Dynamics of the swelling or collapse of a homopolymer

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Abstract

We study the dynamics of a polymer when it is quenched from a $\theta$ solvent into a good or bad solvent by means of a Langevin equation. The variation of the radius of gyration is studied as a function of time. For the first stage of collapse or swelling, the characteristic time-scale is found to be independent of the number of monomers. Other scaling laws are derived for the diffusion regime at larger times. Although the present model is solved only for homopolymers and doesn’t include hydrodynamic interactions, these results may be a first step towards the understanding of the early stages of protein folding.

Under certain conditions (such as a temperature decrease or exposure to a bad solvent), homopolymers undergo a collapse (coil-globule) transition. This has been studied quite extensively, and it has regained some interest since it may be the simplest model to describe the first stages of protein folding. Few experimental data are available [1] [2], but a lot of theoretical work and computer simulations have been done, leading to a large diversity of results. Although the thermodynamic properties of the homopolymer problem have been

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quite well understood, there is at present no analytical derivation of the kinetics laws for the polymer collapse. Since one might expect the first stages of protein folding to be dominated by non-specific hydrophobic forces, this phenomenon should be quite similar to the collapse of a homopolymer chain. It is thus highly desirable to develop a general analytical technique in order to study the kinetics of polymer collapse.

According to de Gennes’ theory [3], the process of collapse of a flexible coil leads to the formation of crumples on a minimal scale along the linear chain, which thickens and shortens under diffusion of the monomers, then forms new crumples of growing scale, until the final state of a compact globule is reached; the total time of collapse is estimated as

$$\tau_c = \frac{\eta a^3}{k_B \theta} \left| \Delta T \right| \theta N^2$$

where $\eta$ is the viscosity of the solvent, $\theta$ is the $\theta$ temperature, $a$ is the monomer size and $\Delta T$ is the temperature quench. This time $\tau_c$ has a very strong dependence on molecular weight. For the case of proteins (see reference [2]), $N = 300$, which yields a collapse time of $\tau_c \sim 1\ \mu s$.

In a revised model, A.Buguin et al. [4] consider a different mechanism, in two steps: first a fast formation of ”pearls” along the chain, followed by a slower stage of compaction.

Grosberg et al. [5] have included the role of self entanglement to de Gennes’ model, and consider a two stage mechanism: first a collapse leading to a crumpled globule with characteristic time $\sim N^2$, and then a chain knotting driven by reptation with a longer characteristic time $\sim N^3$.

Monte Carlo studies (Ostrowsky&Bar-Yam [6], Milchev&Binder [7]) and Langevin dynamics simulations (Byrne et al. [8]) lead to diverging interpretations concerning the mechanisms of collapse.

In a series of articles, Timoshenko et al. [9] have developed an alternative theory based on a self-consistent method using Langevin equations that can be analyzed numerically; kinetics laws for the collapse of a homopolymer are obtained with or without hydrodynamics, at early and later stages.
Experimentation in this field is quite difficult since one has to work in a very dilute regime in order to avoid aggregation of chains and observe a collapse. Experiments by Chu et al. [1] on polystyrene in cyclohexane reveal a two-stage kinetics of approximately equal times. The most promising experiments are those by Chan et al. [2] who study sub-millisecond protein folding by ultra-rapid mixing; based on optical techniques, these experiments can monitor folding up to the microsecond time-scale.

In the following, we shall present an analytical method to study the kinetics of a homopolymer in a \( \Theta \) solvent when it is quenched into good solvent conditions (swelling into a coil) or into bad solvent conditions (collapse into a globule).

We consider a homopolymer chain in a \( \Theta \) solvent - i.e a Gaussian coil- consisting of \( N \) monomers, obeying the Langevin dynamics as the chain is quenched into good or bad solvent conditions (equations (1) and (2)).

Neglecting hydrodynamical interactions (the Oseen tensor) the equations of motion for the system read:

\[
\frac{\partial r}{\partial t} = -\Gamma_0 \frac{\partial H}{\partial r} + \eta(s, t) \tag{1}
\]

\[
H = \frac{1}{a_0^2} \int_0^N \left( \frac{\partial r}{\partial s} \right)^2 \, ds + V(r(s, t)) \tag{2}
\]

where \( N \) is the total number of monomers, \( r(s, t) \) is the position of monomer \( s \) in the chain, \( a_0 \) is the monomer length and \( \Gamma_0 = \frac{D}{k_BT} \) where \( D \) is the diffusion constant of a monomer in the solvent and \( k_BT \) is the temperature. The intra-molecular as well as intermolecular interactions of the chain are contained in the potential \( V(r(s, t)) \). The thermal noise \( \eta(s, t) \) is a Gaussian noise with zero mean and correlation given by:

\[
< \eta(s, t)\eta(s, t') > = 2D\delta(t - t')
\]

The method consists in finding a virtual homopolymer chain which obeys a simpler Langevin equation, chosen so that its radius of gyration best approaches the radius of gyration of the real chain at each time \( t \).

The virtual chain, defined by \( r^{(v)}(s, t) \) satisfies the Langevin equation:
\[
\frac{\partial r^{(v)}}{\partial t} = -\Gamma_0 \frac{\partial H_v}{\partial r^{(v)}} + \eta(s, t) \tag{3}
\]

\[
H_v = \frac{1}{a^2(t)} \int_0^N \left( \frac{\partial r^{(v)}}{\partial s} \right)^2 \, ds \tag{4}
\]

with the same diffusion constant and noise as the original equation, but with a much simplified Hamiltonian \(H_v\). Indeed this Hamiltonian \(H_v\) represents a Gaussian chain, but with a time dependent Kuhn length \(a(t)\).

Our method is a generalization of Edwards’ Uniform Expansion Model \([10]\) to dynamics. This method consists in calculating the radius of gyration of a polymer in a good solvent by using perturbation theory, and adjusting the simplified Hamiltonian so that the first order perturbation to the radius of gyration vanishes. If \(v\) denotes the excluded volume, the method gives the Flory radius \([11]\) for large \(N\) and agrees with the result of the first-order perturbation expansion for small \(v\). Note that it would seem natural to use the most general quadratic Hamiltonian rather than that of (4), but this was shown by des Cloizeaux \([12]\) to yield the incorrect exponent \(\nu = 2/d\).

Let’s define

\[
\chi(s, t) = r(s, t) - r^{(v)}(s, t)
\]

\[
W = H - H_v
\]

Assuming that (3) is a good approximation to (1), \(\chi(s, t)\) and \(W\) can be regarded as small, and to first order in these quantities, the dynamical equations become:

\[
\frac{\partial r^{(v)}}{\partial t} = \frac{\Gamma_0}{a^2(t)} \frac{\partial^2 r^{(v)}}{\partial s^2} + \eta(s, t) \tag{5}
\]

\[
\frac{\partial \chi}{\partial t} = \frac{\Gamma_0}{a^2(t)} \frac{\partial^2 \chi}{\partial s^2} + \Gamma_0 \left[ \left( \frac{1}{a^2(t)} - \frac{1}{a^2(t)} \right) \frac{\partial^2 r^{(v)}}{\partial s^2} + F(r^{(v)}(s, t)) \right] \tag{6}
\]

where \(F(r(s, t)) = -\frac{\partial V}{\partial r(s, t)}\) is the driving force for the swelling or collapse of the chain.

In this approximation, the radius of gyration of the chain becomes:

\[
R_g = \frac{1}{N} \int_0^N \frac{\partial}{\partial s} \left( r^2(s, t) \right) \, ds \tag{7}
\]

\[
\simeq \frac{1}{N} \int_0^N \left( \frac{\partial}{\partial s} \left( r^{(v)}(s, t) + 2r^{(v)}(s, t)\chi(s, t) \right) \right) \, ds \tag{8}
\]

4
The brackets denote the thermal average (that is an average over the Gaussian noise $\eta(s,t)$). Our approximation consists in choosing the parameter $a(t)$ in such a way that the first order in (8) vanishes:

$$\int_0^N < r^{(v)}(s,t) \chi(s,t) >= 0 \quad (9)$$

or in Fourier coordinates:

$$\sum_{n \neq 0} < \tilde{r}^{(v)}_n(t) \tilde{\chi}^*_n(t) >= 0 \quad (10)$$

where the Fourier transform is given by:

$$\tilde{r}_n(t) = \frac{1}{N} \int_0^N e^{i\omega_n s} r(s,t) ds$$

$$r(s,t) = \sum_{n \neq 0} e^{-i\omega_n s} \tilde{r}_n(t)$$

We have used periodic boundary conditions, so that $\omega_n = \frac{2\pi n}{N}$. In addition, to get rid of the center of mass diffusion, we constrain the center of mass of the system to remain at fixed position, $\bar{r}_0(t) = \tilde{r}^{(v)}_0(t) = \tilde{\chi}_0(t) = 0$.

Equations (5) and (6) can easily be solved in Fourier space. We assume that at time $t = 0$, the chains are in a $\theta$ solvent, so that the initial condition $\{r(s,0)\}$ obeys Gaussian statistics. We choose the initial virtual chain to coincide with the real one, so that $r^{(v)}(s,0) = r(s,0)$ for any $s$. Denoting by $\cdots$ the average over the initial conditions, the correlation function of $r(s,0)$ (in Fourier space) is taken as:

$$\bar{r}_n(0) = 0 \quad (11)$$

$$\bar{r}_m(0) \bar{r}^*_n(0) = \frac{N a_0^2}{4\pi^2 n^2} \delta_{mn} \quad (12)$$

Replacing $\tilde{r}^{(v)}_n(t)$ and $\tilde{\chi}^*_n(t)$ by their expression in (10), and taking thermal and initial condition averages, we obtain an implicit equation for $a(t)$.

This equation can be solved analytically in both limits $t << \tau_R$ (short time limit) and $t >> \tau_R$ (long time limit) where $\tau_R = \frac{N^2 a_0^2}{4\pi^2 D}$ is the Rouse time.
In the following, we neglect all hydrodynamic interactions and consider only two-body and three-body interactions between monomers.

More precisely, for a chain in a good solvent, we consider excluded volume interactions:

$$V(r(s, t)) = \frac{v}{2} \int_0^N ds \int_0^N ds' \delta(r(s, t) - r(s', t))$$

and for a chain in a bad solvent, we take attractive two-body interactions and repulsive three-body interactions:

$$V(r(s, t)) = -V_2(r(s, t)) + V_3(r(s, t))$$

$$V(r(s, t)) = -\frac{v}{2} \int_0^N ds \int_0^N ds' \delta(r(s, t) - r(s', t))$$

$$+ \frac{w}{6} \int_0^N ds \int_0^N ds' \int_0^N ds'' \delta(r(s, t) - r(s', t)) \delta(r(s', t) - r(s'', t)), $$

where $v > 0$ and $w > 0$.

In good solvent conditions, at short times $t \ll \tau$, the radius of gyration increases like a power law, which we recast in the form of a stretched exponential:

$$R_g^2(t) = N a_0^2 e^{\sqrt{t / \tau_c}},$$

where the characteristic time $\tau_c$ is defined below in (19).

For large time $t \gg \tau_R$, the radius of gyration relaxes to its Flory value:

$$R_g(t) \sim N a_0^2 (1 - e^{-\frac{t}{\tau_1}}),$$

with a relaxation time $\tau_1$ given by:

$$\tau_1 \sim N^{\frac{d+8}{4+2}}$$

Note that this relaxation time is much larger than the Rouse time, for dimensions lower than 4. For example in $d = 3$, $\tau_1 \sim N^{\frac{4}{3}}$.

In a bad solvent, at short times $t \ll \tau_R$, the radius of gyration decreases as above:

$$R_g^2(t) = N a_0^2 e^{-\sqrt{t / \tau_c}},$$

(15)
with a characteristic time $\tau_c$ defined in (13) and for large times $t \gg \tau_R$, the radius of gyration relaxes to that of compact globule according to

$$R_g(t) \sim \left(\frac{w}{v}\right)^{\frac{1}{2}} N^{\frac{d}{2}} (1 - e^{-\frac{t}{\tau_2}}),$$  \hfill (16)

where

$$\tau_2 \sim \left(\frac{w}{v}\right)^{\frac{3}{2}} N^{1 + \frac{2}{d}}.$$  

Note that for dimensions larger than 2, the relaxation time is much shorter than the Rouse time. For example in $d = 3$, $\tau_2 \sim N^{\frac{5}{3}}$.

In the two cases discussed above, the dynamic relaxation exponent $z$, relating the relaxation time of the system to its radius of gyration:

$$\tau \sim R_g^z$$  \hfill (17)

satisfies the exponent relation:

$$z = 2 + \frac{1}{\nu}$$  \hfill (18)

This relation was derived by de Gennes [13].

The first stage of the swelling or collapse can be described by a stretched exponential with characteristic time $\tau_c$ given by:

$$\tau_c^{\frac{1}{2}} = \frac{2}{3} \frac{\pi^{\frac{d}{2}} a_0^{d+1}}{\sqrt{2 D \pi v I_d N^{d+1}}}$$  \hfill (19)

where

$$I_d = \int_0^1 du \int_0^1 du' \frac{1}{|u - u'| (1 - |u - u'|)}$$  

with $|u - u'| > \Lambda$

and $\Lambda = 1/N$ is a short distance cut-off.

For $d < 2$, the integral converges for small $\Lambda$, and $I_d$ is independent of $N$. On the other hand, for $d \geq 2$, the integral is infra-red divergent and thus there is an explicit dependence on the cut-off. It is easily seen that this $N$ dependence exactly cancels out the $N$ dependence.
in (19) so that the final characteristic time $\tau_c$ is finite (independent of $N$). In particular, for $d = 3$, we find

$$\tau_c \sim \frac{2\pi^2}{9D} \left( \frac{a_0^3}{v} \right)^2 \left( \frac{a_0}{5.22} \right)^2.$$ 

The typical order of magnitude of this short time collapse can be calculated for a typical protein in water. The diffusion constant of an amino-acid in water is typically $D \sim 10^{-7} \text{cm}^2/\text{s}$ . Taking a monomer length of $a_0 \sim 4\text{Å}$, for a chain of 100 aminoacids, we find a microscopic characteristic time $\tau_c \sim 10^{-9}\text{s}$ (in these conditions, the Rouse time is $\tau_R \sim 4.10^{-6}\text{s}$). Note that in these conditions, the relaxation time $\tau_2$ is of the order of magnitude of the Rouse time. This time is several orders of magnitude lower than other estimates in the literature (see references [14], [2]). The fact that this characteristic time is independent of $N$ shows that in the early stage, the collapse is a very local phenomenon, where nearby monomers aggregate into small domains.

Whereas previous mechanisms relied mainly on pure diffusion, we have introduced here explicit attractive hydrophobic forces for the collapse of the chain. These forces are determinant at the early stages of the process, and make it much faster than pure diffusion.

At larger time scales, we find other scaling laws for the relaxation towards equilibrium (which is either the collapsed globule or the swollen coil within the Flory theory). Let us mention that we find the same relaxation time for the collapse as in Kuznetsov et al. [9], namely ($\tau_2 \sim N^{\frac{4}{3}}$). This time is several orders of magnitude larger than $\tau_c$.

Although in this work we did not take into account the role of hydrodynamic interactions, we expect their effect to be weak, at least at the early stage of the collapse. However, these effects might become important in later stages of folding.

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