Lecture 12: Polymer Dynamics

Imagine observing the motion of a tagged point on the DNA of a cell. What motion do we expect? How is polymer motion different from the motion of a particle that moves freely (Figure 1A)?

A common feature of any motion in the cell is randomness. If you repeat the experiment many times, you get different trajectories. The coordinate $x(t)$ at time t, given that you started at $x(0)$, will be a random variable with a distribution $p(x(t) \mid x(0))$ called the transition probability (Figure 1B). The square of the width of the distribution is called the mean-squared displacement (MSD) and it measures how far the particle has moved on average

$$\mu(t) = \left\langle (x(t) - x(0))^2 \right\rangle . \tag{1}$$

To describe the motion of our polymer-bound particle, we choose to study the MSD as a function of time. It is a classical result that the MSD of a freely diffusing particle grows linearly with time, $\mu(t) = 2Dt$, where D is the diffusion constant. In general, we could envision an MSD of the form $\mu(t) = 2Dt^{\alpha}$. Will the DNA-bound particle be superdiffusive ($\alpha > 1$), subdiffusive ($\alpha < 1$), or diffusive ($\alpha = 1$) (Figure 1C)? We might expect the DNA to somehow constrain the motion, leading to subdiffusion, but what will be the value of α?

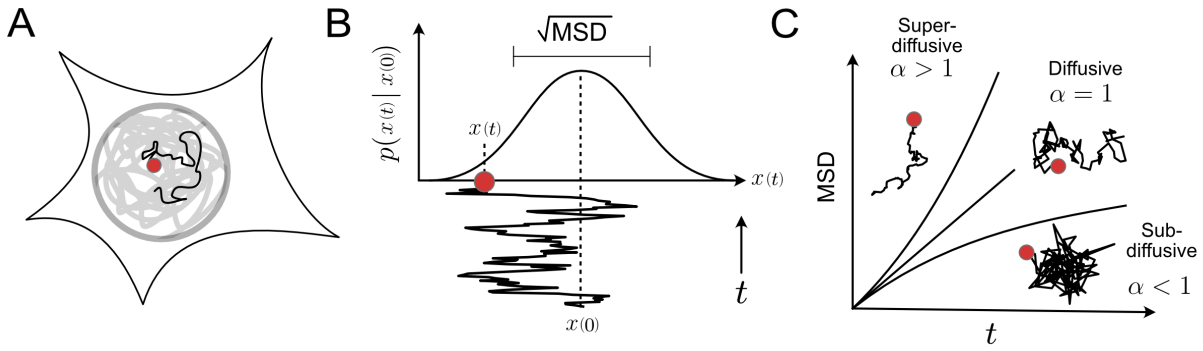


Figure 1: A) A cell with a tagged particle on the DNA moving in the nucleus. B) Graphical depiction of the transition probability. C) Three MSD curves with different exponents, defining the different diffusion regimes.

The overdamped Langevin equation

To model the motion of a point on a polymer, we need an equation of motion for microscopic particles in a fluid. A particle in a fluid experiences a drag force that is proportional to its velocity,

and Newton's law of motion then reads

$$\dot{v} = \frac{1}{m}\left(F^{\text{external}} - \gamma v\right), \qquad \dot{x} = v\,. \tag{2}$$

Microscopic particles in biological systems are typically very small so the drag force is very large compared to the inertia. A way to see this is to compute the velocity relaxation after an external force is turned off. The solution to the equation of motion is then ($F^{\text{external}} = 0$)

$$\begin{aligned} v(t) &= v(0)e^{-\frac{\gamma}{m}t} \\ x(t) &= x(0) + \frac{m}{\gamma}v(0)\left(1 - e^{-\frac{\gamma}{m}t}\right). \end{aligned} \tag{3}$$

The characteristic coasting time is therefore $\tau_c = \frac{m}{\gamma}$ and the total displacement is

$$\Delta x = \int_0^\infty v(t)\mathrm{d}t = \frac{m}{\gamma}v(0)\,. \tag{4}$$

To get a sense for the scales, take a bacterium of radius $R = 1\,\mu$m and mass $m = 10^{-15}\,$kg moving at swimming speed $v = 10\,\mu$m/s in water with viscosity $\eta = 10^{-3}\,$Pa s. The drag coefficient is then (Stokes' law)

$$\gamma = 6\pi\eta R \approx 2\cdot 10^{-8}\,\text{kg/s}\,, \tag{5}$$

giving a coasting time of

$$\tau_c = \frac{m}{\gamma} \approx 0.05\mu\text{s}\,. \tag{6}$$

and a coasting distance of

$$\Delta x = \frac{m}{\gamma}v(0) \approx 5\cdot 10^{-13}\,\text{m} = 0.005\text{Å}\,. \tag{7}$$

This is a much bigger and faster object than the tagged particle we have in mind, and yet it coasts for a distance that is less than the size of a single atom before coming to a stop! The motion of microscopic particles in a fluid is therefore very overdamped, and we can always take velocity to be at steady state with the forces acting on the particle (i.e. $\dot{v} = 0$). This gives the overdamped Langevin equation

$$\dot{x} = \frac{1}{\gamma}F^{\text{external}}\,. \tag{8}$$

Thermal motion and the Langevin equation

While damping transfers energy to the bath, the particle also receives energy from the bath through random collisions with the fluid. We therefore envision two kinds of external forces on the particle, one which is deterministic and one which is random

$$\dot{x} = \frac{1}{\gamma}\left(F^{\text{deterministic}} + F^{\text{thermal}}\right). \tag{9}$$

The simplest choice for the thermal force is a Gaussian path with zero mean and no correlations in space and time

$$F^{\text{thermal}} = \xi(t)\,, \quad \langle\xi(t)\rangle = 0\,, \quad \left\langle\xi(t)\xi(t')\right\rangle = \sigma^2\delta(t-t')\,. \tag{10}$$

In the absence of an external force, the overdamped Langevin is seen to just state that the position is the integral of the thermal force

$$\dot{x} = \frac{1}{\gamma}\xi(t)\,, \qquad x(t) = x(0) + \frac{1}{\gamma}\int_0^t \xi(t')\,\mathrm{d}t'\,. \tag{11}$$

This is the motion we expect for the particle in the absence of any external forces, and we can compute its MSD from the properties of the noise

$$\begin{aligned}
\mu(t) &= \left\langle (x(t) - x(0))^2 \right\rangle \\
&= \frac{1}{\gamma^2}\int_0^t \int_0^t \langle \xi(u)\xi(v)\rangle \,\mathrm{d}u\,\mathrm{d}v \\
&= \frac{\sigma^2}{\gamma^2}\int_0^t \int_0^t \delta(u-v)\,\mathrm{d}u\,\mathrm{d}v \\
&= \frac{\sigma^2}{\gamma^2}\int_0^t \mathrm{d}v \\
&= \frac{\sigma^2}{\gamma^2} t\,,
\end{aligned} \tag{12}$$

from which we see that the particle undergoes diffusion with diffusion constant $D = \sigma^2/(2\gamma^2)$. The noise strength σ^2 is therefore related to the diffusion constant. This is a manifestation of the fluctuation-dissipation theorem, which states that the strength of the fluctuations is related to the dissipation in the system. In particular, we can write

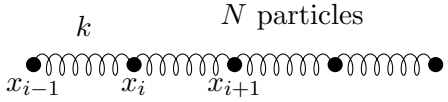
$$\sigma^2 = 2D\gamma^2 = 2k_\mathrm{B}T\gamma\,, \tag{13}$$

where we used the Einstein relation $D = k_\mathrm{B}T/\gamma$ to relate the diffusion constant to the temperature of the bath. The Langevin equation is therefore a model for a particle in a fluid that experiences both drag and random kicks from the surrounding fluid. We can now write the equation of motion for our tagged particle in a thermal bath as

$$\dot{x} = \frac{1}{\gamma}F^{\text{deterministic}} + \sqrt{2D}\,\eta(t)\,, \qquad \langle \eta(t)\rangle = 0\,, \qquad \left\langle \eta(t)\eta(t')\right\rangle = \delta(t-t')\,. \tag{14}$$

The Rouse model

The chromatin in the nucleus is tightly packed. From the previous models described in the class, a natural null model might therefore be the compact globule. For this reason, we expect repulsive interactions to be screened, and the end-to-end distance of the polymer might approximately have random walk statistics. The simplest model for the dynamics of such a polymer is called the Rouse model, which is obtained by modeling the polymer as a point on a chain consisting of N beads connected by springs with spring constant k.



The force on the ith bead on the chain has a term from each neighbor. Denoting the position of the ith bead by $x_i(t)$, the deterministic force on the ith bead is

$$\begin{aligned} F_i^{\text{deterministic}} &= F_i^- + F_i^+ \\ &= -k\big[(x_i(t) - x_{i-1}(t)) + (x_i(t) - x_{i+1}(t))\big] \\ &= -k\big[2x_i(t) - x_{i-1}(t) - x_{i+1}(t)\big]\,, \end{aligned} \tag{15}$$

yielding the following Langevin equation for the ith bead

$$\dot{x}_i = -\frac{k}{\gamma}\left(2x_i - x_{i-1} - x_{i+1}\right) + \sqrt{2D}\,\eta_i\,, \qquad \langle\eta\rangle = 0\,, \qquad \big\langle \eta_i(t)\eta_j(t')\big\rangle = \delta_{ij}\delta(t-t')\,. \tag{16}$$

This couples the position of our particle of interest to the positions of its neighbors, and in time, to the positions of all the other particles on the chain. In general, such a system can be solved by transforming to the normal modes of the system. To focus on the essential physics, we shall instead solve the system in the continuum limit.

In the continuous polymer limit, the discrete index i becomes a continuous parameter s and the coupling can be Taylor expanded to give a second derivative in s

$$\begin{aligned} F^{\text{deterministic}}(s) &= -k\left[2x_s - \left(x_s - \partial_s x_s + \frac{1}{2}\partial_s^2 x_s\right) - \left(x_s + \partial_s x_s + \frac{1}{2}\partial_s^2 x_s\right)\right] + \mathcal{O}(\partial_s^3 x_s) \\ &= k\partial_s^2 x_s + \mathcal{O}(\partial_s^3 x_s)\,, \end{aligned} \tag{17}$$

which gives the following Langevin equation for the Rouse model in the continuum limit

$$\dot{x}_s = \frac{k}{\gamma}\partial_s^2 x_s + \sqrt{2D}\,\eta_s\,, \qquad \langle\eta\rangle = 0\,, \qquad \big\langle \eta_s(t)\eta_{s'}(t')\big\rangle = \delta(s-s')\delta(t-t')\,. \tag{18}$$

You may recognize this as a diffusion equation in the backbone coordinate s with a random forcing term.

We can now diagonalize the laplacian straight-forwardly with a Fourier transform in s:

$$x_s = \int_{-\infty}^{\infty} \frac{\mathrm{d}q}{2\pi}\, x_q e^{-iqs}\,, \qquad \eta_q = \int_{-\infty}^{\infty} \mathrm{d}s\, e^{iqs}\eta_s\,. \tag{19}$$

Then

$$\partial_s^2 \to (-iq)^2 = -q^2\,, \tag{20}$$

and the noise satisfies

$$\begin{aligned} \langle\eta_q\rangle &= 0\,, \\ \big\langle \eta_q(t)\eta_{q'}(t')\big\rangle &= \int_{-\infty}^{\infty}\mathrm{d}s\int_{-\infty}^{\infty}\mathrm{d}s'\langle\eta_s(t)\eta_{s'}(t')\rangle e^{iqs}e^{iq's'} \\ &= \int_{-\infty}^{\infty}\mathrm{d}s\int_{-\infty}^{\infty}\mathrm{d}s'\delta(s-s')\delta(t-t')e^{iqs}e^{iq's'} \\ &= \delta(t-t')\int_{-\infty}^{\infty}\mathrm{d}s\, e^{i(q+q')s} \\ &= 2\pi\delta(t-t')\delta(q+q')\,. \end{aligned} \tag{21}$$

Under these transformations, the Rouse model becomes a set of independent differential equations for each mode q:

$$\dot{x}_q = -\frac{kq^2}{\gamma} x_q + \sqrt{2D}\,\eta_q\,. \tag{22}$$

What this equation says is that the dynamics of mode q is a competition between a restoring force that wants to bring the mode back to zero and a random force that kicks it around. The correlation time of mode q is given by $\tau_q = \gamma/(kq^2)$, and so modes with small q (long wavelength) relax slower than modes with large q (short wavelength). This makes sense given the fact that the dynamics of the Rouse model really is a diffusion in the backbone coordinate as seen from the definining equation (18). The larger wavelength modes (small q) are more weakly bound than shorter wavelength modes (large q), giving rise to larger fluctuations in the long wavelength modes since the noise strength is independent of q.

The solution is obtained by integrating the equation from $-\infty$ to t in which case the initial condition is forgotten and we get:

$$x_q(t) = \sqrt{2D}\int_{-\infty}^{t} e^{-\frac{kq^2}{\gamma}(t-t')}\eta_q(t')\,\mathrm{d}t'\,. \tag{23}$$

Transforming back to the s coordinate, we get

$$x_s(t) = \sqrt{2D}\int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\int_{-\infty}^{t}\mathrm{d}t'\,e^{-\frac{kq^2}{\gamma}(t-t')-iqs}\eta_q(t')\,. \tag{24}$$

This is a Gaussian random path with moments

$$\langle x_s\rangle = 0 \tag{25}$$

and, ($t \geq 0$),

$$\begin{aligned}
\langle x_s(t)x_{s'}(0)\rangle &= 2D\int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\int_{-\infty}^{\infty}\frac{\mathrm{d}q'}{2\pi}\int_{-\infty}^{t}\mathrm{d}u\int_{-\infty}^{0}\mathrm{d}u'\,e^{-\frac{k}{\gamma}[q^2(t-u)-q'^2u']-iqs-iq's'}\langle\eta_q(u)\eta_{q'}(u')\rangle\\
&= 2D\int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\int_{-\infty}^{\infty}\mathrm{d}q'\int_{-\infty}^{t}\mathrm{d}u\int_{-\infty}^{0}\mathrm{d}u'\,e^{-\frac{k}{\gamma}[q^2(t-u)-q'^2u']-iqs-iq's'}\delta(q+q')\delta(u-u')\\
&= 2D\int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\int_{-\infty}^{0}\mathrm{d}u\,e^{-\frac{kq^2}{\gamma}(t-2u)-iq(s-s')}\\
&= 2D\int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}e^{-\frac{kq^2}{\gamma}t-iq(s-s')}\int_{-\infty}^{0}\mathrm{d}u e^{\frac{2kq^2}{\gamma}u}\\
&= \frac{D\gamma}{k}\int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\frac{1}{q^2}e^{-\frac{kq^2}{\gamma}t-iq(s-s')}\,.
\end{aligned} \tag{26}$$

Formally, eq. (26) is infinite due to the $1/q^2$ factor in the integrand giving arbitary large amplitudes to the small-q, long-wavelength modes. Physically, this comes from the fact that we have an inifinately long chain (not from it being continuous as we shall see later). This is not a physical problem since we are only interested in differences in position, which are finite.

To see how this plays out, we begin by assessing the static properties of the chain. The key quantity of interest is the average distance between a point at s and a point at s' on the chain

$$R^2(s-s') \equiv \langle(x_s - x_{s'})^2\rangle = 2\left(\langle x_s^2\rangle - \langle x_s x_{s'}\rangle\right)\,, \tag{27}$$

where we used the translational invariance of the chain in s. Inserting eq. (26) with $t = 0$, we get

$$\begin{aligned} R^2(s-s') &= 2\left(\langle x_s^2\rangle - \langle x_s x_{s'}\rangle\right) \\ &= 2\frac{D\gamma}{k}\int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\frac{1-e^{-iq(s-s')}}{q^2}\,. \end{aligned} \tag{28}$$

The trick to evaluate this integral is to differentiate it with respect to $s - s'$. Defining the integral

$$I_R(r) = \int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\,\frac{1-e^{-iqr}}{q^2}\,, \qquad r = s - s'\,, \tag{29}$$

we can compute its derivative twice to get a simple integral

$$\frac{\mathrm{d}^2 I_R}{\mathrm{d}r^2} = \int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}e^{-iqr} = \delta(r)\,. \tag{30}$$

Since $I_R(r)$ is even and $I_R(0) = 0$. Integrating twice gives

$$\begin{aligned} \frac{\mathrm{d}I_R}{\mathrm{d}r} &= \frac{1}{2}\,\mathrm{sgn}(r) \\ I_R(r) &= \frac{|r|}{2}\,. \end{aligned} \tag{31}$$

Inserting this back into the expression for $R^2(s)$, we get

$$R^2(s-s') = \frac{D\gamma}{k}|s-s'|\,. \tag{32}$$

This result says that the mean square distance between two points on the polymer scales linearly with the amount of polymer connecting them. The Rouse model statistics are therefore the continuum analog of a random walk. From eq. (32), we may read off the Kuhn length to be $b = \sqrt{D\gamma/k}$ which essentially represents the expected distance between one pair of Rouse monomers.

The Rouse MSD

We are now in a position to compute the MSD for the Rouse model. For the tagged point s on the chain, we have

$$\mu(t) = \left\langle (x_s(t) - x_s(0))^2\right\rangle = 2\left(\left\langle x^2\right\rangle - \langle x_s(t)x_s(0)\rangle\right)\,. \tag{33}$$

Again, inserting eq. (26), now for $s = s'$ in both terms and also $t = 0$ for $\langle x^2\rangle$, we get

$$\begin{aligned} \mu(t) &= 2\left(\left\langle x^2\right\rangle - \langle x_s(t)x_s(0)\rangle\right) \\ &= 2\frac{D\gamma}{k}\int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\frac{1-e^{-\frac{kq^2}{\gamma}t}}{q^2}\,. \end{aligned} \tag{34}$$

Write

$$\mu(t) = \frac{2D\gamma}{k}I(\tau)\,, \qquad \tau = \frac{kt}{\gamma}\,, \tag{35}$$

where

$$I(\tau) = \int_{-\infty}^{\infty}\frac{\mathrm{d}q}{2\pi}\frac{1}{q^2}\left(1-e^{-\tau q^2}\right)\,. \tag{36}$$

We again perform the integral by differentiating under the integral sign. Differentiate with respect to τ:

$$\frac{\mathrm{d}I}{\mathrm{d}\tau} = \int_{-\infty}^{\infty} \frac{\mathrm{d}q}{2\pi} e^{-\tau q^2} = \frac{1}{2\pi}\sqrt{\frac{\pi}{\tau}} = \frac{1}{2}\sqrt{\frac{1}{\pi\tau}}\,. \tag{37}$$

which can be integrated to give

$$I(\tau) = \sqrt{\frac{\tau}{\pi}}\,. \tag{38}$$

Inserting this back into the expression for $\mu(t)$, we get

$$\boxed{\mu(t) = \frac{2D\gamma}{k}\sqrt{\frac{kt}{\pi\gamma}} = 2D\sqrt{\frac{t\gamma}{\pi k}}.} \tag{39}$$

With that, we have our answer. The polymer-attached particle is seen to diffuse with a *subdiffusive* MSD with $\alpha = 1/2$: This is a strikingly different dynamical behavior than the freely diffusing particle, and one way to reason about it is that the motion of the particle is hindered by the points connected to it. As the particle diffuses, the effective diffusion constant

$$D_{\text{eff}} = \frac{1}{2}\frac{\mathrm{d}\mu}{\mathrm{d}t} = \frac{D\gamma}{k}\frac{\mathrm{d}I}{\mathrm{d}\tau}\frac{\mathrm{d}\tau}{\mathrm{d}t} = \frac{D}{2}\sqrt{\frac{1}{\pi\tau}}\,, \tag{40}$$

is seen to get diffusively smaller with time. Essentially $n(t) = \sqrt{\tau}$ can be thought of as the stretch of polymer which co-moves with the point at time t. The point moves as if it grows larger and larger as it diffusively (along the backbone, not in space!) correlates with more and more of the chain giving an effectively decaying diffusion coefficient

$$D_{\text{eff}}(t) \sim \frac{D}{n(t)}\,. \tag{41}$$

Real chains

No chain is of course infinite, nor continuous. Here we treat superficially how our results differ from the discrete bead model we started with. It differs in two key respects: the finite length of the chain and the finite size of the monomers. We treat these two effects in turn.

1. Finite length: whole coil diffusion after the Rouse time

The finite chain turns the Fourier transform into a discrete cosine transform (cosine rather than Fourier series due to the boundary conditions), and the wave number is therefore discrete.

$$\int \frac{\mathrm{d}q}{2\pi} \to \frac{1}{N}\sum_{n=0}^{\infty}, \qquad q_n = \frac{\pi n}{N}\,. \tag{42}$$

Thus

$$\mu(t) \approx \frac{2D\gamma}{kN}\sum_{n=0}^{\infty}\frac{N^2}{\pi^2 n^2}\left(1 - e^{-\frac{k\pi^2 n^2}{N^2\gamma}t}\right)\,. \tag{43}$$

From this expression it can be seen that there is a maximal time-scale

$$t_R = \frac{\gamma}{k\pi^2} N^2 \,, \qquad \text{i.e. when } \sqrt{\tau} \sim N \,, \tag{44}$$

after which all the modes will have relaxed and the exponential terms are zero. This time is referred to as the Rouse time, and after it, the MSD becomes

$$\begin{aligned}
\lim_{t \gg t_R} \mu(t) &\approx \frac{2D\gamma}{kN} \left[\frac{N^2}{\pi^2 n^2} \left(1 - e^{-\frac{k\pi^2 n^2}{N^2 \gamma} t} \right) \right]_{n \to 0} + \frac{2D\gamma}{kN} \sum_{n=1}^{\infty} \frac{N^2}{\pi^2 n^2} \left(1 - 0 \right) \\
&\approx \frac{2D\gamma}{kN} \left[\frac{N^2}{\pi^2 n^2} \left(\frac{k\pi^2 n^2}{N^2 \gamma} t \right) \right]_{n \to 0} + \frac{2D\gamma}{kN} \sum_{n=1}^{\infty} \frac{N^2}{\pi^2 n^2} \\
&= \frac{2D}{N} t \text{const.} \,.
\end{aligned} \tag{45}$$

This is a diffusive MSD! The constant is there to make it continuous with the previous regime, and the diffusion constant has exactly the scaling we would have predicted from the effective diffusion constant picture in eq. (41) when inserting $n(t) = N$. We therefore see that the effect of a finite chain is to introduce an upper time-scale after which the whole chain moves together as a single object.

2. Finite monomer size: monomer diffusion before feeling the springs

Finite monomer size introduces an upper cutoff rather than a lower cutoff, as the sum can only run up to the number of modes in the chain

$$\mu(t) \approx \frac{2D\gamma}{kN} \sum_{n=0}^{N-1} \frac{N^2}{\pi^2 n^2} \left(1 - e^{-\frac{k\pi^2 n^2}{N^2 \gamma} t} \right) \,. \tag{46}$$

There thus exists a lower time-scale

$$t_0 \sim \frac{\gamma}{k} \,, \qquad \text{when } \sqrt{\tau} \sim 1 \,, \tag{47}$$

below which all the modes have yet to equilibrate and we may expand all exponentials for small t to get

$$\begin{aligned}
\mu(t) &\approx \frac{2D\gamma}{kN} \sum_{n=0}^{N} \frac{N^2}{\pi^2 n^2} \left(1 - e^{-\frac{k\pi^2 n^2}{N^2 \gamma} t} \right) \\
&= \frac{2D\gamma}{kN} \sum_{n=0}^{N} \frac{N^2}{\pi^2 n^2} \left(\frac{k\pi^2 n^2}{N^2 \gamma} t \right) + \mathcal{O}(t^2) \qquad (48) \\
&= 2Dt \,. \qquad (49)
\end{aligned}$$

i.e. monomer diffusion at short times before the beads feel each other. Again, we predict this from the effective diffusion constant picture in eq. (41) when inserting $n(t) = 1$.

Putting it all together

So what is the motion of a point on DNA? According to the Rouse model, we expect the MSD to have three regimes: At short times, the point moves with free diffusion as it has yet to feel the attachment to the neighboring points. Once $\tau \sim 1$, the point starts to feel the springs and moves subdiffusively with $\alpha = 1/2$ as it correlates with more and more of the chain. Finally, after the Rouse time, the whole chain moves together and the point again moves diffusively but with a smaller diffusion constant that is $1/N$ times the monomer diffusion constant. The MSD is therefore

$$\mu(t) \sim \begin{cases} 2Dt, & t \ll t_0, \\ 2D\sqrt{\dfrac{t\gamma}{\pi k}}, & t_0 \ll t \ll t_R, \\ \dfrac{2D}{N}t + \text{const.}, & t \gg t_R\,. \end{cases} \tag{50}$$

Compared to the freely diffusing particle, we therefore have significantly slower motion at intermediate times, which for large polymers may last for a long time.

