

# Intracavity Nuclear Elastography

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## Article

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# Intracavity Nuclear Elastography

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## **Abstract**

The mechanical state of the cell nucleus encodes and regulates fundamental cellular processes. However, sensitive and non-invasive imaging of nuclear mechanics remains challenging. Existing optical approaches are fundamentally constrained by linear transduction, where subtle mechanical variations produce proportionally small optical responses that are susceptible to measurement noise. Here we introduce intracavity elastography, a nonlinear sensing platform that overcomes this limitation by harnessing the bifurcation dynamics of competing transverse laser modes. By integrating living cells into a Fabry-Pérot microcavity laser, ultrasound-induced nuclear deformations introduce phase perturbations to intracavity modes, triggering pronounced transverse laser mode redistribution near the bifurcation point. This nonlinear transduction converts minute mechanical perturbations into amplified optical modes, achieving over 120-fold higher sensitivity than conventional interferometric phase transduction and enabling quantitative mapping of nuclear mechanics across distinct cellular states. The platform further provides simultaneous access to nuclear optical and mechanical signatures, establishing a multidimensional optical-mechanical framework for cellular phenotyping. Our work establishes nonlinear laser dynamics as an intrinsic physical amplification mechanism for biomechanical sensing, opening a new intracavity paradigm for quantitative mechanophenotyping and probing dynamic mechanobiological processes in living cells.

**Keywords:** Fabry-Pérot microlaser; mode competition; bifurcation dynamics; optical elastography; ultrasound

## 1. Introduction

The mechanical properties of the cell nucleus encode critical information about cellular state and function, governing processes ranging from mechanotransduction<sup>1-4</sup>, cell migration<sup>5,6</sup>, differentiation<sup>7,8</sup>, and cancer progression<sup>9,10</sup>. However, quantitatively characterizing nuclear mechanics in living cells remains challenging. Conventional approaches, including micropipette aspiration<sup>11-13</sup>, substrate strain assays<sup>14-16</sup>, atomic force microscopy (AFM)<sup>17-19</sup>, and particle-tracking microrheology<sup>20-23</sup>, typically rely on direct mechanical contact or exogenous probes, which can perturb the native cellular state and limit their application for dynamic biomechanical investigations.

Optical elastometry has emerged as a powerful strategy for non-invasive biomechanical characterization. Optical tweezers utilize tightly focused optical forces to mechanically perturb cells while tracking deformation through imaging-based measurements, enabling minimally invasive quantification of cellular mechanical properties<sup>24-26</sup>. Brillouin microscopy exploits inelastic light scattering from thermally excited acoustic phonons to enable label-free mapping of intracellular viscoelastic properties<sup>27,28</sup>. Digital holographic microscopy further enables sensitive detection of cellular vibrations through interferometric phase modulation<sup>29</sup>. Optical coherence elastography combines optical coherence tomography with mechanical excitation to quantify tissue and cellular mechanical properties<sup>30-32</sup>. However, current optical techniques generally rely on linear transduction, in which subtle mechanical perturbations produce proportionally weak optical responses that are susceptible to measurement noise. Amplifying the weak mechanical signals through nonlinear optical dynamics could therefore provide a pathway toward ultrasensitive biomechanical sensing<sup>33</sup>.

Here, we employed the nonlinear bifurcation dynamics of a microlaser cavity as an intrinsic amplification mechanism to transduce subtle mechanical perturbations into pronounced transverse mode competition dynamics. As shown in [Fig. 1a](#), the living cells were sandwiched into a Fabry-Pérot (FP) microcavity laser. The ultrasound was applied as a mechanical stimulus to the cell nucleus, inducing acousto-mechanical

vibrations and corresponding phase shifts in the intracavity laser modes (Figs. 1b and 1c). We observed pronounced competition among multiple transverse mode families supported within the microcavity, which drives the system toward a bifurcation point. Near this critical regime, ultrasound-induced nuclear deformations modulate the balance between competing lasing states, leading to amplified optical responses (Fig. 1d). Substantial laser mode redistribution was observed in response to nanoscale nuclear mechanical perturbations, enabling highly sensitive transduction of nuclear mechanics beyond conventional interferometry (Fig. 1e). Leveraging this bifurcation-enhanced sensing mechanism, our platform achieves high-sensitivity mapping of nuclear mechanical heterogeneity (Fig. 1f) and reveals dynamic nuclear biomechanical responses under different cellular states. Our platform provides simultaneous access to nuclear optical and mechanical signatures, establishing an optical-mechanical framework for phenotyping. This work establishes a new paradigm for nonlinear intracavity biomechanical sensing and introduces a new dimension for quantitative cellular mechanophenotyping.

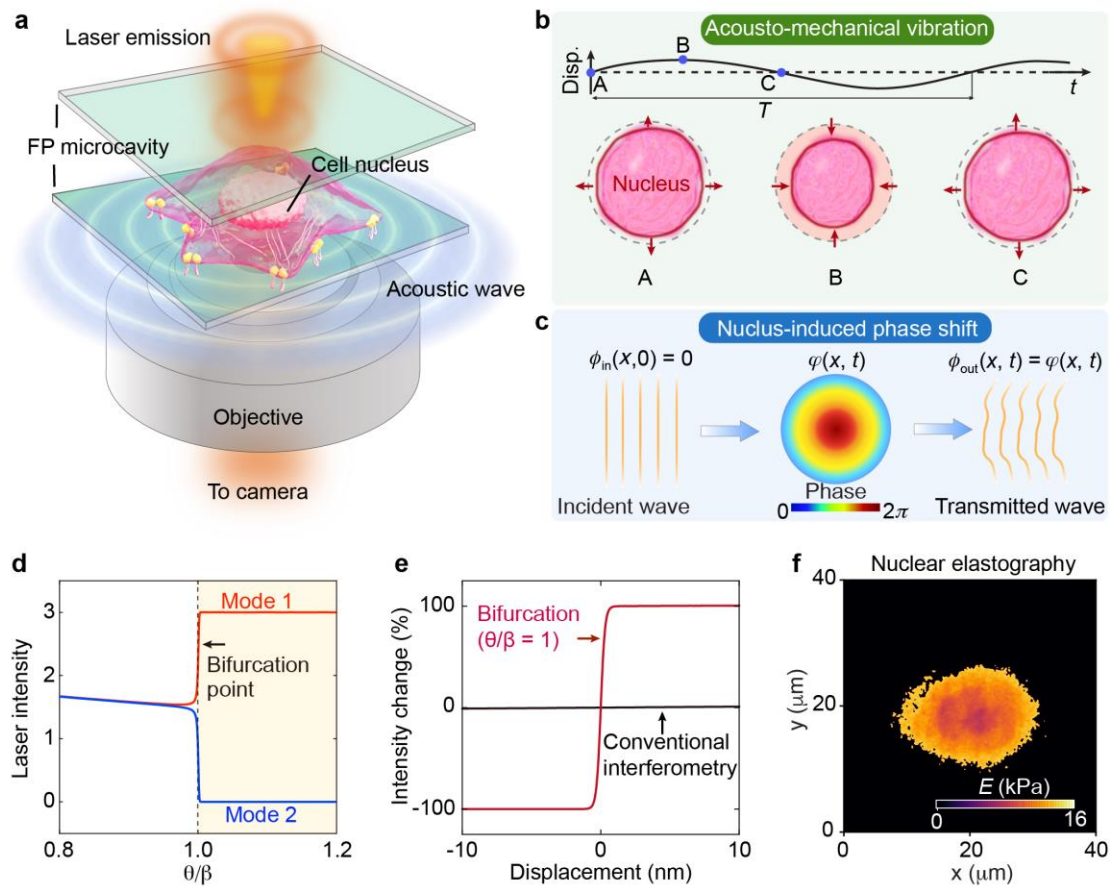


**Figure 1. Principle of nuclear elastography using a Fabry-Pérot (FP) microcavity laser.** (a) Experimental setup. (b) Illustration of acousto-mechanical vibration of the cell nucleus. (c) Illustration of nucleus-induced phase shift. (d) Simulation of bifurcation phenomenon. Near the bifurcation point, the system exhibits bistable behavior, where two competing lasing modes (Mode 1 and Mode 2) can switch in response to external perturbations. (e) Sensitivity enhancement under bifurcation condition. The black curve represents the response of conventional interferometry. (f) Young's modulus map of the cell nucleus.

## 2. Results

### 2.1 Bifurcation in an FP microcavity laser

Multimode lasing in an FP microcavity is inherently governed by nonlinear interactions between transverse modes. The steady state is determined by the balance between intracavity gain and loss. When this balance is perturbed, the stability of the steady state can be analyzed by introducing a small intensity perturbation,  $\delta I$ , around the equilibrium<sup>34</sup>. The temporal evolution of the perturbation follows  $\delta I \propto e^{\mu t}$  (See [Supplementary Information](#) for more details). Here,  $\mu$  is the eigenvalue of the Jacobian matrix, which is given by

$$\begin{cases} \mu_1 = -\beta I_s(1 + \eta) \\ \mu_2 = -\beta I_s(1 - \eta) \end{cases} \quad (1)$$

where  $\beta$  and  $\theta$  represent the self- and cross-saturation coefficients, respectively.  $\eta = \theta/\beta$  is defined as the competition factor. For  $\eta < 1$ , both eigenvalues are negative, indicating that the steady state is stable and the modal intensity return to equilibrium after perturbation. When  $\eta > 1$ ,  $\mu_2 > 0$ , the perturbation grows exponentially, which drives the system toward a new stable lasing state with a different spatial distribution, giving rise to bifurcation ([Fig. 1d](#)). At the critical condition,  $\eta = 1$ ,  $\mu_2 = 0$ , the system reaches the bifurcation point where the steady state reaches marginal stability<sup>35,36</sup>. As shown in [Fig. 1e](#), the FP microcavity laser exhibits a sharply enhanced response at the bifurcation point, in striking contrast to the linear response of conventional interferometric detection. This critical enhancement enables nanometric displacements to induce dramatic redistribution of optical energy between competing laser modes, thereby enabling ultrasensitive mechanical detection.

To validate the theoretical prediction, we characterized the laser emission in an FP microcavity laser. A hydrogel microdroplet sandwiched in an FP microcavity was employed as a model to mimic the biological cell (Fig. 2a). An inverted microscope system was employed for laser excitation and signal collection (Supplementary Fig. S1). When the pump laser energy exceeds the lasing threshold<sup>37</sup>, several individual peaks appear on the emission spectrum, corresponding to the longitudinal laser modes (Fig. 2b). Owing to the high reflectivity of the cavity mirrors (Supplementary Fig. S2), fluorescence emission below the lasing threshold was largely suppressed, yielding a high signal-to-noise ratio of  $\sim 55$  dB. As shown in Fig. 2c, the low lasing threshold of  $P_{\text{th}} = 6.9 \mu\text{J}.\text{mm}^{-2}$  corresponds to an optical power density of only  $0.14 \text{ mW}.\text{mm}^{-2}$ , which is approximately eight orders of magnitude lower than that typically required for Brillouin microscopy ( $\sim 2.3 \times 10^7 \text{ mW}.\text{mm}^{-2}$ )<sup>38</sup>. Such a low excitation power density minimizes photodamage and phototoxicity, thereby ensuring excellent biocompatibility for biological samples<sup>39</sup>.

Pronounced mode competition was observed within the FP microcavity. As shown in Fig. 2d, the laser emission consists of a superposition of multiple transverse modes (See Supplementary Information for details). Among them, Mode 1 and Mode 2 are the dominant components (over 85% of the total energy) and were therefore selected to characterize the intracavity mode competition. Figure 2e shows that Mode 1 and Mode 2 exhibit a complementary intensity evolution, where the growth of one mode is accompanied by the suppression of the other. The corresponding temporal evolution of the mode intensities further confirms the competitive dynamics (Fig. 2f). Notably, the intensity variations of Mode 1 and Mode 2 statistically satisfy a ratio of  $\Delta I_1 / \Delta I_2 \approx -1$  (Fig. 2g), serving as a hallmark of operating near the bifurcation point (see Supplementary Information for more details).

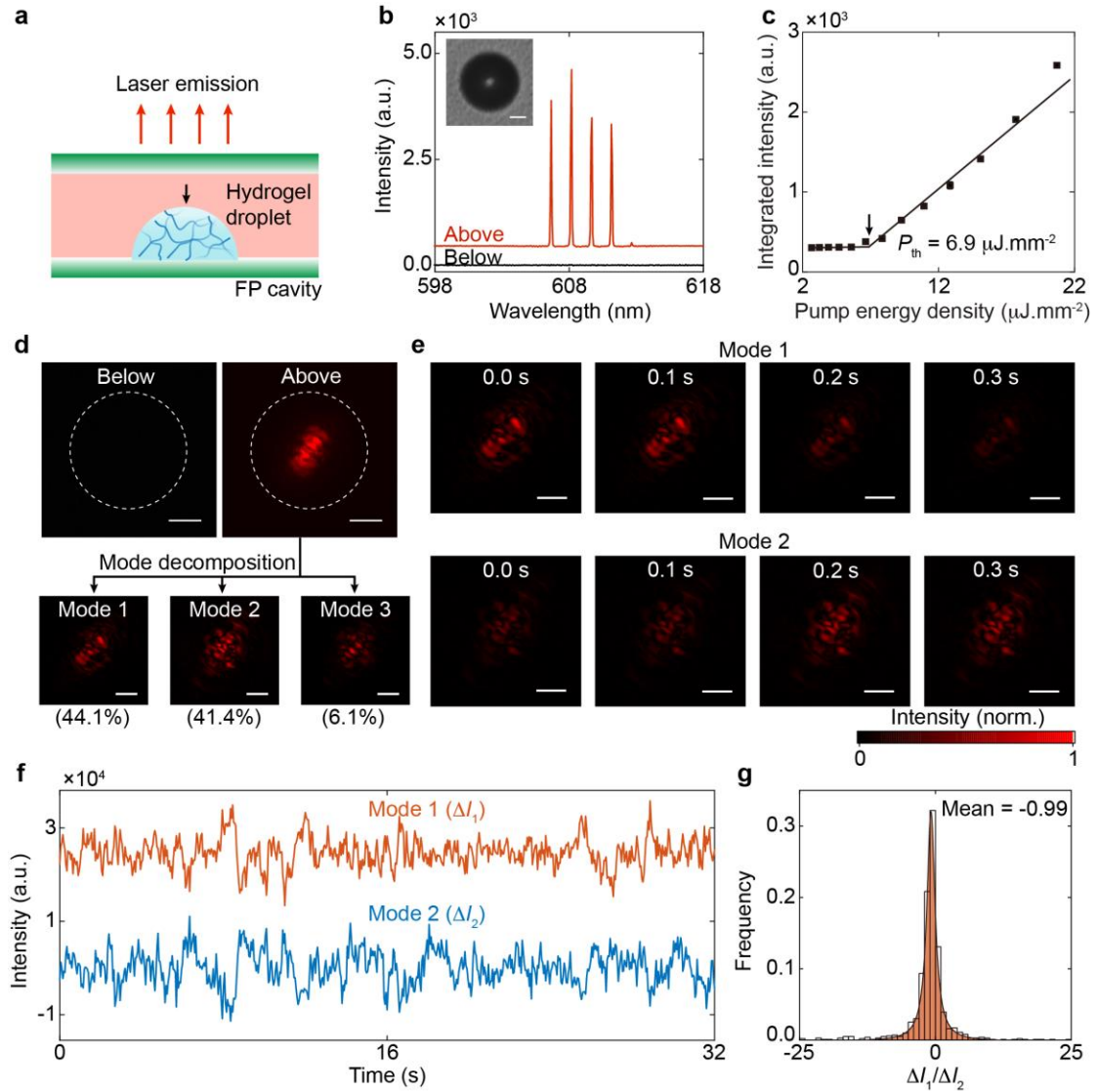


**Figure 2. Experimental observation of bifurcation behavior during mode competition.** (a) Illustration of a hydrogel droplet within FP cavity. (b) Emission spectrum before and after reaching the lasing threshold. Inset, bright field image of the intracavity hydrogel droplet. Scale bar: 5  $\mu\text{m}$ . (c) Integrated intensity as a function of pump energy density. (d) Illustration of mode decomposition. Values in parentheses denote the energy fraction of each mode. Scale bar: 5  $\mu\text{m}$ . (e,f) Dynamic evolution of mode 1 and mode 2 (e) and their corresponding temporal intensity profiles (f). Scale bar: 5  $\mu\text{m}$ . The curves in (f) are vertically shifted for clarity. (g) Statistical distribution of  $\Delta I_1/\Delta I_2$ . The  $\Delta I_1/\Delta I_2 \approx -1$  provides evidence for bifurcation during mode competition.

## 2.2 Response of transverse laser modes to ultrasound

Ultrasound was employed as an external stimulus to induce mechanical perturbations in the FP microcavity laser. As illustrated in Fig. 1b, ultrasound generated time-varying mechanical stresses in the hydrogel droplets, leading to periodic morphological deformations. These deformations drive the redistribution of energy among competing transverse laser modes by dynamically modulating the phase of the cavity modes. In contrast to the chaotic mode competition dynamics in Fig. 2e, periodic mode switching was observed under ultrasound excitation (Fig. 3a). The temporal intensity evolution of Point A was recorded in Fig. 3b. The modulation of mode competition can be further confirmed by the presence of two distinct peaks at  $f_1 = 8.0$  Hz and  $f_2 = 4.0$  Hz in the fast Fourier transform (FFT) spectrum<sup>40-42</sup> (Fig. 3c), corresponding to the aliased signals of the fundamental ultrasound frequency and its harmonic component (Supplementary Fig. S3)<sup>43-46</sup>. After applying a bandpass filter, the temporal signal at Point A exhibited a pronounced sinusoidal waveform under ultrasound excitation (Fig. 3b), whereas only weak fluctuations were observed in the absence of acoustic stimulation (Supplementary Fig. S4). These results indicate that the dynamic evolution of transverse laser modes reveals the mechanical vibration of the intracavity structure. Even though the aliased frequencies differ from the actual ultrasound frequency, the amplitude of the mechanical vibrations can still be quantified with the aliased signals.

The stimulus-response of the transverse laser modes under ultrasound excitation can reveal the intracavity mechanics. As illustrated in Fig. 3d, hydrogel droplet samples with different Young's moduli were fabricated by controlling the ultraviolet (UV) radiation illumination time, and the corresponding Young's moduli were calibrated by using atomic force microscopy (AFM). The aliased signals of samples with different Young's moduli under ultrasound excitation are shown in Supplementary Fig. S5, revealing a pronounced decrease in vibration amplitude with increasing Young's modulus. The statistical distribution of the time-varying signal intensity follows a Gaussian distribution, with a progressively narrower spread as the Young's modulus increases (Fig. 3e). The relative variance (RV) of the signal intensity distribution was calculated and employed as the sensing output to characterize the intracavity Young's modulus throughout the experiments (see Methods for more details). The curve in Fig. 3f establishes the correlation between the stimulus-response of the transverse laser modes and Young's modulus, which can serve as a calibration curve for intracavity mechano-assays. Further experiments show that the calibration is insensitive to the pump position, confirming the robustness of our method (Supplementary Fig. S6).

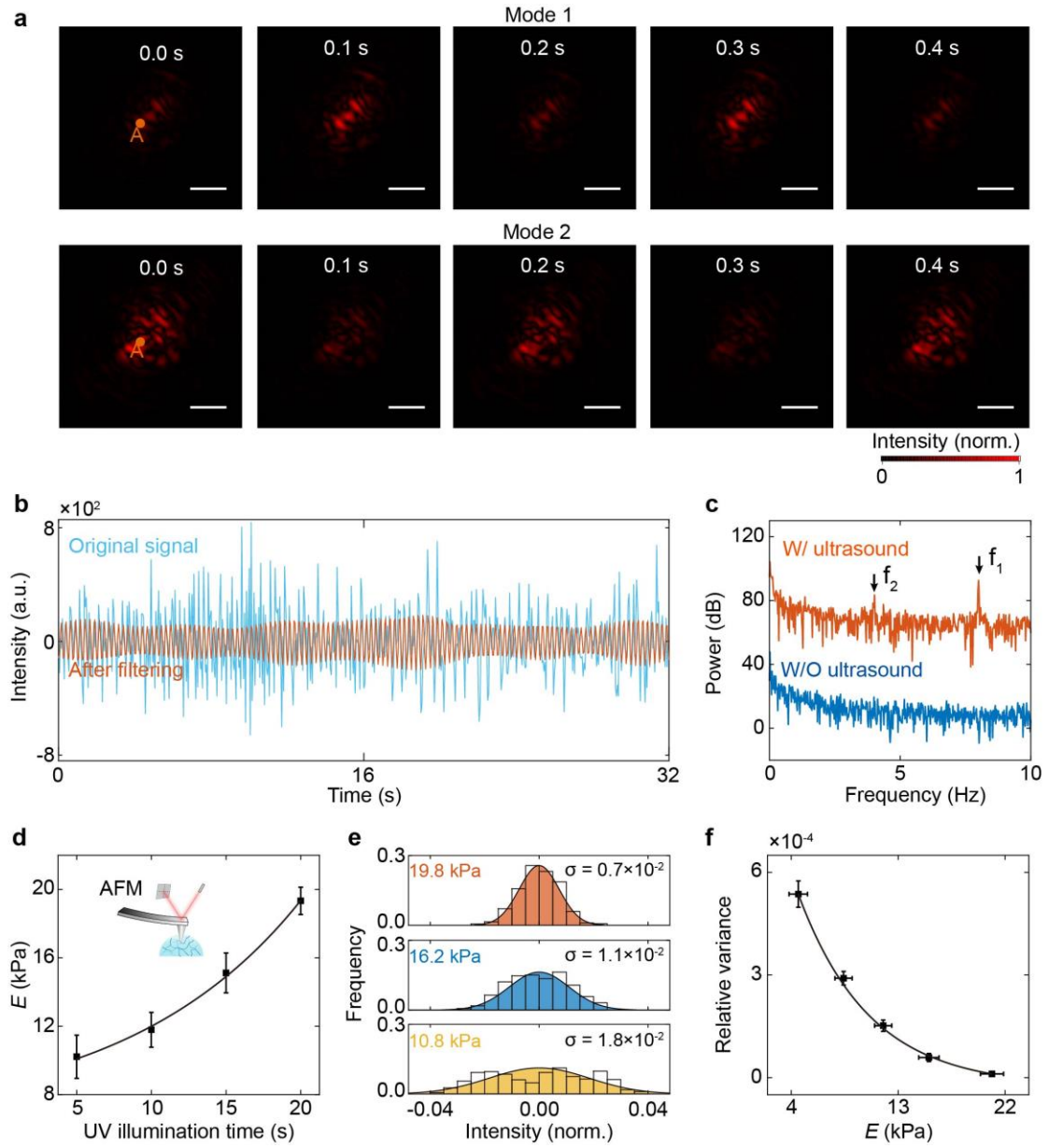


**Figure 3. Ultrasound-modulated transverse laser mode dynamics.** (a) Ultrasound-induced periodic mode switching. Scale bar: 5  $\mu\text{m}$ . (b) Intensity evolution before and after filtering. Data were extracted from point A in (a). (c) Comparison of the FFT spectra with and without ultrasound excitation. (d) Young's moduli of hydrogel samples fabricated using different UV irradiation times. (e) Gaussian distribution of aliased signal intensity with various Young's moduli.  $\sigma$  denotes the standard deviation, representing the width of the Gaussian distribution. (f) Calibration curve for intracavity Young's modulus measurement.

### 2.3 Mechanical mapping of a single-cell nucleus

The transverse mode competition can also be observed in the intracavity cell nucleus. The A549 cell line was employed as a model system due to its widespread use in cancer biology studies. The cells were seeded on the bottom mirror overnight to enable stable attachment on the mirror surface (Fig. 4a). The cells proliferate from  $0.7 \times 10^4$  to  $5.9 \times 10^4$  cells.cm<sup>-2</sup> after 48 hours of incubation, indicating good biocompatibility (Supplementary Fig. S7). As shown in Fig. 4b and Supplementary Fig. S8, owing to the higher refractive index of the cell nucleus, the transverse laser modes are preferentially confined within the nucleus. This behavior is consistent with previous observations in FP cavity-based cell lasers<sup>47-49</sup>. Similar to the results shown in Fig. 2, the mode patterns generated from the cell nucleus consist of multiple transverse modes that compete for optical gain, resulting in dynamic variations in the spatial distribution of the modes across consecutive frames (Fig. 4c). As illustrated in Supplementary Fig. S9, the system operates near the bifurcation point, where the coupled modes exhibit enhanced sensitivity to perturbation.

We further demonstrated that the ultrasound-mediated mode competition reveals the spatial heterogeneity of mechanical properties, enabling mechanical mapping of a single-cell nucleus. Once ultrasound was applied, the cell nucleus experienced periodic compression and expansion, leading to dynamic modulation of the chaotic mode competition. Interestingly, the differential patterns under ultrasound excitation exhibited periodic grid-like features, which were absent in both the hydrogel model and the control experiment performed without ultrasound (Fig. 4c). This phenomenon is likely attributed to the formation of interference patterns during ultrasound propagation through the complex anisotropic architecture of the cell nucleus. This ultrasound interference pattern periodically modulates the spatial distribution of the transverse laser modes, giving rise to the observed grid-like differential patterns. Since the transverse mode patterns contain spatially resolved information, the dynamic intensity evolution at different locations can be simultaneously extracted from the laser mode patterns (Fig. 4d). The statistical intensity distributions of these signals exhibit substantial variations in distribution width, revealing pronounced spatial heterogeneity

in nuclear mechanics (Fig. 4e). Moreover, unlike the spectral interrogation method, the transverse mode patterns distinguish nuclear vibrations from background cavity vibrations, enabling more sensitive quantification of nuclear mechanics (Supplementary Figs. S10 and S11).

Based on the calibration curve in Fig. 3f, a mechanical map of the single-cell nucleus was reconstructed by calculating the RV value at each pixel (Fig. 4f). The reconstructed map reveals pronounced mechanical heterogeneity within the nucleus, with nucleoli (arrows in Fig. 4f) exhibiting substantially higher Young's moduli than the surrounding nucleoplasm. This increased Young's modulus is attributed to the densely packed ribonucleoprotein assemblies and highly concentrated biomolecular constituents within nucleoli<sup>50</sup>. These findings highlight the capability of intracavity elastography to resolve mechanical heterogeneity at the subnuclear scale. To validate the reliability of the Young's modulus map in characterizing nuclear mechanics, we examined its response following DNA cleavage. Deoxyribonuclease I (DNase I) enzymatically cleaves phosphodiester bonds in DNA and degrades chromatin structure, resulting in a reduced Young's modulus of the cell nucleus. As shown in Supplementary Fig. S12, Young's modulus decreases by ~23% after 1 h of DNase I treatment. This result confirms that the mechanical map is sensitive to changes in nuclear mechanical properties.

The bifurcation-induced nonlinear response effectively amplifies weak mechanical perturbations and enables substantially higher perturbation sensitivity than conventional interferometry. Traditional interferometry relies on linear phase modulation, in which the phase shift induced by external mechanical perturbations is linearly converted into optical intensity variations. For a 2 nm nuclear vibration amplitude, the induced phase modulation is estimated to be only  $\sim 2.5 \times 10^{-3}$  rad at a wavelength of 600 nm. Such a weak phase perturbation would generate an intensity modulation on the order of  $10^{-3}$  in conventional interferometric detection, which is difficult to distinguish from laser intensity noise (~1%) in practical measurements. In contrast, the transverse laser modes become highly sensitive to external perturbations near the bifurcation point, where minute mechanical deformations can induce abrupt

redistribution of the transverse mode patterns. According to the results in Fig. 4g, our method exhibits a sensitivity enhancement of  $\sim 120$ -fold compared with conventional interferometry (Supplementary Fig. S13), demonstrating the capability of our method for high-sensitivity mechano-assay of individual cell nuclei.

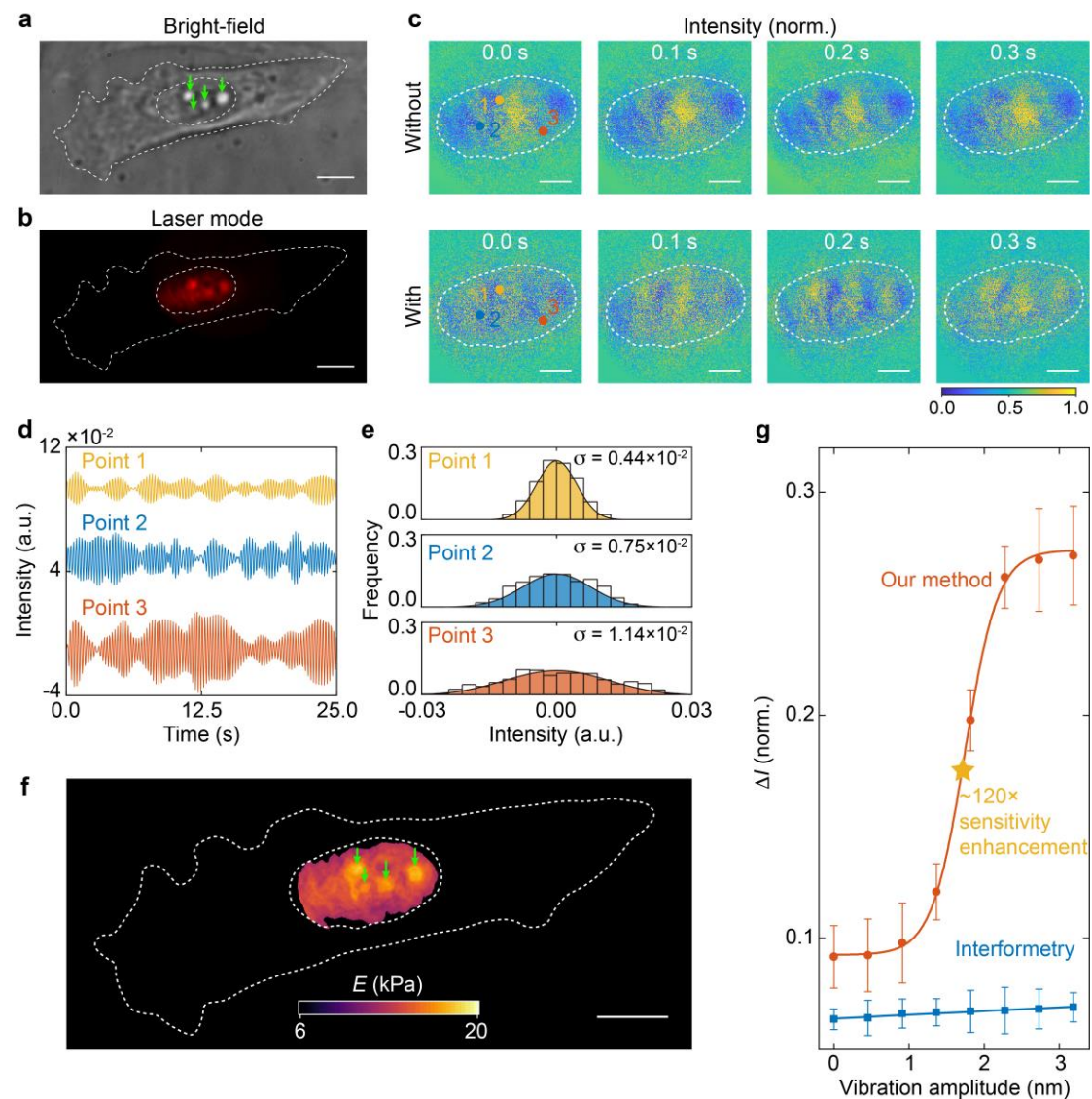


**Figure 4. Mechanical mapping of a single-cell nucleus.** (a,b) Bright-field image (a) and transverse laser modes (b) of the cell. The dashed lines indicate the outlines of the cell and nucleus, respectively. Arrows indicate the locations of nucleoli. Scale bar: 10  $\mu\text{m}$ . (c) The differential patterns of laser modes without (top) and with (bottom) ultrasound excitation. Scale bar: 5  $\mu\text{m}$ . (d,e) The time-varying intensity signal at different locations (d) and the corresponding statistical distributions (e). Data were extracted from points marked in (c). (f) The Young's modulus maps of the cell nucleus.

Scale bar: 10  $\mu\text{m}$ . (g) Comparison of the sensing performance between our method and conventional interferometry at different vibration amplitudes. The curves are vertically shifted for clarity.

## 2.4 Dynamic mechanical responses of the cell nucleus

We employed intracavity elastography to investigate the mechanical responses of the cell nucleus across different cell spreading states. As shown in [Supplementary Fig. S14](#) and [Fig. 5a](#), we characterized nuclear mechanics under different cell spreading conditions. It is worth noting that the reconstructed map shows a relatively higher Young's modulus at the nuclear boundary. This can be attributed to the reinforcing effect of the nuclear lamina and its mechanical coupling with the cytoskeleton in live cells<sup>51</sup>. This result is consistent with previous observations reported in the literature<sup>52,53</sup>. We found that the mechanical difference between the central and peripheral regions becomes more pronounced in larger nuclei. In larger nuclei, the increased nuclear volume is often accompanied by chromatin decondensation, which contributes to a lower Young's modulus in the nuclear interior<sup>54,55</sup>. This nuclear softening effect becomes increasingly significant with increasing nuclear size, leading to a transition in the statistical distribution of Young's modulus from a single-peak Gaussian profile to a bimodal (double-peak) Gaussian distribution. The average nuclear Young's modulus of cells in [Fig. 5b](#) exhibits a strong negative correlation with cell spreading area, indicating that cellular spreading state is closely coupled with nuclear mechanical remodeling. According to the control experiments shown in [Supplementary Fig. S15](#), variations in nuclear size have a negligible influence on mechanical quantification.

We investigated the dynamic mechanical response of the cell nucleus during apoptosis. Apoptosis is a programmed cell death process accompanied by nuclear morphological and biomechanical transformations<sup>56</sup>. To evaluate the capability of our proposed method in capturing the nuclear biomechanical changes during apoptosis, we employed paclitaxel (PTX) to induce programmed cell death in A549 cells. PTX stabilizes microtubules, inhibits their depolymerization, and induces mitotic arrest and apoptosis<sup>57</sup>. The flow cytometric analysis results in [Fig. 5c](#) indicate an increasing

proportion of dead cells, rising from 2.1% to 41.3% after 12 hours of PTX incubation. These results confirm the successful triggering of apoptosis. The reconstructed nuclear Young's modulus maps in [Fig. 5d](#) reveal distinct mechanical characteristics associated with different stages of apoptosis. As shown in [Fig. 5e](#), the average nuclear Young's modulus initially increased and then decreased with prolonged PTX treatment. The biphasic evolution of nuclear mechanics during PTX treatment reflects the sequential mechanical remodeling of the nucleus during apoptosis. During the early stage (0-4 h), PTX-induced mitotic arrest triggers chromatin condensation and nuclear compaction<sup>58,59</sup>, resulting in increased nuclear stiffness. At later stages (4-12 h), activation of apoptotic pathways leads to lamina degradation<sup>60</sup>, chromatin fragmentation<sup>61</sup>, and loss of nuclear structural integrity<sup>62</sup>, thereby causing a decrease in nuclear Young's modulus. In contrast, the average nuclear Young's modulus in the control group remained relatively stable over the same period ([Supplementary Fig. S16](#)). These findings demonstrate that nuclear stiffness serves as a dynamic mechanical biomarker of apoptosis progression, characterized by a transition from early-stage stiffening to late-stage softening.

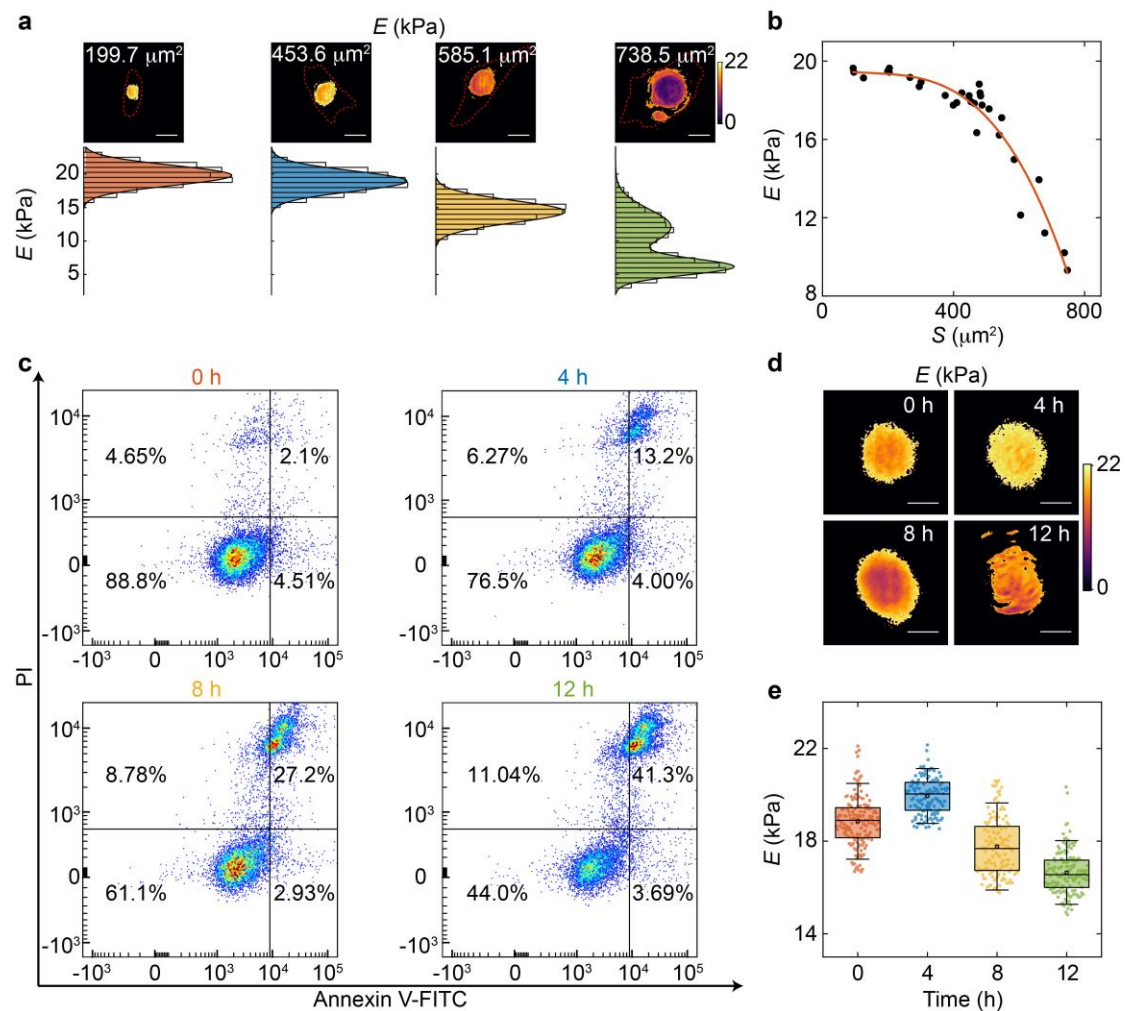


**Figure 5. Mechanical responses of the cell nucleus.** (a) Young's modulus maps of cells with different spreading areas (**top**) and the corresponding statistical distribution of Young's modulus (**bottom**). Scale bar:  $10 \mu\text{m}$ . (b) Average nuclear Young's modulus as a function as spreading areas. (c) Flow cytometric analysis of cellular states following drug treatment at 0 h, 4 h, 8 h, and 12 h. (d) Young's modulus maps at corresponding time points. Scale bar:  $5 \mu\text{m}$ . (e) Statistical analysis of nuclear mechanical evolution during apoptosis. Error bars are obtained over 126 measurements.

## 2.5 Multidimensional optical-mechanical phenotyping

We further demonstrated that the mechanical properties of the nucleus provide a complementary dimension to optical information, enabling optical-mechanical phenotyping of cells. We first extracted the optical features of the cells from the laser spectra. As illustrated in Fig. 6a, the distinct nuclear refractive index, absorption, and

scattering characteristics of different cell types modulate the intracavity optical modes, resulting in variations in the emission wavelength and intensity. Accordingly, the centroid wavelength and integrated intensity were extracted as representative optical features for cellular phenotypic characterization. The centroid wavelength is defined as the intensity-weighted average wavelength of the laser emission spectrum, representing the overall spectral distribution of the emitted light (see Methods for more details). As shown in [Figs. 6b and 6c](#), C2C12 and 4T1 cells exhibited relatively longer centroid wavelengths, whereas PC-9 and H1975 cells displayed stronger laser emission. These differences reflect distinct nuclear optical properties among cell types.

We next quantified the mechanical properties of cell nuclei using intracavity nuclear elastography ([Fig. 6d](#)). The progressive decrease in nuclear Young's modulus from PC-9 to H1299 is consistent with the increasing malignancy and invasive potential of these lung cancer cell lines. PC-9 cells, which retain a predominantly epithelial phenotype, exhibited relatively stiff nuclei, whereas H1975 cells with partial epithelial-mesenchymal transition characteristics and highly invasive H1299 cells displayed progressively softer nuclei. Such nuclear softening is expected to enhance nuclear deformability, thereby facilitating migration through confined environments and contributing to metastatic dissemination. Similarly, highly metastatic 4T1 breast cancer cells also exhibited a low nuclear Young's modulus, further supporting the association between nuclear mechanical compliance and metastatic potential. In contrast, C2C12 myoblasts showed a markedly higher nuclear Young's modulus than cancer cells, likely reflecting the greater mechanical robustness required for skeletal muscle cells to withstand repetitive mechanical loading.

Multidimensional optical-mechanical phenotyping was finally achieved by integrating optical signatures with mechanical properties, enabling label-free identification and clustering of diverse cell types. As shown in [Fig. 6e](#), the cells occupied distinct regions in the optical-mechanical phenotypic space, revealing cell-type-specific biophysical signatures. Furthermore, t-SNE visualization demonstrated that the extracted multidimensional features preserved clear intercellular separability ([Fig. 6f](#)). These results indicate that nuclear mechanics provides a complementary

dimension to conventional biomarkers, substantially improving the discriminatory power of label-free cellular phenotyping. Such multidimensional phenotypic profiling establishes a powerful platform for label-free cellular analysis, with broad translational potential in precision diagnostics, cancer stratification, therapeutic response assessment, and personalized medicine.

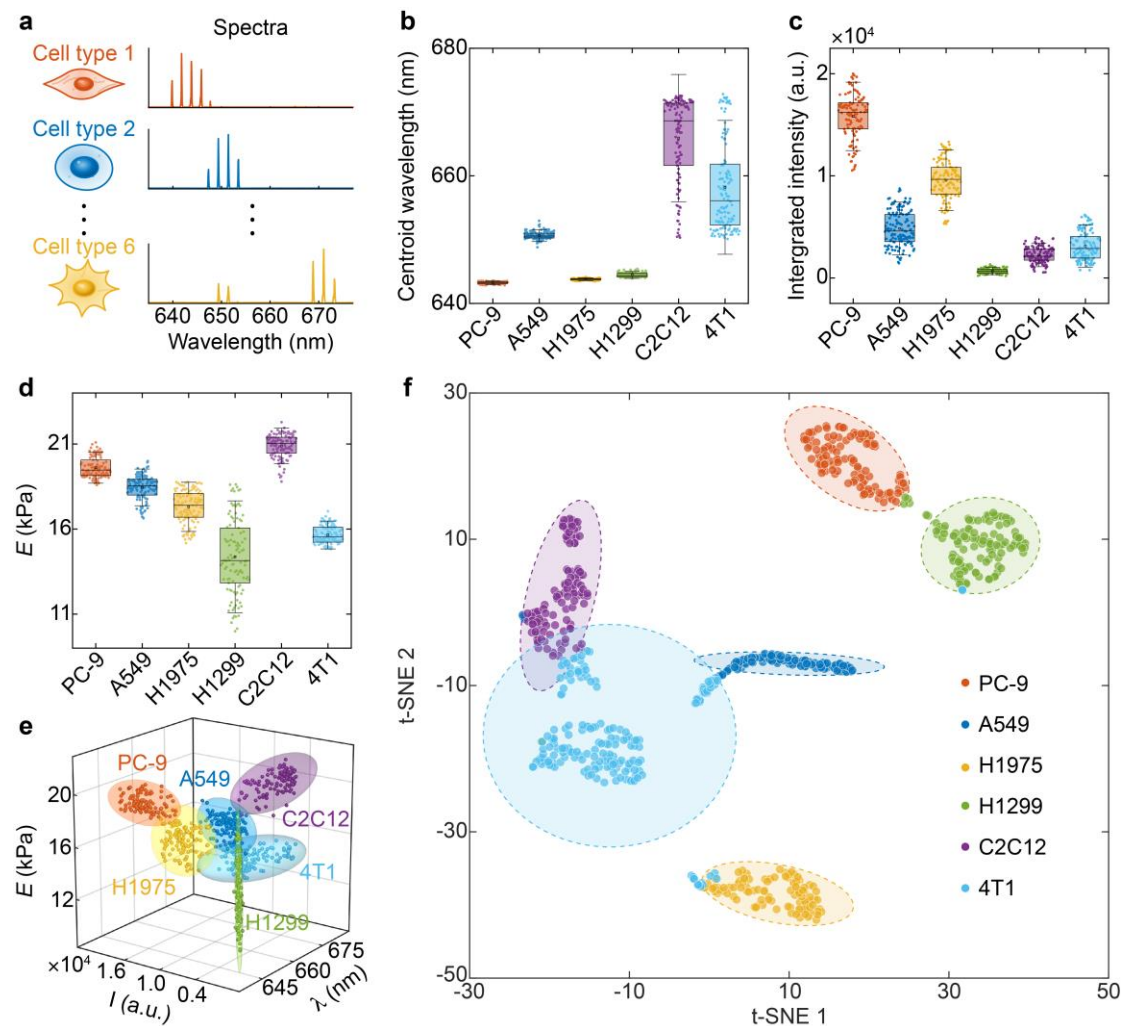


**Figure 6. Optical-mechanical phenotyping.** (a) Conceptual illustration of optical features of different cells. (b,c) Centroid wavelengths (b) and integrated intensities (c) of laser spectra across different cell types. Error bars are obtained from over 110 measurements. (d) Statistical Young's modulus of different cell types. Error bars are obtained from 110 measurements. (e) 3D visualization of cellular features in optical-mechanical phenotypic space. (f) t-SNE visualization of cellular phenotypic clustering.

### 3. Discussion

We developed an intracavity nuclear elastography technique that exploits the nonlinear bifurcation dynamics of a microlaser cavity to amplify optical responses to ultrasound-induced mechanical perturbations. Leveraging the enhanced response arising from transverse-mode competition near the bifurcation regime, our approach converts subtle nuclear deformations into pronounced optical mode redistribution, enabling highly sensitive mapping of nuclear mechanical properties beyond the conventional linear-response limit. The proposed platform reveals the spatial heterogeneity of nuclear mechanics and dynamic biomechanical remodeling across different cellular states. Our results demonstrate that nuclear mechanical properties offer complementary information beyond conventional optical readouts, establishing an optical-mechanical framework for cellular phenotyping. This work provides a highly sensitive mechanobiological sensing platform that advances our understanding of nuclear mechanics and its role in regulating cellular states and functions.

As summarized in [Table S1](#), established mechanical techniques predominantly operate within a linear transduction regime, in which the measured response scales approximately proportionally with the applied mechanical perturbation. Consequently, subtle mechanical variations generate correspondingly small changes in displacement, phase, or frequency, making their detection increasingly susceptible to measurement noise. In contrast, intracavity nuclear elastography harnesses bifurcation-enabled nonlinear transduction, whereby subtle nuclear deformations perturb the competition between transverse laser modes and trigger pronounced redistribution of optical energy. This mechanism provides an approximately 120-fold enhancement in optical response relative to conventional interferometric phase transduction. Meanwhile, the low optical power density of  $10^{-1} \text{ mW} \cdot \text{m}^{-2}$  provides better compatibility with live-cell measurements.

Although the present proof-of-concept experiments were performed at the single-cell level, intracavity elastography is compatible with scanning and microfluidic architectures. Such integration could enable higher-throughput measurements across large cell populations, thereby improving the statistical robustness of mechanical

phenotyping. More broadly, this capability may facilitate systematic investigation of nuclear mechanics across physiological and pathological states and support the development of nuclear mechanical properties as quantitative biomarkers for disease characterization and therapeutic assessment.

## **4. Materials and methods**

### **4.1 Optical system setup**

An inverted microscope system with a  $\times 50$  objective (NA = 0.55) was used for excitation and signal collection ([Supplementary Fig. S1](#)). The 532 nm pulsed laser (CNI, MPL-H-532-2  $\mu$ J) with a 20 Hz repetition rate served as an optical pump. The pulsed pump laser was coupled into the inverted microscope system and focused to a small spot with a diameter of 1  $\mu$ m. The lasing emission from the cell nucleus within the FP cavity was split by a beam splitter and sent to a scientific complementary metal-oxide-semiconductor (sCMOS) camera (Tucsen, Dhyana 400BSI V3) and a spectrometer (Princeton Instruments, SpectrPro-500i) for image and spectra acquisition, respectively. The pump laser, sCMOS camera, and spectrometer were synchronized throughout the experiment to ensure that each spectrum and image corresponded to a single pump pulse.

### **4.2 Fabrication of FP microcavity laser**

The cavity mirrors employed for the lasing emission possessed a high reflectivity of  $\sim 98.9\%$  in the spectral range from 630 to 650 nm. A 10 mM Rhodamine solution was prepared by dissolving Rhodamine 6G powder (Aladdin, R105624) in a 4:1 (v/v) mixture of phosphate buffered saline (PBS) (Aladdin, C0221A) and dimethyl sulfoxide (DMSO) (Aladdin, D103281), served as gain medium within the FP cavity. Silicon microbeads with 50  $\mu$ m diameter were used as spacers to fix the cavity length.

### **4.3 Fabrication of the hydrogel droplets**

The hydrogel droplets were fabricated on the bottom mirror. The mirror was cleaned using a plasma cleaner (PLUTOVAC, PLUTO-T) for 1 minute. The cleaned mirror was immersed in a fluorosilane-modified silicon dioxide coating solution and incubated for

1 minute. After heating at 50 °C on a hot plate for 3 minutes, hydrophobic layer was formed on the mirror. A commercial inkjet printer (EPSON, L130) was used for hydrogel microdroplet generation.

#### **4.4 Ultrasound actuation**

A piezoelectric transducer attached to the bottom mirror was used to generate ultrasound. A square wave with an amplitude of 4 V and a frequency of 20.008 kHz was employed to drive the piezoelectric transducer.

#### **4.5 Transverse mode decomposition**

The transverse mode decomposition was performed using singular value decomposition (SVD)<sup>63,64</sup> (see [Supplementary Information](#) for details). Each recorded image was represented as a two-dimensional matrix, and the static background was removed by subtracting the average intensity. The resulting matrices were vectorized and sequentially arranged to construct a spatiotemporal matrix, which was subsequently decomposed by SVD. Each decomposed mode was reconstructed by multiplying its spatial profile by the corresponding temporal coefficient.

#### **4.6 Quantification of mechanical vibration**

The detailed procedural for the quantification of mechanical vibration can be found in [Supplementary Information](#). Briefly, each image frame was first spatially denoised using a two-dimensional Gaussian filter. The slow temporal intensity drift at each pixel was then removed by second-order polynomial detrending. The detrended signals were further processed using a fourth-order zero-phase Butterworth bandpass filter with cutoff frequencies of 7.5 and 8.5 Hz to isolate the response near 8 Hz. The vibration response at each pixel was quantified by the standard deviation of the filtered signal and normalized by the corresponding average intensity of the original image sequence.

#### **4.7 Calibrating Young's modulus**

The Young's modulus of hydrogels was characterized using a Cypher VRS AFM

(Oxford Instruments). An AC160 AFM probe (Olympus,  $k = 0.0255 \text{ N/nm}$ ) with a radius of 7 nm was employed. The force-distance curves of hydrogels were acquired in contact mode to determine the mechanical properties.

#### **4.8 Cell culture**

To facilitate cell attachment on the bottom mirror, the mirror was treated with plasma cleaner for 1 min to enhance surface hydrophilicity. After being sterilized with 75% ethanol for 10 min, the mirror was washed with PBS and was ready for the following cell culture experiment.

The cells were cultured in Dulbecco's modified Eagle medium (DMEM) (Cytiva, SH30243.01) supplemented with 10% fetal bovine serum (FBS) (Cytiva, SH30406.05) and 1% penicillin-streptomycin (Beyotime, C0222). After being seeded onto the mirror, the cells were incubated in a standard incubator with 5%  $\text{CO}_2$  at 37 °C for 8 h in the incubator to enable stable attachment to the mirror.

#### **4.9 Fluorescence image of cell nucleus**

The cells were cultured on the bottom mirror of the FP cavity for 12 h and gently washed twice with PBS. The cells were then stained with 50  $\mu\text{M}$  SYTO<sup>TM</sup> 9 (Thermo Fisher Scientific, S34854) for 30 min and subsequently washed twice with PBS. The FP cavity was filled with PBS, and the fluorescence from the cell nuclei was recorded using the sCMOS camera under illumination at 450-490 nm.

#### **4.10 DNA cleavage**

Cells cultured on the bottom mirror were washed twice with PBS and fixed with a paraformaldehyde solution (Solarbio, P1110) for 12 min. After two additional washes with PBS, the cells were permeabilized with a permeabilization solution (Aladdin, I743383) for 20 min and then washed twice with PBS. The permeabilized cells were subsequently incubated with 0.1 U/ $\mu\text{L}$  deoxyribonuclease I (Aladdin, D406460) for 1 h to induce DNA cleavage.

#### 4.11 Apoptosis analysis

To monitor the Young's modulus of cell nucleus after drug treatment, the cells on the mirror were further cultured in medium supplemented with 10  $\mu\text{M}$  paclitaxel (Aladdin, P408076). Then, the nuclear Young's modulus was evaluated at various incubation time points.

#### 4.12 Calculation of cell spreading area

To quantify cell spreading area, the bright-field images of cells were segmented using the Cellpose algorithm (v4.0) with the pre-trained 'Cellpose-SAM' model. Subsequently, the resulting segmentation masks were used to calculate the spreading area of individual cells.

#### 4.13 Flow cytometry analysis

A549 cells were seeded in six-well plates and cultured in DMEM until reaching approximately 70% confluence. The cells were then treated with 10  $\mu\text{M}$  paclitaxel (Aladdin, P408076) for 0, 4, 8, and 12 h. Cells treated with an equivalent volume of PBS served as the negative control. After treatment, cells were collected and stained with an Annexin V-FITC apoptosis detection kit (Beyotime, C1062) for 15 min at room temperature in the dark. The stained samples were subsequently analyzed by flow cytometry (BD Biosciences, FACSymphony™ A5 SE).

#### 4.14 Analysis of the Young's modulus map

The Young's modulus map of cell nucleus was obtained through tracking dynamic variations in the nuclear transverse modes under ultrasound stimulation. The average Young's modulus was used to quantify the overall Young's modulus of the entire nucleus.

#### 4.15 Calculation of the spectral centroid

The spectra data acquired by the spectrometer consists of the wavelength array  $\Lambda = [\lambda_1, \lambda_2, \dots, \lambda_l]^T$  and the corresponding intensity array  $\Gamma = [a_1, a_2, \dots, a_l]^T$ .  $l$  is

sampling points in spectrum. First, the fluorescence background was subtracted to obtain laser emission  $\Gamma_{Laser} = \Gamma - \Gamma_{Fluor} = [b_1, b_2, \dots, b_l]^T$ .  $\Gamma_{Fluor}$  is the baseline of  $\Gamma$ , corresponding to the fluorescence emission. Then, a threshold was applied to  $\Gamma_{Laser}$  to eliminate the influence of high-frequency shot noise on the centroid calculation. After applying the threshold, the laser emission can be written as

$$\Gamma_{Laser}(j) = \begin{cases} b_j & (\Gamma_{Laser}(j) \geq I_{th}) \\ 0 & (\Gamma_{Laser}(j) < I_{th}) \end{cases} \quad (1)$$

Here,  $I_{th} = 0.05 \max\{b_1, b_2, \dots, b_l\}$  is the threshold intensity. Finally, the spectral centroid  $\lambda_c$  is derived as

$$\lambda_c = \frac{\sum_{j=1}^{l-1} (\lambda_j \Gamma_{Laser}(j) + \lambda_{j+1} \Gamma_{Laser}(j+1)) (\lambda_{j+1} - \lambda_j)}{\sum_{j=1}^{l-1} (\Gamma_{Laser}(j) + \Gamma_{Laser}(j+1)) (\lambda_{j+1} - \lambda_j)} \quad (2)$$

### Author contributions

C. G. and Z. L. conceived the idea. Z. L. and Z. C. performed the experiments and analyzed the data. G. L. and G. W. contributed to the numerical simulations. Y. Z., H. Z., and Y. L. provided guidance on the biological experiments. X. Y. and Y. G. contributed to the optical theoretical analysis and interpretation. Y. Z., H. Z., Y. L., C. G., and T. Z. provided scientific guidance and supervision. C. G. and Z. L. drafted the manuscript. All authors contributed to the interpretation of the results and finalized the manuscript.

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### Data availability

All data are available within the Article and Supplementary Files, or available from the

corresponding authors on reasonable request.

### Conflict of interest

All the authors declare no conflict of interest.

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