MR guided Focused Ultrasound for Intraventricular Hemorrhage of Prematurity, and Pediatric Epilepsy

James M. Drake FRCSC

11th SANS & 2nd APNS Annual Meeting Joint Conference Riyadh April 2017

The Centre of Image Guided Innovation and Therapeutic Intervention (CIGITI)
The Hospital for Sick Children
University of Toronto, Canada
Objectives

• Discuss the MRgFUS program at CIGITI
• Focus on the progress to date in terms of modelling, technology enhancement in broad applications.
• Outline pre-clinical research in a treatment system for Intraventricular Hemorrhage of Prematurity in an animal model.
• Outline pre-clinical research in an application for targeting disconnection sites for epilepsy applications, with MRgFUS in an animal model.
CIGITI – Therapeutic Imaging

• “Incision-less” surgery with ultrasound and MRI guidance and Robotics

Philips 3T MRI with Integrated HIFU

Transducer
Embedded in
Therapy Table

Focus

Transducer

3D anatomy
and
temperature
mapping

Target
selection
and
treatment

Therapy Console
Sickkids HIFU Program

Core Faculty

- Karl Price
- Jeremy Tan
- Alex Chisholm
- Justin Wee
- Thomas Hudson
- Matt Walker
- Jonathan Murley
- Luc Larocque
- Maggie Hess

Students

- Adam Waspe
- Thomas Looi
- Vivian SiN
- Karolina Piorkowska
- Charles Moughenot
- Maria Lamberti-Pasculli
- Elodie Constanciel
- Jidan Zhong

Collaborating Faculty

- Agostino Pierro
- Roman Maev

U of T and beyond

- Elizabeth Donner
- Emily Tam
- Sevan Hopyan
- Sylvain Baruchel
- Abha Gupta
- Meredith Irwin
- Alisha Kassam
- Andrew Goldenberg
- Siv Sivaloganathan

- Samuel Pichardo
- Greg Czarnota
- Mojgan Hodaie
- Margaret Cheng
- Andrew Goldenberg
- Siv Sivaloganathan
- Roman Maev
Equipment and Resources

- Sickkids – Philips Sonalleve V1, Philips 3T - preclinical only
  - Small animal MRgFUS system FUS Instruments RK-100
- Sunnybrook – Philips Sonalleve V2, Philips 3T; InSightec Neuro, GE 3T, preclinical/clinical, major research group, Kullervo Hynynen/Greg Czarnota
- Toronto Western – InSightec Neuro, GE 3T clinical, Andres Lozano/Mojgan Hodaie
- Toronto General – InSightec Body, GE 1.5T clinical, Walter Kucharczyk
- Thunder Bay – Philips Sonalleve V2; Philips 3T, preclinical/clinical, Laura Curiel/Samuel Pichardo
Pre-Clinical Research Interests  MRgFUS

• Bone
  – Bone/Marrow Thermometry
  – Mathematical modeling of bone heating

• Brain
  – Pediatric skull ultrasound transmission characterization and refocusing
  – Sonothrombolysis of intraventricular hemorrhage of prematurity
  – MRI compatible robotic transducer positioning device
  – Thermal ablation of focal epilepsy targets

• Soft Tissue
  – Thermal ablation of neuroblastoma, pancreatic tumours, thyroid nodules
  – Motion compensation algorithms

• Vascular
  – Deep-vein thrombolysis, flow phantom

• Fetal
  – Thermal ablation placenta, lung cystic malformation, sacrococcygeal teratoma
Clinical Motivation – Neonatal
Clinical Motivation – IVH of Prematurity and Epilepsy

- IVH of Prematurity

Hypothalamic Hamartoma and Epilepsy

DTI images of Forniceal Fibre tracts Neonatal Piglet

Grade 2
Grade 3
Results – Enlarged Workspace

Bio-heat Computation

- Calculated using Pennes’ bioheat equation [7].
- Maximum in cortical: 68.5°C, muscle: 50.2°C, marrow: 52.2°C (true marrow max: 56.0°C).
- Parallel GPU computation time: Acoustic 20-22 seconds, Bio-heat 6-9 seconds (40x40x100 grid).
In Vivo Experiments

- Temperature map and thermocouple data from a 40W porcine femur therapy.
In Vivo Experiments

- Actual max temperature: 73.4°C
- Simulated maximum: 77.2°C

Phase 1 Clinical Trial - Bone HiFU

- First case of Osteoid Osteoma HiFU treatment in North America
  - 16 years old male
  - Incisionless and no radiation

Figure 32: Maximum temperature vs time for Patient 1, Sonication 11
(a) Sagittal slice, thermometry temperature distribution

(b) Sagittal slice, simulated temperature distribution

(c) Maximum temperatures along the Y axis

(d) Maximum temperatures along the Z axis
Comprehensive Correction

<table>
<thead>
<tr>
<th>Method</th>
<th>PCA-PDF</th>
<th>Benchmark PCA-Polynomial Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Stability (°C)</td>
<td>0.75</td>
<td>1.88</td>
</tr>
<tr>
<td>Mean Precision (°C)</td>
<td>0.99</td>
<td>2.05</td>
</tr>
</tbody>
</table>
Temperature Standard Deviation

Non-Cumulative Subtraction
Motion Compensation using Principal Component Analysis and Projection onto Dipole Fields for Abdominal Magnetic Resonance Thermometry. Jeremy Tan1,2,3, Adam C. Waspe1,2, Charles Mougenot4, Samuel Pichardo3,6 and James M. Drake1,2
MRgHIFU for Clot Lysis in IVH

Can we use the unique anatomical properties of neonates to treat them non-invasively with HIFU?

Developing an animal model and acoustic parameters to mechanically lyse clots

In-vitro Clot Lysis
Porcine Model

- Neonatal piglets ~ 3-5 kg
- Cranial Window
- Injection of 1 cc/kg fresh blood into lateral ventricle
- MRgFUS thromolysis

Clot Treatment. Left: Pre-treatment, Right: Post-Treatment
Research Progress – In-vivo Lysis

- IVH563301
Research Progress – In-vivo Lysis

- Imaging of last 2 animals
Research Progress – Clot Quantification Method

1) Preprocessing

T2-w DICOM

2) Registration

Normalized T2-w

3) Threshold

Ventricle Mask

Threshold Label

4) Select

Edited Threshold

5) Label Combine

Combined Label

6) GrowCut

Segmented Ventricles

7) Quantification
Research Progress – Chronic Model (T2)

Day 7

CSF accumulation


Day 14

Ventricle change

Day 21
Research Progress – In vitro clots testing with Boiling Histotrypsy technique

- Results: Porcine clots showed BH effect for power >325 with focused treatment zone

<table>
<thead>
<tr>
<th>Cell</th>
<th>Pre-treatment volume (ml)</th>
<th>Post-treatment volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*In vitro* Clot with BH Treatment (Left: Before, Right: After)
Research Progress – In vitro clots testing with BH technique

- Comparison to Cloud Cavitation technique, Boiling Histotripsy more focused and repeated with Sonalleve

*In vitro* Clot – Left: CC and Right: BH

Unchanged

Dissolved
Research Progress – In vivo testing with BH technique

• Goal: Can BH be used to induce cavitation in a control brain and clot model?
• Method:
  • Similar animal setup but completed 2 control piglets and 4 IVH piglets
Research Progress – Control cases 10ms

• Methods:
• 100-500W Acoustic
• Secondary testing 325-425W
• Long treatment
  • 12000 cycles, 10 ms pulse duration, 1.2MHz, 1% duty cycle, 1s pulse repetition and 25s treatment duration
• Short treatment
  • 1200 cycles and 1ms
Research Progress – Control cases
10ms

*In vivo* – Left: Pre-treatment, Right: Post-treatment (100-500W)
Results – Histology
10ms
Research Progress – Treatment Cases 10ms

*In vivo* – Left: Pre-treatment, Right: Post-treatment (IVH584448)
Research Progress – Treatment Cases 10ms

*In vivo* – Left: Pre-treatment, Right: Post-treatment (IVH584449)
Research Progress – Treatment Cases

*In vivo* Histology – Treated blood clot (Boiling histotripsy) Left:584448
Right:584449

“In Vivo Feasibility Study of Boiling Histotripsy with Clinical Sonalleve System in a Neurological Porcine Model” – T. Looi et al. ISTU 2016
## Research Progress – Summary of Treatment Cases

<table>
<thead>
<tr>
<th>Date</th>
<th>Animal ID</th>
<th>Pre-treatment Clot Volume</th>
<th>Post-treatment Clot Volume</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 7, 2015</td>
<td>584448</td>
<td>3113.98</td>
<td>1971.57</td>
<td>36.7%</td>
</tr>
<tr>
<td>March 28, 2016</td>
<td>584449</td>
<td>2585.08</td>
<td>1788.61</td>
<td>30.8%</td>
</tr>
<tr>
<td>March 29, 2016</td>
<td>577998</td>
<td>1291.63</td>
<td>923.64</td>
<td>28.5%</td>
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</table>
Acoustic characterization of a neonate skull using a clinical MR-Guided High Intensity Focused Ultrasound System for pediatric neurological disorder treatment planning

Elodie Constanciel Colas¹, Adam C. Waspe¹, Charles Mougenot², Thomas Looi¹,³, Samuel Pichardo⁴,⁵ and James M. Drake¹,³
8 yr old skull and phantom

Table 2: Ultrasonic attenuation of real skull and its phantom measured at 2.25 MHz. The measurements were done at four different spots (Figure 1) but due to irregular shape of samples the spots for the real skull and for the phantom may not be exactly the same.

<table>
<thead>
<tr>
<th>Attenuation at 2.25 MHz [dB/cm]</th>
<th>Real Skull</th>
<th>Phantom</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 - 70</td>
<td>34 - 43</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Measurements were done at four different spots of the skull and phantom (left picture – real skull; right picture – fabricated phantom).
Design of a Robotic Device for the Delivery of Transcranial, Magnetic Resonance Guided Focused Ultrasound for Intraventricular Hemorrhage of Prematurity

Karl D. Price, Vivian Sin, Charles Mougnot, Thomas Looi, Samuel Pichardo, Adam C. Waspe and James M. Drake
HOPE System

Surgical planning and treatment

Sonalleve Electronics

HIFU Robotic Positioner

Philips 3.0TX MRI

Neuro-interventional Coil
HIFU Robotic Positioner
Results – System testing
Calibration Method

- Imaged using T1-W 3D GE sequence with the cardiac coil
- Noise thresholding, volume selection and K-means
- Registration between image space to robot space
System Demonstration

- Treatment paradigm for MR guided US thrombolysis simulated
- Transducer mounted to robot in MR bore
- Simulated patient (gel phantom) with multiple ablation targets
- Imaging, targeting, thermal maps, robot motion, acceptable artefact
- Targeted and resultant lesions correspond

MR image showing transducer (red) and gel phantom (yellow) in water tank.

MR thermal image showing FUS 6 distinct focal points heating to a temperature of 60°C inside gel phantom.

Software - Robot Control

“HIFU for Pediatric Operations (HOPE) – A pediatric neurosurgical treatment system” – Drake et al. FUS Foundation Meeting 2016
MRgFUS for Drug Resistant Epilepsy

• 1% of population will develop epilepsy
• 1/3 of pediatric patients develop drug resistant epilepsy
• major source of behavioural, cognitive, developmental disability
• Epilepsy surgery significant morbidity, risk.
• Recent interest MRg laser thermal ablation
• UVA Opening protocol for MRgFUS for epilepsy
MRgFUS for Epilepsy
Targeting White Matter Tracts
High Resolution DTI, Porcine Model.

ISTU 2016
target 1
target 2
target 1
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
</table>
| Active cluster     | Treatment Cell Cluster 4
|                    | 2 mm Regular Cell 2 |
| Sonication Parameters |               |
| Test Sonication    |                 |
| 1.2 MHz            |                 |
| 1.4 MHz            |                 |
| Power (W)          | 60             |
| Duration (s)       | 20             |
| Temperature Curve  | Auto range     |
|                    | max 63.0 °C, 21.0 s |

Use Hardware Controls when ready to proceed.

Scanner Time Settings Differ
Non-default Scan Protocol
Available Secondary Disk Space Getting Low
Start Scan Protocol
T1w: Pre vs. Post

target 1

Histotripsy: 375W; 1% duty cycle; 10 ms pulse duration 1s repetition; 25s duration.
MDWI Pre vs. Post

Pre vs. Post

target 1
Tracts: Pre vs. Post
(SD_stream, full view)

Pre vs. Post

Target 1

Target 2
Tracts: Pre vs. Post
(ST Deterministic, full view)

target 1

Pre

vs.

Post

pig14
Tracts: Pre vs. Post
(whole brain, SD_stream)

“In Vivo And Post-Mortem Brain Analysis of Diffusion Tensor Tensor Images And Diffusivities - Application and Relevance to MR-Guided Focused Ultrasound Treatment” – Walker et al. ISTU 2016
target 2

784_L2
Conclusions

• MRgFUS has myriad applications to pediatric neurological disorders including hemorrhage, epilepsy, neoplasms, and beyond

• The pediatric skull may broaden potential applications due to its relative ultrasound transparency

• New ultrasound energy deposition strategies and targeting may similarly increase the range of applications, their accuracy and effectiveness