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Perra, Emanuele; Hayward, Nick; Pritzker, Kenneth P.H.; Nieminen, Heikki J. **An ultrasonically actuated fine-needle creates cavitation in bovine liver** 

Published in: Journal of the Acoustical Society of America

*DOI:* 10.1121/10.0010534

Published: 01/06/2022

Document Version Publisher's PDF, also known as Version of record

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Please cite the original version:

Perra, E., Hayward, N., Pritzker, K. P. H., & Nieminen, H. J. (2022). An ultrasonically actuated fine-needle creates cavitation in bovine liver. *Journal of the Acoustical Society of America*, *151*(6), 3690-3702. https://doi.org/10.1121/10.0010534

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## An ultrasonically actuated fine-needle creates cavitation in bovine liver

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Citation: The Journal of the Acoustical Society of America **151**, 3690 (2022); doi: 10.1121/10.0010534 View online: https://doi.org/10.1121/10.0010534 View Table of Contents: https://asa.scitation.org/toc/jas/151/6 Published by the Acoustical Society of America

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# An ultrasonically actuated fine-needle creates cavitation in bovine liver

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## **ABSTRACT:**

Ultrasonic cavitation is being used in medical applications as a way to influence matter, such as tissue or drug vehicles, on a micro-scale. Oscillating or collapsing cavitation bubbles provide transient mechanical force fields, which can, e.g., fractionate soft tissue or even disintegrate solid objects, such as calculi. Our recent study demonstrates that an ultrasonically actuated medical needle can create cavitation phenomena inside water. However, the presence and behavior of cavitation and related bioeffects in diagnostic and therapeutic applications with ultrasonically actuated needles are not known. Using simulations, we demonstrate numerically and experimentally the cavitation phenomena near ultrasonically actuated needles. We define the cavitation onset within a liver tissue model with different total acoustic power levels. We directly visualize and quantitatively characterize cavitation events generated by the ultrasonic needle in thin fresh bovine liver sections enabled by high-speed imaging. On a qualitative basis, the numerical and experimental results show a close resemblance in threshold and spatial distribution of cavitation. These findings are crucial for developing new methods and technologies employing ultrasonically actuated fine needles, such as ultrasound-enhanced fine-needle biopsy, drug delivery, and histotripsy.

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(Received 24 March 2022; accepted 26 April 2022; published online 2 June 2022)

[Editor: Keith A. Wear]

Pages: 3690-3702

#### I. INTRODUCTION

In recent years, ultrasonic cavitation has emerged in various medical applications as a way to influence matter noninvasively. Cavitation is a phenomenon that can be described as the interaction between small spherical gas bubbles and pressure perturbations taking place in a medium. When the peak rarefactional pressure amplitude (PRPA) of an ultrasound field is low enough, gas bubbles can undergo stable oscillations about their equilibrium radius, which is usually referred to as stable cavitation.<sup>1</sup> However, at elevated PRPAs, if certain threshold conditions are met,<sup>2</sup> gas bubbles can collapse, giving rise to transient cavitation.<sup>3</sup> The collapse of a cavitation bubble may generate different nonlinear acoustic phenomena in the surrounding medium, such as generation of rapid liquid microjets, acoustic emission in the form of shock waves and formation of high stress fields. These physical effects have been widely investigated and employed in different medical applications with the intent to, e.g., ablate tumors,<sup>4</sup> fractionate calculi<sup>5</sup> or tissue,<sup>6</sup> and enhance the permeability of cells for drug delivery applications.

In our recent study, we have demonstrated that cavitation events can be generated in water by an ultrasonically actuated medical needle.<sup>8</sup> Moreover, it has been shown that at  $\sim 30 \text{ kHz}$ , ultrasound-enhanced fine-needle aspiration biopsy (USeFNAB) enhances the yield of a biopsy by  $3-5\times$ in liver compared to when a fine-needle aspiration biopsy (FNAB) procedure is conducted using a similar needle. These results suggested that the nonlinear acoustic phenomena generated at the needle tip, including cavitation, might play an important role in the tissue cutting mechanism in the context of biopsy applications and beyond. However, the potential presence of cavitation and related bioeffects in diagnostic and therapeutic applications with ultrasonically actuated needles require a more thorough understanding.

Actuation of medical needles by ultrasound is not a new concept, and a number of studies related to the topic can be found in the literature.<sup>9–13</sup> However, the applications have been limited to improve the needle visibility in ultrasound-guided regional anaesthesia and tissue biopsy<sup>9–11</sup> or to reduce the penetration force of a standard needle.<sup>12,13</sup> So far, no research seems to have been conducted on studying the potential generation of nonlinear acoustic phenomena and their interaction with soft tissue.

In this study, we aim at studying the influence of cavitation on soft tissue under the action of an ultrasonically actuated needle. Numerical modeling is first used to simulate the time-dependent acoustic field generated by the ultrasonic needle and the cavitation bubble dynamics in a liver tissue model. The numerical results provided fundamental understanding of

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the cavitation nucleation threshold, spatial distribution, maximum size of the cavitation bubbles, and their influence on the tissue, according to a cavitation–tissue interaction model proposed by Mancia *et al.*<sup>14</sup> Experimentally, we developed a method to visualize cavitation bubbles in thin portions of fresh liver tissue, involving high-speed (HS) imaging using light transmission. Such understanding is crucial for optimising the safety and efficacy of clinical interventional procedures, including many for diagnostics and cancer treatments.<sup>15</sup>

#### **II. METHODS**

#### A. Numerical simulation

The computational software COMSOL Multiphysics  $v5.5^{16}$  was used to solve the different equations governing the cavitation bubble dynamics taking place in soft tissue. We assumed a scenario where a 21 G × 80 mm hypodermic needle is used, since it represents a common medical needle normally employed in FNAB applications. The needle was partially placed into a 10 mm × 12 mm cylinder representing a liver tissue sample and actuated at the ultrasonic frequency of 33 kHz and total acoustic power (TAP) of 0.2, 0.5, and 0.8 W. Ultrasonic flexural standing waves were enabled in the needle shaft *via* an ultrasonic device with similar geometry and material properties to the one employed in the actual experiments (Fig. 1).

The displacement of the needle was calculated in the frequency domain by solving the equation of motion within the ultrasonic device ("Solid Mechanics" module) when a positive potential difference is applied between the faces of the piezoelectric rings. The structural velocity of the portion of the needle immersed into the sample domain was used as a boundary condition for the calculation of the pressure field within the sample ("Pressure Acoustics, Frequency Domain" module), whose outer boundaries were assumed to be perfectly absorbing. The sets of equations describing the needle motion and the radiated pressure field were solved in the frequency domain (f = 33 kHz) in a fully coupled approach by using the multifrontal massively parallel sparse direct solver (MUMPS).

The threshold for enabling cavitation events was first investigated. In the simulation, a single cavitation nucleus of initial size varying from 1 to 1000 nm (1, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 nm), surrounded by liver tissue, was subjected to acoustic forcing pressure amplitudes varying from 1 to 10 MPa (step size = 100 kPa), while the cavitation bubble dynamics was modeled by adopting the Keller-Miksis equation<sup>17</sup> [Eq. (3)]. An inertial cavitation event is assumed to take place when the radius R of a cavitation nucleus becomes as large as  $2R_0$ .<sup>18</sup> In a separate simulation study, the Keller-Miksis equation was then solved in the liver domain as a system of point ordinary differential equations (ODEs), by having the surroundings of the needle seeded with cavitation nuclei periodically spaced by  $50 \,\mu m$ . For simplicity, initial radii of 200, 500, and 800 nm were selected to exemplify the dependence of the cavitation phenomena and the initial bubble radius, when the needle was made to vibrate at the frequency of (f = 33 kHz) inside the

#### Experimental setup



FIG. 1. (a) and (b) Schematics representing the experimental setup. (c) A custom-made glass sample holder was used as housing for a thin liver tissue slice. (d) and (e) The ultrasonic needle was made to oscillate sideways along the *xz*-plane inside the sample in the direction of the positive *x*-axis, while the generated cavitation events are recorded with an HS camera using a collimated beam of light to produce back-lit shadowgraph footage.

liver model. The acoustic forcing pressure  $p_f$  is given by the pressure field calculated in a separate study step; hence, the bubble motion was assumed not to contribute to the total pressure field. For simplicity, inter-bubble interactions and shock wave formation were neglected. The equation describing the bubble dynamics was solved in the time domain in a fully coupled approach by using the parallel direct solver (PARDISO). The chosen time stepping algorithm was the generalized alpha method, in which the used time step resolution was set to be automatic.

The three-dimensional (3D) model was meshed with free tetrahedral elements, considering at least 20 nodes per



Properties	Values	References
Ultrasound frequency, f	33 kHz	
Speed of sound, $c_{\infty}$	1575 m/s	Ref. 53
Density, $\rho_{\infty}$	$1060  \text{kg/m}^3$	Ref. 54
Attenuation coefficient, $\alpha$	1.39 dB/m	Ref. 53
Ambient pressure, $p_{\infty}$	101.325 kPa	Ref. 14
Polytropic index, $\kappa$	1	Ref. 24
Surface tension, S	56 mN	Ref. 55
Viscosity, $\mu$	30 mPa s	Ref. 55
Shear modulus, G	1.8 kPa	Ref. 56
Initial bubble radius, $R_0$	1-1000 nm	Ref. 57

wavelength, which was considered an appropriate number for minimizing the local approximation errors.<sup>19</sup> A detailed list of the model parameters is given in Table I.

#### 1. Acoustic wave propagation in tissue

The acoustic wave propagation in soft tissue was modeled by adopting the linear acoustic wave equation for viscous fluids:<sup>20</sup>

$$\nabla^2 p - \frac{1}{c_\infty^2} \frac{\partial^2 p}{\partial t^2} + \frac{\delta}{\rho_\infty c^2} \frac{\partial}{\partial t} \nabla^2 p = 0, \tag{1}$$

where p is the pressure, and  $c_{\infty}$  and  $\rho_{\infty}$  are the speed of sound and the density of the medium, respectively. The term  $\delta$  is the sound diffusivity, which accounts for viscous losses in a viscous fluid, and it is defined as<sup>21,22</sup>

$$\delta = \frac{2c_{\infty}^3 \alpha}{\omega^2},\tag{2}$$

where  $\omega$  is the angular frequency, and  $\alpha$  (1/m) is the acoustic absorption coefficient.

#### 2. Cavitation model

The Keller–Miksis equation was used to describe the bubble dynamics in soft tissue:

$$\left(1 - \frac{\dot{R}}{c_{\infty}}\right) R\ddot{R} + \frac{3}{2} \left(1 - \frac{\dot{R}}{3c_{\infty}}\right) \dot{R}^{2}$$

$$= \frac{1}{\rho_{\infty}} \left(1 + \frac{\dot{R}}{c_{\infty}} + \frac{R}{c_{\infty}} \frac{d}{dt}\right) \left[p_{B} - (p_{\infty} + p_{f}(t)) - \frac{2S}{R} + J\right].$$

$$(3)$$

In Eq. (3), *R*,  $\dot{R}$  and  $\ddot{R}$ , denote the radial displacement, velocity, and acceleration of the cavitation bubble wall, respectively, and the constants  $c_{\infty}$  and  $\rho_{\infty}$  denote the speed of sound and the density of the medium. The driving pressure is expressed by  $p_f(t)$ , while the pressure at the air–liquid interface of the bubble is defined as<sup>18</sup>

$$p_B = p_0 \left(\frac{R_0}{R}\right)^{3\kappa},\tag{4}$$

where  $R_0$  is the bubble radius at rest and  $\kappa$  is the polytropic exponent. The term  $p_0$  represents the internal pressure of the bubble when the bubble is at equilibrium, expressed as

$$p_0 = p_\infty + 2\frac{S}{R_0},\tag{5}$$

where  $p_{\infty}$  indicates the ambient pressure and *S* the surface tension of the bubble. Equation (3) is combined with the Kelvin–Voigt model,<sup>23</sup> which leads the integral of the deviatoric stress *J*, accounting for the viscoelastic behaviour of soft tissue with isotropic properties, to be expressed as follows:<sup>24</sup>

$$J = 2 \int_{R}^{\infty} \frac{\tau_{rr} - \tau_{\theta\theta}}{r} dr = \frac{-4\mu \dot{R}}{R} - \frac{G}{2} \left[ 5 - 4 \left( \frac{R_0}{R} \right) - \left( \frac{R_0}{R} \right)^4 \right],$$
(6)

where  $\mu$  is the tissue viscosity and *G* is the tissue shear modulus. The terms  $\tau_{rr}$  and  $\tau_{\theta\theta}$  represent the radial and tangential stresses, respectively, due to the bubble deformation. They are related as follows:

$$\tau_{rr} = -4\mu \frac{R^2 \dot{R}}{r^3} + 2G \left[ \left( \frac{r_0}{r} \right)^4 - \left( \frac{r}{r_0} \right)^2 \right] = -2\tau_{\theta\theta},$$
(7)

where *r* is the radial coordinate and  $r_0 = \sqrt[3]{r^3} - R^3 - R_0^3$ relates the coordinate *r* to its initial position in the undeformed configuration of the surrounding tissue. The strain field in the surrounding tissue is defined as<sup>14</sup>

$$E_{rr} = -2\ln\left(\frac{r}{r_0}\right) = -2E_{\theta\theta},\tag{8}$$

 $E_{rr}$  and  $E_{\theta\theta}$  being the radial and tangential strain, respectively.

The model for cavitation–tissue interaction proposed by Mancia *et al.*<sup>24</sup> was adopted to estimate the amount of tissue volume influenced by the cavitation activity. Specifically, this is evaluated by identifying the regions where the von Mises strain [Eq. (9)] exceeds the ultimate fractional strain measured for liver (0.38  $\mu$ m/ $\mu$ m),<sup>25</sup>

$$E_{mises} = \sqrt{\frac{2}{3} \left[ E_{rr}^2 + 2 + \left( -\frac{1}{2} E_{rr} \right)^2 \right]} = |E_{rr}|.$$
(9)

#### B. Experiments with ex vivo tissue

#### 1. Experimental arrangement

A custom-built ultrasonic device<sup>8</sup> was used to excite a flexural vibration mode (f = 33 kHz) in a 21 G hypodermic needle (length = 80 mm) (model: 4 66 54 65 100 Sterican, B



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Braun, Melsungen, Germany) [Fig. 1(a)]. The needle was coupled to an S-shaped 3D-printed aluminum waveguide (3D Step Oy, Ylöjärvi, Finland) that acts as a mode converter, translating the longitudinal motion provided by the Langevin transducer into a flexural motion of the needle [Fig. 1(b)]. The flexural mode was selected as operating resonant mode since it is able to provide large lateral displacements at the needle tip [Fig. 2(a)], which we have found in a previous experimental study to be optimal for generating cavitation in water or to enhance the yield of a biopsy sample.<sup>8</sup> The operating frequency was chosen based on the electrical impedance measurement of the needle, which showed a main resonance frequency of 33 kHz Fig. [2(b)]. The ultrasonic device was driven by an RF amplifier (model: AG 1012LF, Amplifier/ Generator, T&C Power Conversion, Inc., Rochester, NY) controlled by a function generator (model: Analog Discovery 2, Digilent, Inc., Henley Court Pullman, WA). The spatial coordinates of the needle were controlled by using a motorized three-axis translation stage (model: 8MT50-100BS1-XYZ, Motorized Translation Stage, Standa, Vilnius, Lithuania). The cavitation events induced by the needle action were filmed in liver tissue using a HS camera (model: Phantom V1612, Vision Research, Wayne, NJ) in combination with a macro lens (model: Canon MP-E 65 mm f/2.8 1-5x Macro Photo, Canon Inc., Ōta, Tokyo, Japan). A collimated beam of light (model: OSL2COL, Collimation Package for OSL2IR, Thorlabs, Inc., Newton, NJ), generated by a halogen fiber optic illuminator (model: OSL2IR, High-Intensity Fiber-Coupled Illuminator, Thorlabs, Inc., Newton, NJ), was used to produce back-lit shadowgraph footages of the needle actuation inside tissue.

#### Device characterization

a. Needle flexural mode (33 kHz, numerical)







FIG. 2. (a) Cross section of the 3D COMSOL model showing the simulated displacement field (deformation scale factor = 1000) of the ultrasonic device at the frequency of 33 kHz. The color code represents the magnitude of the displacement normalized by the global maximum. At this frequency, a flexural eigenmode is induced in the needle structure, resulting in the needle tip being displaced the most. (b) The impedance curve of the needle, which was measured when the needle was embedded in air, exhibits a resonance peak at 33 kHz, which was adopted in the simulations.

#### 2. Sample preparation

The liver specimen (from a 26-month-old female cow) was retrieved from the slaughterhouse (Vainion Teurastamo Oy, Orimattila, Finland) within 2 h post mortem and experiments were performed within 6h post mortem at room temperature (22 °C-24 °C). The specimen was first rinsed with  $1 \times \text{phosphate-buffered saline (PBS) (BP399-4, Phosphate)}$ Buffered Saline, 10× Solution, Fisher BioReagents, Fisher Scientific, Hampton, NH) to wash away any excess of blood from its surface. Thin slices, approximately 1 mm thick, were carefully extracted from the specimen by using a pair of microtome blades (12101840 Epredia Ultra Disposable Microtome Blades, Epredia, Portsmouth, NH) fixed to a spacing of 1 mm from each other. The liver slices were further washed in  $1 \times PBS$ , cut into  $2 \text{ cm} \times 1 \text{ cm}$  portions and inserted into a custom-made glass sample holder [Fig. 1(c)]. The sample holder was created by cutting a  $2 \text{ cm} \times 1 \text{ cm}$  portion of glass from the upper part of a  $51 \text{ mm} \times 75 \text{ mm}$  microscope slide (J1800BMNZ, Epredia SuperFrost Plus Adhesion slides, Special Size, Epredia, Portsmouth, NH), which was placed between two intact microscope slides, in order to form a pocket for the tissue sample [Figs. 1(c) and 1(d)].

#### 3. High-speed recordings of cavitation

Since the penetration depth  $\delta$  of light into bovine liver is estimated to be, for example, 1.44 mm for a wavelength of 635 nm,<sup>26</sup> the thickness of the sample and the light source spectrum were considered appropriate to ensure a good visibility of the needle inside tissue during the HS recordings. During the experiments, the needle was first carefully inserted into the specimen at a depth of 5 mm and penetration speed of 50  $\mu$ m/s. Ultrasound waves [33 kHz, pulse repetition frequency (PRF) = 55 Hz, duty cycle (DC) = 50\%) at three different TAP levels [0.2 W (n=5), 0.5 W (n=5) and 0.8 W(n = 5)] were then applied to the device, while the needle movement inside tissue was recorded with the following settings: sample rate =  $130\,000$  fps, exposure = 7.1  $\mu$ s, resolution = 256 pixels  $\times$  256 pixels, lens aperture = 2.8, spatial resolution = 5.5  $\mu$ m/pixel. The sample number n = 5 represents the technical replicates per each group and was chosen to both demonstrate the repeatability of the studied phenomenon and to minimize the experimental time window to 1 h, which mitigated the potential bias from the post mortem degeneration of the sample.

#### 4. Hydrophone measurements

The acoustic emission arising from cavitation activity generated in bulk tissue was recorded with an Aquarian hydrophone (AS-1 Hydrophone, Aquarian Audio & Scientific, Anacortes, WA). Experiments were conducted by having the needle inserted 5 mm into a 1 cm  $\times$  1 cm  $\times$  1 cm portion of fresh bovine liver tissue (from an 18-month-old female cow), and finalized within 6 h *post mortem*. The specimen was kept inside an acrylic chamber (external dimensions = L  $\times$  W  $\times$  H = 250 mm  $\times$  250 mm  $\times$  250 mm, wall thickness = 4 mm) filled with 1  $\times$  PBS (BP399–4, PBS,



 $10 \times$  Solution, Fisher BioReagents, Fisher Scientific, Hampton, NH). The hydrophone was immersed into the solution and placed on the outer surface of the sample 5 mm away from the needle tip, with the probe pointing towards the needle tip location and direction parallel to the needle vibration (x-axis). The walls of the chamber were covered with sound absorbing material. This helped to minimize the reflections from the surrounding walls, which could potentially contribute to standing wave or shock wave formation. Ultrasound waves [33 kHz, pulse repetition frequency (PRF) = 55 Hz, duty cycle (DC) = 50%] were applied to the needle at three different TAP levels [0.2 W (n=5), 0.5 W](n=5) and 0.8 W (n=5)]. The pressure signals were acquired and stored with a digital oscilloscope (DSO-X 3014 T, Keysight Technologies, Santa Rosa, CA), which was set to display 18 ms of the signal, corresponding to 1 pulse duration. The fast Fourier transform (FFT) was then calculated for the recorded signal with the built-in function of the oscilloscope (number of averages = 100 pulses).

#### 5. Data analysis

The HS frames were analysed in MATLAB (R2020b)<sup>27</sup> to quantify the projected area of cavitation and the needle displacement using a similar method presented in our recent publication<sup>8</sup> (Fig. 3). A cross correlation–based image registration was performed along the *x*-axis between the reference frame  $I_1$  and the i-th frame  $I_i$ , in order to estimate the needle displacement  $\Delta x_i$  from its reference position. The image  $I_1$ was then rigidly translated by  $\Delta x_i$  and thresholded with the Otsu method,<sup>28</sup> while an Otsu thresholding followed by a morphological closing operation (circular structuring element, diameter = 7 pixels) was applied to the image  $I_i$ . The segmented image  $I_{cav,i}$  showing only the cavitation activity is obtained by subtracting the binarized reference image  $I_{bw,1}$ from the closed image  $I_{bw,i}$ . Since the needle shape in  $I_{bw,1}$  opening operation (circular structuring element, diameter = 3 pixels) was applied to the output  $I_{cav,i}$  in order remove any pixels that may have remained after the subtraction operation and that are not representative of the cavitation activity.

Probability maps [Eq. (10)], showing the probability of cavitation manifesting around the needle tip, and projected areas of cavitation activity over time [Eq. (11)] were finally calculated as follows:

$$P_{cav} = \frac{100}{N} \sum_{i=1}^{N} I_{cav,i},$$
 (10)

$$A_{cav,i} = \iint I_{cav,i} dx dy, \tag{11}$$

where  $N = 25\,000$  is the total number of frames.

Velocity maps, shear, and strain rate maps were generated using the PIVlab toolbox.<sup>29</sup>

An index describing the intensity of cavitation activity inside liver was estimated by analysing the hydrophone signals in MATLAB (R2020b). The method is similar to that reported previously,<sup>30,31</sup> and consists of calculating the root mean square (RMS) of the signal amplitude spectrum across a frequency window of 26 kHz between the third and the fourth harmonics. The RMS amplitude of the baseline, which was determined as the FFT of the signal when no ultrasound was employed, was then subtracted from the calculated RMS amplitudes. This method gives an estimation of broadband noise level, which is an indicator of the presence of inertial cavitation.<sup>31,32</sup>

#### **III. RESULTS**

#### A. Simulation of cavitation in liver

Since the actual size distribution of cavitation nuclei in bovine liver in our experimental arrangement is not known,



FIG. 3. General description of the segmentation process of the HS video frames. A cross correlation–based image registration is applied along the *x*-axis between (a) the reference frame and the (b) i-th frame, in order to estimate the displacement  $\Delta x_i$  of the needle tip from its reference position. (c) The reference frame is then translated horizontally by  $\Delta x_i$ , while (d) the input frame is thresholded with the Otsu method. (e) The binary image showing the translated reference frame is subtracted to (f) the thresholded input frame, which was previously closed with a morphological closing operation. (g) The result of the subtraction is finally filtered with a morphological opening operation, in order to produce (h) the binary mask for the cavitation activity.



the pressure threshold of cavitation of a single bubble embedded in liver tissue and its maximum radius expansion were first investigated numerically for a range of initial bubble radii between 1 and 1000 nm [Fig. 4(a).1]. Nuclei as small as 1 nm require a peak negative pressure (PNP) greater than 5 MPa in order to expand beyond their critical radius, defined as  $2R_0$ ,<sup>18</sup> where  $R_0$  is the initial size of a cavitation nucleus. The pressure threshold drastically drops to 800 kPa for bubbles greater than 400 nm. Bubbles undergoing inertial cavitation can reach dimensions as large as 80, 155, and 165  $\mu$ m, when the PNP is 900 kPa for  $R_0$ =200, 500, and 800 nm, respectively [Fig. 4(a).2].

In order to investigate the spatial occurrence and the extent of cavitation activity, the space around the needle tip was seeded with cavitation nuclei ( $R_0 = 200$ , 500, or 800 nm), which were subjected to the pressure field generated by the ultrasonically actuated needle [Fig. 4(a).3]. Based on the simulations, the ultrasonic action of the needle-induced expansion of bubbles in the proximity of the needle tip, when the needle was driven by ultrasonic waves at the frequency of 33 kHz and TAP levels of 0.2, 0.5, and 0.8 W. At TAP = 0.2 W, no inertial cavitation was detected.

At TAP = 0.5 W bubbles with initial radius of 500 and 800 nm experienced a transient expansion, while at the highest power employed, all cavitation nuclei (200, 500, and 800 nm) went through an inertial cavitation event.

The cavitation activity generated in the proximity of the needle tip can mechanically influence the surrounding tissue, due to high deformation induced on the tissue at the air-tissue interface. The volume of tissue influenced by cavitation activity can be calculated by identifying the regions where the von Mises strain exceeds the ultimate fractional strain measured for liver ( $E_{mis} > 0.38$ ). The volume of influenced tissue was negligible at low TAP (0.2 W), suggesting that no important deformations were induced in the surrounding tissue for any of the initial sizes of the cavitation nuclei considered in the simulation [Fig. 4(b)]. However, higher strains can be generated in tissue at higher TAP levels due to the elevated cavitation bubble activity, leading to an increase in the influenced volume of tissue by cavitation up to 1.8, 3.2, and 3.5 mm<sup>3</sup> after two acoustic cycles at TAP = 0.8 W for  $R_0 = 200$ , 500, and 800 nm, respectively.

In an effort to better understand the simulation results, Fig. 5(a) represents the pressure field generated around the flexurally oscillating needle tip, evaluated on a cross section



FIG. 4. (a1) Amplitude of the driving pressure required to expand a bubble with an initial size of  $R_0$  beyond its critical radius  $2R_0$ , assuming the bubble is embedded in liver tissue. The solid line corresponds to the numerical estimation of the cavitation threshold, while the dashed line corresponds to the analytical prediction given by the Blake's pressure. (a2) Maximum bubble deformation as a function of the initial bubble size  $R_0$  and the driving pressure. (a3) Simulation of cavitation around the tip of an ultrasonic hypodermic needle embedded in liver tissue, where the selected time points represent fractions of an acoustic cycle of duration T = 1/f. The surrounding medium is seeded with three exemplary cavitation nuclei sizes ( $R_0 = 200, 500$ , and 800 nm) and the needle is actuated at TAP levels of 0.2, 0.3, and 0.8 W at the frequency of 33 kHz. These numerical results suggest that cavitation takes place around the needle tip. Moreover, the cavitation threshold is inversely proportional to the size of the cavitation nuclei, while the maximum bubble expansion is directly proportional to the amplitude of the driving pressure and to the initial bubble radius. (b) The amount of tissue volume influenced by cavitation activity is suggest that cavitation events are triggered at TAP > 0.2 W, with bubbles having a more likely influence on tissue at higher TAP levels than at lower TAP levels.



parallel to the *xz*-plane and coincident with the needle center axis, and on a cross section parallel to the *xy*-plane evaluated at z = -1.5 mm. The magnitude of the acoustic field induced by the oscillating needle can be as high as 900 kPa close to the needle boundary, when the power level of 0.8 W is employed. The pressure field emanates outwards from the needle walls in a dipole-like fashion, being the strongest along the direction of the needle motion [Fig. 5(a)].

The spatial likelihood of generating cavitation around the needle tip is presented through probability maps, where each pixel indicated the probability of belonging to a cavitation bubble [Fig. 5(b)]. A cavitation event is assumed to occur when the radius *R* of a cavitation nucleus becomes as large as  $2R_0$ .<sup>18</sup> According to this criterion, no cavitation activity was detected at TAP = 0.2 W for any of the considered initial bubble sizes. At TAP = 0.5 W, slight cavitation activity can be observed for nuclei with  $R_0 = 200$  nm, while greater cavitation activity can be seen for nuclei with initial radii of 500 and 800 nm. At TAP = 0.8 W, the probability of cavitation occurrence became greatest, being up to 40% when the initial bubble radius was 800 nm.

#### B. Observation of cavitation events in ex vivo liver

Thin slices of liver tissue were sonicated at different TAP levels [0.2 W (n=5), 0.5 W (n=5) and 0.8 W (n=5)]with the ultrasonically actuated needle. Figure 6(a) shows some exemplary frames acquired with the HS camera, when a halogen fiber optic light source was used to produce shadowgraph images of the needle movement inside tissue. When the delivered TAP was 0.2 W, no cavitation activity was detected. At the TAP level of 0.5 W, the needle motion induced the formation of cavitation bubbles, which mostly took place at the distal end of the needle. However, when the delivered TAP was increased to 0.8 W, multiple cavitation bubbles can be noticed along the needle tip, extending to a few hundreds of  $\mu m$  from the needle boundaries along the directions parallel to the needle motion. Figure 6(b)shows the cavitation probability maps calculated across the entire duration of the HS footages, which suggest that no cavitation events were observed at the lowest TAP 0.2 W employed. By increasing the TAP, the probability of seeing cavitation bubbles was up to 10% in the region within  $100 \,\mu\text{m}$  from the needle tip along the positive x-axis and  $300 \,\mu\text{m}$  along the negative z-axis, while this region became considerably greater in area and uniformly distributed around the needle tip, when the highest TAP of 0.8 W was employed.

Figure 7(b) represents the time evolution of the needle tip peak displacement, obtained by computing the moving maximum of the raw data and using a window with a size of approximately two acoustic cycles (60  $\mu$ s). In all experiments, the peak displacement reached its maximum value within the first pulse, being ~9, 45, and 100  $\mu$ m at the TAP levels of 0.2, 0.5, and 0.8 W, respectively. Figure 7(c) shows the projected area of the cavitation activity (filtered with a moving average, window size ~10 acoustic cycles) as a



FIG. 5. (a) Simulation of the absolute pressure field radiated from the needle boundary, visualized on a cross section of the needle geometry coincident with its plane of symmetry (*xz*-plane), and on a cross section parallel to the *xy*-plane evaluated at z = -1.5 mm (red dashed line). The pressure field emanates outwards from the needle walls in a dipole-like fashion, whose magnitude can be as high as 900 kPa close to the needle boundary, when the highest power level (0.8 W) is employed. (b) The probability maps show the probability of a pixel representing a cavitation bubble, when TAP levels of 0.2, 0.3, and 0.8 W are delivered to the needle and when considering cavitation nuclei of sizes  $R_0 = 200$ , 500, and 800 nm. These results would indicate that cavitation takes place in the proximity of the needle tip, and it is strongly dependent on the initial bubble size and on the magnitude of the radiated pressure field.

function of time. It can be noted that no cavitation activity was present at 0.2 W, while some activity was detected at 0.5 W, and, at 0.8 W, the measured cavitation activity was relatively elevated.

Measurements of needle displacement and cavitation activity exhibited high repeatability within the same power groups, as shown in Fig. 7(d). In the first pulse, the needle tip peak displacements were  $9.5 \pm 6.4 \,\mu\text{m}$  (average  $\pm$  standard deviation, n = 5),  $34.3 \pm 1.0 \,\mu\text{m}$ , and  $61.6 \pm 1.9 \,\mu\text{m}$ , when the employed TAP levels were 0.2, 0.5, and 0.8 W, respectively. The needle tip peak displacement stabilised within 3 pulses, reaching the values of  $10.8 \pm 8.5 \,\mu m$  (0.2 W),  $41.5 \pm 1.4 \,\mu m$  (0.5 W), and  $91.9 \pm 2.3 \,\mu\text{m}$  (0.8 W) after 10 pulses. Figure 7(e) shows the time integral of cavitation activity calculated for each individual pulse. In all experiments, no cavitation activity was recorded for TAP = 0.2 W, while it slowly built up over time at TAP = 0.5 W, being  $0.014 \pm 0.002 \text{ mm}^2 \text{ ms}$  after the first pulse and reaching the value of  $0.055 \pm 0.002 \text{ mm}^2 \text{ ms}$  during the 10th pulse. At the highest TAP employed, the cavitation level observed during the first pulse was  $0.177 \pm 0.060 \,\mathrm{mm^2 ms}$ and reached its maximum intensity in the last pulse





(a) Observation of cavitation events in liver  $a.1 \quad 0.2W \qquad a.2 \quad 0.5W \qquad a.3 \quad 0.8W$ 

FIG. 6. (a) Exemplary HS video frames showing cavitation events taking place at the needle tip at three different TAP levels. (b) The probability maps, which show the probability of each pixel belonging to a cavitation bubble, demonstrate that no cavitation activity is recorded at 0.2 W, while it is more frequent at higher TAP levels. These results show how cavitation can be generated on-demand and in a localized manner near the needle tip.

(0.386  $\pm$  0.016 mm<sup>2</sup> ms). Overall, the temporally local peak displacement of the needle tip measured for each TAP level were 11.3  $\pm$  6.8  $\mu$ m, 44.4  $\pm$  1.5  $\mu$ m, and 97.2  $\pm$  1.8  $\mu$ m, which led to total cavitation activity values of ~0  $\pm$  0 mm<sup>2</sup> ms, 0.459  $\pm$  0.032 mm<sup>2</sup> ms, and 3.44  $\pm$  0.078 mm<sup>2</sup> ms for TAP = 0.2, 0.5, and 0.8 W, respectively.

Velocity maps were generated out of two consecutive frames of the HS videos in order to estimate the velocity field of the tissue at the moment of a cavitation bubble collapse. Figure 8(a) shows the velocity vector field distribution overlapped to a HS frame showing a cavitation event, when the highest TAP is employed. The velocities are the highest at the very tip of the needle, being approximately 3 m/s in this region [Fig. 8(b)]. Importantly, according to the simulation, the velocity of the tissue–air interface can be remarkably greater, i.e., up to 100 m/s. However, the limited frame rate adopted during the recordings (130 000 fps) did not permit capture of the very moment of the cavitation collapse, which resulted in underestimation of its maximum velocity. Figure 8(c) shows the shear rate distribution around the needle, being the highest in magnitude  $(20 \text{ ms}^{-1})$  at the proximity of the cavitation bubble boundary. This is reasonable since the cavitation bubble deformation is known to exert considerably high shears and stresses in the surrounding medium.<sup>24,33</sup> In Fig. 8(d), the strain rates assume negative values, which denote a compression state, on the left hand side of the needle and positive values in the proximity of the cavitation bubble. The needle movement is in the direction of the negative *x*axis, which causes the adjacent portion of tissue to be compressed on the left-hand side of the needle, and to be stretched on the right-hand side.

# C. Passive detection of cavitation activity in *ex vivo* liver

In order to quantify the cavitation activity inside bulk tissue, hydrophone measurements were performed, when the needle was inserted into small portions of liver tissue (dimensions:  $1 \text{ cm} \times 1 \text{ cm} \times 1 \text{ cm}$ ) and sonicated at TAP = 0.2 W (n = 5), 0.5 W (n = 5), and 0.8 W (n = 5).Figure 9(a) shows the amplitude spectrum of the pressure signals, recorded by having the hydrophone placed 5 mm away from the needle tip. At low power (0.2 W), the amplitude spectrum of the pressure signal exhibits 4 peaks located at the fundamental frequency of the needle vibration  $(\sim 33 \text{ kHz})$ , and at its 2nd, 3rd, and 4th harmonics. At 0.5 W sub- and ultra-harmonics can be observed, suggesting the presence of stable cavitation. Slight broadband noise can be noticed, hinting the presence of inertial cavitation.<sup>32</sup> At the highest power employed (0.8 W), pronounced broadband noise can be observed, and the harmonic components of the pressure field become less noticeable, indicating that moderate inertial cavitation activity is predominant at this power level.<sup>31</sup> The measured peak-peak pressure amplitudes recorded with the hydrophone, evaluated across a 200 ms time window, were  $15.0 \pm 1.6$  kPa,  $71.8 \pm 5.3$  kPa, and  $144.9 \pm 5.4$  kPa, and at TAP = 0.2, 0.5, and 0.8 W, respectively [Figs. 9(b) and 9(c)]. Figure 9(d) shows the cavitation activity index, normalized by the maximum value identified across all 3 power groups, being  $0.02 \pm 0.08$ ,  $0.22 \pm 0.06$ , and  $0.97 \pm 0.02$  for TAP = 0.2, 0.5, and 0.8 W, respectively.

#### **IV. DISCUSSION**

The results indicate that cavitation events can be triggered by actuating a standard medical needle with ultrasonic flexural waves in liver tissue at the frequency of 33 kHz. The numerical results suggested that the cavitation activity mostly took place at the needle tip, which was optically confirmed with HS photography. This is explained by the flexural vibration mode induced in the needle, which makes the needle oscillate with its highest displacements at its tip, thus enabling higher pressure amplitudes in this region. Since cavitation is a strictly related threshold phenomenon, cavitation events are most likely to appear at the needle tip location, where most of the acoustic intensity is concentrated. Moreover, due to the geometric spreading of the acoustic

https://doi.org/10.1121/10.0010534





FIG. 7. Representation of relevant parameters calculated based on the analysis of HS images of the needle activity. (a) Ultrasonic sequence adopted during the experiments [f=33 kHz, pulse repetition frequency (PRF)=55 Hz, duty cycle (DC)=50%]. (b) Time evolution of the needle-tip displacements, obtained by computing the moving maximum of the raw HS images (window size ~ 2 acoustic cycles), and (c) projected area of the cavitation activity (filtered with moving average, window size ~10 acoustic cycles). (d) and (e) represent the peak-tip displacement and time integral of cavitation activity calculated for each individual pulse of the ultrasonic sequence, while (f) represents the same information evaluated across a time window of 180 ms. In the bar charts, the bar height represents the mean of the dataset and the error bar indicates the standard deviation.

wavefront, directed outwards from the needle shaft, the acoustic intensity decays rapidly further away from the needle; hence, limiting the cavitation effects to the proximity of the needle tip.

The experimental results showed that the probability of triggering cavitation events in soft tissue is a function of TAP, suggesting the existence of a threshold (0.2 W < TAP < 0.5 W) for enabling cavitation, when a standard medical needle is actuated in soft tissue. Based on the simulation results, this threshold is a function of the initial cavitation bubble radius, e.g., being 500, 250, and 200 kPa for the initial radii of 200, 500, and 800 nm, respectively. Assuming an initial size of the cavitation nuclei in the range between 1 nm and 1000 nm, the natural frequency  $f_n$  of such bubbles would fall within the MHz range.<sup>34</sup> Since the excitation frequency  $f_0 = 33 \text{ kHz}$  used in this study is far below the resonant

frequency  $f_n$  of the bubbles, the cavitation threshold criterion is governed by the Blake's pressure,<sup>34</sup> which determines the critical negative pressure below which a cavitation event will occur:

$$P_B = P_{\infty} + \frac{8\sigma}{9} \sqrt{\frac{3\sigma}{2R_B^3(P_{\infty} + (2\sigma/R_B))}},\tag{12}$$

where  $P_B$  is the Blake pressure,  $\sigma$  is the surface tension, and  $R_B$  is the Blake bubble radius. Under these assumptions, the Blake thresholds for bubbles of, e.g.,  $R_0 = 200,500$ , and 800 nm are 600, 250, and 150 kPa, which show a close resemblance with the numerical predictions.

According to the numerical estimations, the maximum pressure amplitudes involved in the experiments are  $\sim 100$ ,



FIG. 8. (a) Velocity vector field distribution overlapped to an exemplary HS frame showing a cavitation event and (b) the velocity magnitude map, when the highest TAP (0.8 W) is employed. (c) and (d) show the shear and strain rate distribution in the tissue surrounding the needle tip.

600, and 900 kPa for TAP = 0.2, 0.5, and 0.8 W. As a consequence, only bubbles with an initial radius greater than 200 nm underwent inertial cavitation when the highest TAP (0.8 W) was employed. However, as reported in previous experimental and numerical studies,<sup>14,24,35</sup> the estimated size of cavitation nuclei inside liver tissue is approximately 5 nm. The Blake's pressure for bubbles of such size  $(\sim 18 \text{ MPa})$  exceeds by far the pressures generated by the ultrasonic needle used in this study. Hence, cavitation would be very unlikely to take place with our current experimental arrangement for such small bubbles. However, since cavitation activity was directly observed under HS imaging when the needle actuated inside tissue, we could estimate that the size of the cavitation nuclei involved in the experiment would fall in the range of hundreds of nm, according to our numerical simulation. A possible explanation of the presence of such large nuclei might be found in the needletissue interaction, which can cause the formation of crevices at the needle-tissue boundary generated by the needle insertion, constituting potential locations for nucleation sites to grow into. This can represent an advantage for applications aiming at, e.g., tissue disruption by collapsing bubbles, as it provides a lower threshold to enable cavitation in the vicinity of the ultrasonically actuated needle.

The interpretation of the results here presented is of fundamental importance in the context of different medical



FIG. 9. (a) Frequency spectrum of the pressure signals acquired with a hydrophone, while the needle was actuated in a small portion of tissue at TAP = 0.2, 0.5, and 0.8 W. At 0.2 W, only the peaks corresponding to the harmonics of the pressure field can be noticed, while at 0.5 W sub- and ultraharmonics can be detected. At 0.8 W, an increase in the broadband noise can be also observed, which is an indicator of the presence of inertial cavitation. (b) Represents the time dependent pressure signals recorded at different power levels when the hydrophone was placed 5 mm away from the needle tip, while (c) shows the peak–peak pressure amplitude of the signals evaluated across a time window of 180 ms, and (d) shows a metric describing the cavitation activity as a function of TAP (values are normalized by the maximum value identified across all three power groups). In the bar charts, the bar height represents the mean of the dataset and the error bar indicates the standard deviation.

https://doi.org/10.1121/10.0010534



applications. In our recent study, the influence of the ultrasonic action of a medical needle was exemplified in liver tissue by comparing the yield mass collected with the USeFNAB technique to the one obtained with the conventional FNAB approach. The major finding was that, by increasing the TAP level, the yield of a liver biopsy was increased up to  $5 \times$  as compared to when a standard FNA was performed, without inducing major alterations to the sample quality up to a TAP of 0.8 W. More importantly, a TAP of 0.2 W was enough to increase the biopsy yield by almost  $2\times$ . Based on the findings of the present study, it seems that this TAP level is unlikely to generate detectable cavitation events in liver. This indicates that the tissue yield increase observed at this TAP can be in part associated with the tissue cutting mechanisms arising from shear and hydrodynamic effects promoted by the ultrasonic vibration of the needle tip, rather than being induced by cavitation. However, higher TAP levels allowed us to obtain even larger tissue sample masses<sup>8</sup> as well as more frequent cavitation activity. Although a clear correlation between the cavitation activity and the tissue yield is yet to be proven, these observations do not exclude the possibility for cavitation to be contributing to the enhancement of tissue collection. In fact, the high strain rates generated in the proximity of the gas-tissue interface<sup>24,33</sup> can potentially induce different viscoelastic mechanical responses (namely stiffening, softening, hardening, and tissue failure observed in porcine liver under high strain rate compression testings<sup>36</sup>) that might facilitate the tissue cutting mechanisms that yield an increase in sample extraction.

Regarding the safety aspects of the biopsy application in relation to the potential cavitation-induced effects in tissue, one should consider the mechanical index  $MI = P_r/P_r$  $\sqrt{f_c}$ , where  $P_r$  is the peak negative pressure (MPa), and  $f_c$  is the excitation frequency (MHz). According to our simulations, when the employed TAP is 0.2 W, the MI is approximately 0.4, which would ensure a cavitation-free biopsy procedure, since cavitation is unlikely to take place at MI <  $0.5.^{37}$  At 0.5 W, the MI is approximately 2.7, which will most likely induce the formation of cavitation bubbles; this might impact on the safety, as at MI values greater than 1.9, potential bioeffects might be induced in the tissue.<sup>38</sup> These bioeffects may include cell lysis and extravasation of blood.<sup>39–41</sup> The highest TAP employed should be avoided for biopsy applications, as the high MI value (4.9) suggests that bioeffects and tissue damage due to the bubble collapses are likely to appear.

If uncontrolled, cavitation events can lead to deleterious effects in soft tissue. However, this could be turned into a therapeutic advantage if one aims to treat unhealthy tissue, such as tumors. At high levels (TAP > 0.8 W), the needle vibration is anticipated to cause the formation of large clouds of cavitation bubbles and elevated tissue heating, which may arise from the viscous friction forces that can appear at the bubble surface. These effects can be used in medical applications, such as tumor ablation,<sup>42</sup> histotripsy, or lithotripsy,<sup>43</sup> where the medical intent is to achieve a

complete or partial destruction of the target by mechanical and thermal means. Since a fine hypodermic needle is employed to bring the acoustic energy directly into the target, one may be able to easily access different locations inside the body to provide minimally invasive treatment of solid organ cancers of the prostate,<sup>44</sup> thyroid,<sup>45</sup> and pancreas,<sup>46</sup> and other lesions, too.<sup>47</sup> In addition, the cavitation phenomena generated with this technology could potentially find use in other applications as a way to ultrasonically activate sonosensitive carriers for the release of drugs,<sup>48–50</sup> mediate drug or gene delivery into cells,<sup>51</sup> or to improve the permeation of tissue allowing the entry of therapeutic agents (e.g., as with ultrasonically mediated blood–brain barrier opening).<sup>52</sup>

The limitations of this study include the inability to replicate a numerical model representative of the real-world scenario. The equations adopted in the simulations are highly parameter-dependent, and since some of the viscoelastic and acoustic properties of tissue are largely unknown, some assumptions had to be made, for example, on the tissue viscosity, surface tension, and initial radius of cavitation nuclei. The interaction between individual bubbles and thermal effects, likely to be more pronounced at TAP levels, were neglected for simplicity, since the intention was to understand the onset behavior of cavitation rather than the behavior of the full cavitation cloud. Moreover, the use of thin portions of liver tissue might not allow one to reveal all the cavitation bubble dynamics that would normally take place in bulk tissue during needle sonication, or to replicate the same acoustic and mechanical conditions as in an USeFNAB procedure. However, such an approach was necessary to visualize the needle and cavitation activity inside tissue

Nevertheless, the presented results offer an understanding of the cavitation phenomena in liver tissue near the ultrasonically actuated medical needle. Such findings could serve as a starting point for designing and developing an ultrasonic biopsy device in compliance with the safety standards for clinical applications, and for exploring its potential in other medical applications involving pathological destruction of tissue.

#### **V. CONCLUSION**

To conclude, we have studied numerically the dynamics of cavitation bubbles generated in liver tissue near the tip of an ultrasonically actuated needle. Experimentally, we have developed a method to capture and quantify the cavitation activity within thin slices of fresh bovine liver. The main finding was that cavitation exhibited a TAP dependent behavior, manifesting at TAP > 0.2 W and with intensity proportional to the TAP level. Based on a qualitative comparison, the numerical and the experimental results presented similarities concerning the cavitation threshold and the spatial probability of cavitation occurrence around the needle tip. The results are important since they broaden the understanding of the onset and spatiotemporal behavior of https://doi.org/10.1121/10.0010534

cavitation near ultrasonically actuated medical needles. This is especially relevant for ensuring appropriate safety in clinical scenarios, but also for employing the information in the development of USeFNAB and other new applications of ultrasonically actuated medical needles.

#### ACKNOWLEDGMENTS

JASA

We thank all members of the Medical Ultrasonics Laboratory (MEDUSA) at Aalto University and Professor Edward Hæggström at the University of Helsinki for correspondence related to the topic. Professor Tapio Lokki and the Aalto Acoustics Lab are also acknowledged for providing the necessary equipment used in the experiments. The Academy of Finland is acknowledged for financial support (Grant Nos. 314286, 311586, and 335799). E.P. produced all data and conducted the data analyses.

#### **CONFLICT OF INTEREST**

H.J.N. and K.P.H.P. have stock ownership in Swan Cytologics Inc., Toronto, ON, Canada and are inventors within the patent application WO2018000102A1. H.J.N. is also an inventor within the patent application WO2020240084A1. E.P. and N.H. do not have any competing interests in relation to this work.

#### CODE AVAILABILITY

The codes are available upon request.

#### DATA AVAILABILITY

The datasets are available upon request.

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