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Modeling of Thermal Damage from Focused Ultrasound Exposures for Heterogeneous Tissues

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* Some content adapted from lecture notes from Rajiv Chopra and Charles Mougenot and cited references

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What is Focused Ultrasound?

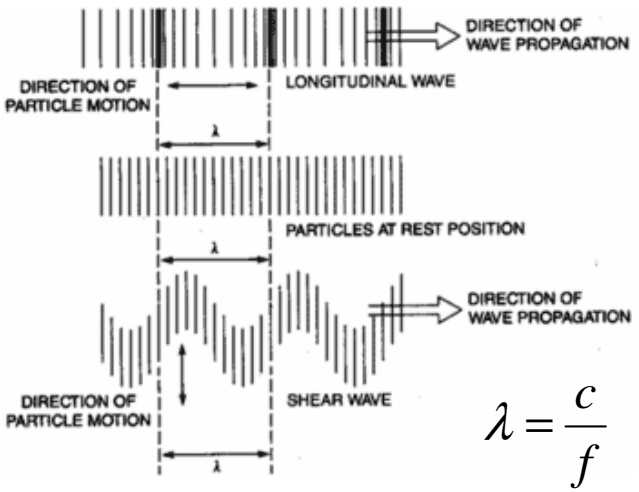
- Focused ultrasound is a noninvasive technique to enhance biological therapies by exposing tissues to acoustic energy:
  - Spatial / temporal control over temperature
  - Localized drug delivery (thermal, mechanical)
  - Functional / structural modification of tissues

- Clinical adoption of FUS has expanded rapidly in recent years due to an active research community, strong commercial support, and better visualization/thermometry tools

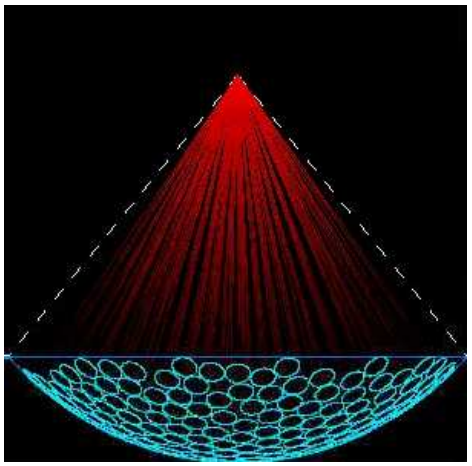
- Paediatric/foetal applications are starting to be explored, due to the potential to delivery a non-ionizing energy based therapy, in a noninvasive manner

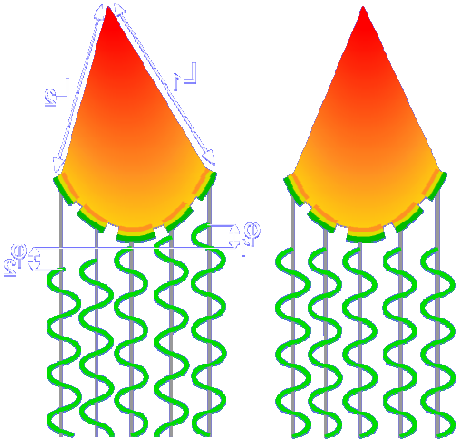
Focused Ultrasound Principles

- Ultrasound generates 2 types of waves when interacting with tissue
  - **Longitudinal** (fluids, soft tissue and bone), and shear waves (bone only)
  - Pressure is positive during compression and negative during rarefaction of the wave
- As waves traverse a lossy medium, attenuation (**absorption**, scattering and mode conversion) reduces the energy delivery
- Waves are focused geometrically, mechanically, or electronically to aim all the energy emitted from the transducer into a small target
- Acoustic intensity (power focused over a small area) determines the amount of thermal energy deposited at the focus



$$\lambda = \frac{c}{f}$$





How is Acoustic Energy Described

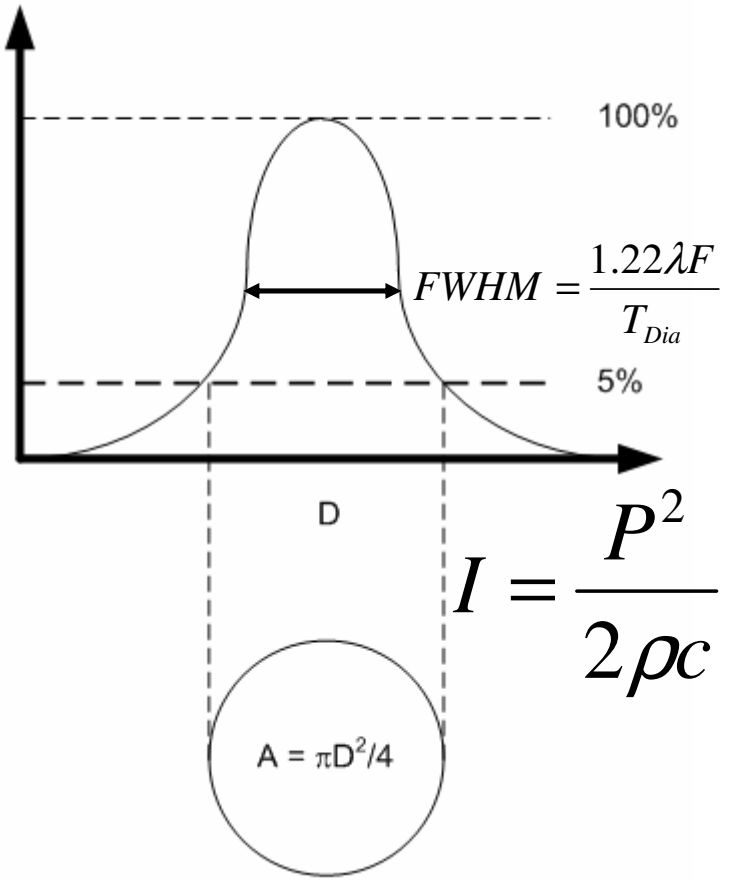
- **Electrical Power:** delivered to the transducer by the RF amplifier [W]

$$Power = \iint_{\infty} I(x, y)dxdy$$

- **Acoustic Power:** electrical power de-rated by the measured transducer efficiency (η) [W]

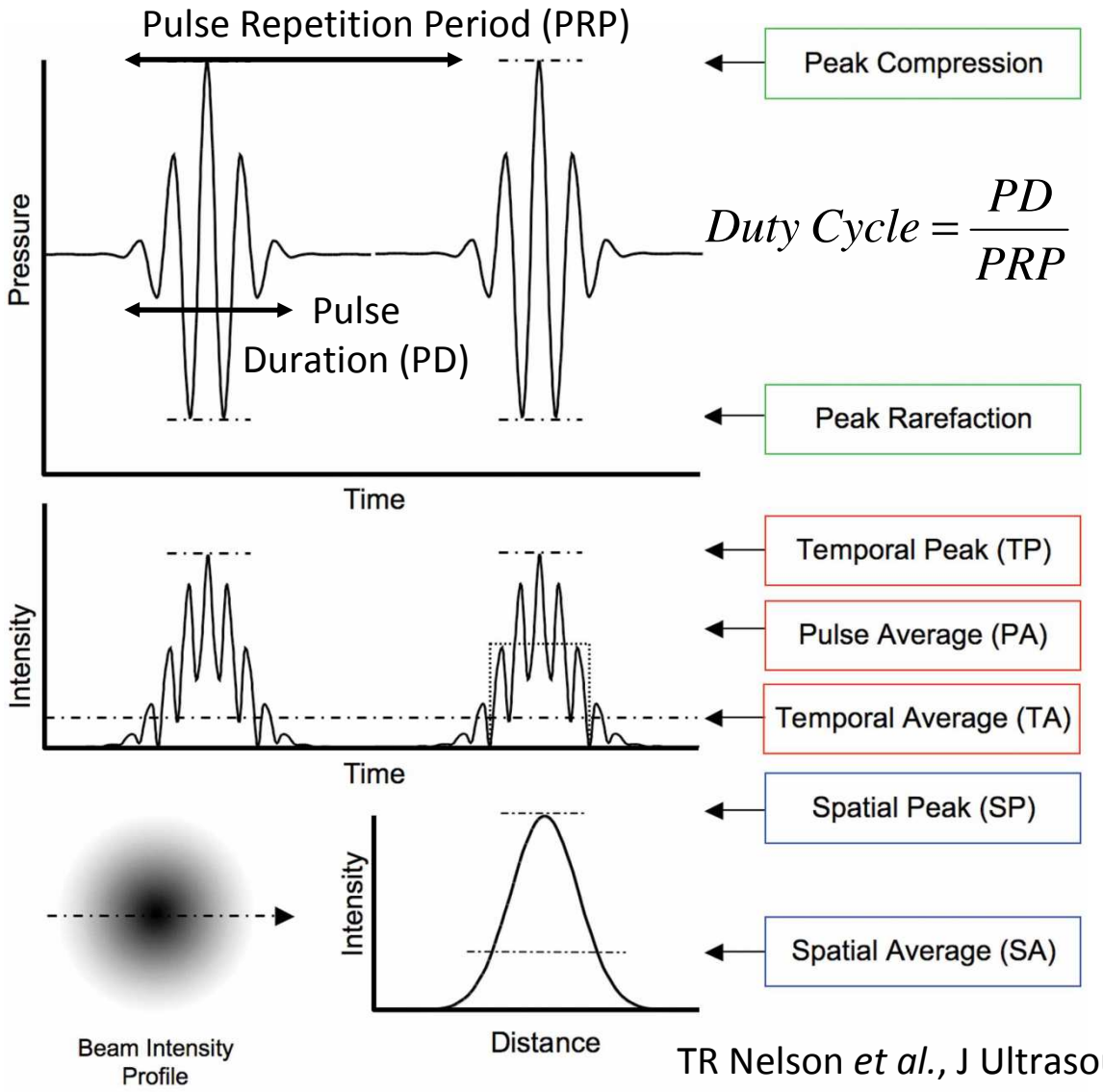
- **Acoustic Intensity (*I*):** Majority of the acoustic power traverses through the FWHM of the focus [W/cm^2]

- **Acoustic Pressure (*P*):** Peak positive (compressional) and peak negative (rarefactional) pressure of the longitudinal ultrasound wave [MPa]



$$I = \frac{P^2}{2\rho c}$$

Definitions of Intensity



$$Duty\ Cycle = \frac{PD}{PRP}$$

- I_{SPTP}: related to mechanical bioeffects and cavitation [~MPa^2]
- I_{SATA}: related to the magnitude of thermal bioeffects [~W/cm^2]
- I_{SPPA}
- I_{SPTA}
- I_{SATP} $\quad I_{TA} = I_{PA} \times Duty\ Cycle$
- I_{SAPA}

TR Nelson *et al.*, J Ultrasound Med, 28:139–150, 2009

Attenuation of Ultrasound Waves

- As sound traverses tissue, pressure (amplitude) and intensity are derated with distance by the same ratio
- **Absorption (*α*)**: conversion of acoustic energy into heat
- Attenuation is frequency dependent and is approximately linear for most soft tissues [dB/cm/MHz]

$$\alpha[dB/cm] = a[dB\ cm^{-1}MHz^{-1}]f^{b} \quad b \approx 1.2 \text{ for most soft tissues}$$

- The goal with thermal FUS therapies is to minimize the attenuation in the near field of the transducer and maximize thermal absorption at the focus

Attenuation of Ultrasound Waves

- Attenuation at a depth (d) is modeled as an exponential decay of the wave amplitude (base$_e$) $P_d(d) = P_o e^{-\mu_a d}$
- Attenuation is reported using dB (base$_{10}$)

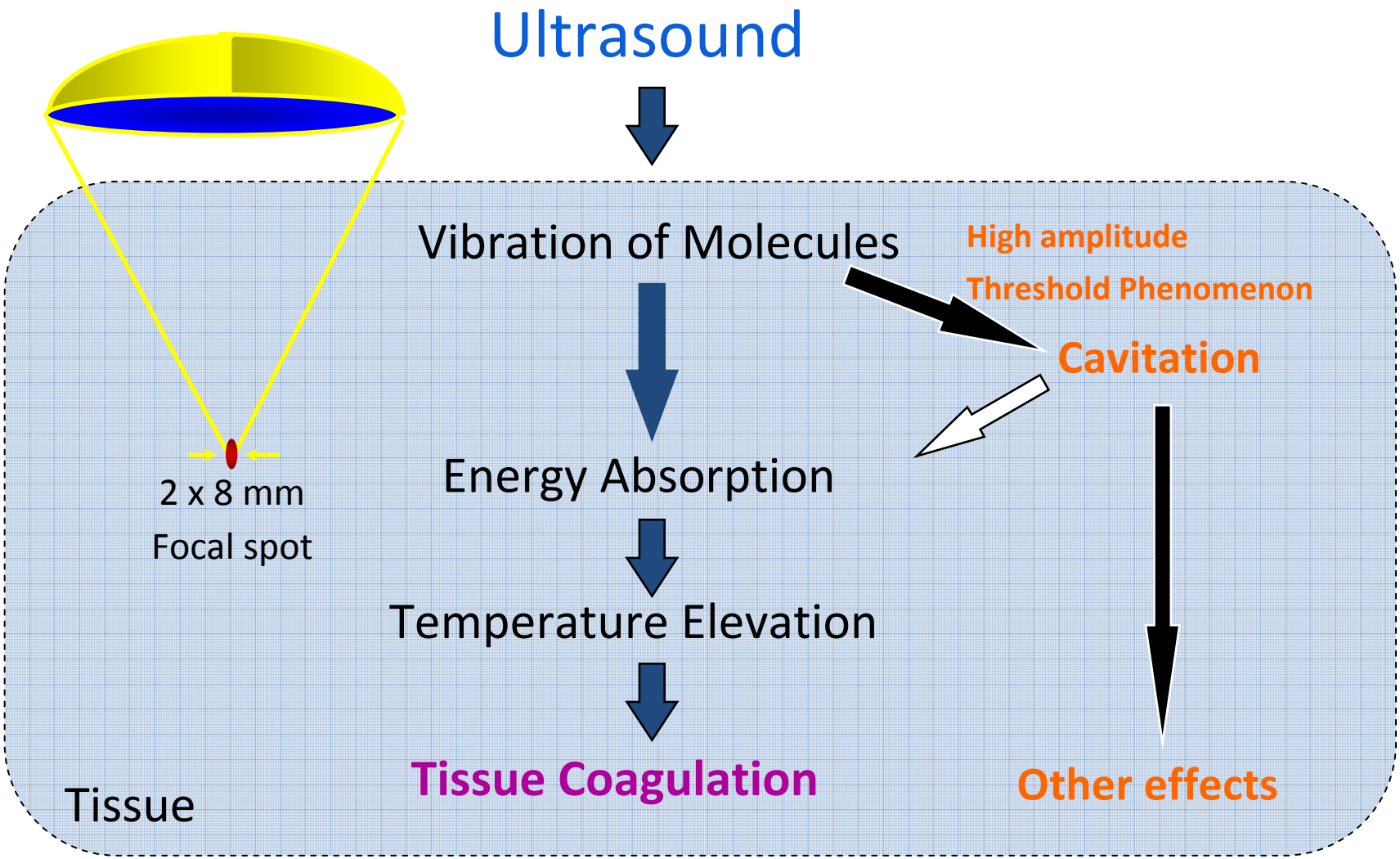
$$\text{Relative pressure level (dB)} = 20\log_{10}\frac{P_d}{P_o} \equiv 10\log_{10}\frac{I_d}{I_o} = \text{Relative intensity level (dB)}$$

- The Neper [Np] is a base$_e$ logarithmic ratio

$$\alpha[dB/cm] = 20(\log_{10} e)\mu_a \approx 8.7\,\mu_a[Np/cm] \rightarrow 1Np = 8.7dB$$

$$\text{Relative Pressure}[dB] = 20\log_{10}\frac{P_d}{P_o} = 20\log_{10}\left[\exp\left(-\frac{\alpha}{8.7}d\right)\right]$$

Therapeutic Ultrasound Interaction with Tissue



Ultrasound Treatment Techniques

- **Cavitation:** high-power pulsed-wave (PW) exposures (100-500W, 0.1-10% duty cycle, 1um to 100 ms burst durations) to mechanically break up tissues
- **Ablation:** high-power continuous-wave (CW) exposures (10-200W, 5-60s exposures) to thermally coagulate tissues
- **Hyperthermia:** low-power CW exposures to locally control temperatue without coagulation
- **Sonoporation:** low-power PW exposures (usually combined with a microbubble contrast agent) to mechanically weaken cell membranes, open tight-junctions between cells, etc.

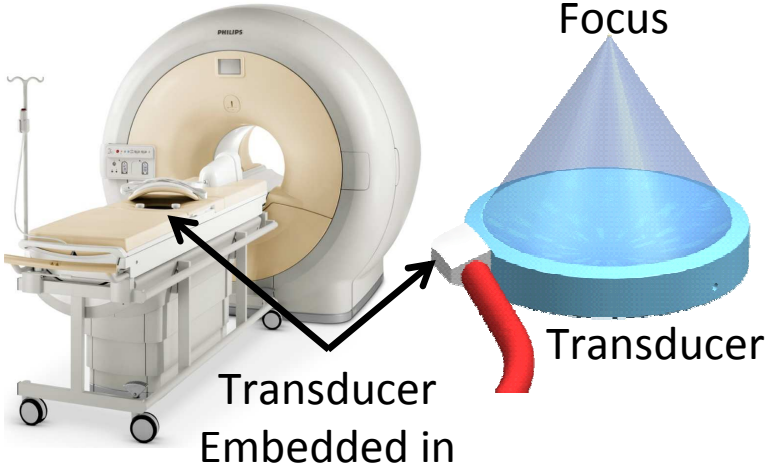
HIFU Treatment of Bone Tumours

Gd-T_1-w MRI of an 18-year-old woman who underwent HIFU ablation for tibia osteosarcoma. (a) Before HIFU treatment shows a hypervascular lesion (arrow) in the tibia. Images obtained (b) 2 weeks and (c) 12, (d) 24, and (e) 36 months after HIFU show no evidence of enhancement in treated tumor region (arrow).

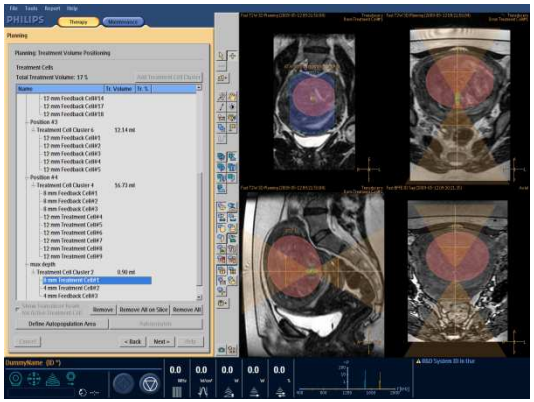
[1] Primary Bone Malignancy: Effective Treatment with High-Intensity Focused Ultrasound Ablation *Chen W., et al., Radiol., 2010; 255(3):967-78.*

How Does MR-HIFU Work?

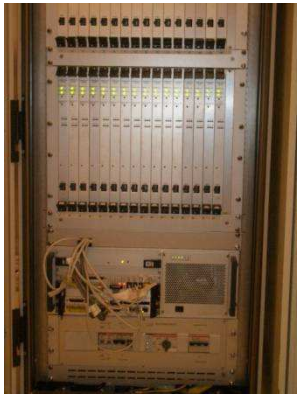
Philips 3T MRI with Integrated HIFU



3D anatomy and temperature mapping



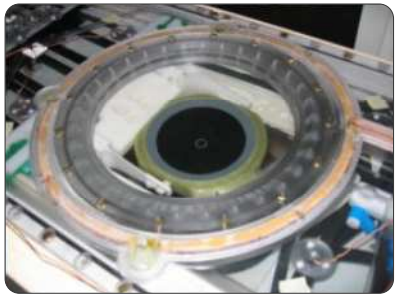
Therapy Console



Ultrasound Driving Electronics

RF Power

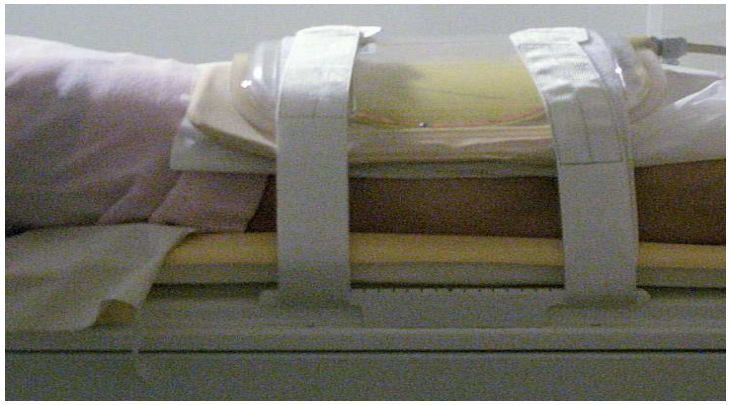
Motor Control

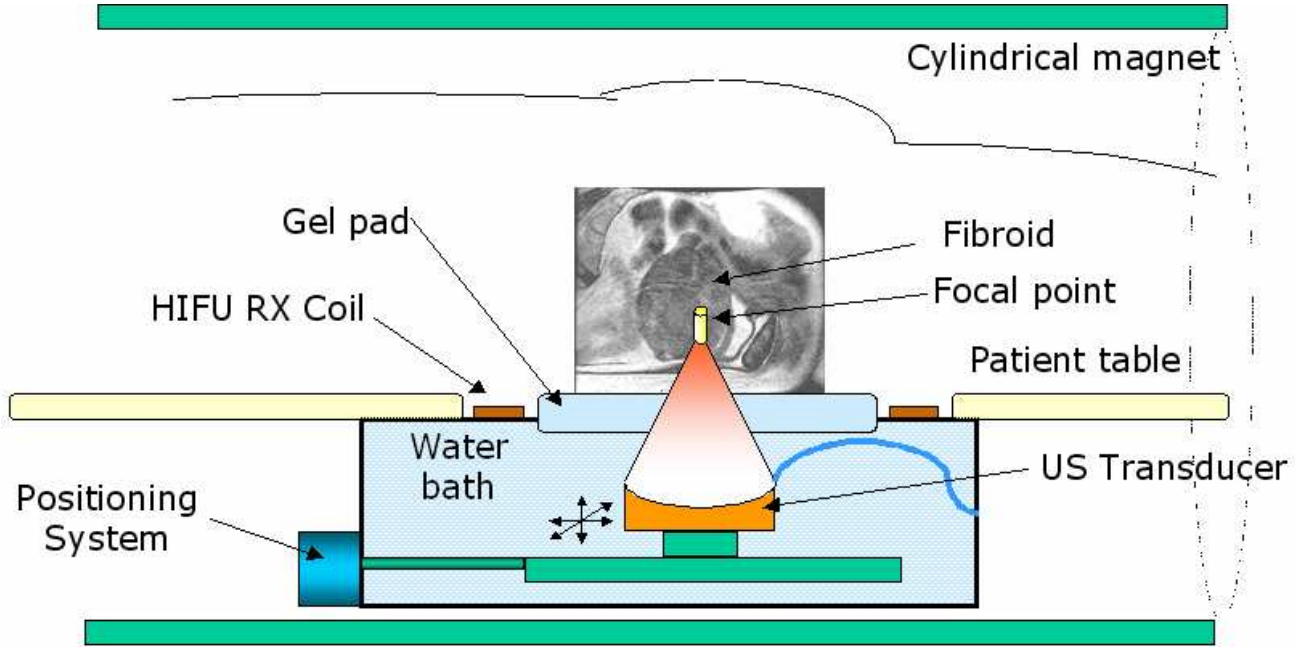


Phased Array Transducer

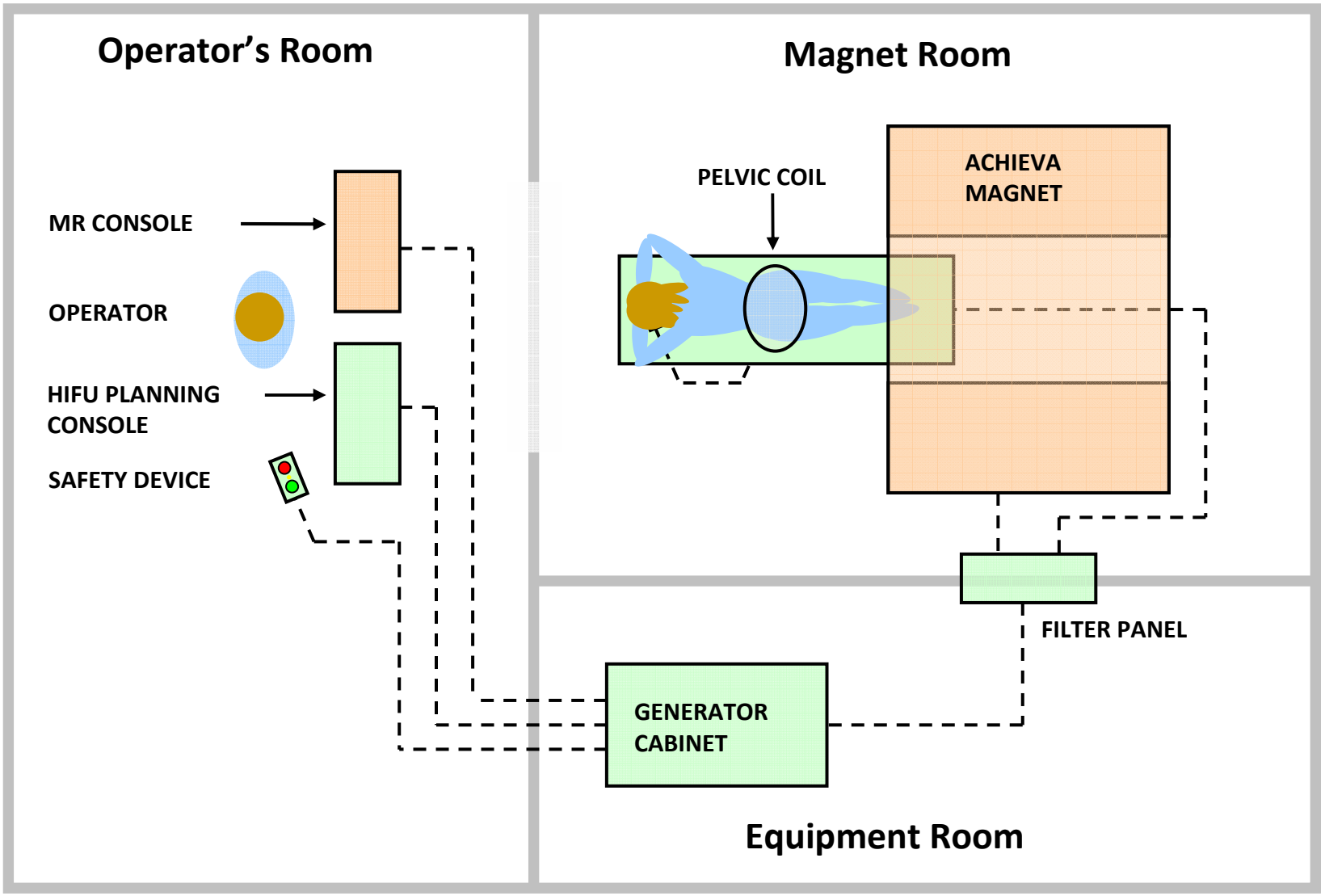
Thermotherapy

System Setup





MR-HIFU Treatment Facility



MRI Thermometry

- Temperature measurement is based on the water proton resonance frequency (PRF) shift induced phase differences between dynamic frames
- Temperature in bone and fat tissue can not be measured with the PRF method
- From MR dynamic phase images a relative frequency shift is be calculated
- The phase of a MR image is sensitive to disturbances such as transducer movement and magnetic field drift and to patient movement

MR Thermometry

- Temperature maps calculated from phase differences between successive dynamic frames as

$$\Delta T = \frac{\Delta\phi}{2\pi\alpha\gamma B_0 \cdot TE}$$

$\Delta\phi$ = Phase Shift [rad] $\rightarrow$ bounded by $[-\pi : \pi]$

α = Temperature Sensitivity Coefficient = 0.01 ppm / °C

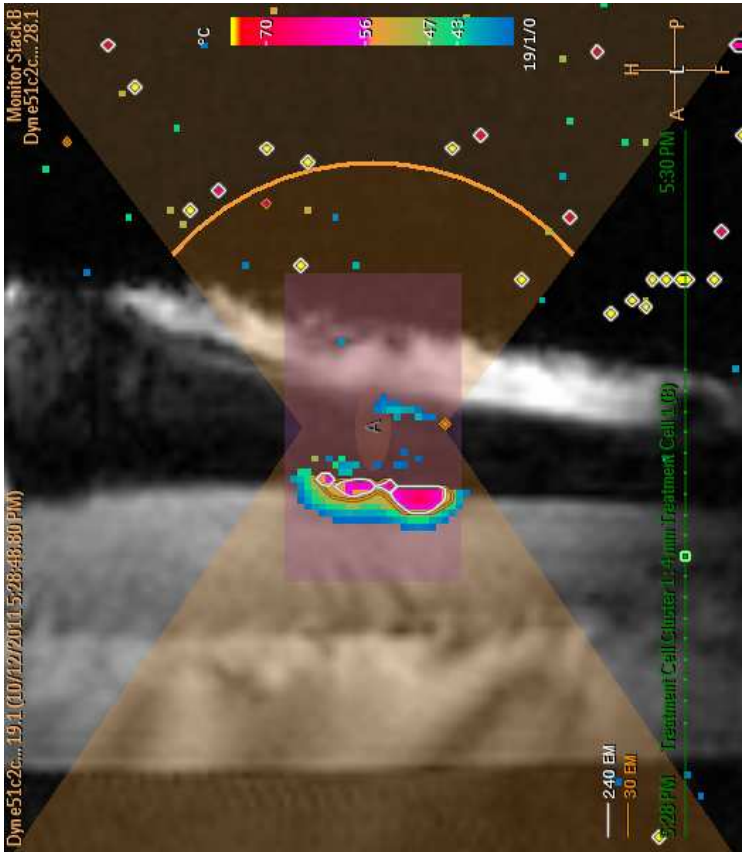
γ = Gyromagnetic Ratio [MHz/T] = 42.58 MHz/T for ^{1}H

B_o = Magnetic Field Strength [T]

T_E = Echo Time [s]

- Temperature maps are calculated on-line during sonication and displayed as overlays on the magnitude image

Bone MR Thermometry Example



Heating signal is strong at bone surface but non-existant in the cortical bone and fatty bone marrow.

Thermal Dose Model

- Thermal dose is calculated on a voxel-by-voxel basis as a time integral as temperature is measured throughout treatment

$$TD(t) = \int_0^t r^{(43 - T(t))} dt$$

$$r = 0.25 (T < 43°C)$$

$$r = 0.50 (T > 43°C)$$

- 240 EM (**equivalent minutes**) at 43℃ is sufficient to cause thermal necrosis in “soft tissue”

- **Caution**: a 1 second exposure at 57℃ can produce thermal necrosis (273 EM)

Advantages with this Model

- The ***increase*** in the rate of cell killing with temperature is relatively constant (for T>43, T<43)
  - For every degree above 43°C the required time to coagulate the tissue halves (120 minutes @ 44°C, 60 minutes @ 45°C)
- Formulation relates all time-temperature curves back to a single temperature, chosen arbitrarily as 43°C – trend seems to be conserved across multiple cell types, even though sensitivity to heat will differ
- Model valid for high temperatures seen in HIFU
- Valid for tissues with different thermal sensitivity but threshold for thermal dose required for cell death changes

Problems with this Model

- Different tissues have varying thermal sensitivity and will ablate at different thermal doses:
  - "soft tissue" will become necrotic at 240 EM
  - Nerve tissue may damage at much lower doses
  - Bone may require much higher dose for ablation
- Non-linear response between temperature and cell death higher probability of dying with increasing temperature and time of exposure
- Measuring dose does not directly predict damage
- Model primarily validated for cell cultures so ambiguity between calculated thermal dose and ablation volumes from imaging/pathology

Pennes Bioheat Transfer Model

- Proposed in 1940s for modeling heat transfer in the body due to an externally applied heating/cooling sources
- Harry Pennes (a Neurologist at Columbia Univ) experimented on patients by inserting thermocouples into patients' forearms
- Model accounts the thermal conductivity, specific heat capacity, and blood perfusion of specific tissue types (muscle, organs, skin, etc)

Pennes Bioheat Transfer Equation

- Validated heating model (does not predict dose or thermal damage) that has "stood the test of time" against other models and is applicable to many different heating source types (ultrasonic, RF, laser, etc.)

$$\rho c = \frac{\partial T}{\partial t} = \nabla \cdot k \nabla T - \omega c_b \left(T - T_b \right) + Q$$

- Highly dependent on "good" tissue properties

ρ = Tissue Density [kg/m^3]
c = Specific Heat Capacity [J/kg/°C]
k = Thermal Conductivity [W/m/°C]
ω = Blood Perfusion [kg/m^3/s]
Q = Heat Deposition from Ultrasound [W/m^3]
T = Temperature [°C]
T_b = Arterial Blood Temperature [37°C]
t = Time [s]

Modeling Questions

1. Can a tissue type dependant thermal damage model (similar to the Pennes Bioheat model for tissue heating) be derived that takes into account the thermal dose, thermal conductivity, thermal diffusion, specific heat, and perfusion of the tissue of interest and surrounding structures?

1. Can a spatially dependant (and perhaps a patient specific) thermal damage model be derived which can work directly with intraoperative temperature measurements to better predict the volume of ablated tissue during a MR-HIFU treatment?

Some Tissue Properties

- Wide range of tissue properties reported in literature spanning over > 50 years.

Table I. Material properties of tissues.

Medium	Density (kg/m^3)	Velocity (m/s)	Attenuation (Np/m/MHz)	Thermal conductivity (W/m/°C)	Specific heat (J/kg/°C)	Perfusion rate ($kg/m^3/s$)
Muscle	1041 [35]	1576 [35]	5 [75]	0.5 [35]	3430 [35]	0.6923 [35]
Bone	1420 [35]	3260 [35]	105 [35]	0.38 [35]	1700 [35]	0.892 [76]
Spinal canal and nerves	1038 [35]	1542 [35]	12† [35]	0.515‡ [35]	3640‡ [35]	3.63 [77]
Intervertebral disc	1165* [35]	1627** [78]	53.3* [35]	0.61 [79]	2713 [79]	0 [80]
Carbon dioxide	1.66 [81]			0.018 [81]	871.5 [81]	0
Blood					3800 [35]	

Tumour tissue is assumed to have the same properties as muscle, but with a higher perfusion of 2.4 $kg/m^3/s$ [82,83]. Values for nerve (†) and brain (‡) were used for some spinal canal properties. Values for tendon (*) and cartilage (**) were used for some intervertebral disc properties.

- Conductivity, specific heat, and perfusion vary greatly over tissue types.

* Adapted from Scott et al, Int. J. Hyperthermia, 2014; 30(4): 228-244.

CEM 43°C	Tissue type	Type and degree of change				Species
		Acute		Chronic		
		Minor	Significant	Minor	Significant	
0–20	BBB		F			Dog
	Bone marrow	F/H				Mouse
	Brain	H		H		Dog/cat
	Conjuctiva	G				Rabbit
	Kidney	H				Mouse
	Retina			G/H		Rabbit
	Spleen	F (enzyme)				Mouse
	Testicle	F	H	F	F	Mouse
21–40	BBB		F			Dog
	Brain	H/G		H/G		Dog
	Cornea	G				Rabbit
	Eyelid	G				Rabbit
	Prostate			H		Dog
	Rectum	H				Pig
	Retina	G				Rabbit
	Rodent appendage	G		G		Mouse/rat
	Skin	F				Mouse
	Small intestine		H			Mouse
41–80	Anterior chamber	G				Rabbit
	Brain		H/G		H/G	Dog
	Choroid			G		Rabbit
	Cilliary body	G				
	Cornea		G			Rabbit
	Fat	H				Pig
	Lens		G		G	Rabbit
	Liver	H				Rabbit
	Muscle	H				Pig
	Peripheral nerve		F/H		F/H	
	Rectum	H				
	Retina		G	G		Rabbit
	Rodent appendage		G	G		Mouse/rat
	Sclera	G				Rabbit
	Skin		G/H		G/H	Mouse
>80	Anterior chamber	G				Rabbit
	Bladder				G	Dog
	Choroid			G		Rabbit
	Cilliary body		G			Rabbit
	Conjunctiva	G				Rabbit
	Cornea		G			Rabbit
	Esophagus	H	H	H	H	Pig
	Eyelid	G				Rabbit
	Fat			G/H	G/H	Pig
	Lens		G		G	Rabbit
	Liver	H				Rabbit
	Muscle			G/H	G/H	Pig
	Peripheral nerve		H/F/G		F/G	
	Prostate	H	G			Dog
	Rectum		H			
	Retina		G			Rabbit
	Rodent appendage		G		G	Mouse/rat
	Sclera	G		G		Rabbit
	Skin		G/H		G	Pig
	Small intestine		H		G/H	Pig/dog

Acute (Tissue evaluated 0–30 days after heat exposure); Chronic (Tissue evaluated >30 days fater heat exposure); BBB = blood brain barrier.

Histolopathology (H); Gross appearance (G); Function (F).

More Tissue Properties

- Temperature sensitivity varies greatly across tissue types and species

- Values in literature are mostly determined from in vitro cell cultures and vary greatly and span many decades

- In practice: disconnect between temperature measurement and prediction of resulting thermal damage/dose

* Adapted from Dewhirst et al, Int. J. Hyperthermia, 2003; 19(3): 267-294.

Summary of HIFU

- MR-HIFU is a flexible energy-based treatment modality
- Focusing the ultrasound beam enhances the treatment over a small target area by a factor of ~1000X
- Attenuation is the primary contributor to both losses on the way to the target **AND** is the mechanism for thermal treatment at the target
- MR thermometry “closes the loop” to monitor and control treatment temperatures in real time
- **Caution:** thermal dose builds up cumulatively and at an increasing rate with temperature Current models do not account for differences in tissue types (may under/ over dose thermo-resistive/sensitive tissues)

References

[1] Sapareto S.A. and Dewey W.C., Thermal dose determination in cancer therapy. Int J Radiat Oncol Biol Phys, 10(6): p. 787-800 (1984).

[2] Sassaroli E., Li K.C.P., O'Neill B.E., Modeling focused ultrasound exposure for the optimal control of thermal dose distribution. The ScientificWorld Journal, Article ID 252741, 11 pages, (2012).

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[6] Dewhirst M.W., et al, Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. Int J Hyperthermia, 19(3): p. 267-294 (2003).

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