{x}Dk_{cn}(\beta,N), \tag{55}$$

where

$$k_{cn}(\beta,N) = A_{c,c}-\sum_{l,m\neq c}A_{l,c}A_{m,c}\tilde{C}^{-1}_{l,k}. \tag{56}$$

While for a Rouse polymer the force depends only on the distance along the chain $|c-n|$, for a β-polymer, the effective spring coefficient depends on all monomers.

1 Extracting the strength of two potential wells for a Rouse polymer

For a Rouse polymer subjected to two gradient forces, the energy $U_{\text{ext}}(\boldsymbol{R})$ can now described by

$$\tilde{\Phi}(\boldsymbol{R}) = \frac{\kappa}{2}\sum_{j=2}^{N}(\boldsymbol{R}_j - \boldsymbol{R}_{j-1})^2 + \frac{1}{2}k_n(\boldsymbol{R}_n - \boldsymbol{\mu}_n)^2 + \frac{1}{2}k_m(\boldsymbol{R}_m - \boldsymbol{\mu}_m)^2. \tag{57}$$

The external potentials represent the interaction of two monomers. We compute here the average position $\langle \boldsymbol{R}_c \rangle$ of monomer c, which is situated between monomers n and m. For that goal, we rewrite the potential $\tilde{\Phi}(\boldsymbol{R})$ in a quadratic form

$$\tilde{\Phi}(\boldsymbol{R}) = \frac{1}{2}\sum_{p,q} A_{p,q}\boldsymbol{R}_p\boldsymbol{R}_q + \sum_p B_p\boldsymbol{R}_p + \frac{1}{2}k_n\boldsymbol{\mu}_n^2 + \frac{1}{2}k_m\boldsymbol{\mu}_m^2, \tag{58}$$

where the matrix A is made of d blocks, each of size $N \times N$, where each block i is given by

$$A^i = \begin{pmatrix} \kappa & -\kappa & 0 & \cdots & \cdots & \cdots & 0 \\ -\kappa & 2\kappa & -\kappa & \cdots & \vdots & \vdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \\ 0 & \cdots & -\kappa & 2\kappa + k_n & -\kappa & 0 & \cdots \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \\ \vdots & \vdots & 0 & -\kappa & 2\kappa + k_m & -\kappa & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 0 & -\kappa & \kappa \end{pmatrix} \tag{59}$$

and the vector $\boldsymbol{B}$ is compose of d blocks, each given by

$$B^i = \begin{pmatrix} 0 \\ \vdots \\ k_n\mu_n \\ 0 \\ \vdots \\ k_m\mu_m \\ 0 \\ \vdots \end{pmatrix}. \tag{60}$$

Since A^i is a tridiagonal matrix, we use the algorithm proposed in [34] to calculate its determinant and inverse of matrix. For $a, b < m$, $A^i_{a,b}$ has the same structure as the matrix 7. Thus

$$\theta_l = \kappa^l \quad \text{for} \quad l < n, \tag{61}$$

$$\theta_n = \kappa^n + k_n \kappa^{n-1}, \tag{62}$$

$$\theta_l = \kappa^{l-1} \left(\kappa + (l - n + 1)k_n\right), \quad \text{for } n \leq l < m. \tag{63}$$

We next find the series solution at position m:

$$\theta_m = (2\kappa + k_m)\theta_{m-1} - \kappa^2 \theta_{m-2} = \kappa^{m-2} \left[\kappa^2 + k_n \kappa(m - n + 1) + k_m(\kappa + (m - n)k_n)\right] \tag{64}$$

and

$$\theta_{m+1} = 2\kappa\theta_m - \kappa^2\theta_{m-1} = \kappa^{m-1} \left[\kappa^2 + k_n\kappa(m - n + 2) + 2k_m(\kappa + (m - n)k_n)\right]. \tag{65}$$

Again, we solve the recurrence relation

$$\begin{aligned}
&\theta_l = 2\kappa\theta_{l-1} - \kappa^2\theta_{l-2}, \quad \text{for } m + 1 < l < N, \\
&\theta_m = (2\kappa + k_m)\theta_{m-1} - \kappa^2\theta_{m-2} = \kappa^{m-2} \left[\kappa^2 + k_n\kappa(m - n + 1) + k_m(\kappa + (m - n)k_n)\right], \\
&\theta_{m+1} = 2\kappa\theta_m - \kappa^2\theta_{m-1} = \kappa^{m-1} \left[\kappa^2 + k_n\kappa(m - n + 2) + 2k_m(\kappa + (m - n)k_n)\right].
\end{aligned} \tag{66}$$

Eq.(66) has the characteristic polynomial (eq.12), thus using the initial conditions (eq.66), we find

$$\theta_l = \kappa^{l-2} \left(\kappa^2 + \kappa(k_n(l - n + 1) + k_m(l - m + 1)) + k_n k_m (m - n)(l + 1 - m)\right) \quad \text{for } \; m \leq l < N. \tag{67}$$

Using that

$$\theta_N = \kappa\theta_{N-1} - \kappa^2\theta_{N-2}, \tag{68}$$

we obtain that the determinant is given by

$$\det A^i = \theta_N = \kappa^{N-2} \left((k_m + k_n)\kappa + (m - n)k_n k_m\right). \tag{69}$$

The inverse of the matrix A^i is given by [34]

$$(A^i)^{-1}_{ij} = \begin{cases} (-1)^{i+j} c_i c_{i+1} \ldots c_{j-1} \frac{\theta_{i-1}\phi_{j+1}}{\theta_N}, \; i \leq j \\ (-1)^{i+j} a_j a_{j+1} \ldots a_{i-1} \frac{\theta_{j-1}\phi_{i+1}}{\theta_N}, \; i > j \\ \frac{\theta_{i-1}\phi_{i+1}}{\theta_N} \quad i = j, \end{cases} \tag{70}$$

where

$$\begin{aligned}
&\phi_l = b_l\theta_{l+1} - a_{l+1}c_l\theta_{l+2} \quad \text{for } l \leq N, \\
&\phi_{N+1} = 1, \\
&\phi_{N+2} = 0.
\end{aligned} \tag{71}$$

Solving the recurrence relation 71 we find

$$\begin{aligned}
&\phi_l = \kappa^{N-l+1} \quad \text{for } \; m < l < N, \\
&\phi_l = \kappa^{-m-1} \left[\kappa^{N+m-l+2} + (m - l + 1)k_m\kappa^{N+m-l+1}\right] \quad \text{for } \; n < l \leq m, \\
&\phi_n = \kappa^{N-n-1} \left[\kappa^2 + k_m\kappa(m - n + 1) + k_n(\kappa + (m - n)k_m)\right].
\end{aligned} \tag{72}$$

The normalization factor is

$$\begin{aligned}\mathcal{N}^{-1} &= \int_\Omega .. \int_\Omega \prod_{i=1}^N d\boldsymbol{R}_i P(\boldsymbol{R}) = \int_\Omega .. \int_\Omega \prod_{i=1}^N d\boldsymbol{R}_i \exp\Big(-\frac{1}{2}\sum_{p,q} A_{p,q}\boldsymbol{R}_p\boldsymbol{R}_q \\ &+ \sum_p B_p \boldsymbol{R}_p + \frac{1}{2}k(\boldsymbol{\mu}_n^2 + \boldsymbol{\mu}_m^2)\Big) = \left[\frac{(2\pi)^N}{\prod_i \mathrm{detA^i}}\right]^{3/2} e^{-\frac{1}{2}k(\boldsymbol{\mu}_n^2+\boldsymbol{\mu}_m^2)} e^{\frac{1}{2}\boldsymbol{B}^T A^{-1}\boldsymbol{B}} \quad (73)\end{aligned}$$

Substituting eq.(60) in the exponential term of the last equation, we get

$$\boldsymbol{B}^T A^{-1}\boldsymbol{B} = \sum_i (k\mu_n^i)^2 (A^i)^{-1}_{nn} + (k\mu_m^i)^2 (A^i)^{-1}_{mm} + k^2\mu_n^i\mu_m^i (A^i)^{-1}_{nm} + k^2\mu_n^i\mu_m^i (A^i)^{-1}_{mn}. \quad (74)$$

We now estimate these elements of $(A^i)^{-1}$:

$$\begin{aligned}(A^i)^{-1}_{nn} &= \frac{\theta_{n-1}\phi_{n+1}}{\theta_N} = \frac{\kappa + k_m(m-n)}{k_n k_m(m-n) + (k_n+k_m)\kappa}, \\ (A^i)^{-1}_{mm} &= \frac{\theta_{m-1}\phi_{m+1}}{\theta_N} = \frac{\kappa + k_n(m-n)}{k_n k_m(m-n) + (k_n+k_m)\kappa}, \\ (A^i)^{-1}_{nm} &= (-1)^{n+m}(-\kappa)^{m-n}\frac{\theta_{n-1}\phi_{m+1}}{\theta_N} = \frac{\kappa}{k_n k_m(m-n) + (k_n+k_m)\kappa} \quad (75)\end{aligned}$$

Finally, we compute the average position of monomer c

$$\begin{aligned}\langle \boldsymbol{R}_c\rangle &= \int_\Omega .. \int_\Omega \prod_{i=1}^N d\boldsymbol{R}_i \boldsymbol{R}_c P(\boldsymbol{R}) = \mathcal{N}\int_\Omega .. \int_\Omega \prod_{i=1}^N d\boldsymbol{R}_i \boldsymbol{R}_c \exp\Big(-\frac{1}{2}\sum_{p,q} A_{p,q}\boldsymbol{R}_p\boldsymbol{R}_q \\ &+ \sum_p B_p\boldsymbol{R}_p + \frac{1}{2}k_n\boldsymbol{\mu}_n^2 + \frac{1}{2}k_m\boldsymbol{\mu}_m^2\Big) = \sum_i k_n\mu_n^i (A^i)^{-1}_{cn} + k_m\mu_m^i (A^i)^{-1}_{cm}, \quad (76)\end{aligned}$$

where

$$\begin{aligned}(A^i)^{-1}_{cn} &= (-1)^{c+n}(-\kappa)^{c-n}\frac{\theta_{n-1}\phi_{c+1}}{\theta_N} = \frac{\kappa + (m-c)k_m}{k_n k_m(m-n) + (k_n+k_m)\kappa}, \\ (A^i)^{-1}_{cm} &= (-1)^{c+m}(-\kappa)^{m-c}\frac{\theta_{c-1}\phi_{m+1}}{\theta_N} = \frac{\kappa + (c-n)k_n}{k_n k_m(m-n) + (k_n+k_m)\kappa}. \quad (77)\end{aligned}$$

Thus

$$\langle \boldsymbol{R}_c\rangle = \frac{1}{k_n k_m(m-n) + (k_n+k_m)\kappa}\sum_i \mu_n^i k_n(\kappa + (m-c)k_m) + \mu_m^i k_m(\kappa + (c-n)k_n). \quad (78)$$

We now estimate the conditional expectation of the velocity for the observed monomer c, in the small time step regime

$$\lim_{\Delta t\to 0}\mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t) - \boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{R}_c = \boldsymbol{x}\}. \quad (79)$$

The conditional expectation of the velocity of monomer c is

$$\lim_{\Delta t\to 0}\mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t)-\boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{R}_c=\boldsymbol{x}\}=D\int\left[-\nabla_{\boldsymbol{R}_c}\tilde{\Phi}(\boldsymbol{R})\right]_{\boldsymbol{R}_c=\boldsymbol{x}}P(\boldsymbol{R}|\boldsymbol{R}_c=\boldsymbol{x})\prod_i d\boldsymbol{R}_i$$

$$= D\int\left(\kappa\left(\boldsymbol{x}-\boldsymbol{R}_{c-1}\right)-\kappa\left(\boldsymbol{R}_{c+1}-\boldsymbol{x}\right)\right)P(\boldsymbol{R}|\boldsymbol{R}_c=\boldsymbol{x})\prod_i d\boldsymbol{R}_i=-\tilde{\mathcal{N}}De^{-\kappa\boldsymbol{x}^2-\frac{1}{2}k_n\boldsymbol{\mu}_n^2-\frac{1}{2}k_m\boldsymbol{\mu}_m^2}$$

$$\int\left(\kappa\left(\boldsymbol{x}-\boldsymbol{R}_{c-1}\right)-\kappa\left(\boldsymbol{R}_{c+1}-\boldsymbol{x}\right)\right)e^{-\frac{1}{2}\sum_{i,p,q}\tilde{A}^i_{p,q}R_pR_q+\sum_{i,p}\tilde{B}^i_pR^i_p}\prod_{i\neq c}d\boldsymbol{R}_i$$

$$= -D\kappa\sum_i\left(2x^i-\sum_l\tilde{B}^i_l\left((\tilde{A}^i)^{-1}_{c-1,l}+(\tilde{A}^i)^{-1}_{c+1,l}\right)\right), \quad (80)$$

where $\tilde{\mathcal{N}}$ is the normalization as computed in 73 when the c column is removed. $\tilde{A}^i$ is a block matrix of size $N-1\times N-1$

$$\tilde{A}^i=\begin{pmatrix}\tilde{A}^i_1 & 0\\ 0 & \tilde{A}^i_2\end{pmatrix} \quad (81)$$

with

$$\tilde{A}^i_1=\begin{pmatrix}\kappa & -\kappa & 0 & \cdots & 0 & 0\\ -\kappa & 2\kappa & -\kappa & \cdots & 0 & 0\\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots\\ \vdots & 0 & -\kappa & 2\kappa+k_n & -\kappa & \vdots\\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots\\ \vdots & 0 & 0 & -\kappa & 2\kappa & -\kappa\\ \vdots & 0 & 0 & 0 & -\kappa & 2\kappa\end{pmatrix} \quad (82)$$

which is of size $(c-1)\times(c-1)$ and

$$\tilde{A}^i_2=\begin{pmatrix}2\kappa & -\kappa & 0 & \cdots & 0 & 0\\ -\kappa & 2\kappa & -\kappa & \cdots & 0 & 0\\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots\\ \vdots & 0 & -\kappa & 2\kappa+k_m & -\kappa & \vdots\\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots\\ \vdots & 0 & 0 & -\kappa & 2\kappa & -\kappa\\ \vdots & 0 & 0 & 0 & -\kappa & \kappa\end{pmatrix} \quad (83)$$

which is of size $(N-c)\times(N-c)$. The vector $\tilde{\boldsymbol{B}}$ is compose of d blocks, each given by

$$\tilde{B}^i = \begin{pmatrix} 0 \\ \vdots \\ k_n\mu_n \\ \vdots \\ \kappa x^i \\ \kappa x^i \\ \vdots \\ k_m\mu_m \\ \vdots \end{pmatrix}. \tag{84}$$

To find the determinant $\det\tilde{A}_1^i$, we use eq.(63):

$$\det\tilde{A}_1^i = \kappa^{c-2}(\kappa + (c-n)k_n) \tag{85}$$

and using eq.(72)

$$\det\tilde{A}_2^i = \kappa^{N-c-1}(\kappa + (m-c)k_m). \tag{86}$$

The elements of the inverse matrix are given by

$$\begin{aligned}
(\tilde{A}_1{}^i)^{-1}_{c-1,c-1} &= \frac{\kappa + (c-n-1)k_n}{\kappa^2 + (c-n)k_n\kappa} = \frac{1}{\kappa} - \frac{k_n}{\kappa(\kappa + (c-n)k_n)}, \\
(\tilde{A}_2{}^i)^{-1}_{c+1,c+1} &= \frac{\kappa + (m-c-1)k_m}{\kappa^2 + (m-c)k_m\kappa} = \frac{1}{\kappa} - \frac{k_m}{\kappa(\kappa + (m-c)k_m)}, \\
(\tilde{A}_1{}^i)^{-1}_{c-1,n} &= (-1)^{c+n-1}(-\kappa)^{c-n-1}\frac{\theta_{n-1}}{\theta_{c-1}} = \frac{1}{\kappa + (c-n)k_n}, \\
(\tilde{A}_2{}^i)^{-1}_{c+1,m} &= \frac{1}{\kappa + (m-c)k_m}.
\end{aligned} \tag{87}$$

Now, we estimate the term in the parenthesis in eq.(80) by substituting eqs.(87)

$$\begin{aligned}
K^i &= 2x^i - \sum_l \tilde{B}_l^i \left((\tilde{A}^i)^{-1}_{c-1,l} + (\tilde{A}^i)^{-1}_{c+1,l}\right) \\
&= 2x^i - \left(\kappa x^i(\tilde{A}_1{}^i)^{-1}_{c-1,c-1} + \kappa x^i(\tilde{A}_1{}^i)^{-1}_{c+1,c+1} + k_n\mu_n(\tilde{A}_1{}^i)^{-1}_{c-1,n} + k_m\mu_m(\tilde{A}_2{}^i)^{-1}_{c+1,n}\right) \\
&= 2x^i - \kappa x^i\left(\frac{\kappa + (c-n-1)k_n}{\kappa^2 + (c-n)k_n\kappa} + \frac{\kappa + (m-c-1)k_m}{\kappa^2 + (m-c)k_m\kappa}\right) - \frac{k_n\mu_n^i}{\kappa + (c-n)k_n} - \frac{k_m\mu_m^i}{\kappa + (m-c)k_m} \\
&= 2x^i - x^i\left(\frac{\kappa + (c-n-1)k_n}{\kappa + (c-n)k_n} + \frac{\kappa + (m-c-1)k_m}{\kappa + (m-c)k_m}\right) - \frac{k_n\mu_n^i}{\kappa + (c-n)k_n} - \frac{k_m\mu_m^i}{\kappa + (m-c)k_m} \\
&= 2x^i - x^i\left(2 - \frac{k_n}{\kappa + (c-n)k_n} - \frac{k_m}{\kappa + (m-c)k_m}\right) - \frac{k_n\mu_n^i}{\kappa + (c-n)k_n} - \frac{k_m\mu_m^i}{\kappa + (m-c)k_m} \\
&= x^i\left(\frac{k_n}{\kappa + (c-n)k_n} + \frac{k_m}{\kappa + (m-c)k_m}\right) - \frac{k_n\mu_n^i}{\kappa + (c-n)k_n} - \frac{k_m\mu_m^i}{\kappa + (m-c)k_m}
\end{aligned} \tag{88}$$

We introduce into expression eq.(88) the position of monomer c with respect to its mean position ($\tilde{\boldsymbol{x}} = \boldsymbol{x} - \langle \boldsymbol{R}_c \rangle$) (eq.78)

$$\begin{aligned} K^i &= \left[\tilde{x^i} + \frac{1}{k_n k_m (m-n) + (k_n + k_m)\kappa} \sum_i \mu_n^i k_n (\kappa + (m-c)k_m) + \mu_m^i k_m (\kappa + (c-n)k_n) \right] \\ & \left(\frac{k_n}{\kappa + (c-n)k_n} + \frac{k_m}{\kappa + (m-c)k_m} \right) - \frac{k_n \mu_n^i}{\kappa + (c-n)k_n} - \frac{k_m \mu_m^i}{\kappa + (m-c)k_m} \\ &= \tilde{x^i} \left(\frac{k_n}{\kappa + (c-n)k_n} + \frac{k_m}{\kappa + (m-c)k_m} \right). \end{aligned} \tag{89}$$

Finally, substituting eq.(89) into expression (80), we find

$$\lim_{\Delta t \to 0} \mathbb{E}\{ \frac{\boldsymbol{R}_c(t+\Delta t) - \boldsymbol{R}_c(t)}{\Delta t} | \tilde{\boldsymbol{x}} \} = -D(k_{c,n} + k_{c,m}) \tilde{\boldsymbol{x}}, \tag{90}$$

where

$$k_{c,n} = \frac{k_n \kappa}{\kappa + (c-n)k_n} \tag{91}$$

and

$$k_{c,m} = \frac{k_m \kappa}{\kappa + (m-c)k_m}. \tag{92}$$

1.1 Variance of monomer c position

We now find the variance of a monomer position $\langle \boldsymbol{R}_c^2 \rangle$ with respect to its average position

$$\langle (\boldsymbol{R}_c - \langle \boldsymbol{R}_c \rangle)^2 \rangle = \langle \boldsymbol{R}_c^2 \rangle - \langle \boldsymbol{R}_c \rangle^2, \tag{93}$$

We begin by calculating

$$\begin{aligned} \langle \boldsymbol{R}_c^2 \rangle &= \int_\Omega .. \int_\Omega d\boldsymbol{R}_1 d\boldsymbol{R}_2 ... d\boldsymbol{R}_N \boldsymbol{R}_c^2 P(\boldsymbol{R}) = \mathcal{N} \left[\frac{(2\pi)^{d(N-1)}}{\det A} \right]^{1/2} \sum_i \frac{\partial^2}{\partial (R_c^i)^2} \exp\left(\frac{1}{2} \sum_i \sum_{pq} A^{i\,-1}_{\ pq} \right) \\ &= \sum_i (A^i)^{-1}_{cc} + \left((A^i)^{-1}_{cn} k_n \mu_n^i + (A^i)^{-1}_{cm} k_m \mu_m^i \right)^2, \end{aligned} \tag{94}$$

where

$$(A^i)^{-1}_{cc} = \frac{\theta_{c-1}\phi_{c+1}}{\theta_N} = \frac{(\kappa + (c-n)k_n)(\kappa + (m-c)k_n)}{(k_m + k_n)\kappa^2 + (m-n)k_n k_m \kappa}. \tag{95}$$

Substituting (94), (95) and (78) into eq.(93) we find

$$\langle (\boldsymbol{R}_c - \langle \boldsymbol{R}_c \rangle)^2 \rangle = \frac{1}{k_{cn} + k_{cm}}. \tag{96}$$

1.2 Two potential wells located on the left side of the observed locus ($n < m < c$)

Finally, we solve for the case $n < m < c$. We being with the average position of monomer c

$$\langle \boldsymbol{R}_c \rangle = \sum_i k_n \mu_n^i (A^i)^{-1}_{cn} + k_m \mu_m^i (A^i)^{-1}_{cm}, \tag{97}$$

where A^i is given in eq.(59). Thus

$$\begin{aligned} (A^i)^{-1}_{cn} &= (-1)^{c+n}(-\kappa)^{c-n}\frac{\theta_{n-1}\phi_{c+1}}{\theta_N} = \frac{\kappa}{k_n k_m(m-n)+\kappa(k_n+k_m)}, \\ (A^i)^{-1}_{cm} &= (-1)^{c+m}(-\kappa)^{m-c}\frac{\theta_{m-1}\phi_{c+1}}{\theta_N} = \frac{\kappa+(m-n)k_n}{k_n k_m(m-n)+\kappa(k_n+k_m)}. \end{aligned} \tag{98}$$

The average position of c is

$$\langle \boldsymbol{R}_c \rangle = \frac{1}{k_n k_m(m-n)+\kappa(k_n+k_m)} \sum_i k_n \mu_n^i \kappa + k_m \mu_m^i (\kappa + (m-n)k_n). \tag{99}$$

The conditional expectation of the velocity of monomer c for a small time step is defined as

$$\begin{aligned} &\lim_{\Delta t \to 0} \mathbb{E}\{\frac{\boldsymbol{R}_c(t+\Delta t)-\boldsymbol{R}_c(t)}{\Delta t}|\boldsymbol{x}\} = D\int \left[-\nabla_{\boldsymbol{R}_c}\tilde{\Phi}(\boldsymbol{R})\right]_{\boldsymbol{R}_c=\boldsymbol{x}} P(\boldsymbol{R}|\boldsymbol{R}_c=\boldsymbol{x})\prod_i d\boldsymbol{R}_i \\ &= -D\kappa\sum_i\left(2x^i - \sum_l V_l^i\left((U^i)^{-1}_{c-1,l}+(U^i)^{-1}_{c+1,l}\right)\right), \end{aligned} \tag{100}$$

where U^i is also a block matrix of size $N-1 \times N-1$

$$U^i = \begin{pmatrix} U_1^i & 0 \\ 0 & U_2^i \end{pmatrix} \tag{101}$$

with

$$U_1^i = \begin{pmatrix} \kappa & -\kappa & 0 & \cdots & 0 & 0 & 0 \\ -\kappa & 2\kappa & -\kappa & \cdots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ \vdots & 0 & -\kappa & 2\kappa+k_n & -\kappa & 0 & \vdots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ \vdots & 0 & 0 & -\kappa & 2\kappa+k_m & -\kappa & \vdots \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ \vdots & 0 & 0 & 0 & -\kappa & 2\kappa & -\kappa \\ \vdots & 0 & 0 & 0 & 0 & -\kappa & 2\kappa \end{pmatrix} \tag{102}$$

which is of size $(c-1)\times(c-1)$ and

$$U_2^i = \begin{pmatrix} 2\kappa & -\kappa & 0 & \cdots & 0 & 0 \\ -\kappa & 2\kappa & -\kappa & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \vdots & 0 & 0 & -\kappa & 2\kappa & -\kappa \\ \vdots & 0 & 0 & 0 & -\kappa & \kappa \end{pmatrix} \tag{103}$$

which is of size $(N-c)\times(N-c)$. The vector $\boldsymbol{V}$ is composed of d blocks, each given by

$$V^i = \begin{pmatrix} 0 \\ \vdots \\ k_n\mu_n \\ \vdots \\ k_m\mu_m \\ \vdots \\ \kappa x^i \\ \kappa x^i \\ \vdots \end{pmatrix}. \tag{104}$$

To find the determinant $\det\tilde{U}_1^i$, we use eq.(67):

$$\det U_1^i = \theta_{c-1} = \kappa^{c-3}\left(\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_nk_m\right) \tag{105}$$

and using eq.(61), we get

$$\det U_2^i = \kappa^{N-c}. \tag{106}$$

The (c-1,c-1) term of the inverse matrix is given by

$$\begin{aligned} (U^i)^{-1}_{c-1,c-1} &= \frac{\theta_{c-2}\phi_{c+1}}{\det(U_2^i)\det(U_1^i)} \\ &= \frac{\kappa^2 + ((c-n-1)k_n + (c-m-1)k_m)\kappa + (m-n)(c-m-1)k_nk_m}{\kappa\left(\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_nk_m\right)} \\ &= \frac{1}{\kappa} - \frac{\kappa(k_n+k_m) + (m-n)k_nk_m}{\kappa\left(\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_nk_m\right)}, \end{aligned} \tag{107}$$

where we used eqs.(72),(67). For simplicity we name the indices of the matrix U $(i = 1, 2..c-1, c+1, ..N)$

$$(U^i)^{-1}_{c+1,c+1} = \frac{\theta_{c-1}\phi_{c+2}}{\det(U_2^i)\det(U_1^i)} = \frac{1}{\kappa}, \tag{108}$$

$$(U^i)^{-1}_{c-1,n} = \frac{(-1)^{c+n-1}(-\kappa)^{c-n-1}\theta_{n-1}}{\det(U^i_1)} = \frac{\kappa}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m} \quad (109)$$

and

$$(U^i)^{-1}_{c-1,m} = \frac{(-1)^{c+m-1}(-\kappa)^{c-m-1}\theta_{m-1}}{\det(U^i_1)} = \frac{\kappa + (m-n)k_n}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m} \quad (110)$$

We estimate the term in the parenthesis in eq.(100) by substituting eqs.(107)-(110)

$$\begin{aligned} J^i &= 2x^i - \sum_l V^i_l \left((U^i)^{-1}_{c-1,l} + (U^i)^{-1}_{c+1,l} \right) \\ &= 2x^i - \left(\kappa x^i (U^i)^{-1}_{c-1,c-1} + \kappa x^i (U^i)^{-1}_{c+1,c+1} + k_n \mu_n (U^i)^{-1}_{c-1,n} + k_m \mu_m (U^i)^{-1}_{c+1,n} \right) \\ &= 2x^i - \kappa x^i \left(\frac{2}{\kappa} - \frac{(k_n + k_m)\kappa + (m-n)k_n k_m}{\kappa \left(\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m\right)} \right) \\ &- \frac{\kappa k_n \mu^i_n + (\kappa + (m-n)k_n) k_m \mu^i_m}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m} \\ &= x^i \left(\frac{(k_n + k_m)\kappa + (m-n)k_n k_m}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m} \right) \\ &- \frac{\kappa k_n \mu^i_n + (\kappa + (m-n)k_n) k_m \mu^i_m}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m}. \end{aligned} \quad (111)$$

We introduce into expression eq.(111) the position of monomer c with respect to its mean position ($\tilde{\boldsymbol{x}} = \boldsymbol{x} - \langle R_c \rangle$) (eq.99)

$$\begin{aligned} J^i &= \left[\tilde{x^i} + \frac{1}{k(m-n) + 2\kappa} \sum_i \mu^i_n \kappa + \mu^i_m (\kappa + (m-n)k) \right] \\ &\times \left(\frac{(k_n + k_m)\kappa + (m-n)k_n k_m}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m} \right) \\ &- \frac{\kappa k_n \mu^i_n + (\kappa + (m-n)k_n) k_m \mu^i_m}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m} \\ &= \tilde{x^i} \frac{(k_n + k_m)\kappa + (m-n)k_n k_m}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m}. \end{aligned} \quad (112)$$

Finally, substituting eq.(112) into expression (100) we find

$$\lim_{\Delta t \to 0} \mathbb{E}\left\{ \frac{\boldsymbol{R}_c(t + \Delta t) - \boldsymbol{R}_c(t)}{\Delta t} | \tilde{\boldsymbol{x}} \right\} = -D k_{c,nm} \tilde{\boldsymbol{x}}, \quad (113)$$

where

$$k_{c,nm} = \kappa \frac{\kappa(k_n + k_m) + (m-n)k_n k_m}{\kappa^2 + ((c-n)k_n + (c-m)k_m)\kappa + (m-n)(c-m)k_n k_m}. \quad (114)$$

2 Computing the auto-correlation function of the tagged locus when a force is applied

We now study the effect of the potential well on the second moment of the locus dynamics by calculating its auto-correlation function. The external potential can be written in term of the modes $\boldsymbol{u}_p$

$$U_{\text{ext}}(\boldsymbol{R}_n) = \frac{1}{2}k(\boldsymbol{\mu} - \boldsymbol{R}_n)^2 = \frac{1}{2}k\left(\boldsymbol{\mu} - \sum_{p=0}^{N-1} \alpha_p^n \boldsymbol{u}_p\right)^2, \tag{115}$$

where we used the orthogonal transformation which diagonalize the Rouse potential [21]

$$\alpha_p^c = \begin{cases} \sqrt{\frac{1}{N}}, & p = 0 \\ \sqrt{\frac{2}{N}} \cos\left((c - 1/2)\frac{p\pi}{N}\right), & \text{otherwise.} \end{cases} \tag{116}$$

In the presence of the potential, the Langevin equations for the modes are

$$\frac{d\boldsymbol{u}_p}{dt} = D\left(k\alpha_p^n \boldsymbol{\mu} - ((\alpha_p^n)^2 k + \tilde{\kappa}_p)\boldsymbol{u}_p\right) - Dk\alpha_p^n \sum_{q=0, q\neq p}^{N-1} \alpha_q^n \boldsymbol{u}_q + \sqrt{2D}\frac{d\tilde{\boldsymbol{w}}_p}{dt}, \tag{117}$$

with $\tilde{\kappa}_p = 4\kappa \sin\left(\frac{p\pi}{2N}\right)^\beta$ $(\beta > 1)$ [24]. Thus, the potential on monomer n couples the dynamical equations for the modes. When the strength of the coupling term is relatively weak $(\alpha_p^n)^2 k \ll \tilde{\kappa}_p$, we can neglect the coupling term. This will be the case for the higher modes given that $k < \kappa$ and N large. In this case, the Langevin equations 117 can be approximated by

$$\begin{aligned} \frac{d\boldsymbol{u}_p}{dt} &= D\left(k\alpha_p^n \boldsymbol{\mu} - ((\alpha_p^n)^2 k + \tilde{\kappa}_p)\boldsymbol{u}_p\right) + \sqrt{2D}\frac{d\tilde{\boldsymbol{w}}_p}{dt}, \\ \frac{d\boldsymbol{u}_0}{dt} &= D_{\text{cm}}\alpha_0^n \left(\boldsymbol{\mu} - \alpha_0^n \boldsymbol{u}_0\right) + \sqrt{2D_{\text{cm}}}\frac{d\tilde{\boldsymbol{w}}_0}{dt}. \end{aligned} \tag{118}$$

We denote $b_p = (\alpha_p^n)^2 k + \tilde{\kappa}_p$. The solutions of the eqs.(118) is

$$\boldsymbol{u}_p(t) = \boldsymbol{u}_p(0)e^{-Db_p t} + \frac{k\alpha_p^n \boldsymbol{\mu}}{b_p}\left(1 - e^{-Db_p t}\right) + \sqrt{2D_p}\int_0^t e^{Db_p(s-t)} d\tilde{\boldsymbol{w}}_p(s), \tag{119}$$

while the expectation values are

$$\begin{aligned} \langle \boldsymbol{u}_p(t) \rangle &= \boldsymbol{u}_p(0)e^{-Db_p t} + \frac{k\alpha_p^n \boldsymbol{\mu}}{b_p}\left(1 - e^{-Db_p t}\right), \\ \langle \boldsymbol{u}_0(t) \rangle &= \boldsymbol{u}_0(0)e^{-D_{\text{cm}}k(\alpha_0^n)^2 t} + \frac{\boldsymbol{\mu}}{\alpha_0^n}\left(1 - e^{-D_{\text{cm}}k\alpha_0^n t}\right). \end{aligned} \tag{120}$$

The time auto-correlation function of mode p in the spatial direction i is [26]

$$\begin{aligned} &\left\langle \left[u_p^i(t_1) - \langle u_p^i(t_1)\rangle\right]\left[u_p^i(t_2) - \langle u_p^i(t_2)\rangle\right]\right\rangle = 2D\left\langle \int_0^{t_1} e^{Db_p(s_1-t_1)} d\omega_p^i(s_1) \int_0^{t_2} e^{Db_p(s_2-t_2)} d\omega_p^i(s_2)\right\rangle \\ &= \frac{1}{b_p}\left(e^{-Db_p(t_2-t_1)} - e^{-Db_p(t_1+t_2)}\right) \approx \frac{1}{(\alpha_p^n)^2 k + \tilde{\kappa}_p} e^{-D((\alpha_p^n)^2 k + \tilde{\kappa}_p)(t_2-t_1)}, \end{aligned} \tag{121}$$

for $t_2 > t_1$, where we approximated for long times and introduced back the expression for b_p. Similarly, for the center of mass we have

$$\langle \left[u_0^i(t_1) - \langle u_0^i(t_1)\rangle\right] \left[u_0^i(t_2) - \langle u_0^i(t_2)\rangle\right]\rangle \approx \frac{1}{(\alpha_0^n)^2 k} e^{-D_{\rm cm}(\alpha_0^n)^2 k(t_2-t_1)}. \quad (122)$$

Thus, the auto-correlation function of monomer c is

$$\langle [\boldsymbol{R}_c(t_1) - \langle \boldsymbol{R}_c(t_1)\rangle] [\boldsymbol{R}_c(t_2) - \langle \boldsymbol{R}_c(t_2)\rangle]\rangle = \frac{d}{k} e^{-D(\alpha_0^n)^2 k(t_2-t_1)} + \sum_{p=1}^{N-1} \frac{d(\alpha_p^c)^2}{(\alpha_p^n)^2 k + \tilde{\kappa}_p} e^{-D((\alpha_p^n)^2 k + \tilde{\kappa}_p)(t_2-t_1)}, \quad (123)$$

where $(\alpha_0^n)^2 = \frac{1}{N}$.

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