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Supplementary Information for "Time-resolved nanomechanics of a single cell under the depolymerization of the cytoskeleton"

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Hydrodynamic Drag Correction

The hydrodynamic drag force opposes the motion of a body through a fluid. This hydrodynamic drag force F_{drag} in the absence of turbulence (Reynold Number Re < 1) can be approximated by

$$F_{drag} = - b\, v \tag{S.1}$$

where b is a damping factor and v is the cantilever speed. For our complex set up, the damping factor is an empirical feature which depends on the cantilever and sample shape.

Fig. S1 shows an example of force-distance curves before being corrected by the hydrodynamic effect. This hydrodynamic drag introduces an effective repulsive force during the approach and an effective attractive force during the retraction. This effect increases with the modulation frequency.

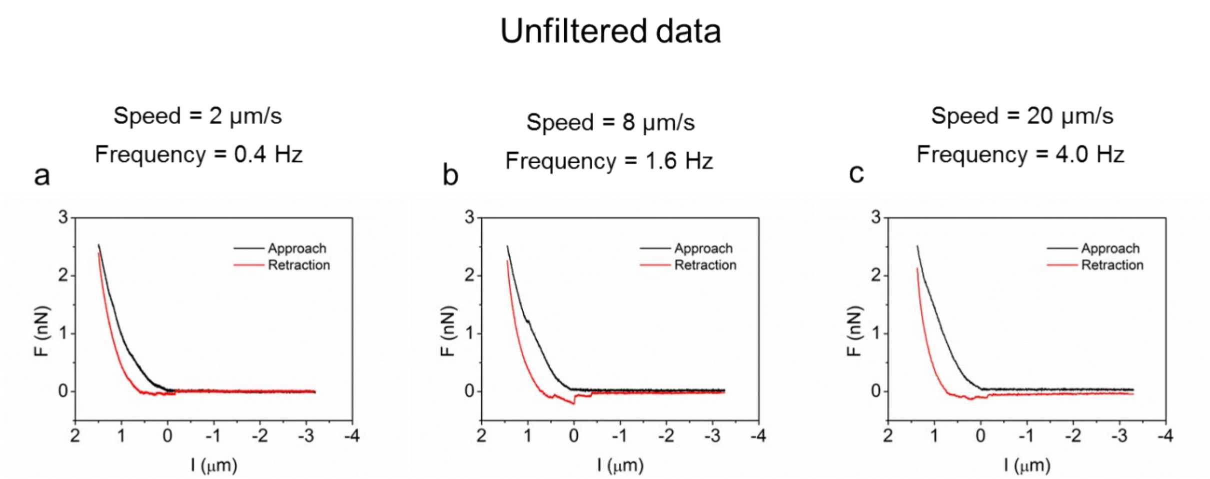

Fig. S1. Force distance curves on a cell for different modulation frequencies. (a)-(c), Representative examples of uncorrected force-distance curves for three modulation frequencies. With increasing frequency, the baselines corresponding to the approach and retraction separate. This is the hydrodynamic drag effect.

Fig. S2 illustrates the method to correct the hydrodynamic drag. First, we have calculated the difference between the approach and withdraw force baselines (Fig. **S**2a). The half of this value represents the drag force.

$$|F_{drag}| = \frac{F_1 - F_2}{2} \tag{S.2}$$

Finally, the value of the drag force ($|F_{drag}|$) is subtracted from the original section of the force curve in the approach and added to the original section of the force curve in the retraction (Fig. S2b). The tails of the approach and retraction sections of the force-distance overlap once the drag force has been suppressed.

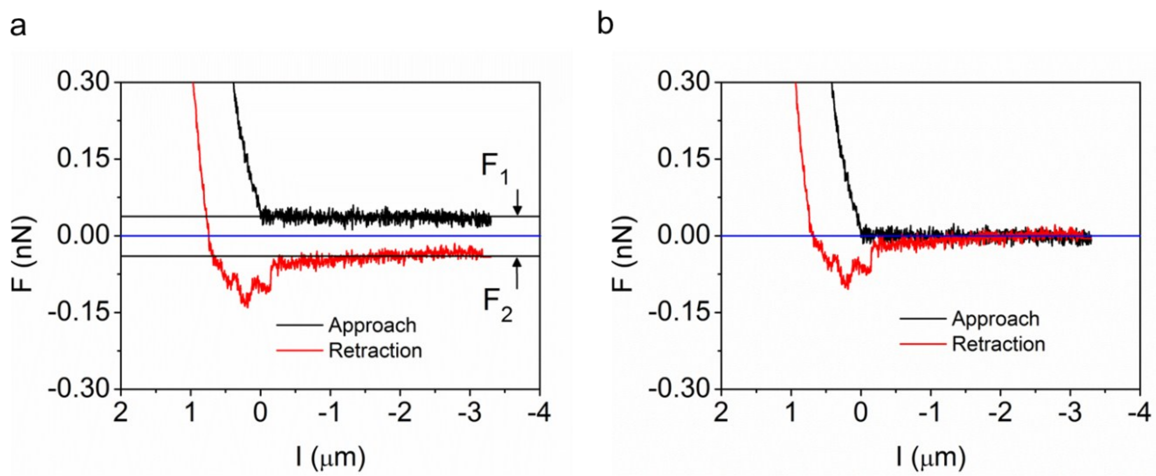

Fig. S2. (a) Force-distance curve on a cell for a modulation frequency of 4 Hz. Far from the cell surface there is a significant separation between approach and retraction sections. (b**)** Corrected force-distance curve by applying the method described in the text.

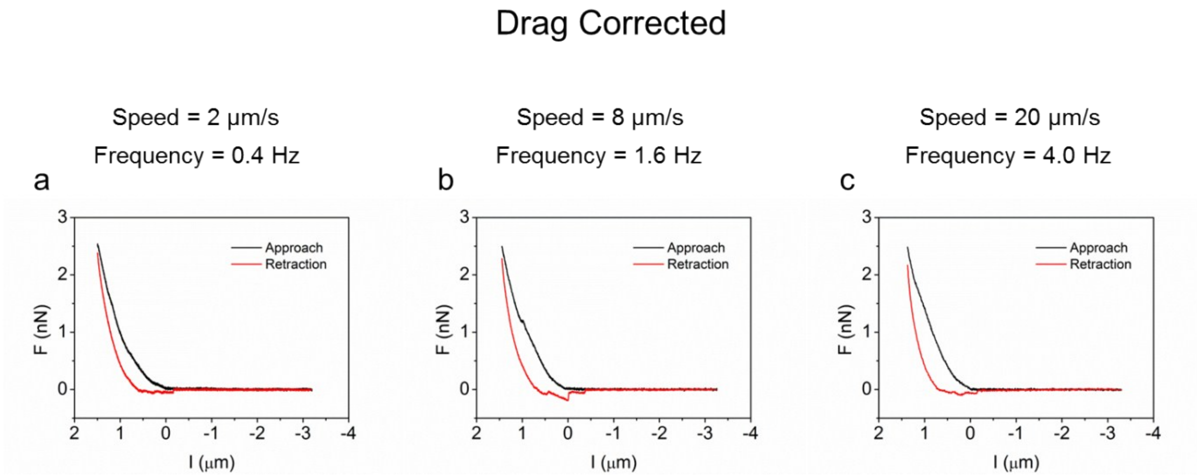

Fig. S3. Force distance curves on a cell for different modulation frequencies. (a)-(c), Representative examples of force-distance curves affected by drag effects after being corrected.

To determine the damping factor b of eqn (S.1) we have plotted the drag force with respect to the tip's speed (modulation frequency) (Fig. **S**4). After fitting the experiment data on Fig. **S**4 to a straight line, we have obtained a value of b = 1.8 ± 0.2 Kg/s.

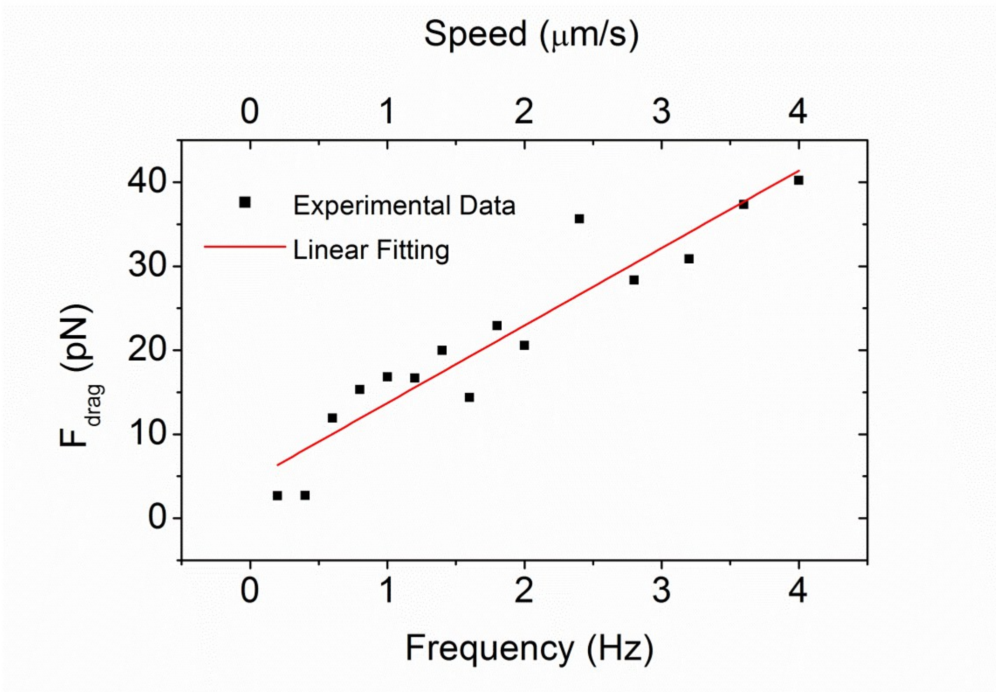

Fig. S4. Drag force as function of the frequency. The red line represents the linear fitting obtained applying a less square method.

General Kelvin-Voight equivalency

The Kelvin-Voight model has been used to obtain the viscoelastic parameters. However, this approximation does not restrict the generality of the method because it can be demonstrated that any one-dimensional linear viscoelastic system, modulated at a fixed frequency, can be approximated by a Kelvin-Voigt system.

To show that, we recall that the force in a linear system is the convolution of the velocities and the load relaxation function of that system:

$$F(t) = \int_0^t \psi(t - t') \frac{d}{dt'}[x(t')]dt' \tag{S.3}$$

By applying the Fourier transform to this expression and the property which states that the Fourier transform of the convolution of two functions is the product of the Fourier transforms of such functions, eqn (S.3) can be transformed into

$$\hat{F}(\omega) = \hat{\psi}\,(\omega) \cdot i\omega \cdot x\,(\omega) \tag{S.4}$$

The above expression is valid for any linear viscoelastic system such Standard Linear Solid or Maxwell. The key point is that for a given modulation frequency ω, all the viscoelastic information is given by the complex function $\hat{\psi}(\omega)$

$$\hat{\psi}(\omega) = \psi_R\,(\omega) + i\,\psi_I\,(\omega) \tag{S.5}$$

For Kelvin-Voigt model, the above function is

$$\hat{\psi}_{KV}(\omega) = \int_{-\infty}^{\infty} e^{-i\omega t}\psi_{KV}(t)dt = \int_{-\infty}^{\infty} e^{-i\omega t}[kH(t) + c\delta(t)\,]dt = \int_{0}^{\infty} e^{-i\omega t}kdt + c = - i\frac{k}{\omega} + c$$

(S.6)

We can always find (for certain frequency) a couple of values k and c in such a way that eqn (S.5) and (S.6) are exactly the same complex number

$$\hat{\psi}_{KV}(\omega) = \hat{\psi}(\omega) \tag{S.7}$$

But, as all the information about the behavior of the system is condensed in this complex number, both systems are totally equivalent.

Expression for the loss modulus

The Young modulus is defined (without viscosity), as the ratio between the strain and the stress

$$\sigma(t) = E\varepsilon(t) \tag{S.8}$$

We can apply the Fourier transform to this equation, obtaining:

$$\sigma(\omega) = E\varepsilon(\omega) \tag{S.9}$$

The complex Young modulus is then defined with more generality, for a 1D system, as the ratio between the stress and the strain in the Fourier domain.

$$\frac{\sigma(\omega)}{\varepsilon(\omega)} = E^*(\omega) \tag{S.10}$$

This definition holds perfectly in the case of the simple elastic case (zero viscosity), because then the complex number E^* is equivalent to E.

The above relationship implies a linear relationship between stress and strain. This is no longer the case for a 3D geometry where the force depends on a non-linear manner on the indentation and the velocity. In the particular case of Sneddon model for the indentation plus the Kelvin-Voigt model for viscoelasticity, we have the next expression:

$$F(t) = \frac{1}{1-\nu^2}\frac{2\tan(\phi)}{\pi}I(t)\left[2\eta_E\dot{I}(t) + EI(t)\right] \tag{S.11}$$

However, a linear relationship for the 3D case can be obtained by considering small displacements $\Delta I(t)$ around a fixed indentation I_0:

$$I(t) = I_0 + \Delta I(t) \tag{S.12}$$

$$F(t) = F_0 + \Delta F(t) \tag{S.13}$$

For our particular case, we obtain (substituting (S.12) and (S.13) in eqn (S.11))

$$F_0 + \Delta F(t) = \frac{1}{1-\nu^2}\frac{2\tan(\phi)}{\pi}(I_0 + \Delta I(t))\left[2\eta_E(\Delta \dot{I}(t)) + E(I_0 + \Delta I(t))\right] \tag{S.14}$$

If we assume that ΔI is very small we can keep just the terms proportional to ΔI and to I_0, obtaining two equations:

$$F_0 = \frac{1}{1-\nu^2}\frac{2\tan(\phi)}{\pi}EI_0^2 \tag{S.15}$$

$$\Delta F(t) = \frac{1}{1-\nu^2}\frac{2\tan(\phi)}{\pi}I_0\left[2\eta_E\Delta \dot{I}(t) + 2E\Delta I(t)\right] \tag{S.16}$$

The first one is the expression of the constant force due to the constant indentation. We can apply (as in the one-dimensional case) the Fourier transform to the second expression, obtaining:

$$\Delta F(\omega) = \frac{1}{1-\nu^2}\frac{2\tan(\phi)}{\pi}I_0\Delta I(\omega)\left[2\eta_E(-i\omega) + 2E\right] \tag{S.17}$$

If we analyze eqn (S.17) in the case of an elastic material (no viscosity, $\eta_E = 0$), we can see that E is defined as:

$$E = \frac{\Delta F}{\Delta I}(1 - \nu^2)\frac{\pi}{4I_0 \tan(\phi)} \quad \text{(S.18)}$$

We want to generalize this definition for the viscoelastic case, so we hold the viscosity terms in eqn (S.17), obtaining the general complex Young modulus:

$$E^* = \frac{\Delta F}{\Delta I}(1 - \nu^2)\frac{\pi}{4I_0 \tan(\phi)} = - i\omega\eta_E + E \quad \text{(S.19)}$$

This complex Young modulus can be separated in imaginary and real parts, which are respectively the loss and the storage modulus:

$$E_{storage} = Re[E^*] = E \quad \text{(S.20)}$$

$$E_{loss} = Im[E^*] = - i\omega\eta_E \quad \text{(S.21)}$$