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Models for the Length Distributions of Actin Filaments: I. Simple Polymerization and Fragmentation

LEAH EDELSTEIN-KESHET*
Department of Mathematics,
University of British Columbia,
Vancouver, BC,
Canada, V6T 1Z2

G. BARD ERMENTROUT
Department of Mathematics,
University of Pittsburgh
Pittsburgh, PA 15260, U.S.A.

We studied mathematical models for the length distributions of actin filaments under the effects of polymerization/depolymerization, and fragmentation. In this paper, we emphasize the effects of these two processes acting alone. In this case, simple discrete and continuous models can be derived and solved explicitly (in several special cases), making the problem interesting from a modeling and pedagogical point of view. In a companion paper (Ermentrout and Edelstein-Keshet, 1998, *Bull. Math. Biol.* **60**, 477–503) we investigate what happens when the processes act together, with particular attention to fragmentation by gelsolin, and with a greater level of biological detail.

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1. GLOSSARY OF PARAMETERS

A_j	An actin filament consisting of j monomers
A_1	An actin monomer
A_{total}	Total concentration of actin in all forms
$\mathcal{A}$	$= A_{total} - [A_1]$, concentration of actin in polymerized form
n	Number of monomers required to nucleate an actin filament ($n = 3$ or 4)
x_n	Concentration of actin filament nuclei
$x_j = [A_j]$	Concentration of actin j-mers
L_n	Number-average length of filaments
L_w	Weight-average length of filaments

*Author to whom correspondence should be addressed.

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a=$[A_1]$	Concentration of free-actin monomers
k_+	Polymerization rate constant for actin
k_-	Depolymerization rate constant for actin
a_{crit}	$= k_-/k_+$ critical actin concentration at which polymerization just balances depolymerization
r	$= k_+a/k_- = a/a_{crit}$ (dimensionless parameter)
J	Maximal size (in monomer units) of a filament, where applicable
k_b	Rate of breakage of an actin filament
k_{init}	Initiation rate of an actin filament from n monomers
σ	$= k_{init}a^n/k_-$ (dimensionless parameter)

2. INTRODUCTION

Actin is a polymer, a peptide of molecular weight 42 kDa that exists in monomeric (G-actin) or filamentous (F-actin) forms. Actin plays an essential role in the cytoskeleton, the structural framework that determines the shape of an otherwise fluid-like animal cell. Aside from its purely structural properties, the dynamic formation and breakdown of actin filaments are implicated in cellular motility, in cellular response to external stimuli, and in a variety of physiological functions such as mitosis and chemotaxis. In this paper we consider simple polymerization which gives rise to an exponential length distribution. We then discuss the case in which fragmentation of the filaments takes place.

There are several reasons for an interest in a theoretical analysis of actin length distributions:

1. Actin filaments grow only at their two ends (Pollard, 1986). A single, long filament would thus contribute much less to actin polymerization than many short filaments (Zigmond, 1993; Theriot, 1994). Knowledge of the length distribution is equivalent to knowledge of the potential for further growth (Redmond and Zigmond, 1993).
2. Properties of solutions containing filamentous components are known to vary with lengths of these components. In particular, the viscosity of such solutions is correlated to the filament length distributions. The viscosity of the cytoplasm, which influences other important properties and functions in the cell, depends in part on its actin composition (Janmey *et al*., 1986; Oster, 1994) and on other components, such as intermediate filaments, microtubules, and organelles.
3. Actin filaments have translational and rotational degrees of freedom in the cytoplasm, but rates of diffusion depend on the length of the molecule: the longer the filament, the slower its rate of diffusion (Doi and Edwards, 1986; Zaner, 1995).
4. The physicochemical literature on rod-like molecules emphasizes the effects of filament lengths on the spontaneous formation of structures such as liquid crystals, in which the axes of the molecules are aligned. Actin is

known to form such structures under appropriate *in vitro* conditions, and filament alignment is correlated with the filament lengths (Suzuki *et al*., 1991; Furukawa *et al*., 1993; Käs *et al*., 1996).

5. Actin filaments interact with other filaments *in vivo* through crosslinking and bundling; these interactions are mediated by a variety of actin-associated proteins, and depend on the lengths of the filaments relative to intermolecular distances (Suzuki *et al*., 1991; Coppin and Leavis, 1992; Furukawa *et al*., 1993; Wachsstock *et al*., 1993, 1994).

As a further indication of the importance of considering filament lengths, it has recently been shown (Sechi *et al*., 1996) that both very long (in the order of a few microns) and short (in the order of 0.1 μm) filaments coexist in the actin tail of the intracellular parasitic bacterium, *Listeria*. It is believed that this may have an impact on the propulsion of Listeria. See also Marchand *et al*. (1995) for a discussion of tail length and propulsion speed.

Ideally, one would like to describe not only filament lengths, but also how these filaments are arranged spatially in the leading edge, or lamellipod, of the cell, and how they contribute to the motion of a cell in response to external signals. (Lauffenburger and Horowitz, 1996; Mitchison and Cramer, 1996). Related work in this direction includes that by Mogilner and Oster (1996) and Edelstein-Keshet and Ermentrout (1998). As a first step, the analysis of actin length distributions without the explicit modeling of their spatial distribution is carried out in this paper.

3. SIMPLE POLYMERIZATION

Actin is a protein which can link with many copies of itself (like interlocking beads on a necklace) to form linear filaments called F-actin. Before a filament can start to form, it must be nucleated by some minimal number of actin monomers. The filament can then add or lose monomers, G-actin, at either end. Addition of monomers is called polymerization. This process depends both on the availability of monomers in the solution and on the kinetic rate constants for binding of the monomers to the actin filament and for unbinding. Loss of monomers, depolymerization, from a filament end is a spontaneous process, i.e., it is independent of the monomer pool. As the molecule is asymmetric, the ends are not identical and have distinct polymerization properties. The so-called barbed end (also called the plus end) can grow much more rapidly than the pointed end (also called the minus end). *In vitro* actin polymerization has been well characterized in numerous 'test-tube' experiments with actin purified from several sources. Some of these results are summarized in Section 3.4 and in Table 1. There are many factors, including binding proteins, ionic composition and other effects that influence actin polymerization, but these will be ignored in this first stage of treatment of the problem.

The kinetics of actin polymerization have been described in many papers, and mathematical models have been applied to this problem. Many papers are essentially computer simulations of the relevant chemical reactions, with a variety of assumptions about the system—some more detailed than others (Frieden, 1983; Tobacman and Korn, 1983; Korn *et al*., 1987). Others include some analytic formulation of differential equations and their solutions for simplified versions of the system (Fesce *et al*., 1992; Houmeida *et al*., 1995). (The latter is a particularly clear exposition of the problem.) However, these papers, like many others in the literature, are concerned only with the total amount of polymerized versus monomeric actin, and do not discuss the distribution of filament lengths.

In this section, we will consider the distribution of lengths of polymer given simple polymerization–depolymerization reactions at fixed rates k_-, k_+. It is well known that, under such circumstances, the equilibrium length distribution that develops is exponential (Oosawa and Kasai, 1962; Kawamura and Maruyama, 1970; Lumsden and Dufort, 1993). A simple derivation of this result, is, however, difficult to find in the literature, and is thus included here for completeness.

3.1. ***A model for the distribution of sizes.*** Consider a filament consisting of j actin monomers, represented by the symbol A_j. If one monomer dissociates, the complex becomes A_{j-1}. If a monomer is added, the complex becomes A_{j+1}. This polymerization and depolymerization takes place at both ends of an actin filament. Assuming that both the barbed and the pointed ends are in a similar environment (an assumption which must eventually be relaxed in models for the spatiotemporal distribution of actin), the processes are additive, as they occur simultaneously. Thus, we define the combined rate constants for polymerization at both ends of the filament as follows:

$$k_+ = k_+^{barbed} + k_+^{pointed}. \tag{1}$$

$$k_- = k_-^{barbed} + k_-^{pointed}. \tag{2}$$

These aggregate constants are sometimes called 'operational parameters' (Fesce *et al*., 1992). The system to be studied then consists of the set of reactions:

$$A_j + A_1 \underset{k_-}{\overset{k_+}{\rightleftharpoons}} A_{j+1}. \tag{3}$$

To simplify the notation, we will use the following abbreviations for the concentrations (in arbitrary units):

$$x_j = [A_j]. \tag{4}$$

Note that x_1 represents monomers, so that:

$$x_1 = a. \tag{5}$$

The chain of reactions shown above implies that the concentrations of j-mers for $j > n$ (where n is the size of the nucleus that can form a stable actin filament) satisfy the system of differential equations:

$$\frac{dx_j}{dt} = k_- x_{j+1} - (k_- + ak_+)x_j + k_+ a x_{j-1}. \tag{6}$$

The terms in equation (6) include appearance of j-mer via depolymerization of a $(j+1)$-mer and polymerization of a $(j-1)$-mer, and loss of j-mer to larger and smaller sizes. If the units used for rate constants and for monomer concentrations are consistent (e.g., μM), all the coefficients in the above equation will have units of (1/time). Thus, the units of concentration for the j-mers are, up to this point, arbitrary, and if we look for the steady-state distribution of this equation alone, it can tell us about only the relative prevalence of the various sizes, not their absolute levels.

The process of nucleation is a complicated one which may require many steps. An elegant summary of the possible schemes is given in Fesce *et al*. (1992). There is still controversy in the literature about the size of the nucleus for spontaneous nucleation of actin filaments, but the most commonly cited values are $n = 3$ (Frieden, 1983; Korn *et al*., 1987; Alberts *et al*., 1989) and $n = 4$ (Tobacman and Korn, 1983; Fesce *et al*., 1992). In several sources, a differential equation for the nucleation of actin filaments is based on the assumption that the nucleus is in quasi-equilibrium with monomer (Wegner and Engel, 1975; Tobacman and Korn, 1983). We adopt the following equation for nuclei, $j = n$, which is consistent with the literature models[†]:

$$\frac{dx_n}{dt} = k_- x_{n+1} - (k_- + ak_+)x_n + k_{init} a^n. \tag{7}$$

This equation contains an apparent 'source' term $k_{init}a^n$ that describes formation of nuclei from n monomers. (It is assumed that aggregates of actin smaller than the size of a nucleus are highly unstable.) The constant k_{init}, which represents the rate of filament initiation, is an 'operational parameter' in the sense of Fesce *et al*. (1992) where it is called k_{nuc}. Generally, the quantities $k_-, ak_+, k_{init}a^{n-1}$ have units of (1/time), and now the units of concentration for x_j must match with those used for monomers. Thus, this equation determines the dimensions appropriate for the concentration of j-mers.

It is convenient to work with a rescaled version of the above system of equations,

$$\frac{dx_j}{dt} = x_{j+1} - (1+r)x_j + r x_{j-1}, \qquad j > n \tag{8}$$

$$\frac{dx_n}{dt} = x_{n+1} - (1+r)x_n + \sigma, \tag{9}$$

[†]The correspondence between the literature models and the length distribution model requires a careful consideration and interpretation. We comment on this correspondence in the Appendix.

where

$$r = \left(\frac{k_+ a}{k_-}\right) = \left(\frac{a}{a_{crit}}\right), \tag{10}$$

$$a_{crit} = \frac{k_-}{k_+}, \tag{11}$$

$$\sigma = \left(\frac{k_{init}}{k_-}\right) a^n. \tag{12}$$

In this formulation, time is rescaled by the depolymerization time constant $(k_-)^{-1}$. It is worth noting that r represents the ratio of the free-actin monomer concentration, a, to an important parameter grouping with dimensions of concentration, the so-called critical actin concentration, a_{crit}. This concentration represents the level of monomers at which polymerization just balances depolymerization[‡].

From the values of concentrations of j-mers (for all possible js), we can compute the total amount of actin in polymerized form, $\mathcal{A}$, by summation.

$$\mathcal{A}(t) = \Sigma_{j=n}^{\infty} j x_j(t). \tag{13}$$

The summation starts at the nucleus size $j = n$, under the assumption that smaller complexes are unstable, and thus negligible.

We now make an important remark about two distinct situations, leading to two different realizations of the models discussed in this paper. We will refer to these distinct cases as the *in vitro* and the *in vivo* cases. The model for actin has associated with it a different constraint on the amount of available actin in each of these situations.

The *in vitro* case refers to experiments done *in vitro*, where the total amount of actin is fixed. (For example, the experimenter may supply some prescribed amount of actin in monomeric form.) In that case,

$$A_{total} = a + \mathcal{A} = \text{constant}. \tag{14}$$

The *in vivo* case reflects cellular conditions, where it is inaccurate to assume that the total amount of available actin is fixed. A large pool of sequestered monomeric actin is held in reserve, and the cell can keep the concentration of free monomers available for binding at a controlled level. In that case, in the regime of polymerization of interest here, it is more accurate to assume that the concentration of free monomers is constant, i.e.,

$$a = \text{constant}. \tag{15}$$

[‡]An actin filament has two different values of a_{crit}, one at the pointed end, $a_{crit,p} = k_{p,-}/k_{p,+}$ and another at the barbed end, $a_{crit,b} = k_{b,-}/k_{b,+}$; however, in the model we have used the 'operational parameters' k_+, k_- that represent both ends of the molecule combined. Thus, the value of a_{crit} is related to but not equal to these individual end-specific values.

Clearly, this assumption is valid for a limited time scale over which changes in the actin make up are taking place inside the cell.

3.2. ***Steady-state solution: An exponential length distribution.*** From equation (8), we find that the equilibrium concentrations of the actin j-mers satisfy:

$$0 = x_{j+1} - (1+r)x_j + rx_{j-1} \qquad j > n. \tag{16}$$

This equation is a linear difference equation with constant coefficients. We look for solutions $x_j > 0$. In the *in vitro* case where the total amount of actin is fixed, we also require that A_{total} and $\mathcal{A}$ be bounded. Experience with such equations (Edelstein-Keshet, 1988) suggests a solution of the form

$$x_j = C\lambda^j \tag{17}$$

for constant C, and λ (the eigenvalue) to be determined. By substituting this form into equation (16), canceling common factors, and solving the resultant quadratic equation for λ we find that $\lambda = r$ or $\lambda = 1$. The second possibility would imply that every length occurs with equal probability. This is unrealistic for large lengths, and also leads to an unbounded sum for the total amount of actin. It is thus a case we reject. Thus, we conclude that the only biologically relevant solution is

$$x_j = Cr^j. \tag{18}$$

A comment about this result is appropriate. If we permit equations (8) and (16) to describe a system of possibly unbounded size (in the sense that the lengths of the filaments are not limited), then the solution given above is relevant only for $r < 1$, i.e., as long as the free-actin concentration is smaller than a_{crit}. [For $r \geq 1$ the total amount of polymerized actin, a sum of infinitely many terms of the form given by equation (18) would be infinite.] We later avoid this difficulty by restricting attention to filaments that cannot grow beyond some maximal size, J.

The value of the constant C is obtained by using the equation for actin filament nuclei, i.e., equation (9). This equation acts like a boundary condition for the length-distribution equations model. By plugging in the form (18) into equation (9), we find that, at equilibrium, terms of the form r^{n+1} cancel, and we are left with

$$0 = Cr^n - \sigma \tag{19}$$

[This result implies that, at equilibrium, breakdown of actin filament nuclei 'balances' with their formation from actin monomers, and growth of nuclei balances with the depolymerization of the $(n+1)$-mers.]

(i) *In vivo* case: As argued above, it is sensible to consider the free-actin monomer concentration constant (or buffered close to some constant level) inside the cell. We can then plug in the value of the constants r and σ into the above equation and determine that

$$C = \frac{\sigma}{r^n} = \left(\frac{k_{init}}{k_-}\right) a_{crit}^n. \tag{20}$$

Thus,

$$x_j = Cr^j = C\left(\frac{a}{a_{crit}}\right)^j = \frac{k_{init}}{k_-}(a_{crit})^{n-j} a^j. \tag{21}$$

Since a is constant in this case, we could also express this solution in the form $x_j = C' r^{j-n}$ for a slightly redefined multiplicative constant[§].

(ii) *In vitro* case: In this case, the actin monomer concentration is not known *a priori*. C is still determined as above, using the condition for nuclei, but we must solve a complicated nonlinear equation to find a and hence r, using the fact that the total amount of actin is A_{total}. Depending on the size of the nuclei, n, this procedure may be cumbersome. We illustrate the general idea in the Appendix.

3.3. ***Mean filament lengths for simple polymerization.*** It is straightforward to compute derived quantities such as the number-average length of filaments, L_n, and the weight-average length of filaments, L_w (Janmey *et al*., 1986) from the expression for x_j given in the previous section, using the definitions

$$L_n = \frac{\left(\sum_{j=3}^{\infty} j x_j\right)}{\left(\sum_{j=3}^{\infty} x_j\right)} \tag{22}$$

$$L_w = \frac{\left(\sum_{j=3}^{\infty} j^2 x_j\right)}{\left(\sum_{j=3}^{\infty} j x_j\right)} \tag{23}$$

The summation is taken only over actin filaments, starting with nuclei, which, in the case of simple polymerization we take to be trimers, as in Korn *et al*. (1987), Frieden (1983) and Alberts *et al*. (1989). When the appropriate series are computed in the above expressions with $r < 1$, we find that

$$L_n = \frac{(3 - 2r)}{(1 - r)} \tag{24}$$

$$L_w = \frac{(4r^2 - 11r + 9)}{(2r^2 - 5r + 3)} \tag{25}$$

[§]This form proves useful when we discuss polymerization in the presence of a very small amount of fragmenter.

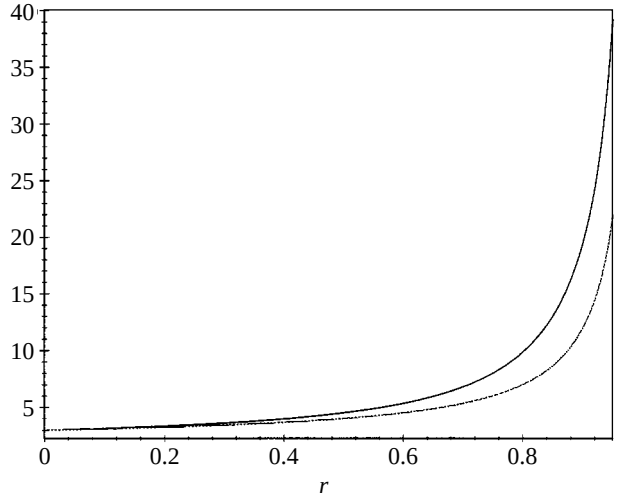

Figure 1. A plot of average filament length as a function of the parameter $r = a/a_{crit}$. Length (vertical axis) is given in terms of the number of monomers in the polymer chain. The number-average length (L_n, top curve) and the weight-average length (L_w, bottom curve) of the actin filaments are shown for the case of simple polymerization with trimers as nuclei. Note that the average filament length increases sharply as r gets closer to 1.0, i.e., as the concentration of monomers approaches a_{crit}.

Note that these expressions depend only on r, and not on the value of the constant C that appears in the size distribution x_j. The dependence of these averages on the parameter r is shown in Fig. 1.

3.4. ***Parameter values for polymerization.*** Some of the parameter values associated with actin polymerization have been identified in a variety of experimental conditions. Pollard (1986) measured rates of elongation at barbed and pointed ends of actin (*in vitro*, using the sperm acrosomal process of *Limulus* as nuclei and electronmicroscopic methods). He found that elongation rates depend linearly on ATP–actin concentration from a critical concentration up to a high concentration of 20 μM actin monomers (Pollard, 1986). For example, a typical value for the barbed-end-on-rate is $k_+ = 10\ \mu\text{M}^{-1}\ \text{s}^{-1}$, compared with roughly $2\ \mu\text{M}^{-1}\ \text{s}^{-1}$ at the pointed end. Depolymerization takes place at a rate roughly $k_- = 2\ \text{s}^{-1}$. Rather different results were obtained by Korn *et al*. (1987) for rabbit skeletal muscle actin. Bonder *et al*. (1983) also used *Limulus* sperm and electronmicroscopy. The rates and critical concentrations depend on the ionic make up of the solutions, and particularly on divalent cations such as Mg^{2+} and Ca^{2+} (Bonder *et al*., 1983).

There is some controversy about whether *in vitro* and *in vivo* behavior are comparable (Selve and Wegner, 1986; Cano *et al*., 1992; Theriot, 1994); for a review, see Cooper (1991). Further, the polymerization in the cell is mediated and controlled by many influences which are not yet fully understood. Some

groups have also estimated the values of polymerization rates *in vivo*, and in cell preparations (Cano *et al*., 1991). Rate constants under their conditions used by Cano *et al*. were: $k_- = 6.3\ \mathrm{s}^{-1}$ (both pointed and barbed ends together), $k_+ = 0.9\ \mu\mathrm{M}^{-1}\ \mathrm{s}^{-1}$. According to Zigmond (1993), in polymorphonuclear leukocytes (PMNs) there is about 100 μM G-actin, and about the same F-actin. Most is sequestered (reserved in an inactive form) by other proteins. Profilin, whose role is still being elucidated, is thought to prevent spontaneous formation of new filaments, while allowing elongation at the barbed end of an actin filament. β-Thymosine is another sequestering protein currently believed to maintain the large actin monomer pool in cells in a manner still not fully understood (Sun *et al*., 1996).

A summary of the values of experimental rate constants is given in Table 1. It appears that the polymerization rate at the barbed end of a filament is faster than that at the pointed end by nearly an order of magnitude. However, it is clear from the literature that rate constants for actin polymerization vary widely with the type of actin, ionic composition, and other experimental conditions. Estimates of the nucleation rate of actin filaments (here called k_{init}) have been made experimentally (Tobacman and Korn, 1983). What emerges is an even more astonishing prediction, namely that the rate of nucleation of filaments can vary by a factor of 50 000 under different ionic compositions of the medium.

Because experimentally derived estimates for the various rate constants come from different conditions, it is not particularly meaningful to choose values for each of the parameters that appear in the solution given by equation (21), unless one also specifies the detailed experimental conditions. (A particular difficulty is the nucleation rate, k_{init} which is so highly sensitive to conditions.) However, the general characteristics of the solution can be displayed. From the parameter values taken from the literature, we see that $a_{crit} = k_-/k_+$ is roughly 0.1 μM. Assuming a monomeric actin concentration at 90% of this critical concentration, i.e., $a = 0.09$ in the *in vivo* case, and arbitrarily choosing $C = 1$ for illustrative purposes, we have

$$x_j = Cr^j = (0.9)^j = 0.1(\exp(\ln 0.9))^j = 0.1e^{(-0.105j)}. \tag{26}$$

The behavior of this exponential solution is shown in Fig. 2. (An accurate value for the nucleation constant and, hence, for C would clearly rescale the vertical axis without changing the shape.) A similarly shaped length distribution, namely an exponential decay with increasing length, would also occur in the *in vitro* case. Calculation of the constant C would be more cumbersome, even for a specified set of parameters (see Appendix). Not surprisingly, an experimentally determined length distribution shown in Kawamura and Maruyama (1970) has a form similar to the one shown in Fig. 2.

3.5. ***Time-dependent behavior: evolution of the exponential distribution.*** The time behavior of the system of linear differential equations (8) and (9), can be

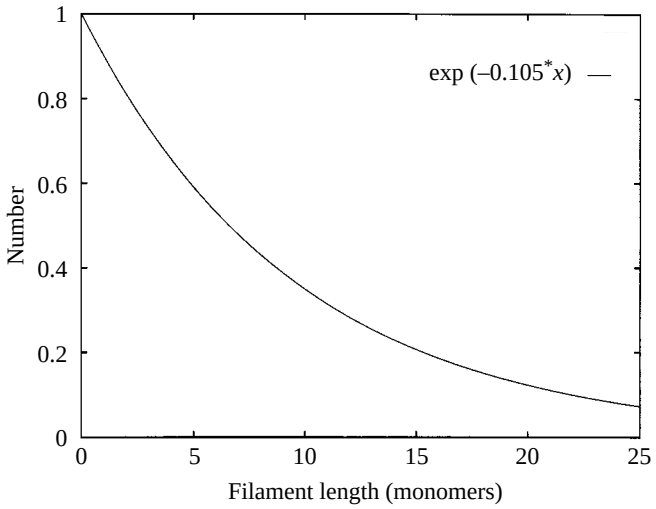

Figure 2. An exponential filament-length distribution in the case of simple polymerization. The vertical axis represents the relative number (or frequency) of filaments at different size classes. The explicit solution [given by equation (26)] is plotted in the in vivo case, with $r = a/a_{crit} = 0.9$ and the constant C arbitrarily set to 1.0.

characterized in a relatively straightforward way. In particular, we ask whether the steady-state solution discovered in the previous section is stable. To avoid problems with infinite mass or unbounded systems, we assume that there is some filament size J beyond which no actin polymerization will occur. (This size can be arbitrarily large, e.g., of the order of the size of the cell, but our assumption ensures that the system of equations studied below is finite. The assumption also supplies a 'right boundary condition', i.e., a condition imposed on the largest size.)

We observe that the character of the system under investigation is

$$\frac{d\boldsymbol{x}}{dt} = \mathsf{M}\boldsymbol{x} + \mathsf{s}, \tag{27}$$

where

$$\boldsymbol{x}(t) = \begin{pmatrix} x_n(t) \\ x_{n+1}(t) \\ . \\ . \\ x_J(t) \end{pmatrix}, \tag{28}$$

$$\mathsf{M} = \begin{pmatrix} -(1+r) & 1 & 0 & 0 & . & 0 \\ r & -(1+r) & 1 & 0 & . & 0 \\ 0 & r & -(1+r) & 1 & . & 0 \\ 0 & & & & & \\ 0 & . & 0 & r & -(1+r) & 1 \\ 0 & . & 0 & 0 & r & -(1+r) \end{pmatrix}, \tag{29}$$

and where the 'source term', i.e., *de novo* appearance of n-mers from n monomers is

$$\mathsf{s} = \begin{pmatrix} \sigma \\ 0 \\ . \\ . \\ 0 \end{pmatrix}. \tag{30}$$

There are $m = J - n + 1$ equations, since clusters of size smaller than nuclei are not considered. Since this system of differential equations is linear, solutions are of the form

$$\boldsymbol{x} = \boldsymbol{x}_{ss} + \boldsymbol{v}_1 e^{\lambda_1 t} + \ldots + \boldsymbol{v}_n e^{\lambda_m t}, \tag{31}$$

where $m = J - n + 1$, and where the steady-state solution as found in the previous section is,

$$\boldsymbol{x}_{ss} = \begin{pmatrix} x_n \\ x_{n+1} \\ \vdots \\ x_J \end{pmatrix} = C \begin{pmatrix} r^n \\ r^{n+1} \\ \vdots \\ r^J \end{pmatrix} \tag{32}$$

and where $\boldsymbol{v}_i$ are the eigenvectors and λ_i the associated eigenvalues of the matrix M. It is a tedious task to find the eigenvalues and eigenvectors of M for $n > 2$ or 3, and the results are not insightful. (But see the Appendix, where some examples are given for $n = 2, 3$.) Rather, we can use more general arguments to find conditions for these eigenvalues to be negative. We first note that M is a tridiagonal linear system of equations. The matrix of coefficients a_{ij} satisfies the condition $a_{i,i+1}a_{i+1,i} > 0$, and thus the eigenvalues of the matrix are all real and simple (Fiedler, 1986).

By the Geršgorin disk theorem (Horn and Johnson, 1985), the eigenvalues of the matrix M are contained in the union of disks defined as follows:

$$D_{n+i-1} = \{|\lambda - a_{ii}| \leq \Sigma_{j \neq i} |a_{ij}|\} \tag{33}$$

(The numbering scheme refers to successive rows in the matrix M, which we index by the size of the actin-cluster they represent.) The centers of all the disks are determined by the terms on the diagonal, and the radii of the disks are the sum of off-diagonal terms in a given row. Thus, we note that for the first disk, which we will label D_n, the center is at $-(1+r)$ and the radius is 1. For all disks D_{n+1} through D_{J-1}, the centers are $a_{ii} = -(1+r)$ and the radii are $(1+r)$. All these disks are, therefore, contained in the nonpositive quadrants of the complex plane. For the last disk, D_J, the center is at $a_{JJ} = -1$ and the radius is r. This disk, too, will be contained in the nonpositive semiplane provided that

$$r \leq 1, \tag{34}$$

or, equivalently,

$$a \leq a_{crit}. \tag{35}$$

(We have already noted that this condition must be satisfied for a bounded steady-state solution to exist.) If this condition is satisfied, then the union of all disks is in the nonpositive part of the complex plane.

It remains only to verify that there are no zero eigenvalues, i.e., that the real parts of all eigenvalues are strictly negative. This is illustrated on a 3×3 matrix in the Appendix. We have shown that all eigenvalues, $\lambda_1 \ldots \lambda_m$ ($m = J - n + 1$) are negative. Thus, the transient behavior dies out and the steady state found in the previous section is stable.

4. FRAGMENTATION AND BREAKAGE OF FILAMENTS

Actin filaments can break spontaneously, under certain experimental manipulations (Janmey *et al*., 1994), and through the action of filament-cutting proteins such as gelsolin and cofilin. Details about the types of proteins involved in fragmenting actin filaments and how they act will be described in the sequel to this paper (Ermentrout and Edelstein-Keshet, 1998). Briefly, gelsolin is a fragmenter that stays attached to the filaments that it severs (Janmey and Matsudaira, 1988; Hartwig and Kwiatkowski, 1991), while cofilin gets 'recycled' after it breaks a filament (Maciver *et al*., 1991; Hawkins *et al*., 1993; Hayden *et al*., 1993; Moon and Drubin, 1995; Aizawa *et al*., 1996).

An accurate representation of the dynamics of actin filament lengths in the cell would require a detailed description of many factors, including ionic effects and interactions of many molecules. This level of detail is beyond the scope of this initial study, whose purpose is to develop the mathematical tools and gain some initial insight into the processes of fragmentation and growth of filaments. A greater level of detail is given in Ermentrout and Edelstein-Keshet (1998).

In the following sections, we consider the action of a generic breakage: for example, through a recycled fragmenting molecule such as cofilin. We develop simple mathematical models for this fragmentation process.

4.1. ***A discrete model for fragmentation acting alone.*** We first discuss how an actin filament would be broken spontaneously or by a generic chopping molecule. Suppose that breakage occurs with equal probability at any bond in the actin polymer. For example the 'chopper' binds with equal probability at any site along the actin filament. If the filament is a j-mer, it would break into two pieces: a k-mer and a $(j-k)$-mer. This can happen in one of two possible ways, i.e., at position k or at position $j-k$ along the length of the filament from a given end [¶]. Further, a j-mer will break up if any of its $j-1$ bonds are broken.

[¶]Recall that an actin filament is polarized; the two ends are not equivalent.

We first consider a system in the absence of polymerization, with fragmentation (or spontaneous breakage) of filaments only. In the case of active 'chopping,' we assume that the concentration of the chopper is kept constant. This would be true if the chopper is an enzyme that is 'recycled' after each use: for example, in the case of cofilin, as discussed above. The system to be studied is

$$A_{j+k} \xrightarrow{k_b} A_j + A_k, \tag{36}$$

If we consider the action of a recycled chopper, k_b is replaced by gk_g, where g is the concentration of the chopper and k_g the rate that the chopper binds to actin and cuts the actin filament at a given bond. (In spontaneous breakage, k_b represents the average rate that a filament breaks per bond.) Note that longer filaments have more bonds and thus a higher probability of being broken or chopped, a feature incorporated into the model. The system of equations for the filament length distribution with fragmentation alone (and no polymerization) is:

$$\frac{dx_j}{dt} = k_b \left(2 \sum_{k=1} x_{j+k} - (j-1)x_j \right). \tag{37}$$

The term in summation represents the total accumulation of j-sized pieces by breakage of larger sizes. The term $(j-1)x_j$ is elimination of j-mers by further breakage at any of the $j-1$ bonds. (The model is identical, but with $k_b + gk_g$ replacing k_b if both breakage and fragmentation are superimposed.)

The only parameters appearing so far in the above system of equations are k_b or its equivalent for chopping. It is interesting to note that the steady-state size distribution discussed below will not depend at all on these rates, since when we set $dx_i/dt = 0$, the rate constants cancel out. This implies that the steady-state distribution where it exists, should thus be exactly the same whether the filaments break spontaneously, are severed by a 'chopper,' or both. (The time for steady state to be reached, if such a state exists, will, however, depend on these rates.) We can eliminate the parameters in the differential equations by rewriting the equations in a rescaled form as follows:

$$\frac{dx_j}{dt} = 2 \sum_{k=1} x_{j+k} - (j-1)x_j, \tag{38}$$

where time has been rescaled in units of the breakage-time constant $(k_b)^{-1}$, (or possibly $(k_b + gk_g)^{-1}$, the time during which the fraction of bonds left unbroken is $1/e = 36\%$[‖].

[‖]This interpretation of the parameters follows from the fact that the total number of unbroken bonds in the actin network satisfies an equation of the form $dn/dt = -k_b n$. Thus, $n(t) = n_0 \exp(-k_b t)$, and, after a time $t = (k_b)^{-1}$, the number of unbroken bonds has dropped to $n(t) = n_0 e^{-1}$.

We now comment on the behavior of this system of equations. First, it is intuitively clear that if a fixed amount of polymerized actin is supplied to choppers that act continuously, then eventually the filaments will be broken up into smaller and smaller pieces. If the fragmenter can chop filaments of all sizes, then eventually only monomers will be left. This is not necessarily the case if the choppers are supplied in a limited amount and are used up in the process before the filaments are completely broken up. For a steady-state length distribution other than this trivial result, it is necessary to consider a situation in which polymerized actin is continuously supplied.

4.1.1. *Example: Continuous supply of size* J *filaments and solution to the boundary-value problem.* Consider a situation in which long actin filaments are continually fed into the system. (An approximate example is the continual accumulation of actin filaments from dying cells in the lungs of cystic fibrosis patients, but it is stressed that this is only a rough approximation.) Suppose we assume that the density of filaments of some large size, J, is maintained at a constant level, C, i.e.,

$$x_J = C. \tag{39}$$

Equations (38) and (39) form a boundary-value problem in which the behavior at the boundary size $= J$ is prescribed. Although this situation is artificial from the biological perspective, it leads to a particularly simple solution. Note that, as filaments must be constantly added to keep the number of J-mers constant, the total amount of actin increases. We can still determine the relative proportions of the various size classes. Setting $dx_j/dt = 0$ in equation (38), and subtracting two consecutive equations, leads to a recursion relation:

$$x_j = \left(\frac{j+2}{j-1}\right) x_{j+1}. \tag{40}$$

This permits an explicit formulation of the relative ratios of successive size classes. Observe that

$$x_j > x_{j+1}. \tag{41}$$

Further, the size distribution can be worked out explicitly, leading to the result:

$$x_j = \frac{J(J+1)(J-1)}{j(j+1)(j-1)} C = C' \frac{1}{(j^3 - j)}. \tag{42}$$

where

$$C' = C\,J(J+1)(J-1) \tag{43}$$

is a known constant. We can make the following observations about this result:

(i) If the maximal size, J, is rather large, the numbers of large filaments is roughly constant, since $x_j \approx x_{j+1}$ for large j. The length distribution appears flat for large sizes, as long as size J is continuously supplied.

(ii) The length distribution obtained with this process is monotonic. The most prevalent size class consists of the very small pieces. The frequency of larger sizes drops off thereafter, and the size distribution does not have a peak.

(iii) For small j, the number of filaments is roughly an inverse cubic, but the solution predicted by the model blows up at $j = 1$, suggesting that monomers are accumulating in an unbounded way. To keep the total amount of actin bounded, monomers would have to be removed at a rate that matches the rate of addition of mass to the size class J.

4.1.2. *Mean filament length for simple fragmentation.* Using the explicit formula for the size distribution given above, we can compute the number-average length, L_n, and the weight-average length, L_w, of the actin filaments by performing the appropriate summations. (See Section 3.3 for the detailed definitions of these averages, but note that here the sums are taken over sizes $j = 2 \ldots J$ since there is a maximum size, and since in principle dimers can occur as breakdown products of larger sizes.) We find that the number-average length is

$$L_n = (3J + 2)/(J + 2). \tag{44}$$

Note that for large values of J this ratio approaches the length 3. This simply means that the number of tiny fragments is so large that the average is around three monomers long. The weight-average length is a more complicated expression that includes the special function $\Psi(J+2)$, and its form is not particularly revealing. However, the dependence of both L_n and L_w on the size J can be plotted and is shown in Fig. 3.

This model is oversimplified in that it has omitted polymerization kinetics (which would prevent monomers from exceeding a critical concentration in general). It has also ignored the possibility that severing proteins may need some minimum-sized filament on which to act. Furthermore, the assumption that the number of large actin filaments at size J are constant is at best an approximation and not fully realistic in the biological situation. (Thus, the prediction that monomers accumulate in an unbounded way is probably an artifact of the model.) In the next section we discuss the situation of fragmentation from some predetermined initial filament-length distribution, without constraints on the largest filament size and without addition of mass.

4.2. ***Continuous formulation of the fragmentation model.*** The system of discrete equations can be explored numerically at this stage. However, with the relatively elementary form of the equations, it is possible to restate the model in a continuous version, and this version is helpful in finding an explicit solution to an initial-value problem. In the continuous counterpart, the frequency of filaments of length ℓ, is denoted $N(\ell, t)$. (Note that in this version, $\ell = 0$ corresponds to the smallest size, i.e., to monomers.)

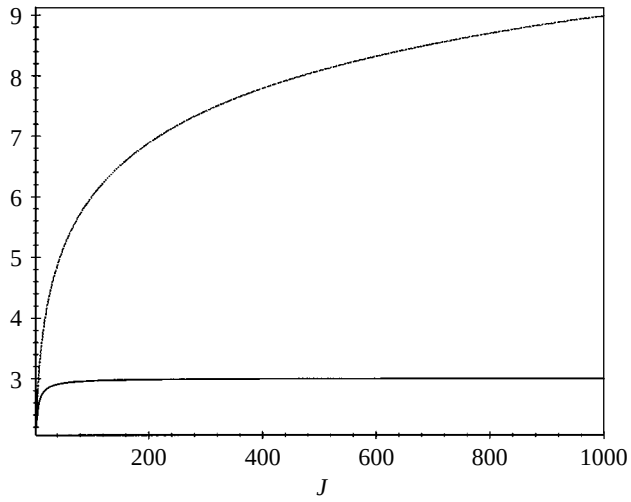

Figure 3. Average filament lengths predicted by the steady state of equation (38) for filament breakage. The average length (in monomer units, vertical axis) is shown as a function of the length J (in monomer units) of the biggest filaments continually supplied to be fragmented. The number-average length (L_n, bottom curve) and the weight-average length (L_w, top curve) of the actin filaments is shown for the case of simple fragmentation. Note that as J increases up to the 1000 monomer length, the number-average length approaches a constant level at three monomer units, but the weight-average length increases to about nine monomer units.

Rewriting equation (38) in a continuous version leads to

$$\frac{\partial N(\ell, t)}{\partial t} = -\ell N(\ell, t) + 2\int_{\ell}^{L} N(s, t)\, ds, \tag{45}$$

We explore how some fixed amount of actin, initially distributed in some arbitrary length distribution would change if the filaments were continually being cut by a chopper molecule. To do so, we complement equation (45) with an initial condition, i.e., we assume that at time $t = 0$, the distribution of lengths is given by

$$N(\ell, 0) = C(\ell). \tag{46}$$

where $C(\ell)$ is a known function.

In view of comments in the previous section, we would expect that this model (in the absence of polymerization) should predict that eventually only monomers are left. This is confirmed by the explicit solution described below.

4.2.1. *Example: Fragmentation from a given initial length distribution and solution to the initial value problem.* Equation (45) with the initial condition (46) form an initial-value problem and can be solved explicitly. Some experimentation with the symbolic manipulation software MAPLE was helpful in leading us to

'guess' an explicit form for the solution of the length distribution starting from an arbitrary initial distribution, $C(\ell)$. In the Appendix, we show that the solution of this equation is

$$N(\ell,t) = e^{-\ell t}\left(C(\ell) + 2t\int_{\ell}^{L} C(y)dy + t^2\int_{\ell}^{L}(y-\ell)C(y)dy\right). \tag{47}$$

The main feature of the solution given in equation (47) is that every size decays exponentially, with a rate that is proportional to the size ℓ. Thus, the bigger the filament, the shorter its decay time. This result makes intuitive sense, since the longer the filament, the more opportunities there are for breakage at any one of its bonds. The pool of monomers (whose size is represented by $\ell = 0$) grows quadratically with time. Eventually, as $t \to \infty$, there will be only monomers left. This means that the process of fragmentation from an initial distribution does not lead to a nontrivial stable length distribution. While initial stages of the process may be associated with nonmonotonic length distributions [depending on the function $C(\ell)$], the eventual outcome is always a concentration of mass at the smallest size class.

This comment reveals that, while the continuum equation gives a closed-form solution, it has artifacts that are undesirable: for example, since fragmentation preserves the total amount of actin in this case, the area under the curve representing the initial distribution must be preserved for the final distribution, in which all the mass is concentrated at the origin. This means that the solution approaches a delta function. The discrete model avoids this discontinuity at the origin.

4.2.2. *Mean filament length in the continuum case.* The mth moment of the distribution is defined by

$$\bar{N}_m = \int_0^L \ell^m N(\ell,t)d\ell \tag{48}$$

We find that the general formula for the mth moment is dependent on the $m+1$st moment:

$$\frac{d\bar{N}_m}{dt} = \left(\frac{2}{m+1} - 1\right)\bar{N}_{m+1} \tag{49}$$

This is found by multiplying equation (45) by ℓ^m and integrating (using integration by parts on the integral term). The following are immediate consequences:

(a) $\bar{N}_1$ is a constant independent of time, since $d(\bar{N}_1)/dt = 0$. Thus, it is obtained simply from the initial distribution as follows

$$\bar{N}_1 = \int_0^L \ell C(\ell)d\ell. \tag{50}$$

(b) $d\bar{N}_0/dt = \bar{N}_1$ so that

$$\bar{N}_0(t) = \int_0^L C(\ell)d\ell + \bar{N}_1(0)t. \tag{51}$$

Thus, the number-average length $L_n = \bar{N}_1/\bar{N}_0(t)$ decreases with time with a dependence like $1/t$ regardless of the initial concentration.

The behavior of the weight-average length is not as easily found, since from the above results the differential equation for the moment $\bar{N}_2$ depends on $\bar{N}_3$, and so on. Only the first two equations form a closed system.

5. Discussion and Comparison with the Literature

Papers in the literature contain various treatments of actin polymerization kinetics. Some of the early descriptions of the process included equations for filament elongation (Kirschner, 1980; Pollard and Mooseker, 1981; Selve and Wegner, 1986; Korn *et al*., 1987) and verbal descriptions of various aspects of polymerization. Several of these papers give experimental values of parameters (see Table 1). Equilibrium analysis of particle-length distributions for simple polymerization were given explicitly, for example in the introduction to a paper on linear and helical aggregations of macromolecules (Oosawa and Kasai, 1962). An exponential distribution of sizes, as in our case of simple polymerization, was found analytically. We were not able to find as simple a pedagogical treatment of the dynamics as the one given here. Other papers incorporate a greater level of detail, for example, of the effects of ions such as magnesium and calcium on polymerization (Frieden, 1983), but no analytical results are given. Still other papers focus on interactions of actin with other factors in the nucleation step (Tobacman and Korn, 1983; Fesce *et al*., 1992; Houmeida *et al*., 1995) and give partial analytical insight, though simulations and experimental observations are more numerous.

Models for the fragmentation of polymers and the resulting size distributions are more difficult to find. Results of experimental manipulations in which filament-length distributions were measured are available (Janmey *et al*., 1986), but the kinetics of the process have not been fully explored. In many cases, the agents causing fragmentation have many effects on the actin filaments, other than simple fragmentation. Such is the case of gelsolin, which will be described in more detail in the sequel to this paper (Ermentrout and Edelstein-Keshet, 1998).

The results of this study can be summarized briefly as follows:

(i) The models described here are simple enough that their solutions can be characterized fully. Moreover, properties such as the average filament length (calculated both as a number average and a weight average) can be found explicitly.

(ii) Polymerization or fragmentation acting individually generally lead to monotonic length distributions, i.e., distributions without peaks. There tends to be a concentration of small pieces. This is true both in the fragmentation-dominated case and in the simple polymerization case under limited actin availability.

(iii) Simple polymerization creates an exponential filament length distribution (Fig. 2). That length distribution is a stable one (see Section 3.5).

(iv) A dichotomy exists between the character of the model in the case of constant total actin available (A_{total} constant; here referred to as the '*in vitro* case') and in the case of the constant free-actin monomer pool (a constant; '*in vivo* case'). The model is linear in the second case and nonlinear in the first.

(v) For simple polymerization, increasing the ratio of free actin to the actin critical concentration causes the average length of filaments to increase, as expected (see Fig. 1).

(vi) The type of continual fragmentation described in Section 4, produces a size distribution that does not depend on the detailed rate constant of breakage or on which agent causes the effect. The steady-state size distribution depends only on boundary conditions (how filaments are supplied). There is a tendency for accumulation of small pieces, but the size distribution is not exponential.

(vii) For fragmentation acting alone from an initial filament distribution, the number-average filament length for continual fragmentation decreases as the function $1/t$, where t is time. This is independent of the initial supply of actin filaments.

Experimental length distributions are shown in various papers (Kawamura and Maruyama, 1970; Brenner and Korn, 1983; Janmey *et al*., 1994; Käs *et al*., 1996), and descriptions of growth in length in others (Coluccio and Tilney, 1983; Podolski and Steck, 1990). It is premature at this point to do detailed comparisons, since the models in this paper are necessarily simplifications. We leave some of the detailed biological connections to the next treatment, in which the fragmenting agent is gelsolin, and in which biological parameter values are incorporated.

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APPENDIX

A1. Actin nucleation: correspondence with the literature. Papers in the literature commonly use the following differential equation to describe actin nucleation (Wegner and Engel, 1975; Tobacman and Korn, 1983):

$$\frac{dC}{dt} = K_{n-1}k_{+}a^{n-1}(a - a_{crit}). \tag{52}$$

Here, C is the concentration of polymers, and $k^{+}K_{n-1} = k_{nucl}$ is an 'operational parameter' called the apparent nucleation rate. This equation stems from the underlying assumptions that the rate of change of polymer concentration stems from formation of nuclei and disappearance of prenuclei, i.e., that

$$\frac{dC}{dt} = k_{+}ax_{n-1} - k_{-}x_{n-1}, \tag{53}$$

and that the prenuclei are in quasi-equilibrium with monomers,

$$x_{n-1} \sim K_{n-1}a^{n-1}. \tag{54}$$

We observe that, while the second term (which is a loss of prenuclei x_{n-1}) is considered in the total budget of polymer concentration, it does not enter into the net loss or gain of nuclei, x_n per se. Thus, this term does not appear in our equation for x_n. Moreover, our tally for net gain and loss of nuclei has to keep track of the exchange with the next size class as we keep a more detailed classification of the polymerized forms. From the above equations we also observe that the first term, namely $k_{+}ax_{n-1} = k_{+}a(K_{n-1}a^{n-1}) = (k_{+}K_{n-1})a^{n} = k_{nuc}a^{n}$, corresponds precisely to the term $k_{init}a^{n}$ for formation of new nuclei from monomers.

A2. Solving for the constant C ***in the in vitro case (Section 3.2).*** In the *in vitro* case, the value of a, the free-actin monomer concentration is not predetermined, but rather is calculated from the total amount of actin supplied, A_{total}. We illustrate the idea in the situation when nuclei are dimers and comment on the real case of nuclei of size $n = 3$ or $n = 4$.

If dimers are the smallest filaments, then we readily calculate by a simple summation exercise that

$$A_{total} = C\Sigma_{1}^{\infty} jr^{j} = C\frac{r}{(1-r)^{2}}. \tag{55}$$

Rearranging this equation in the form of a quadratic equation with known coefficients C and A_{total}, we obtain

$$r^{2} - (2 + \frac{C}{A_{total}})r + 1 = 0. \tag{56}$$

We can use the equation for nuclei to solve for the constant C (as shown in Section 3.2 for the *in vivo* case). The above quadratic equation then allows us to solve for the parameter r. This completely specifies the form of the solution, which can get expressed in terms of A_{total}.

In the case of nuclei of size n, the constant C is still obtained in a manner identical to the one outlined in the *in vivo* case described in Section 3.2. However, finding r or, equivalently, solving for a is more challenging. If smaller complexes are highly unstable, the summation in equation (55) must start at $j = n$. In that case, we find that

$$A_{total} - a = Cr^{n+1}\left(\frac{1 + n(1-r)}{(1-r)^2}\right). \tag{57}$$

Using the definition $r = a/a_{crit}$, we obtain a nonlinear equation in a that must be solved (in general, a polynomial of degree $n + 2$). We can then express the solution to the simple polymerization problem in terms of the known value of A_{total}. Solving for a may necessitate a numerical technique such as Newton's method in this case.

A3. Rate constants for actin polymerization. Table 1 gives representative values of the rate constants for actin polymerization cited in the literature. These are *in vitro* results, and their relevance to rates of reactions in the cell have come into question.

Table 1. Polymerization rate constants for actin from literature sources.

Parameter	Units	Barbed end	Pointed end	Source
k_+	$\mu M^{-1}\ s^{-1}$	11.6	1.3	ATP-actin (Pollard, 1986)
		3.8	0.16	ADP-actin (Pollard, 1986)
		1.4	0.1	ATP-actin (Korn *et al*., 1987)
		0.75	0.05	ADP-actin (Korn *et al*., 1987)
		8.8	2.2	Microvilli (Bonder *et al*., 1983)
		12.3	1.5	Acrosome (Bonder *et al*., 1983)
			0.1	Coppin and Leavis (1992)
k_-	s^{-1}	1.4	0.8	ATP-actin (Pollard, 1986)
		7.2	0.27	ADP-actin (Pollard, 1986)
		0.14	0.4	ATP-actin (Korn *et al*., 1987)
		6	0.4	ADP-actin (Korn *et al*., 1987)
		2.0	1.4	Microvilli (Bonder *et al*., 1983)
		2-3.5	1.5	Acrosome (Bonder *et al*., 1983)
			0.4	Bonder *et al*. (1983)
$[a]_{crit}$	μM	0.12	0.60	ATP-actin (Pollard, 1986)
		0.1	4	ATP-actin (Korn *et al*., 1987)
		0.1-0.4	0.4-0.6	Bonder *et al*. (1983)

A4. No zero eigenvalues (Section 3.4). We illustrate the fact that there are no zero eigenvalues on a small subsystems of size $n = 2, 3$, but the idea can be generalized in a straightforward manner.

For $n = 2$ the matrix M is simply

$$\mathsf{M} = \begin{pmatrix} -(1+r) & 1 \\ r & -(1+r) \end{pmatrix}. \tag{58}$$

The eigenvalues of this matrix can be computed simply and are $-1, -(1+r)$, so that for $r > 0$ these are nonzero negative real numbers.

For $n = 3$, let $\mathsf{M}_{3\times 3}$ be given by:

$$\mathsf{M} = \begin{pmatrix} -(1+r) & 1 & 0 \\ r & -(1+r) & 1 \\ 0 & r & -1 \end{pmatrix}. \tag{59}$$

The eigenvalues of this matrix can be found using standard symbolic software such as MAPLE, but they are messy expressions involving r. Their general forms are not very revealing. However, in specific cases we have the following situations: (a) for $r = 0.5$, the eigenvalues are: -0.328, -2.4 and -1.2; (b) for $r = 0.75$ they are -0.25, -1.4 and -2.8; (c) for $r = 0.85$ they are -0.226, -3.00 and -1.46. We can show that the eigenvalues are nonzero by showing that the determinant of M is nonzero. To do so, we add rows 1 and 3, to obtain

$$\begin{pmatrix} -(1+r) & 1 & 0 \\ -(1+r) & (1+r) & -1 \\ 0 & r & -1 \end{pmatrix}. \tag{60}$$

Finally, adding row 2 to 1 and row 3 to 2, we get :

$$\begin{pmatrix} -1 & 0 & 0 \\ r & -1 & 0 \\ 0 & r & -1 \end{pmatrix}. \tag{61}$$

This is a triangular matrix whose determinant is clearly nonzero. Thus, there is no zero eigenvalue. The same idea can be used for an arbitrarily large system, though the steps involved are more numerous.

A5. Solution to the continuous fragmentation equation (Section 5.2). We define the variable

$$V(\ell, t) = e^{\ell t} N(\ell, t) \tag{62}$$

which has the property that

$$V(\ell, 0) = C(\ell) \tag{63}$$

and further satisfies the equation:

$$\frac{\partial V}{\partial t} = 2 \int_{\ell}^{L} e^{t(\ell - y)} V(y, t) dy. \tag{64}$$

We will show that

$$V(\ell,t) = C(\ell) + 2t\int_\ell^L C(y)dy + t^2\int_\ell^L (y-\ell)C(y)dy \tag{65}$$

First we plug equation (65) into equation (64) and see that if V is a solution then the following must hold:

$$\begin{aligned}\frac{\partial V}{\partial t} &= \int_\ell^L e^{t(\ell-y)}\left[4t\int_y^L C(s)ds + 2t^2\int_y^L (s-y)C(s)ds + 2C(y)\right]dy \\ &\equiv I(\ell,t)\end{aligned}$$

Direct differentiation of equation (65) with respect to t yields

$$\frac{\partial V}{\partial t} = 2\int_\ell^L C(y)dy + 2t\int_\ell^L (y-\ell)C(y)dy \equiv G(\ell,t).$$

Thus, if we can show that $G(\ell,t) = I(\ell,t)$, we will be done. We have the following:

$$\frac{\partial I}{\partial \ell} = tI - 4t\int_\ell^L C(y)dy - 2t^2\int_\ell^L (y-\ell)C(y)dy - 2C(\ell)$$

On the other hand,

$$\frac{\partial G}{\partial \ell} - tG = -4t\int_\ell^L C(y)dy - 2t^2\int_\ell^L (y-\ell)C(y)dy - 2C(\ell)$$

so that

$$\frac{\partial G}{\partial \ell} - tG = \frac{\partial I}{\partial \ell} - tI$$

and thus, we have

$$G(\ell,t) = I(\ell,t) + \alpha e^{\ell t}.$$

Since $G(L,t) = 0 = I(L,t)$ it follows that $\alpha = 0$ and, thus, that $G = I$ as required.

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