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Syllabus contribution for:

Physics of Focused Ultrasound

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Highlights:

Who will benefit from this information?

Any medical practitioner or researcher involved in the adoption of Focused Ultrasound Surgery into clinical practice, or Focused Ultrasound research at large, with limited or no technical background in ultrasound physics. The lecture will cover several principles at the undergraduate physics level, avoiding complicated mathematical expressions, but delivering general '*rules-of-thumb*' (with associated expressions in their simplest format) that may be implemented to determine the degree to which the principles are of significance, to a given Focused Ultrasound application.

"How was a problem determined?"

Focused Ultrasound research has always been a highly multi-disciplinary endeavor – perhaps now more than ever, requiring close collaboration throughout a 'pipeline' of physicists, engineers (from electrical through to biomedical), cell biologists, life scientists and ultimately, of course, medical practitioners. This course is particularly aimed at professionals toward the latter stages of this pipeline, with an interest in the physical principles underpinning Focused Ultrasound application.

"What will learners be able to do differently because of this information?"

Attendees will be benefit from an overview of basic concepts, as well as an introduction to several 'advanced' topics associated with Focused Ultrasound. The *rules-of-thumb* are intended to allow a quick and easy (if informal) assessment as to the degree to which any particular topic is an issue, in their particular application of Focused Ultrasound.

Course content:

§1 *Key parameters*

1.1 Frequency

The fundamental property of any wave; the number of oscillations undergone per second (unit: Hertz (Hz); typically MegaHertz (MHz)) for medical ultrasound. This parameter underpins much of the physics of interaction between ultrasound and tissue.

1.2 Propagation speed*

For any wave c (ms^{-1}) = f (Hz) λ (m). For sound, speed of propagation depends on material properties (and temperature), where

* '*group'* and '*phase*' speeds not distinguished

K – bulk modulus (GPa) (measurement of stiffness, or pressure required to deform a material) ρ – density (kg m^{-3})

$$c = \sqrt{\frac{K}{\rho}} \qquad \text{Eq. 1}$$

Generally, denser materials will have a much higher stiffness, and as a *rule-of-thumb*, ultrasound will propagate faster within them.

Values for speed of sound, in common materials
air ≈ 340 ms^{-1}; water ≈ 1500 ms^{-1}; fat ≈ 1450 ms^{-1}; brain ≈ 1520 ms^{-1}; muscle ≈ 1630 ms^{-1}; bone ≈ 3000 ms^{-1}; iron ≈ 5130 ms^{-1}; diamond ≈ 12000 ms^{-1}.

1.3 Pressure Amplitude and Intensity

In essence, ultrasound constitutes a periodic pressure fluctuation propagating through a host medium. The pressure amplitude thus represents the maximum instantaneous pressure exerted during the exposure, either positive (i.e. compressive) or negative (i.e. rarefactional), depending on the phase of the cycle.

Pressure amplitudes are measured via hydrophone devices as a principal mechanism to calibrate ultrasound (including focused, although specialised robust – fibre-optic, for example – hydrophones are required)

The *intensity* (energy flow through unit area) of any wave, is related to the square of its amplitude. Thus for ultrasound, the acoustic intensity is given by;

I - 'instantaneous' intensity (Wcm^{-2}) p - pressure amplitude (MPa) ρ – density (kg m^{-3}) c – propagation speed (m s^{-1})

$$I = \frac{P^2}{\rho c} \qquad \text{Eq. 2}$$

Different types of Intensity
There are many *types* of intensity, depending on the nature of the exposure, that give an average temporal (in the case of pulsed HIFU) and/or average spatial values; for example: temporal-average, spatial-peak temporal-peak, spatial-peak temporal-average, etc. Typical values for spatial-average intensity, I_{sa}, of HIFU employed during FUS = 100 – 10000 W cm^{-2}.

1.4 Radiation force

Ultrasound incident to an object will exert a force on it, due to a momentum transfer between the wave and the object, related to the acoustic power, W, of the beam. For ultrasound incident to an absorbing rigid surface, this is given by;

F_{rad} – radiation force
W – ultrasound power incident
c – propagation speed

$$F_{rad} = \frac{W}{c} \qquad \text{Eq. 3}$$

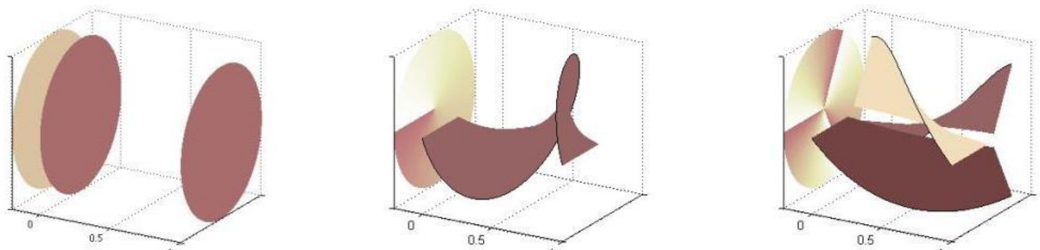
On a (perfectly) reflecting object, F_{rad} is doubled, as the momentum is not simply absorbed, but the direction reversed.
Note, if ultrasound is focused into liquid, this force induces flow, known as *acoustic streaming*.

Acoustic Radiation Force Impulse imaging

This is the principle underpinning ARFI [1], where the precise location of the ultrasound focal volume is determined via the slight physical displacement incurred by the absorption of a short burst of HIFU, through MR-imaging.

†Advanced concept: **The Real 'Sonic Screwdriver'**

Using a 2-d, 1000 element matrix array (InSightec ExAblate 2100) at 550 kHz, researchers have recently demonstrated that encoding a helical phase profile to a focused ultrasound beam, allows the transfer of angular momentum to a target object, causing it to rotate [2].



(a) (b) (c)

Fig 1. (a) planar ultrasound wave (with azimuthal index, l = 0). (b) Helical phase profile, encoded via incorporating a 2π phase discontinuity across the phased array, with azimuthal index, l = 1). (c) azimuthal index, l = 3.

§2 *Frequency effects*

2.1 Absorption; heating vs penetration

When ultrasound propagates through a host medium, various interactions occur that result in energy loss, known collectively as attenuation (measured in decibels, dB). This includes *reflections* at interfaces (the mechanism underpinning diagnostic imaging), *scattering* and *absorption*. The latter is the mechanism that mediates thermal ablation in Focused Ultrasound Surgery, whereby heat is generated via viscous absorption (frictional effects), which causes coagulative necrosis in the targeted tissue. The following expression can be used to approximate the attenuation characteristics;

A – attenuated amplitude A_0 – amplitude at source α_s – scattering coefficient (dB cm^{-1}) α_a – absorption coefficient (dB cm^{-1}) z – unit propagation distance

$$A = A_0 e^{-(\alpha_s(f)+\alpha_a(f))z}; \quad \alpha_a = \alpha_o f^{\gamma} \qquad \text{Eq. 4}$$

α_a (f) is the frequency dependent absorption coefficient, which can be quite variable (for tissue 1 > γ > 2), even in tissue of the same type.

As a *rule-of-thumb*, this parameter increases with increasing frequency. This has two direct consequences; higher frequencies will achieve the temperature increases required for FUS more quickly, however cannot be used to access deeper-seated pathologies. This influences the frequencies (and transducers) selected for FUS applications, such as prostate which is performed trans-rectally with a high-frequency device, and the brain, or uterine fibroid, which employs lower frequencies and larger aperture HIFU sources.

§3 ***Amplitude effects***

3.1 Nonlinear propagation

For high intensity focused ultrasound applications, the localised pressure changes of the wave impose an asymmetry in the propagation speed for the component phases of the wave itself. This is manifested as higher propagation speeds for positive pressure, compressional phases and reduced speeds for the negative pressure, rarefactional phases. Thus, an initially monochromatic sinusoid wave (of a single frequency) will adopt a saw-tooth profile on nonlinear propagation, fig. 2 (a)(i-iii).

3.1.1 *Dependence on pressure amplitude*

One consequence of such a distorted waveform is the addition of new frequency components within the spectrum of the wave. A Fourier analysis, whereby every signal can be represented by a sum of sinusoidal waves, describes this effectively. For nonlinear HIFU, higher harmonic component frequencies, at multiples of the fundamental frequency are generated, with larger amplitudes for more nonlinear propagation (at higher pressure amplitudes), fig 2 (b)(i-iii).

3.1.2 *The nonlinearity parameter*

The degree of nonlinearity also has a dependence on the host medium properties, and temperature. This is denoted by the nonlinearity parameter B/A, that derives from the 2^{nd} order term of a Taylor series relating the perturbed pressure, p', to the perturbed density ρ'

$$p' = c^2 \rho' \left[1 + \frac{1}{2}\frac{B}{A}\left(\frac{\rho'}{\rho_0}\right) + \cdots.\right] \qquad \text{Eq. 5}$$

Typical B/A values at room/body temperature: air ≈ 0.4; water ≈ 5.0; liver ≈ 6.5; fat ≈ 9.9

A significant consequence for nonlinear propagation of focused ultrasound in tissue, is the higher absorption associated with higher frequency harmonic components, apparent from eq 4 for α(f) §2. This has been postulated as a mechanism for *enhanced* (rapid) *heating* in FUS, for example [3]

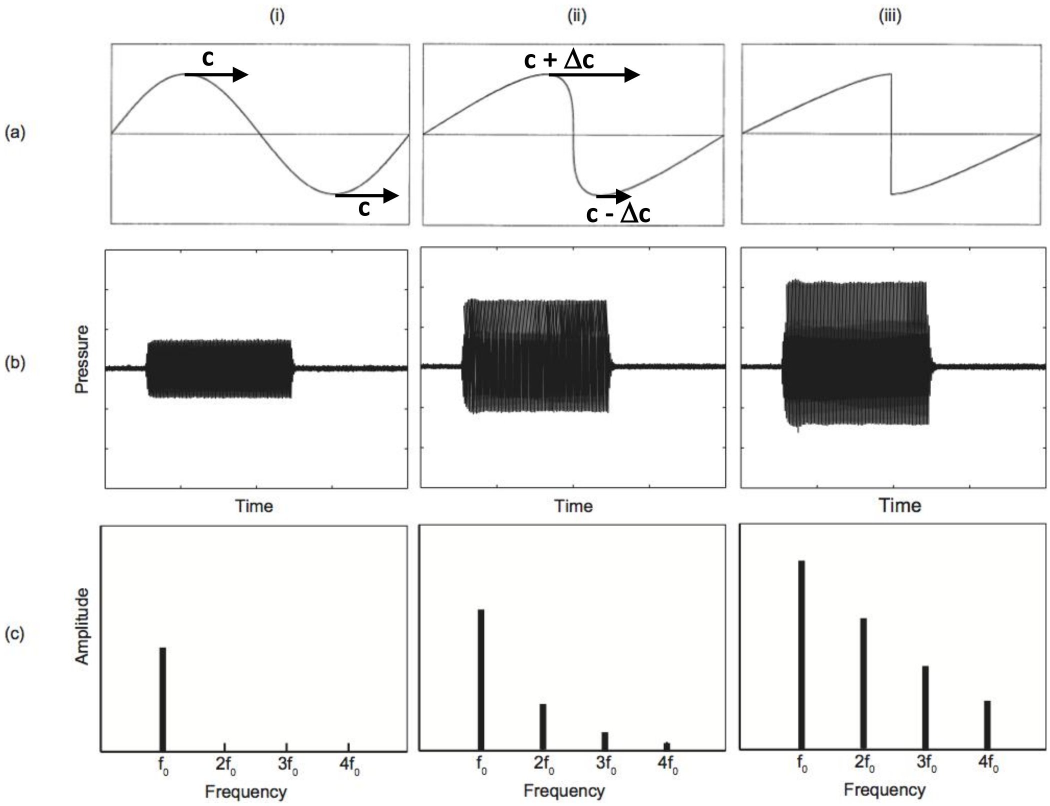


Fig 2. Principles of nonlinear ultrasound propagation. (a) at higher amplitudes, an initially sinusoidal waveform (i), will become distorted due to the effects of the local pressure fluctuation on the local propagation speed (ii), such that the waveform becomes distorted, toward a saw-tooth profile (iii). (b) Typical hydrophone traces detecting a burst of nonlinear HIFU, will often exhibit a larger peak-positive pressure amplitude, than peak-negative pressure amplitude. (c) A Fast Fourier Transform (converting from time- to frequency-domain) reveals higher harmonic components to the fundamental driving frequency, with higher amplitudes for more nonlinear propagation.

3.2 Cavitation

(Acoustic) cavitation refers to the formation of bubbles in a host medium, exposed to a sound field, which will then oscillate in response to it. The quiescent (at equilibrium) size of the bubbles formed is related to the frequency of the sound, via a resonance condition.

R_0 – Resonant bubble radius f_0 – (resonant) frequency

$$R_0 f_0 \approx 3 \text{ (m.Hz)} \qquad \text{Eq. 6}$$

A MHz ultrasound field may therefore be expected to generate bubbles, initially in the range of a few microns in diameter. However, cavitation in FUS is a highly complex and rapidly developing phenomenon, interacting strongly with the HIFU field itself (includes significant scattering), and is associated with transient high temperatures and pressures, light and plasma production (so-called sonoluminesence), free-radical generation (sonochemistry), destructive and erosive effects.
Cavitation is conventionally avoided during clinical FUS, although the activity is receiving renewed interest as a mechanism for tissue permeabilisation and drug delivery, as well as enhanced heating, localised boiling [4, for an excellent review for potential applications of cavitation in FUS].

3.2.1 *Mechanical Index*

The likelihood of cavitation activity in response to a given ultrasound exposure (both diagnostic and therapeutic) in tissue, may be qualitatively predicted via the Mechanical Index, given by

MI – Mechanical Index (dimensionless)
PNP – Peak Negative Pressure amplitude (normalised to MPa)
f' – frequency (normalised to MHz)

$$MI = \frac{PNP\ (MPa)}{\sqrt{f'\ (MHz)}} \qquad \text{Eq. 7}$$

However, it is generally recognised that MI is rather limited as a concept, and in remit. For example, there is no account taken for the duration of the exposure that may precede cavitation inception, or the prevalence of cavitation nuclei in the medium.

3.2.2 *Cavitation nucleation*

A significant difficulty in studying cavitation, or indeed utilising it for a potential therapeutic effect, is predicting exactly where (and when) bubble activity will arise, during exposure. In cavitating liquids or tissue, discontinuities, impurities and pre-existing nano/microscopic gas pockets often provide a nucleation site – even cosmic rays are thought to be responsible!

The dissolved gas content is an important parameter for the resulting activity – indeed cavitation studies are often performed in degassed media (via boiling, or subjecting the medium to prolonged tension) to achieve a degree of reproducibility.

Ultrasound Contrast Agents

Essentially suspensions of stabilised and long-lived microbubbles, contrast agents were originally developed for increasing vascular contrast during diagnostic scanning. Researchers are exploring potential therapeutic applications for microbubbles, such that they are often added, particularly for *in-vivo* experiments for drug delivery, to promote cavitation (effectively lowering the MI threshold), see for example [5].

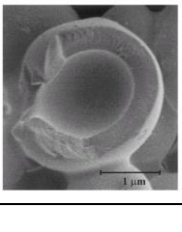


Fig. 3 SEM image of a sheared, albumin-shelled commercial contrast agent microbubble, revealing shell structure and gas core 'pocket'.

3.2.3 *Cavitation clouds*.

In reality, cavitation in focused ultrasound forms as ‘clouds’ of bubbles, originating from the nucleation site. A process known as fragmentation (the generation of multiple bubbles from a single, strongly collapsing cavity) will produce clouds within a few cycles of HIFU. These bubbles will interact with each other via the acoustic fields re-radiated by the individual bubble oscillations, driven by the primary field (so-called secondary Bjerknes forces).

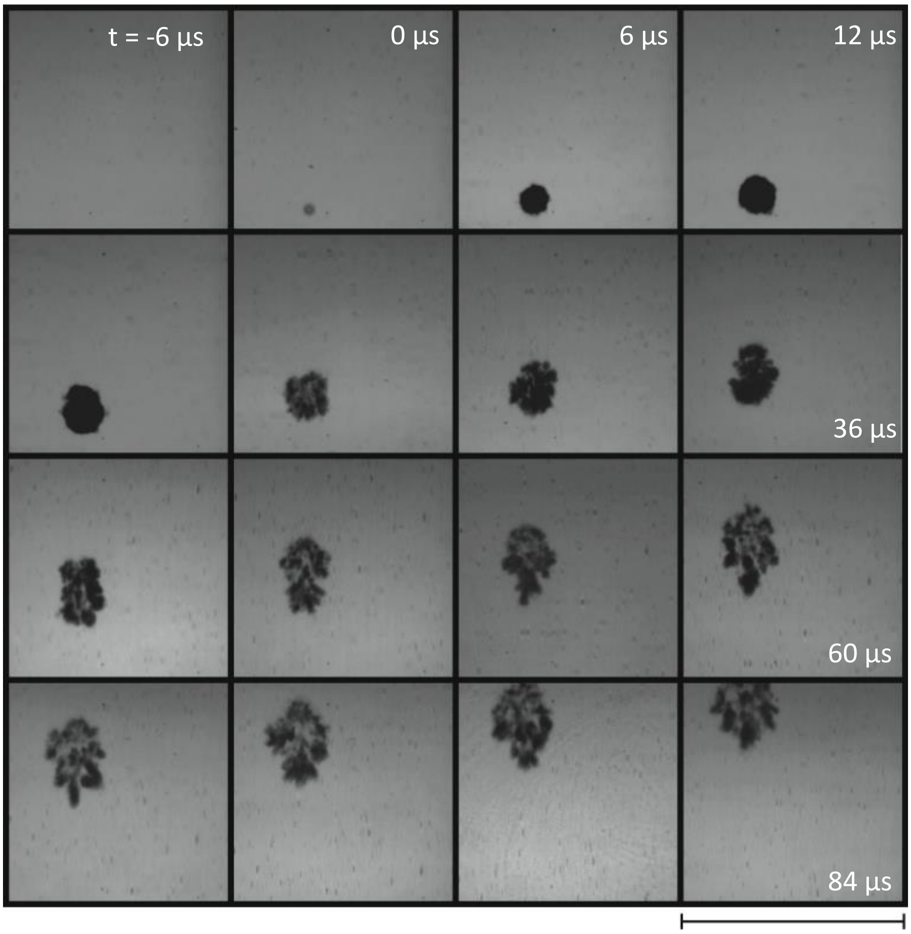


Fig 4. A cavitation cloud in degassed water nucleates and evolves under exposure to focused ultrasound, of frequency 1.47 MHz and MI = 3.4, imaged via high-speed photography recording at 0.5 million frames per second. Bubbles ‘stick’ together via secondary Bjerknes forces, and the cloud translates upwards (away from the HIFU source) under the action of the radiation force. Note, the action of F_{rad} in this situation is complicated by the fact that a bubble is an oscillating ‘target’. Scale bar, bottom 670 μm.

The Cavitation Research Team, at IMSaT, University of Dundee, UK, has developed a laser-nucleation technique to pre-determine the location and moment of cavitation inception, in a pre-established propagating HIFU field [6] (note, cavitation dynamics are very sensitive to the local pressure fluctuation, so standing waves or scattering are significant issues). This is allowing us to study idealised (in degassed water) cloud behaviour, and develop acoustic devices (hydrophones), with the intention of correlating detected signal to physical dynamics, observed via ultra-high speed photography [7].

†Advanced concept: **Bubble acoustic emissions: the origin of sub-harmonics**

Cavitation has traditionally been categorised as *transient* and *stable*, according to the bubble dynamic. The former refers to violently collapsing bubbles associated with higher amplitude ultrasound, the latter with periodic bubble oscillations, driven by lower amplitudes. The acoustic emissions associated with each type is *broadband* and the *half-harmonic* ($f_{emitted} = f_0/2$, where f_0 is the HIFU driving frequency), respectively. To date, the origin of the sub-harmonic signal and the transition to broadband noise, has remained the subject of debate.

The temporal resolution afforded by our laser-nucleation approach has allowed us to identify nonlinear cloud oscillation behaviour – where the cloud responds 'not-in-phase' to the incident HIFU driving field. Early work indicates that the physical cloud oscillation may provide the source for these signals, and that it may well bifurcate many times, on increasing the pressure amplitude [7], in the transition to becoming broadband.

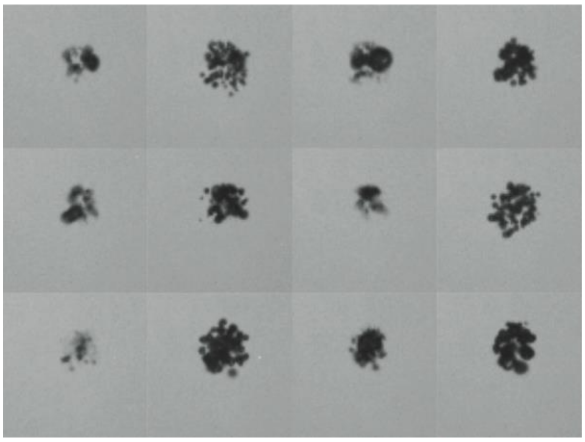


Fig 5 (right) A cloud exhibiting nonlinear oscillatory behaviour, in f = 0.521 MHz, PNP = 1.04 MPa, imaged at 1×10^6 frames per second.

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