Les ultrasons focalisés: une chirurgie non invasive en plein essor

Jean-François Aubry

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2. Visiting Associate Prof, Department of Radiation Oncology, Univ. of Virginia, USA
Biological effects of ultrasound
Biological effects of ultrasound
Biological effects of ultrasound

Mechanical effect
Kidney stones destruction (Lithotripsy)
Biological effects of ultrasound

Cavitation: Histotripsy

Boat propellers

+40 MPa during 1 µs

transducer

skin
Biological effects of ultrasound

Cavitation: Histotripsy

+40MPa during 1μs

Histotripsy generated “M” shaped lesion shown in ultrasound imaging

transducer

skin
Biological effects of ultrasound

Cavitation: Histotripsy

Pictures from University of Michigan: Parsons J et al; Xu Z et al

+40MPa during 1µs

Skin

Transducer
Biological effects of ultrasound

**Frontier of the lesion**

- Dead Cells
- Normal Cells

 Thermal effect: Tissue ablation

- **liver**
- **transducer**
- **skin**

- 1 mm

- $\sim 60^\circ C$ during 10s 4MPa
FUS – Overview (partial)  ~1, 400,000 patients treated to date

Philips Sonalleve

More than 30 companies

Exablate 2000

GE- InSightec

Edap TMS, France

Focus Surgery, USA

Theraclion, France

Chongqing HAIFU, China

Shanghai Aishen, China

Beijing Yuande, China
21 Indications = 21 devices! (+ competitors)

Courtesy of The FUS foundation
Schematic diagram of a FUS Device

- **Imaging unit**
- **Positioning unit**
- **Console operator** controls all treatment planning and operation
- **Treatment unit**
  - Function generator
  - Power-Amplifier
  - Power-Meter
  - Matching circuit
  - Transducer (Focused US probe)
  - Cooling device

Step motors
Schematic diagram of a FUS Device

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**Ultrasound** or **MRI?**
- USgFUS
- MRgFUS

**Step motors**
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Step motors

Ultrasound USgFUS or MRI? MRgFUS

Single element or Multielement phased array?
FUS Device

- Imaging unit
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Fry, HIFU System Integrated with Ultrasound B-Mode Imaging, 1972

Courtesy of N. Sanghvi
State of the art FUS Device... in the 70s

Ultrasound Images during the HIFU treatment
R. Heimburger et al -- 1974

Courtesy of N. Sanghvi
Therapeutic ultrasound: Cumulative Indications

Courtesy of The FUS foundation
From 1970 to 2010: what changed?
Therapeutic ultrasound: Cumulative Indications

Courtesy of The FUS foundation
Example of Ultrasound-guided Therapeutic Ultrasound

Haifu Model JC Focused Ultrasound Tumour Therapeutic System

Courtesy of J. Kennedy, F. Wu
Integrated Treatment Transducer (diagnostic US probe and HIFU transducer) in degassed water reservoir

Ideal focal region for treatment:
1.1mm \times 3.3mm

Range of acoustic intensity within focal field:
5000 \text{ W/cm}^2 \text{ to } 25000 \text{ W/cm}^2

Therapeutic frequency:
0.8\text{MHz—}2.4\text{MHz}

*Courtesy of J. Kennedy, F. Wu*
Example of change seen on ultrasound image during treatment
(Left = Before, Right = After)

Courtesy of J. Kennedy, F. Wu
Changes in real-time US images during HIFU procedure for Large human HCC


FIG. 3. Gray-scale changes of large high intensity focused ultrasound (HIFU) obtained on real-time ultrasound (US) images during HIFU procedure. (A) US image obtained before HIFU shows a large hepatocellular carcinoma lesion present in left lobe of liver (arrows). (B–C) US images obtained during the HIFU procedure show hyperechogenicity in the treated tumor (arrows). (D) US images obtained immediately after the one-slice HIFU procedure show the hyperechogenicity of treated tumor in the one-slice lesion (arrows).

Example of Ultrasound-guided Therapeutic Ultrasound

Haifu Model JC Focused Ultrasound Tumour Therapeutic System (Liver Carcinoma)
Example of MR-guided Therapeutic Ultrasound

(Uterine Fibroid)

Courtesy of Y. Medan and A. Hananel, Insightec
What does MR guidance provide?

- 3D anatomic information for tumor targeting
- Beam path representation for safe treatment

Courtesy of Y. Medan and A. Hananel, Insightec
Example of MR-guided Therapeutic Ultrasound

Courtesy of Y. Medan and A. Hananel, Insightec
Example of MR-guided Therapeutic Ultrasound

What does MR guidance provide?

- Real time MR thermometry to achieve planned outcome

- Thermal Dose evaluation

\[
t_{eq,43} = \int_{0}^{t} R^{43-T(t)} dt
\]

\[R = \begin{cases} 
0.25 & \text{if } T < 43^\circ C \\
0.5 & \text{if } T > 43^\circ C 
\end{cases}
\]

Equivalent exposure time at 43°C (necrosis if >240eq min in muscle)

Courtesy of Y. Medan and A. Hananel, Insightec
Example of MR-guided Therapeutic Ultrasound

What does MR guidance provide?

- Post treatment T1 images
- (+ Gd injection)

- Thermal Dose evaluation

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Schematic diagram of a HIFU Device

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Ultrasound or MRI?
Advantages of ultrasound:
- less expensive
- high frame rate (20 to 1000 images per second)
- handheld

Advantages of MR:
- anatomical imaging
- quantitative measurement of thermal dose
Schematic diagram of a HIFU Device

- **Imaging unit**
- **Positioning unit**

**Console operator**
controls all treatment planning and operation

- **Treatment unit**
  - Function generator
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Ultrasound or MRI?

Monoelement or Multielement phased array?
Volumetric ablation, with feedback control to automatically stop heating when thermal dose is reached.

Cell

Outwards-moving concentric circles
4 – 16 mm Ø

Courtesy of Philips
Treatment time 142min
Transribs focusing


S. Bobkova, L. Gavrilov, V. Khokhlova, A. Shaw, Focusing of high-intensity ultrasound through the rib cage using a therapeutic random phased array UMB (2010)
3D Motion tracking system for liver – Animal studies (pigs)

Pig, in vivo, IMM research, Paris

3D motion of a ventilated pig

Superior-Inferior motion
Lateral motion
Anterior-Posterior motion

Targeting the brain with ultrasound: promises and challenges

MR guided Focused Ultrasound:
An appealing non-invasive non-ionizing method to target the brain
Targeting the brain with ultrasound: promises and challenges

**Challenge:**

How to focus ultrasound through the disorting skull bone?
How to determine the appropriate time shifts?
Simulation of transcranial wave propagation

Non invasive procedure

3D finite difference time domain simulation using CT scans

Virtual point source

Transcranial aberration correction: a long way...2002-2013


High Frequency Brain therapy (1MHz)

**Ultrasonic array**
- 512 elements, 1 MHz, $\varnothing$ 6mm, 20 W/cm²

**Electronics**
- 512 channels, 10 W/channel

Human skull mounted on a stereotactic frame in front of the array
Clinical device developed with SSI

Planning Software
Validation on cadaver heads

MR temperature imaging

Precision on 13 cadavers:
axial plane: 0.7±1.2mm
along the ultrasonic beam: 0.5±2.4mm

Size of the MR temperature voxel: 1.5mm×1.5mm×3mm

ExAblate 4000 Neuro: 1024 elements operating at 670-720 kHz

Focused Ultrasound thalamotomy on medication resistant Essential Tremor

Focused Ultrasound Excellence Center, University of Virginia, USA
Essential Tremor Treatment
Targeting

Elias et al, NEJM, 2013
Essential Tremor Treatment

Awake, no anesthesia
No incisions
No burr holes
No electrodes
No infection
No blood clots
No brain damage

Courtesy of Uva
Courtesy of InSightec
Essential Tremor: Clinical results

- 18 Patients
- 75% reduction in hand tremor
- 85% improvement in quality of life

MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study

Nir Lipsman, Michael L. Schwartz, Yuexi Huang, Leslie Lee, Tejas Sankar, Martin Chapman, Kullervo Hynynen, Andres M. Lozano

The Lancet, 2013

- 4 patients
- >80% reduction in dominant hand tremor

Unilateral magnetic resonance guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes

Won Seok Chang,1 Hyun Ho Jung,1 Eun Jung Kweon,1 Eyal Zadicario,2 Itay Rachmilevitch,2 Jin Woo Chang1

- ~70% tremor reduction
Can we induce more subtle effects in the brain?
Ultrasonic Neurostimulation

Why use ultrasound for brain stimulation?

- Surface Electrodes
- Implanted Electrodes
- Transcranial Magnetic Stimulation (TMS)
- Optogenetic
Ultrasonic Neurostimulation

Why use ultrasound for brain stimulation?

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<thead>
<tr>
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Sprague Dawley rats / transcranial (n=10; all male, body weight 150-250 g)

Ketamin (66mg/Kg) / Xylazin (13 mg/Kg)

35-40 min

10-15 min search & work time

Wake up phase

Y Younan, T Deffieux, B Larrat, M Fink, M Tanter, J-F Aubry, Medical Physics, 2013
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Younan, T Deffieux, B Larrat, M Fink, M Tanter, J-F Aubry, Medical Physics, 2013
Low-Intensity Focused Ultrasound Modulates Monkey Visuomotor Behavior

Thomas Deffieux,1,3 Youliana Younan,1,3 Nicolas Wattiez,2 Mickael Tanter,1 Pierre Pouget,2,4,* and Jean-François Aubry1,4,*

a) Antisaccades / FEF region

Latency (ms)

350
300
250
200
150

ipsilateral
contralateral
NoStim
Stim
NoStim
Stim

**
***
NS

monkey Y
monkey L
Blood Brain Barrier

from Bellavance 2008
FUS Opening of the Blood Brain Barrier

Blood Brain Barrier

from Bellavance 2008

Courtesy of N. de Jong

from Vykhodtesva 2008
FUS Opening of the Blood Brain Barrier

Micro-bubbles injection + low pressure UltraSound (US)

Transient opening of endothelial tight junctions

from Bellavance 2008

from Vykhodtesva 2008

Courtesy of N. de Jong
BBB opening on rodents

MR compatible stereotactic brain system for rodents


T_{1w} Before

- 200μL Sonovue®
- 60s US bursts
  (3/100ms)

T_{1w} post Gd

BBB opening on rodents

**MR compatible stereotactic brain system for rodents**


\[ T_{1w} \text{ Before} \quad T_{1w} \text{ post Gd} \]

Blood brain barrier opening in monkeys with the pre-clinical prototype

Clinical Blood brain barrier opening with skull bone removed

17 patients with recurrent GBM before receiving systemic chemotherapy with carboplatin (dose escalating study)

Carpentier et al, Clinical trial of blood-brain barrier disruption by pulsed ultrasound, Science Translational Medicine, 2016
Ultrabrain project (transcranial focused ultrasound)

Collaboration Institut Langevin / Institut du Cerveau et de la Moelle (ICM)
Thermal Therapy

Ultrabrain project (transcranial focused ultrasound)

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Thermal Therapy

Ultrasonic Neurostimulation
Ultrabrain project (transcranial focused ultrasound)

Collaboration Institut Langevin / Institut du Cerveau et de la Moelle (ICM)

- Thermal Therapy
- Ultrasonic Neurostimulation
- Blood Brain Barrier Opening
Ultrabrain project (transcranial focused ultrasound)

Collaboration Institut Langevin / Institut du Cerveau et de la Moelle (ICM)

- Thermal Therapy
- Ultrasonic Neurostimulation
- Blood Brain Barrier Opening
- Ultrafast Functional Imaging
Ultrafast Functional Imaging

Ultrasonic Neurostimulation

Blood Brain Barrier Opening

Ultrafast Functional Imaging

**Ultrabrain project (transcranial focused ultrasound)**

Collaboration Institut Langevin / Institut du Cerveau et de la Moelle (ICM)

- Thermal Therapy
- Ultrasonic Neurostimulation
- Blood Brain Barrier Opening
- Ultrafast Functional Imaging

Small animal system

Primate system (neuronavigator)

Clinical system
Equipe Physique des Ondes pour la Médecine at Institut Langevin

Equipe Physique des Ondes pour la Médecine at Institut Langevin

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Jeff Elias & Robert Dallapiazza, UVA

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Bettencourt – Schueller foundation:
Save the date:

Winter School on THERAPEUTIC ULTRASOUND
Les HOUCHES, France
Directors:
G. ter Haar (UK), V. Khokhlova (Russia)
& J.-F. Aubry (France)

March 26-31, 2017
Save the date

17th ISTU meeting, **Nanjing, May 30-June 2 2017**

Jinling Hotel, Nanjing

www.istu.org
Thank you