Nanoscale Viscosity of Cytoplasm Is Conserved in Human Cell Lines

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ABSTRACT: Metabolic reactions in living cells are limited by diffusion of reagents in the cytoplasm. Any attempt to quantify the kinetics of biochemical reactions in the cytosol should be preceded by careful measurements of the physical properties of the cellular interior. The cytoplasm is a complex, crowded fluid characterized by effective viscosity dependent on its structure at a nanoscopic length scale. In this work, we present and validate the model describing the cytoplasmic nanoviscosity, based on measurements in seven human cell lines, for nanoprobes ranging in diameters from 1 to 150 nm. Irrespective of cell line origin (epithelial–mesenchymal, cancerous–noncancerous, male–female, young–adult), we obtained a similar dependence of the viscosity on the size of the nanoprobes, with characteristic length-scales of 20 ± 11 nm (hydrodynamic radii of major crowders in the cytoplasm) and 4.6 ± 0.7 nm (radii of intercrowder gaps). Moreover, we revealed that the cytoplasm behaves as a liquid for length scales smaller than 100 nm and as a physical gel for larger length scales.

Metabolism at the cellular level is considered as a network of reactions between biomolecules.1–3 These reactions maintain a balance where any prolonged disturbance can lead to pathological changes, including cell death or systemic diseases.4,5 From the physical point of view, a reaction can occur when molecules of reagents approach each other. In an equilibrium-state solution, Brownian motion (free diffusion) is a source of the movement of particles, and an increase of diffusion rate increases the probability of molecular encounters leading to biochemical reactions. The cytoplasm is a complex and crowded medium, where diffusion of biomolecules is hindered, and therefore diffusion can be treated as a factor limiting reaction rates in a cell.6,8 Decrease of diffusion rates would decrease rates of metabolic reactions and could lead to cell damage. According to the Stokes–Sutherland–Einstein relation,8,9 the diffusion coefficient depends inversely on hydrodynamic drag, \( f = 6\pi \eta_{\text{eff}} r^2 \), where \( r \) is the hydrodynamic radius of a probe and \( \eta_{\text{eff}} \) is an effective viscosity of the medium. Many reports show that viscosity of the cytoplasm is not constant, but rather spatially heterogeneous.10–12 Additionally, according to our research, scale-dependent heterogeneity of cytoplasmic viscosity is even more pronounced.13–15 We found that objects of different sizes can experience different viscosities: the viscosity increases with the increasing size of the object.13 It is an outcome of the complex composition of cytoplasm—various components provide obstacles at different length-scales: the only obstacle of similar or smaller size can hinder the diffusion of a probe (see Figure 1: 1). Our previous, detailed works on polymer and colloidal solutions resulted in a comprehensive model of length-scale dependent viscosity (LSDV), applicable for complex fluids.13,16–19

\[
\eta_{\text{eff}} = \eta_0 A \exp \left( \frac{\xi^2}{R_H^2} + \frac{\xi^2}{r^2} \right)^{-a/2}
\]

where \( \eta_0 \) is the viscosity of a reference buffer, \( A \) is a pre-exponential factor of the order of 1, \( \xi \) and \( R_H \) are length scales characteristic for a given system, and \( a \) is an exponent of the order of unity. \( R_H \) can be interpreted as a hydrodynamic radius of the main crowders, while \( \xi \) refers to an effective intercrowder gap, including a weak interactions factor.18,20 In such a fluid, small molecules (\( r_p \ll \xi \)) experience viscosity of the solvent, while big tracers (\( r_p \gg R_H \)) experience viscosity measurable by macroscopic methods. To distinguish viscosity experienced by nanoobjects, we introduce a term of nanoviscosity. We further presented applicability of this model to complex biological fluids, like cytosol of prokaryotic and eukaryotic cells,5,13 and we experimentally proved and applied this model for determination of oligomerization state of proteins in living cells.15,21

The LSDV model relies on \( R_H \) and \( \xi \) parameters, which reflect the length scales characterizing the structure of the fluid. For the simplest case of complex fluid—a single polymer in a continuous solvent—\( R_H \) is defined as a hydrodynamic radius of polymer molecules, while \( \xi \) is mesh size or distance between intersections

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Figure 1. Principle of the research on cytoplasmic nanoviscosity. (I) Assumptions of the length-scale dependent viscosity (LSVD) model: (Ia) cytoplasm is a complex liquid containing components of various sizes. Thus, diffusion of the probes of different hydrodynamic radii \( r_p \) is hindered by different cytoplasmic obstacles. In the result (Ib), effective viscosity \( \eta_{eff} \) probed by tracers of different sizes increase with the size of the tracer. (II) To examine \( \eta_{eff} \), fluorescently labeled tracers are introduced to the cytoplasm—the mode of introduction is optimized for a given probe. (III) Next, FCS measurements are performed: (IIia) Confocal spot is positioned in the cytoplasmic area of the cell, and fluorescence fluctuations are registered, (IIib) autocorrelation curve (ACC) is calculated for the acquired data, and (IIic) ACC is fitted with a proper diffusion model, and diffusion coefficient of the tracer is derived. (IV) Data collected for a set of tracers in a given cell line is used for quantitative description of the LSDV model: (IVa) the majority of human cell lines. (IVb) results are plotted and fitted with eq 1; (IVc) LSDV profiles are compared between different cell lines.

The LSVD model predicts that tracers of different hydrodynamic radii would experience different effective viscosity of cytoplasm, as only those obstacles which are of similar or smaller size than the tracer would have an impact on \( \eta_{eff} \) (Figure 1, panel I). To confirm this prediction, tracers of defined hydrodynamic radii, ranging from 0.65 to 81 nm, were introduced to cytoplasmic area of cells via microinjection (dextrans and nanoparticles), passive inflow (Calcein-AM), or biosynthesis upon transfection (proteins) (Figure 1, panel II). We applied the core–shell type of nanoparticles to avoid the impact of nanoparticle size on FCS measurements. Diffusion coefficients were derived for each type of probe (see SI 3 for details), and results were averaged for each of the cell lines considered in this study. Diffusion coefficients obtained in the cytoplasm (D) were compared to diffusion coefficients measured in water (\( D_0 \)) for the same probes and temperature. Following the Stokes–Sutherland–Einstein relation, relative viscosity was calculated as follows: \( \eta_{eff}/\eta_0 = D_0/D \). \( \eta_{eff}/\eta_0 \) experienced by the probe was plotted against \( r_p \) for each of the cell lines (Figure 1, panel IV).

The results obtained for six cell lines (HeLa, HepG2, MCF-7, AS49, HSAEC, and U2-Os) are compiled in Figure 2. Error bars represent standard deviations reflecting the intercellular variability of the results. Possible intracellular variability was neglected, as discussed in SI 4. For each of the cell lines listed above, the effective viscosity of the cytoplasm is increasing with the size of the probing tracer. Although absolute values of \( \eta_{eff} \) slightly differ in particular cell lines, the trend is common in all cells of this group. The results were fitted with the LSDV model (eq 1), with following parameters: \( R_H = 20 \pm 11 \text{ nm}, \xi = 4.6 \pm 0.7 \text{ nm, } a = 0.57 \pm 0.14. \) A was fixed to 1.3 following our previous results. The values of the parameters of the LSDV model provide information regarding the rheological structure of the cytosol. Exponent \( a < 1 \) is characteristic for entangled polymer solutions. \( R_H \) is attributed to the size of major crowders in the complex liquid. \( R_H = 20 \text{ nm} \) suggests that major crowders are of diameters ~40 nm, which correspond to large cytoplasmic structures, such as vesicles, mRNA molecules, or ribo-
GEL-LIKE STRUCTURE OF CYTOPLASM

Diffusion coefficients of the probes of hydrodynamic radii smaller than 50 nm could have been measured in the cytoplasm using FCS. Larger probes, however, were more challenging: only a few autocorrelation curves were interpretable, and it was much too little for proper data analysis. We decided to support the FCS technique with its variant—Raster Image Correlation Spectroscopy (RICS).41

Fluorescent nanoparticles of diameters exceeding 100 nm were introduced via microinjection to the cytoplasm of HeLa cells and fibroblasts, and RICS analysis was performed. It turned out that no diffusion-dependent correlation could have been detected using RICS. Frame-by-frame analysis of the pictures revealed that long time and range translational diffusion could have been studied using RICS.41 In our previous work,42,43 we presented that nanoviscosity sensed by EGFP (r_p = 2.3 nm) is constant (with a slight, 30% increase during S phase) during the whole cell cycle of HeLa cells. These results, together with those presented in the present work, provide a picture of stable nanoviscosity in human cells. Future questions arise from these observations: whether nanoviscosity has a biological impact and is conserved on a level optimal for cell homeostasis.

FIBROBLASTS EXHIBIT DIFFERENT NANOVISCOSITY THAN OTHER CELLS

Primary skin fibroblasts are the only cells for which nanoviscosity profile is not length-scale dependent in the range of length scales of 1 nm < r_p < 20 nm. Thus, the nanoviscosity profile of fibroblasts deviates from the results for all other cell lines (Figure 3: e). It is a surprising result, as other mesenchymal cells exhibited “usual” LSDV profiles.44 On the other hand, cytoplasmic viscosities were similar in fibroblasts and other cells for the probes larger than 20 nm. The nanoviscosity for smaller probes in the cytoplasm of fibroblasts was independent of the passage number (see SI7).

To investigate a potential source of differences in nanoviscosity, we imaged large cytoplasmic obstacles (cytoskeleton: actin and tubulin, and endoplasmic reticulum, ER) in fibroblasts, HeLa, A549, and U2-Os cells (Figure 4). Fibroblasts were imaged as cells of interest, according to their extraordinary nanoviscosity. HeLa and A549 were chosen as control cancer
epithelial cells, while U2-Os were selected as control cancer mesenchymal cells. In the first experiment (Figure 4: a), actin and tubulin were stained using ligands specific for these proteins (phalloidin-based and paclitaxel-based, respectively). At least ten cells were imaged for every cell type. No distinct differences in cytoskeleton abundances were observed. The second experiment (Figure 4: b) included the immunostaining of ER. Again, at least ten cells were imaged for every cell type. In this variant, it was observed that the ER is much more abundant in fibroblasts than other cells. The abundance of the stained ER was quantified (see SI 8), and results are presented in Figure 5. We decided to take into account the total size of the ER, rather than the signal intensity, which may vary from cell to cell according to different protein expression levels. A significant difference in ER abundance was observed between fibroblasts and other cells: ER covered an average of 67% of the cytoplasmic

Figure 3. Comparison of nanoviscosity in different cell types. Graphs represent average relative nanoviscosity measured in the cytoplasm of different cells and plotted against hydrodynamic radii of the tracers probing the viscosity (data consistent with Figure 2) (a−d) Cell lines used in the study were divided into groups (see SI 5), according to (a) tissue origin, (b) disease, (c) gender of donor, or (d) age of donor. No deviations of the viscosity could have been observed between these groups. (e) Fibroblasts were the only cell line in which nanoviscosity was found to differ from the major trend for small probes ($r_p < 10 \text{ nm}$).
area in fibroblasts, while in A549, HeLa, and U2-Os, it was 37%, 43%, and 38%, respectively. As a complement, the cytosol (liquid phase of cytoplasm) of the fibroblasts was compressed into 33% of the cytoplasmic volume, while in other cells, it is an average of 61%.

From the diffusion point of view, the endoplasmic reticulum is a set of membrane walls crossing the medium. Its presence is included in the $\eta_{\text{eff}}$ measured in our FCS experiments. The focal volume has a cross section of diameter $\sim 400$ nm, which can consist of ER cisterna or other membrane obstacles (such as mitochondria, lysosomes, etc.). With the higher ER or organelle abundance, the number of membrane walls increases. There is a known phenomenon of near-wall diffusion hindrance,\textsuperscript{47} causing an increase of effective viscosity. Also, our previous studies on lamellar phases revealed an increase of continuous phase viscosity, comparing to the same solvent with no lamella.\textsuperscript{48} These observations are consistent with our measurements in fibroblasts—more abundant ER can possibly cause matrix viscosity increase. This effect is less pronounced for bigger length scales—for tracers of $r_p > 20$ nm, cytoplasmic viscosities of fibroblasts reach values similar to every other cell line examined in this study.

To conclude, we performed a systematic study on cytoplasmic nanostucture in seven different cell types. Cell lines used in this study represented different origins (epithelial or mesenchymal, cancer or healthy, male or female, young or adult). We probed cytoplasmic nanoviscosity at length scales in the range of $1 - 150$ nm, revealing length-scale dependent viscosity profiles present in the majority of cells. We provided the model equation describing nanoviscosity, and derived length scales characteristic for the cytoplasm. It was shown that mRNA, ribosomes, and vesicles are major cytoplasmic crowders. It was also demonstrated that nanoparticles of diameters bigger than 100 nm are unable to diffuse freely through the cytoplasm, suggesting a critical length scale crossover to gel-like structure in the cytoplasm.
The cytoplasmic nanoviscosity is preserved in the majority of human cell lines. The only cells differing from the major trend are fibroblasts. The potential source of this discrepancy can be the abundance of intracellular membrane structures, which we identified at the example of the endoplasmic reticulum. Though, the length-scale dependent viscosity model seems to be universal for human cells, regardless of age, disease, or type of tissue. Moreover, in our previous work, we presented the stability of nanoviscosity for the whole cell cycle. All these results indicate that nanoviscosity can play a vital role in cellular homeostasis maintenance, and some unknown mechanism keeps it stable in single cells and between cell types. These observations open a new field of questions about the role and regulation of the physical properties of cells.

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