

THE KINETICS LAWS FOR POLYMER
COLLAPSE AND BIOPOLYMER FOLDING

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Abstract: We discuss some recent ideas relating to the folding and other conformational transitions of polymers. In particular we emphasize that it is possible to conceive the accompanying kinetic processes as a problem in non-equilibrium statistical mechanics. In this sense it should be possible to develop such methods to deduce the kinetic laws in the vicinity of various conformational transitions. To establish the ideas we first study the well known problem of the collapse transition of a homopolymer. We then turn to conformational transitions in periodic and random copolymers. We offer a brief survey of the status of these ideas in applications to biopolymeric conformational kinetics.

INTRODUCTION

The endeavour to understand the equilibrium aspects of polymer collapse finds its roots to a large degree in Russian science, under the hand of I. M. Lifshitz (Ref. 1) and coworkers. Subsequent works on the collapse or folding process have followed in that same tradition including those of O. Ptitsyn (Ref. 2), A. Yu. Grosberg (Ref. 3) and of E. I. Shakhnovich (Ref. 4). Numerous other fine articles, not mentioned here, have emerged from the Russian school on these matters. It is therefore fitting at a conference where many of the modern Russian scientists in the area are represented that we offer a view of our current thinking on this field.

We aim in this paper to give a brief and rather broad overview of our work on the kinetics of polymer collapse. We caution the reader that we omit many details, referring to the literature for these. Also, as it befits a conference paper we report some work that is far from mature with the aim of stimulating further discussion rather than offering definitive results.

THE KINETICS LAWS FOR POLYMER COLLAPSE

In this section we present the results from some recent theory, simulation, and experimental work that has aimed to uncover the fundamental laws of kinetics across the collapse

transition. We suppress as many details as possible, referring the reader to more full treatments in the literature.

Theoretical Development

The theory that has been developed in this field is based on the Langevin equation, and any hydrodynamic effects that we incorporate are accommodated by leading orders of the Oseen tensor. Now, beginning from this point we approximate the Langevin dynamics using an effective time-dependent dynamics (Ref. 5, 6, 7). We will discuss no details, except to point out that this formalism is different from the traditional Hartree non-equilibrium methods mainly in that it describes the evolution of a fractal object, and is therefore not based on the density but averages of coordinates, \mathbf{x}_n , where $n = 0, \dots, N-1$, N being the degree of polymerization. We calculate the observables,

$$\mathcal{F}_q(t) = \frac{1}{3} \langle |\mathbf{x}_q(t)|^2 \rangle, \quad \mathcal{G}_q(t) = \frac{1}{3} \langle \mathbf{x}_{-q}(0) \mathbf{x}_q(t) \rangle, \quad (1)$$

where $\mathbf{x}_q(t)$ are Fourier conjugated variables to space coordinates $\mathbf{x}_n(t)$. Time evolution of observables in (1) is given by the equations,

$$\begin{aligned} \frac{\zeta_q(t) d\mathcal{F}_q(t)}{2 dt} &= k_B T - \Delta V_q(t) \mathcal{F}_q(t), \\ \zeta_q(t) \frac{d\mathcal{G}_q(t)}{dt} &= -\Delta V_q(t) \mathcal{G}_q(t). \end{aligned} \quad (2)$$

The effective time-dependent potential $\Delta V_q(t)$ and friction $\zeta_q(t)$ are determined self-consistently. Keeping the first two terms in the virial expansion series of hard core potential, they may be written as (Ref. 7, 8),

$$\begin{aligned} \Delta V_q(t) &= k_q - \hat{u}_2 \sum_{m \neq m'} \frac{d_{mm'}^{(q)}}{\mathcal{D}_{mm'}^{5/2}} \\ &\quad - \hat{u}_3 \sum_{m \neq m' \neq m''} \frac{d_{mm'}^{(q)} \mathcal{D}_{m'm''} + d_{m'm''}^{(q)} \mathcal{D}_{mm'} - 2d_{mm'm''}^{(q)} \mathcal{D}_{mm'm''}}{(\mathcal{D}_{mm'} \mathcal{D}_{m'm''} - \mathcal{D}_{mm'm''}^2)^{5/2}}, \end{aligned} \quad (3)$$

$$\frac{1}{\zeta_q(t)} = \frac{1}{N\zeta_b} + \frac{1}{3(2\pi)^{3/2} \eta_s N^2} \sum_{n \neq n'} \frac{2 - d_{nn'}^{(q)}}{\mathcal{D}_{nn'}^{1/2}(t)}, \quad (4)$$

\hat{u}_2 and \hat{u}_3 are rescaled second and third virial coefficients, η_s denotes the viscosity of the solvent, and ζ_b is the bare friction coming from the diagonal element of the hydrodynamic Oseen tensor. Two- and three-body space correlations are defined as,

$$\begin{aligned} \mathcal{D}_{mm'm''}(t) &= \frac{1}{3} \langle (\mathbf{x}_m(t) - \mathbf{x}_{m'}(t)) (\mathbf{x}_{m''}(t) - \mathbf{x}_{m'}(t)) \rangle, \\ \mathcal{D}_{mm'} &\equiv \mathcal{D}_{mm'm} = \sum_q d_{mm'}^{(q)} \mathcal{F}_q(t), \quad d_{mm'}^{(q)} = 2 - 2 \cos \frac{2\pi q(m-m')}{N}. \end{aligned} \quad (5)$$

Note that $k_q = \kappa d_{01}^{(q)}$, where κ is the spring constant. In neglect of the back flow effect ($\eta_s = \infty$) the friction is a constant, $\zeta_q \equiv \zeta = N\zeta_b$.

It is possible to solve these equations numerically, and analyse their behaviour in the vicinity of the initial Flory state and final collapsed state. We shall return to the results later.

Finally, it is clear that we can generalize all of this treatment and deal with periodic and random copolymers in an analogous manner. We shall not present any details here, instead referring the reader to papers on the subject (Ref. 9, 10).

Monte Carlo and Langevin Simulations

To support the theory and give a visual impression of the processes we can describe also the results of some Monte Carlo calculations (Ref. 11). Langevin simulations have also been carried out (Ref. 12), but where they may be compared they give essentially the same results, but with less reliability, this arising from the fact that the lattice model is much more readily studied in an exhaustive manner (Ref. 13).

We carry out calculations using the traditional ideas of non-equilibrium statistical mechanics. That is we equilibrate in the Flory phase, quench to the condensed phase, and calculate the time evolution of a number of observables. Quantities such as the mean number of monomers in cluster $S(t)$, calculated using definitions of clusters familiar in areas such as diffusion limited aggregation and percolation, as well as the mean number of cluster $\langle n \rangle(t)$ on collapsing chains, are obtained. We also find the time-dependent effective Flory exponent $\beta(t) = \nu(t) + 1/2$ thereby probing the change of fractal dimension with time.

Results from Theory and Simulations

Including both three- and four-body as well as the normal two-body terms we find a phase diagram exhibited in the Fig. 1 (Ref. 14). Thus, at equilibrium we find three collapsed phases with different orientational order. Phase (I) may be described as a conventional phase with effective three-body attraction. In Fig. 2a we exhibit an example of particular polymer configuration representative of this phase. Two other phases are observed in the region of the phase diagram corresponding to effective three-body repulsion. Phase (II) is characterized by local orientational order within the globule (see Fig. 2b). Finally, phase (III) possesses global orientational order and it appears to be analogous to the nematic phase of a liquid crystal (see Fig. 2c).

In essence we believe that that there are four characteristic stages in the kinetics from the Flory coil to the conventional collapsed phase. The stages are as follows,

(a) At early stages we find a sort of spinodal decomposition where many of the internal modes of the polymer coil become unstable. To make relation to common features of polymers we comment that the Flory coil is a fractal and therefore the spinodal waves

are not described by density, but in the metric of the polymer chain. Initially the chain undergoes formation of small locally collapsed globules that grow for some time at the expense of their neighbours in the chain. This process leads to an essential decrease of amplitudes of large- q modes, these describing the local structure of the chain. There is also a much slower decrease of low- q modes, describing the polymer at large distances along the chain.

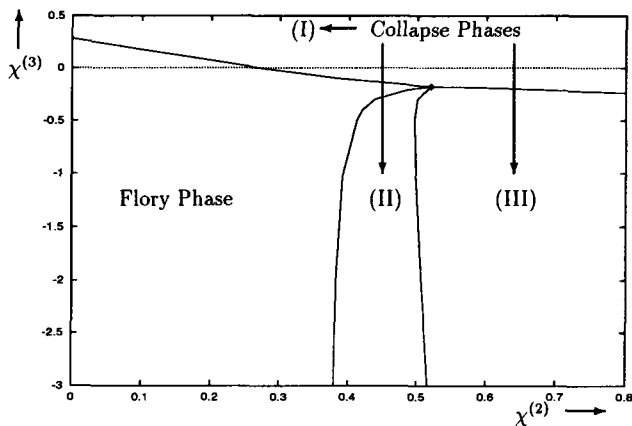
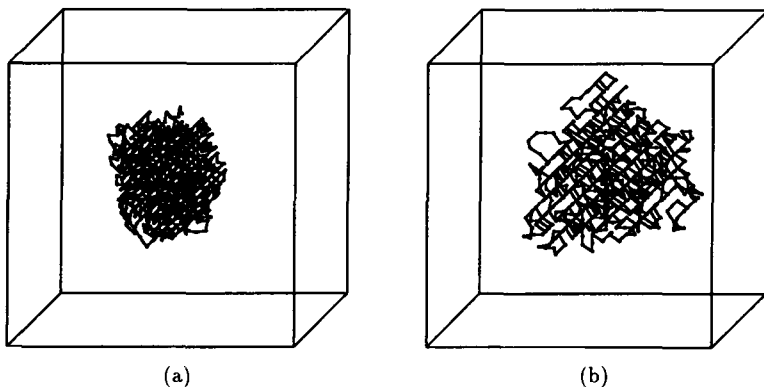


Fig. 1. Phase diagram for homopolymer model which includes three-body interaction in terms of Flory interaction parameters $\chi^{(2)}$ and $\chi^{(3)}$. Lower left region corresponds to Flory state $\nu = 3/5$, other three regions to different collapse phases $\nu = 1/3$. Region (I) of the phase diagram corresponds to the isotropic liquid compacted state. Region (III) corresponds to the anisotropic collapsed state, which is analogous to the nematic state of a liquid crystal. In region (II) the single globule consists of several locally ordered regions.



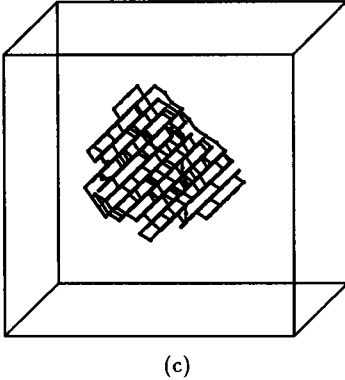


Fig. 2. Equilibrium collapsed polymer configurations for degree of polymerization $N = 768$. The size of the framing box is equal to $L = 32$. Pictures (a), (b) and (c) correspond, respectively, to states found in the regions of the phase diagram labeled by (I), (II) and (III) in Fig. 1.

By linearizing the equations (2) and (3) the deviation $\Delta\mathcal{F}_q$ from the initial equilibrium value for sufficiently small times may be written as,

$$\Delta\mathcal{F}_q(t) \equiv \mathcal{A}_q (1 - e^{-\lambda_q t}), \quad (6)$$

and we calculate the Lyapunov exponent λ_q and corresponding amplitude \mathcal{A}_q of the internal modes. These possess positive λ_q for $q < q_c$, where q_c is some critical value of the chain index.

Using the spectrum and amplitudes at early times we can find that the squared radius of gyration, $R_g^2(t) = \sum_{q \neq 0} \mathcal{F}_q(t)$ decreases according to the power law (Ref. 7),

$$R_g^2(t) = R_g^2(0) - A_1 t^{\alpha_i}, \quad (7)$$

where $\alpha_i = 7/11$ ($\alpha_i = 9/11$) without (with) hydrodynamic interaction. We also find that this result is in a good agreement with Monte Carlo simulations (Ref. 11) performed without account of hydrodynamics.

At the end of this stage (see Fig. 3) most of the slack polymer has been gathered up into small more condensed clusters with relatively tight chain between them. The effective Flory exponent has risen to be unity, characterising a rigid rod of clusters, and thereafter begins to fall rapidly until it reaches a near-ideal Gaussian value.

(b) The second stage involves cluster coarsening, the analogue of Lifshitz-Slyozov cluster growth after a quench into the liquid-gas coexistence region. However, we emphasise that this chain of clusters is essentially an ideal coil at long lengths with a set

of topologically connected locally collapsed clusters. The evidence is that the average effective swelling exponent during this stage corresponds to an ideal coil $\nu_T = 1/2$, and we therefore have a set of clusters growing against the tension of an ideal coil elasticity. The characteristic time expected from elementary arguments is

$$\tau_m = AN^{2\beta_T}, \quad (\tau_m = A'N^{3\nu_T}) \quad (8)$$

for the model without (with) hydrodynamic interaction. We find that this expectation is justified by both simulations and numerical analysis of the self-consistency equations (Ref. 11, 8). Thus, we get the cluster growth law without hydrodynamics,

$$S(t) = A_s t^Z, \quad Z = 1/2. \quad (9)$$

These then are the fundamental laws of collapse throughout the predominant stage of kinetics, for beyond this stage the polymer coil is space-filling, though not yet compacted.

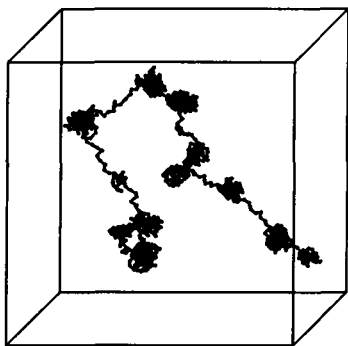


Fig. 3. The kinetic evolution of a particular polymer configuration after the first kinetic stage. The degree of polymerization and the size of the framing box are equal to $N = 768$ and $L = 64$, respectively.

(c) The next stage corresponds to shape optimization and further compaction of the globule to a higher density. Here the mean squared radius of gyration tends exponentially slowly to the final equilibrium value,

$$R_g^2(t) = R_g^2(\infty) + A_f \exp(-t/\tau_f). \quad (10)$$

The relaxation time scales in the degree of polymerization $\tau_f \sim N^{\gamma_f}$ in the following way (Ref. 8) $\gamma_f = 2\nu_c + 1$ ($\gamma_f = 3\nu_c$) without (with) hydrodynamics, where $\nu_c = 1/3$ is the collapsed swelling exponent.

(d) Due to topological restrictions the late state of kinetics for a nonphantom chain will have a different structure than for a phantom one. For an open polymer topological restrictions may be removed via self-reptations of the chain, and it has been argued that this leads to an even longer final kinetic stage with the time scale $\tau_{reptations} \sim N^3$ (Ref. 3).

In conclusion let us mention that kinetics after the quench to the region (III) of the phase diagram in Fig. 1 is very slow compared to other collapse regions. The origin of this metastable long-lived state in kinetics at the intermediate stage is in formation of locally collapsed clusters with different orientations (Ref. 14).

Laws for Periodic Copolymers

The analytical approach just described has the great benefit that it can be applied to more complex systems. In particular we have recently followed the kinetics of folding of a periodic copolymer with hydrophobic elements 'a' and hydrophilic elements 'b' (Ref. 9). We here present only a brief summary of the conclusions.

(a) The form of the kinetic stage corresponding to collective or spinodal effects is unmodified, as one might expect.

(b) The coarsening stage proceeds at first in the same manner as the homopolymer with no microscopic microphase separation of the 'a' and 'b' units. However, towards the end of the coarsening stage if one examines the order parameter corresponding to such a phase separation, there arises a rather sharp transition leading to,

(b') a new stage where there is a large-scale separation of the hydrophilic and hydrophobic species.

The remaining stages are comparable in principle to the homopolymer. However, the interested reader should consult the literature (Ref. 9).

The Laws for Random Copolymers

The homopolymer studies are of great significance in forming basic opinions about the kinetic laws of collapse or folding. However, part of our overall vision involved the derivation of kinetic laws for bipolymer folding, and therefore we must make further progress if we are to establish connection to these issues. As an intermediate stage of challenge we wish to study a random copolymer composed of units that are entirely hydrophilic and units that have the possibility to become hydrophobic, as for the polymer discussed above. An example of the sort that we seek to study is a copolymer of N-isopropylacrylamide and acrylamide. Evidently when we have a homopolymer that undergoes a collapse transition we have the relative concentration $n_a = 1$ whilst an entirely hydrophilic polymer corresponds to $n_a = 0$. On the basis of simulations alone (Ref. 11) we have determined

the phase diagram as below in Fig. 4.

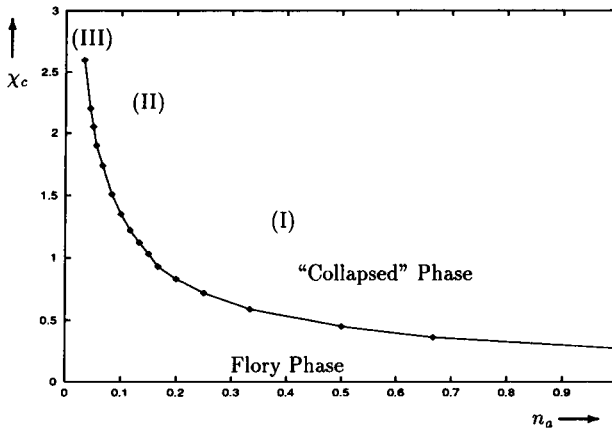


Fig. 4. Phase diagram for random copolymer with the degree of polymerization $N = 180$. Solid line corresponds to the dependence of the critical point value χ_c on the hydrophobic beads concentration n_a . Regions of the diagram are labelled by the numbers, (I), (II) and (III). Region (III) corresponds to a chain of small micelles, probably a renormalized Flory coil. Region (II) may be a crossover between these, but it corresponds to a few quite large micellar objects.

The radius of gyration of the “collapsed” state and, more importantly, its swelling exponent ν , appears to be dependent on the concentration n_a of hydrophobic beads in the polymer chain. For concentrations in the range $1/5 \lesssim n_a \lesssim 1$ the collapse exponent is essentially unaffected (region I in phase diagram Fig. 4). The main point is indeed that novel phenomena are found in the intermediate regime of concentrations and there we find first microphase separation or single-chain micellization with hydrophilic groups expressed on the exterior and hydrophobic groups in the interior (region II). There then appears to be a disordered glass phase about which we understand relatively little as yet, though it is probably related to the phases discussed by previous writers. Finally, for the smallest concentrations of hydrophobic monomers (region III) the effective swelling exponent ν_c^{eff} is close to the Flory exponent value. The polymer once more becomes a coil-like chain with only small micelles distributed along the chain. The transition curve therefore terminates in a sort of end point of collapse transitions. It is of interest that the curve of transitions is well described through most of the concentration range by,

$$\chi_c = \chi_c^{(h)} n_a^{-2/3}, \quad (11)$$

where $\chi_c^{(h)}$ is the value of the Flory interaction parameter at the theta-point for homopolymer.

The kinetics of the conformational change across the curve is a rich study which is far from complete. Clearly the results depend on whether one quenches from the Flory coil to regions (I), (II) or (III). The case of the homopolymer has been discussed earlier. The cases of the micelle formation at the transition to the glass-like state are more complex.

Thus, at early stages we find once more a process that is analogous to binary fluid spinodal phase separation such that small micelles of A units form quite quickly. At this stage the kinetics becomes fundamentally different from that of the homopolymer, because at the end of this first kinetic stage we find a chain that is essentially locally stable with the small micelles screened by hydrophilic material. We know that, much later, there will be considerable rearrangement to allow the small micelles to grow, however, there is relatively little force to do so, and such reorganizations occur on a very much longer time scale than the complete collapse time for a homopolymer. We believe therefore, that after an early fast stage there is kinetic arrest ended, for the simple micelle region when the system escapes from the local minimum into which it has fallen. In the case of the putative glass-like phase we believe that there is a range of barriers such that the kinetics is appropriate to glass relaxation. In this case we believe that the initial stage corresponds roughly to β -relaxation, and the slow stage corresponds to a type of α -relaxation. There are Monte Carlo calculations of these phenomena that we present below, and in considerably more detail in the literature (Ref. 11). We conjecture that there is first a relatively fast spinodal-like process which nevertheless seems to be of stretched exponential form in terms of the variables \mathcal{F}_q . There follows a very slow kinetic regime, possibly with a weak power-law dependence, and then what may well be another stretched exponential regime. These three stages correspond to the two much simpler stages that emerge from the homopolymer studies. It is clear that there is still much uncertainty about this aspect of the research program, but there seems no particular reason that the methods discussed earlier cannot be applied here (Ref. 10), too. We may note also that there are later stages of kinetics where a density-type theory will be more appropriate, and careful consideration of this aspect of the problem has been given in various recent works.

CONCLUSION AND DISCUSSIONS

It seems clear now that good theoretical and computational approaches based on simple polymer models that are flexible and solvable are possible. Based on these we believe it will be possible, within a relatively short time, to elucidate most of the kinetic laws for homopolymers and copolymers.

We point out that the forms of those homopolymer laws that were earlier discussed on a phenomenological basis (Ref. 15) correspond to what we find in our theory, although

we have a different microscopic picture of some of the processes. The theory exhibits the other kinetic stages clearly. However, the simplicity of the models means that we are unable to give an absolute time scale, though reasonable estimates of the parameters such as A' in equation (8) seem to lead to "collapse times" of the order of milliseconds.

However, the connection of the theoretical pictures to experiment is still lacking. At this conference results were presented by Professor B. Chu (Ref. 16) indicating that the "collapse time" of polystyrene in an organic solvent is of the order of seconds, or larger. We have no real answer to this dilemma at the moment. However, we do have a few preliminary results from our own experimental work, and some suggestions that may lead to one possible resolution of the dilemma. We emphasize the preliminary and informal nature of these comments, as appropriate for the conference, that are not to be regarded as firmly established.

Firstly, we have carried out rapid temperature jump and fixed-angle static light scattering experiments (Ref. 17) to probe all the kinetic time scales of poly(*N*-isopropylacrylamide) collapse in water¹. This experiment can probe time scales from microseconds to one second because of the laser temperature jump and the fact that photon correlation is unnecessary. We find evidence of two clear and well separated processes, one in the millisecond regime, the other in the regime of seconds. The latter may be shown to be mainly associated with aggregation, but may cover some part of the coil collapse process which would be in agreement with Chu's result. However, the short time scale process is much weaker and may correspond to another part of the isolated globule collapse process. The structure factors at short time that we have measured are certainly consistent with shrinkage of the isolated globules. One wonders if there can be a resolution along these lines. That is, part of the shrinkage does indeed occur rapidly, but the coil then experiences some barriers that require thermal or other activation before further collapse, and then aggregation occurs on a similar time scale.

This is a field of study that deserves the attention of theorists and experimentalists for its implications are of great fundamental interest in terms of understanding biopolymer kinetics and practical concern as in, for example, the field of the kinetics of responsive gels. It will be interesting to see how the field evolves.

Undoubtedly, however, this conference has stimulated much discussion in these and related issues and the authors wish to acknowledge the organizers' contribution in assisting communication and academic exchange in their area of study.

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¹ Poly(*N*-isopropylacrylamide) has a lower consolute point and collapses with increasing temperature

and A. Byrne, P. Kiernan, A. Moskalenko from whom they have learned much about the collapse phenomena. Numerous discussions, and the cumulative results of these colleagues has lead the authors to deepen their perspective on the problem. A longstanding collaboration with colleagues in Pushchino, Russian Academy of Sciences has also been of great assistance. Besides these collaborators, other colleagues have been of considerable assistance, including Professors A. Yu. Grosberg, A. R. Khokhlov, Y. Rabin and K. Yoshikawa who communicated many of their results and much of their thinking often prior to publication. In addition Professors P. G. de Gennes and P. Pincus were both sources of interesting background to the problem. This work was supported in part by the Irish Government, by a grant from Forbairt, and by INTAS.

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