

## **Irreversible polymer collapse by Monte-Carlo simulations**

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We investigate the problem of polymer collapse using a modified two-space Monte-Carlo dynamics. The modified simulations eliminate the excluded volume constraint and move aggregates by Stokes' law diffusion. The results suggest that collapse of long polymers is dominated by diffusion of the polymer ends which accrete monomers and small aggregates. We also develop a scaling relation that relates the growth of the end mass to the growth of the average mass along the contour. Results in both 2 and 3-dimensions agree with the scaling relation. In 3-dimensions the collapse time scales only linearly with the polymer mass suggesting other collapse processes would be significantly slower.

### **I. Introduction**

Homo-polymer collapse upon rapid change from good to poor solvent conditions is a comparatively simple problem which may shed some light on the much more difficult problem of protein folding.<sup>1</sup> Motivated by these considerations, deGennes has described a mean field argument for the behavior of polymer collapse during slight departures from  $\theta$ -solvent conditions.<sup>2</sup> Under these conditions he suggests the polymer initially collapses into a sausage shape. Then diffusion thickens the sausage uniformly as the ends contract.

We have investigated the polymer collapse problem in the limit of large departures from good solvent conditions so that monomers that encounter each other stick irreversibly. We also restrict

our study to diffusive monomer motion and short range interactions. In order to investigate polymer collapse in this regime we have performed simulations and developed a scaling argument. Simulations were performed in both 2 and 3 dimensions. Our analysis suggests that in direct contrast to the mean field scenario discussed by deGennes polymer collapse is dominated by the motion of the ends of the polymer that diffuse along the polymer contour accreting monomers and smaller aggregates.

The dominance of the end motion in collapse arises from the greater mobility of the ends when compared with an aggregate along the contour. The motion of an aggregate along the contour is constrained by its two neighbors. Without curvature in the chain the aggregate is unable to move to coalesce with either neighbor because it is bonded to the neighbor on the other side.

## **II. Methodology of the simulations**

Our simulations are based on a lattice Monte-Carlo algorithm recently developed for simulating high-molecular-weight polymers.<sup>3</sup> This novel two-space algorithm, in its original form, has been shown to be significantly faster than previous state-of-the-art techniques.<sup>4</sup> Odd monomers and even monomers of a polymer are distinct and may most easily be described as residing in two separate spaces. Each monomer occupies one cell of a square lattice. Both connectivity of the polymer and excluded volume are imposed by requiring that in the opposite space only the nearest neighbors along the contour reside in the 3x3 neighborhood of cells around each monomer. Motion of monomers is performed by Monte-Carlo steps which satisfy the polymer constraints. Since adjacent monomers (and only adjacent monomers) may lie on-top of each other the local motion of the polymer is flexible. Despite the unusual local polymer properties the behavior of long polymers is found to agree with conventional scaling results.

The simulation of polymer collapse starts from a set of equilibrium polymer configurations generated by Monte-Carlo simulations of two kinds with no theoretical or measured difference in properties. The first is the local polymer Monte-Carlo two-space dynamics which satisfies dynamic scaling. The second is a non-local 'reptation' Monte-Carlo process which randomly moves

monomers from one end to the other and is faster than the local Monte-Carlo dynamics but for equilibrium geometries provides equivalent results.

Polymer collapse is simulated by eliminating the excluded volume constraint. Local Monte-Carlo (diffusive) dynamics are then performed. Monomers are no longer stopped from entering the neighborhood of another monomer, however, they continue to be required not to leave any neighbors behind. This enables monomers of the same type (odd or even) to aggregate by moving on top of each other. Once more than one monomer lands on the same site they are no longer moved independently but rather as an aggregate. The mass of an aggregate is set to the total number of monomers which reside on the same site. Aggregates are moved as a unit but are assigned a diffusion constant which scales by Stokes' law for spherical bodies in d-dimensions  $D \sim 1/M^{1/d}$ . The diffusion constant enters through the probability of taking a Monte-Carlo step.

The polymer dynamics during collapse are simulated by selecting an aggregate (monomers are included as aggregates of mass 1) and moving the aggregate in one of four compass directions with a probability given by the diffusion constant and only if connectivity constraints allow -- the aggregate does not leave any neighbors behind. The next aggregate to move is selected at random since the modified algorithm does not allow parallel motion of the aggregates. Since the number of aggregates is changing over time, care must be taken to define what is meant by a single time interval. One time interval consists of performing a number of aggregate moves equal to the number of remaining aggregates -- taken to be the number at the end of the time interval. It is possible to choose slightly different conventions such as taking the number of moves equal to the average of the number of aggregates at the beginning and end of the time interval. This convention, of course, does not affect the behavior of the collapse and should not affect the scaling relation or exponents.

### **III. Results on end-dominated collapse**

Simulation results are presented in Figs. 1-3. Fig. 1 shows frames from the collapse of a polymer in 2-dimensions. These frames illustrate clearly the central result -- the dominance of aggregation at the polymer ends as the mechanism of collapse. Some small aggregates may be seen to form along the contour of the polymer which are then accreted by the ends. The statistical dominance of the end collapse is shown in the time evolution of the distribution of aggregate sizes in Fig. 2. A horizontal slice through Fig. 2 is a histogram of the aggregate sizes at a particular instant. The first moment of the collapse is the topmost slice where all aggregates have unit mass. Aggregation is seen by the shift of aggregates to higher mass over time. Because of the large number of small aggregates, the contours are cut off at a low value (.20 per bin) to show the higher mass aggregates. If collapse of a polymer occurred uniformly into a sausage shape, the histogram, over time, would show a systematic shift of all aggregates to higher mass. In contrast, the large majority of aggregates are found to remain with a mass close to 1. Aggregates at the ends increase in mass eventually reaching an average of 25% of the total mass of the polymer (in the two-space algorithm there are two aggregates at each end, one of odd monomers and one of even monomers). This is seen in Fig. 2 by the presence of a second peak in the distribution of aggregate sizes that separates from the low mass distribution and increases until it reaches a mass of 25%. The final event consists of the coalescence of the ends.

### **IV. Scaling relations**

To develop a scaling argument for irreversible collapse we assume that both (a) uniform collapse along the contour and (b) ends which diffuse and accrete monomers, play a role in collapse. Let  $M(t)$  be the mass of a site along the polymer. Let  $M_0(t)$  be the mass of the aggregate at either end of the polymer. At every time step the end aggregate has a probability proportional to its diffusion constant of collecting more mass by accreting its immediate neighbor aggregate assumed to be a distance  $d_0$  away with a mass  $M(t)$ . Thus  $M_0(t)$  satisfies

$$\frac{dM_0(t)}{dt} = M(t)D_0(t)/d_0^2 \quad (1)$$

Where  $D_0(t) = 1/M_0(t)^{1/d}$  is the diffusion constant of the end at time  $t$ . Assuming scaling:

$$M_0(t) = t^{s_0} \quad (2)$$

$$M(t) = t^s$$

We obtain:

$$s_0 = (s+1)d/(d+1) \quad (3)$$

For  $s < d$   $s_0 > s$  and the growth of the ends is faster than the growth of the width of the chain and end collapse dominates for long enough polymers. Some insight to this relationship may be reached by considering a point on the chain and allowing all of the mass in the volume given by  $V = (ct)^d$  (the light cone) to be aggregated onto this point assuming an initial uniform density. In this unrealistic case  $s = d$ . This is the highest possible value of  $s$ , and thus, either  $s = s_0 = d$  or  $s < s_0$ . In the former case the polymer thickens uniformly, and in the latter case the end kinetics dominates the collapse.

## **V. Exponents from simulations**

Fig. 3 shows the time evolution of the average mass of the polymer ends and the average mass of aggregates not including the ends. Longer polymers follow the collapse of the shorter polymers but extend it to longer times. This is consistent with the end dominated collapse where the length of the polymer only enters through the time at which the ends meet. The scaling behavior follows the exponents shown in Table I. Values are compared with the scaling relation result and are in close agreement with a small but possibly non-zero deviation. The agreement with the scaling relationship is striking since there are corrections which may be expected due to the neglect of changes in both curvature and compression of the polymer at the ends. Finally, the small values of  $s$  and a slight curvature may indicate that the non-zero  $s$  results from a logarithmic correction rather than a power law. Efforts to fit the curves to logarithmic scaling are not conclusive. We note that consistent with the rapidly diminishing probability of long rings<sup>5</sup> we find they have a negligible significance in collapse.

The scaling time of collapse may be seen in end-dominated collapse to follow  $\tau \sim N^{1/s_0}$ . We find  $1/s_0 = 1.293 \pm 0.001$  in 2-D and  $1.018 \pm 0.005$  in 3-D (errors are statistical). Thus the collapse time is predicted to scale linearly with polymer length in 3-D. The maximum values allowed by the scaling relations are  $3/2$  in 2-D and  $4/3$  in 3-D. This result also addresses the question: Are the polymers simulated long enough to show the asymptotic collapse mechanism? The scaling of the collapse time is significantly lower than other collapse mechanisms. The sausage collapse scaling of deGennes is 2 or 2.2 (without hydrodynamic interactions) in 3-d. Thus it is unlikely that for longer polymers a faster process will dominate.

## **VI. Discussion and conclusions**

Returning to the problem of protein folding, we point out both differences and connections. In these simulations homopolymer collapse in the irreversible regime is found to possess a non-trivial behavior dominated by end motion. The relevance of this behavior to hetero-polymer collapse including reversible kinetics remains to be fully assessed. The relevance of these simulations to protein folding is limited also by the neglect of hydrophobic interactions and other long-range interactions that violate the assumptions of these simulations and may force significant corrections. Despite these significant differences, these simulations may help explain the success of *in vitro* refolding experiments. *In vivo* conditions may directly promote end dominated collapse -- a protein may fold as it is synthesized, during extrusion from the ribosome. The probable *in vivo* end-dominated-collapse during extrusion taken with our results implying *in vitro* end-dominated-collapse may explain the success of many *in vitro* refolding experiments.

Our simulation of collapse in both 2- and 3-dimensions leads to an interesting suggestion. The dominance of end motion in the collapse is greater in 2 compared to 3 dimensions as seen in the smaller value of  $s$ . This could be further extended by noting that in 1-dimension  $s_0 = 1/2$  and  $s = 0$ . Dimensional restriction from 3 to 2 dimensions may be achieved *in vivo* by proximity of the polypeptide to the ribosome or other 'chaperone' proteins.<sup>6</sup> It may be possible by weakly

adsorbing a protein on a surface *in vitro*, to achieve proper refolding for proteins which do not normally refold correctly. To act correctly the adsorption must be without self-crossings.

In conclusion, we have found that polymer collapse in both 2- and 3- dimensions appears to reduce essentially to the behavior of 1-dimensional collapse. In 1-dimension, collapse proceeds by the driven diffusion of the polymer ends. The driving force is the aggregation of the monomers. The only modification of the simple diffusion is the change in the diffusion constant due to the accretion of mass onto the ends. In 2- and 3- dimensional simulations the results are similar. Ends diffuse along the contour accreting monomers and smaller aggregates. The dominance of the end motion arises because of their greater mobility since they are not subject to the constraint of attachment to two nearest neighbors. Aggregation along the contour does occur. This aggregation is slow but is fastest in regions of high curvature because of the greater mobility of monomers. The progressive aggregation results in an increasing mass density with a small exponent and a decrease in polymer curvature. The importance of the aggregation along the contour increases with increasing dimensionality as may be expected by the decreasing importance of the connectivity constraint in reducing the mobility. It is not clear at this time if there is a finite crossover dimension to the mean-field infinite-dimension behavior of uniform-polymer-collapse where all points along the contour have equal aggregation probability.

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<sup>1</sup> for a review of homo-polymer collapse theories and protein folding see H. S. Chan and K. A. Dill, *Annu. Rev. Biophys. Biophys. Chem.* 20, 447-90 (1991)

<sup>2</sup> P. G. deGennes, *J. Physique Lett.*, 46 L639-42 (1985)

<sup>3</sup> Y. Bar-Yam, Y. Rabin, and M. A. Smith, *Macromolecules Reprints*, 25, 2985-6 (1992)

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<sup>4</sup> M. A. Smith, Y. Bar-Yam, Y. Rabin, C. H. Bennett, N. Margolus and T. Toffoli, in *Complex Fluids*, (E. B. Sirota, D. Weitz, T. Witten and J. Israelachvili eds.) MRS Symp. Proc. Vol. 248 (1992) p. 483; *Journal of Computational Polymer Science*, 2, 165-171 (1992)

<sup>5</sup> J. des Cloizeaux, *Phys. Rev. A*, 10, 1665-9 (1974)

<sup>6</sup> M.-J. Gething and J. Sambrook, *Nature*, 355, 33-45 (1992)

Table I: Power law behavior exponents defined in the text and fitted to the simulation results between the dashed lines in Figs. 2 & 3. Fits were chosen to minimize standard errors. Errors given are only statistical. Results are compared to the scaling relation given by Equation 3. Results in 1-D are exact.

	$s_0$	$s$	$s_0(s)$ [Eq. 3]	$s_0-s_0(s)$
1-D	0.5	0	0.5	0
2-D	$0.7734\pm 0.0006$	$0.154\pm 0.001$	$0.7695\pm 0.0006$	$0.004\pm 0.001$ (0.5%)
3-D	$0.982\pm 0.005$	$0.337\pm 0.002$	$1.003\pm 0.002$	$-0.021\pm 0.005$ (2%)

Figure Captions:

Fig. 1: Frames 'snapshots' of the collapse of a single polymer of length  $N=500$  monomers in 2-dimensions. The plot is constructed by placing dots of area  $M^{1/2}$  for an aggregate of mass  $M$ . This does not reflect the excluded volume of the aggregates which is zero during collapse. Successive snapshots are taken at intervals of approximately  $1/4$  of the collapse time with the initial configuration shown as (a). The results demonstrate the end dominated collapse process where the ends diffuse along the contour of the polymer accreting small aggregates.

Fig. 2: Time evolution of the distribution of aggregate sizes shown as a contour map. The vertical axis is time with the initial state at the top. The horizontal axis is the aggregate size with a maximum of  $1/2$  the length of the polymer. (a) is the result of averaging over 500 collapses of polymers of length 1000 in 2-D. (b) is the result of averaging 1000 collapses of polymers of length 500 in 3-D. The time scale of (b) is expanded compared to (a) by a factor of 2. The distinctive separation of high-mass aggregates from the peak at a mass of 1 (individual monomers) shows the time evolution of the mass of the ends of the polymer which form the high mass peak. In contrast, a uniform collapse would appear as an evolution of a single peak whose average mass would increase.

Fig. 3. Plot of the time evolution during polymer collapse of the average total mass of the polymer ends  $M_0(t)$  and of the average mass  $M(t)$  of aggregates not including the ends. (a) Shows collapse in 2-D of polymers of length  $N=1000$  (500 samples), and  $N=500$  (1000 samples). (b) Shows collapse in 3-D of polymers of length  $N=500$  and  $N=250$  (1000 samples). Scaling exponents fitted to the longer polymer collapse for times between the vertical dashed lines are given in Table I and discussed in the text.