## Controlling tissue size by active fracture

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Groups of cells, including clusters of cancerous cells, multicellular organisms, and developing organs, may both grow and break apart. What physical factors control these fractures? In these processes, what sets the eventual size of clusters? We develop a framework for understanding cell clusters that can fragment due to cell motility using an active particle model. We compute analytically how the break rate of cell-cell junctions depends on cell speed, cell persistence, and cell-cell junction properties. Next, we find the cluster size distributions, which differ depending on whether all cells can divide or only the cells on the edge of the cluster divide. Cluster size distributions depend solely on the ratio of the break rate to the growth rate—allowing us to predict how cluster size and variability depend on cell motility and cell-cell mechanics. Our results suggest that organisms can achieve better size control when cell division is restricted to the cluster boundaries or when fracture can be localized to the cluster center. Our results link the general physics problem of a collective active escape over a barrier to size control, providing a quantitative measure of how motility can regulate organ or organism size.

How does an organ or an organism control its size? Size is thought to be tightly regulated by feedbacks controlling cell division [1]. However, two recent experiments suggest a different possibility—that the size of a group of cells can arise from a competition between growth, which tends to make the group larger, and random cell motility, which can make the group fracture into multiple pieces, reducing group size. In the metazoan Trichoplax adhaerens, asexual reproduction by fission is driven by motility-induced fractures [2]. Similarly, germline cysts in mice are formed by a combination of cell division and fracture of intercellular bridges by random cell motility [3]. These mechanisms are more reminiscent of how cancerous cells can break from an invading front [4–6] than a well-regulated organism. Can motility-driven fracture reliably regulate the size of a group of cells? Both T. adhaerens and germline cysts show significant variability in size [2, 3]. What physical factors control the group size and its variability?

We argue that the size of cell clusters controlled by fracture is set by competition between the break rate of cell-cell junctions  $k_b$  and the cell division rate  $k_d$ . We model break rate  $k_b$  from a mechanical perspective, using a simple one-dimensional model of cells as active particles connected by springs. The break rate depends on typical cell speed, cell-cell junction strength, and the cell's persistence time. We then develop models of cluster growth and fracture. We derive the exact steady-state cluster size distribution, finding that cluster sizes depend solely on the ratio  $k_b/k_d$ , allowing us to link cluster size to cell adhesion and motility. The quality of cluster size control can be improved if only cells on the edge of the cluster divide or if only cell-cell junctions near the cluster middle can fracture.

*Mechanics.*—We model our cell cluster as a one-dimensional chain of cells. This geometry is reasonable

for the germline cysts [3], and is often found in cells confined in extracellular matrix [5–8]. One dimension may be appropriate for T. adhaerens when it takes on an elongated string-like shape [2], though a higher-dimensional model is necessary for a full study of T. adhaerens. We treat our chain of cells as self-propelled active particles with positions  $\{x_n\}$  connected by springs [Fig. 1(a)], assuming an overdamped environment:

$$\dot{x}_n = -\mu \nabla_n \Phi + v_n(t),\tag{1}$$

where  $\mu$  is the particle mobility and  $\Phi = (1/2)k\sum_{\langle i,j\rangle}(|x_i-x_j|-\ell_0)^2$  is the cell-cell interaction energy. Here, k is the spring constant,  $\ell_0$  is the natural length of the springs, and  $\langle i,j\rangle$  denotes the

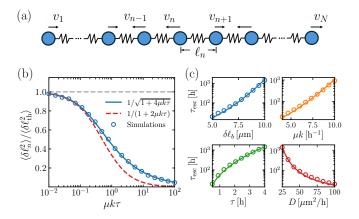


FIG. 1. (a) Illustration of the active chain model. Cells are connected by springs; each cell has active velocity  $v_n$ . (b) Variance of the spring stretch  $\langle \delta \ell_n^2 \rangle$  as a function of  $\mu k \tau$ . Gray dashed line is the thermal variance  $\langle \delta \ell_{\rm th}^2 \rangle = D/\mu k$ . We change  $\mu k \tau$  by varying  $\tau$  while fixing  $\mu k$  in the simulations. Red dashed line is the two-particle result  $\langle \delta \ell^2 \rangle_2$ . (c) Mean escape time  $\tau_{\rm esc} = 1/k_b$ . Empty circles are simulation results with N=1000 cells; solid lines are theory, Eq. (4).

summation over nearest neighbors. The active velocities  $v_n$ —the velocities the cell would have in the absence of cell-cell interactions—are Ornstein-Uhlenbeck (OU) processes [9]:

$$\tau \dot{v}_n = -v_n + \sqrt{2D}\xi_n(t), \tag{2}$$

where  $\xi_n(t)$  are independent, zero-mean, unit-variance Gaussian white noises.  $\tau$  is the persistence time of the cell, while D controls the typical cell speeds— $v_n$  have mean zero and correlations  $\langle v_n(t)v_{n'}(t')\rangle = \delta_{nn'}(D/\tau)\mathrm{e}^{-|t-t'|/\tau}$  if  $t,t'\gg\tau$ . In the limit  $\tau\to 0$ , the active velocities  $v_n$  reduce to Gaussian white noises with correlations  $\langle v_n(t)v_{n'}(t')\rangle = \delta_{nn'}2D\delta(t-t')$ —in this limit the system is in thermal equilibrium, but will be out of equilibrium for a finite  $\tau$ .

What is the mean first time to rupture for a given link, i.e., the time required for the spring to be stretched to a specified threshold? Our initial intuition was that the rupture rate within a cluster would be the same as that of a two-particle link, as in thermal equilibrium. To explore this, we first compute the variance of the stretched length  $\delta \ell = \ell - \ell_0$  (where  $\ell$  is the distance between the particles) in the two-particle case. Extending the approach of Ref. [10], we can map this problem to an inertial Brownian particle in a harmonic potential  $U(\delta \ell) = \mu k \delta \ell^2$  experiencing a friction  $\eta = 1 + 2\mu k\tau$ , and an effective temperature  $k_B T_{\text{eff}} = 2D/\eta$  (see the Supplemental Material [11]). The distribution of  $\delta \ell$  in the steady state is Boltzmannlike  $\sim \exp(-U/k_BT_{\rm eff})$ , i.e., a Gaussian distribution with zero mean and variance  $\langle \delta \ell^2 \rangle_2 = k_B T_{\text{eff}} / U'' = D / \mu k (1 +$  $2\mu k\tau$ ). The subscript indicates this is the two-particle result. When  $\tau=0$ ,  $\langle\delta\ell^2\rangle_2$  approaches the thermal equilibrium solution  $\langle\delta\ell^2_{\rm th}\rangle=D/\mu k$ . If the spring breaks when stretched beyond a critical length  $\delta \ell_b$ , the mean escape time can be estimated using standard Kramers' theory. For small effective temperatures, the time for the pair to break is given by  $\tau_{\rm esc}^{\rm pair} = \tau_0 \exp(\Delta U/k_B T_{\rm eff}) =$  $\tau_0 \exp[\mu k \delta \ell_b^2 (1 + 2\mu k \tau)/2D]$ , where  $\tau_0$  is a subexponential correction [10, 12–15].

For a long chain of  $N \gg 1$  cells, we use a discrete Fourier transform to compute the variance of  $\delta \ell_n = \ell_n - \ell_0$ , where  $\ell_n = x_{n+1} - x_n$  are the interparticle distances (see SM [11]). We find

$$\langle \delta \ell_n^2 \rangle = \frac{D}{\mu k \sqrt{1 + 4\mu k \tau}},\tag{3}$$

different from the two-particle result  $\langle \delta \ell^2 \rangle_2$  at large  $\mu k \tau$  [Fig. 1(b)]. Notably,  $\langle \delta \ell_n^2 \rangle = \langle \delta \ell_{\rm th}^2 \rangle$  when  $\tau \to 0$ , but  $\langle \delta \ell_n^2 \rangle$  also converges to the two-particle result  $\langle \delta \ell^2 \rangle_2$  when  $0 < \mu k \tau \ll 1$ , as shown in Fig. 1(b). This implies that when  $\mu k \tau$  is small but finite, the system resides in an effective equilibrium regime [16], and such a convergence can be understood through a modified equipartition theorem (see SM [11]). In the steady state, the distribution of  $\delta \ell_n$  follows a Gaussian form,  $P_s(\delta \ell_n) \sim$ 

 $\exp(-\delta \ell_n^2/2\langle \delta \ell_n^2 \rangle)$ . The escape rate will be proportional to the probability density at the breaking length  $P_s(\delta \ell_b)$ , yielding [10]

$$k_b = \tau_0^{-1} \exp\left(-\frac{\mu k \delta \ell_b^2 \sqrt{1 + 4\mu k \tau}}{2D}\right),\tag{4}$$

where we have found the subexponential correction  $\tau_0 = \pi \eta/\mu k$  leads to a good fit to the escape time from our simulation of active cell motion [see Fig. 1(c)]. Time to rupture increases with a higher break threshold  $\delta \ell_b$ , stiffer springs, or greater cell persistence, while it decreases if cells are faster (larger D). Unlike the two-particle problem, where the mean escape time grows exponentially with k in equilibrium and  $k^2$  in the  $\mu k \tau \gg 1$  nonequilibrium limit, it grows here exponentially in  $k^{3/2}$  for large k.

Growth models.—We have described an active chain in which links can break at a rate  $k_b$ , while cells can also divide at some rate, leading to an increase in the chain length. What controls the cluster size, and how broad is its distribution? As in germline cysts, where all cells can divide [3], we first assume that each cell divides independently with the same division rate  $k_d$ . To analyze the distribution of the chain length, we randomly pick one of the daughter chains to track once fragmentation occurs. The selected daughter chain then continues to grow and rupture in the same manner as the original chain, as illustrated in Fig. 2(a).

Assuming  $p_n(t)$  gives the probability that the length of the tracked chain at time t is n, the master equation governing such a process is, generalizing [17],

$$\frac{\mathrm{d}p_n}{\mathrm{d}t} = \sum_{m>n} k_b p_m - p_n \sum_{i+j=n} k_b + k_d (n-1) p_{n-1} - k_d n p_n,$$
(5)

where the first two terms on the right-hand side describe the fragmentation process while the last two terms represent the growth of the chain through cell division.  $\sum_{m>n} k_b p_m$  corresponds to the rate of obtaining an nmer through the fragmentation of a longer chain. Though there are two possible rupture points (at n and m-n) when an m-mer breaks to form an n-mer, the random selection of one daughter chain causes the prefactors to cancel out. In the second term,  $\sum_{i+j=n} k_b = (n-1)k_b$ describes the rupture of the n-mer chain into two daughter fragments of lengths (i, j), where (n - 1) is exactly the number of connections within an n-mer chain. The two terms for the growth process give the rates that an (n-1)-mer grows into an *n*-mer, and an *n*-mer grows into an (n+1)-mer, respectively. Using generating functions, we find the steady-state solution:

$$p_n = \frac{\gamma}{(1+\gamma)^n},$$
 (all-cell growth) (6)

where  $\gamma \equiv k_b/k_d$  is the ratio of the break rate to the division rate [11].

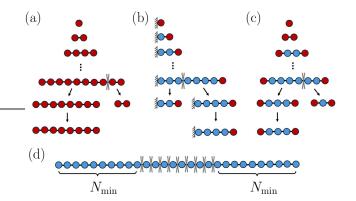


FIG. 2. Growth and fracture of cell groups under different assumptions. (a) All cells can divide. After a rupture occurs, one daughter chain is selected at random. (b) Only the cell at one end of the chain can divide. (c) Only the cells at the two ends can divide. (d) Potential rupture points when a minimum cluster size  $N_{\min}$  is enforced. Rupture can only occur when the chain length  $n \ge 2N_{\min}$ . Red cells have a nonzero division rate  $k_d$ , while blue cells have a division rate of zero; gray crosses indicate actual or potential rupture points.

So far, we have assumed that all cells in the chain can divide. However, cell division may be regulated by mechanical and spatial constraints. Cells with fewer neighbors or experiencing lower compression are more likely to divide—"contact inhibition of proliferation" [18]. As an extreme limit of contact inhibition, we develop alternate models where only cells at the chain ends divide. First, consider the case where only one end of the chain grows—e.g., if the other end is constrained by a barrier. In contrast to the all-cell growth model, where the total growth rate scales as  $k_d n$  (proportional to chain length), in one-end growth, the total growth rate is fixed at  $k_d$  [Fig. 2(b)]. Here, the master equation becomes

$$\frac{\mathrm{d}p_n}{\mathrm{d}t} = \sum_{m>n} k_b p_m - p_n \sum_{i+j=n} k_b + k_d p_{n-1} - k_d p_n.$$
 (7)

We find that the steady-state solution is

$$p_n = n\gamma^{1-n} / \left(\frac{1+\gamma}{\gamma}\right)_n$$
, (one-end growth) (8)

where  $(x)_n = x(x+1)(x+2)\cdots(x+n-1)$  is the Pochhammer symbol [11]. When  $\gamma \ll 1$ ,  $p_n$  can be approximated by a Rayleigh distribution  $n\gamma e^{-\gamma n^2/2}$  with mode  $1/\sqrt{\gamma}$ .

If the chain can grow from both ends, i.e., only the two cells at the two ends can divide, the total growth rate is  $2k_d$ , except when n=1 (the chain has only one particle) where the total growth rate is  $k_d$  [Fig. 2(c)]. For this case, the steady-state solution is [11]

$$p_{n} = \begin{cases} \gamma/(1+\gamma)^{n}, & n = 1, 2, \\ \frac{2+\gamma}{2(1+\gamma)} \frac{n(\gamma/2)^{1-n}}{((2+\gamma)/\gamma)_{n}}, & n > 2. \end{cases}$$
 (two-end)

In the limit of rare breaking  $\gamma \ll 1$  when clusters almost always have two ends,  $p_n$  converges to Eq. (8) with a doubled division rate.

Figure 3(a) shows our theoretical predictions  $p_n$  for the three growth models, validated by Monte Carlo simulations of chain evolution [11]. If all cells can divide, the cluster size distribution is extremely broad with a peak at n = 1; if only end cells divide, we have a better-defined peak at  $n \approx 1/\sqrt{\gamma}$ .

Larger growth rates relative to break rates lead to larger clusters, but does this also result in greater variability of cluster size? With the distributions  $p_n$ , we can compute the means and variances of n [Figs. 3(b) and 3(c)]. In the limit  $\gamma \to 0$ , fragmentation is rare, leading to both increased growth and increased variability in all models, while in the limit  $\gamma \gg 1$ , fragmentation dominates, and clusters become single-celled. To quantify the relative variability, we plot the ratio of the standard deviation of cluster size to the mean (coefficient of variation CV) in Fig. 3(d). We see a key difference between the end-growth models and the all-growth model when  $\gamma \ll 1$ and cluster sizes are large—CV approaches 1 for the allgrowth model, while it approaches  $\sqrt{(4-\pi)/\pi} \approx 0.523$ for end-growth. The CV for end-growth is roughly half that for all-growth, indicating better size control. If the interior cells can still divide, but at a lower rate, the CV is intermediate between end- and all-growth [11].

We have so far assumed all rupture rates to be identical, but secreted factors [19] or stress [20] may vary across the cluster. As a simple model of these effects, we assume that only the junctions sufficiently far from the cluster edge break. This is equivalent to introducing a minimum cluster size  $N_{\min}$  [Fig. 2(d)]. Once we include the constraint that all clusters are larger than  $N_{\min}$ , we cannot solve the master equation analytically. However, in the steady state, we can write it simply as a matrix equation  $\mathbf{Kp} = \mathbf{0}$  which can be easily solved numerically to find  $\mathbf{p}$  [11]. This method leads to good agreement with stochastic simulations [Fig. 3(e)].

In the absence of a minimum cluster size, large cluster sizes always come with an unavoidable variability [Figs. 3(b)-3(d)], while large rupture rates  $\gamma \gg 1$  lead to sizes being precise but  $\langle n \rangle \to 1$ . Given a minimum cluster size, it's possible to have precise size control and finite clusters [Figs. 3(e)-3(h)]. In the limit  $\gamma \gg 1$ , cell clusters grow from size  $N_{\min}$  to  $2N_{\min}$ , then fragment in half. This is very similar to the dynamics of a single cell's growth, akin to a sizer model [21, 22], and leads to distributions  $p_n$  [Fig. 3(e)] like those of single cell size distributions [21–24]. During each growth cycle  $t \in [0, t_c]$ , we have  $\langle n \rangle = N_{\min} e^{k_d t}$  if all cells can divide, where  $t_c = \ln 2/k_d$  is the time required to double the chain's length. Over a long trajectory, any moment within the chain's lifecycle is equally likely to be sampled [21]. If t is uniformly distributed in one cycle  $[0, t_c]$ , then  $p_n$  should obey a log-uniform distribution, as shown in Fig. S1(e)

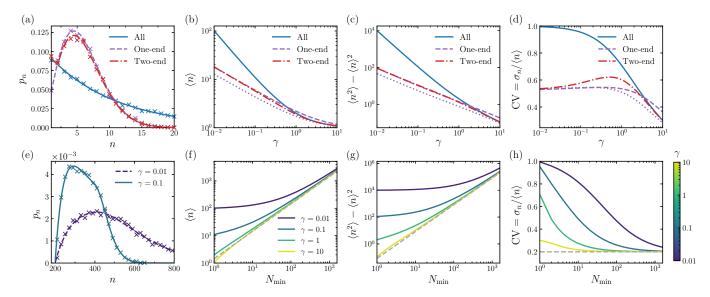


FIG. 3. (a) Steady-state distribution of chain length  $p_n$  for the three growth modes, with  $\gamma=0.1$  for the all-cell growth and two-end growth models, and  $\gamma$  replaced by  $\gamma'=\gamma/2=0.05$  for the one-end growth model (doubled division rate). Crosses represent simulation results, while lines correspond to theoretical predictions. Panels (b)–(d) display the mean  $\langle n \rangle$ , variance  $\langle n^2 \rangle - \langle n \rangle^2$ , and coefficient of variation  $\text{CV} = \sigma_n/\langle n \rangle$ , where  $\sigma_n = \sqrt{\langle n^2 \rangle - \langle n \rangle^2}$ . Purple dashed lines are the one-end result after doubling the division rate  $[\gamma \to \gamma' = \gamma/2 \text{ in Eq. (8)}]$ , while the purple dotted lines show Eq. (8). (e) Steady-state distribution  $p_n$  when minimum cluster size  $N_{\text{min}} = 200$ . Crosses are simulation results, lines are theoretical predictions by the matrix method [11]. Panels (f)–(h) show how mean, variance, and CV vary with  $N_{\text{min}}$  in the all-cell growth model. Gray dashed lines show predictions assuming log-uniform distributions [Eq. (10)].

in the Supplemental Material [11]:

$$p_n = \frac{1}{n \ln 2}, \quad n \in [N_{\min}, 2N_{\min}],$$
 (10)

where the mean is  $\langle n \rangle = N_{\rm min}/\ln 2$  and the variance is  $\langle n^2 \rangle - \langle n \rangle^2 = (3 \ln 2 - 2) \langle n \rangle^2/2$ , i.e., the coefficient of variation CV is independent of  $N_{\rm min}$ , as shown in Figs. 3(f)–3(h). Similarly, if only edge cells can divide, the chain length increases linearly with time.  $p_n$  is then uniformly distributed in  $[N_{\rm min}, 2N_{\rm min}]$ , leading to a mean of  $3N_{\rm min}/2$  and a variance of  $N_{\rm min}^2/12$ . When  $\gamma\gg 1$ , we see mean cluster size scales as  $N_{\rm min}$  and the variance scales as  $N_{\rm min}^2$ , but the CV goes to a nonzero constant as  $\gamma\gg 1$ , and is smaller than for clusters with no minimum size. If we weaken the strict assumption of a minimum cluster size by assuming a basal break rate  $k_b^0$  for all junctions, even small  $k_b^0$  creates a relevant population of small clusters [11].

Combining mechanics and statistics.—According to our theory, the break rate  $k_b$  depends on four key parameters related to cell motility and mechanical properties of the cluster— $\tau$ ,  $\mu k$ , D, and  $\delta \ell_b$ . While these parameters have not yet been measured simultaneously for a single cell type, we can provide reasonable estimates. Experiments measuring velocity correlations of HaCaT cells [25] give a persistence time  $\tau$  of roughly 0.5 hour and D of around  $\sim 100 \, \mu \text{m}^2/\text{h}$ , leading to an active velocity  $v_n$  on the order of  $\sqrt{D/\tau} \approx 15 \, \mu \text{m/h}$ . The mobility  $\mu$  and spring constant k together create a relaxation timescale

 $1/\mu k$ , estimated to be approximately 15 min based on measurements for MDCK cells [8] (details in SM [11]). According to Eq. (4), the break rate  $k_b$  is highly sensitive to the critical break length  $\delta \ell_b$ . As a rough guess,  $\delta \ell_b = 5 \,\mu \text{m}$  yields a mean escape time  $\tau_{\rm esc} \approx 17.6 \,\text{h}$ , or a break rate of approximately  $0.057 \,\text{h}^{-1}$ . This is the right order of magnitude for experiments in germline cyst fracture [3] and cancer cell dissociation [5, 6]. We use these values as our default parameters (Table S1 in [11]).

Our results suggest that clusters of cells may regulate their size not only by changing division rate but also by changing cell motility or persistence or cell-cell adhesion. Recent experiments found that germline cells have motility that decreases as cysts develop, decreasing fracture over time and controlling cyst size [3]. How much does a change in cell properties change cluster size? The break rate and division rate of germline cysts are approximately  $0.02 \,\mathrm{h^{-1}}$  and  $0.04 \,\mathrm{h^{-1}}$  [3], i.e., the ratio  $\gamma \approx 0.5$ , corresponding to a mean cluster size  $\langle n \rangle \approx 3$  in the allcell growth model. (We note this is not the value found by Ref. [3]—their germline cysts do not reach the steady state. If we simulate for only 5 division times, we get similar results to their experiment and model [11].) For germline cysts, we set  $\delta \ell_b = 6.5 \,\mu\mathrm{m}$  to match  $k_b$  to experiment. Cell motility and cell-cell adhesion change  $k_b$  and thus change  $\gamma$ , changing cluster size distributions. For instance, if cells double their adhesiveness by increasing k,  $\gamma$  decreases to approximately 0.0067, leading to a larger cluster size  $\langle n \rangle \approx 150$  with significantly higher variability

 $\sigma_n \approx 150$ . At long developmental times, the break rate of germline cysts drops to under  $1/190\,\mathrm{h^{-1}}$ , which Ref. [3] attributes to changes in cell motility. We find this drop does not require a dramatic change in cell speed. To decrease the break rate to this level, D must decrease by more than a factor of 1.5, i.e., the typical speed of cells needs to decrease by more than a factor of 1.2.

Discussion.—Our work provides a route to understand quantitatively how the size of groups of cells ranging from cancer to organs to organisms can emerge from balancing growth and random cell motility. Our model shows that differences in where cell division and rupture occur can lead to different characteristic distributions of cluster sizes, and that biologically relevant regulation of cluster size can occur from relatively small changes in cell motility. From a physics standpoint, our results show that even in a very simple one-dimensional active material, the collective rupture of a link is nontrivial and can't be understood from the properties of a single pair of cells—unlike in an equilibrium version of our model. This qualitative difference with the simple active trap model [10] suggests that rupture rates may be sensitive to other collective features, e.g., differing between branched and linear chains of cells, or reflecting the degree of cellcell correlation of velocities.

We have generally chosen analytic tractability over biological detail in our approach to capture the key elements of this problem. There are many possible generalizations. These include polymer networks within the cell [26], cell-matrix interactions [27, 28], cell shape [6, 29] and its coupling to division [18, 30], or mechanosensitive feedback [31], as well as cell-cell interactions like contact inhibition of locomotion [32–34] and collective alignment of cell polarity [8, 35]. Determining to what extent these features only change the relevant energy barrier, rescaling k, or qualitatively change our picture is an important open question.

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### **Supplemental Material: Controlling Tissue Size by Active Fracture**

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## I. RATES FOR BREAKING CHAINS USING KRAMERS' THEORY

#### A. Results for two particles

The rupture rate of a pair of cells can be found straightforwardly through a very simple generalization of the approach of Ref. [1], who mapped overdamped active Ornstein-Uhlenbeck particles (AOUPs) in a harmonic well to an equivalent thermal system. Here, we show that the same holds for a pair of harmonically bound AOUPs. For a pair of particles  $\{x_1, x_2\}$  with a distance  $\ell = x_2 - x_1$  between them, we have

$$\dot{x}_1 = \mu k \delta \ell + v_1,$$
  
$$\dot{x}_2 = -\mu k \delta \ell + v_2,$$

where  $\delta\ell = \ell - \ell_0$  is the stretched length of the spring. Thus we can obtain  $\dot{\delta}\ell = -2\mu k\delta\ell + \delta v$ , where  $\delta v = v_2 - v_1$  is the solution of  $\tau \dot{\delta}v = -\delta v + \sqrt{4D}\xi(t)$ —i.e.,  $\delta v$  is still an Ornstein-Uhlenbeck process but with correlation  $\langle \delta v(t) \delta v(t') \rangle = (2D/\tau) \mathrm{e}^{-|t-t'|/\tau}$ . By a standard change of variable  $p = -2\mu k\delta\ell + \delta v$ , we obtain a new set of Langevin equations for a thermal Brownian particle with displacement  $\delta\ell$  [1, 2]:

$$\begin{cases} \dot{\delta \ell} = p, \\ \tau \dot{p} = -\eta p - U' + \sqrt{4D} \xi(t), \end{cases}$$
 (S1)

where the potential  $U(\delta \ell) = \mu k \delta \ell^2$  is harmonic, the persistence time  $\tau$  is acting as a mass, and the drag  $\eta = 1 + 2\mu k \tau$ . Thus an effective temperature can be defined by

$$k_B T_{\text{eff}} := \frac{2D}{\eta} = \frac{2D}{(1 + 2\mu k\tau)}.$$
 (S2)

Then we can write out the Fokker-Planck equation (aka Klein-Kramers equation) from Eq. (S1):

$$\partial_t P(\delta \ell, p, t) = -p \partial_{\delta \ell} P + \frac{1}{\tau} \partial_p (\eta p + U') P + \frac{2D}{\tau^2} \partial_p^2 P,$$

and the stationary solution is given by a Boltzmann-like measure

$$P_s(\delta\ell, p) = \mathcal{Z} \exp\left(-\frac{U}{k_B T_{\text{eff}}} - \frac{\tau p^2}{2k_B T_{\text{eff}}}\right), \quad (S3)$$

where  $\mathcal{Z}$  is the partition function. The variance of  $\delta \ell$  follows directly,

$$\langle \delta \ell^2 \rangle = \frac{k_B T_{\text{eff}}}{U''} = \frac{D}{\mu k (1 + 2\mu k \tau)}.$$

From standard Kramers' theory, for a trap in the potential  $U(\delta \ell)$  of size  $\delta \ell_b$ , the mean escape time, when the effective temperature is small compared to the potential barrier height  $\Delta U = U(\delta \ell_b) - U(0)$ , is given by [3–5]

$$\tau_{\rm esc} = \frac{2\pi}{\omega_0} \exp\left(\frac{\Delta U}{k_B T_{\rm eff}}\right) = \pi \sqrt{\frac{2\tau}{\mu k}} \exp\left[\frac{\mu k \delta \ell_b^2 (1 + 2\mu k \tau)}{2D}\right],$$

where  $\omega_0 = \sqrt{U''/\tau} = \sqrt{2\mu k/\tau}$  is the undamped angular frequency of the system. The subexponential correction  $\tau_0 = 2\pi/\omega_0$  applies in the limit of moderate friction but may vary under different friction regimes [4, 6].

#### B. Results for a long chain

We can explicitly write Eq. (1) in the main text as:

$$\dot{x}_n = \mu k(x_{n+1} - 2x_n + x_{n-1}) + v_n.$$

Assuming that  $x_n(t) = n\ell_0 + \delta x_n(t)$ , where  $\delta x_n$  represents the deviation of  $x_n$  around the lattice point  $n\ell_0$ , we find that  $\delta x_n$  obeys the same equation as  $x_n$ :

$$\dot{\delta x}_n = \mu k (\delta x_{n+1} - 2\delta x_n + \delta x_{n-1}) + v_n. \tag{S4}$$

For a long chain with  $N \gg 1$  particles, it is simpler to solve for the fluctuations of cell-cell distances if we impose periodic boundary conditions,  $\delta x_{n+N} = \delta x_n$ . In principle this could change the amplitude, but we find that in our simulations in Sec. IVA with free boundaries at the end of the chain, the variance  $\langle \delta \ell_n^2 \rangle$  does not depend on n when the number of cells N is large. An alternate approach would be to use a continuum approximation  $(\delta x_{n+1} - 2\delta x_n + \delta x_{n-1}) \approx \partial^2 \delta x / \partial n^2$  as in the Rouse model [7]. We have done this, and the results can well describe the long-wavelength behaviors, but when  $\mu k \tau \ll 1$ , the high-frequency terms become more and more important, and such a long-wavelength approximation breaks down. Therefore, we introduce a standard discrete Fourier transform to the equations of motion for an N-particle chain, as given in Eq. (S4):

$$\tilde{x}_q = \frac{1}{N} \sum_{n=0}^{N-1} \delta x_n e^{-iqn},$$

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where  $q=2\pi m/N$  and the index  $m=0,1,\cdots,N-1$ . The inverse transform is given by  $\delta x_n=\sum_q \tilde{x}_q \mathrm{e}^{iqn}$ . By substituting the inverse transforms into the above Eq. (S4) and matching terms for each mode q, we can then obtain

$$\dot{\tilde{x}}_q = -\mu k_q \tilde{x}_q + \tilde{v}_q, \tag{S5}$$

where  $k_q = 2k(1 - \cos q)$  and  $\tilde{v}_q = (1/N) \sum_{n=0}^{N-1} v_n e^{-iqn}$  is the Fourier amplitude of  $v_n$ . The mean is simply  $\langle \tilde{v}_q \rangle = 0$ , and the time correlation is

$$\langle \tilde{v}_{q}(t)\tilde{v}_{q'}^{*}(t')\rangle = \frac{1}{N^{2}} \sum_{n=0}^{N-1} \sum_{n'=0}^{N-1} \langle v_{n}(t)v_{n'}(t')\rangle e^{-iqn-iq'n'}$$

$$= \delta_{qq'} \frac{D}{N\tau} e^{-|t-t'|/\tau}, \qquad (S6)$$

where we have used the mean and time correlation of  $v_n$ , along with the orthogonality relation  $\sum_{n=0}^{N-1} \mathrm{e}^{i(q-q')n} = N\delta_{qq'}$ . Equation (S5) can be solved by using the exponential ansatz  $\delta \tilde{x}_q = \mathcal{R}_q(t)\mathrm{e}^{-\mu k_q t}$ . When  $t \gg 1/\mu k_q$ , we have

$$\tilde{x}_q(t) = \int_0^t dt' e^{-\mu k_q(t-t')} \tilde{v}_q(t').$$

Thus, for the zeroth mode  $\tilde{x}_0 = (1/N) \sum_n \delta x_n$  (center of mass), which is special because  $k_0 = 0$ , we obtain  $\langle \tilde{x}_0 \rangle = 0$  and  $\langle |\tilde{x}_0(t)|^2 \rangle = 2Dt/N$ . For other modes with  $q \neq 0$ ,  $\langle \tilde{x}_q \rangle = 0$  and

$$\langle \tilde{x}_q(t)\tilde{x}_{q'}^*(t)\rangle = \delta_{qq'}\frac{D}{N\mu k_q(1+\mu k_q\tau)}.$$
 (S7)

Ref. [8] shows that active Brownian particles (ABPs) exhibit a similar relationship, as their active velocities share the same Gaussian colored noise temporal correlations as those of AOUPs. Then we can calculate the stretched lengths of the springs by  $\delta \ell_n = x_{n+1} - x_n - \ell_0 = \delta x_{n+1} - \delta x_n = \sum_{q \neq 0} \tilde{x}_q e^{iqn} (e^{iq} - 1)$ , where the mean is simply  $\langle \delta \ell_n \rangle = 0$ , and the variance is

$$\begin{split} \langle \delta \ell_n^2 \rangle \; &= \; \sum_{q \neq 0} \sum_{q' \neq 0} \langle \tilde{x}_q \tilde{x}_{q'}^* \rangle \mathrm{e}^{i(q-q')n} (\mathrm{e}^{iq} - 1) (\mathrm{e}^{-iq'} - 1) \\ &= \; \frac{D}{N \mu k} \sum_{q \neq 0} \frac{1}{1 + 2 \mu k \tau (1 - \cos q)}. \end{split}$$

In the limit  $N \gg 1$ , we can replace the sum by integral

$$\sum_{q \neq 0} \frac{1}{1 + 2\mu k \tau (1 - \cos q)} \approx \frac{N}{2\pi} \int_0^{2\pi} \frac{\mathrm{d}q}{1 + 2\mu k \tau (1 - \cos q)},$$

which equals  $N/\sqrt{1+4\mu k\tau}$ . Then, we obtain the variance of  $\delta \ell_n$  given in the main text:

$$\langle \delta \ell_n^2 \rangle = \frac{D}{\mu k \sqrt{1 + 4\mu k \tau}}.$$
 (S8)

Thus, in the steady state, the marginal distribution of  $\delta\ell_n$  follows a Gaussian distribution  $P_s(\delta\ell_n) = \mathcal{Z} \exp(-\delta\ell_n^2/2\langle\delta\ell_n^2\rangle)$  since each  $\delta\ell_n$  is the sum of Gaussian processes, and each  $\delta x_n$  is similarly a Gaussian process. In the small noise limit, the system rapidly relaxes from  $P_s(\delta\ell_n)$  to a quasi-stationary state described by  $P_{\rm QS}(\delta\ell_n,t) \sim P_s(\delta\ell_n)\,{\rm e}^{-t/\tau_{\rm esc}}$ , indicating that the escape process is Poissonian with a rate of  $1/\tau_{\rm esc}$  [1]. Therefore, the mean escape time follows an effective "Arrhenius law" where the rate of rupture is proportional to the probability density at the breaking stretch  $\delta\ell_b$ ,  $\tau_{\rm esc}^{-1} \sim P_s(\delta\ell_b)$  [1]. We then can find the mean escape time is given by

$$\tau_{\rm esc} \sim \exp\left(\frac{\mu k \delta \ell_b^2 \sqrt{1 + 4\mu k \tau}}{2D}\right).$$

We propose the result

$$\tau_{\rm esc} = \frac{2\pi\eta}{\omega_0^2 \tau} \exp\left(\frac{\mu k \delta \ell_b^2 \sqrt{1 + 4\mu k \tau}}{2D}\right).$$
 (S9)

We originally derived this as  $2\pi\eta/\sqrt{U''(0)|U''(\delta\ell_b)|}$ , which is the prefactor appropriate to an overdamped thermal escape [4]. However, its application to this case, where the potential is a cusp, is somewhat ad hoc—we view this as a reasonable first approximation, and it has a good fit to the simulated rates. While the prefactor may be slightly different under different parameter regimes, the leading behavior for small effective temperatures is dominated by the exponential term [1]—so the prefactor is essentially only serving to set the units of the problem, and its magnitude can be neglected.

## C. When is the two-cell result the *N*-cell result?—an effective equipartition theorem

For the thermal equilibrium case where  $\tau=0$ , the variances of stretched lengths for both a cell pair  $\langle \delta \ell^2 \rangle$  and a chain  $\langle \delta \ell^2_n \rangle$  are identical, given by  $\langle \delta \ell^2_{\rm th} \rangle = D/\mu k$ . This result can be easily verified using the equipartition theorem. For a long chain, the energy of the system is expressed as  $\Phi=(1/2)k\sum_n \delta \ell^2_n$ . Due to translational symmetry in the limit  $N\gg 1$ , we have

$$\langle \Phi \rangle = \frac{N}{2} k \langle \delta \ell_n^2 \rangle = \frac{N}{2} k_B T,$$

where  $k_BT = D/\mu$  from the Einstein relation, thus we obtain  $\langle \delta \ell_n^2 \rangle = D/\mu k$ . For a particle pair,  $\Phi = (1/2)k(x_2 - x_1 - \ell_0)^2 = (1/2)k\delta\ell^2$ , we then get the same result by applying the equipartition theorem.

However, we note that the results for both the pair and the chain also converge to the same non-equilibrium value when  $\mu k \tau \ll 1$  because  $\sqrt{1+4\mu k \tau} \to 1+2\mu k \tau$  for small  $\mu k \tau$ . Why should an active system with a finite persistence time  $\tau$  (nonequilibrium) still show that

 $\langle \delta \ell^2 \rangle_{\rm pair} = \langle \delta \ell_n^2 \rangle_{\rm chain}$ , as if some equipartition theorem applied? In Ref. [9], Fodor *et al.* found that for a system of interacting AOUPs, at small but finite persistence time  $\tau$ , there exists an *effective equilibrium* regime—the particle dynamics still respects detailed balance and timereversal symmetry—the entropy production rate vanishes. Rather than defining an effective temperature as in Sec. IA, the authors stated that the system could be equivalently described using an effective potential, while defining  $k_B T = D/\mu$  [9, 10]:

$$\tilde{\Phi} = \Phi + \tau \left[ \frac{\mu}{2} (\nabla_n \Phi)^2 - D \nabla_n^2 \Phi \right] + \mathcal{O}(\tau^2).$$
 (S10)

Note that we have restored the mobility  $\mu$  which was set to one in Refs. [9, 10], and  $\nabla_n \equiv \partial/\partial x_n$  denotes the derivative with respect to  $x_n$ , not  $\delta \ell_n$ . The Einstein summation convention is applied here, i.e.,  $(\nabla_n \Phi)^2 = \sum_n (\partial_{x_n} \Phi)^2$  and  $\nabla_n^2 \Phi = \sum_n \partial_{x_n}^2 \Phi$ . For a particle pair, we have  $(\nabla_n \Phi)^2 = 2k^2(x_2 - x_1 - \ell_0)^2 = 2k^2\delta\ell^2$ , and  $\nabla_n^2 \Phi = 2k$ , which is a constant and can therefore be disregarded. Applying equipartition on this effective potential,

$$\langle \tilde{\Phi} \rangle = \frac{1}{2} k (1 + 2\mu k \tau) \langle \delta \ell^2 \rangle = \frac{1}{2} k_B T,$$

the variance derived in Sec. IA follows immediately. For a long chain, it yields  $(\nabla_n \Phi)^2 = k^2 \sum_n (x_{n+1} - 2x_n + x_{n-1})^2 = k^2 \sum_n (\delta \ell_{n+1} - \delta \ell_n)^2$ , and  $\nabla_n^2 \Phi = 2Nk$ , which is also a constant. Therefore, we have

$$\frac{N}{2}k\left[\left\langle\delta\ell_{n}^{2}\right\rangle+2\mu k\tau\left(\left\langle\delta\ell_{n}^{2}\right\rangle-\left\langle\delta\ell_{n}\delta\ell_{n+1}\right\rangle\right)\right]=\frac{N}{2}k_{B}T,$$

where we have used the translational symmetry of the system. We can directly calculate  $\langle \delta \ell_n \delta \ell_{n+1} \rangle$ , the correlation between adjacent stretched lengths as

$$\begin{split} &\sum_{q\neq 0} \sum_{q'\neq 0} \langle \tilde{x}_q \tilde{x}_{q'}^* \rangle \mathrm{e}^{iqn-iq'(n+1)} (\mathrm{e}^{iq}-1) (\mathrm{e}^{-iq'}-1) \\ &= \frac{D}{N\mu k} \sum_{q\neq 0} \frac{\cos q}{1+2\mu k \tau (1-\cos q)} \\ &\approx \frac{D}{2\pi\mu k} \int_0^{2\pi} \mathrm{d}q \; \frac{\cos q}{1+2\mu k \tau (1-\cos q)} \\ &= \langle \delta \ell_n^2 \rangle \frac{1+2\mu k \tau - \sqrt{1+4\mu k \tau}}{2\mu k \tau}. \end{split}$$

Since  $\sqrt{1+2x}=1+x-x^2/2+\mathcal{O}(x^3)$ , we have  $\langle \delta \ell_n \delta \ell_{n+1} \rangle \approx \mu k \tau \langle \delta \ell_n^2 \rangle \ll \langle \delta \ell_n^2 \rangle$  when  $\mu k \tau \ll 1$ . Thus, the above equation for a chain yields the two-particle result  $\langle \delta \ell_n^2 \rangle \approx D/\mu k (1+2\mu k \tau)$  when  $\mu k \tau \ll 1$ .

# II. SOLVING THE MASTER EQUATION FOR DIVISION AND FRACTURE WITH GENERATING FUNCTIONS

#### A. All particles can divide

To solve the master equation (5) in the main text, we first define a generating function as

$$G(z,t) := \sum_{n \ge 1} p_n(t) z^n. \tag{S11}$$

We then multiply the master equation by  $z^n$  and sum over all n, so the left-hand side becomes  $\partial G(z,t)/\partial t$ . On the right-hand side, the first term is

$$k_b \sum_{n \ge 1} z^n \cdot \sum_{m > n} p_m$$

$$= k_b \sum_{m > 1} p_m \cdot \sum_{n = 1}^{m - 1} z^n = k_b \sum_{m > 1} p_m \frac{z - z^m}{1 - z}$$

$$= k_b \frac{z}{1 - z} \sum_{m > 1} p_m - k_b \frac{1}{1 - z} \sum_{m > 1} p_m z^m$$

$$= \frac{k_b z}{1 - z} (1 - p_1(t)) - \frac{k_b}{1 - z} (G(z, t) - p_1(t)z)$$

$$= \frac{k_b}{1 - z} (z - G(z, t)),$$

where we interchange the order of summation in the first step, and we have used the normalization condition  $\sum_{m} p_{m} = 1$  in the penultimate step. The second term is

$$-k_b \sum_{n>1} z^n (n-1) p_n = -k_b \left( z \frac{\partial G}{\partial z} - G \right),$$

and the third term is

$$k_d \sum_{n \geqslant 1} z^n (n-1) p_{n-1} = k_d z^2 \frac{\partial}{\partial z} \sum_{n \geqslant 1} p_{n-1} z^{n-1} = k_d z^2 \frac{\partial G}{\partial z},$$

where we have used the condition  $p_n(t) \equiv 0$  when n = 0. The last term is

$$-k_d \sum_{n \geqslant 1} z^n n p_n = -k_d z \frac{\partial G}{\partial z}.$$

Hence, we obtain a partial differential equation (PDE) for the generating function:

$$\frac{\partial G}{\partial t} = (k_d z - k_b - k_d) z \frac{\partial G}{\partial z} - k_b \frac{z}{1 - z} G + k_b \frac{z}{1 - z}, \text{ (S12)}$$

where the steady-state solution is

$$G(z) = \frac{k_b - (1 - z)C}{k_b + k_d - k_d z},$$
 (S13)

where C is a constant we have to set. Expanding G(z) in powers of z, we get

$$G(z) = \frac{k_b - C}{k_b + k_d} + \frac{k_b(C + k_d)}{(k_b + k_d)^2} z + \mathcal{O}(z^2).$$

By construction, our function G(z) has no zeroth-order term, so the constant must be  $C=k_b$ . We could also find this constant by explicitly solving the original master equation for  $p_1$ :  $\mathrm{d}p_1/\mathrm{d}t = \sum_{m>1} k_b p_m - k_d p_1 = k_b (1-p_1) - k_d p_1$ . In the steady state, setting  $\mathrm{d}p_1/\mathrm{d}t = 0$  gives  $p_1 = k_b/(k_b + k_d)$ . This result holds for all three growth models, as the master equation for n=1 remains the same in each case. Matching the first-order coefficient to  $p_1$  gives the same value of  $C=k_b$ . Using this value of C in Eq. (S13), we find the steady-state generating function is given by

$$G(z) = \frac{k_b z}{k_b + k_d - k_d z} = \sum_{n \ge 1} \frac{k_b}{k_d} \left(\frac{k_d}{k_b + k_d}\right)^n z^n.$$
 (S14)

We can read the value of  $p_n$  directly from this formal series, finding Eq. (6) in the main text:

$$p_n = \frac{k_b}{k_d} \left( \frac{k_d}{k_b + k_d} \right)^n = \frac{\gamma}{(1 + \gamma)^n}, \quad (S15)$$

where we define the ratio  $\gamma := k_b/k_d$ . When  $\gamma \to 0$ ,  $p_n \approx \gamma(1 - n\gamma)$ ; when  $\gamma \gg 1$ ,  $p_n \approx 1/\gamma^{n-1}$  decreases exponentially with n. The first two moments are

$$\langle n \rangle = \sum_{n} p_n n = \frac{1+\gamma}{\gamma},$$
 (S16a)

$$\langle n^2 \rangle = \sum_n p_n n^2 = \frac{(1+\gamma)(2+\gamma)}{\gamma^2}, \quad \text{(S16b)}$$

and the variance is

$$\langle n^2 \rangle - \langle n \rangle^2 = \frac{1+\gamma}{\gamma^2} = \frac{\langle n \rangle}{\gamma}.$$
 (S17)

We can also calculate the coefficient of variation (CV) as

$$CV := \frac{\sigma_n}{\mathbb{E}[n]} = \frac{\sqrt{\langle n^2 \rangle - \langle n \rangle^2}}{\langle n \rangle} = \frac{1}{\sqrt{1+\gamma}}, \quad (S18)$$

where  $\sigma_n$  represents the standard deviation of n, and  $\mathbb{E}[n]$  denotes the expected value of n.

#### B. One-end growth

To solve Eq. (7) in the main text, we can still apply the generating function method. The first two terms on the right-hand side are the same as in the all-cell growth case, but the last two terms after multiplication by  $z^n$ and summing over n become

$$k_d \sum_{n>1} z^n p_{n-1} = k_d z \sum_{n>1} z^{n-1} p_{n-1} = k_d z G,$$

and

$$-k_d \sum_{n \ge 1} z^n p_n = -k_d G.$$

Hence, the PDE for G(z,t) for the one-end-growth model is given by

$$\frac{\partial G}{\partial t} = -k_b z \frac{\partial G}{\partial z} - \left(k_d (1-z) + k_b \frac{z}{1-z}\right) G + k_b \frac{z}{1-z}.$$

Then the steady-state solution is

$$G(z) = \frac{(1-z)}{z^{1/\gamma}} e^{z/\gamma} \left( \int_1^z \frac{x^{1/\gamma}}{(1-x)^2} e^{-x/\gamma} dx + C \right).$$

Similarly, we can determine the constant C by matching the conditions  $p_0 = 0$  and  $p_1 = k_b/(k_b + k_d)$ :

$$C = \int_0^1 \frac{x^{1/\gamma}}{(1-x)^2} e^{-x/\gamma} dx,$$

so the generating function is given by

$$G(z) = \frac{(1-z)}{z^{1/\gamma}} e^{z/\gamma} \int_0^z \frac{x^{1/\gamma}}{(1-x)^2} e^{-x/\gamma} dx.$$
 (S19)

Expanding G(z) around z = 0, we obtain Eq. (8) in the main text:

$$p_n = \frac{n\gamma}{\prod_{m=1}^n (1+m\gamma)} = \frac{n\gamma^{1-n}}{((1+\gamma)/\gamma)_n},$$
 (S20)

where  $(x)_n = x(x+1)(x+2)\cdots(x+n-1) = \sum_{k=0}^{n-1}(x+k)$  denotes the Pochhammer symbol. The distribution  $p_n$  for one-end growth is shown in Fig. S1(b), where a distinct peak (or typical scale of n) is observed. When  $\gamma \gg 1$ ,  $p_n \approx \gamma^{1-n}/(n-1)!$  deceases faster than the all-cell growth results. Since n=1 becomes the most probable outcome when  $\gamma$  is large, statistical quantities such as the mean and variance should converge to those of the all-cell growth model. For small  $\gamma$ , to determine the location of the peak in  $p_n$ , we compute the ratio:

$$\frac{p_{n+1}}{p_n} = \frac{n+1}{n} \frac{1}{1 + (n+1)\gamma}.$$

By setting  $p_{n+1}/p_n = 1$ , we arrive at the equation  $n(n+1) = 1/\gamma$ , which implies the peak  $n^* \approx 1/\sqrt{\gamma}$ , and  $n^* \gg 1$  when  $\gamma \ll 1$ . The log-probability function is given by

$$\ln p_n = \ln(n\gamma) - \sum_{m=1}^n \ln(1 + m\gamma).$$

For large n and small  $\gamma$ , the sum can be approximated by  $\int_0^n \ln(1+m\gamma) \, \mathrm{d}m \approx \int_0^n m\gamma \, \mathrm{d}m = \gamma n^2/2$ . Thus, when  $\gamma \ll 1$ , the distribution near the peak  $n=n^*$  can be approximated as

$$p_n \approx f(n; \sigma) = n\gamma e^{-\gamma n^2/2},$$
 (S21)

where  $f(n; \sigma)$  is a Rayleigh distribution with mode  $\sigma = 1/\sqrt{\gamma}$ . Therefore, when  $\gamma \ll 1$ , we can use the saddle-point approximation to compute the average of any X(n):

$$\langle X(n) \rangle = \sum_{n} p_n X(n) \approx \int_0^\infty p_n X(n) dn$$
  
  $\approx \int_0^\infty f(n; \sigma) X(n) dn.$ 

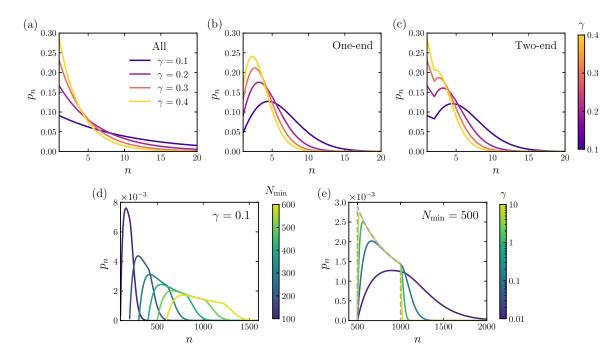


FIG. S1. How the steady-state distributions  $p_n$  vary with  $\gamma$  and  $N_{\min}$  across different growth models. (a) Steady-state distribution  $p_n$  for various values of  $\gamma$  in the all-cell growth model [Eq. (S15)]. (b) Steady-state distribution  $p_n$  for different  $\gamma$  in the one-end growth model, where we have doubled the division rate  $[\gamma \to \gamma' = \gamma/2 \text{ in Eq. (S20)}]$ . (c) Steady-state distribution  $p_n$  for different  $\gamma$  in the two-end growth model from Eq. (S25). (d) Steady-state distribution  $p_n$  obtained from the matrix equation  $K\mathbf{p} = \mathbf{0}$  incorporating different values of minimum cluster size  $N_{\min}$  with  $\gamma = 0.1$ . (e) Steady-state distribution  $p_n$  obtained from the matrix equation method for different values of  $\gamma$  with  $N_{\min} = 500$ . The gray dashed line represents the corresponding log-uniform distribution  $1/(n \ln 2)$  within the range  $[N_{\min}, 2N_{\min}]$ .

Thus, the mean and variance of n are directly obtained from the Rayleigh distribution:

$$\langle n \rangle = \sigma \sqrt{\frac{\pi}{2}}, \quad \langle n^2 \rangle - \langle n^2 \rangle = \frac{4 - \pi}{2} \sigma^2,$$
 (S22)

and the coefficient of variation is

$$CV = \frac{\sqrt{\langle n^2 \rangle - \langle n^2 \rangle}}{\langle n \rangle} = \sqrt{\frac{4 - \pi}{\pi}}.$$
 (S23)

#### C. Two-end growth

For the two-end growth scenario, the master equation is described by Eq. (5) for n = 1 and n = 2, and by Eq. (7) with a doubled division rate for n > 2:

$$\frac{\mathrm{d}p_n}{\mathrm{d}t} = \begin{cases} \mathcal{F}(k_b) + 0 - k_d p_n, & n = 1, \\ \mathcal{F}(k_b) + k_d p_{n-1} - 2k_d p_n, & n = 2, \\ \mathcal{F}(k_b) + 2k_d p_{n-1} - 2k_d p_n, & n > 2, \end{cases}$$

where  $\mathcal{F}(k_b) = k_b \sum_{m>n} p_m - k_b(n-1)p_n$  represents the fragmentation process which remains unchanged. Using the generating function method, multiplying the master equation by  $z^n$  and summing over n, the generating function corresponding to  $\mathcal{F}(k_b)$  are just the ones we derived

before. However, the last two terms in the master equation become

$$0 + k_d p_1 z^2 + 2k_d \sum_{n>2} p_{n-1} z^n = -k_d p_1 z^2 + 2k_d z G,$$

and

$$-k_d p_1 z - 2k_d \sum_{n \geqslant 2} p_n z^n = k_d p_1 z - 2k_d G.$$

In the steady state, we have  $p_1 = k_b/(k_b + k_d)$  and  $\partial G/\partial t = 0$ , so we obtain the equation:

$$k_b z \frac{\partial G}{\partial z} = -\left(2k_d(1-z) + k_b \frac{z}{1-z}\right) G + k_b \frac{z}{1-z} + \frac{k_b k_d}{k_b + k_d} z (1-z).$$
(S24)

The solution is given by

$$G(z) = \frac{(1-z)}{z^{2/\gamma}} e^{2z/\gamma} \int_0^z \frac{x^{2/\gamma} (x^2 - 2x + 2 + \gamma)}{(1+\gamma)(1-x)^2} e^{-2x/\gamma} dx,$$

where the integration constant has been set as

$$C = \int_0^1 \frac{x^{2/\gamma}(x^2 - 2x + 2 + \gamma)}{(1+\gamma)(1-x)^2} e^{-2x/\gamma} dx,$$

to match  $p_0 = 0$ , and  $p_1 = k_b/(k_b + k_d)$ . By expanding G(z) around z = 0, we derive the exact analytical solution for two-end growth case:

$$p_n = \begin{cases} \gamma/(1+\gamma), & n = 1, \\ \frac{2+\gamma}{2(1+\gamma)} \frac{n(\gamma/2)^{1-n}}{((2+\gamma)/\gamma)_n}, & n \geqslant 2. \end{cases}$$
 (S25)

Observe that the results are quite similar to the oneend growth case, but with a doubled division rate  $2k_d$ [equivalent to replacing  $\gamma$  with  $\gamma/2$  in Eq. (S20)]. When  $\gamma \to 0$ , meaning only growth without fragmentation, the two scenarios converge. In contrast, when  $\gamma \gg 1$ , the chain is most likely to be a monomer  $(p_1 \approx 1)$ , and  $p_n$  is reduced by half compared to the one-end growth scenario with  $2k_d$  for  $n \geqslant 2$ .

# III. GENERALIZATIONS TO THE MODEL WITH A MATRIX EQUATION METHOD

A general master equation with a minimum cluster size  $N_{\min}$  and different growth mechanisms can be written as

$$\frac{\mathrm{d}p_n}{\mathrm{d}t} = k_b \sum_{m \ge n + N_{\min}} p_m - k_b \max(n - 2N_{\min} + 1, 0)p_n + g(n - 1)p_{n-1} - g(n)p_n, \quad (n \ge N_{\min})$$
 (S26)

where we have incorporated in the first term that given a minimum cluster size  $N_{\min}$ , a cluster of size m can only break into one of size n if  $m \ge n + N_{\min}$ . In the second term, we require that both daughter clusters must satisfy  $i, j \ge N_{\min}$ , i.e., this term is

$$p_n \sum_{\substack{i+j=n\\i,j \geqslant N_{\min}}} k_b = k_b \max(n - 2N_{\min} + 1, 0) p_n, \quad (S27)$$

where max acts as an activation function indicating that the chain can only break once it has grown to at least  $2N_{\min}$ . In the third and fourth terms of our general master equation [Eq. (S26)], g(n) describes how the total growth rate scales with the length of the chain:

$$g(n) := \begin{cases} k_d n, & \text{all-cell,} \\ k_d, & \text{one-end,} \\ k_d [1 + \Theta(n-2)], & \text{two-end,} \end{cases}$$
 (S28)

where  $\Theta(x)$  is the Heaviside step function, with the convention  $\Theta(0) = 1$  adopted throughout this paper. Then, the master equation can be organized as

$$\frac{\mathrm{d}p_n}{\mathrm{d}t} = k_b \sum_{m \geqslant n + N_{\min}} p_m + g(n-1)p_{n-1} - \lambda(n)p_n, \text{ (S29)}$$

where  $\lambda(n) := k_b \max(n-2N_{\min}+1,0) + g(n)$  is the total transition rate from n-mer state to other states. As a continuous-time Markov chain, Eq. (S29) can be written in the matrix form as  $\dot{\mathbf{p}} = K\mathbf{p}$ , where K is the generator on the state space  $\{N_{\min}, N_{\min}+1, N_{\min}+2, \cdots\}$ . For simplicity, we decompose K = A + B, where A is a

smaller upper triangular matrix:

and B is a lower bidiagonal matrix:

$$\boldsymbol{B} = \begin{pmatrix} -\lambda(N_{\min}) & 0 & 0 & \cdots \\ g(N_{\min}) & -\lambda(N_{\min}+1) & 0 & \cdots \\ 0 & g(N_{\min}+1) & -\lambda(N_{\min}+2) & \cdots \\ 0 & 0 & g(N_{\min}+2) & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix},$$

i.e., the main diagonal  $B_{nn}=-\lambda(n)$  and subdiagonal  $B_{n+1,n} = g(n)$ . Note that the transition-rate matrix **K** satisfies the property  $K_{nn} = -\sum_{m \neq n} K_{mn}$ , namely, the columns of the matrix sum to zero. In the steady state, we obtain a homogeneous equation Kp = 0. We can then find the null space of K and normalize it to obtain the steady-state distribution **p**, ensuring that  $\sum_{n\geqslant N_{\min}} p_n = 1$ . Note that to solve this equation numerically, we must truncate to a maximum possible cluster size  $N_{\text{max}} \gg 2N_{\text{min}}$ , where  $p_n$  is negligible for  $n > N_{\text{max}}$ .  $N_{\rm max}$  is set to  $N_{\rm min}$  + 5000 by default in our calculations. It is also possible to incorporate the normalization condition into the matrix K by adding an extra row  $(1, 1, 1, \cdots)$  at the top, forming a new matrix K'. Then the matrix equation becomes K'p = c, where  $\mathbf{c} = (1, 0, 0, \cdots)^{\top}$ . Note that  $\mathbf{K}'$  is not a square matrix after adding the normalization row. However, by

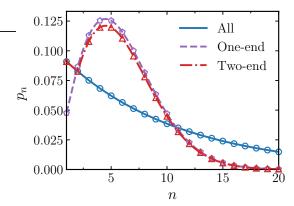


FIG. S2. Comparison of the analytical solution obtained using the generating function method with numerical results from the matrix equation method. Lines represent the same analytical solutions for  $\gamma=0.1$  as shown in Fig. 3(a) in the main text ( $\gamma'=\gamma/2=0.05$  for the one-end growth model). Empty symbols denote exact numerical results from the matrix equation  $K\mathbf{p}=\mathbf{0}$ .

multiplying the matrix equation by  $\mathbf{K}'^{\top}$  from the left, the product  $\mathbf{K}'^{\top}\mathbf{K}'$  becomes square again, allowing us to compute its inverse. The final solution is given by  $\mathbf{p} = (\mathbf{K}'^{\top}\mathbf{K}')^{-1}\mathbf{K}'^{\top}\mathbf{c}$ . When setting  $N_{\min} = 1$ , the solutions  $\mathbf{p}$  match those derived in Sec. II using the generating function method (see Fig. S2).

#### A. Basal rates

So far we have assumed that both the end-growth and minimum cluster size models are strictly enforced, meaning that break and division rates are either at their maximum values or completely suppressed. However, in real cell clusters, it is not clear whether breakage would be completely absent, even if its rate is larger near the cluster center. Similarly, cells within a cluster may still divide despite contact inhibition of proliferation. Therefore, it is reasonable to incorporate basal rates into our model—changing the model so that every cell has a basal rate of division and every junction has a basal rate of fracture. This is straightforward with the matrix equation method.

We first consider a scenario where, in addition to the regulated break rate  $k_b$  (restricted by the minimum cluster size), there exists a basal break rate  $k_b^0$  that applies uniformly to all links. In our matrix equation formulation, we solve  $\mathbf{K}\mathbf{p} = \mathbf{0}$ , where now  $\mathbf{p} = (p_1, p_2, p_3, \cdots)^{\top}$ , rather than  $(p_{N_{\min}}, p_{N_{\min}+1}, p_{N_{\min}+2}, \cdots)^{\top}$ . We continue to decompose the transition-rate matrix as  $\mathbf{K} = \mathbf{A} + \mathbf{B}$ , where  $\mathbf{A}$  remains an upper triangular matrix, but with modified elements  $A_{mn} = \Theta(n - m - 1)k_b^0 + \Theta(m - N_{\min})\Theta(n - m - N_{\min})k_b$ . Note that the second term corresponds exactly to the original matrix  $\mathbf{A}$ .  $\mathbf{B}$  remains the bidiagonal matrix but is updated with the total transition

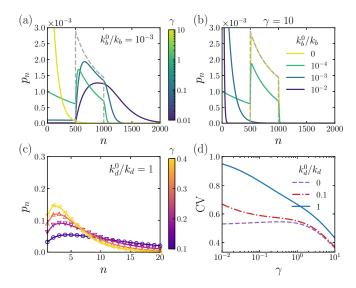


FIG. S3. Effect of basal break and division rates on the steady-state distributions  $p_n$ . (a) Cluster sizes when  $N_{\min} = 500$  and  $\gamma$  is varied, but with a basal break rate  $k_b^0 = 10^{-3} k_b$ , i.e., the basal break rate varies when  $\gamma$  changes; this figure should be compared to Fig. S1(e). (b) The near-deterministic case  $\gamma = 10$  with varying basal break rates  $k_b^0$ . Minimum cluster size is set to  $N_{\min} = 500$ ; gray dashed lines are the corresponding log-uniform distributions. (c) The same distribution as in Fig. S1(b), but with a basal division rate  $k_d^0 = k_d$ . (d) Coefficients of variation (CV) as a function of  $\gamma$  for different basal division rates  $k_d^0$ . Note that we have used  $\gamma \to \gamma' = \gamma/2$ , as in Figs. S1(b) and 3(d).

rate  $\lambda(n) = k_b^0(n-1) + k_b \max(n-2N_{\min}+1,0) + g(n)$ . Figure S3(a) illustrates how the steady-state distributions change, as in Fig. S1(e), when a small basal break rate  $k_b^0 = 10^{-3} k_b$  is applied to all links, while keep the definition  $\gamma := k_b/k_d$ . For small  $k_b^0$  (low  $\gamma$ ), the distribution remains nearly unchanged, but as  $k_b^0$  increases with increasing  $\gamma$  (near-deterministic), it effectively relaxes the minimum cluster size constraint, shifting the distribution toward an exponential decay. Figure S3(b) further demonstrates this effect for a near-deterministic break case ( $\gamma = 10$ ), where the distribution gradually leaks into  $n < N_{\min}$ . We note that the basal break rate does not have to be very large in order to qualitatively change our results—even if the basal break rate is a factor of 100 lower than  $k_b$ , it can overwhelm the "controlled" break rate that respects  $N_{\min}$ , leading to a system dominated by small clusters, as when all links break at the same rate. This may argue that the limit of fast rupture  $\gamma \gg 1$  is not a biologically robust way to control size, since it requires a very small basal break rate.

If a basal division rate  $k_d^0$  is introduced, the results are relatively straightforward—the system simply transitions from the end-growth case to the all-growth case. Within our matrix equation framework—e.g., in the one-end growth model—the total growth rate becomes:  $g(n) = k_d^0 n + k_d$ . This modification allows all cells to divide

at a small but finite rate  $k_d^0$ . In the near-deterministic limit  $\gamma \gg 1$ , the distribution transitions from a uniform distribution in the range  $[N_{\min}, 2N_{\min}]$  to the predicted log-uniform distribution in the all-cell growth model. To check whether some of the key qualitative results in the end-growth model are still preserved, we set  $N_{\min} = 1$ and observe that the steady-state distribution remains largely unchanged until  $k_d^0$  becomes comparable to  $k_d$ . Figure S3(c) shows the distributions  $p_n$  corresponding to Fig. S1(b), but with a basal division rate  $k_d^0 = k_d$ . While the peaks persist,  $p_n$  increasingly resembles the all-growth case [Fig. S1(a)] with long exponential tails. Regarding relative errors, the coefficients of variation remain < 1 and gradually approach the all-growth results as  $k_d^0$  increases. We expect the key factor of the relevance of the basal growth rate is whether growth is dominated by basal growth or end-growth, i.e., for the most common cluster sizes n, whether  $nk_d^0$  or  $2k_d$  is larger. This means that if there is a basal growth rate, as cluster sizes get larger and larger, we would expect that the system looks more and more like the all-growth case. We see this in Fig. S3(d) for  $k_d^0 = 0.1k_d$ : As  $\gamma \ll 1$ , the CV transitions from the end-growth value and starts to increase, presumably reaching eventually to CV = 1 as  $\gamma$  becomes small enough.

#### IV. MONTE CARLO SIMULATIONS

#### A. Active-particle simulations

We simulate the dynamics of N active Ornstein-Uhlenbeck particles (AOUPs) described by Eq. (1) using the forward Euler method (Euler-Maruyama method [11]) as in Ref. [9]. We integrate the dynamics with a time step  $\Delta t = 10^{-3}\,\mathrm{h}$  over a total simulation time  $T = 10^3\,\mathrm{h}$ . The variances of the stretched lengths of the springs  $\langle \delta \ell_n^2 \rangle$  are calculated from 4800 independent simulation runs. We have verified that  $\langle \delta \ell_n^2 \rangle$  does not depend on the position n within the chain when N is large in the simulations. Therefore,  $\langle \delta \ell_{N/2}^2 \rangle$  for the central link is used to represent the variance in Fig. 1(b).

To measure the mean escape time  $\tau_{\rm esc}$ , we first allow the chain to relax to its steady state by running the simulation for  $10^3$  h. After relaxation, we track the stretched length of the central link  $\delta\ell_{N/2}$ , starting the timer when it approaches zero, i.e.,  $|\delta\ell_{N/2}| < \varepsilon = 0.1 \,\mu{\rm m}$  in our simulations. The break time  $\tau_{\rm esc}$  is recorded as the time at which  $\delta\ell_{N/2}$  reaches the critical break length  $\delta\ell_b$ . The final results shown in Fig. 1(c) are averaged over  $10^3$  independent simulations.

TABLE S1. Table of simulation parameters.

Parameter	Description	Dimension	Value <sup>a</sup>
N	Number of particles	1	1000
$\Delta t$	Simulation time step	T	$10^{-3}  \mathrm{h}$
$1/\mu k$	Spring relaxation time	T	$0.25 \mathrm{h}  [12]$
au	Persistence time	T	0.5 h [13]
D	Diffusion coefficient	$L^2/T$	$100  \mu \text{m}^2/\text{h}  [13]$
$\delta \ell_b$	Critical break length	$\dot{L}$	$5\mu\mathrm{m}$

<sup>&</sup>lt;sup>a</sup> These serve as the default parameter values for the AOUP simulations; any deviations from them are explicitly specified.

#### 1. Details of parameter estimates

The default parameter values used in our model are listed in Table S1. These values have been calibrated using experimental data as discussed in the main paper. We provide a few additional details here. We estimated  $D=100\,\mu\mathrm{m}^2/\mathrm{h}$  and  $\tau\approx0.5\,\mathrm{h}$  from data on HaCaT cells (a human keratinocyte cell line) from Ref. [13] (Fig. 4E of that paper). Selmeczi *et al.* show in their paper that the Ornstein-Uhlenbeck model is not a complete representation of their velocity correlation data [13], so our application here is only to get a reasonable order-of-magnitude.

We estimate the spring relaxation time  $1/\mu k$  based on the results of Jain et al., who calibrated a self-propelled particle model of collective cell migration using their experimental measurements [12]. We want to note how our model maps to their calibration briefly, since it might not be immediately obvious. The model of Ref. [12] essentially assumes a force balance between a self-propulsion force of the cell  $F_M$ , a viscous drag, and a cell-cell interaction force,  $0 = -\xi v + F_M + f_{\text{cell-cell}}$ . In the absence of cell-cell contact, then the cell velocity is given by  $v = F_M/\xi$  ( $\xi$  is called  $\mu$  in Ref. [12]; we have changed this to avoid confusion with our mobility  $\mu$ , which is  $1/\xi$ ). Based on typical cell velocities in their experiment, it's possible to set  $F_M/\xi = 30 \,\mu\text{m/h}$ . If one cell is colliding into a stationary cell, the cell-cell interaction force is nonzero, and they assume it to be  $f_{\text{cell-cell}} = F_C[1 - (d/2R)], \text{ where } d \text{ is the cell-cell dis-}$ tance. Within our model, the force would be  $-k\delta\ell$ —so with a typical spacing of  $\ell_0 = 2R$  of twice the radius of the cell, we see that our k value corresponds to  $F_C/2R$ in their model. By measuring how much a cell is compressed when another cell is pushing against it, Ref. [12] estimated the ratio of cell stiffness  $F_C$  to the persistent motile force  $F_M$  to be approximately  $F_C/F_M \approx 5.5$ . This means our value of  $k = F_C/2R \approx 5.5 F_M/2R$ , or in our notation,  $k/\xi \approx 5.5 F_M/2R\xi$ . Using the speed of the cell for  $F_M/\xi$  and the value from Ref. [12] of  $R=20\,\mu\mathrm{m}$  for MDCK cells, we find  $k/\xi = \mu k \approx 4 \,\mathrm{h}^{-1}$ , or our timescale  $1/\mu k \approx 0.25 \,\mathrm{h} = 15 \,\mathrm{min}$ . We note that other papers have come up with different estimates for this timescale [14], which may vary significantly from cell type to cell type

and depending on the context (e.g., cells being on a substrate vs in a 3D aggregate likely have very different frictions).

#### B. Fragmentation-growth simulations

We implement a rejection-free kinetic Monte Carlo (rfKMC) algorithm to simulate the fragmentation-growth processes. The initial chain length is set to  $n_0 \gg N_{\rm min}$ . For a chain of N particles, there are N-1 connections, each with a break rate. If breaking a connection violates the minimum cluster size  $N_{\rm min}$ , the break rate is set to zero. Each particle has a division rate, which is set to zero for particles not allowed to divide (e.g., in the end-growth mechanism).

In our simulations, we fix the division rate  $k_d = 1$  and vary the ratio  $\gamma$  by adjusting the break rate  $k_b = \gamma$ , i.e., the time unit is  $1/k_d$ . In the rfKMC algorithm, the time step for each MC step is calculated as  $\Delta t = Q_k^{-1} \ln(1/u)$ , where the total rate  $Q_k$  is the sum of all break and division rates, and u is a uniform random number in (0,1]. Each step permits either a fragmentation or a division event. If a particle division occurs, the chain length increases by one. If fragmentation occurs, one of the daughter chains is randomly selected as the new tracked chain. Then, we update all rates for particles and connections according to the specific fragmentationgrowth mechanism. Since the time step  $\Delta t$  in rfKMC is not constant, the output is a time series  $\{t_0, t_1, t_2, \cdots\}$ . To determine the chain size at a specific time T, we identify the first time  $t_{i+1} > T$ , and then record the chain size at  $t_i$  as n(t = T). To obtain the steadystate distribution  $p_n$ , we must wait for a sufficiently long time T for the chain length n(t) to reach a stable increase-then-drop pattern (as shown in Fig. S4), akin to cell size control [15, 16]. The distribution is then generated from the results of 10<sup>4</sup> independent simulation runs. There is an alternative, faster way to obtain the same distribution from simulations. We expect that the steady-state distribution  $p_n$  is equivalent to the lineage distribution of the tracked chains as  $T \to \infty$ , i.e.,  $\lim_{T\to\infty} T^{-1} \int_0^T p_n(t) dt = \lim_{t\to\infty} p_n(t)$  [17]. We can get the lineage distribution by measuring the length n(t) of the tracked chain over a long period and calculating the fraction of time spent at each n. We have computed these lineage distributions and confirmed that they agree with our distributions shown in Figs. 3(a), 3(e), and theory.

We note that the cluster sizes of germline cysts shown in Fig. 5 of Ref. [18] are smaller than our steady-state predictions using their measured break and division rates, as their system has not yet reached steady state. For instance, the break rate is approximately  $0.015\,\mathrm{h^{-1}}$  at E11.5 and E12.5 ovaries (Fig. 4C of Ref. [18]), while the division rate for germline cysts is about  $\ln 2/16\,\mathrm{h^{-1}}$ . Our steady-state solution predicts a mean cluster size

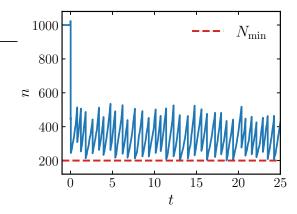


FIG. S4. A representative time trajectory of chain length n(t) from rfKMC simulation with  $N_{\rm min}=200$  and  $\gamma=0.1$ . The initial chain length is set to  $n_0=1000$ , and the simulation begins at t=0. The time unit is  $1/k_d$ .

 $(1+\gamma)/\gamma \approx 4$ , whereas their simulated average cyst sizes are 1.73 and 3.26 at E11.5 and E12.5, respectively. If we similarly evolve a single cell only from E10.5 to E11.5 and E12.5, as in Ref. [18], we obtain mean cluster sizes of approximately 2 and 3, which closely match their results. We note the simulations of Ref. [18] also include variability in cell division rates, which we do not include in order to allow us to get a simple analytic answer.

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