BIOELECTRONIC DEVICES

Palpating biopsy needles

A stiffness-sensing piezoelectric microsystem that can be mounted onto conventional biopsy needles distinguishes abnormal tissue from healthy tissue.

Pengfei Song and James F. Greenleaf

Biopsies play essential roles in cancer diagnosis and in the development of individualized cancer therapies. But they have low targeting accuracy, which can lead to the inadequate sampling of malignant cells and therefore high rates of false negatives and failed genomic analysis[1,2]. Also, complications involved with biopsy procedures such as bleeding, tumour seeding and patient discomfort make repeated biopsies undesirable and, in practice, unfeasible[3]. More accurate biopsy procedures are therefore needed in existing clinical cancer care and in the rapid development of personalized biomarker-driven treatments. Now, Yonggang Huang, Rahmi Oklu, John Rogers and colleagues report in *Nature Biomedical Engineering* a biopsy device based on a needle-shaped ultrathin piezoelectric microsystem that can sense the stiffness of surrounding tissues to guide tissue targeting during a biopsy[4]. Essentially, the researchers equipped a needle with a 'palpating finger' that can sense local tissue stiffness.

The needle-shaped microsystem can be injected or mounted directly onto conventional biopsy needles, and it can measure tissue modulus in real time, with a spatial resolution of 1 mm in length and width, and 1.5 mm in thickness. The researchers made two designs of the modulus-sensing probes (Fig. 1a,b): a free-standing device in the shape of a penetrating pin that can be directly injected into targeted soft tissues; and a device that can be placed on the tip of a biopsy needle to target tissues deep in the body. Both devices use a two-microcomponent set-up (constructed with the piezoelectric material lead zirconate titanate (PZT), which is commonly used in ultrasound transducers), with one microcomponent (the actuator) generating a mechanical strain that bends the needle substrate and deforms the surrounding tissue, and the other microcomponent (the sensor) detecting the tissue deformation through the inverse piezoelectric effect (proportionality of strain and applied field in the same direction). The amount of tissue deformation reflects the stiffness of the surrounding tissue, and could be directly measured via voltage readout from the sensor owing to a scaling law that associates tissue modulus with the detected sensor voltage for tissue moduli ranging from 1 kPa to 1 MPa. The monotonic relationship between tissue Young's modulus and sensor voltage readout was adjusted by varying the modulus of the needle substrate, its thickness, and the spacing between the actuator and the sensor.

Rogers and co-authors first showed that the modulus-sensing probe differentiated thin layers of agarose gel of varying stiffness. They then conducted both in vivo and ex vivo experiments to measure the stiffness of a variety of soft tissues. In an in vivo rat model, the probe showed consistent stiffness measurements of the liver, fat, spleen, lung and kidney. And ex vivo measurements of human lung, adrenal gland and kidney tissues, cirrhotic liver tissue, hepatocellular carcinoma (HCC) tissue and thyroid tissue showed that abnormal tissues had significantly higher modulus than normal tissues (Fig. 1c). The authors then focused on the application of the probe to sense HCC tissue, as there is a strong clinical need for improving the performance of biopsies in HCC (especially for small lesions[5]). An ex vivo human liver with cirrhosis and HCC was biopsied with the modulus-sensing needle probe, and imaged with magnetic resonance elastography (MRE) — a clinically available elasticity-imaging technique that can quantitatively measure tissue stiffness in the body by using shear waves generated from an acoustic driver coupled to the surface of the body. By measuring the propagation speed of the shear wave in the targeted tissue, the modulus of the tissue can be calculated[6]. The stiffness measurements of both cirrhotic liver tissue and HCC tumours from the probe (Fig. 1c), although displaying significant spatial variability (as expected from the known spatial variability of stiffness in tumours), were consistent and comparable to those from MRE and from the literature. Importantly, the amount of actuator-induced strain was small (<0.1%), the constituent materials of the probes showed no evidence of toxicity[7], and the probe constructs were encapsulated and shown to be impermeable to biofluids.

The use of the mechanical properties of tissues as biomarkers for detecting tissue pathology can be traced back to 400 BC, when Hippocrates noted in *The Book of Prognostics* that hard swellings were more dangerous than soft ones. Hippocrates also first described the art of palpation by noting that soft swellings "yield when pressed with finger". For millennia, palpation has been widely used to identify tissue malignancy. Interestingly, one strong motivation for the development of elastography, which is based on the same idea of non-invasively 'palpating' tissue stiffness[8], was to reduce and even replace biopsies. After over two decades of technical developments and clinical trials, elastography has found a niche in the staging of liver fibrosis, with MRE having the most reliable and robust clinical performance[9]. It has greatly reduced the need for a liver biopsy for fibrosis staging, and largely replaced follow-up biopsies for treatment evaluation[10].

However, in cancer, imaging elastography (including MRE and ultrasound-based elastography methods) is fundamentally challenged by the limited spatial resolution of the shear waves that can be generated inside the human body. For both MRE and ultrasound shear-wave elastography, shear-wave frequency in vivo is typically 50–200 Hz. To accurately measure lesion stiffness, the size of the lesion cannot be smaller than half of the wavelength of the interrogating shear wave. Therefore, even with a 200-Hz shear wave, the smallest lesion (assuming a 30-kPa modulus) that can be reliably measured is approximately 8 mm. Achieving the 1-mm resolution of the modulus-sensing needle probe would require a shear-wave frequency of approximately 1,600 Hz, which is extremely challenging to achieve in vivo. Even if future technical advances in elastography could reach spatial resolutions of 1 mm, elastography may never replace biopsies in the context of aetiology and genomic testing for cancer, fibrosis and other pathologies.

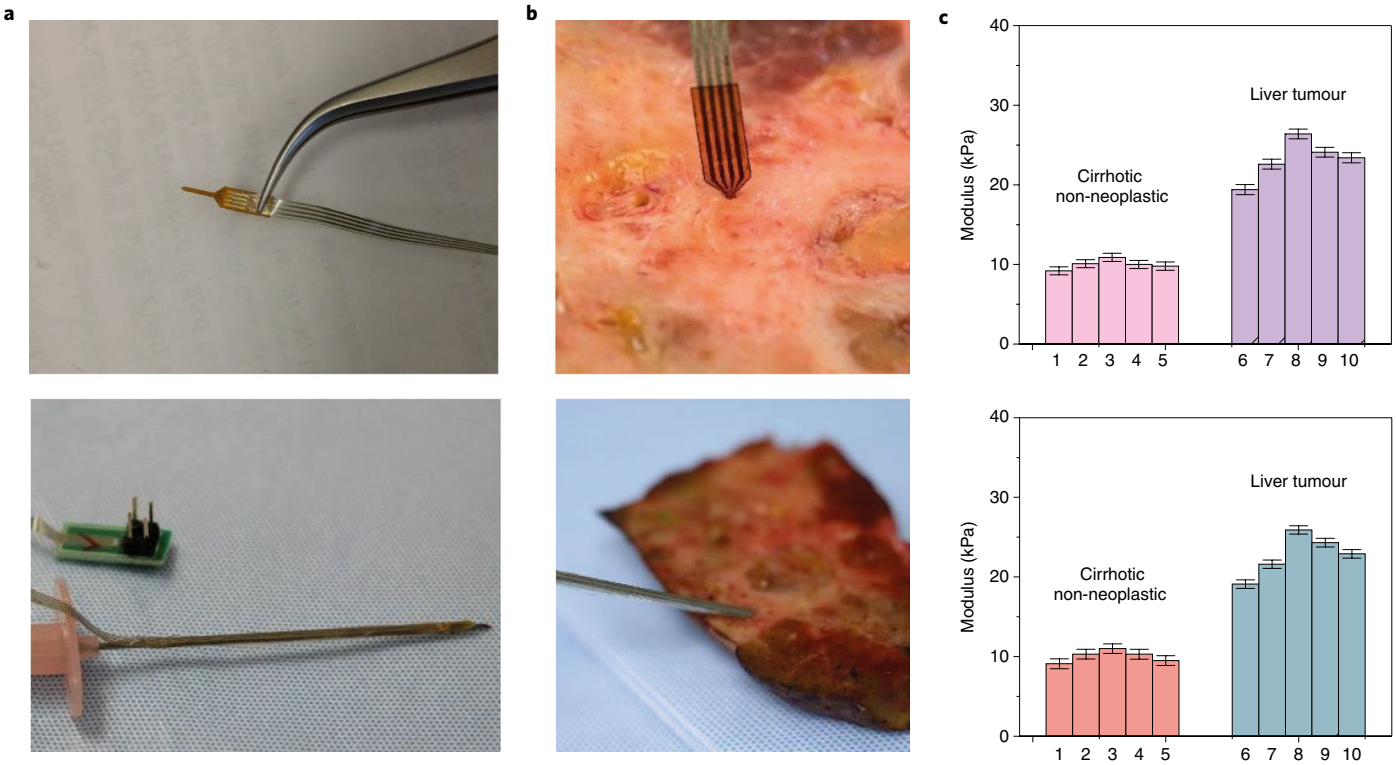

Fig. 1 | Modulus-sensing probes. a, Free-standing (top) and needle-based (bottom) versions of the probe. **b**, Biopsies (top, free-standing probe; bottom, needle-based probe) of ex vivo liver tumours. **c**, Young's modulus of cirrhotic liver tissue and liver tumour tissue at ten different tissue sites, measured by the free-standing (top) and needle-based (bottom) probes. Error bars, s.d. of ten measurements. Figure adapted from ref. [4], Macmillan Publishers Ltd.

Rogers and co-authors' modulus-sensing device synergistically combines elastography and biopsy to achieve capabilities that cannot be achieved by either method alone. In addition to the main application of improving biopsy for cancer, the device could be implanted in tumours to monitor treatment responses. It may also be mounted on a radio-frequency ablation-catheter tip to monitor tissue ablation. In addition to measuring elasticity, the device may be used to measure tissue viscosity, which is another sensitive biomarker for a variety of diseases, such as fibrosis and cancer. The device may also be used to perform creep-recovery mechanical testing by continuously deforming the tissue with increasing actuator voltages, followed by strain release, as well as to measure viscosity based on the time delay between the displacement profile at the actuator and the measured tissue-displacement profile at the sensor.

Clinical translation of the modulus-sensing probe may require the establishment of cut-off stiffness values for differentiating benign tissue from malignant tissue inside tumours as well as for the categorization of different cancer stages. The influence of tumour interstitial pressure on local tissue stiffness may need to be studied and accounted for when interpreting measurements from the probe. In practice, conventional imaging guidance such as computed tomography or ultrasound may still be necessary during a biopsy to guide the insertion of the needle into the targeted tissue; the stiffness-sensing needle can then help fine-tune the sampling location before extraction of the tissue sample. For clinical use, the modulus-sensing biopsy needle may need to be disposed of after each biopsy; therefore, unit costs will be an important factor. Nevertheless, the combination of stiffness measurements and tissue sampling in a biopsy needle that can be directed with high-resolution guidance should significantly decrease false-negative rates in tumour detection via biopsy (particularly the ~30% false-negative rates in the detection of liver nodules smaller than 2 cm). ❐

Pengfei Song[1] and James F. Greenleaf[2]
[1]*Department of Radiology, Mayo Clinic, Rochester, MN, USA.* [2]*Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA.*
e-mail: song.pengfei@mayo.edu; jfg@mayo.edu

Published online: 7 March 2018
https://doi.org/10.1038/s41551-018-0205-2

References

1. Sherman, C. B., Zhao, W., Corley, D. A. & Guy, J. *Gastroenterology* **142**, S-927–S-928 (2012).
2. Saggese, M., Dua, D., Simmons, E., Lemech, C. & Arkenau, H.-T. *Oncol. Rev.* **7**, e5 (2013).
3. Shyamala, K., Girish, H. C. & Murgod, S. *J. Int. Soc. Prev. Community Dent.* **4**, 5–11 (2014).
4. Yu, X. et al. *Nat. Biomed. Eng.* https://doi.org/10.1038/s41551-018-0201-6 (2018).
5. Forner, A. et al. *Hepatology* **47**, 97–104 (2008).
6. Muthupillai, R. et al. *Science* **269**, 1854–1857 (1995).
7. Dagdeviren, C. et al. *Nat. Mater.* **14**, 728–736 (2015).
8. Ophir, J., Cespedes, I., Ponnekanti, H., Yazdi, Y. & Li, X. *Ultrason. Imaging* **13**, 111–134 (1991).
9. Yin, M. & Venkatesh, S. K. *Abdom. Radiol.* https://doi.org/10.1007/s00261-017-1340-z (2017).
10. Tapper, E. B. & Lok, A. S.-F. *N. Engl. J. Med.* **377**, 756–768 (2017).