Actin, a model semi-flexible polymer

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Actin is a filamentary protein which has many remarkable properties making it an ideal system for the study of the dynamics and mechanics of semi-flexible polymer solutions and gels; actin has a persistence length of over 10 microns and can polymerize to lengths of several tens of microns, this permits the use of video microscopy and other optical methods in the study polymer dynamics. Many associated proteins exist which can be used to regulate length or crosslink filaments. We discuss the dynamics and rheology of these solutions.

Actin, a self assembling protein

For the rheologist the biological world is a source of a number of interesting materials with properties which are not easily reproduced with synthetic polymers. In particular actin forms remarkably stiff structures which are very good realizations of semi-flexible polymers [1]. A number of experimental and theoretical results are available for this system which we now review. The actin experimental system is not without disadvantages, in particular it is mechanically fragile and subject to bio-degradation, however it allows the direct, visual observation of a number of fundamental processes in polymer dynamics, including reptation. A number of novel regimes, without direct equivalents in the case of flexible polymers, are still to be explored.

Actin is a widely spread protein, occurring in almost all higher cells. Starting from a rich source of actin (such as muscle) efficient purification protocols are easy to apply, giving a relatively pure solution of monomeric actin proteins. In the presence of a polymerization buffer [2] (containing divalent ions and a source of energy in the form of the molecule ATP), the actin monomers spontaneously assemble to form filaments, fig. (1). The filaments can also assemble without the energy source by replacing the molecule ATP by ADP, however higher concentrations of actin monomers are then required and the quality of the filaments formed seems to be not as good. These filaments are made of double helixes of monomers where each monomer is in an equivalent position. The diameter of the filaments thus formed is about 7 nm. The filament length can reach some tens of microns, a length scale easily studied with optical techniques and at the limit between the microscopic and the macroscopic, where micro-manipulation techniques using optical and magnetic tweezers can be used to study macromolecular systems undergoing Brownian motion.

A single filament of actin is just a little bit too fine to be seen with direct optical microscopy, however addition of a fluorescent probe renders the filament easily visible. These fluorescence techniques have been used to determine the persistence length of the filaments via Brownian spectroscopy. One records a large number of images of a filament using a video camera and performs an analysis in terms of normal modes. A simple theory of bending elasticity (see below) gives the elastic constants and thus the persistence length [3]. This persistence length is close to 15 microns, with perhaps a moderate dependency on buffer conditions [3]. The accuracy of these
FIG. 1. A schematic drawing of an actin filament showing the double helical structure. The two filaments are oriented in the same sense so that the global symmetry of the filament is polar as well as chiral. This should be contrasted with other helical biopolymers such as DNA where the two backbones are anti-parallel and thus form a non-polar structure.

methods is very good with error bars on the persistence length of less than 10 per cent. Thus actin filaments are rather good realizations of semi-flexible polymers with $d \ll l_p < L$, where $d$ is the filament diameter, $l_p$ the persistence length and $L$ the filament length. One should note that the persistence length is enormous even compared with that of other biological molecules. For comparison DNA has a persistence length of 30nm a factor of more than 100 smaller. Another cytoskeletal protein, tubulin, forms structures which are even more rigid, and polymerize to a similar length; microtubules thus behave as rigid elastic rods, thermal fluctuations are probably to small to be important in most situations.

The process which polymerizes the filaments is reversible (though dissipative due to the turnover in ATP which occurs during the assembly process). A given filament continually gains and looses monomers at its ends. Due to the dynamic processes of filament formation it is difficult to dilute filaments to study individual filament dynamics in the absence of steric interactions; on extreme dilution the solution depolymerizes. This depolymerization can be prevented by using an associated molecule such as phalloidin which modifies the disassembly dynamics or by working at a sufficiently high concentration [6]. Polymerization is usually carried out in conditions such that the final distance between the filaments formed is between $0.2\mu$ and $1\mu$. In these conditions the solution is semi-dilute but with properties which must be contrasted with those in semi-dilute solutions of normal flexible polymers. Firstly the volume fraction is extremely small, of the order of 1 per thousand. Secondly the sequence of length scales that we are used to in flexible polymers has been changed. In the physics of flexible polymer solutions we are used to the length hierarchy $d < l_p \ll \xi$, where $\xi$ is the length scale of density fluctuations. Here we are in the regime, $d \ll \xi \ll l_p$ with $\xi$ the typical distance between filaments ($d=7nm, \xi = 1\mu, l_p = 15\mu$). We have already noted that it is not possible to decrease the density to very low levels because of filament depolymerization. Increasing the volume fraction leads to a nematic transition [7]. One is thus confined to a relatively narrow window of concentration if one wishes to study isotropic actin solutions.

As well as being studied by video methods, actin has been the subject of investigation by light scattering, macroscopic rheology, magnetic bead rheology and other physical techniques which we shall also discuss. We note that this article, presented at the colloquium in honor of the late Jacques Bastide, is partly review and partly a summary of some unpublished ideas; some parts of the presentation have been worked out in full, while others (such as the arguments as to the nature of long range order in actin solutions) await disproof by more rigorous approaches to the problem.
The length of actin filaments can be regulated by many proteins

Actin is remarkable for the number of other proteins which interact with it. Many tens of other proteins are available to modify the properties of an individual filament or to regulate the degree of polymerization. Some of these molecules have been exploited in physical measurements but many other proteins are relatively poorly studied. A general review of associated proteins can be found in [8]. These associated molecules are used to regulate the rheological state of actin in the cellular environment.

Too many classes of regulating proteins exist to be discussed here, but we will speak of some of the molecules which have the most interest for the polymerist. Often used in rheological experiments, gelsolin caps the end of a growing filament and thus can be used to regulate the average filament length in a solution. When added to an already polymerized solution gelsolin cuts the actin filaments in presence of calcium, thus provoking a gel-sol transition. Since unbound gelsolin also acts as a nucleating center for actin filament growth one could imagine a protocol involving gelsolin and phalloidin to generate relatively mono-disperse actin solutions [9]. It would be interesting to perform rheological experiments on such mono-disperse samples to see how the usual polydispersity affects the mechanical properties.

There are many other regulating proteins that interact with monomeric actin, including profilin and thymosin-β_4. These proteins sequester actin in a non-polymerizable form and allow the cell (in particular platelets) to stock very high concentrations of actin. A chemical signal [10] then starts an explosive polymerization of filaments. This polymerization is into a disordered phase but the concentration is high enough for nematic effects to be important. There are some interesting problems in the rearrangement dynamics to be answered. Does the solution re-orient via classical rotational dynamics or does the dynamic growth and depolymerization of the filaments play and important role in the re-orientational dynamics? Or does the system remain blocked in a metastable glass like phase as described by [11].

Observation of individual filament dynamics

Despite the fact that most of the the solutions studied are semi-dilute a number of the experimental results can be understood from the dynamics of individual filaments, in particular recent experiments of dynamic light scattering and micro-rheology with magnetic beads. The dynamics of a free actin filament are determined, for wavelength small compared with \( l_p \), by the bending elastic modes. To a good approximation, [12], one can write that the bending energy is

\[
E = \kappa \int \frac{1}{R^2(s)} \, ds \approx \frac{\kappa}{2} \int \left( \frac{d^2r_\perp}{ds^2} \right)^2 \, ds = \frac{\kappa}{2} \int q^4 r_\perp r_{-q} \, dq
\]

(1)

Where \( R(s) \) is the curvature of the filament at the position \( s \), \( \kappa = l_p k_B T \) and \( r_\perp \) is the fluctuation of the filament about its mean position. Eq. (1) shows that the fluctuations in position are characterized by a \( q^4 \) dispersion relation. Fitting the observed mode amplitudes to the functional form (1) gives the bending constant \( \kappa \) [3,4], as noted above.

If we neglect hydrodynamic interactions (which give small corrections) we find that the bending dynamics are described by a Langevin equation
\[ \rho \frac{\partial r_\bot}{\partial t} = -\kappa \frac{\partial^4 r_\bot}{\partial s^4} + f_\bot(s, t) \]  

where \( \rho \) is a friction coefficient and \( f_\bot(s, t) \) is the force acting perpendicular to the filament. From eq. (2) we deduce the relaxation time for bending excitations on the filament. Typical times for a ten micron filament are several tens of seconds. Thus normal video cameras (with 30 frames per second) are adequate for the study of filament dynamics. Higher resolution methods (in time and space) involve interferometric and other optical techniques [13], [14].

In the presence of a constant force, \( \delta(s) f_0 \), on the filament at the origin one can solve the differential equation (2) for the displacement of the filament. To understand, simply, the result of the full calculation one can make the following simple scaling argument. The equation (2) resembles that of normal diffusion except that the second spatial derivative has been replaced by a fourth spatial derivative. This implies that the perturbation due to a small perturbation at \( t = 0, s = 0 \) will propagate with the law \( r_\bot \sim G(s^4 / \kappa t) / (\kappa t^{1/4}) \). Thus after a time \( t \) a length \( (t \kappa)^{1/4} \) has been perturbed and is in movement. The friction coefficient of this section will increase with its length and thus with the same power law. The approximate differential equation for the movement is thus \( \frac{dr_\bot}{dt} \sim f / (t \kappa)^{1/4} \). Integrating this equation we find that under constant force, \( f_0 \),

\[ r_\bot(0, t) \sim \frac{f_0 t^{3/4}}{\kappa^{1/4}} \]  

Such experiments have been realized using small magnetic beads [15–17], fig. (2). One polymerizes a solution of actin in presence of a small number of magnetic particles. One chooses the size of the beads such that they are trapped by the mesh formed by the actin filaments but the beads are small enough that one is sensitive to individual filament fluctuations. Thus the particles are trapped in a small cage and pulling on the bead disturbs only a few filaments. The experiments are in very good agreement with the prediction (3), both the power law dependence in time and the linearity in force. Independent examination of the experimental curves of other experimental groups is also consistent with the anomalous time dependence in eq. (3) [14]. The forces applied in these experiments are very large compared with the thermal energy scale: they are of the order of \( 1 \mu N \), whereas the natural force unit for this system would be \( k_B T / \xi \) which is much smaller, comparable to \( 10^{-3} \mu N \). These experiments are thus only weakly sensitive to thermal fluctuations; the force constraining a given filament to its tube is also comparable to \( k_B T / \xi \) perhaps explaining why tube constraints do not seem to be important in these experiments, and why one is able to displace the bead rather large distances before eq. (3) breaks down.

Many approximations are involved in the application of (3) to actin solutions. On further reflection is is even surprising that the experimental data show such good power law behavior over several decades. Some of the points to consider are

- The approximation of a point force acting on a filament: The beads must couple by hydrodynamic interactions to a finite portion of the filament. Thus one expects to see important corrections to (3) due to crossovers in hydrodynamic couplings. In addition, at the shortest times the friction of the bead should be larger than of the section of filament of length \( (t \kappa)^{1/4} \), due to the constant friction on the bead. At longer times constraints due to filament contact must also become important.
FIG. 2. Displacement as a function of time of a bead in a actin network under a constant force. The scale is log-log. The dashed line corresponds to a slope of 3/4 as predicted by eq. (3). Each curve corresponds to a different applied force, allowing one to check the linearity of the response as a function of $f_0$. For long times and larger forces there is a saturation of the response, presumably due to steric hindrance coming from interactions between several filaments.

- Eq. (3) is only valid in the absence of tension. Addition of a term in $\sigma \partial^2 r_\perp / ds^2$ in eq. (2) should change the exponent in (3) to $1/2$. Such tension terms could be generated by crosslinks, or disruption of the equilibrium structure of the network under large forces.

- The bead can be dragged through the sample in a stochastic manner as pores in the network open and close [16]. We also note that a very interesting non-linear dynamic regime has been discussed [18], where thermal fluctuations in a filament are pulled out via a large forces. This too may be important when dragging beads through the sample.

The nature of the crossover from local dynamics dominated by bending elasticity described by (3) to the macroscopic bulk modulus has yet to be fully explored. It is not clear whether such a crossover should occur for particles of size comparable to $\xi$, or whether there is a novel viscoelastic regime all the way out to $l_p$. Recent experiments [14] observing thermal fluctuations of beads with sizes up to 20 times the mesh (but smaller than $l_p$) still seem to be sensitive to the internal mode dynamics, though they are interpreted in terms of macroscopic elastic theory. We argue later that elasticity on the scale $\xi$ to $l_p$ is non-classical, perhaps resembling smectics or columnar liquid crystals rather than isotropic solids.

Individual filament dynamics can also be studied in dynamic quasi-elastic light scattering experiments. One illuminates a solution with a coherent source which is scattered by a wave-vector $q$ and observes the time-time correlations in the scattered beam. The Munich biophysics group [19,20] observed unusual results in their light scattering experiments. In particular they found that the results scaled with the combination $tq^{2.7}$ rather than $tq^3$ or $tq^4$ expected in Rouse or Zimm dynamics [21,22]. The dynamic light scattering experiments measure the density density correlation function. These experiments are again sensitive to the transverse fluctuations of the filaments described by eq. (2) with $f_\perp(s, t)$ now interpreted as the Brownian noise of the solvent. The transverse fluctuations can, as usual, be characterized by the correlation function.
\[ G(s, t) = \langle (\mathbf{r}_\perp(s, t) - \mathbf{r}_\perp(0, 0))^2 \rangle \] (4)

indeed the experiments are sensitive to
\[ I(t, q) = \int \exp(-q^2 G(s, t)/4) \, ds \] (5)

For times that are not too short one finds that the correlation function is dominated by the contribution coming from \( s = 0 \) and that we need only calculate \([23]\)
\[ G(s = 0, t) = \int \frac{1 - \exp(-2\kappa q^4 t/\rho)}{\kappa q^4} \frac{dq}{2\pi} = A t^{3/4}/\kappa^{1/4} \] (6)

thus
\[ I(t, q) \sim \exp(-A' q^2 t^{3/4}/\kappa^{1/4}) \] (7)

The intensity scales with the combination \( t q^{8/3} \approx t q^{2.7} \) as found in the experiments. More detailed calculations, including hydrodynamic interactions, allow one to extract a value for \( \kappa \) from the light scattering data which is consistent with that found in Brownian spectroscopy \([23]\), \([24]\). Recently a more detailed study has been performed to examine the short time behavior \([24, 25]\) where the full functional form of (4) has to be examined. Other experimental studies have confirmed these results \([26]\). Another dynamic light scattering approach to measuring the rigidity of actin filaments involves using short filaments and studying corrections to the rigid rod behavior \([26]\) in an expansion in normal modes of the filament.

### Tube dynamics of actin filaments

A rather pretty series of experiments have been performed \([27]\) in order to visualize the movement of actin filaments in semi-dilute solutions. As we have already remarked it is possible to examine a filament with an optical microscope by adding a fluorescent probe to the sample. However, marking an entire semi-dilute sample swamps any image detection system. One gets around this problem by using a two stage polymerization process. Firstly polymerizing in presence of a dye, fixed to phalloidin, secondly diluting the fluorescent actin in a new polymerizing solution containing unmarked phalloidin. In this way non-fluorescent filaments reform around the now dilute marked filaments. Thus one directly observes filament movement, the existence of the tube, as well as events such as constraint release as the geometry of the tube changes in time.

Equally important for the general study of actin solutions the observations show that the samples studied are not too contaminated by crosslinking and cutting agents (see below) and that the samples studied are really semi-dilute fluids rather than gels: A major problem in the literature on actin mechanics is that it is very difficult to have precise information on the degree of crosslinking, or the distribution of filament lengths in a given sample. This leads to many divergences between experimental groups as to the state of the sample. Joint mechanical/optical experiments such as those performed already in \([28]\) should lead to a much better understanding of the problems of sample preparation.

While the dynamics of a free filament is largely dominated by transverse fluctuations these modes are clearly blocked by the tube constraints \([22, 21]\). Thus one expects that there is a characteristic length \( l_e \) below which the filament fluctuations are essentially free but beyond which
FIG. 3. The fluctuations of an actin filament in the confining tube. Collisions occur between the tube and the filament every $l_e$. Notice that the filament is rigid on the scale of $l_e$ which should be contrasted with the case of flexible polymers where one imagines a Gaussian, or Flory like structure on length scales smaller that the tube diameter.

fluctuations are suppressed. This length is comparable to the distance between the filaments, $\xi$, but does show a slightly different scaling $l_e \sim \xi^{4/5} l_p^{1/5}$, [29–31]. As a consequence of the presence of several length scales in actin solutions direct application of scaling ideas in dynamics is sometimes a difficult and ambiguous enterprise.

In the interior of the tube the filament behaves in a very anisotropic manner. A segment of filament of length $l_e$ is characterized by two elastic moduli, the first characterizes its transverse response and fluctuations and is quite soft. The second which characterizes the longitudinal fluctuations and response is much harder. To understand the macroscopic elastic behavior of a actin solution we need to understand these two moduli and their coupling to macroscopic degrees of freedom. The transverse elastic constant of a filament of length $l_e$ follows from eq. (1). Applying a static force $f_\perp$ transverse to a filament gives rise to a displacement $r_\perp \sim f_\perp l_e^3 / l_p$, thus we characterize the section of filament by a transverse elastic constant

$$K_t \sim k_B T l_p / l_e^3.$$  \hfill (8)

This elastic response is purely mechanical in origin.

The origin of the longitudinal elastic constant is however more subtle; thermal fluctuations “eat up” a part of the length of a filament. Imagine a filament aligned at temperature zero along the $z$ axis. The addition of thermal fluctuations in the $x$-$y$ plane will cause the filament to shorten in the $z$ direction. Thus the projected length will fluctuate. The extra length of a filament undergoing small fluctuations about its mean position can be calculated from

$$S = \int_0^{l_e} (\sqrt{1 + (dr_\perp/ds)^2} - 1) ds \approx 1/2 \int_0^{l_e} (dr_\perp/ds)^2 ds$$  \hfill (9)

Using equipartition for the energy (1) one finds that the mean excess of material in a tube of length $l_e$ is

$$S \approx l_e \int_{1/d}^{l_e} q^2 / kq^4 \sim l_e^2 / l_p$$  \hfill (10)

Similarly the elasticity is calculated by examining the fluctuations of $S$ in particular $(S^2) - (S)^2$.

A similar calculation to (10), [29,52,53] shows that this fluctuation can be interpreted as an elastic constant
When \( l_e \ll l_p \) the longitudinal constant becomes very hard and \( K_l \gg K_t \). According to whether one is coupled to the transverse or the longitudinal fluctuations one feels very different elastic constants. In the case of micro-rheology, discussed above one is sensitive to the transverse fluctuations, in the case of macroscopic rheological measurements to be discussed below the larger longitudinal elastic constant can dominate.

\[
K_l \sim k_B T l_p^2 / l_e^4
\]

(Eq. 11)

**Elasticity of crosslinked actin**

In [32] the authors consider the effect of a large degree of crosslinking on actin solutions and conclude that in this case the longitudinal constant dominates the macroscopic rheological behavior. They find that the shear modulus, \( G \sim k_B T l_p^2 / l_e^5 \). However, as a function of the degree of crosslinking one may expect a number of distinct regimes. The modulus is high at high crosslinking densities because the constraints on the distances become very severe and it is impossible to shear the sample without compressing longitudinally the filaments. At low degrees of crosslinking this is no longer the case; one can imagine configurations where the sample is linked in a three dimensional manner but the number of constraints is to low to impose compressive strains on the actin filaments. In such loosely crosslinked systems, under shear, there is no reason either to bend or to compress the filaments (unless the crosslinks themselves impose specific angles between the filaments). In cases of weak crosslinking one is probably dominated by entropic contributions to the free energy and should count \( k_B T \) towards the modulus for each effective degree of freedom in the gel. This would lead to a low modulus comparable to \( k_B T / \xi^3 \). If the filaments are crosslinked by angularly stiff elements which impose a given angle between two filaments one can only shear the sample by bending the individual filaments; in such a case one would estimate \( G \sim l_p / l_e^2 \xi^2 \), due to a coupling to \( K_t \). Thus, for crosslinked samples one expects a wide variety of elastic moduli as a function of the type and concentration of crosslinking elements in the solution.

There are clearly some interesting problems in the percolation of elastic constraints [35] in actin networks. Indeed the nature of the transmission of stress by directional and non-directional bonds in diluted networks has been intensively studied over the last decade and one finds that there are very different critical behaviors as a function of crosslinking. In particular the percolation threshold for bending and compressional degrees of freedom can be rather different, as is also the case for the exponents. There must surely be a rather rich series of crossovers in the presence of actin crosslinking agents and as a function of mean filament length due to the large difference in \( K_t \) and \( K_t \). The exact nature of the possible regimes still have to be elucidated however. In fact the nature of the percolation transition in even simple elastic networks is still an active subject of research [36].

\[\text{1An analogy is the problem of regular lattices in two dimensions: A three dimensional triangular lattice is rigid due to the fact that the number constraints is superior to the number of translational degrees of freedom. The hexagonal lattice however is floppy since the number of constraints per lattice site is lower. The marginal case is the square lattice. See [34].}\]
We note also that the nature of entanglements is very different in semi-flexible solutions compared to solutions of flexible polymers. Because of the convoluted nature of the path followed by flexible polymers in space knots, or entanglements, are very easily formed on a length scale which is comparable to \( \xi \). In the case of actin filaments there are important transverse constraints on the scale of \( l_e \), which is comparable to \( \xi \), however there is no longitudinal hindrance to movement. We shall argue that despite the lack of parallel entanglement the storage modulus of actin solutions can still be rather high.

**Shear couples to length fluctuations**

One of the most important differences in the mechanics of semi-flexible and flexible polymers concerns the coupling of external shear to length fluctuations of the molecule in a semi-dilute solution. Shear does not couple to the length fluctuations of a flexible polymer in linear response \[21\]. This is due to the fact that the confining tube contains a coil in which all orientations are present; the extensional component of the shear is thus unable to couple to the orientation of the polymer tube. The situation is very different for actin filaments where no averaging occurs within the tube. One expects that locally the filament can be placed under tension or compression according to its orientation with respect to the extensional component of the shear fig. (4).

The exact coupling of actin filaments to a shear flow is difficult to calculate. We have calculated \[37\] the contribution of the longitudinal degrees of freedom to the modulus using a single chain in mean field picture with the usual assumptions about affine shear in the sample. We estimated the modulus \[37\] by calculating the relaxation of the stress in a sample to which a sudden shear, \( \gamma_0 \), has been applied. When we apply a macroscopic shear to a actin solution a test chain will feel the effect of the distortion via hydrodynamic coupling with the tube. During the fast application of the shear the internal modes of the filament relax quickly. For the later relaxation of the sample we have the following relationship between the stress \( \sigma(t) \) and the modulus \( G(t) \), \[21\]

\[
\sigma(t) = \gamma_0 G(t)
\]

Thus we calculate the modulus \[37\] by studying the relaxation from an initial perturbed configuration of alternate compression and tension, fig. (4). We summarise the results in the next two sections.

**Time scales in semi-dilute solutions**

A number of interesting times scales exist in semi-flexible polymer solutions which have no direct analogy in the dynamics of flexible polymers. Indeed the nature of the time scales and dissipation occurring in semi-flexible polymer solutions is sufficiently different from those in flexible polymers that the experimental similarities between the two must be considered rather fortuitous. The shortest characteristic bending time in our problem is that corresponding to the length scale \( l_e \). From eq. \[2\] one can estimate that the tube constraint becomes important for \( \tau_e \sim l_e^4/l_p \) \[3\].

\[2\]Note that we choose for the rest of this article to work in the *natural* units for this problem; all lengths are in microns while time has the units of microns cubed. This is rather convenient because the volume 1
FIG. 4. Coupling of shear to length: (A) The shear has both rotational and elongational components, so that a tube with initial shape (B) containing a filament is alternatively lengthened and shortened (C).

Thus \( \tau_e \) is typically somewhat smaller than a second. The longest natural time in the problem is that needed for a filament to diffuse completely out of its tube. From the diffusion equation \( R^2 = Dt \) and using the fact that the diffusion coefficient varies with the length of a filament as \( D_L \sim 1/L \) one finds that the reptation time, \( \tau_{\text{rept}} \sim L^3 \). For filaments which are tens of microns long this latter time can be hours, as seems to be seen in experiments of the Munich group [38,39]. However, we note that even a small degree of crosslinking (far below that needed for gelling) will be sufficient to produce star like clusters for which the dependence of the relaxation time on the length is exponential, \( \tau_{\text{rept}} \sim \exp(\alpha L) \), probably beyond any experimentally reasonable limit.

Between these two times a number of other important time scales exist which we shall now discuss. These other time scales come from the relaxation of the internal longitudinal modes of the filament. As we have argued above, for length scales longer than \( l_e \) the degrees of freedom available to a filament are longitudinal. The filament can thus be modeled as a series of hard springs, of elasticity \( K_l \). Each spring has a relaxation time of \( \tau_e \). The dynamics of each cell are coupled together, the long wavelength dynamics are those of a one dimensional elastic chain in a dissipative environment. Thus one can write

\[
\frac{\partial r}{\partial t} = D_e \frac{\partial^2 r}{\partial s^2} \tag{13}
\]

where \( D_e \) is the effective spring constant over a dissipation coefficient, \( r \) is the longitudinal displacement. Since we know that the time \( \tau_e \) corresponds to the length scale \( l_e \) one expects that \( D_e \sim l_e^2/\tau_e \).

From eq. (13) one can deduce other characteristic time scales. Firstly \( \tau_L \) the relaxation time for internal modes in the whole filament and secondly \( \tau_{l_p} \) the relaxation time for fluctuations coherent over the persistence length \( l_p \). Since eq. (13) has the form of a diffusion equation we have that \( \tau_L \sim \tau_e (L/l_e)^2 \) and that

\[
\tau_{l_p} = \tau_e \left( l_p/l_e \right)^2 \tag{14}
\]

This final time scale is most important in the macroscopic relaxation of density fluctuations. As we have seen above shearing a sample leads to stresses which are coherent over the length \( l_p \), \( \mu^3 \) corresponds to a few seconds.
they can only relax slowly via eq. (13) on a time scale comparable to $\tau_l$. This time is of the order of a tens of seconds under typical experimental conditions. A number of experiments of the Munich group \cite{38,39} indeed have a dynamic crossover at this time scale in macroscopic rheological experiments. A fuller discussion of time scales is given in \cite{29}.

**Plateau Moduli of actin solutions**

Much of the rheological literature on actin solutions has concentrated on the existence and value of a plateau modulus. Analogies are often made with the rheology of flexible polymers where an elastic plateau is seen. To what extent can one take over the standard results of polymer rheology to the case of semi-flexible polymers with the length hierarchy $d \ll \xi \ll l_p$? A number of models have been proposed for the plateau modulus of actin solutions. However many of these models are probably too mechanical to be taken seriously. In particular to delimit the frequency range in which a plateau is observed one needs some ideas of the dynamical processes and the mechanisms of dissipation present as well as the dynamical mode implicated in energy storage. Many of the simplest models in the literature have no dynamic component \cite{40,41}.

The quality of the plateau observed is sometimes not very good; for instance we can cite the creep experiments of \cite{42}, or of \cite{43}. Other experimental groups see quite a flat plateau \cite{44,45}. It is unclear why the experimental literature is so disperse. Perhaps a number of experiments are in fact seeing a slow variation of the storage modulus rather than a real plateau. Certainly the experiments are difficult to perform and there are perhaps important and interesting effects coming from polydispersity, nonlinearity and sample history which need to be cleared up. We believe that two mechanisms are able to give rise to real plateau regimes and that some of the discrepancies in the experimental literature could be due to the fact that different storage processes are being observed in different experimental setups. However, we shall also argue that over certain frequency ranges, one might expect a behaviour in $G(\omega) \sim \omega^{1/4}$ for some systems or even a stretched exponential decay in $G(t)$. These slow frequency variations could in some cases be confused with a poor quality plateau.

We have argued \cite{29} that on time scales larger than $\tau_L$ all longitudinal stress in a filament has been dissipated, but that there is still a large frequency range between $\tau_L \sim L^2$ the slowest internal mode and $\tau_{rept} \sim L^3$. Over this time scale the backbone of the tube is in a sheared, non-Gaussian form, there must be some residual entropic contributions to the free energy due to this modified tube geometry. We have thus suggested a small low-frequency contribution to the modulus of the form $G \sim k_B T/\xi^2 l_e$ \cite{29}. This comes from the modification of the confinement energy in the tube which is equal to $k_B T$ for each segment of length $l_e$ of filament in the solution. This very low modulus seems to be seen by some experimental groups working with very low frequency viscoelastic response \cite{38,39}. Recent experiments interpreting bead fluctuations also find small elastic moduli \cite{14}.

As we have noted many groups see a much larger modulus at higher frequencies, how can one explain these results? As argued above the effect of shear on a filament is to produce tension and compression on filaments which are coherent over a distance of the order of $l_p$. Since the longitudinal displacement variable, $r$ of eq. (13) follows a diffusive type law the applied strains remain high on a time scale varying from $\tau_e$ to $\tau_{rept}$ (ie fractions of a second to a few tens of seconds). One expects a see a plateau over this frequency range which is high since one couples to the longitudinal
FIG. 5. Schematic representation of the storage modulus of a solution of actin filaments showing a number of regimes (A) fluid behaviour at very low frequencies. (B) entropic plateau. (C) crossover between the two plateau, which is expected to be a sensitive function of the distribution of filament lengths in the solution. (D) plateau due to longitudinal elasticity. (E) crossover to independent filaments.

elastic constant $K_l$. In [32] a high modulus of this form was derived by assuming that the solution is completely entangled on the scale $l_e$ and that longitudinal dynamics as well as transverse dynamics are hindered. We see that this hypothesis is unneeded, the dynamics of longitudinal fluctuations are already very slow due to the large length scales involved. This slow dynamics gives a modulus similar to that estimated in [32] for the case of strong local entanglement, $G \sim l_p^2/\xi^2 l_e^3$.

At longer times there are two possibilities as a function of the lengths of the filaments. For filaments which are only somewhat longer than $l_p$ one expects that the stress in a filament should decay to zero exponentially for long times, when $t > L^2/D_e$. However if the distribution of filament length is itself exponential [40] a convolution of the length distribution with the exponential decay of stress in each filament should give a stretched exponential form to the function $G(t) \sim \exp(-t/t_0)^{1/3}$.

In the case of very long filaments the following simple scaling argument can be applied. The stress in a long filament is a random alternation of compression and tension which we can consider as a sequence of random positive and negative initial conditions in a diffusion equation. Since the initial conditions in space are random the Fourier coefficients of the initial condition are close to Gaussian white noise. Each mode in the system decays as $a_q \sim \exp(-D_e q^2 t)$. After a time $t$ only modes with $q < 1/\sqrt{D_e t}$ remain. Again these modes are Gaussian, of mean zero and independent. Going back into real space one thus concludes that the typical value of the stress in a filament must decay as $(D_e t)^{-1/4}$ and thus that the system as a contribution to the low frequency modulus of the form $G(\omega) \sim (D_e^{-1} \omega)^{1/4}$, as confirmed by more elaborate treatments [37].

To resume, we believe two mechanisms are present, fig. (5), which can lead to plateau like behaviour in different frequency ranges. No experimental data is available to confirm this point, but the experiments from the various groups use a variety of experimental methods and preparation conditions. The data is not always available over the complete frequency and dynamic range that one might wish. The crossovers between these two regimes can be quite rich and varied, depending on the sample preparation.
Breakage, work-hardening and other non-linearities

Solutions of actin filaments have a relatively small strain where one observes linear response. There are a number of mechanisms which lead to non-linear effects.

- The filaments are relatively fragile [44,47]. Pipetting a sample breaks longer filaments, the act of filling a rheometer is thus relatively delicate. Best results are to be expected from in-situ polymerization.

- Even very small shear rates are capable of aligning samples. In long experiments where the filaments are still dynamic one could worry about progressive alignment of filaments due to the flow [28], even in samples polymerized in situ.

- Extensional elasticity described by eq (8) depends on the small fluctuations in length of each cell of size \( l_e \). From eq. 10 we see that a filament has about 10% excess material. Strains larger than this exhaust the excess length generated by the fluctuations, the sample should thus become extremely non-linear for larger strains.

- It is relatively easy to buckle filaments. Under oscillatory excitation one can imagine that filaments are able to buckle out of the confining tube forming hernias, similar to those observed in DNA electrophoresis. Once a hernia has formed it should considerably change the nature of the longitudinal tube dynamics. Multiple interacting hernias could even act as longitudinal entanglements and serve as a source of work hardening in actin solutions.

- Very low levels of crosslinking, below that needed to produce gelling can introduce exponentially long, \( \tau_{\text{rept}} \sim \exp(\alpha L) \), relaxation times in solutions. In creep experiments this will probably drive the system into highly non-linear regimes, since the slowest modes are very far from equilibrium.

Actin, Peirls and St Vernet

What is the nature of the deformation field around a particle, such as a small magnetic bead, on length scales between \( \xi \) and \( l_p \). We argue here that it can be rather different from that found in conventional elastic solids. Normal elastic materials are described by longitudinal or transverse elastic modes, each solutions of Laplace’s equation. Thus the static deformations can be considered the solution of the equation \( \nabla^2 \phi = 0 \) with the appropriated boundary conditions; for normal solids we are interested in systems with a \( q^2 \) dispersion relation. This has two important consequences

- As pointed out by Peirls there is long range order in three dimensions due to the infra-red convergence of the integral \( \int d^4q/q^2 \) in three dimensions (to be contrasted with the divergence in one and two dimensions).

- As pointed out by St Vernet a force applied over a radius \( R \) will also decay in a material over a distance which scales as \( R \).
We are interested in how these points are modified in actin solutions. We first resume the Peirls argument in a real space form which can be applied to the actin case with just a little modification. When we apply a force on a solid then we can suppose that the solid reacts in a sphere of diameter $L$. If the amplitude of the displacement at the point of force is $a$ then the total energy stored is equal to $E \sim (a/L)^2 L^d$ in $d$ dimensions. The first term in the energy comes from the bending elasticity described by the $q^2$ dispersion law and the second factor is the volume excited. In three dimensions this energy diverges with $L$ thus small forces only excite movements locally about the point of force application. In low dimensional systems we can disorder the system with the application of arbitrarily small forces since $E$ goes to zero for large $L$.

Let us now pass to actin. If we consider only the transverse component of the fluctuations then we have seen that actin solutions are characterized, on lengths less than $l_p$ by a $q^4$ dispersion law. Naive application of the Peirls arguments would then suggest that there is no long range order on scales out to $l_p$. (We expect that the system is described by an normal $q^2$ law beyond $l_p$). We now give a more careful argument to show that the longitudinal and transverse modes are probably strongly coupled so that long range order is almost restored even for lengths smaller than $l_p$, however the same argument gives an anomalous penetration of excitations into the gel which should be contrasted with the result of St Vernet. There is also an important difference in the scaling of the amplitude of response with the particle size. In the case of standard elasticity the amplitude of the response scales inversly with the particle size, for actin the response is predicted to be independent of the size of the probing beads.

The weak existence of long range order also has implications as to the coherency of the picture of a tube in the dynamics. The tube geometry may fluctuate more in semi-flexible polymer solutions than in classical solutions of flexible polymers.

Consider an excitation in an actin gel (perhaps excited by a small bead on which one pulls with a constant force) fig. (6), characterized by its width $L_w$ and its length (parallel to the force) $L_l$. The energy of this excitation has two sources, bending of filaments perpendicular to $f$ and longitudinal compression of filaments parallel to $f$. The first contribution can be estimated as

$$E_1 \sim (L_w^2 L_l)(k_B T l_p a^2 / L_w^4)(1/\xi^2)$$  \hspace{1cm} (15)$$

with the first factor the excitation volume, the second factor the energy eq. (14) and the third factor the length of filament per unit volume. The longitudinal contribution to the energy is given by

$$E_2 \sim (L_w / \xi)^2 (l_e / L_l)(a^2 k_B T l_p^2 / l_e^4)$$  \hspace{1cm} (16)$$
The three factors here are the number of filaments crossing an area $L_w^2$, the number of segments of length $l$, in the length $L$, and the longitudinal spring constant $K_l$. If the bead sets the scale for the transverse variations then minimizing the sum of the energies over $L$ implies that

$$L_t \sim L_w^2$$

(17)

in contrast with classical elastic behaviour.

Note, in this suggestive argument, there are a number of hidden assumptions as to the time scales involved. For the description of the longitudinal modes in terms of longitudinal elasticity to be valid we must be studying times such that $t > \tau_e$. Clearly for the description in terms of a solid rather than a liquid to be valid we require $t < \tau_{rept}$. However the longitudinal stress can only be maintained for the shorter time span of $t < \tau_{lp}$. Thus we might hope that the above description is valid for $\tau_e < t < \tau_{lp}$.

In three dimensions the total energy $E_1 + E_2$ (obtained by substituting (17) in (15) and (16)) remains bounded, suggesting that the lower critical dimension for this problem is three dimensions and that the amplitude of fluctuations diverges logarithmically with distance up to a scale of $l_p$, rather like elastic solids in two dimensions, or certain liquid crystals in three dimensions. It will be interesting to try and understand how this argument generalizes to times shorter than $\tau_e$ to fully understand the experiments [33].

**Statics and dynamics of twist**

Until now we have been concerned largely by the bending dynamics of actin filaments, however an elastic filament has two degrees of freedom. It is characterized both by bending and torsional elastic constants. These two quantities should be comparable; for a cylinder with Young modulus $E$, Poisson ratio $\sigma$, and diameter $d$ we can calculate that the bending elastic constant and twist elastic constants are given by [12],

$$\kappa_{twist} = \frac{E\pi d^4}{64(1 + \sigma)}$$

(18)

$$\kappa_{bend} = \frac{E\pi d^4}{64}$$

(19)

Since the Poisson ratio is normally between 0 and $1/2$, the torsional persistence length $l_r$ must be comparable to $l_p$. Clearly the approximation of a uniform cylindrical material is not very good, and one is sensitive to the internal modes of the filament which may give important corrections [48].

Most experiments discussed up to now have only been sensitive to the bending degrees of freedom. Firstly because they couple most directly to the bending modes. Secondly because the time scales of bend and twist dynamics are very different as we shall now discuss. One of the few experiments which is directly sensitive to the twist dynamics of actin filaments is [49] where the dynamics are observed by depolarized light scattering. With this technique the sample is marked with a fluorescent dye and illuminated by polarized light. During the time between the absorption and the emission of photons the filament can turn and thus the distribution of emitted light depends on the twist dynamics. In principle this should allow a determination of the twist persistence length. The experiments of [49] find rather strange behavior of the measured constants on filament length. This may be due to the extremely complicated numerical fitting methods used in the
treatment of the data. We have arguments, however, that the twist and bending modes are coupled giving rise to new sources of dissipation. Thus the friction coefficient may be underestimated in the standard theories of twist dynamics; the twist elastic constant is less well characterized than the bending constant.

The theory of the twist dynamics of semi-flexible polymers has been discussed in [50,51] in conjunction with DNA dynamics. The twist dynamics of a straight filament are over-damped. Thus the twist angle $\phi$ in the laboratory frame obeys the equation

$$\frac{\partial \phi}{\partial t} = K \frac{\partial^2 \phi}{\partial s^2}$$

with $K$ a rotational diffusion coefficient depending on the torsional rigidity of the filament and the solvent friction coefficient.

One should note the large difference in time scales between the relaxation of bending and torsional modes. Whereas a ten micron filament will take several seconds to relax its fundamental bending mode the relaxation time of its torsional modes occurs on the scale of microseconds to milliseconds. This is due to the very different length scales upon which dissipation takes place for bending and translational modes. Consider a bending excitation of length scale $L$ and amplitude $a$ on a semi-flexible filament. The total energy of the excitation is $E \sim (a^2 l_p/L^4) L$. The dissipation in the solvent is caused by the time evolution of the amplitude and can be estimated to be $\eta L^3 (\dot{a}/L)^2$ where $\eta$ is the viscosity $L^3$ is the volume of fluid implicated in the flow and $\dot{a}/L$ is a typical shear around the filament. Thus we find the approximate equation in real space for the evolution of the amplitude $a$.

$$\eta L \dot{a} \sim -al_p/L^3$$

or

$$\dot{a} \sim -al_p/L^4$$

This is the equivalent in real space of the dispersion relation $\omega \sim q^4$ deduced above from the Langevin equation (2).

How does this argument change for twist dynamics? The hydrodynamic field due to rotation of the filament has typical shear values of $\dot{\phi}$ and occurs throughout a volume $Ld^2$. The energy stored is $E \sim L(\dot{\phi}^2 l_r/L^2)$. Thus we deduce the approximate equation

$$\eta L d^2 \dot{\phi} \sim -\phi l_r/L \implies \dot{\phi} \sim -l_r \phi/d^2 L^2$$

In agreement with (20) we find a $q^2$ dispersion relation due to the short range nature of the dissipation. A filament of length $L$ thus has two relaxation times with a ratio $\tau_L/\tau_{\text{twist}} \sim (L/d)^2$. Since $L/d \sim 1000$ these times are very different indeed. The rotational relaxation occurring of sub-millisecond time scales is well adapted to times scales of fluorescent re-emission. Video techniques are far to slow to capture these movements though perhaps more sophisticated techniques such as those developed by [14] or [13] are able to resolve such high frequency fluctuations. Our picture of bending fluctuations should thus be modified. During the slow relaxation of the bending modes the filament must be considered as rotating at very high frequencies. The bending occurs subject to a very high frequency “noise” due to the rotational motion.
The de-polarizing experiments are sensitive to correlation functions of the form

$$I(q, t) = \exp\left(-\langle (\phi(t) - \phi(t'))^2 \rangle\right) = \exp(-H(t - t')).$$  \hspace{1cm} (24)

we can find the form of these correlation function $H(t)$ with the following simple argument similar to that used to derive eq. (3). Eq. (24) has the normal diffusive form thus in a time $t$ a length $\sim \sqrt{t}$ of filament moves coherently. This section of length $\sqrt{t}$ has a rotational diffusion constant $D_r \sim 1/\sqrt{t}$ thus after a time $t$ we deduce that $|\phi(t) - \phi(0)| \sim t^{1/4}$ (as confirmed by more elaborate treatments). This slow decay of the rotational correlations is valid for as long as one is dominated by the internal modes of the filament. For longer times the filament is going to turn freely on its axis and thus $|\phi(t) - \phi(0)| \sim t^{1/2}$ as expected for a diffusive process.

In polydisperse samples it may well be difficult to separate the effects of polydispersity from the internal dynamics. The signal from a short filament has the form $I(t) \sim \exp(-t/d^2 L)$ which when convolved with the length distribution $P(L) \sim \exp(-L/l_0)$ gives a dominant contribution in $< I(t) > \sim \exp(-t(t_0/1)^{1/2})$ this is perhaps partly the cause of the difficulty of deconvolving the signal found in [49].

What are the effects of bending on the rotational dynamics? Does the filament keep a constant shape in the body frame of reference or is the converse true, that the filament twists with a constant real space shape, imposing a rapid bending on the filament as it spins. The first scenario is rather unlikely due to the high frictional coefficient of a bent object turning in space. Since the typical transverse fluctuations of a filament of length $L$ vary as $L^{3/2}/l_p^{1/2}$ one can redo the above arguments as to the typical gradients and volumes involved in dissipation to find that the rotational diffusion coefficient should vary as $D_r \sim l_p/L^4$ rather than the more usual $D_r \sim 1/d^2 L$. It is more reasonable to expect that the approximate torsional mode is a combined spin and bend such that the shape of the filament remains the same in the laboratory reference frame. Indeed one can formally let the bending friction diverge in which case this combined bending and torsional mode becomes the exact dynamical eigenmode of the filament. Clearly, as well, in dense solutions this must be the physical torsional mode due to the strong steric hindrance present. Note that due to the non-diagonal nature of the frictional couplings the eigenmodes for the statics and for the dynamics can be expected to be very different.

Since in the frame of the rotating filament, the filament is bending very rapidly we can find new sources of dissipation in the dynamics. Until know we have considered that the filament is in effect a perfect solid with no dissipation occurring due to internal motion, however, in general a protein is expected to be described by both an elastic modulus, $E$ and a loss modulus. The simplest model is

$$E(\omega) = E/(1 + i\omega \tau_i)$$  \hspace{1cm} (25)

Where $\tau_i$ is an internal frequency that one could perhaps place at about 1MHz. Thus by avoiding spinning in the laboratory frame the one finds a new source of dissipation, internal friction. It is to be seen whether these effects are large enough to be seen experimentally.

As well as coupling to twisting modes, the bending modes also contribute to the depolarized scattering; bending a filament changes its orientation in space giving a contribution to the rotation of the filament analogous to (3)

$$< (\phi(t) - \phi(0))^2 > \sim \int q^2 \frac{1 - \exp(-2\kappa q^4 t/\rho)}{\kappa q^4} dq \frac{1}{2\pi}$$  \hspace{1cm} (26)

$$= B t^{1/4}/\kappa^{3/4}$$  \hspace{1cm} (27)

$$= B t^{1/4}/\kappa^{3/4}$$
FIG. 7. Illustration of the relative rotation of a filament due to the non commutative nature of the rotation group in three dimensions. We start at the vertical arrow on the upper side of the cube and follow two paths. The first goes clockwise around the from face, the second anti-clockwise. At each corner we imagine that we are allowed to bend a filament but not twist it. We see that as the arrows finish at 90 degrees to one another. Thus we can twist the filament in space by only bending distortions. Bending fluctuations of a filament can thus give rise to an apparent twist of the filament in the laboratory frame, which adds to the internal twist dynamics of the filament.

Since the twist modes are so much more rapid than the bending modes we would normally expect that this contribution is to slow to be observed, however in the presence of crosslinking agents which freeze some of the twist degrees of freedom one might hope to observe such terms.

It will be interesting to think about the problem of back reaction of the rotational degrees of freedom on the bending. At the shortest length and time scales the bending and twist should be weakly coupled; whereas as we have argued above in long filaments the twisting eigenmode is really a combined twist/bend mode. Fig. (7) shows that the bending and twisting degrees of freedom are indeed strongly coupled in long filaments. Is there a dynamic crossover between a short time regime where the bending and the twisting of a filament do not see each other and a long time regime where the modes are coupled dynamically? It may be possible to make an adiabatic expansion in the dynamic equations using the enormous difference in time scales as a separation parameter to answer this question. Such effects may give crossovers in the dynamic light scattering experiments especially at shorter times when the ratio of characteristic time for twist and bend are not too different.

A simple simulation, [59], to measure the coupling between the twist and bend described by fig. (7) shows that the filament twists in the laboratory frame in the following manner: $|\phi(s) - \phi(0)| \sim s/l_p$. Thus from a simple scaling argument we expect that the mechanism of fig. (7) contributes a term $|\phi(t) - \phi(0)| \sim t^{1/4}/\kappa^{3/4}$ to the scattering (24)

Ref. [52] has shown that small asymmetries in coupling constants can give rise to a static, though weak, cross talk between torsion and bending. Similar effects are also probable in the case of actin filament though are probably as in DNA small corrections. Here we note that twist-bend coupling terms are always present in the dynamics due to the non-diagonal nature of the hydrodynamic couplings, even when the modes are statically independent.
Actin forms active materials

Reversible and irreversible crosslinking proteins exist with several attachment geometries. Again to many such proteins exist to be fully treated here [8] but one can note in particular the existence of proteins with variable crosslinking properties. The exact geometry of interaction varies with a tendency to form parallel bundles for the case of $\alpha$-actinin and perpendicular link for actin binding protein-120. The crosslinks can be either irreversible or reversible depending upon the molecule involved and the exact chemical nature of the buffer (many molecules are sensitive to energy sources such as ATP, and signaling ions such as calcium).

Until know we have discussed actin in the relation to classical mechanical and rheological properties. However, actin is a molecule which crucial in the transduction of chemical into mechanical energy and thus is potentially much richer than classical polymer systems. Already the filament undergoes a active polar polymerization process which means that a single filament can move forwards by depolymerizing behind while polymerizing in front, a process known as treadmilling [53].

In the cell actin has many independent roles. It is a major component of muscle where it is present in the form of aligned fibers. However it is also present in many other cells in both higher and lower eucaryotes (such as yeast or slime molds). In these cells the actin is often present in the form of a complex gel like environment forming the cellular cortex. This structure is essential to movement of many cells.

In both muscle and in other cells the actin is associated with active molecules, in particular molecules from the myosin family [54]. These molecules are molecular motors, that is they transform chemical energy (in the form of ATP) into mechanical force. Recent experiments extract myosin from the cell and use it to coat either surfaces or beads. The filaments then slide over the glass surface or the beads are transported along an actin filament as a consequence. It would be of the greatest interest to study the effect of myosin in a gel. One could imagine a solution with multiple beads where the motors on each bead interact with several filaments. These experiments appear quite difficult to perform, however recent results similar to this are available for the more rigid microtubule in the presence of a kinesin construct [55].

One of the most remarkable manifestations of the variety of behaviors shown by actin is the listeria locomotion system. Listeria is a pathogenic bacterium of the gut which is able to catalyse the polymerization of free cellular actin into hollow tube. By an unknown mechanism the bacterium can “push” against the tube to propulse itself forwards. Highly simplified extracts now exist where the bacterium remains active; the system in being actively studied by a number of biophysics groups, in particular to characterize the mechanical properties of this actin tube, made out of short crosslinked filaments.

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