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# Magnetic wires as probes for active microrheology: applications to the cytoplasm of living cells

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## 1. Introduction

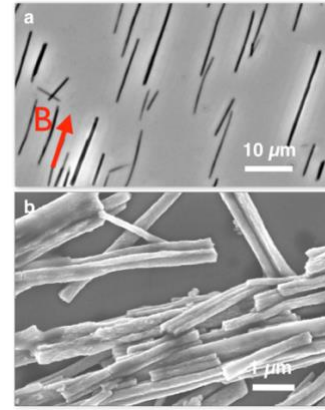
The past 20 years have seen increasingly rapid advances in the realm of cell and tissue biomechanics. For living cells, techniques including atomic force microscopy, optical and magnetic tweezers, parallel microplates and active tracking of internalized particles have been developed (Alibert et al. 2017). These studies were successful in probing cellular mechanics and establishing the viscoelastic nature of the cytoplasm. By design, they focus on different cellular compartments, such as intracellular medium, cortical actin, or the whole cell, making it difficult to reach a consensus on the mechanics of mammalian cells in culture. One feature of cellular biomechanics is that most techniques measure mechanical response at frequencies typically between 1 Hz to 10<sup>6</sup> Hz. The 1 Hz limit is imposed by the design of the experiment, as for optical or magnetic tweezers. In this experimental context, it was concluded that the intracellular medium is a weak elastic solid (Guo et al. 2014). Surprisingly, few studies have focused on the low frequency region, ( $\nu = 10^{-4}$  Hz – 1 Hz) which is this range of interest for cellular flow (Berret 2016). Here we address the question of the mechanical properties of living cells using a microrheology platform based on the video-microscopy tracking of magnetic wires. Wires are submitted to an external magnetic field of increasing frequencies. Measurements performed on NIH/3T3 mouse fibroblasts and HeLa cervical cancer cells confirm the viscoelastic character of the cytoplasm (Berret 2016).

## 2. Methods

### 2.1 Magnetic wire synthesis and structure

Magnetic wires were made from iron oxide nanoparticles ( $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>) and PDADMAC cationic copolymers. The nanoparticles were coated with poly(sodium acrylate). The wires result from a bottom-up co-assembly process based on electrostatic interaction between oppositely charged particles and polymers. Wire structures were assessed by optical and scanning electron microscopy. Figure 1 illustrates the wire nanostructure acquired using

scanning electron microscopy. After sonication, wires were sorted by magnetic separation, resulting in a dispersion of wires of median length 4  $\mu$ m.



**Figure 1** a) Optical microscopy of magnetic wires. b) SEM image of a 4  $\mu$ m sonicated wires.

### 2.2 Magnetic rotational spectrometry (MRS)

The microrheology technique used here is based on magnetic rotational spectroscopy (MRS) (Berret 2016, Yan et al. 2010). MRS advantages are its broad frequency range, from 10<sup>-3</sup> and 10<sup>2</sup> rad s<sup>-1</sup>, together with its ability to measure both low and high viscosities, from 10<sup>-3</sup> to 10<sup>3</sup> Pa s (Berret 2016, Thai et al. 2020). The technique consists in applying a rotating magnetic field and monitoring the rotation of the wires using optical microscopy. The viscosity of the fluid is obtained from the critical frequency between a synchronous and an asynchronous regime, occurring at the S/AS transition. The critical frequency  $\omega_c$  is expressed as :

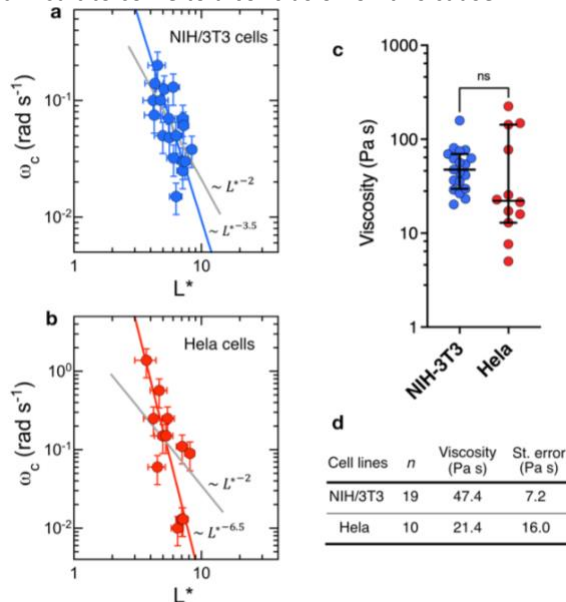
$$\omega_c = \frac{3}{8\mu_0} \frac{\Delta\chi}{\eta} g\left(\frac{L}{D}\right) \frac{D^2}{L^2} B^2 \quad (1)$$

where  $\mu_0$  is the vacuum permeability,  $L$  and  $D$  the wire length and diameter,  $B$  the magnetic field,  $\Delta\chi$  the anisotropy of susceptibility and  $g(x) = \ln(x) - 0.662 + 0.917x - 0.050x^2$  (Chevry et al. 2013). Eq. 1 was verified for fluids of known viscosity and tested for an 85% glycerol/water mixture for  $\Delta\chi$  determination. The S/AS transition has been observed in many complex fluids and it was used to measure the viscosity of biofluids available only in minute quantities (Radiom et al. 2021, Thai, et al. 2020).

## 3. Results and discussion

NIH/3T3 and HeLa cells were incubated 24h with 150×10<sup>3</sup> wires per well and within this period they spontaneously internalized the wires. At this stage,

neither morphology nor cell cycle seems to be disturbed. Cells and wires were then placed in a home-made rotating field device and submitted to a rotational magnetic field of frequencies from 1.5 mHz to 15 Hz while the wire rotation was recorded. To investigate the viscous behavior of cytoplasm probed with wires, we examined the transition between the synchronous and asynchronous regimes. Within each cell line, we observed a good agreement between runs. Figures 2a and 2b display the dependences of the critical frequency  $\omega_c$  as a function of the reduced wire length  $L^* = L/D\sqrt{g(L/D)}$  for the two cell lines studied. Least square calculations using a power law dependence of the form  $\omega_c(L^*) \sim 1/L^{*\alpha}$  provide exponents  $\alpha = 3.5 \pm 0.5$  and  $\alpha = 6.5 \pm 0.5$  for NIH/3T3 and HeLa, respectively. Two effects could account for the discrepancy with respect to Eq. 1 which predicts  $\alpha = 2$ : a the heterogeneities of the intracellular medium, and potential dependence of the mechanical response on the length scale. For now, and considering the statistic of available data, it is difficult to come to a conclusion on this cause.



**Figure 2:** Variation of the critical frequency  $\omega_c$  as a function of the reduced wire length  $L^*$  for a) NIH/3T3 mouse fibroblasts and b) HeLa cervical cancer cells. c) Boxplot comparing the viscosity data series obtained on the two cell lines. d) Table providing the median cellular viscosity and standard error for the data in Figures 2a and 2b.

The intracellular viscosity could however be computed from  $\omega_c$  and  $L^*$ -values for each of the 29 internalized wires in the two cell lines. Figure 2c shows a boxplot of the viscosity of NIH/3T3 and HeLa cells for the  $n = 19$  and  $n = 10$  data points obtained. Median

viscosities were found at  $\eta_{\text{NIH/3T3}} = 47.4 \pm 7.2$  Pa s,  $\eta_{\text{HeLa}} = 21.4 \pm 16.0$  Pa s (Figure 2d). Statistical significance using Student's t-test for unpaired samples was found to be non-significant. These results point to the need to operate on larger wire statistics to be able to draw final conclusions on intracellular viscosity.

#### 4. Conclusions

In this work, we used 2-6  $\mu\text{m}$  long magnetic wires to measure the static viscosity of the cytoplasm of living cells. This wire-based technique has been known for over 20 years, but has only recently been applied to living environment and biofluids. Contrary to several cell biomechanics studies (Guo, et al. 2014), we conclude that the interior of living cells is described as a viscoelastic liquid, not an elastic gel. This conclusion was made possible by gaining access to a previously unexplored frequency range, between 0.001-1 rad s<sup>-1</sup>, and for which cytoplasm has been shown to exhibit purely viscous flow. In conclusion, the present work demonstrates the potential of this microrheology technique as an accurate tool to explore biological soft matter and tissue dynamics.

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