Estimation of *in situ* medical ultrasound fields based on measurements in water and nonlinear simulations

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Introduction
- nonlinear fields of high power therapeutic transducers
- thermal and mechanical bioeffects in HIFU due to presence of shocks

Combined measurement and modeling characterization method:
1) nonlinear propagation models of different complexity
   - 3D full diffraction Westervelt equation
   - axially symmetric parabolic KZK equation
2) Setting a boundary condition from measurements
   - acoustic holography method
   - 1D field scans for simplified “equivalent” source

Examples of characterizing high power fields:
- 256-element array of a clinical HIFU
- diagnostic linear array probe

Derating water measurements to in situ fields
- direct modeling in inhomogeneous tissue
- source amplitude scaling method to compensate for attenuation

Conclusions
Therapeutic applications of ultrasound

HIFU surgery:

- **frequency**: 0.7 – 4 MHz
- **Intensity in situ**: 500 – 30 000 W/cm²

**Major bioeffects of HIFU**
- **thermal**: tissue heating due to absorption of ultrasound energy
- **thermal dose for necrosis**: 120-240 min at 43°C, 1 c at 56°C, 0.1 c at 59°C
- **mechanical**: cavitation, shear stresses

High Intensity Focused Ultrasound = nonlinear acoustic fields

No characterization methods have been established for strongly nonlinear HIFU fields with shocks
Nonlinear effects in HIFU
acoustic characterization and newer bioeffects

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
- histotripsy
- 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
Characterization of HIFU fields: combined measurement and modeling approach

Specific steps of the approach:

1. Choose a nonlinear propagation model
   ⇒ 3D Westervelt or axially symmetric KZK

2. Reconstruct a model boundary condition based on experimental measurements conducted under linear conditions
   ⇒ acoustic holography or an equivalent source that matches axial focal beam profiles

3. Experimentally relate changes in source settings to changes in pressure at the source for output levels of interest

4. Simulate the nonlinear acoustic field using the reconstructed boundary condition scaled for different output settings

5. Validate modeling results through independent hydrophone measurements at the focus

6. Simulate the nonlinear acoustic field in tissue
   ⇒ direct simulation or nonlinear derating
Nonlinear propagation models: 3D full diffraction

Westervelt equation:

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

\[ \tau = t - \frac{z}{c_0} \]

diffraction nonlinearity absorption

P.V. Yuldashev, V.A. Khokhlova. 
Simulation of three-dimensional nonlinear fields of ultrasound therapeutic arrays. 


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 models: reduced diffraction

Axially symmetric KZK equation:

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

\[\tau = t - z / c_0\]


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
Sample results from medical ultrasound sources

<table>
<thead>
<tr>
<th>1</th>
<th>MR-guided HIFU system (Sonalleve V1, Philips)</th>
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<tbody>
<tr>
<td></td>
<td>256 element array</td>
</tr>
<tr>
<td></td>
<td>128 mm diameter</td>
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<td></td>
<td>120 mm focus</td>
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<thead>
<tr>
<th>2</th>
<th>Diagnostic linear array probe Philips C5-2</th>
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<tbody>
<tr>
<td></td>
<td>128 element array</td>
</tr>
<tr>
<td></td>
<td>38 mm width, 12.5 mm height</td>
</tr>
<tr>
<td></td>
<td>50 – 70 mm focus</td>
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Nonlinear acoustic fields from two transducers of different geometry were characterized in water and derated into tissue.
**Example 1: Characterization of the array field using acoustic holography and Westervelt modeling**

reconstruction of vibration velocity at the surface of the transducer

experimental arrangement
Philips MR-guided HIFU source

O.A. Sapozhnikov *et al.*
Boundary condition to the model
reconstructed experimentally using acoustic holography

2D multi element clinical phased array
Philips MR-guided HIFU source


Acoustic holography is an accurate method to set a boundary condition
Calibrate initial pressure amplitude for nonlinear modeling

Experimentally relate the source pressure in the modeling to the source settings over a range of output levels

Direct hydrophone measurements at the beam axis close to the source

Power of scaled hologram compared to Philips radiation force balance data

Pressure output is expected to be proportional to driving voltage up to very high output levels — but it should be verified
Validation of the combined measurement and modeling characterization method

Linear projections of holography measurements match direct hydrophone measurements (dots)

Nonlinear waveforms with shock amplitudes of up to 100 MPa modeled and measured at the focus agree very well

Setting an “equivalent source” boundary condition by matching linear field of the therapeutic array in the focal region.

Linear modeling: array *versus* single element equivalent transducer (linearized KZK and WE)

Along the axis

Across the axis in the focal plane

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P.B. Rosnitskiy, P.V. Yuldashev, B.A. Vysokanov, and V.A. Khokhlova.
Comparison of 256-element array and “equivalent source” boundary condition

Boundary conditions in the plane $z = 0$
defined using different methods

Hologram, 256-element array, 3D Westervelt

Equivalent single element focused bowl, 3D Westervelt

Equivalent single element focused source, KZK model
Linear field: 2D pressure distributions (logarithmic scale)

2D array Westervelt

in the axial plane

in the focal plane

single element Westervelt

single element KZK
Validation of nonlinear simulation results for equivalent source modeling *versus* experiment measurements, full diffraction (Westervelt), parabolic (KZK) modeling.

Nonlinear pressure waveforms, measured at the focus agree well with those, simulated based on the KZK and Westervelt equations with equivalent-source boundary condition.
Example 2: Diagnostic probe used for ultrasonic propulsion of kidney stones

Ultrasonic propulsion system

Pushing residual fragments

2.3 MHz, Philips C5-2

Setting a boundary condition to the Weatervelt model by varying “equivalent source” parameters to match linear axial scans

**Boundary condition:**
- cylindrical surface
- uniform amplitude distribution
- continuous phase distribution
- fitting parameters: $R, \theta, l_y, F_{x,y}$

**Parameters:**
- $R = 38$ mm, $l_y = 12.5$ mm,
- $F_x = 50$ mm, $F_y = 70$ mm

40 elements

acoustic lens in the $yz$ plane

On-axis pressure amplitude

Pressure amplitude in the focal plane
Validation of nonlinear simulation results for diagnostic probe

3D Westervelt modeling with the equivalent-source boundary condition

40 elements, \( z = 73 \text{ mm} \)

Pressure waveforms, MPa

Saturation of peak pressures

Good agreement between measurements and simulations through a whole range of operational power outputs
Derating nonlinear measurements in water to tissue

Direct modeling of the 3D Westervelt modeling equation in inhomogeneous absorptive tissue

\[ \rho_0 \nabla \left( \frac{1}{\rho_0} \nabla p \right) - \frac{1}{c_0^2} \frac{\partial^2 p}{\partial t^2} + \frac{\varepsilon}{\rho_0 c_0^4} \frac{\partial^2 p^2}{\partial t^2} + \frac{\delta}{c_0^4} \frac{\partial^3 p}{\partial t^3} + L_a(p) = 0. \]

Focusing a HIFU beam transcutaneously onto a liver mass (arrow) below the costal margin

Use CT images (or MRI, or potentially 3D ultrasound) for modeling propagation in tissue:
- sound speed and density are determined from the CT contrast
- attenuation and nonlinearity are set within the contours of different tissue types

Accurate approach possible for HIFU treatment planning. It requires CT data therefore not reasonable for US diagnostic applications.
Derating nonlinear HIFU fields compensating for absorption

Source pressure scaling method for strongly focused beams

\[ p_0(\text{tissue}) = p_0(\text{water}) \exp(A) \]

\[ p(\text{focus})_{\text{tissue}} = p(\text{focus})_{\text{water}} \]

\[ A = \alpha F \]

On-axis linear propagation curves

<table>
<thead>
<tr>
<th>[ p/p_0 ]</th>
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<tbody>
<tr>
<td>[ \text{water, } A=0 ]</td>
</tr>
<tr>
<td>[ \text{tissue, } A=1 ]</td>
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Initial pressure is scaled to compensate absorption losses assuming linear wave propagation to equalize focal pressures
Theoretical validation of pressure scaling method in absorptive medium

\[ p_0^{\text{tissue}} = p_0^{\text{water}} \exp(A) \quad A = \alpha F \]

\[ A = 0 \text{ (water)}, \quad A = 1 \text{ (tissue)}, \quad G = 40 \]

peak pressures at the focus

versus source amplitude

in water and in tissue

peak pressures versus

DERATED source amplitude

in water and in tissue


Nonlinear derating method is valid for strongly focused fields
Experimental validation of derating method: measurements behind *ex vivo* bovine liver

HIFU source

\[ f_0 = 2 \text{ MHz} \]

\[ F = 2r_0 = 45 \text{ mm} \]

\[ G = \frac{p_F}{p_0} = 48 \]

\[ p_0(\text{tissue}) = p_0(\text{water}) \cdot \exp(\alpha L) \]

\[ p_0 = 0.14 \text{ MPa – water} \]

\[ p_0 = 0.24 \text{ MPa – liver} \]

\[ \alpha = 0.7 \text{ dB/cm/MHz} \]

Liver, 27 mm thick

**Measured focal waveforms: water versus liver**

Matching nonlinear focal waveforms in water and behind tissue for different source amplitudes gives an attenuation factor of 0.7 dB/(cm MHz) for deration
Derating nonlinear diagnostic fields compensating for absorption

Focused ultrasound beam produced by C5-2 array probe with 64 active elements

Peak positive and peak negative pressures at the beam axis

Free field propagation in water

Propagation in the presence of tissue

Nonlinear and absorption effects interplay over larger distances than in HIFUI fields: predicting in situ pressures based on data obtained in water is challenging
Derating nonlinear diagnostic fields
compensating for absorption

Derating focal waveforms into tissue
at different source outputs

Peak pressures at the focus
\textit{versus} source amplitude
in water and in tissue

\begin{align*}
  p_{0}^{\text{tissue}} &= p_{0}^{\text{water}} \exp(\alpha L) \\
  p_{F}^{\text{tissue}} &= p_{F}^{\text{water}} \exp(-\alpha L)
\end{align*}

Nonlinear derating method
(source scaling)

Standard derating method
(focal waveform scaling)

Both nonlinear and conventional derating methods do not accurately predict \textit{in situ} pressures: direct modeling is necessary
Conclusions

- Combined measurement and modeling approaches are powerful tools in characterization of medical transducers and their fields.
- Modeling based on Westevelt equation with boundary condition obtained from acoustic holography has shown the most accurate results for nonlinear field characterization.
- “Equivalent source” boundary conditions can be used for characterizing the nonlinear focal region if parameters are set to match focal beam characteristics under linear conditions.
- Source pressure scaling method is proposed and validated for high gain HIFU sources; derating is more challenging for diagnostic sources.

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Nonlinear propagation effects in HIFU fields

- Ultrasound propagation speed depends on local pressure.
- High pressure regions (compressions) travel faster than low pressure regions (rarefactions).
- Harmonic wave transforms to sawtooth wave.

\[ p(x = 0) = p_0 \sin(\omega_0 \tau) \]

\[ x_{sh} = \frac{c_0^3 \rho_0}{\beta p_0 \omega_0} \] - Shock formation distance

\[ p_0 = 10 \text{ MPa}, \, f_0 = 1 \text{ MHz}, \, x_{sh} = 1.5 \text{ cm} \]
\[ p_0 = 25 \text{ MPa}, \, f_0 = 2 \text{ MHz}, \, x_{sh} = 3 \text{ mm} \]

\[ H = \frac{\beta f A_s^3}{6 c_0^4 \rho_0^2} \]

Heat deposition at the shocks:

- Clinically relevant focal values: 10 MPa – 3 300 W/cm²
Linear modeling: 2D pressure distributions

- **2D array Westervelt**
- **single element Westervelt**
- **single element KZK**
Modeling results: nonlinear propagation

Waveforms at the focus

- Saturation effects do limit peak positive and negative pressures
- Shock front formation occurs starting at ~ 30 V source level
- Using of a larger number of elements provide higher peak pressure values
Practical implementation of the KZK modeling results for users of HIFU arrays

focal pressures of an arbitrary HIFU source:
• find equivalent aperture and pressure; calculate linear focusing gain $G$,  
• find the point on the calibration curve for a given output $N$,  
• determine the degree of nonlinear effects

correction factors to focusing gain $K = \frac{G_{\text{nonlinear}}}{G_{\text{linear}}}$, $N \sim p_0$

peak positive pressure

peak negative pressure