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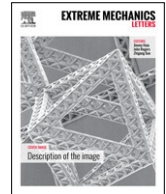


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Dampening effects on the polymerization rate of actin gel surface growth



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ABSTRACT

This letter addresses the delicate balance between a local surface growth mechanism, driven by actin polymerization, and the resulting macroscopic stress field, with emphasis on the effect of external dampening on the growth process. In connection with available experimental studies, we consider a spherically symmetric setting in which new mass is constantly being formed on the surface of a bead. In that unique growth process the previously formed layers are constantly being pushed outwards by new mass, thus resulting in an internal stress field which, in turn, effects the growth process. It is shown that external dampening effects the growth rate as well as the steady-state thickness in the treadmilling regime.

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1. Introduction

The molecular mechanism of actin polymerization drives cell movement. Fascinating examples of such phenomena have been observed in embryonic cells and several intracellular pathogens such as *Listeria monocytogenes* [1]. The latter example has motivated Noireaux et al. [2] to perform a series of experiments designed to obtaining further insight into the chemo-mechanical process. Therein actin gel was grown on spherical beads under varying conditions (i.e. bead radius and concentration of necessary proteins to promote the reaction). It was shown that if symmetry is maintained the growth process eventually assumes a steady-state treadmilling response. Van der Gucht et al. [3] later explained, based on experimental observations in a similar setting, that stress release due to symmetry breaking of the actin layer can drive movement. In that study it is further shown that the symmetry breaking can

occur before or after arriving at the treadmilling state, is independent on the bead size, but is sensitive to the growth rate.

In the present study we suggest a simplified framework which ties the microscopic growth process to the macroscopic evolution of mass, to expose the sensitivity of the process and specifically the growth rate to external dampening effects. That sensitivity may play a key role in the limit state of symmetry breaking and thus in actin based motility.

Actin polymerization and depolymerization is widely considered in the scope of Brownian dynamics and is thus an 'overdamped' dynamic process at the limit where no average acceleration takes place. The dampening is a product of the crowding of solvent molecules which causes friction. Specifically, considering the growth of actin gel on a spherical bead, the process requires inflow of solid mass (monomers) through the out-flowing material at an identical rate, to sustain the growth. Hence the process and the resulting stress field are expected to depend on the growth rate. On the other hand, the bio-chemical process of polymerization (and depolymerization) depends on the

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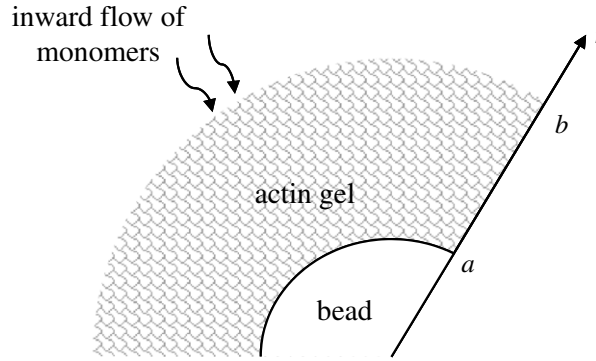


Fig. 1. Illustration of actin layer grown on a bead in a spherically symmetric setting. The spatial radial coordinate is denoted by r , the radius of the bead is a and the external radius of the grown mass is b . Actin polymerization takes place only on the bead surface at $r = a$, while inward flow of monomers is required to maintain the growth.

stress. Therefore there is a coupled relation between the growth rate and the stress.

Considering the collective behavior of the solid mass at the continuum limit, the present derivation by-passes the stochastic aspects of Brownian dynamics which is then plugged back into the model through the chemo-mechanical coupling with the rate of polymerization dictated by a simplified form of Kramers equation [4], which was previously suggested by Noireaux et al. [2] and applied therein, in comparison with experimental results. Employing an incompressible continuum model of finite strain elasticity it will be shown that external dampening influences not only the time required to achieve a steady thickness of the actin gel but also the steady thickness itself.

Recent studies [5–7] account for the growth process and induced stress fields considering several constitutive models of compressible and incompressible elasticity and hyperelasticity for both infinitesimal and finite strains in spherical and cylindrical geometries. It is shown therein that material compressibility can have a profound effect on the stress field and thus on the steady thickness in the treadmilling state. In the present study we restrict the discussion to an incompressible material response. The novel ingredient of the present study compared to the aforementioned ones is the role of the external dampening effects.

2. Problem setting and formulation

We consider the spherically symmetric growth of actin gel on a bead of radius a , as illustrated in Fig. 1, where the spatial radial coordinate is denoted by r and the external radius of the actin layer is b . New mass is formed only on the bead surface ($r = a$), hence the previously formed layers are constantly being pushed outwards by new mass, thus resulting in an internal stress field which, in turn, effects the growth process.

The formulation centers on the simplifying assumption that the actin gel is an isotropic homogeneous continuum. However, the interactions with solvent molecules and the constant inward flow of monomers is accounted for by considering an external dampening effect.

We consider the grown mass to be an incompressible Hookean elastic medium while accounting for finite

strains. Therefore, by inserting Poisson's ratio $\nu = 0.5$ (for incompressibility) into the regular Hookean elastic relations in spherical symmetry, we have

$$h_r = \frac{1}{E} (\sigma_r - \sigma_\theta), \quad h_\theta = h_\varphi = -\frac{1}{2E} (\sigma_r - \sigma_\theta) \quad (1)$$

where E is the elastic modulus, $(\sigma_r, \sigma_\theta = \sigma_\varphi)$ are the radial and tangential stress components and $(h_r, h_\theta = h_\varphi)$ are the radial and tangential logarithmic (Hencky) strains, respectively. Note that in the present analysis compressive stress has a negative sign.

According to (1) we have the relation $h_r + 2h_\theta = 0$ which is a basic requirement for conservation of mass in an incompressible medium. In that context, it should be mentioned that, being a polymeric gel, actin can have some level of compressibility. Since the network alone (without the surrounding fluid) is compressible, outflow of fluid through the network allows for change in volume. This is a subtle time dependent effect which depends on the boundary conditions and is apparent only in the low frequency loading regime [8]. Poisson ratio measurements reported in [9] are near the incompressibility limit. Nevertheless, in previous studies [5–7] the effect of compressibility on the stress field, without consideration of dampening effects, has been thoroughly addressed, hence, the combined damped-compressible response can be accounted for in the future.

By employing kinematic considerations as in [7] we find that the tangential stretch of any material segment is the ratio between its initial length and current length, hence the logarithmic tangential strain component is

$$h_\theta = \ln \left(\frac{r}{a} \right). \quad (2)$$

Conservation of mass of the incompressible medium implies that the inward mass flow due to polymerization on the bead surface (with velocity $v(a) = v_p$) must be equal to the outward flow through the spherical surface at any radius, thus bringing us to the relation for the material velocity

$$v = v_p \left(\frac{a}{r} \right)^2. \quad (3)$$

Note that the velocity v_p , which represent the rate of polymerization (hence the subscripted p), plays a key role in the present chemo-mechanically coupled growth process, as will be discussed in the next section.

We now proceed to write the equation of motion in spherical geometry

$$\frac{d\sigma_r}{dr} + \frac{2}{r}(\sigma_r - \sigma_\theta) = \mathcal{D}(v) \quad (4)$$

where the additional term on the right hand side is a dampening term and thus represents *drag* as a function of the material velocity. Since the polymerization process is widely considered in the scope of Brownian dynamics, and is, namely, an over-damped process in which inertial effects can be neglected, the inertial term in the equation of motion (4) is omitted, and we account for a Stokes' type drag formula

$$\mathcal{D}(v) = cv \quad (5)$$

with a constant coefficient (c).¹ Note that any other dampening relations can be considered without sacrificing the analytical derivation. Nevertheless the linear dampening relation is most commonly applied in the context of Brownian and Langevin dynamics, essentially describing the interaction of the material with a Newtonian solvent where the dampening coefficient is related to the diffusion through the Stokes–Einstein relation [10,11]. A more extensive discussion and review of literature on interaction between Brownian particles with supramolecular polymer solutions can be found in [12].

Inserting relations (1) and (2) into the equation of motion (4) and performing integration with the boundary condition

$$\sigma_r(r = b) = 0 \quad (6)$$

at the free surface ($r = b$) yields the radial stress profile

$$\sigma_r(r) = -2E \ln\left(\frac{b}{r}\right) \ln\left(\frac{rb}{a^2}\right) - cav_p \left(\frac{a}{r} - \frac{a}{b}\right) \quad (7)$$

which for $c = 0$ becomes identical to Eq. (36a) in [7]. According to (7), the radial stress at the bead surface is

$$\sigma_r(a) = -2E \ln^2(1 + h) - cav_p \left(\frac{h}{1 + h}\right) \quad (8)$$

written in terms of the nondimensional thickness of the actin layer $h = (b - a)/a$ (which must not be confuse with the subscript carrying notation of the Hencky strain components in (1)). For further use, we write the circumferential stress at the outer surface, according to (1) with (6) as

$$\sigma_\theta(b) = 2E \ln(1 + h). \quad (9)$$

In the present section we have obtained a complete closed form solution of the stress field in the growing matter with the underlying assumptions of finite strain elasticity of an incompressible medium under the influence of viscous dampening. As shown in (7), that stress field depends on the rate of polymerization through v_p . On the other hand, the reaction rate depends on the stress and therefore the evolution of the actin layer, and its final steady thickness, is a coupled chemo-mechanical process.

3. The chemo-mechanical coupling

The relation between the local microscopic growth process and the resulting macroscopic stress field is discussed in the present section.

The growth process at the bead surface is driven by the molecular motor known as the Brownian Ratchet [13,14]. Such motors transduce chemical bond energy into directed motion by rectifying Brownian motion. A product of this process, in the present context, is actin polymerization. The rate of polymerization\depolymerization depends on the environment in which the process takes place (i.e. temperature, concentration of monomers) and the resisting stress.

Noticing that the dimensionless thickness (h), serves here as an independent variable throughout the growth process, we can write the rates of polymerization and depolymerization as functions of the thickness $v_p = v_p(h)$ and $v_d = v_d(h)$, respectively. The stress-free initial rates are thus $v_p(0)$ and $v_d(0)$. Where, under usual circumstances, we expect the stressed free polymerization rate $v_p(0)$ to be much larger than the depolymerization rate $v_d(0)$ with the necessary inequality $v_p(0) > v_d(0)$ to facilitate initiation of growth.

The effect of the internal stress can now be taken in accordance with Kramers [4] via a Van't Hoff–Arrhenius type equation in the simplified form

$$v_p = v_p(0)e^{c_p\sigma_r(r=a)} \quad (10)$$

for polymerization, and similarly

$$v_d = v_d(0)e^{c_d\sigma_\theta(r=b)} \quad (11)$$

for depolymerization, as suggested in [2]. Derivation of (10) assumes that the activation energy required to add another monomer in the gap between the end of the actin filament and the bead surface is proportional to the work done by applying force on a single filament over a distance equal to the length of the monomer, with a similar argument in derivation of (11). Hence, the energy is proportional to the stress in the direction of the process and c_p, c_d are scaling parameters. Since the stress components in (10) and (11) are proportional to the elastic modulus (E), it is clear that increasing the stiffness of the grown medium increases the rate of polymerization. Dafalias and Pitouras [7] suggested an extension of the rate relations in (10) and (11) to include the effect of the orientation of the free ends of the actin filaments.

Following previous studies [2,15] the rate of change of the thickness of the actin layer is governed by the difference between the rate of polymerization at the bead surface and the rate of depolymerization, or gel dissociation, at the outer surface. Intuitively, if the rate of polymerization and the rate of depolymerization are equal, then the thickness is maintained constant.

Now, by inserting (8) into (10) we have the implicit relation for the growth rate

$$\frac{v_p}{v_p(0)} = \exp \left\{ -c_p \left[2E \ln^2(1 + h) + cav_p \left(\frac{h}{1 + h} \right) \right] \right\} \quad (12)$$

¹ Based on assumed incompressibility one can argue that $2v$ instead of v should enter Eq. (5) as the relative velocity of monomers and solid mass, in which case the factor 2 can be absorbed in c .

which by different choice of parameters can be written as

$$\bar{v}_p = \exp \left\{ -\alpha_p \ln^2(1+h) - \zeta \bar{v}_p \left(\frac{h}{1+h} \right) \right\} \quad (13)$$

where $\bar{v}_p = v_p/v_p(0)$ is the dimensionless growth rate, $\alpha_p = 2c_p E$, and the nondimensional dampening coefficient is $\zeta = c_p c a v_p(0)$. By similar substitution of (9) in (11) we write

$$\bar{v}_d = (1+h)^{\alpha_d} \quad (14)$$

where $\bar{v}_d = v_d/v_d(0)$ is the dimensionless depolymerization rate and $\alpha_d = 2c_d E$.

Finally, we can write the rate of change in the dimensionless thickness as

$$\dot{h} = \frac{1}{a}(v_p - v_d) \quad (15)$$

clearly showing that the thickness would come to a steady state if $v_p = v_d$. At that point mass conservation implies,

$$v_d = v_b \left(\frac{b}{a} \right)^2 \quad (16)$$

since all the mass flowing through $r = b$ is immediately dissociated.

It is also convenient to write the dimensionless rate of change in thickness with respect to the initial rate as

$$\frac{\dot{h}}{\dot{h}(0)} = \frac{\gamma \bar{v}_p - \bar{v}_d}{\gamma - 1}, \quad \gamma = \frac{v_p(0)}{v_d(0)} \quad (17)$$

where the initial rate is

$$\dot{h}(0) = \frac{\gamma - 1}{\gamma} v_p(0). \quad (18)$$

Once the growth rate as a function of the thickness ($v_p = v_p(h)$) is known by solution of (13), differential equation (17) can be integrated with the initial condition

$$h(0) = 0 \quad (19)$$

to obtain the variation of the thickness with time. It should be noted that the solution of (13) cannot be expressed in terms of elementary functions and has only one real branch.

A useful formula for the steady state thickness at the undamped limit, with $\zeta = 0$, can be obtained from (17) with $\dot{h} = 0$ by inserting relations (13) and (14), thus arriving at a quadratic relation with the solution

$$\ln(1+h) = \sqrt{\left(\frac{\alpha_d}{2\alpha_p} \right)^2 + \frac{\ln \gamma}{\alpha_p}} - \frac{\alpha_d}{2\alpha_p}. \quad (20)$$

The steady state thickness in (20) serves as an upper limit in the present growth process. Since the values of α_p and α_d , are proportional to the elastic modulus we find from (20) that there is an inverse effect between E and the steady state thickness of the actin layer.

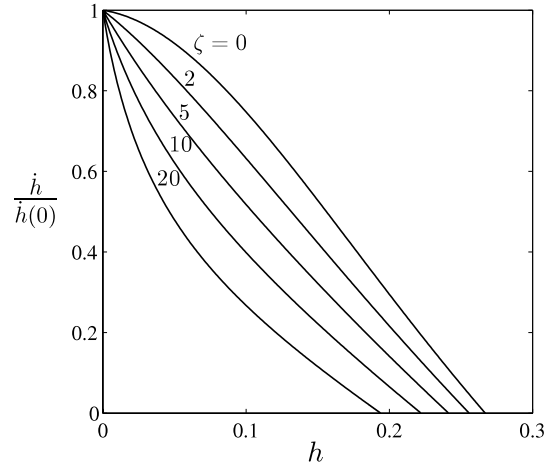


Fig. 2. The state space representation of the growth process. Curves are for various levels of the non-dimensional dampening coefficient.

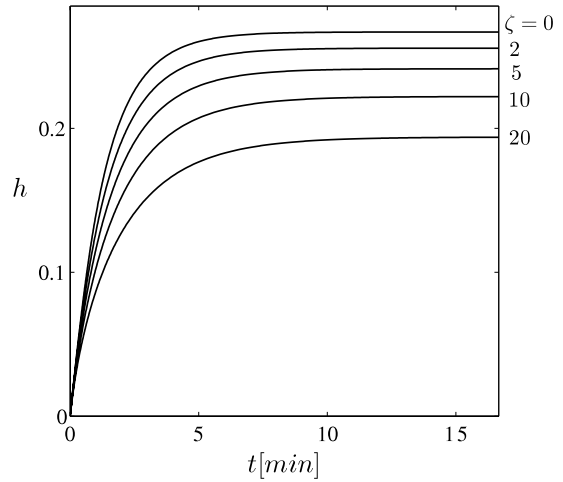


Fig. 3. The thickness as a function of time. Curves are for various levels of the non-dimensional dampening coefficient.

4. Results and discussion

To illustrate the results and examine the sensitivity of the growth process to the external dampening effect, the model parameters are chosen to fit best to the experimental results presented in [2,3]. Thus, we have the bead radius $a = 7 \mu\text{m}$, the polymerization and depolymerization coefficients $\alpha_p = 20$ and $\alpha_d = 5$, respectively and the initial polymerization rate $v_p(0) = 20 \text{ nm/s}$, which is much higher than the initial depolymerization rate, so that the ratio is $\gamma = v_p(0)/v_d(0) = 10$. The results are shown for several values of the dampening coefficient ζ .

The implicit relation in (17) is presented in Fig. 2 and the variation of thickness of the grown material with time, which is merely the result of integration of the relation in (17) with initial condition (19), is shown in Fig. 3. It is observed that as the dampening coefficient increases, the steady thickness decreases, while the time required to approach the steady state increases. Hence, sensitivity to the external dampening is noticeable. We also notice

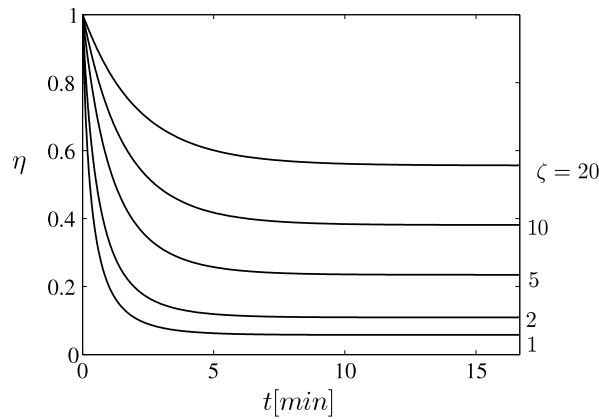


Fig. 4. The percentage of power input invested in dissipation as a function of time throughout the growth process.

a transition from concave to convex behavior of the rate relation.

An important question which arises from the present analysis is how to quantify physical levels of dampening. To that end, it is illuminating to consider the percentage of energy consumed by dissipation, which is a direct outcome of the acting drag force. Accounting for the compressive (negative) nature of the radial stress, the power invested by the molecular motor at the surface of the bead is

$$P = -4\pi a^2 \sigma_r(a) v_p. \quad (21)$$

Part of that power input is converted into potential elastic energy while the remainder is dissipated through the act of the viscous dampening force (\mathcal{D}). The power consumed by dissipation is thus obtained by integration of the dampening force $c v$, (5), multiplied by the velocity over the entire thickness, as

$$D = 4\pi \int_a^b c v^2 r^2 dr = 4\pi a^3 c v_p^2 \left(\frac{h}{1+h} \right). \quad (22)$$

Now we can define the percentage of invested power input being consumed by dissipation as

$$\eta = \frac{D}{P} = - \left(\frac{\zeta h}{1+h} \right) \frac{\bar{v}_p}{\ln \bar{v}_p} \quad (23)$$

which is obtained by substituting relations (21) and (22) for P and D , respectively, in (23), with the radial stress at $r = a$ extracted from (10). We expect that for physical levels of dampening, in the present setting, the percentage of power being dissipated is sufficiently small.

The variation of η throughout the growth process is shown in Fig. 4 for several levels of dampening. It is observed that, at initiation of the growth process, the only mechanism for distribution of energy is by dissipation. That is an expected result since at that point of time there is no elastic stress. However, as the growth process continues the percentage of energy consumed by dissipation reduces and at the steady-state we have $\eta < 0.5$ for $\zeta \lesssim 14$ thus providing some insight into the possible levels of viscous dampening. However, quantifying the actual physical levels of ζ , requires comparison with a designated set of experimental results.

5. Concluding remarks

The effect of external dampening on surface growth of actin gel in a spherically symmetric setting is investigated. While the microscopic growth mechanism of actin polymerization is driven by a molecular motor known as the Brownian Ratchet, which represents a discrete 'over-damped' process with stochastic aspects, the resulting grown actin gel is considered to behave as an isotropic continuum. That solid medium is constantly being deformed and increased in mass, due to the surface growth, while it is simultaneously subjected to an external drag force and a pre-existing stress field dictated by the history of the growth process. This framework facilitates derivation of closed form analytical relations for the evolution of the macroscopic stress field in this unique growth process, accounting for finite strains in an incompressible medium. Considering a Stokes' type drag force, the stress field is shown to depend on the rate of polymerization and the resulting chemo-mechanical coupling is addressed. Since the depolymerization at the external radius is accelerated by the increasing tangential stress, the process is generated by two competing mechanisms and thus tends to a steady treadmilling regime of constant thickness, as observed in available experimental studies. Through the analytical relations, it is shown that the external dampening can have a profound effect, not only on the time required to arrive at the treadmilling regime, but also on the steady thickness itself and therefore on the underlying phenomena of actin based cell motility. The analysis concludes with an energetic evaluation of physical levels of external dampening.

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