Thermal Fracture Kinetics of Heterogeneous Semiflexible Polymers

Alexander Lorenzo,1 Enrique M. De La Cruz,2 and Elena F. Koslover1

1Department of Physics, University of California, San Diego, San Diego, California 92093
2Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT 06520

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The fracture and severing of polymer chains plays a critical role in the failure of fibrous materials and the regulated turnover of intracellular filaments. Using continuum wormlike chain models, we investigate the fracture of semiflexible polymers via thermal bending fluctuations, focusing on the role of filament flexibility and dynamics. Our results highlight a previously unappreciated consequence of mechanical heterogeneity in the filament, which enhances the rate of thermal fragmentation particularly in cases where constraints hinder the movement of the chain ends. Although generally applicable to semiflexible chains with regions of different bending stiffness, the model is motivated by a specific biophysical system: the enhanced severing of actin filaments at the boundary between stiff bare regions and mechanically softened regions that are coated with coflin regulatory proteins. The results presented here point to a potential mechanism for disassembly of filament networks in general and cytoskeletal actin networks in particular by the introduction of locally softened chain regions, as occurs with coflin binding.

The fracture properties of polymeric solids pose a key constraint on the manufacture and design of a vast array of man-made materials for load-bearing or weather-resistant purposes. Furthermore, polymeric materials serve as some of the most important structural and information-bearing components in living organisms, and their rupture (whether through mechanical or environmental stress or through regulated turnover) has a crucial role to play in biological processes ranging from cell division, to tumorigenesis, to cell motility. Theoretical and experimental explorations of failure mechanisms have established that the fracture of polymeric solids relies on the concentration of stress on individual polymer filaments, with the dynamics and stress-dependence of fracture governed by the kinetics of molecular rupture. At the molecular scale, fracture is inherently a thermal process, where the activation energy is lowered by the application of stress on individual bonds along the filament.

Fragmentation of a polymer filament is accelerated when externally applied stresses become locally concentrated in specific regions. This principle underlies, for instance, the fragmentation of DNA at discrete folding points under extensional flow, the rupture of microtubules through buckling during spindle reorganization and traumatic axonal injury, and the severing of actin bundles by myosin-driven compression in motile cells and reconstituted contractile networks. Local discontinuities in mechanical properties tend to concentrate externally applied stress, leading to preferential fracture of materials at these discontinuous regions.

In the case of thermally driven fracture, the effect of mechanical inhomogeneities in a filament is poorly understood. Prior theoretical work showed that thermal energy is equally partitioned among spatial degrees of freedom in general equilibrium one-dimensional systems. However, fracture is inherently a transient, kinetic process. Accordingly, understanding fracture rates requires moving beyond equilibrium models to consider the dynamics of thermal fluctuations in a polymer filament. Here we focus on the role of spatial heterogeneity of mechanical properties in accelerating thermally induced fracture of semiflexible chains.

The general problem of fracture rates in a thermalized, mechanically heterogeneous, polymer filament is motivated in part by a biological system: the coflin-mediated severing of cytoskeletal actin filaments. Actin is a semiflexible polymer that forms bundles and networks responsible for maintaining cell-scale mechanical properties as well as driving processes such as lamellipodial motility, cytokinesis, and embryonic patterning. Much of the biological behavior of actin networks relies on the dynamic turnover of individual actin filaments, which is accelerated by the actin-binding protein coflin. Cofilin assembles cooperatively along actin chains, locally decreasing their bending stiffness and resulting in mechanically heterogeneous partially decorated filaments. Such filaments fragment, without additional energy input, preferentially at the boundary of coflinated segments. While missing bonds at these discontinuities may account for their increased fragility, particularly under stress, an additional contribution to enhanced severing has been proposed that relies on the concentration of stress at the discontinuities between coflinated and bare actin segments. Here, we explore the physical plausibility of enhanced fracture at a junction between soft and stiff regions, in a purely thermal system (ie: in the absence of externally applied compressive forces).

We consider the thermally driven fracture of a mechanically heterogeneous filament, by building upon the well-established continuum “worm-like chain” (WLC) model for semiflexible polymers. Prior work on the sta-
where $h = 0.25, \Delta = 0.1, N = 0.25, \Delta = 0.1, h = 1, N = 0.25, \Delta = 0.1, \hat{\Delta} = 0.1, h = 10$.

(b) Sample configuration of heterogeneous chain ($h = 10$).

(c-d) Free energy landscapes for chains with the same parameters as (a) and (b), respectively, plotted as a function of junction bending ($\rho = \cos \theta$) and normalized end distance $|r = R/(2L)|$. White lines mark the lowest energy path to increasingly sharp junction angles. For a purely stiff chain, junction bending requires a greater reduction of the chain end-to-end distance.

The overall partition function $[G_{\text{tot}}(\hat{R}, \rho)]$ for this model can be computed from prior results derived for worm-like chains with end constraints [28, 32]. Namely, the partition function for a fixed end-to-end vector $\hat{R}$ and junction angle (expressed as $\rho$) is given by,

$$G_{\text{tot}}(\hat{R}, \rho) = \frac{e^{\kappa \rho}}{4\pi^2(2\ell_{p,1})^3} \int_0^\infty \frac{dk}{2N} \frac{k \sin (2kNr)}{k^2} \sum_{l=0}^\infty P_l(\rho) G_0^0(l, N) G_{\text{tot}}(k, N) \left( \frac{k}{h}, hN \right),$$

where $r = |\hat{R}|/(2L)$ is the fractional end separation and $G_{\text{tot}}^0$ refer to previously defined continued fraction terms [22]. The free energy ($F$) of the chain is then defined as the log of the partition function according to $F(r, \rho) = -k_b T \log \left[ 2G_{\text{tot}}(r, \rho) \right]$. This free energy landscape is plotted in Fig. 1c-d for a homogeneous, stiff chain ($L = 0.5\ell_{p,1}$) and a heterogeneous chain.

We focus on filament fracture at the junction point, assuming that fracture will occur when thermal fluctuations push the junction energy ($E_{\text{junc}}$) above some predefined cutoff ($E^*$). This model represents a fracture process where the junction must hop over a transition energy barrier, with the cosine of the bending angle $\rho$ as the reaction coordinate. Chains with a more flexible junction (lower $\kappa$) will have to reach a more extreme cutoff $\rho^* = 1 - E^*/\kappa$ than chains with a more stiff junction (higher $\kappa$). This model is consistent with previous analyses of experimental data on fracture of short cofilin-decorated actin filaments that points to fracture occurring beyond a critical bending angle that increases with lower filament persistence length [22]. Critical energies of approximately 22kT have been estimated for the severing of bare actin filaments [22].

The overall rate of fracture is obtained from the first passage time to the critical value $\rho^*$, as the system fluctuates thermally over the free energy landscape plotted in Fig. 1. The kinetics of fracture are thus determined by a free energy barrier incorporating both the junction bending energy and the configurational energy of the worm-like chains. For a homogeneously stiff chain, surmounting this barrier along the minimum energy path requires bringing the ends of the chain closer together (Fig. 1a). For the heterogeneous chain, by contrast, the cutoff junction angle can be reached without substantial change in the end-to-end distance. The importance of this effect in determining the overall time to fracture depends on the dynamics of the end-to-end coordinate $r$ compared to the dynamics of the junction angle.

To calculate kinetics over the free energy landscape, we make the simplifying assumption that for each value of the end distance $r$, the kinetics of transition to the cutoff $\rho^*$ can be described by a single time-scale — the mean first passage time $\tau(\rho^*; r)$ along a horizontal slice of the landscape. Dynamics along the angular coordinate are defined by a variable friction coefficient that depends on
the value of the junction angle,
\[ \zeta(\rho) = \frac{k_B T}{D_{\rho}^{(0)} 6(1 - \rho^2)} \]

where \( D_{\rho}^{(0)} = \frac{k_B T}{\rho^2 \Delta} \) and \( \mu \) is the translational friction coefficient per unit length of the chain. This expression is derived from the dynamics of two connected rigid links [see Supplemental Information (SI)] \[32\]. The mean first passage time over a one-dimensional landscape can be computed from the Fokker-Planck equation \[34\], appropriately modified for spatially varying diffusivity \[33\] \[36\]. Brownian dynamics simulations of a discretized WLC model are used to validate our calculations of the mean first passage time to junction energy \( E^* \) for fixed values of the end distance (Fig. 2); details in SI \[33\].

The overall mean first passage time to fracture can be computed by considering a system that fluctuates over discrete states in the dimensionless end distance, with state \( i \) corresponding to \( r_i = i \delta r \), and the discretization set to \( \delta r = 0.01 \). The system is assumed to start in thermal equilibrium, with the probability of starting in state \( i \) set by a Boltzmann factor corresponding to the free energy of that state:
\[ F_i = -k_B T \log \int d\rho \exp[-F(r_i, \rho)/k_B T]. \]

Transitions between states occur with a rate constant of
\[ k_i^{(\pm)} = \frac{k_B (E_{i+1} - E_i)}{\exp(F_{i+1} - F_i) - 1}, \]

as derived from a discretization of the Fokker-Planck equation \[27\]. Within each end distance state, fracture is treated as a Poissonian process with average time \( \tau_i = \tau(\rho^*; r_i) \). We compute the overall mean time to fracture for a system that fluctuates over these states using a matrix inversion method, as described in previous work on the kinetics of systems with fluctuating rates\[38\]. This approach for representing the dynamics of the system as movement over a two-dimensional free energy landscape is validated by comparison to Brownian dynamic simulations with unconstrained chains (Fig. 2).

We assume that the chain begins in a configuration selected from its equilibrium distribution and consider the mean time to fracture for two limiting cases of the end-to-end dynamics (Fig. 3). For the case of very rapid end equilibration (high \( k_B / D_{\rho}^{(0)} \)), the chain would be expected to sample all end positions over a time-scale that is short compared to the fracture time. In this limit, the fracture dynamics are determined entirely by the stiffness and friction coefficient for the junction bending \( \rho \) and are independent of the mechanical properties of the rest of the chain.

The opposite regime holds when the dynamics of the end distance are much slower than those of the junction angle. In this case, the end distance remains constant at its starting value, and the mean time to fracture is the weighted average of the individual \( \tau_i \). Softer mechanics in one half of the chain then make it more probable that a lower value of \( r \) will be selected from the equilibrium distribution. This lower \( r \) persists over time and allows
the junction to more rapidly reach the cutoff angle.

Fig. 3b,c show the mean time to fracture for chains with different degrees of heterogeneity $h$ in the case of fixed end-to-end distance (infinitely slow $r$ dynamics). In this limit, a purely stiff chain will be slow to reach fracture at the junction because a higher overall chain deformation energy is required to bend the junction to the point of fracture. A purely soft chain will also be slow to reach fracture because the requisite junction angle $\theta^*$ to achieve the same cutoff energy will be correspondingly larger. Rapid fracture can be achieved by a heterogeneous chain, where the junction stiffness and hence the cutoff angle are set by the stiff side of the chain, while the low persistence length of the soft side enables the junction to reach that cutoff angle without moving the chain ends or incurring a substantial cost in chain deformation energy. The enhancement due to chain heterogeneity can reach several orders of magnitude in cases where the junction must reach very steep bending angles in order to fracture (high $N$ and $\Delta$).

For the case with free chain ends, calculating the fracture rate requires an estimation of the rate of chain end dynamics compared to the dynamics in the junction coordinate. Comparison to Brownian dynamics simulations (Fig. 2a) indicates that a good estimate for the chain end dynamic prefactor is given by $k_R/(\delta r)^2 = \frac{6k_BT}{\mu L(2L\delta r)^2}$, corresponding to three-dimensional translational diffusion of a chain of length $L$, over a length scale $2L\delta r$. The dimensionless parameter describing the rate of equilibration in chain end distance compared to the junction angle is then $k_R/\mathcal{D}^{(0)} = 2\Delta^3$.

For chain heterogeneity to enhance thermal fracture, this ratio of rates must be small (i.e. the sampling of junction angles must be substantially faster than the end-to-end motion). However, when $\Delta$ becomes small for a chain of constant length, the junction stiffness $\kappa$ must increase and the fracture process becomes dominated by junction energetics rather than deformation of larger portions of the chain. The fracture rate becomes similar for heterogeneous and homogeneously stiff chains in this case (Fig. 3a,b,h). If the end-to-end dynamics are slowed down by increasing the chain length $L$ while keeping the junction length $\Delta$ constant (Fig. 4b), then the stiff side of the chain becomes more flexible and the fracture enhancement from chain heterogeneity decreases. Overall, the enhancement in fracture rates for a heterogeneous chain with free end conditions maxes out at approximately 15%, even for the rather extreme heterogeneity $h = \ell_{p,1}/\ell_{p,2} = 10$ (Fig. 4).

Our calculations show that filament heterogeneity can substantially enhance the rate of thermal fracture in the case of restricted end-to-end dynamics of the filament. A very modest enhancement is expected for the case of a chain with freely moving ends. We note that the model developed here differs from previous athermal models for fracture which indicated that a heterogeneous chain concentrates stresses at the junction when the chain is forced into a buckled configuration. The enhancement in thermally driven fracture occurs despite the fact that the initial configuration of the chain is allowed to sample from the equilibrium distribution. The contrast between the case of rapid and slow $r$ equilibration (Fig. 3b) highlights the purely dynamic nature of this effect. Fracture enhancement arises from the separation in timescales between fluctuations at the junction versus moving the ends of the entire polymer. The presence of a softer chain region allows a junction to reach steep bending angles without requiring large movements of the chain ends and without paying a large energetic cost for the chain deformation.

The model with restricted chain ends is particularly relevant for the cofilin-mediated severing of actin filaments within a cytoskeletal network. In such networks cross-links and entanglements can effectively restrict the movement of certain positions along the chain, while allowing rapid equilibration of chain positions between the cross-link points. Our results indicate that in such situations, introducing mechanical heterogeneity into the actin filaments by cofilin binding should substantially enhance thermal severing rates.

It should be noted that, in addition to changing the flexibility of actin filaments, cofilin binding also alters the filament twist density. Recent experiments have shown that constraining filaments to prevent torsional equilibration enhances actin filament severing by cofilin. The effect described here centers on severing due to bending fluctuations and may provide a parallel, unrelated mechanism for cofilin-driven fracture. Both twist-based and bending-based severing are expected to depend on the density and mechanics of cross-links in an actin network. By providing a feedback mechanism
between network structure and actin severing dynamics, these physical effects may play an important role in regulating the self-assembly, turnover, and mechanoresponse of cytoskeletal structures.

In addition to helping unravel the mechanisms of actin severing by coflin, the results presented here are generally applicable to the fracture of any semiflexible thermally fluctuating polymer. Enhanced rates of thermally-activated fracture in mechanically heterogeneous chains point towards general principles for controlling the stability of nanoscale systems, including polymer networks, nanotubules, and molecular threads, for a broad range of biological and industrial applications.

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Appendix

Angular dynamics for coupled rigid links

In this section we derive the angular dynamics for two connected rigid links, each of length $\ell$, in a highly viscous fluid. We assume each of the links has a friction coefficient per unit length $\mu$, and that there is a bending modulus $\kappa$ for the junction between the links. This simplified system serves as a basis for deriving the appropriate dynamics of the junction angle for the heterogeneous worm-like chain.

We define a given configuration of the system by the center of mass positions for the two rigid rods ($\vec{r}_1, \vec{r}_2$) and their normalized orientations ($\vec{u}_1, \vec{u}_2$). The overall energy for this configuration is then given by,

$$E = \kappa (1 - \vec{u}_1 \cdot \vec{u}_2) + \frac{\kappa}{2} \left( \vec{r}_1 + \frac{\ell}{2} \vec{u}_1 - \vec{r}_2 + \frac{\ell}{2} \vec{u}_2 \right). \quad (3)$$

Here, the first term corresponds to the bending energy of the junction between the two rods and the second term uses a Lagrange multiplier $\tilde{\lambda}$ to enforce the connectivity of the two inextensible rods at the junction.

In the freely draining approximation, and in the absence of Brownian forces, the overdamped dynamics of such a system are defined by the equations,

$$\zeta_i \frac{d \vec{u}_i}{dt} = -\vec{u}_i \times \nabla E - \vec{u}_i \times \frac{\partial E}{\partial \vec{u}_i},$$

$$\zeta_i \frac{d \vec{r}_i}{dt} = -\frac{\partial E}{\partial \vec{r}_i}, \quad (4)$$

where $\zeta_i$ gives the rotational velocity for each rod ($i = 1, 2$). Here, $\zeta_i = \mu \ell / 12$ is the rotational frictional coefficient of each rod around its center of mass and $\zeta_i = \mu \ell$

the translational friction coefficient[31]. The Lagrange multiplier $\tilde{\lambda}$ can be obtained from the constraints:

$$\frac{d}{dt} \left( \vec{r}_1 + \frac{\ell}{2} \vec{u}_1 - \vec{r}_2 + \frac{\ell}{2} \vec{u}_2 \right) \cdot \vec{u}_1 = 0,$$

$$\frac{d}{dt} \left( \vec{r}_1 + \frac{\ell}{2} \vec{u}_1 - \vec{r}_2 + \frac{\ell}{2} \vec{u}_2 \right) \cdot \vec{u}_2 = 0. \quad (5)$$

Solving these equations yields $\tilde{\lambda} \cdot \vec{u}_i = \frac{6 \kappa (1 - \rho^2)}{\ell (5 - 3 \rho)}$, where $\rho = \vec{u}_1 \cdot \vec{u}_2$. The dynamics of the angular coordinate $\rho$ are then given by,

$$\frac{d \rho}{dt} = \frac{48 \kappa (1 - \rho^2)}{\mu \ell^3 (5 - 3 \rho)} \quad (6)$$

This expression gives the effective friction coefficient for the coordinate $\rho$ according to

$$\frac{d \rho}{dt} = -\frac{1}{\zeta(\rho)} \frac{\partial E}{\partial \rho} = -\frac{\kappa}{\zeta(\rho)} \quad (8)$$

For the angular dynamics of a junction in a continuum worm-like chain, changes in the angle require dragging along a length of chain that should scale as the junction size $\Delta$. By comparing Brownian dynamics simulations with calculations of first passage times on a free energy landscape over the angular coordinate (Fig. 2a), we find that setting $\ell = 2 \Delta$ gives an accurate representation of the dynamics.

Mean first passage time on a 1D landscape

For one-dimensional systems with spatially varying diffusivity $D(x)$ and free energy landscape $F(x)$, it has been shown that the Fokker-Planck equation which correctly reproduces the Boltzmann distribution in the steady state[32] is given by,

$$\frac{DG(x,t|x_0)}{dt} = \partial_x \left[ D(x) \left( \frac{1}{kT} \frac{\partial F}{\partial x} G + \frac{\partial G}{\partial x} \right) \right] \quad (7)$$

where $G(x,t|x_0)$ is the Green’s function giving the distribution of the coordinate $x$ at time $t$ for a system that started at position $x_0$. A corresponding backward Kolmogorov equation can be derived for this system[33] as,

$$\frac{dG}{dt} = -\frac{D(x_0)}{kT} \frac{\partial F}{\partial x_0} \frac{\partial G}{\partial x_0} + D(x_0) \frac{\partial^2 G}{\partial x_0^2} \quad (8)$$

Assuming the system has an absorbing boundary at $a$ and a reflecting boundary at $L$, the mean first passage time is defined based on the probability $Q(t|x_0) = \int_a^L G(x,t|x_0)dx$ that the absorbing boundary has not yet been reached. Namely, the MFPT is given by $T(x_0) = \int_a^L G(x,t|x_0)dx$.
− \int_0^\infty t^{4q/2} \frac{d^q p}{dt^q}. \) We solve for \( T(x_0) \) using Eq. 8 in a manner analogous to previous calculations with a constant diffusivity [34][42]. Assuming an equilibrated distribution of starting positions, the overall mean first passage time is then given by

\[
\langle T \rangle = \frac{1}{\int_a^L e^{-F(z)/kT} \, dz} \times \left[ \int_a^L d \int_x^z d y \int_y^z d z \frac{1}{D(y)} e^{(F(y) - F(z) - F(x))/kT} \right]
\]

(9)

We use numerical integration of Eq. 9 to calculate the mean first passage time for each fixed value of \( r \) over the energy landscape plotted in Fig. 1.

**Brownian dynamics simulations**

Brownian dynamics simulations are used to verify our simplified model for dynamics over a free energy landscape in the \( \rho \) and \( r \) coordinates. We define a discretized version of the heterogeneous worm-like chain model, using the standard bead-rod formalism [43], with very stiff stretching modulus for constraining the length of the rods. Our chains consist of \( n = 20 \) segments of length \( d \), with bending energy

\[
E_{\text{bend}} = \sum_{i=1}^{n-1} \kappa_i \left[ 1 - \cos(\rho_i) \right]
\]

(10)

for \( \rho_i = \cos \theta_i \) and \( \theta_i \) the angle between orientations of each consecutive pair of segments. The prefactor is set to \( \kappa_i = \frac{\ell_B}{d} \) for \( i \leq 10 \) and \( \kappa_i = \frac{\ell_B}{d} \) otherwise. The central bead represents a junction of size \( \Delta = d \).

Chains are initiated in a thermally equilibrated configuration by direct sampling of the segment angles. A standard Brownian dynamics algorithm [44] with 4th-order Runge-Kutta time integration [45] is used to propagate the system forward in timesteps of \( \Delta t = 10^{-4} \frac{d^2 \mu_B}{k_B T} \), where the \( \mu_B \) is the friction coefficient of each bead. Simulations are run until either the central chain angle \( \rho_{10} \) or the end-to-end distance reaches a cutoff value, up to a maximum of \( 10^4 \) timesteps.

Mean first passage times to cutoff cannot be obtained by direct averaging since many chains to not reach the cutoff over the simulation time. Instead, we fit the empirical cumulative distribution function for first passage times to the functional form \( 1 - \exp(-t/\tau) \), to extract the appropriate time-scale for first passage. \( 10^4 \) chains are simulated for each data point plotted in Fig. 2.

* ekoslover@ucsd.edu

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