Fraunhofer MEVIS

Fraunhofer Institute for Digital Medicine MEVIS

EXAMPLES AND PRINCIPLES OF MATHEMATICAL MODELLING IN MEDICINE: MICROWAVE ABLATION

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- 110 scientists, engineers and software developers
- Headquartered in Germany, with strong international networks
- Part of Fraunhofer Society, Europe's leading institution for applied R&D with >30K employees across all application and technology areas
- Founded 1995 in Bremen
- We partner with industry globally to accompany innovative product development

- Mathematics background: BSc at Imperial College London, MSc University of Bath, PhD at University College London

- PhD in Hamiltonian dynamical system, post-doc on interaction of ensembles of driven nonlinear oscillators also at UCL (cavitation in tissue), another post-doc solving large scale PDEs (focused ultrasound therapy) at the Institute of Cancer Research

- Position at National Physical Laboratory in medical ultrasound group
- Started position at modelling and simulation group in Fraunhofer in late November 2019

Learning Outcomes

- Understanding of requirements of developing solutions in a clinical context
- Knowledge of requirement and constraints on numerical schemes which can be deployed

- Knowledge of treatment pipeline for image-guided thermal therapies

- Difference between radio-frequency ablation and microwave ablation
- Mathematical challenges in solving the curl-curl form of Maxwell's equations
- Challenges in validation when simulating in clinical context
- Knowledge of challenges of ultrasound modelling: power-law absorption and nonlinear wave propagation

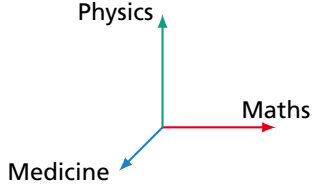
EXAMPLES AND PRINCIPLES OF MATHEMATICAL MODELLING IN MEDICINE: MICROWAVE ABLATION

1. Introduction To Image-Guided Therapies
2. Microwave Ablation
3. Solving
4. Conclusions
5. Open Exercises

1. Introduction To Image-Guided Therapies

Principles of Mathematical Modelling in Medicine

There are a number of areas of expertise which are required.



Physics What are governing equations we need to model?

Medicine What is the clinical endpoint, what are constraints, what are in the inputs, what can be monitored and at what spatial and temporal resolution?

Maths What is the best formulation of the problem and what is the best way of solving the system?

1. Introduction To Image-Guided Therapies

What is Image-Guided Therapy

Image-guided therapy is the process of imaging, during a course of treatment, to direct the treatment, position the patient, and compare to the pre-therapy imaging from the treatment plan.

There are a range of applications: mainly radiotherapy, but also focused ultrasound as another external beam therapy, as well as needle-based interventions such as cryotherapy and microwave and radio-frequency ablation.

A number of therapies will be discussed, but what they will all have in common is that they change the temperature to destroy unhealthy tissue and spare healthy tissue.

1. Introduction To Image-Guided Therapies
Mathematical Challenges

Mathematics can play a vital role in ensuring the correct dose is delivered to the correct location.

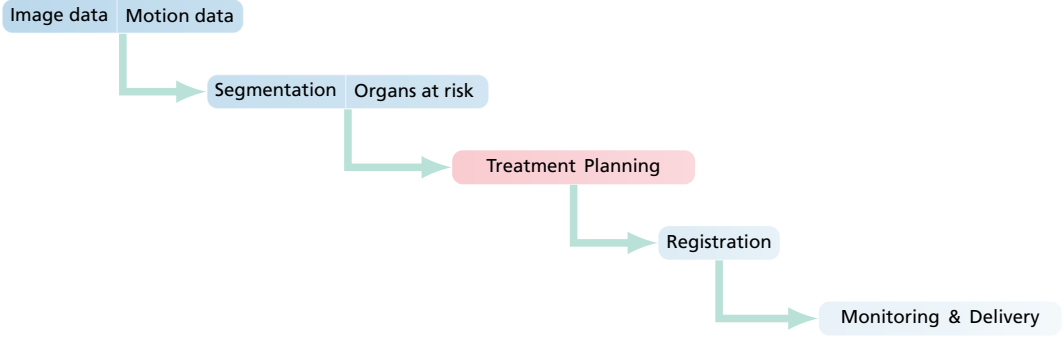
Also, computationally demanding simulations can be a barrier to clinical uptake.

Often the requirements for a numerical scheme are influenced by:

- Speed as treatment planning may need to be re-planned
- Spatial resolution determined by the image, thus stability is, in part, determined by imaging
- Monitoring may require simulation to provide output within a given time
- Simulations will take place in three-dimensions
- Simulations will, ideally, run on-site

1. Introduction To Image-Guided Therapies

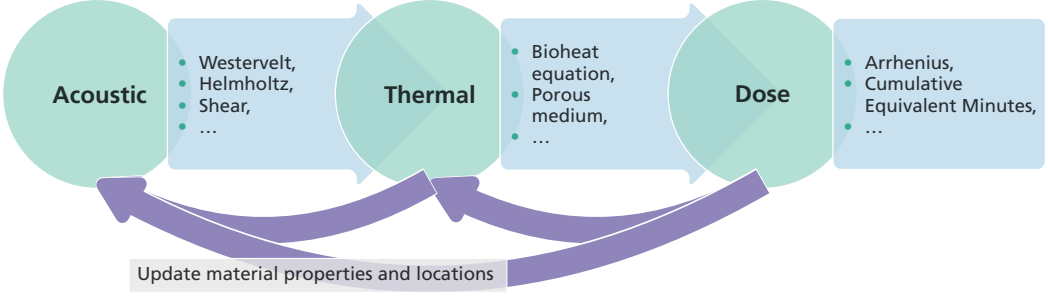
Clinical Pipeline



1. Introduction To Image-Guided Therapies

Typical Simulation Pipeline

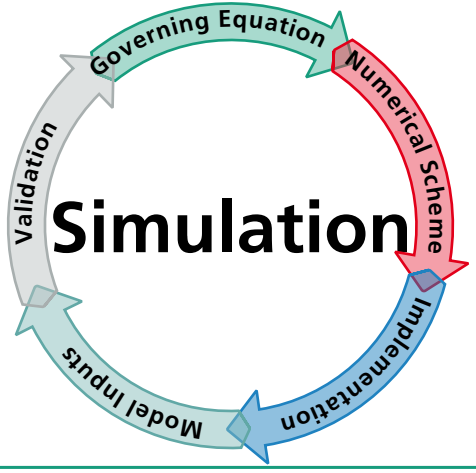
In the context of therapeutic ultrasound:



1. Introduction To Image-Guided Therapies

Simulation Pipeline

A each stage of the simulation pipeline (computation of the source term, the thermal field or the dose field) , it is necessary to perform a number of steps:



Simulation Pipeline

The Pennes bioheat equation is used to compute the thermal field, $T(x, t)$

$$\rho c_v \frac{\partial T}{\partial t} = \nabla \cdot (\kappa \nabla T) + \nu (T - T_\infty) + q$$

where ρ is the density, c_v the specific heat, κ the thermal conductivity, ν the (bulk, isotropic) perfusion term and q the heat source.

- The computation of the source term, q, for the heat equation is typically an order of magnitude longer than the computation of the thermal field.
- The computation of the thermal field is typically an order of magnitude longer than the computation of the dose.
- All parameters are spatially varying and are dependent on the temperature (perhaps also water content or whether coagulated, water content).

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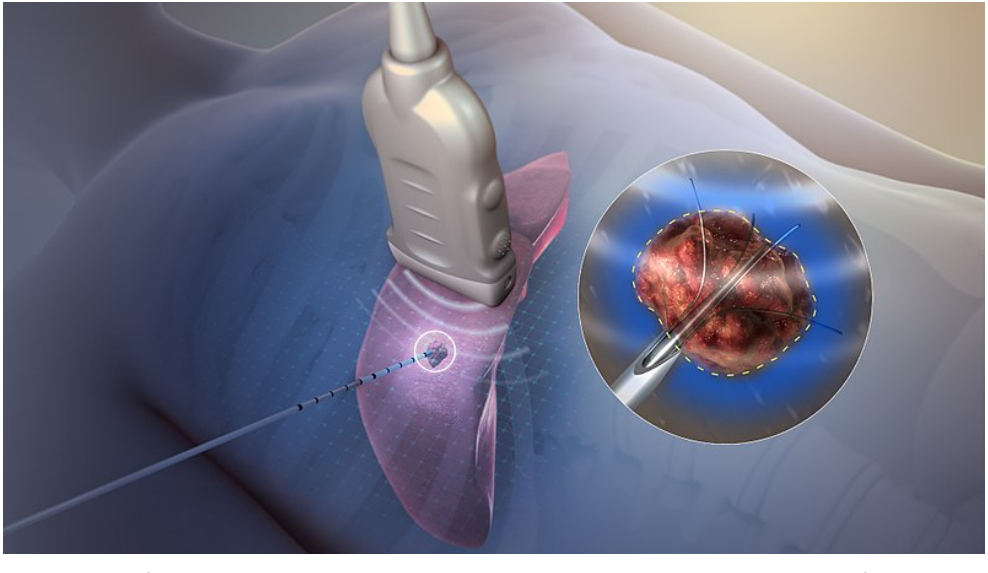


Figure: Schematic of ultrasound guided/monitored needle based ablation. Image courtesy of Wikipedia

Microwave Ablation

There are two ways of using electromagnetic fields in image guided therapies: radiofrequency ablation and microwave ablation.

Radio-frequency ablation is at 250 kHz, where as microwave ablation is performed at either 950 MHz or 2.45 GHz.

How they heat the tissue is different.

2. Microwave Ablation

Governing equations

Maxwell's equations govern the propagation of electro-magnetic waves

$$\varepsilon \frac{\partial \boldsymbol{E}}{\partial t} = \nabla \times \boldsymbol{H} - \boldsymbol{J} \quad \text{and} \quad -\mu \frac{\partial \boldsymbol{H}}{\partial t} = \nabla \times \boldsymbol{E}$$

subject to

$$\nabla \cdot (\sigma \boldsymbol{E}) = 0 \quad \text{and} \quad \nabla \cdot \boldsymbol{H} = 0$$

with $\boldsymbol{E}$ the electric field, $\boldsymbol{H}$ the magnetic field, $\boldsymbol{J}$ the current, where $\boldsymbol{J} = \sigma \boldsymbol{E}$.

These are vector quantities, so at any point $\boldsymbol{E} = \left(E_x, E_y, E_z\right)$ etc.

Given duration of treatments (around 10 minutes) and period of oscillations (nano-seconds), assume continuous wave exposures.

2. Microwave Ablation

Parameters

Where

- Conductivity, σ, is the resistance of a material to the flow of an electric current
- Permeability, μ, is the resistance of a material against the formation of a magnetic field
- Permittivity, ε, is the ability of a material to be electrically polarized, that is the molecules within a material rearrange themselves according to the applied electric field. Typically denote this as the complex $\varepsilon = \varepsilon' + i\varepsilon''$, with a dielectric constant and the dielectric loss factor

Note: conductivity and permittivity are highly frequency-dependent as well as temperature dependent.

2. Microwave Ablation
Heating mechanisms

There are two mechanisms for heating [1]

Resistive heating

The ions in the tissue attempt to follow the changing directions of the alternating current

Dielectric heating

As the polarity changes rapidly, molecules continuously re-align themselves with the electric field

Resistive heating does not penetrate as far as dielectric heating and is more influenced by the tissue properties.

2. Microwave Ablation

Different frequency, different equations

The ratio between the conduction current density and the displacement current density is proportional to $\omega\varepsilon/\sigma$.

When $\sigma \ll \omega\varepsilon$, then dielectric heating will be the dominant mechanism and not resistive heating

Thus, in tissue, as microwave ablation operates at 950 MHz or 2.45 GHz, so the source of heating is dielectric heating, whereas for radiofrequency ablation, at 250 kHz, it is resistive heating [1].

2. Microwave Ablation

RFA: Laplace Equation

At operating frequencies of 250 kHz, it is possible to assume

- negligible displacement currents
- large wavelength relative to the characteristic size of the domain

so that a static equation can be used. This essentially assumes that the electric and magnetic fields decouple and that current behaves as a direct current. The governing equation is

$$\nabla \cdot (\sigma \nabla \varphi) = 0 \quad \text{with} \quad \boldsymbol{E} = \nabla \varphi$$

and the heat source term is given by

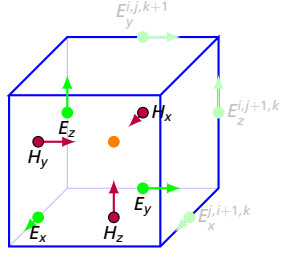
$$q = \boldsymbol{J} \cdot \boldsymbol{E} \quad \text{with} \quad \boldsymbol{J} = \sigma \boldsymbol{E}$$

2. Microwave Ablation

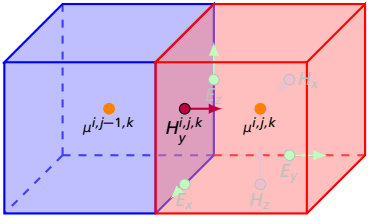
Yee Cell

It is not possible to make the quasi-static assumption for MWA.

Computing on the Yell cell [2] can produce numerical scheme which preserves the divergence



(a) Yee cell



(b) Voxel-to-voxel interpolation

Note that at all computational points it is necessary to interpolate values for the material properties between voxels of the image.

MWA: Curl-Curl Operator

Let $E_x \in \mathbb{R}^N$ be the column vector of the x components of the electric field, where $N = n_x n_y n_z$, and let $\boldsymbol{E} = (E_x, E_y, E_z) \in \mathbb{R}^{3N}$ be the column vector of all components. Then,

$$
\begin{aligned}
-\omega\bar{\mu}\boldsymbol{H} &= \nabla \times E \\
&= A^e \boldsymbol{E} \quad \text{with} \quad A^e = \begin{pmatrix} 0 & -D_z^e & D_y^e \\ D_z^e & 0 & -D_x^e \\ -D_y^e & D_x^e & 0 \end{pmatrix}
\end{aligned}
$$

where D_x^e is the discretization of $\dfrac{\partial}{\partial x}$ for an electric field component by a forward difference.

For $\omega\bar{\varepsilon}\boldsymbol{E} + \boldsymbol{J} = \nabla \times H = A^h \boldsymbol{H}$, the differential operators are given by backwards differences.

Note: the differences in spatial derivatives between fields is due to the Yee cell.

Also note that $\bar{\varepsilon}$ is a diagonal matrix of the interpolated values ε_{xx}, ε_{yy} and ε_{zz}.

Approximating the Differential Operator

Thus, the governing equations

$$\nabla \times \bar{\mu}^{-1} \nabla \times \boldsymbol{E} - \omega^2 \bar{\varepsilon} \boldsymbol{E} = -i\omega \boldsymbol{J}$$

is discretized as

$$A^h \bar{\mu}^{-1} A^e \boldsymbol{E} - \omega^2 \bar{\varepsilon} \boldsymbol{E} = -i\omega \boldsymbol{J}$$

$$\underbrace{\left(A^h \bar{\mu}^{-1} A^e - \omega^2 \bar{\varepsilon}\right)}_{A} \underbrace{\boldsymbol{E}}_{\boldsymbol{x}} = \underbrace{-i\omega \boldsymbol{J}}_{\boldsymbol{b}}$$

The operator [3] is approximated as a linear system as $A\boldsymbol{x} = \boldsymbol{b}$.

The right hand side $\boldsymbol{b}$ is given by the source, but it is necessary to compute the scattered field on the device in order to replicate the feedback which may control the output of the device. This is achieved by splitting the field into scattered and total fields.

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3. Solving
Sparsity

Matrix $A \in \mathbb{C}^{3N \times 3N}$ is complex-valued, large ($N \approx 1 \times 10^6$) but highly sparse (only 13 entries per row). It is most likely not symmetric (depending on spatial discretization and inhomogeneity of μ). It has a huge null-space. It is probably sign-indefinite [4, 5] and ill-conditioned. Thus, it should be solved iteratively.

Iterative schemes construct a series of approximations to the inverse which are iteratively refined. The first step is to handle the matrix in compressed row storage (CSR) format, as three vectors:

- The vector of complex values
- The vector of integers containing the column number of the entry
- The vector of integers which is used to specify the number of non-zero entries per row

Sparse matrix-vector multiplication can be performed, significantly reducing computational cost.

Iterative Solvers

A problem is that many iterative solvers based on relaxation methods or conjugate gradient methods fail for sign indefinite linear problems.

However, GMRes, BiCGStab [6] and other methods do work in these cases.

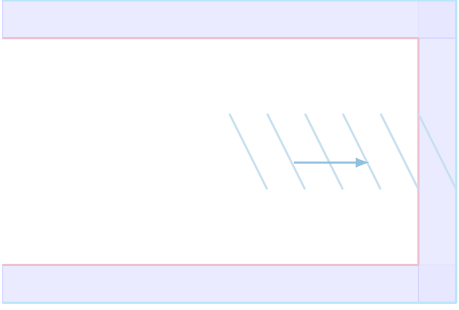
But, the iterations for Maxwell's equations do not show good convergence and often stagnate, with many standard preconditioners failing [7]. This is conjectured to be due to the highly oscillatory nature of the Green's function.

$$G(\boldsymbol{x}, \boldsymbol{y}) = \frac{e^{-ik|\boldsymbol{x}-\boldsymbol{y}|}}{|\boldsymbol{x}-\boldsymbol{y}|}$$

Numerical experiments find that BiCGStab(ℓ) works better than GMRes, BICGStab, COCR [8].

3. Solving

Perfectly Matched Layers



An approach to reduce the size of the system is to truncate the system by a perfectly matched layer [9].

Rather than impose a boundary condition, assume that the domain is surrounded by a (fictitious) anisotropic and highly absorbing layer.

3. Solving
Perfectly Matched Layers

Determine material properties so that waves do not reflect at all angles of incidence at the interface between the computation domain and the fictitious material, i.e. the two materials are perfectly matched.

Increase the attenuation of the material with depth. Impose a reflection boundary condition at the exterior.

There are many formulations (such as the uniaxial PML or the stretched coordinate formulation) but essentially all approaches correspond to a coordinate transformation in which coordinates are mapped to complex numbers – analytic continuation of the wave equation into complex coordinates. The method replaces (attenuating) propagating waves by (weakly oscillating) exponentially decaying waves.

Perfectly Matched Layers

For example, if a wave passes into the perfectly matched layer in *yz* plane (in the *x*-direction) with depth *d*, stretch by a factor

$$s_x(l) = 1 - \frac{i}{\omega\varepsilon_0}\frac{(m+1)\ln(R)}{2\nu_0 d}\left(\frac{l}{d}\right)^m \quad \text{with} \quad \nu_0 = \sqrt{\mu_0/\varepsilon_0}$$

here R is a reflection coefficient, and m characterises how steeply the attenuation increases in the layer. The permittivity and permeability tensors are thus scaled as

$$\bar{\bar{\varepsilon}} = \bar{\varepsilon}\begin{pmatrix} \frac{s_y s_z}{s_x} & 0 & 0 \\ 0 & \frac{s_x s_z}{s_z} & 0 \\ 0 & 0 & \frac{s_x s_y}{s_z} \end{pmatrix}$$

3. Solving
PML Preconditioners

It has been observed [10] that applying the stretched coordinate vectors derived in the perfectly matched layer works effectively as left and right preconditioners.

$$\left(S_a^{-1} A S_l\right) \boldsymbol{y} = S_a^{-1} \boldsymbol{b} \quad \text{where} \quad \boldsymbol{y} = S_l^{-1} \boldsymbol{x}$$

where S_a is the stretched area matrix and S_l is the stretched length matrix.

The advantage of this scheme is that the preconditioners are computed in the construction of the perfectly matched layer and, as diagonal matrices (since tissue is isotropic), are easily invertible.

Attenuation-based preconditioners have been investigated in other wave propagation scenarios.

3. Solving
Steps I

- From the imaging data, compute six materials, $\bar{\bar{\varepsilon}}_{xx}$, $\bar{\bar{\varepsilon}}_{yy}$, $\bar{\bar{\varepsilon}}_{zz}$, $\bar{\bar{\mu}}_{xx}$, $\bar{\bar{\mu}}_{yy}$ and $\bar{\bar{\mu}}_{zz}$
- Construct the differential operators matrices which are the submatrices of A^h and A^e, noting that the submatrices of the matrices are Hermitian transpose of the other to save memory
- Construct the matrix A
- Apply perfectly matched layer
- Construct the right-hand side $\boldsymbol{b}$, first by defining the binary mask, Q from the needle position, then by defining the source, f.
- Apply preconditioners to the linear system using stretch coordinate matrices.
- Invert the system using an iterative scheme such as BiCGStab(ℓ) to solve for $\boldsymbol{E}$
- Solve for the heat source $q = \frac{1}{2}\sigma |\boldsymbol{E}|^2$ on voxel grid by averaging back to voxel centres.

3. Solving
Convergence

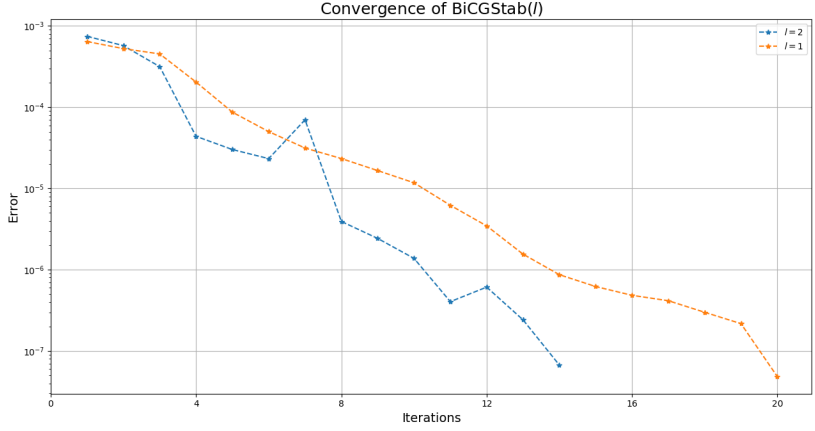


Figure: BiCGStab(ℓ) out-performs the standard BiCGStab scheme

3. Solving

Time Domain Approach

An expensive, but robust approach is to retain the time dependence in Maxwell's equations, although the problem is essentially time-harmonic, and compute until it reaches a steady state and then take the Fourier transform [11].

There are a few problems with the approach:

- It is slower
- It is difficult to know a priori when a steady state has been reached
- As the material properties change due to heating the solution needs to be fully recomputed

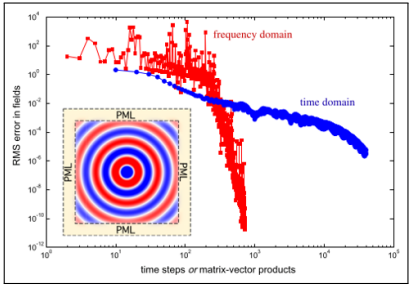


Figure: Figure from [12]

There are a few other approaches which have been used:

- Adding a term with $\nabla\left(\varepsilon^{-1}\nabla\cdot(\varepsilon\boldsymbol{E})\right)$, called the shifted Laplacian. This was derived in the context of homogeneous materials, which is problematic in this case as ε varies spatially, especially when it heats up.
- Schur complement domain decomposition, this defines a number of regions and a coupling between them, in our case this is difficult material properties change.
- Cache-based architectures
- Preconditioners:
  - Jacobi preconditioner
  - Sweeping preconditioners
  - Approximate inverse preconditioner: ideally if the solution is known

Heat Source

The thermal equation is solved on the image grid. The heat source q then requires that the field components are evaluated at the same points, i.e. interpolate the electric field values so that the heat source is evaluated at the centre of the voxel. For the x-component

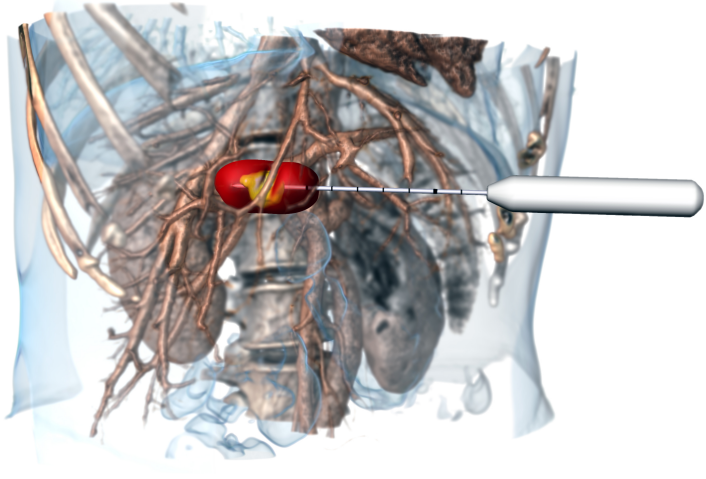
$$E_x^{i,j,k} = \frac{1}{4}\left(E_x^{i,j+1/2,k+1/2} + E_x^{i,j+1/2,k-1/2} + E_x^{i,j-1/2,k+1/2} + E_x^{i,j-1/2,k-1/2}\right)$$

So that the source terms is

$$\begin{aligned} q^{i,j,k} &= \frac{1}{2}\sigma^{i,j,k}\left|\boldsymbol{E}^{i,j,k}\right|^2 \\ &= \frac{1}{2}\sigma^{i,j,k}\left(E_x^{i,j,k}E_x^{i,j,k} + E_y^{i,j,k}E_y^{i,j,k} + E_z^{i,j,k}E_z^{i,j,k}\right) \end{aligned}$$

3. Solving
Steps II

- Compute the solution to Pennes bioheat equation in time up to a point
- Update all material properties which change with temperature
- Recompute the electro-magnetic field, using the last computed solution as an initial guess for the iterative solver
- Interpolate back onto thermal grid and recompute q



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Conclusions

- At high frequencies, curl-curl formulation of Maxwell's equations must be employed, this leads to significant computational challenges.
- To conserved the divergence of the field employ staggered grids. This creates large matrices, and interpolation artefacts.
- Preconditioning challenging, perfectly matched layers help in preconditioning
- Update procedure is challenging, time interval to recompute material properties not optimized

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Open Exercises

1. When updating the material properties there is a trade-off: if you update too often it is costly, but if you update too infrequently the initial guess is inaccurate and will require more iterations in the solver to update the source field, as well as being inaccurate dose. Given some empirical data on how the tissue changes as it heats up, what is a good approach to ensure computationally tractable results?

2. Can machine learning help in the construction of a solution of the iterative scheme [13] or preconditioner?

3. How should averaging over staggered grid be performed when there maybe different materials between voxels?

4. How can the thermal deformation be computed? One approach is a hybrid Lagrangian-Eulerian formulation: compute the thermal heat, then the deformation field, then apply the deformation to each gird point, then interpolate deformed field to find temperature at grid points.

6. Code

- </> Comsol: commercial multiphysics finite element solver – axisymmetric, frequency domain models, with temperature dependency are often used. Interior of device can be modelled.
- </> Sim4Life: combines human phantoms, tissue properties and solvers (commercial)
- </> CST: commercial electromagnetic solvers
- </> FeNiCs: open source automatic finite element library
- </> FD3D and MaxwellFDFD: open source C++ and Matlab finite-difference frequency domain solvers. Can be deployed on HPC systems with PETSc
- </> Jaxwell: open source finite-difference frequency domain solver written in JAX (optimised automatic differentiation framework)
- </> Meep: open source finite-difference time domain
- </> Bempp: open source boundary element solver for wave problems

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Thankyou for your attention

Any questions?

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