Sonication & Feedback Control Strategies for MRg Hyperthermia with the Insightec Prostate Array

Vasant A. Salgaonkar, PhD

Thermal Therapy Group, Radiation Oncology

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Presentation Outline

- Introduction
  - Hyperthermia (HT): Clinical significance, delivery, monitoring
  - Overview: Insightec ExAblate system
- Numerical study & preliminary analysis
  - HT-specific operational modifications to prostate ablation array
  - Experiments in phantom
- Real-time MRTI & Control *in vivo*

Hyperthermia – Clinical Significance

- Typical HT regimen combined with radiation or chemotherapy
  - 40 – 45 ºC, T_{90}>40.5 ºC, CEM43C: 6 – 10 min, time: 30 – 60 min

Compelling Evidence: Recent Randomized Phase III Trials
- Glioblastoma : 2 yr Survival - 15% to 31%
- Melanoma: 2 yr local control - 28% to 46%
- Chest Wall Recurrence (Breast Cancer): CR - 43% to 77%
- Advanced Pelvic Disease: CR - 39% to 55%
- Head & Neck Tumors: 5 yr local control – 24% to 69%
- LA Cervical: 3 yr survival 27 to 51%; local control 41 to 61%
- Sarcoma (HT+-CT): disease free survival – 16.2 to 31.7 mo

HT – Emerging Applications

- Targeted drug delivery – liposomes
- Anti-tumor immunity stimulation
- Immune modulation for cancer vaccines
- Hormone therapy

Temperature sensitive liposomes release drugs (Ponce 2006)

Prostate HT

- Precise delivery of uniform HT to prostate is challenging
- Ultrasound (US) applicators for targeted prostate HT
  - Smith 1999, Nau 2005

Interstitial array for HT + HDR brachytherapy

Endorectal (ERUS) phased array

MRgHIFU – Drug Delivery

- Recent animal studies of HT with MR-guided HIFU systems
  - Scanned focus for liposome drug release (Staruch 2011, Partanen 2012)
  - Pulsed-HIFU for enhanced docetaxel uptake (InSightec, Mu PMB 2012*)

Pulsed-HIFU HT with Insightec fibroid array

MR Thermometry (MRTI) during HT

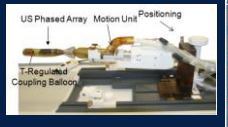
- Precise temperature measurement necessary in HT
- Long-term MRTI during HT is challenging
  - Motion, susceptibility changes, phase drift
- Compensation: Accuracy 0.3 – 1 ºC reported during MRgHT
  - Temp. reference fiducials
  - Multi-baseline
  - Referenceless

Craciunescu, Med Phys, 2011

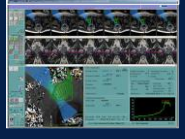
Prostate Treatment with ExAblate 2100

- Clinical trials for focal tumors + whole gland ablation
- ExAblate prostate array at multiple sites
- Motivation: Fast track prostate HT with ExAblate 2100

ERUS phased array (2.3 MHz)



InSightec MRgHIFU for Prostate Ablation



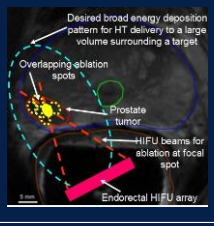
Study Objectives

- Implement HT-specific, long-duration sonications
  - Work within ExAblate system constraints
- Real-time MRTI and control for HT with ExAblate prostate array

Models: Indentify Array Beamforming

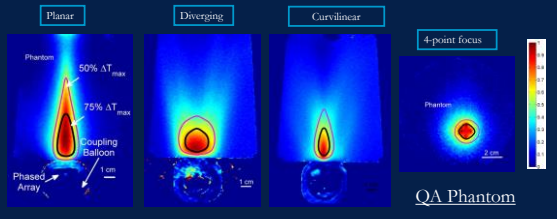
- Hardware and software specs of ExAblate prostate array
  - Proprietary array layout, dimensions
  - Proprietary element interconnection scheme
  - Phase round offs
  - Input power limitations
- Pennes bio-heat model

HIFU ablation vs HT



HT-specific Beamforming Examples

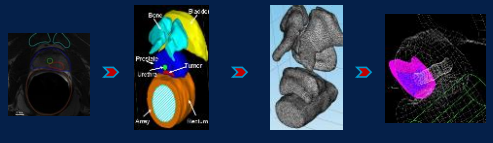
- CW sonications (15 min), time-avg surface intensity = 0.86 W/cm^2
- MRTI - 3.0 T, PRFS, SPGR: TE = 16 ms, FOV = 14 cm, FA = 30^o



QA Phantom

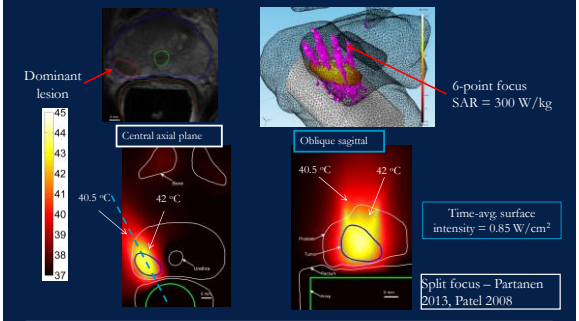
Patient-Specific Models - Feasibility

- Pennes bio-heat transfer equation in 3D
- Patient specific geometry
- Temperatures calculated using commercial FEM solver

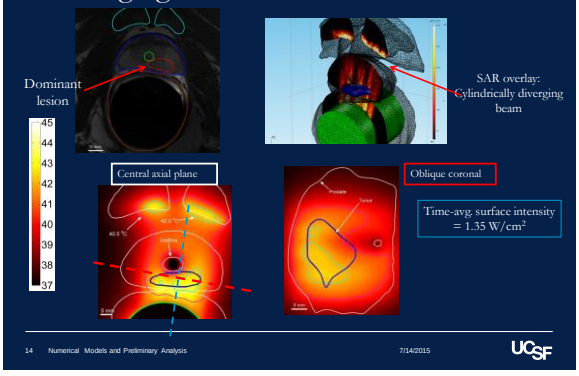


Segmenting MRIs | 3D Rendering in Mimics | FE Mesh in 3-Matic | FEM in Comsol

Conformal HT: Multi-foci Sonication



Diverging Sonication: Volumetric HT

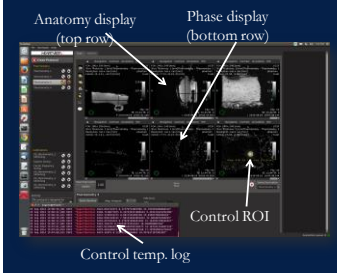


Beam-pattern Analysis

- Useful illumination patterns for HT

Beamforming	Surface Intensity (W/cm²)	Vol. T>40 °C (cm³)	Vol. T>41 °C (cm³)	Targeting capability and caveats
Simultaneous multi-point focusing (Num of foci = 4 – 8)	0.68 – 0.72	8.8 – 10.6	4.5 – 5.8	Selective heating of small targets. Potential unwanted hotspots due to side lobes from shallow or off-axis focusing. Useful for tailored conformal HT
Curvilinear focusing (depth = 25 – 35 mm)	0.7 – 0.75	12 – 12.1	6.0 – 6.6	
Diverging sonication (radius of curvature = 10 – 40 mm)	1.05 – 1.2	24.4 – 37.2	13.3 – 21.5	Uniform energy deposition. Suitable for targeting posterior quadrants and hemi-gland targets. Potential bone heating..
Planar sonication	0.94	35	22.8	

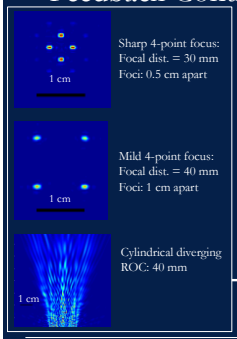
Development of MRTI with Prostate Array

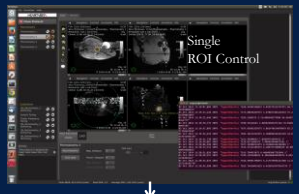


- RTHawk real-time MRI system, GE 3T MR scanner
- SPGR pulse sequence
  - TE = 13.4 ms, FOV = 28-32 cm, 3 s/slice
- PRFS thermometry
- 95% CI for baseline temp
  - 0.4 – 1.2 ºC (5×5 pix ROI)

Multi-slice RT Hawk GUI

Feedback Control





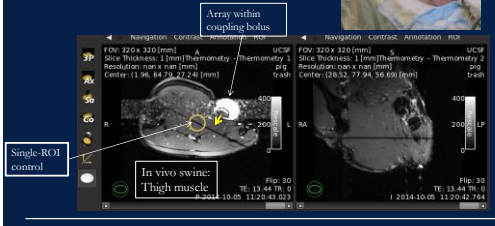
PI Feedback Controller

Sonication duty cycle modulation

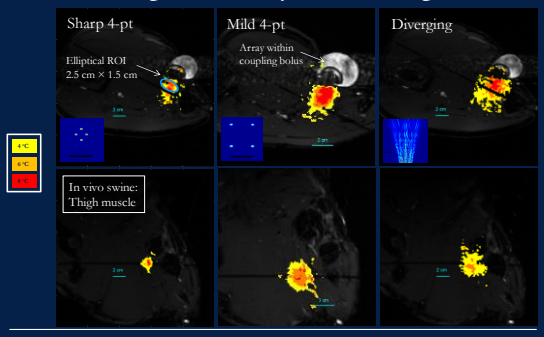
InSightec ExAblate 2100 Ablation System

In vivo Assessment: Swine study

- Acute study - 28.7 kg female swine
- Respiration:10 breaths/min
- Heart rate ~87 beats/min

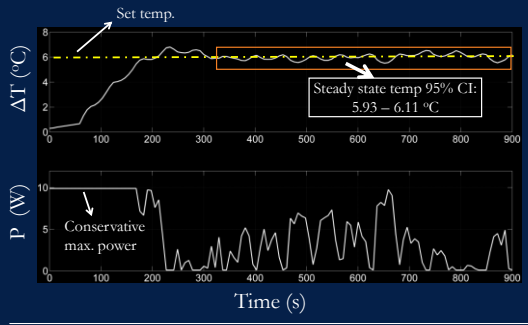


HT examples: Steady-state Temps.



19 Real-time MRTI & Control *In Vivo* 7/14/2015 UCSF

Example: Control Temp. & Power



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Conclusions

- Modifications to ExAblate for HT delivery were successful
- Implemented HT delivery and MRTI/control *in vivo*
- MRgHT with InSightec prostate ablation system feasible
- Additional work necessary for clinical implementation
  - Dynamic beam patterns (FUSIMO)
  - Multi-ROI for volumetric control
  - Extend accuracy of MRTI

21 Concluding Remarks 7/14/2015 UCSF

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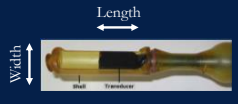
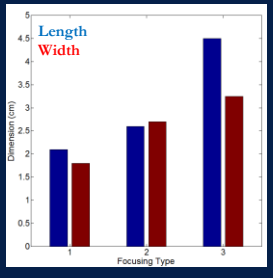
$\Delta T = 4\ ^{o}C$ Dimensions

- 1: Sharp 4-point focusing
- 2: Mild 4-pt focusing
- 3: Diverging





Beam plots – Yuan Zhang, Kim Butts, Stanford University