# Design of HIFU transducers to generate specific nonlinear ultrasound fields

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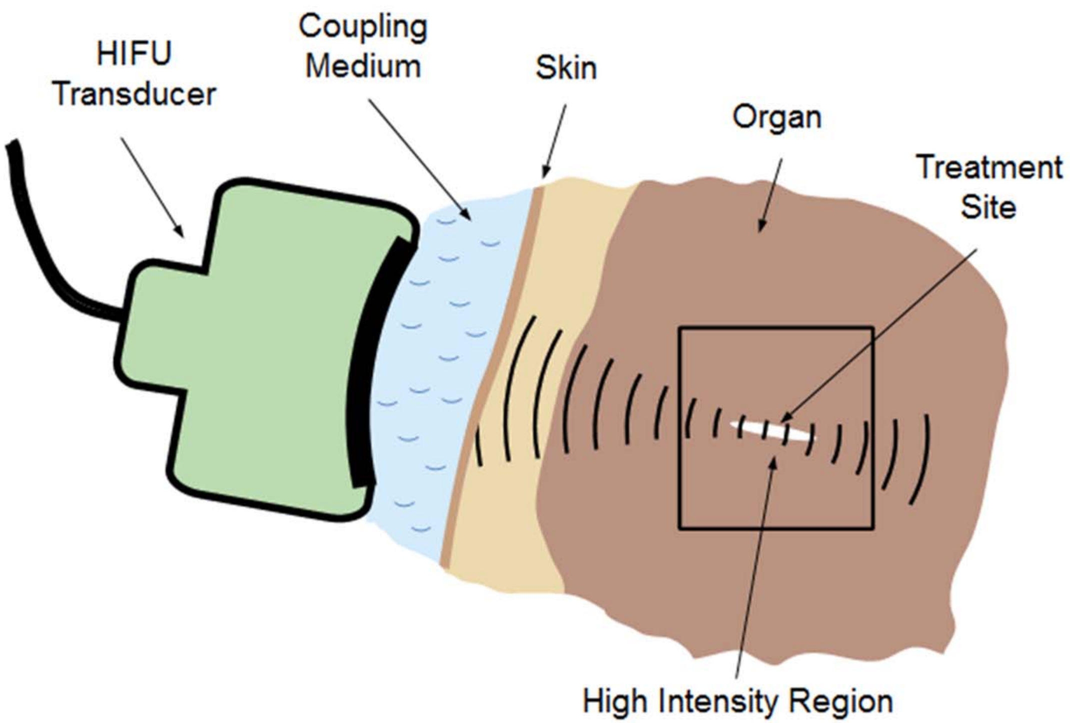
# Outline

- **Introduction and motivation**
  *- nonlinear effects in therapeutic ultrasound fields*
- **Hypothesis and theoretical models**
  *- KZK equation, equivalent source model, Westervelt equation*
- **Solving inverse problem**
  *- multi-parametric solution to the KZK equation
  for focused ultrasound beams*
- **Results**
  *- determine transducer F-number, aperture, and initial intensity
  to achieve certain pressures and degree of nonlinear effects at the focus*
- **Example of HIFU array design**
- **Conclusions**

# Therapeutic applications of ultrasound




**High Intensity Focused Ultrasound**
**= nonlinear acoustic fields**

## HIFU surgery:

**frequency**
0.7 – 4 MHz, up to 20 MHz

***Intensity in situ :***
500 – 30 000 W/см$^2$

## Major bioeffects in HIFU

**thermal**: tissue heating due to absorption of ultrasound energy

**thermal dose for necrosis:**
120-240 min at 43ºC
1 s at 56ºC, 0.1 s at 59ºC

**mechanical**: cavitation
shear stresses
???

# Motivation:

## Some HIFU applications

- rely on the presence of shock fronts and their specific amplitudes at the focus
- are designed to avoid nonlinear effects and shocks
- rely on maximized peak negative pressure preferably without shocks

**How to optimize transducer parameters to control the degree of nonlinear effects at the focus?**

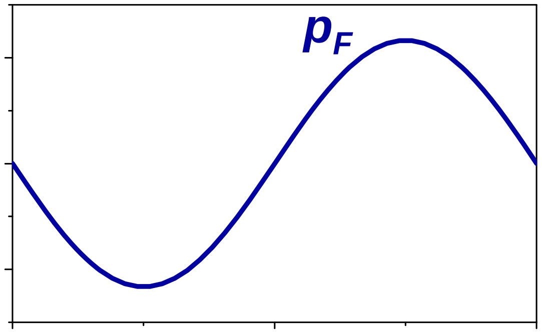
# Nonlinear effects in HIFU

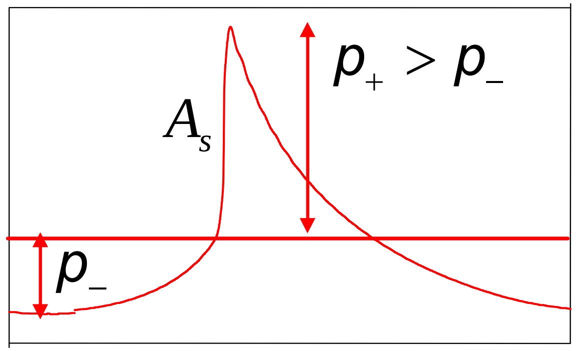
**Linear acoustics**

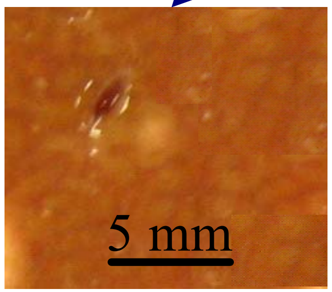
- focal pressure amplitude ($p_F$)
- broader focal zone

**Nonlinear acoustics**

- peak positive and negative pressures ($p_+ > p_-$)
- shock amplitude ($A_s$)
- narrower focal zone, enhanced heat deposition

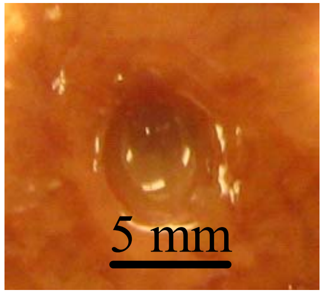


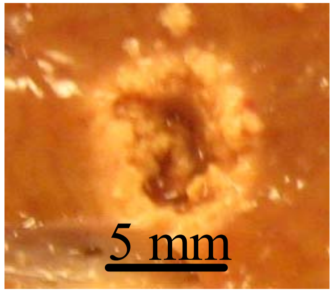




**Different effects in tissue:**

thermal coagulation
boiling
emulsification
shear stresses
immune response
release of biomarkers



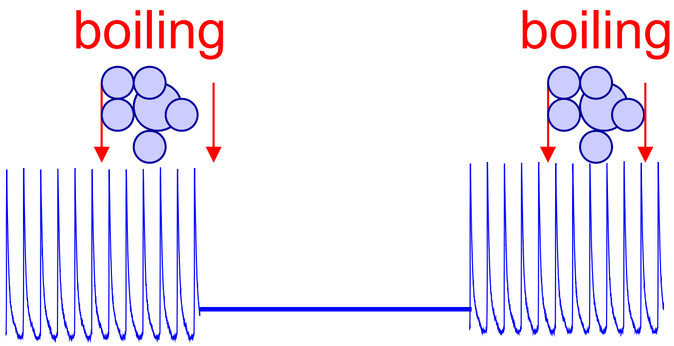



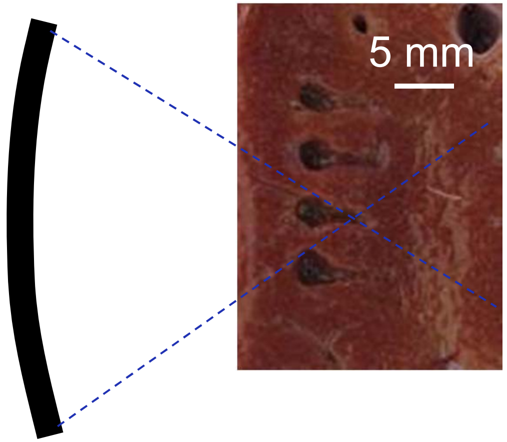

**Nonlinear effects and resulting shocks are important in HIFU**
**as they result in enhanced heating and additional nonthermal bioeffects**

# Example: boiling histotripsy (BH) method in HIFU

**Mechanical tissue disintegration into subcellular debris**

**Pulsing protocol:**
1 – 3 MHz, 10 – 20 ms pulses with shocks,
0.01 duty cycle, vapor bubble within each pulse




Single liquefied lesion
in *ex-vivo* bovine heart

Khokhlova T. *et al.*, JASA 2011

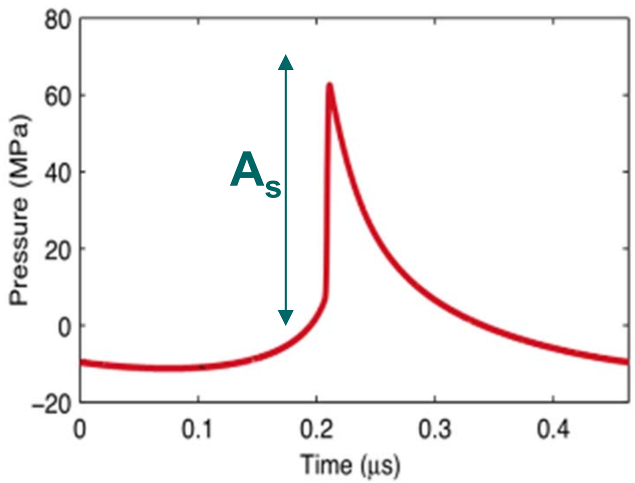
Shock amplitudes of **$A_p$ >60 MPa**

are necessary to generate vapor cavities within each ms-long pulse

**How to determine transducer parameters for most effective BH treatment?**

# Example: boiling histotripsy (BH) method in HIFU

## Mechanisms of tissue disintegration into subcellular debris

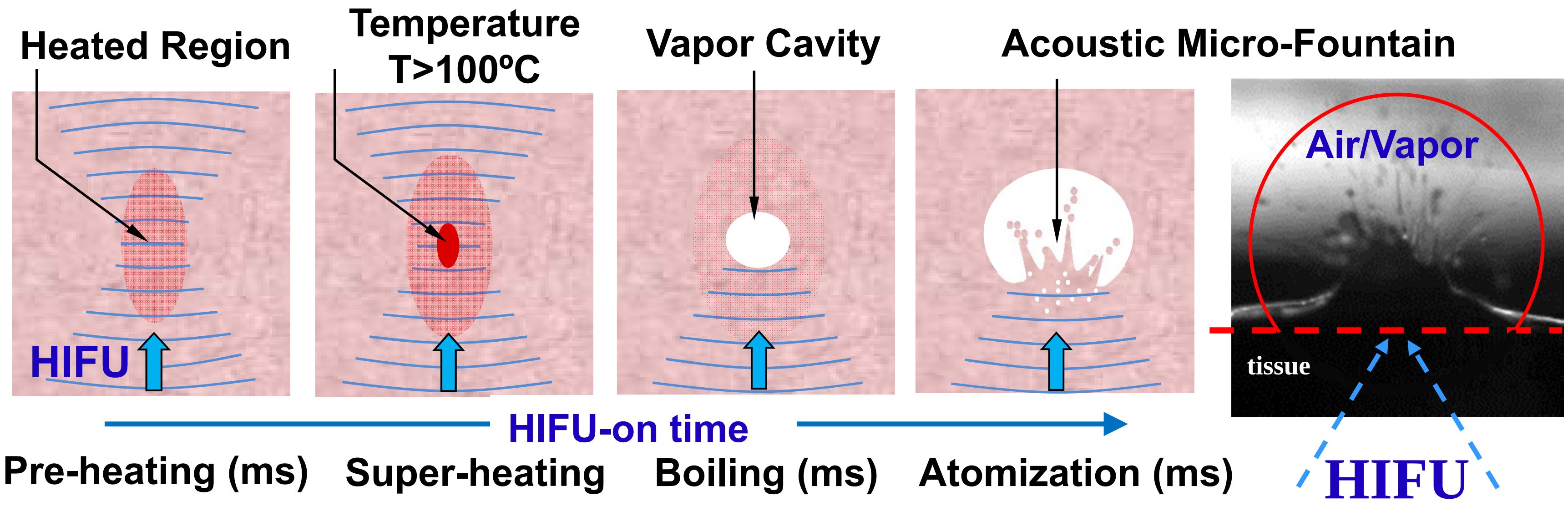



**Weak shock heating:**

$$q = \frac{\beta f_0 A_s^3}{6 c_0^4 \rho_0^2}$$

**Tissue at the focus reaches 100°C in a few ms!**

Canney M. *et al*., UMB 2009




Simon J.C. *et al*., PMB 2012

**Shock amplitude of 60 – 100 MPa are needed, how to choose transducer parameters?**

## Hypothesis:

Pressure levels required

for a certain degree of nonlinear effects

to occur at the focus

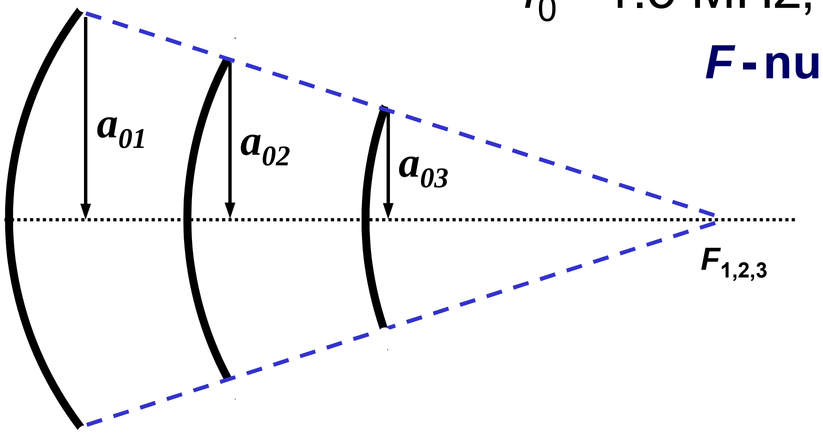
is mainly determined by

**transducer focusing angle (F-number)**

# Transducers with the same angular aperture

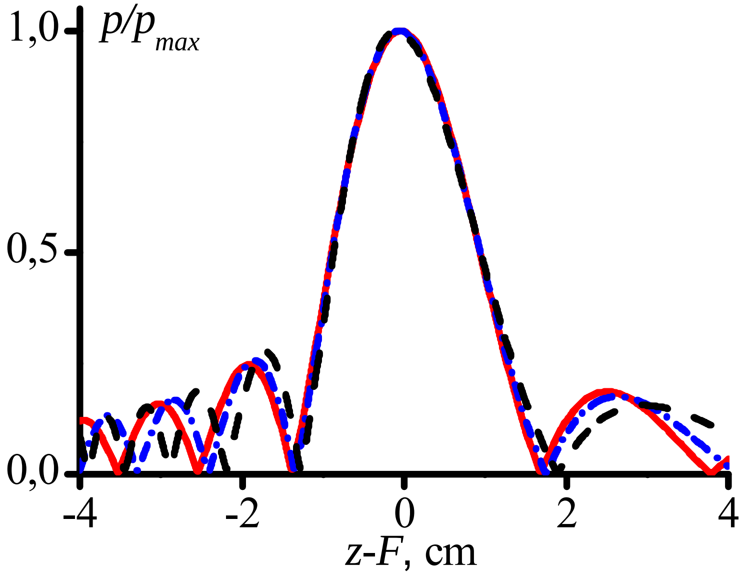
$f_0$ =1.5 MHz, $F_{1,2,3}$ = 8; 12; 16 cm

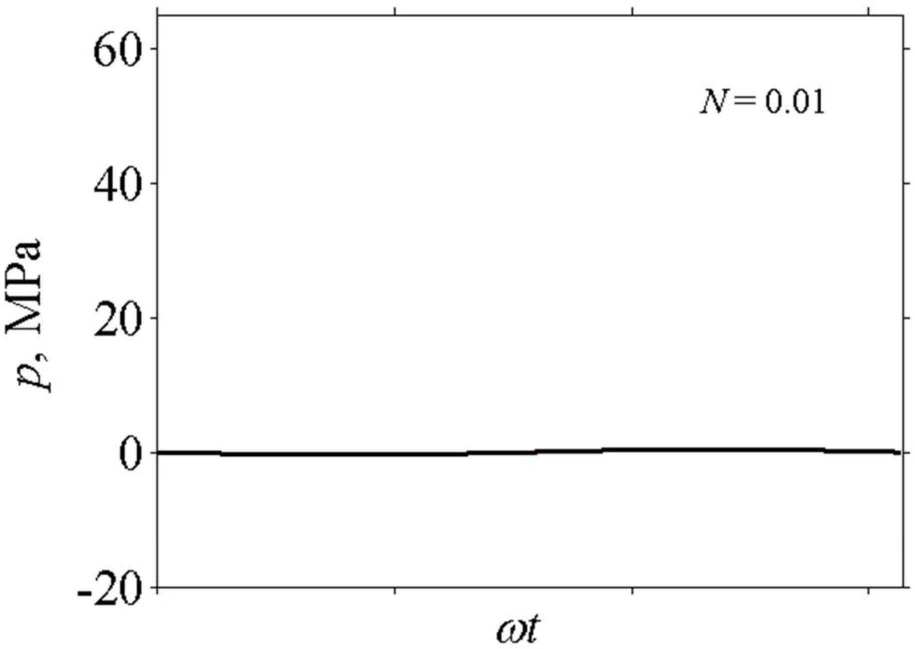
***F*-number = 1.5**




**Pressure waveforms at the focus**
**focal length *F* = 8 and 16 cm**
**for increasing source outputs**

**Axial pressure $p/p_{max}$**



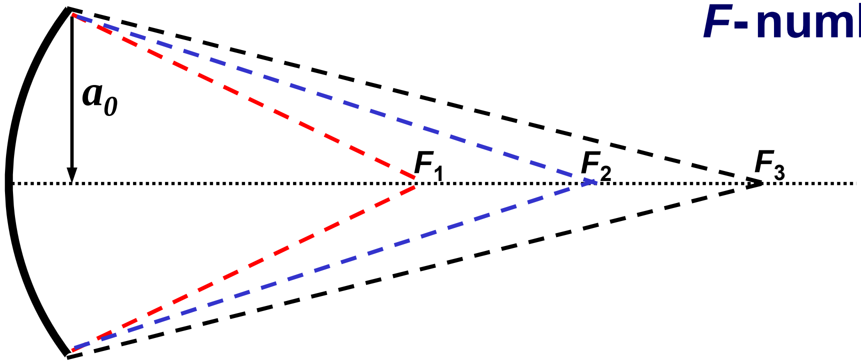




**Transducers with the same *F* – number = $F/2a_0$**
**generate shock fronts of the same amplitude at the focus**

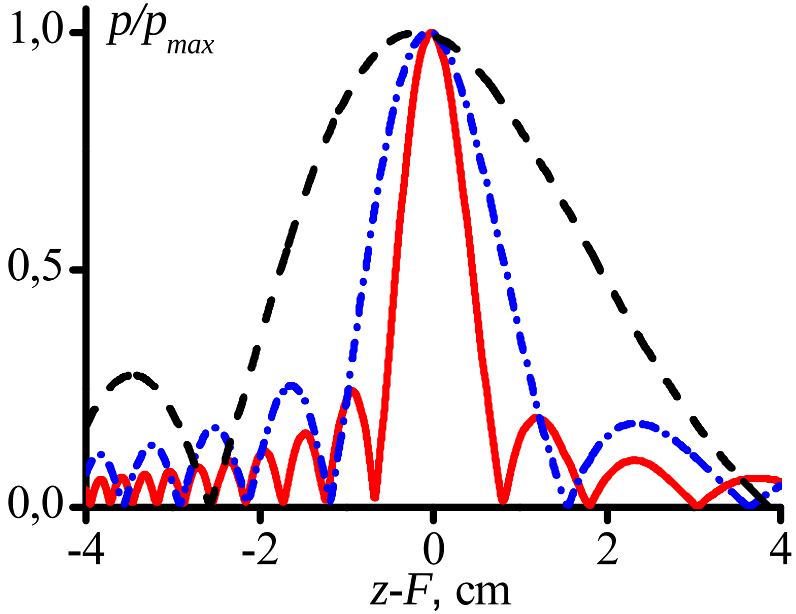
# Transducers with different angular aperture

$f_0$=1.5 MHz, $a_0$ = 4 cm, $F_{1,2,3}$ = 8; 12; 16 cm

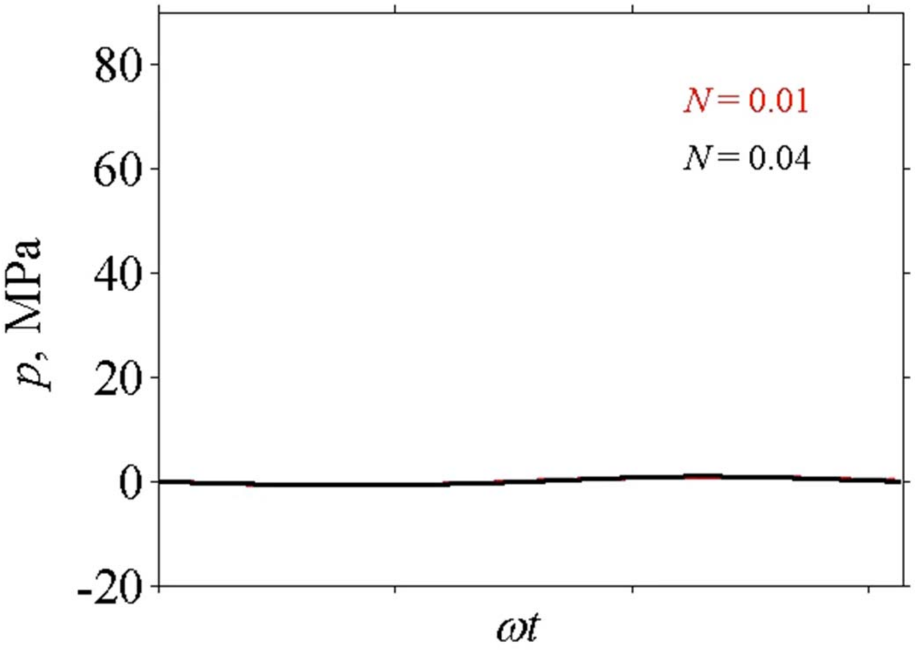
***F*-number = 1; 1.5; 2**




**Axial pressure $p/p_{max}$**




**Pressure waveforms at the focus focal length *F* = 8 and 16 cm for increasing source outputs**




**Hypothesis: shock amplitude at the focus is determined by the angular aperture (*F* – number) of the transducer**

## Numerical methods:

- Most accurate 3D Westervelt equation with holography boundary condition for detail field analysis
- equivalent source model to correlate KZK results with realistic transducer parameters
- axially symmetric KZK equation for solving an inverse problem

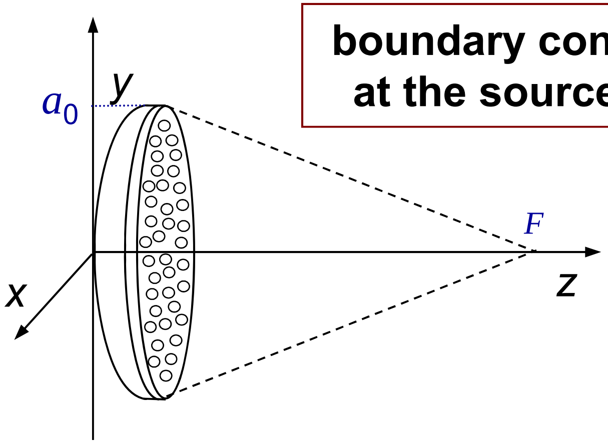
# Nonlinear propagation model: 3D full diffraction

**Westervelt equation:**

$$\frac{\partial^2 p}{\partial \tau \partial z} = \frac{c_0}{2}\left(\frac{\partial^2 p}{\partial x^2} + \frac{\partial^2 p}{\partial y^2} + \frac{\partial^2 p}{\partial z^2}\right) + \frac{\beta}{2\rho_0 c_0^3}\frac{\partial^2 p^2}{\partial \tau^2} + \frac{\delta}{2c_0^3}\frac{\partial^3 p}{\partial \tau^3}$$

$$\tau = t - z / c_0$$

**diffraction** **nonlinearity** **absorption**




**boundary condition set at the source surface**

P.V. Yuldashev, V.A. Khokhlova. **Simulation of three-dimensional nonlinear fields of ultrasound therapeutic arrays.** Acoustical Physics, 2011, 57(3), 334–343.

W. Kreider, *et* al. **Characterization of a multi-element clinical HIFU system using acoustic holography and nonlinear modeling.** IEEE UFFC, 2013, v. 60(8), pp.1683-1698.

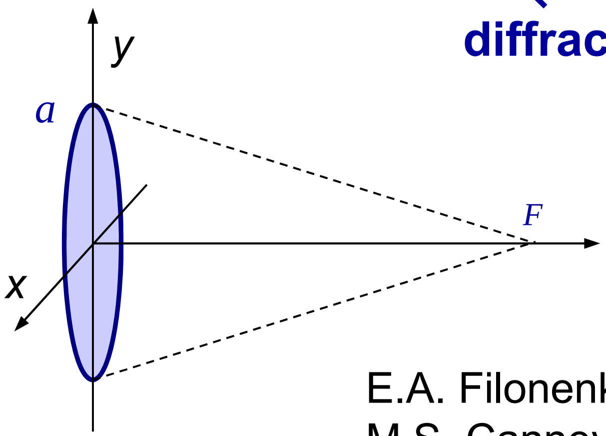
**3D full wave nonlinear models can accurately simulate the entire field of HIFU sources at high outputs in water and in tissue, but they are very intensive computationally**

# Nonlinear propagation model: numerically efficient

**Axially symmetric KZK equation (reduced diffraction):**

$$\frac{\partial^2 p}{\partial \tau \partial z} = \frac{c_0}{2}\left(\frac{\partial^2 p}{\partial x^2} + \frac{\partial^2 p}{\partial y^2}\right) + \frac{\beta}{2\rho_0 c_0^3}\frac{\partial^2 p^2}{\partial \tau^2} + \frac{\delta}{2c_0^3}\frac{\partial^3 p}{\partial \tau^3} \qquad \tau = t - z/c_0$$

**diffraction** **nonlinearity** **absorption**




**boundary condition in the plane z = 0**

E.A. Filonenko, V.A. Khokhlova. Acoust. Phys., 2001, 47(4), 468-475.
M.S. Canney, *et al.* JASA., 2008,124(4), 2406-2420.
O.V. Bessonova, *et al*. Acoust. Phys., 2009, 55(4–5), 463–473.
O.V. Bessonova, *et al*. 2013, IEEE T-UFFC, 60(2), 290-300.

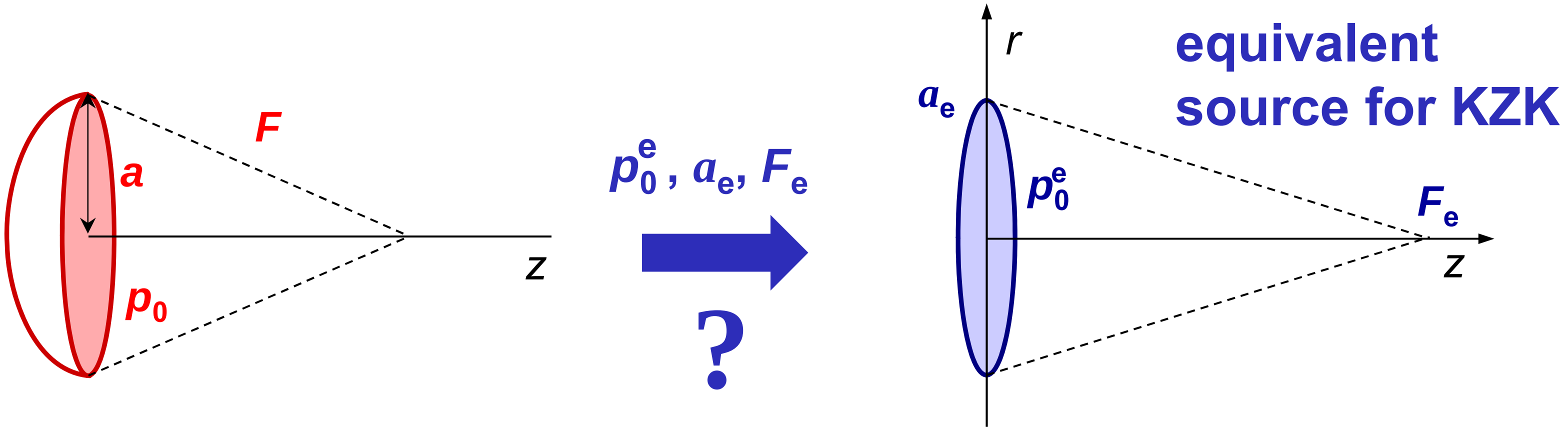
**Axially symmetric KZK model is much less extensive numerically than 3D Westervelt modeling: about 1000 times less memory requirements; computational time for modeling shock waves: from tens of hours to minutes**

# Equivalent source model

relates boundary condition to the KZK equation
to parameters of the designed transducer

**HIFU transducer**

$$p(z=0,r,\tau) = p_0^{\mathrm{e}} \sin\left[\omega_0\left(\tau + r^2/2c_0F_{\mathrm{e}}\right)\right], \quad r \le a_{\mathrm{e}}$$




P.B. Rosnitskiy, *et al*. Acoustical Physics, 2016, 62(2), 151–159.
M.S. Canney, *et al.* JASA., 2008, v.124(4), pp. 2406-2420.
O.V. Bessonova, *et al*. 2013, IEEE T-UFFC, 60(2), 290-300.

**Parameters of the equivalent source boundary condition to the KZK model $p_0^{\mathrm{e}}$, $a_{\mathrm{e}}$, $F_{\mathrm{e}}$ are related to those of the HIFU transducer to achieve the best fit of the pressure distributions on the beam axis measured or modeled at low output level**

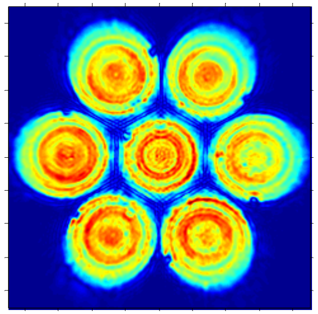
# Example: 1 MHz, 7-element array

## equivalent-source modeling (linear field)

$a$ = 7.4 cm, $F$ = 14 cm

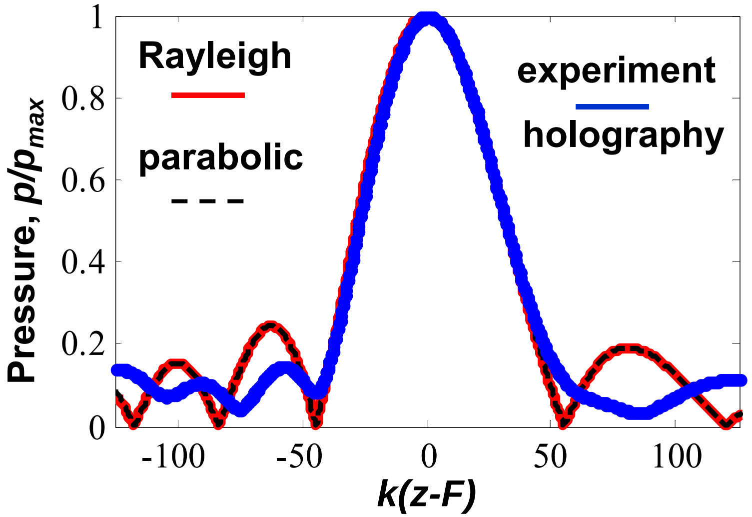
Holographic boundary condition for full diffraction modeling

O.A. Sapozhnikov *et al.* JASA 2015 138(3), 1515-1532.

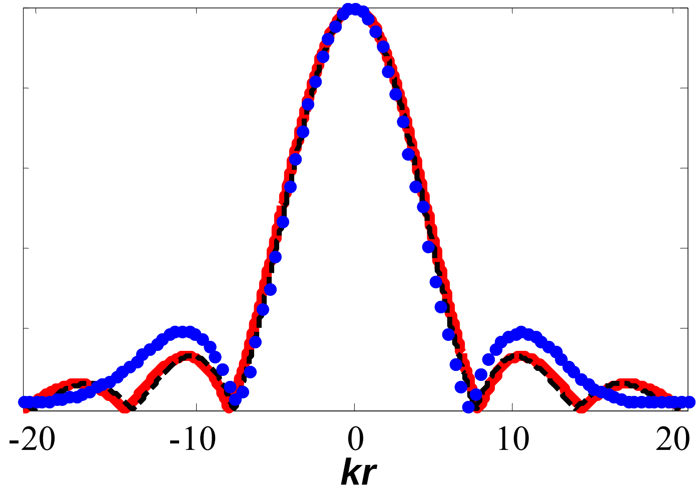


**Measurements, Rayleigh, and parabolic** equivalent-source modeling

**Pressure amplitude at the beam axis**




**and in the focal plane**



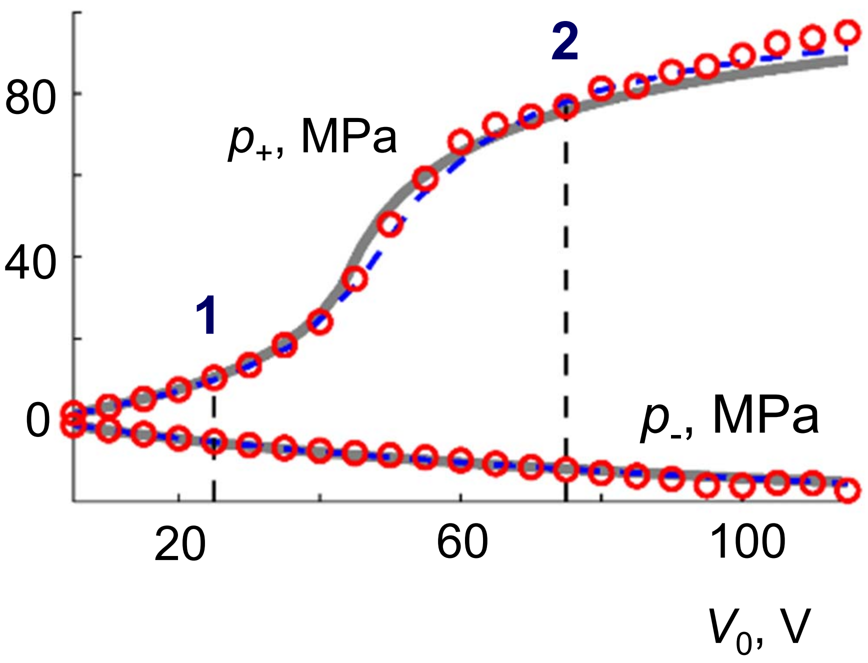

**Measurements, parabolic (KZK) and full diffraction modeling agree well in the focal lobe of the linear beam**

# **Example: Validation of nonlinear simulation results**

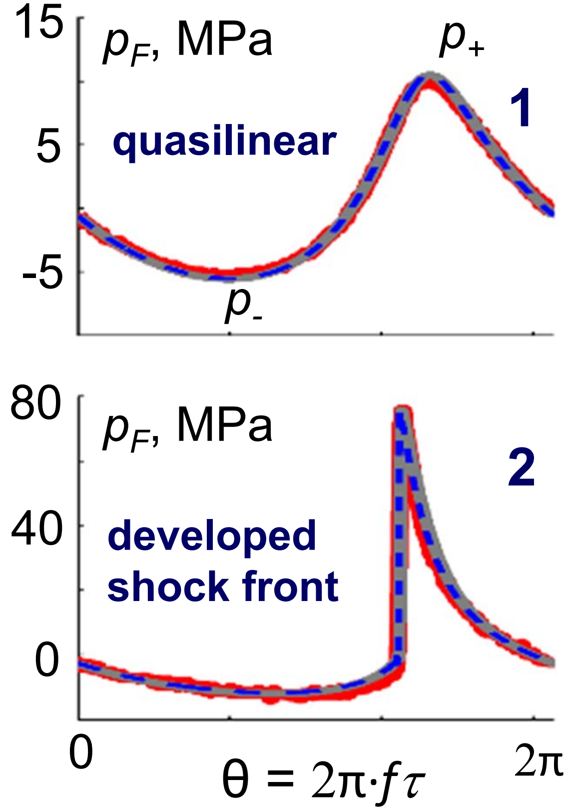
for equivalent-source modeling *versus* experiment

**measurements, full diffraction (3DWestervelt), parabolic (2D KZK) modeling**

Peal positive and peak negative pressures at the focus *versus* transducer output




Pressure waveforms at the focus

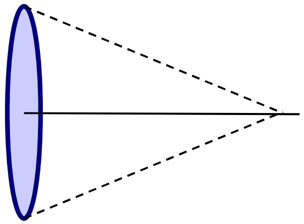



**Nonlinear pressure waveforms, measured at the focus agree well with those simulated based on the KZK and Westervelt equations**

## Solution to the inverse problem:

- Find multiparametric solutions to the KZK equation
- Consider three characteristic nonlinear regimes of focusing:
  - quasilinear
  - developed shock fronts
  - saturation
- Determine transducer focusing angle, aperture, and intensity to achieve chosen regime at specific pressure levels

# Multi-parametric solution to the KZK equation



KZK equation in dimensionless variables

only 2 parameters

$$\frac{\partial}{\partial\theta}\left[\frac{\partial P}{\partial\sigma} - NP\frac{\partial P}{\partial\theta} - A\frac{\partial^2 P}{\partial\theta^2}\right] = \frac{1}{4G}\Delta_\perp P$$

nonlinearity — source amplitude

absorption

diffraction — linear focusing gain

$$N = \frac{F_e 2\pi f_0 \varepsilon p_0^e}{c_0^3 \rho_0}$$

$$G = \frac{\pi f_0 a_e^2}{c_0 F_e}$$

Boundary condition

$$P(\sigma=0,R,\theta) = \begin{cases} \sin\left(\theta + GR^2\right), & R \le 1 \\ 0, & R \ge 1 \end{cases}$$

$$A << 1$$

absorption is negligible when focusing in water

**Water:**
$c_0$ = 1500 m/s
$\rho_0$ = 1000 kg/m³
$\varepsilon$ = 3.5

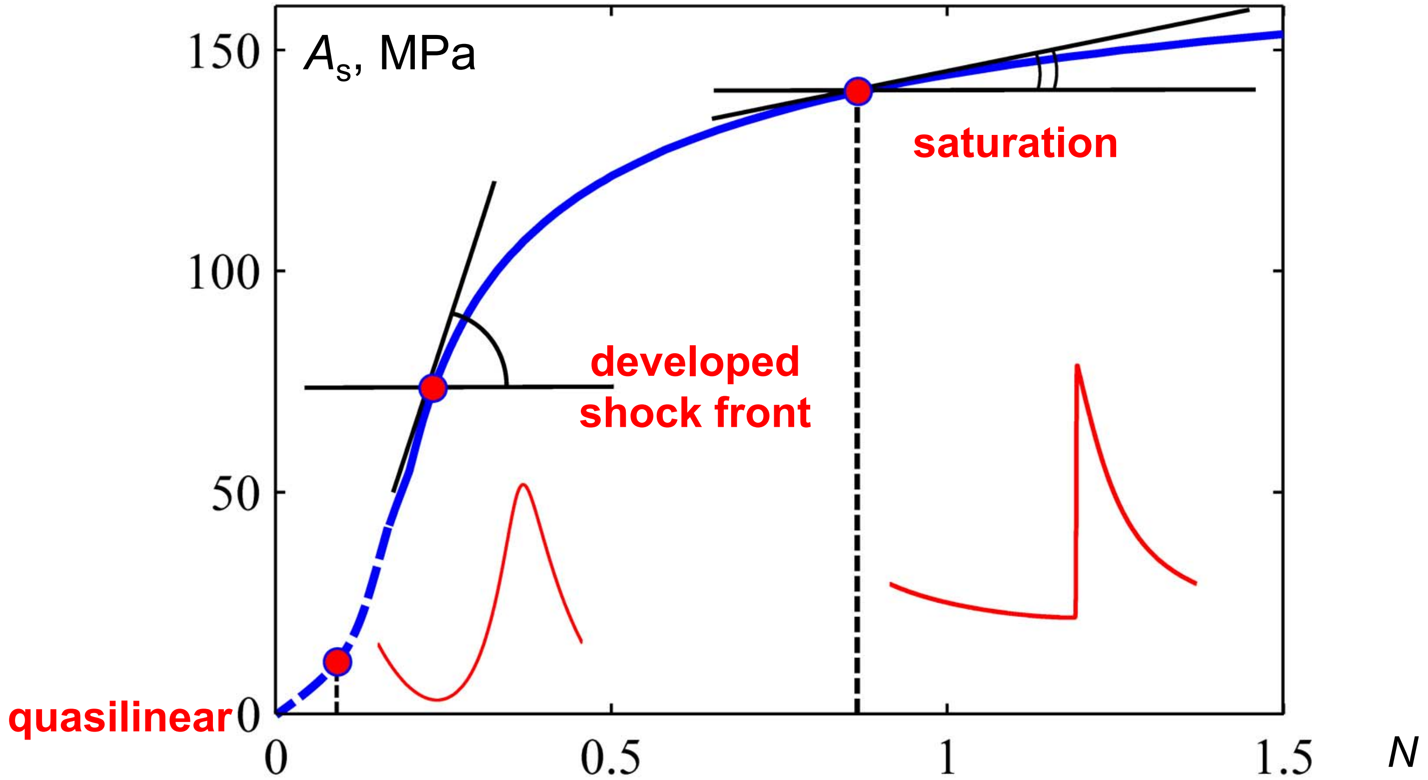
**KZK equation was solved**
**for various values *G* and *N***
10 ≤ $G$ ≤100 **20 points**
for each $G$: 0 < $N$ ≤1.5 **75 points**
**19*75 = 1425 times**

P.B. Rosnitskiy, *et al*. Acoust. Phys., 2015, 61(3), 301–307.

**Solutions in 2D parameter space (*N* and *G*) were used to solve the inverse problem**

# Three characteristic regimes of focusing

Focal peak positive pressure and shock amplitude
versus source pressure



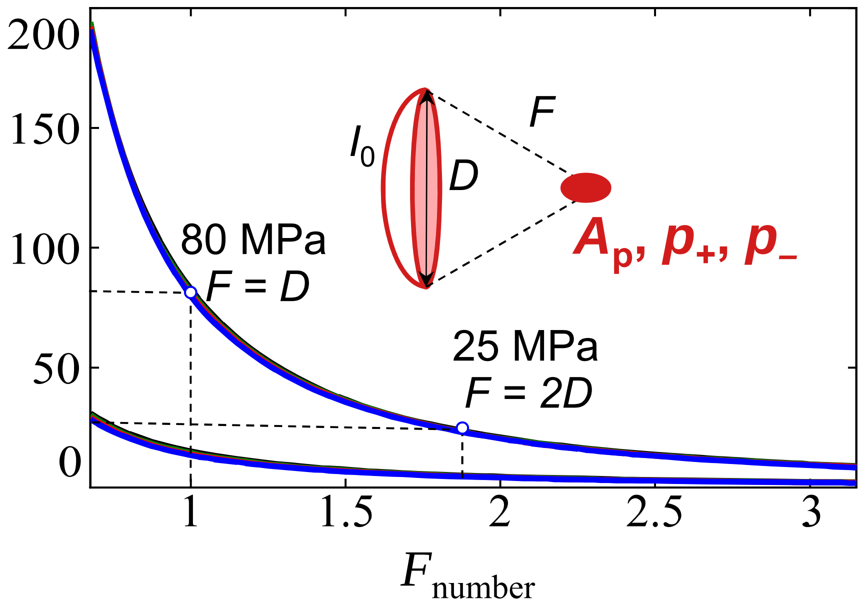

Definitions:

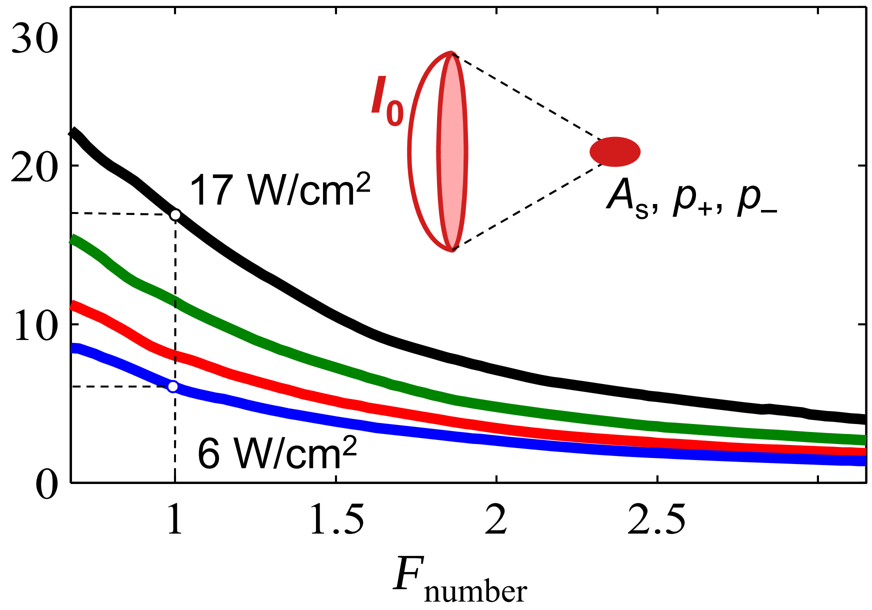
quasilinear focusing – 10% of focal wave intensity is transferred to harmonics
developed shocks - maximum ratio of shock amplitude to initial pressure
saturation - steepness of the saturation curve $As(N)$ is 10% of that for developed shock regime

# Example: regime of developed shock fronts at the focus

**Focal peak pressures and shock front amplitude, MPa**

**Initial intensity, W/cm² at which developed shock front is formed**




**Source aperture measured in wavelengths $ka$ = 126; 147; 168; 188**

**Shock front amplitude at the focus is related to the *F*-number of the transducer and its initial intensity, at which developed shock front forms**

**Shock amplitude is determined by the focusing angle of the transducer and does not depend on its frequency and aperture**

# Recipe

for designing a transducer with specific focal pressures
and controlled degree of nonlinear effects

(quasi-linear, developed shock, saturation)

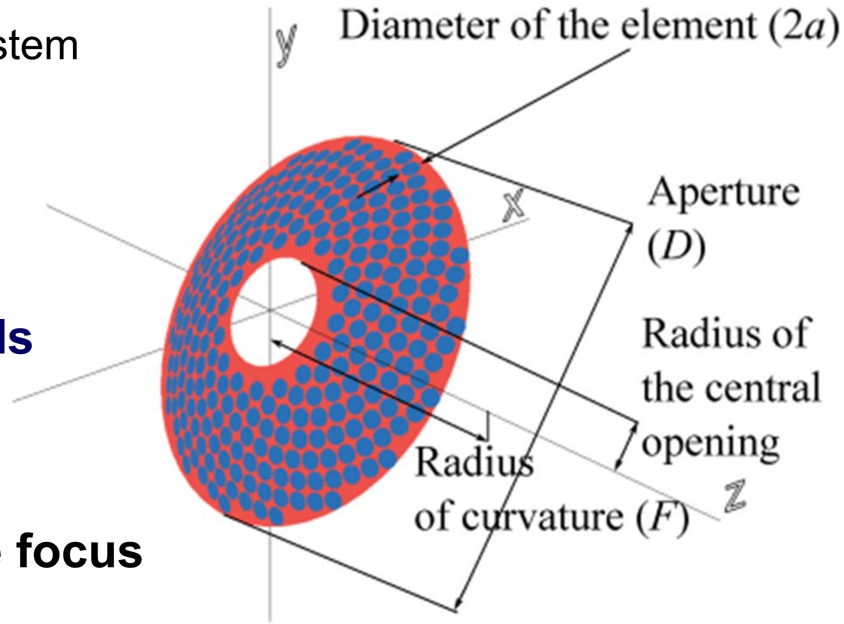
- Decide on desired nonlinear regime of focusing
- Determine focusing angle for the KZK equivalent source
- Tune the angle and aperture of the transducer by matching axial distributions of the linear pressure field with equivalent-source model results.

  *[consider technical limitations on initial peak intensities]*

# Example: Design of a multi-element HIFU array for BH developed shocks of 90 – 100 MPa

**Predetermined parameters**

- **256** elements – number of channels in US system
- **1.5 MHz** frequency – from BH experiments
- **0.5 mm** between elements – array safety
- **4 cm** central hole – fits US imaging probe
- geometry of array location – **compact spirals**
- **30 W/cm²** max intensity at the elements




**Requirements to the nonlinear field at the focus**

- **developed shock front of 90-100 MPa**
- achieved in water at $I_0$ **< 3.75 W/cm²** at the elements (accounting for 9 dB losses for propagation in tissue)

**Unknowns to determine**

**Array aperture?**

**Focusing angle?**

# Choosing focusing angle and diameter of elements

Developed shock front at the focus **90 - 100 MPa** → KZK modeling → **Focusing angle 58º equivalent source**

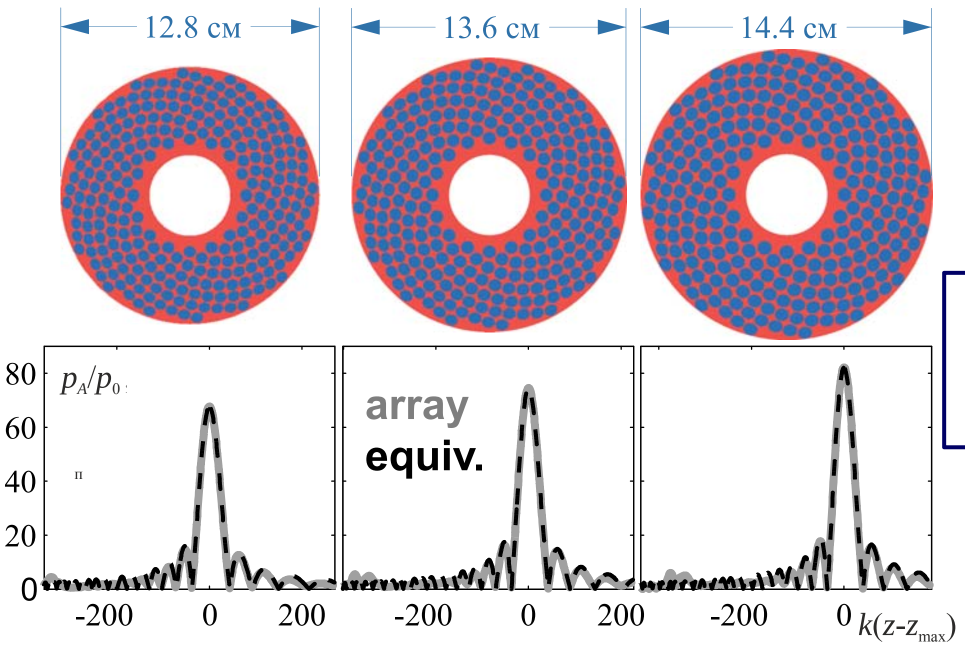
Compare to spiral array

↓

**Focusing angle 74º of the array**

← Vary diameter of elements *D*

**6 мм** | **6.5 мм** | **7 мм**




KZK modeling

**4.7 W/cm²** | **4.4 W/cm²** | **3.4 W/cm²**

**at the elements**

**axial pressure in the linear beam**

array, **equivalent source**

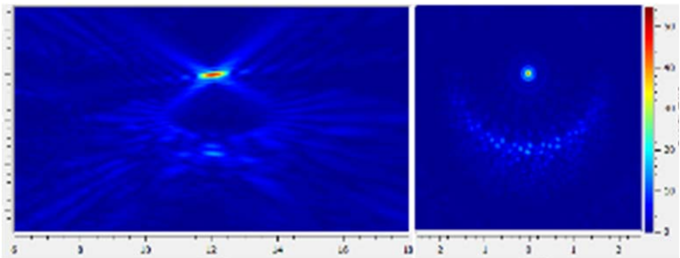
**Parameters of the array are determined to achieve developed shock amplitude of 90-100 MPa**

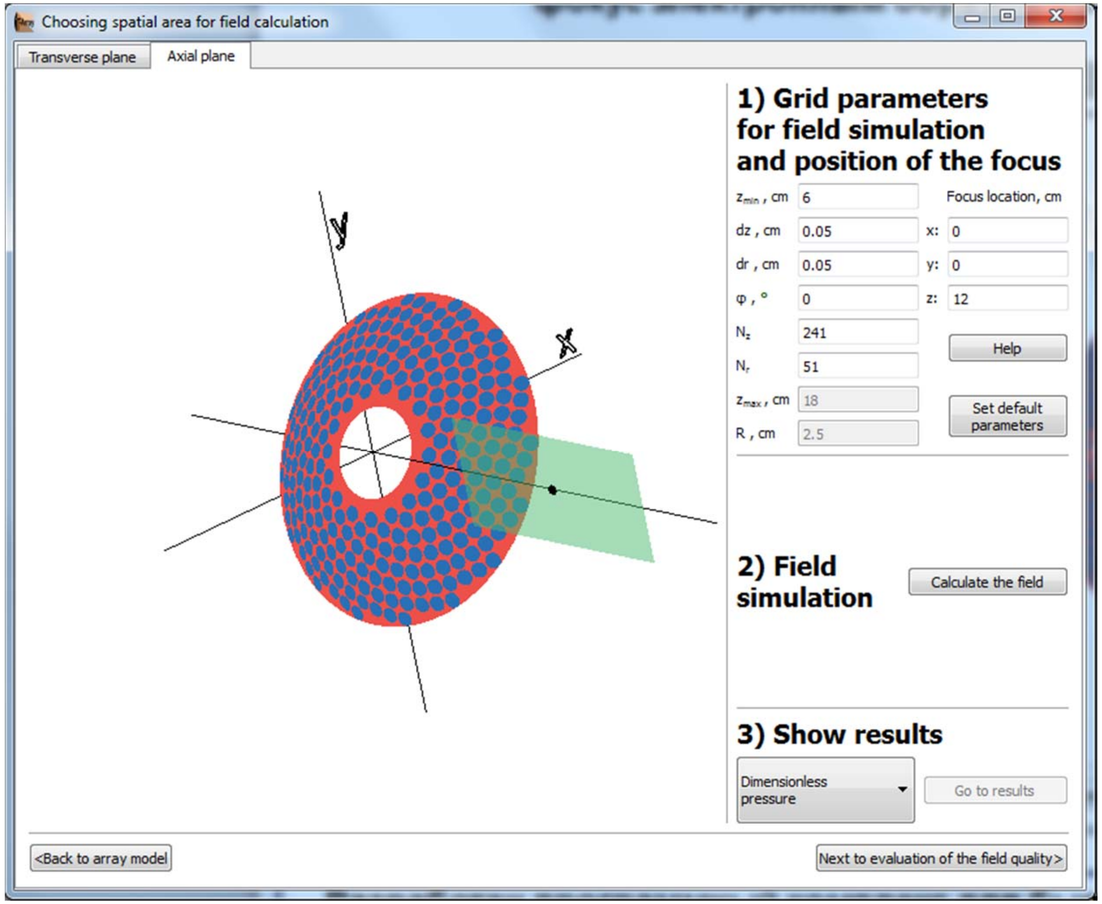
# Evaluating electronic focusing capabilities of the array

**Range of dynamic focusing is established by analyzing the quality of the array field: grating lobes of acceptable level, intensity in the main focus**

S.A. Ilyin, *et al*. Acoust. Phys., 2015, 61(1), 52–59.

T-Array






**T-Array** is free, open-source software with a friendly GUI.

<u>Current capabilities:</u>

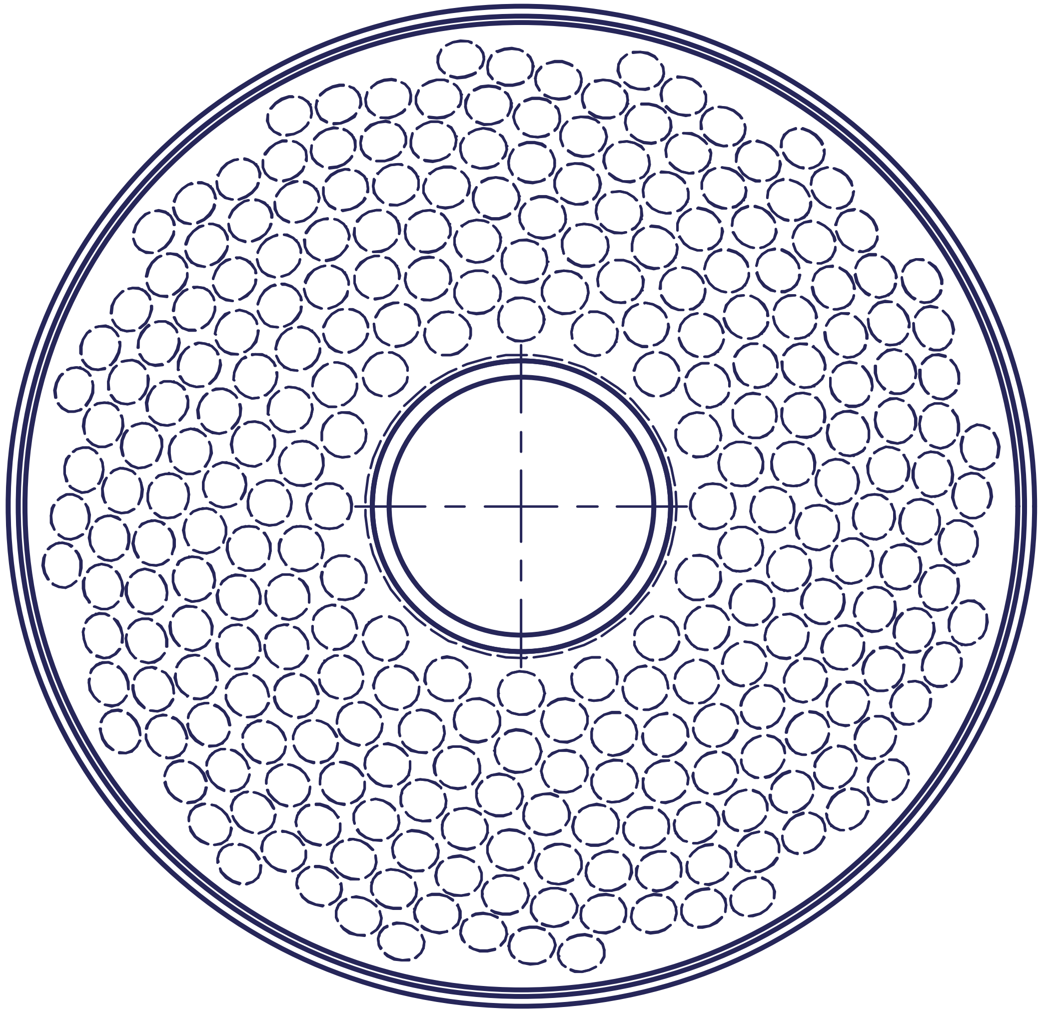
- analyze linear ultrasound fields generated by therapeutic phased arrays
- evaluate beam steering performance

**can be downloaded for free from**

T- Array

**www.limu.msu.ru**

# Final design of the array produced by Imasonic



**Parameters of the array:**

**1.5 MHz**
**144 mm aperture**
**120 mm focal length**
**256 elements of 7 mm diameter**
**positioned with 0.5 mm gaps**
**16-arm spiral**
**40 mm central opening**

# Conclusions

## Transducer design for generating nonlinear HIFU fields

- Method developed to relate transducer parameters to those of the equivalent source in the KZK model
- Accuracy of the method demonstrated
- Inverse problem solved using KZK model
  *desired waveform ⟺ nonlinear effects ⟺ transducer parameters*

## Application of the approach

- Multi-element HIFU array for BH applications designed using the proposed method
- T-Array software developed to analyze steering capabilities of HIFU arrays


# Acknowledgments

NIH EB007643 and RSF 14-12-00974