

## Supporting Information

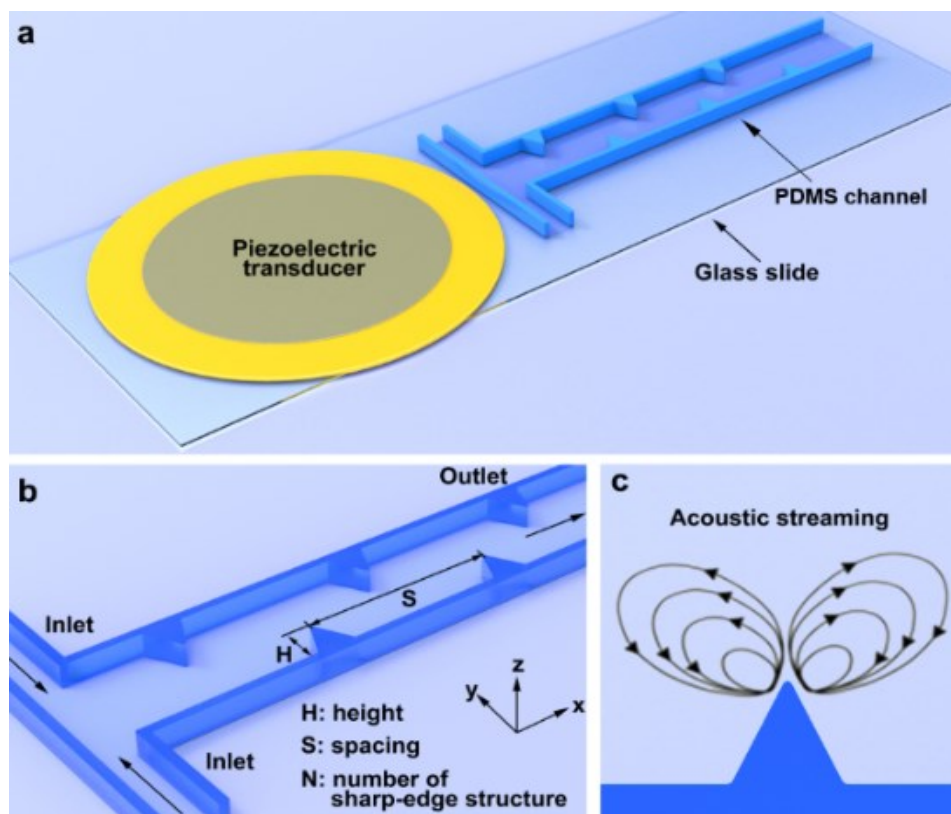
### **Fabrication of tunable, high-molecular-weight polymeric nanoparticles via ultrafast acoustofluidic micromixing**

*Shuaiguo Zhao,<sup>a</sup> Po-Hsun Huang,<sup>a</sup> Heying Zhang,<sup>a</sup> Joseph Rich,<sup>b</sup> Hunter Bachman,<sup>a</sup> Jennifer Ye,<sup>a</sup> Wenfen Zhang,<sup>a</sup> Chuyi Chen,<sup>a</sup> Zhemiao Xie,<sup>a</sup> Zhenhua Tian,<sup>a</sup> Putong Kang,<sup>a</sup> Hai Fu,<sup>a</sup> and Tony Jun Huang<sup>a\*</sup>*

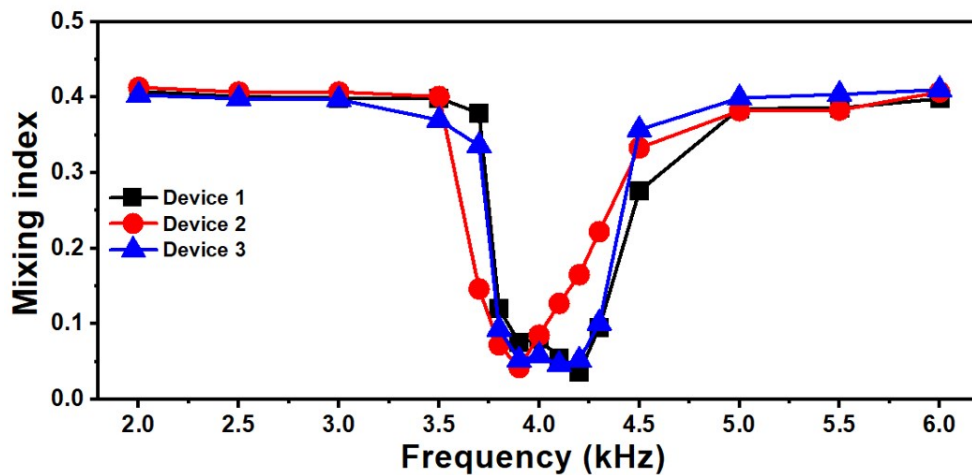
<sup>a</sup>Thomas Lord Department of Mechanical Engineering and Materials Science, Duke University, Durham, NC 27708, USA

<sup>b</sup>Department of Biomedical Engineering, Duke University, Durham, NC 27708, USA

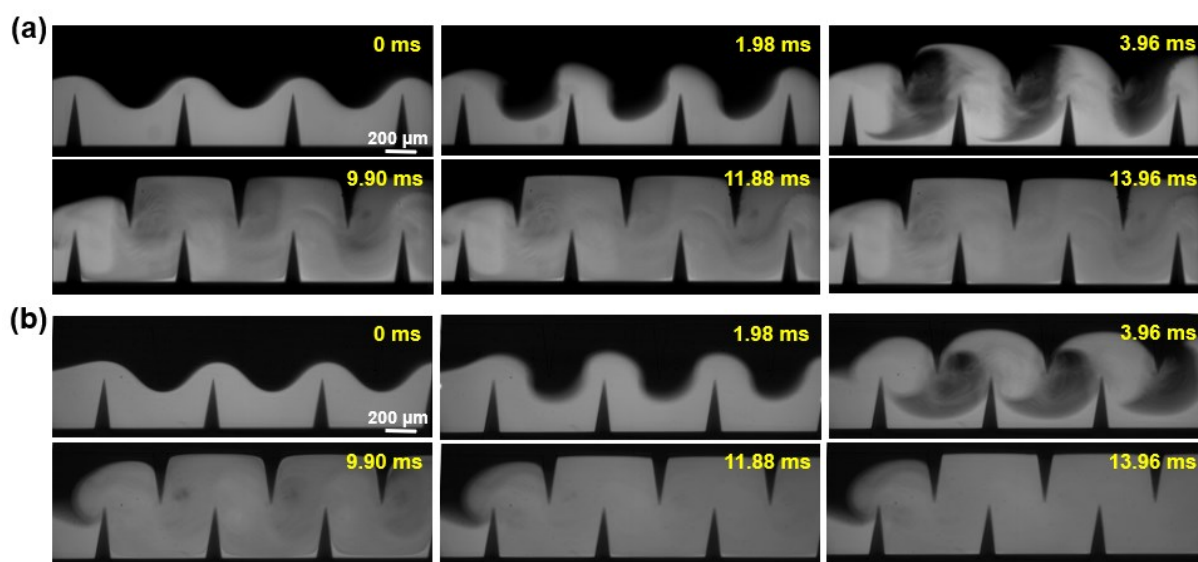
\*Correspondence authors Tel.: 1-919-6845728; E-mail addresses: tony.huang@duke.edu



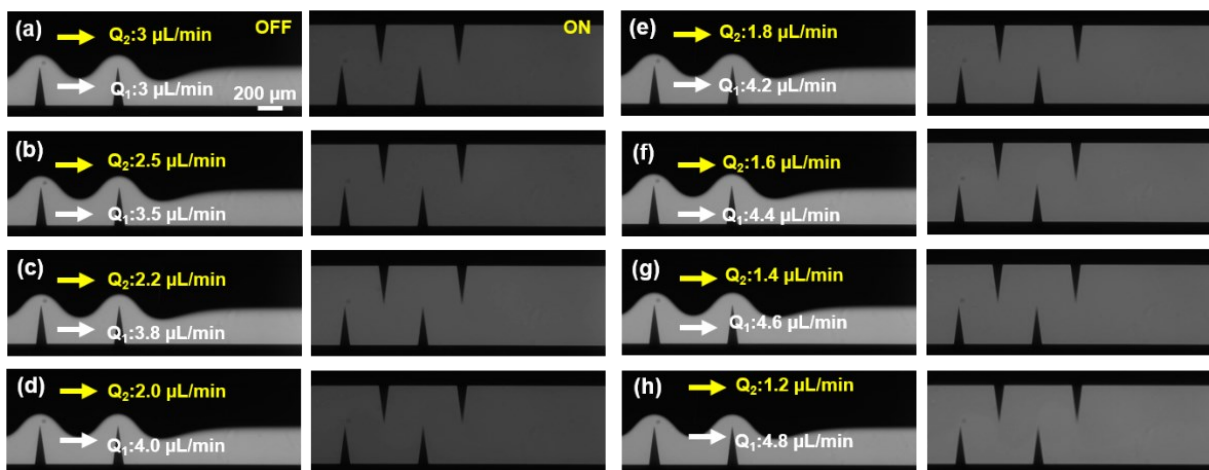
**Figure S1.** Schematic showing (a) the component configuration, (b) sharp-edge structure, and (c) acoustic micro-streaming of acoustofluidic synthesis device. In (b), the sharp-edge structure depends on sharp-edge height (H), spacing (S), and number of pairs (N). Each microchannel designed with different sharp-edge structures is therefore denoted as  $H \times S \times N$ .



**Figure S2.** Plots of mixing indexes versus driving frequency at a driving voltage of 25 V<sub>pp</sub> and a total flow rate of 30  $\mu$ L/min. The device tested has a sharp-edge structure of 300 $\times$ 600 $\times$ 12, a glass thickness of 170-250  $\mu$ m, and a PDMS thickness of 4 mm. Data represents three independent devices.



**Figure S3.** The mixing process of DI water and fluorescence dye under the driving voltage of 50 VPP characterized using a fast camera (Photron, 500K-M1) at different total flow rates: (a) 150  $\mu\text{L}/\text{min}$  and (b) 90  $\mu\text{L}/\text{min}$ . The flow rate ratio of DI water and fluorescence dye is maintained at 1. At the time scale of 0 ms, a clear interface of laminar flow was observed. By increasing the mixing time, the acoustic streaming effect perturbs the interface and enhances the mass transport, leading to slight mixing around the sharp-edge tips (3.96 ms). Acceptable mixing was achieved at the time scale of 11.88 ms for 150  $\mu\text{L}/\text{min}$  and less than 9.90 ms for 90  $\mu\text{L}/\text{min}$ . These results demonstrate that our acoustofluidic device is strong enough to complete ultrafast reagent mixing at the time scale of 10 ms.



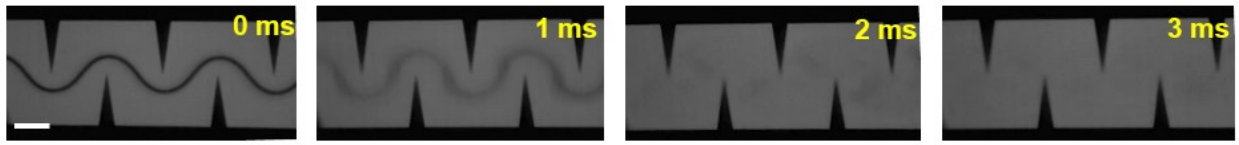
**Figure S4.** Characterization of the mixing performance of DI water-PEGDA700 mixture solutions at different concentrations and dynamic viscosities: (a) 50 vol.% and 18.3 mPa.s, (b) 63 vol.% and 24.5 mPa.s, (c) 67 vol.% and 34.2 mPa.s, (d) 71 vol.% and 41.7 mPa.s, (e) 77 vol.% and 48.8 mPa.s, (f) 83 vol.% and 65.3 mPa.s, (g) 90 vol.% and 77.3 mPa.s, and (h) 100 vol.% and 95.9 mPa.s. The total flow rate for all measurements is fixed at 6  $\mu\text{L}/\text{min}$ . However, due to the difference in viscosity between fluorescent water and viscous PEGDA solution with varying concentration, the ratio of flow rate was changed accordingly to ensure the interface of laminar flow at the middle of the microchannel.



**Figure S5.** Microchannel images showing the macroscopic nanoprecipitation evolution of PLGA<sub>10K</sub>-PEG<sub>5K</sub> at 10 mg/mL by a 2D HFF device. With increasing time from 1 to 6 min, the device always worked well without polymer aggregation. This result demonstrates that hydrophilic PEG can effectively prevent polymer aggregation. Scale bar: 200  $\mu$ m.

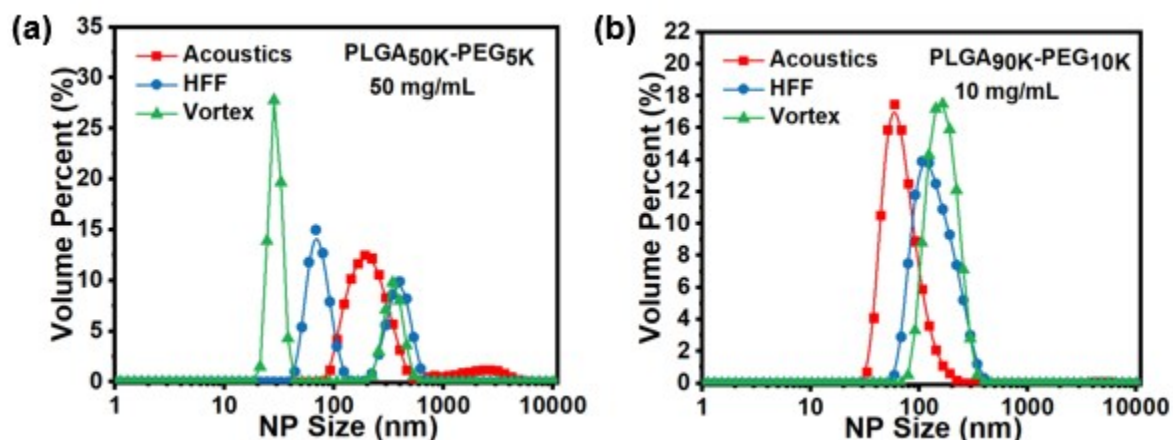


**Figure S6.** Microchannel images showing the polymer aggregation for PLGA<sub>50K</sub>-PEG<sub>5K</sub> at 90 mg/mL at 30 s operation. Scale bar: 200  $\mu$ m.



**Figure S7.** Characterization for the mixing time of water and PLGA<sub>50K</sub>-PEG<sub>5K</sub> at 30 mg/mL. Scale bar: 200  $\mu\text{m}$ .





**Figure S8.** Size distributions for nanoparticles yielded by 2D HFF, bulk vertexing method, and the acoustofluidic device from (a) PLGA<sub>50K</sub>-PEG<sub>5K</sub> at 50 mg/mL and (b) PLGA<sub>90K</sub>-PEG<sub>10K</sub> at 10 mg/mL. The results in (a) show that the failure of bulk and 2D HFF method to generate nanoparticles.

**Table S1** Comparison between our previous work on nanoparticle synthesis and this work.

Features	Our previous acoustofluidic micromixers <sup>1</sup>	This work
Ability to synthesize nanoparticles from high molecular weight polymers (>45 kDa)	No	Yes
Ability to perform multi-step ( $\geq 2$ ) sequential nanoprecipitation	No	Yes
Demonstration of uniform core-shell nanoparticles	No	Yes

## Reference

[1] P. H. Huang, S. Zhao, H. Bachman, N. Nama, Z. Li, C. Chen, S. Yang, M. Wu, S. P. Zhang and T. J. Huang, *Adv. Sci.*, 2019, **6**, 1900913.