

Elastic model of actin polymerization upon processive capping by formin

In this section, we formulate an elastic torsion model for an actin filament that is capped at its barbed end by a formin dimer, which is attached by an elastic link to a substrate. We calculate the energy of this system that accumulated in the course of polymerization and find the energetically most favorable behavior of the formin cap in the course of processive capping.

Energy of filament torsion. Rotation of formin with respect to the filament pointed end will be referred to as the filament torsion. We propose that, in the course of polymerization, the formin dimer can behave in stair-stepping or screw mode. One stair-stepping step of polymerization results in torsion by $\phi_{SS} = 14^\circ$, whereas one screw step leads to torsion by $\phi_{SCR} = -16^\circ$. The numbers of the stair-stepping and screw steps will be denoted by n and m , respectively. The torsion angle that results from unconstrained rotation equals $\phi_S = n\phi_{SS} + m\phi_{SCR}$ and will be referred to as the spontaneous torsion angle. Each polymerization step leads to filament elongation by $\lambda = 2.75 \text{ nm}$ (Lorenz et al., 1993).

We assume that during the first $n_0 + m_0$ steps of polymerization, there are no constraints imposed on the relative rotation of filament ends so that the accumulated torsion angle ϕ_0 is equal to its spontaneous value $\phi_0 = \phi_{0S} = n_0\phi_{SS} + m_0\phi_{SCR}$, and the filament length reaches a value of $L_0 = (n_0 + m_0)\lambda$. Further polymerization proceeds upon fixation of the filament pointed end and attachment of the formin cap to a substrate (a prototype of such a situation is represented by the experimental design of Kovar and Pollard, 2004) and, hence, results in accumulation of the elastic stress that is related to torsion. The next Δn stair-stepping and Δm screw steps generate the torsion angle $\Delta\phi$ and the filament elongation $\Delta L = (\Delta n + \Delta m)\lambda$.

The energy of torsion deformation F_{FIL} of a filament of length L can be presented as (Otomo et al., 2005)

$$F_{FIL} = \frac{1}{2}C\phi^2 L \left(\frac{\phi - \phi_S}{L} \right)^2 \quad (1)$$

where ϕ is the total torsion angle, L is the total filament length, and C is the torsion elastic modulus, which is equal to $C \approx 8 \times 10^{26} \text{ Nm}^2$ (Tsuda et al., 1996). The difference between the actual torsion angle ϕ and its spontaneous value ϕ_S represents the torsion strain $\tau = \phi - \phi_S$. Taking into account that $\phi = \phi_0 + \Delta\phi$, $L = L_0 + \Delta L$, and the above relationships, we obtain for the filament torsion energy

$$F_{FIL} = \frac{1}{2} \lambda \frac{C}{(n_0 + m_0 + \Delta n + \Delta m)} (\Delta\phi - \Delta n \phi_{SS} - \Delta m \phi_{SCR})^2. \quad (2)$$

Energy of formin cap turning. We further assume that the formin cap can rotate to some extent while immobilized on the substrate, generating deformation of formin itself, the link connecting formin to the substrate, or the substrate itself. Resistance to such deformation will be characterized by an effective rigidity of the formin–substrate complex (C_L) and its energy (F_L), which is expressed as

$$F_L = \frac{1}{2} C_L (\Delta\phi)^2. \quad (3)$$

Total energy of the system. The torsion elastic energy that accumulated in the course of processive capping is determined by the number of stair-stepping (n) and screw (m) steps. To obtain an expression for the filament torsion energy, we first minimized the total elastic energy ($F_{TOT} = F_{FIL} + F_L$) with respect to the torsion angle $\Delta\phi$ that accumulated upon restriction of the filament rotation. By using equations 2 and 3, we obtain the expressions for $\Delta\phi$ and the corresponding torsion strain (τ):

$$\Delta\phi = \frac{C}{C + C_L \lambda (n_0 + m_0 + \Delta n + \Delta m)} (\phi_{SS} \Delta n + \phi_{SCR} \Delta m) \quad \text{and} \quad (4 \text{ a})$$

$$\tau = \frac{C_L \lambda (n_0 + m_0 + \Delta n + \Delta m)}{C + C_L \lambda (n_0 + m_0 + \Delta n + \Delta m)} (\phi_{SS} \Delta n + \phi_{SCR} \Delta m). \quad (4 \text{ b})$$

If the rigidity of the formin–substrate complex vanishes ($C_L \Rightarrow 0$), the angle $\Delta\phi$ is simply an addition to the spontaneous torsion angle that accumulated as a result of $\Delta n + \Delta m$ steps of processive capping. In the case of a nonvanishing rigidity ($C_L > 0$), the torsion angle $\Delta\phi$ differs from the spontaneous one and leads to the build up of elastic energy:

$$F_{TOT} = \frac{1}{2} \phi_{SS} (\phi_{SS} \Delta n + \phi_{SCR} \Delta m)^2, \quad (5)$$

where the effective rigidity of the system, C_{EFF} , is determined by the elastic moduli, C , K_L , and the filament length, $L = \lambda(n + m)$, according to

$$C_{EFF} = \frac{C_L \phi C}{C + C_L \lambda (n_0 + m_0 + \Delta n + \Delta m)}. \quad (6)$$

If the formin–substrate link is broken ($C_L = 0$), the effective rigidity vanishes ($C_{EFF} = 0$), and, as expected, the elastic energy is not accumulated for any number of steps (n and m). For an infinitely rigid formin–substrate complex ($C_L \Rightarrow \infty$), the effective rigidity is determined only by the torsion elastic modulus (C) of the actin filament:

$$C_{EFF} = \frac{C}{\lambda (n_0 + m_0 + \Delta n + \Delta m)}. \quad (7)$$

Optimal regime of processive capping. The most favorable regime of processive capping corresponds to a minimal accumulation of the elastic energy. Such regime is determined by an optimal relationship between the number of the stair-stepping (n) and screw (m) steps.

To find the optimal regime of processive capping, we have to determine which of the two modes is most favorable for each step of polymerization. To this end, we find the energy cost of one processive capping step, which is performed after the system underwent $n_0 + \Delta n$ stair-stepping and $m_0 + \Delta m$ screw steps.

Based on equation 5, if the step is performed in the stair-stepping mode, its energy is

$$f_{ss} = \frac{1}{2} \phi_{SS} (2 \phi_{SS} \Delta n + 2 \phi_{SCR} \Delta m + \phi_{SS}) \phi_{SS}. \quad (8)$$

If the step proceeds in the screw mode, the corresponding energy is

$$f_{SCR} = \frac{1}{2} \phi_{EFF} (2 \phi_{SS} \Delta n + 2 \phi_{SCR} \Delta m + \phi_{SCR}) \phi_{SCR}. \quad (9)$$

The relationship between these energies (equations 8 and 9) determines what kind of step will be most probable. A step of stair stepping will be performed if $f_{SS} < f_{SCR}$, whereas in the opposite case of $f_{SS} > f_{SCR}$, a screw step is more favorable.

Let us consider the first step after the beginning of torsion stress accumulation, meaning $\Delta n = 0$ and $\Delta m = 0$. In this case, $f_{SS} = \frac{1}{2} \diamond C_{EFF} \diamond \phi_{SS}^2$ and $f_{SCR} = \frac{1}{2} \diamond C_{EFF} \diamond \phi_{SCR}^2$. Because $\phi_{SS} = 14^\circ$ and $\phi_{SCR} = -168^\circ$, we obtain from equations 8 and 9 that $f_{SS} < f_{SCR}$, so the first step will be performed in the stair-stepping mode.

Calculation of the energies of the following steps shows that several of them will also proceed in the stair-stepping mode. The first screw step comes after Δn^* stair-stepping steps, and the condition for this event is $f_{SCR}(\Delta n = \Delta n^*, \Delta m = 0) < f_{SS}(\Delta n = \Delta n^*, \Delta m = 0)$. According to equations 8 and 9,

$$\Delta n^* = -\frac{1}{2} \frac{\phi_{SCR} + \phi_{SS}}{\phi_{SS}}. \quad (10)$$

Similar analysis shows that in the course of further polymerization, each screw step occurs after a sequence of

$$\Delta n^{**} = -\frac{\phi_{SCR}}{\phi_{SS}} \quad (11)$$

stair-stepping steps.

According to equations 10 and 11 and the specific values of ϕ_{SS} and ϕ_{SCR} , the first screw step occurs after five to six steps in the stair-stepping mode, whereas each other screw step is preceded by 11–12 stair-stepping steps.

In summary, the optimal regime of continuing processive capping consists of repeating cycles, each of which includes a sequences of 11–12 stair-stepping steps followed by one screw step.

Solution of the rotation paradox. Because the optimal regime of processive capping consists of cycles comprising the alternating stair-stepping and screw steps, the torsion angle and elastic energy of the system change periodically and remain within limited ranges during the whole course of polymerization.

To analyze this issue, we assume that the number of polymerization steps ($\Delta n + \Delta m$) that were performed upon accumulation of torsion stress within the filament–formin is much smaller than the number of preceding steps ($\Delta n + \Delta m \ll n_0 + m_0$). This assumption does not change the qualitative predictions of our model but makes the considerations easier.

Based on equations 4 b and 11, within one cycle of the processive capping, the torsion strain changes between $\tau_{in} = -\frac{1}{2} \frac{C_L \lambda \phi(n_0 + m_0)}{C + C_L \lambda \phi(n_0 + m_0)} (\phi_{SCR} + \phi_{SS})$ and $\tau_{fin} = \frac{1}{2} \frac{C_L \lambda \phi(n_0 + m_0)}{C + C_L \lambda \phi(n_0 + m_0)} (\phi_{SCR} - \phi_{SS})$. The larger the rigidity of the formin–substrate complex (C_L) is, the larger the amplitude is of torsion strain variation. A maximum amplitude corresponds to $C_L \gg \frac{C}{\lambda \phi(n_0 + m_0)}$. In this case, the difference between the torsion strain in the beginning and end of the cycle constitutes $\tau_{in} - \tau_{fin} = -\phi_{SCR} = 168^\circ$. This means that the torsion strain does not persistently build up in the course of polymerization but rather varies within a limit of 168° . The periodic variation of the torsion strain as a function of the number of polymerization steps ($\Delta n + \Delta m$) for the case of $C_L \gg \frac{C}{\lambda \phi(n_0 + m_0)}$ is illustrated in Fig. 2 a.

As a consequence of the limited variation of the torsion strain, we predict that processive capping will not result in supercoiling of the actin filament. This is in contrast to what can be expected based on the pure stair-stepping model (Kovar and Pollard, 2004). Indeed, according to the elastic criterion (Landau and Lifshitz, 1959), a filament undergoes supercoiling if its torsion strain exceeds a critical value of

$\tau^* = \frac{8.98 K}{C}$, where K is the filament-bending modulus. The bending modulus of an actin filament has a

value of $K \approx 3.6 \times 10^{26} \text{ J/m}$ (Gittes et al., 1993; Isambert et al., 1995), whereas its torsion rigidity is

$C \approx 8 \times 10^{26} \text{ J/m}$ (Tsuda et al., 1996) so that the critical torsion equals $\frac{8.98 K}{C} \approx 230^\circ$. Within the optimal

regime of processive capping, the maximum absolute value of the torsion strain equals $\approx 83^\circ$ (Fig. 2 a), which is smaller than the critical value. Hence, the actin filament never reaches the torsion angle, generating supercoiling.

The torsion elastic energy (F_{TOT}) that accumulated within the system in the course of polymerization can be determined by combining equations 5 and 11. Variation of energy in the course of polymerization is illustrated in Fig. 2 b. Within one cycle of polymerization, the torsion energy changes between the values

$F_{in} = \frac{1}{8C + C_L \lambda (n_0 + m_0)} (\phi_{SCR} + \phi_{SS})^2$ and $F_{fin} = \frac{1}{8C + C_L \lambda (n_0 + m_0)} (\phi_{SCR} - \phi_{SS})^2$. The lower the rigidity C_L is of the formin–substrate complex, the smaller the elastic energy is. The largest value of elastic energy corresponds to the case $C_L \gg \frac{C}{\lambda (n_0 + m_0)}$. It is accumulated at the end of the cycle and equals

$F_{TOT}^{\max} = \frac{1}{2\lambda (n_0 + m_0)} (\phi_{SCR} - \phi_{SS})^2$. Assuming that before imposing the constraint, actin polymers reach the length of $\lambda (n_0 + m_0) = 1\text{m}$ and by using the parameter values $C = 8 \times 10^{26} \text{J/m}$, $\phi_{SCR} = -168 \approx -29$, and $\phi_{SS} = 14 \approx 0.24$, we obtain for the maximum elastic energy $F_{fin}^{\max} \approx 20k_B T$ (where $k_B T \approx 0.6 \text{kcal}/\text{mol}$ is the product of the Boltzmann constant and absolute temperature).

Altogether, cyclic variations of the torsion strain and the corresponding elastic energy (Fig. 2) within feasible limits demonstrate that the suggested optimal regime of the processive capping combining steps of stair-stepping and screw modes resolves the rotation paradox of the purely stair-stepping model.

References

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