Fraunhofer Institute for Digital Medicine MEVIS

EXAMPLES AND PRINCIPLES OF MATHEMATICAL MODELLING IN MEDICINE: ULTRASOUND

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1. Physical Principles

Piezo-electricity

Ultrasound works because of two related properties: when an electric current is applied the material moves. This is called the inverse piezo-electric effect and this is used to generate the sound field.

When the material experiences a mechanical stress, it generates a charge. This is used the piezo-electric effect and is used to generate the signal which is reconstructed to form an image.

Ultrasound is sound above 26.5 kHz, above the range of human hearing, but in medical applications the frequencies are in the mega Hertz regime (10^6 cycles per second).

1. Physical Principles
Therapeutic Transducers

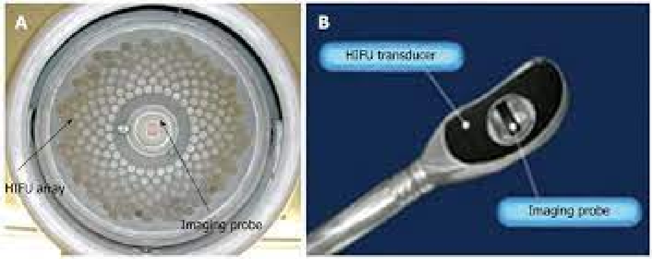

Figure: Image from [17]

1. Physical Principles
Therapeutic Ultrasound

As the acoustic wave (longitudinal) passes through the body it is absorbed. This leads to a rise in temperature.

When a continuous wave, high intensity focused ultrasound, HIFU, can be used as a therapy to heat tissue.

If the waves are very intense, ultrasound can be used to mechanically damage tissue. For the destruction of kidney stones this is call lithotripsy; the destruction of soft tissue this is called histotripsy.

1. Physical Principles

Therapeutic & Diagnostic Ultrasound

Ultrasound is a cheap, real-time, portable imaging modality which can generate lots of data easily. Because of these reasons there are many machine-learning algorithms which are used to enhance the low-contrast, noisy images. A disadvantage is that it is operator dependent.

As a therapy, ultrasound is cost-effective, non-ionising, non-invasive, monitorable and able to selectively destroy small regions of tissue deep with the body.

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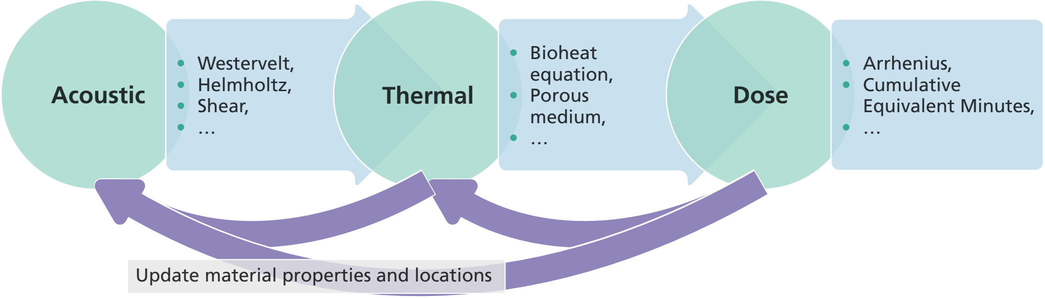
2. Fundamentals of Modelling Ultrasound

Typical Simulation Pipeline

In the context of therapeutic ultrasound:



2. Fundamentals of Modelling Ultrasound

Westervelt Equation

From first principles 14 quantities are required to model the acoustic wave propagation. Fortunately this can be reduced down to 7, then 5, then down to a single variable: pressure, p

$$\frac{\partial p}{\partial z} = \underbrace{\frac{c_0}{2}\int_{-\infty}^{t} \nabla^2 p \,\mathrm{d}\tau}_{\text{Diffraction}} + \underbrace{\frac{2}{c_0^3}\mathcal{L}\left[p; \alpha_0, \eta\right]}_{\text{Attenuation}} + \underbrace{\frac{\beta}{2\rho c_0^3}\frac{\partial p^2}{\partial t}}_{\text{Nonlinearity}}$$

captures the three key physical phenomena of

- Diffraction: the property of a wave to spread as it propagates
- Attenuation: the absorption of the wave by the medium
- Nonlinearity: the change in the wave form as it propagates

2. Fundamentals of Modelling Ultrasound

Computation Challenges

HIFU encounters a challenge in the computation of the state equations: for example implicit, stable finite-difference time-domain codes in a clinically relevant imaging context [12] requires calculations of the order of exaflops

$$\text{exaflop} \quad 10^{18} = 1,000,000,000,000,000,000$$

extremely computationally expensive

Ultrasound

The formulation of the governing equation and, consequently the solution method, is dependent on the application.

- Is the wave pulsed or running continuously? Harmonic solution can be assumed
- Are there significant scatterers in the domain? One-way solutions could be used.
- Is the input power high? Does nonlinear propagation need to be considered?
- Is the transducer a single element or an array? Is it curved or flat?

The review [6] provides an overview of the methods.

2. Fundamentals of Modelling Ultrasound

Linear: Helmholtz

In the linear case, continuous wave case the acoustic Helmholtz equation is derived.

This can be solved by in many ways, for example by finite-elements, or by boundary elements methods.

$$G_{i,j} = \int_{\partial\Omega} G\left(x, x_i\right) \varphi\left(y_i\right) ds \quad \text{and} \quad H_{i,j} = \int_{\partial\Omega} G_n\left(x, x_i\right) \varphi\left(y_i\right) ds$$

The assembly of the boundary element matrix is costly, but can be accelerated by either fast multi-pole methods [3] or hierarchical matrix [7] formulations.

EXAMPLES AND PRINCIPLES OF MATHEMATICAL MODELLING IN MEDICINE: ULTRASOUND

Nonlinearity

Nonlinearity arises from the property that very high/low parts of the waveform travel faster than less intense parts.

The wave steepens.

Consider, in one-dimension, an initially sinusoidal wave $p = p_0 \sin(\omega t)$, then

$$\begin{aligned}\frac{\partial p^2}{\partial t} &= p_0^2 \frac{\partial \sin^2(\omega t)}{\partial t} \\ &= 2p_0^2 \omega \sin(\omega t)\cos(\omega t) \\ &= p_0^2 \omega \sin(2\omega t)\end{aligned}$$

Thus nonlinearity results in the generation of higher frequency components to the wave equation which are integer multiples of the fundamental frequency.

Note: the equations are weakly nonlinear as the particle velocity is less than the speed of sound.

3. Nonlinearity

Burgers Equation

In general it is not possible to write down the solution to nonlinear PDEs, but a one-dimensional version of the Westervelt equation is the acoustic Burger's equation

$$\frac{\partial v}{\partial x} - \beta v \frac{\partial v}{\partial t} - \frac{\partial^2 v}{\partial t^2} = 0.$$

where v is the acoustic velocity.

This is solvable and expressions for nonlinear wave propagation can be derived.

3. Nonlinearity

Wave Steepening

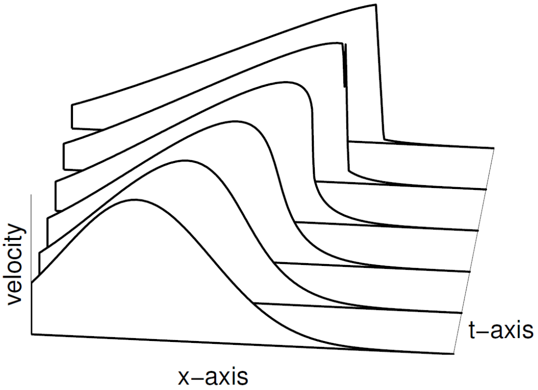


Figure: Evolution of Burgers equation as wave becomes shocked

3. Nonlinearity

Acoustic to Thermal Coupling

The source term in the thermal model is given by the square of the pressure

$$q_n = 2\alpha I, \quad \text{where} \quad I = \sum_{i=1}^{N} \frac{p_i^2}{\rho_0 c_0}$$

which is generalised for nonlinear propagation.

There is another local absorption mechanism which may be included in applications in which shock-like waves may be present

$$q_s = \frac{\beta f_0 A_s^3}{6 c_0^4 \rho_0^2}$$

The heating is independent of attenuation coefficient. It scales against the cube of the shock height, A_s.

3. Nonlinearity

Shock-like Waves

Tissue is attenuating thus “true” shocks will never occur. So how do we specify when this form of heating will occur? That is, what is the difference between a nonlinear wave and a shock-like wave?

The means to distinguish between the two is to observe that shock-like waves will have a finite shock width.

The physical shock width for acoustic Burgers’ equation is of the order $\mathcal{O}(\varepsilon)$, where ε, called the Goldberg number, is the ratio of nonlinearity to attenuation [5].

3. Nonlinearity

Shock Enhances Heating

However, when using an operator-splitting approach the resolution of the shock width [10] is typically $\mathcal{O}\left(\sqrt{k\varepsilon}\right)$. So the spatial resolution, h, must be adjusted accordingly, i.e. $h \sim \varepsilon$, to match the physical shock width.

Thus, by using exact analytical expression for appearance of shock-like wave, it is possible to compute the contribution from shock enhanced heating.

EXAMPLES AND PRINCIPLES OF MATHEMATICAL MODELLING IN MEDICINE: ULTRASOUND

1. Physical Principles
2. Fundamentals of Modelling Ultrasound
3. Nonlinearity
4. Attenuation
5. Dose
6. Open Problems

4. Attenuation

Attenuation

Attenuation is comprised of absorption and scatter. There are two fundamental processes which determine absorption:

- Viscous heating: absorption is proportional to the square of the frequency: $\mathcal{L} \sim \omega^2 \rightarrow \dfrac{\partial^2 p}{\partial t^2}$. At frequencies for medical ultrasound this mechanism is relevant for water.
- Relaxation processes: $\mathcal{L} \rightarrow \dfrac{\partial \xi}{\partial t}$, where $\dot{\xi} = \alpha \xi + \beta + \nabla p$. In media with a complex molecular structure, such as tissue, there are a huge number of relaxation processes and the absorption is accurately modelled by a powerlaw: $\mathcal{L}\left[\omega\right] \sim \omega^{\eta}$, where $\eta = 1 + \nu$.

4. Attenuation
Single Relaxation Process

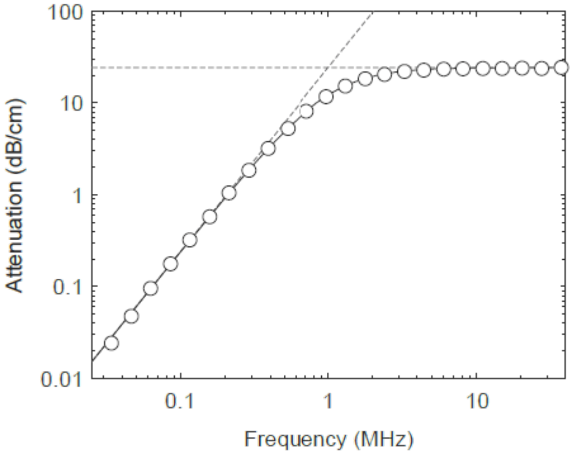


Figure: From [11]

4. Attenuation
Tissue Data

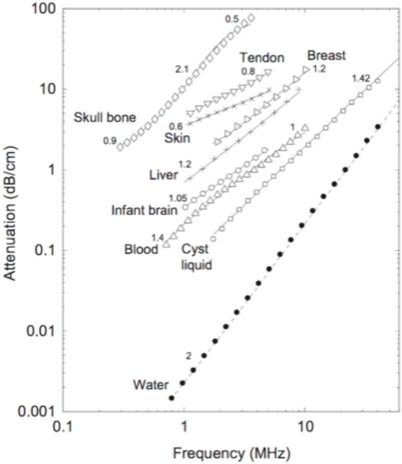


Figure: From [9]

4. Attenuation

Powerlaw Absorption

For linear propagation each frequency can be solved independently for a given attenuation factor derived from experiments.

But in general, the frequency-dependent powerlaw for attenuation can lead to an convolutional integral [15]

$$\mathcal{L}[p] = \int_0^t J(\tau - t_0) \star p(\tau) \mathrm{d}\tau$$

or as via a fractional operator in time

$$= \frac{\partial^{\nu} p}{\partial t^{\nu}}$$

How this is handled is dependent on the clinical context - whether ultrasound is pulsed or continuous wave.

4. Attenuation
Gamma Function

The gamma function is defined as:

$$\Gamma(s) = \int_0^\infty t^{s-1} e^{-t} \,\mathrm{d}t$$

As

- $\Gamma(1) = 1$

and

- $\Gamma(n) = n\Gamma(n-1)$

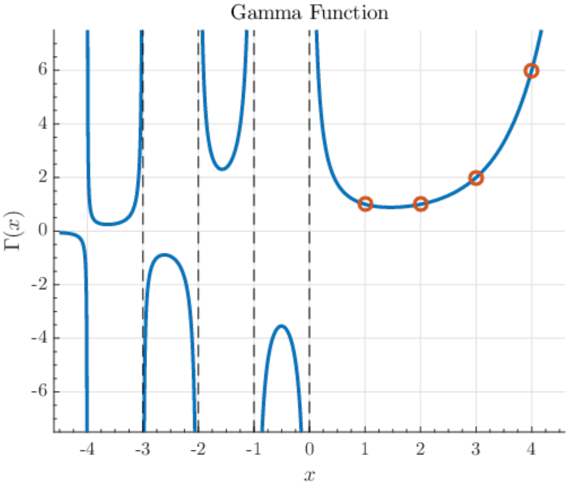
then

- $\Gamma(n) = (n-1)! \quad \forall n \in \mathbb{N}^+$

thus the gamma function can generalise the factorial operator.

4. Attenuation

Gamma Function



Fractional Derivatives for Polynomials

For a simple monomial function $u(x) = x^k$, with $k, a \in \mathbb{N}^+$

$$\frac{\mathrm{d}^a u}{\mathrm{d}x^a} = \begin{cases} \dfrac{k!}{(k-a)!} x^{k-a} & \text{if } k \geq a \\ 0 & \text{if } k < a \end{cases}$$

Now generalise for $a \in \mathbb{R}^+$

$$= \frac{\Gamma(k+1)}{\Gamma(k+1-a)} x^{k-a}$$

4. Attenuation

Riemann-Liouville & Caputo Formulations

The definition of a fractional derivative is more involved for general functions. There are a number of formulations:

- Grünwald-Letnikov
- Riemann-Liouville
- Caputo

Only the Riemann-Liouville formulation ensures that the absorption operator is causal, however, it is more complicated to implement numerically and, requires initial conditions which are difficult to ascertain experimentally.

4. Attenuation

Repeated Integrals

The fractional derivative relies on the definition of the fractional integral. Let an integration operator be:

$$\mathcal{I}_{\alpha}\left[u\right](x) = \int_{\alpha}^{x} u(t)\mathrm{d}t$$

applied again

$$\mathcal{I}_{\alpha}^{2}\left[u\right](x) = \int_{\alpha}^{x} \left(\int_{\alpha}^{t} u(s)\mathrm{d}s \right) \mathrm{d}t.$$

Cauchy showed

$$\mathcal{I}_{\alpha}^{n}\left[u\right](x) = \frac{1}{(n-1)!} \int_{\alpha}^{x} (x-t)^{n-1} \, u\left(t\right) \mathrm{d}t.$$

This is easily generalised to fractional terms.

Fractional Derivatives

The fractional derivative relies on the definition of the fractional integral. But the notion of the fractional integral being the anti-fractional derivative no longer holds.

The fractional derivative, $\mathcal{D}_{\alpha}^{s}$ of order $s \in (k-1, k]$, with $k \in \mathbb{N}$ is defined by the k^{th}-derivative of the $(k-s)^{\text{th}}$-fractional integral

$$\mathcal{D}_{\alpha}^{s}\left[p\right](x) = \frac{1}{\Gamma\left(k-s\right)} \frac{\partial^{k}}{\partial \tau^{k}} \left(\int_{\alpha}^{\tau} \frac{p\left(x, s\right)}{\left(\tau - s\right)^{s+1-k}} \mathrm{d}s \right)$$

The classical derivative depends locally on the point of evaluation, but fractional derivatives are dependent on all values between α and x. It is a non-local operator. In ultrasound computation requires knowledge over the duration of the exposure.

4. Attenuation

Pseudo-Spectral: k-space

A common approach is to model the system in k-space. This means taking the spatial Fourier transform in (x, y, z) and mapping to (k_x, k_y, k_z).

As a wave equation, computations are naturally handled in a frequency domain. Another advantage is that the approximation of the derivative is highly accurate, as

$$\hat{p}\left(k, t+\Delta t\right) - 2\hat{p}\left(k, t\right) + \hat{p}\left(k, t-\Delta t\right) = -4\sin^2\left(ck\Delta t/2\right)\hat{p}\left(k, t\right) \quad (1)$$

The frequency dependent power-low for attenuation law is expressed as a fractional Laplacian [14, 16, 4]

$$\nabla^{\nu/2} p = \nabla^2\left(\mathcal{D}^{2-\nu} p\right)$$

Now, the partial differential equation has been transformed into a system of nonlinear ordinary differential equations which are solved in time.

4. Attenuation

Pseudo-Spectral: Spatial Marching

Another approach is to consider continuous wave exposures and work in pseudo-spectral domain taking the Fourier transform in time and two spatial dimensions (x, y), so that a differential equation, $\hat{p}\left(k_x, k_y, z, \omega\right)$ which is solved in space, stepping forward in $z_i = z_0 + i\delta z$

In this case, the powerlaw, formulated as a fractional operator in time, is simple to handle

$$\frac{\partial^{\nu} p}{\partial t^{\nu}} = \mathcal{F}^{-1}\left(\left(-i\omega\right)^{\nu} \mathcal{F}\left(p\right)\right).$$

This formulation assumes an input plane as an initial condition, which typically is given by measurement data.

4. Attenuation
Simulations from Measurements

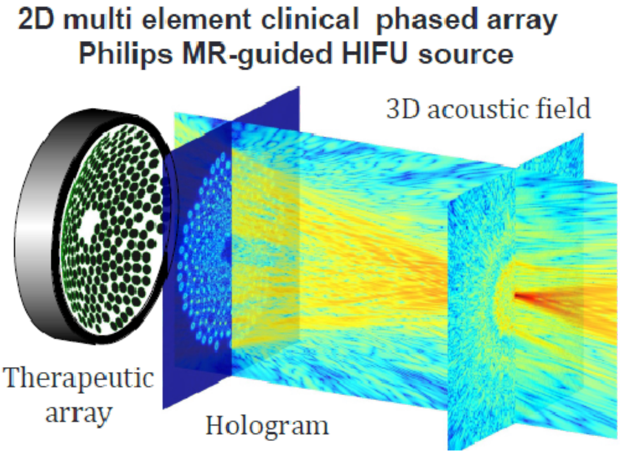


Figure: Image from [13]

4. Attenuation

Quadrature

Another approach is to handle the quadrature directly.

Or use oblivious quadrature [2]: this approximates the fractional operator

$$\frac{\partial^{\nu} p}{\partial t^{\nu}} = \sum_{j=0}^{n} \omega_{n-j} \left(p\left(t_j\right) - \chi p\left(0\right) \right)$$

where the weights ω are determined by solving a

$$\left(\frac{3 - 4\xi + \xi^2}{2h} \right)^{\nu} = \sum_{j=0}^{\infty} \omega_j \xi^j$$

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5. Dose

Dose Equations

Two formulations for the damage, Ω,

- Arrhenuis component models, based on chemical kinetic models. For example, the first-order rate equation

$$[E] \xrightarrow{k_d} [D] \quad \text{leads to} \quad \Omega = \int_0^t A e^{-E_a/(R\bar{T})} \, \mathrm{d}s.$$

- Cumulative equivalent minutes, typically threshold value of an isothermal dose value of 240 min at 43°

$$\Omega = \int_0^t R^{\bar{T}(\boldsymbol{x},t)-\bar{T}_{\mathrm{ref}}} \mathrm{d}s \quad \text{with} \quad \bar{T}_{\mathrm{ref}} = 43^\circ \quad \text{and} \quad R = \begin{cases} 0.25 & \text{for} \quad T < 43^\circ \\ 0.5 & \text{for} \quad T \geq 43^\circ \end{cases}$$

5. Dose

Piecewise Continuous Damage

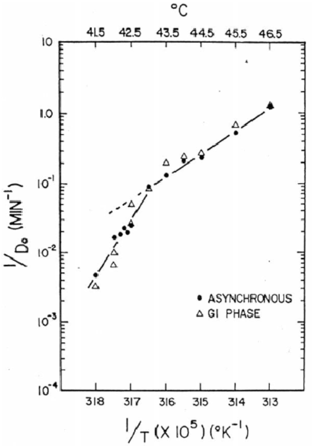

Figure: Many models are based on data from [8] which shows two distinct regimes in which the rates of damage differ.

EXAMPLES AND PRINCIPLES OF MATHEMATICAL MODELLING IN MEDICINE: ULTRASOUND

6. Open Problems
Open Questions

- How does power-law absorption system behave for low power, i.e. discarding nonlinearity, does a Green's function exist for the fractional absorption wave equation?
- In the one-dimensional nonlinear case – fractional Burgers equation – is the system integrable? Does a Cole-Hopf transformation exist? When do shocks form? What is the shock width?
- Can a better formulation of the thermal dose equations be derived from a more complicated rate-reaction scheme?

7. Code

A key reference is [1], which benchmarks ultrasound code for transcranial applications.

- </> Comsol: commercial multiphysics finite element solver – axisymmetric, frequency domain models, with temperature dependency are often used. curvative of transducer accurately resolved
- </> Sim4Life: combines human phantoms, tissue properties and solvers. Can solve nonlinear acoustic equations in time-domain.
- </> k-wave: open-source matlab ultrasound wave pseudo-spectral simulator for diagnostic and therapeutic applications: compiled C++ and cuda binary can accelerate code.
- </> FeNiCs: open source automatic finite element library
- </> HITU_Simulator: A nonlinear axisymmetric beamer simulator (Matlab, GPL-3, GitHub)
- </> j-wave: open source implementation of k-wave in JAX (optimised automatic differentiation framework)
- </> BabelBrain: open source acoustic solver for transcranial applications
- </> Bempp: open source boundary element solver for wave problems

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Thankyou for your attention

Any questions?

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