A Proposal for Dissertation Research on

Development of a Computational Paradigm for
Laser Treatment of Prostate Cancer

David Fuentes
CAM Fellow
Institute for Computational Engineering and Sciences
The University of Texas at Austin

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Goals of the proposed research

To develop a dynamic-data-driven control system for the thermal treatment of prostate cancer wherein the continual interaction between computer simulation of bioheat transfer processes and thermal imaging equipment will enhance the success of thermal therapies.
Contributions of the proposed research

- Development of sufficient conditions to guarantee the well-posedness of optimization problems subject to the constraints of the equations of bioheat transfer.
- Implementation of efficient, parallel algorithms for adaptive hp-FEM models of inverse analysis, calibration, and optimal control
- Development of a computational system that interacts with laboratory treatments in real time at remote sites
- Model validation of the equations of bioheat transfer through the comparison of computational prediction to experiment
Outline

- Prostate Anatomy
- Prostate Cancer and Statistics
- Goals of this Research
- Bioheat Transfer
- Control System
- Current Progress
- CAM Concentration Areas
Anatomy of The Prostate

• located in front of the rectum and underneath the bladder.
• firm partly glandular, partly muscular organ.
• stromal tissue forms a mesh in which the glandular tissue is embedded.
Stages of Prostate Cancer
Cancer Statistics and Standard Treatment Options

- 234,460 new prostate cancer diagnoses in 2006 (33% of all new cancer cases)
- Prostate cancer is a leading cause of cancer deaths in males.
- Prostatectomy usually followed by local radiation therapy
  - major surgery, long recovery time
  - urinary incontinence, urethral stricture, impotence
- 90% of all prostate cancers are discovered in local and regional stages;
- The 5 year survival rates for patients whose tumors are diagnosed at these stages approaches 100%

Basis For Thermal Therapy of Cancer

Current Thermal Treatment Modalities

- Cryo-ablation
- Microwave
- Radiofrequency
- High Intensity Focused Ultrasound
- Ferromagnetic rod
- Laser

Computational Modeling of Bioheat Transfer in Prostate

Optimizing heat shock protein expression induced by prostate cancer laser therapy through predictive computational models

M.N. Rylander, Y. Feng, K.R. Diller et. al.

Numerical Simulation for Heat Transfer in Prostate Cancer Cryosurgery

J. Zhang, G. Sandison, J. Murthy, L. Xu

Perfusion and Heat Transfer in the Canine Prostate

D. Yuan
Proposal Goal: Laser Based Thermal Treatment
Target Patient Class

This research targets sensitizing or ablating a well-defined region of the prostate

- Stage I. Prostate Cancer*
- Stage II. Prostate Cancer*
- Benign Prostatic Hyperplasia

*The treatment would most likely still be followed by regional radiation or chemotherapy.
Equipment

- 7 Planar temperature fields, in the form of 7 *DICOM files, written to a directory on a Linux machine every 5 secs

- Fixed laser source: maximum of 3-4 laser sources

*DICOM Format is the Standard File format in Medical Imaging.
Non-Linear Pennes Model (1948)

Consider a material body $\Omega \subset \mathbb{R}^3$ where $\Omega$ is a Lipschitz domain. Begin with the global equations for conservation of energy under the following assumptions:

- no mass flux across boundary, $\partial \Omega$
- no motion, deformation, or applied forces
- stromal tissue, glandular tissue, blood, etc. is represented as a single homogeneous tissue
- the presence of the blood within the homogenized tissue acts as an isotropic volumetric heating term at every point within the body $\Omega$
- laser heating acts as a spatially varying heat source term
Non-Linear Pennes Model

Find the spatially and temporally varying temperature field $T(x, t)$ such that

$$\rho c_p \frac{\partial T}{\partial t} - \nabla \cdot (k(T) \nabla T) + \omega(T)c_{blood}(T - T_a) = Q_{laser}(x, t) \text{ in } \Omega$$

given the boundary condition

$$-k(T) \nabla T \cdot n = h(T - T_\infty) \quad \text{on } \partial \Omega$$

and the initial condition

$$T(x, 0) = T^0 \quad \text{in } \Omega$$

in the classical sense
Non-Linear Pennes Model

The isotropic volumetric heating of the tissue by perfused blood is driven by mass flow of blood to tissue and the temperature difference between arterial temperature and local homogenized tissue temperature.

\[ Q_{blood} = -\omega(T)c_{blood}(T - T_a) \]

where

- \( c_{blood} \left[ \frac{J}{kg \cdot K} \right] = \text{specific heat of blood} \)
- \( \omega \left[ \frac{kg}{s \cdot m^3} \right] = \text{perfusion coefficient. Has units of mass flow (of blood to tissue) per unit volume of tissue.} \)
Non-Linear Pennes Model

For Physical and mathematical reasons assume that the thermal conductivity and blood perfusivity are smooth, monotone, increasing, bounded, and analytic functions of temperature.
Non-Linear Pennes Model

The laser source term is assumed to be

\[ Q_{\text{laser}}(x) = 3P \mu_{\text{atot}} \mu_{\text{tr}} \frac{e^{-\mu_{\text{eff}} \|x - r_0\|}}{4\pi \|x - r_0\|} \]

where the following coefficients are known

- \( P \) = laser power
- \( \mu_{\text{atot}}, \mu_{\text{tr}}, \mu_{\text{eff}} \) = laser coefficients related to laser wavelength and give probability of absorption of photons by tissue
- \( r_0 \) = position of laser photon source
Pennes Model: Variational Formulation

Standard arguments to obtain the weak form of the equations, integrate in time, and apply the initial conditions weakly

\begin{equation}
B(T, \beta; v) = \int_0^\tau \int_\Omega \left[ \rho c_p \frac{\partial T}{\partial t} v + k(T, \beta) \nabla T \cdot \nabla v + \omega(T, \beta) c_{\text{blood}}(T - T_a) v \right] \, dx \, dt \\
+ \int_0^\tau \int_{\partial\Omega} hT_v \, dA \, dt + \int_\Omega T(x, 0) \, v(x, 0) \, dx
\end{equation}

\begin{equation}
F(\eta; v) = \int_0^\tau \int_\Omega Q_{\text{laser}}(\eta; x) v \, dx \, dt + \int_0^\tau \int_{\partial\Omega} hT_\infty v \, dA \, dt + \int_\Omega T^0 v(x, 0) \, dx
\end{equation}
Pennes Model: Variational Formulation

Given a set of model coefficients, $\beta_0$, and laser parameters, $\eta_0$,

\[
\text{Find } T(x, t) \in \mathcal{V} \text{ such that }
\]

\[
B(T, \beta_0; v) = F(\eta_0; v) \quad \forall v \in \mathcal{V}
\]

where $\mathcal{V}$ is the appropriate function space in which a unique solution exists.
Control Loop

Houston (real time)

Austin (simulation time)

Pre-treatment

Initial Calibration

Dynamic Control

i = i + 1

$t = t_i + \Delta t$

$t = t_{i+1}$

$t_{i+1}$
Mesh created by Y. Zhang using LBIE-mesher suite.
Control Loop: Pre-Treatment

Looking at the computational grid there are three problems to control

- Optimal control of the laser parameters
- Mesh refinement
- Calibration of the bioheat transfer model
Control Loop: Pre-Treatment

Given a set of model coefficients, $\beta_0$, and the ideal temperature field that maximizes damage to cancerous tissue while minimizing damage to healthy tissue

$$\phi(x) \equiv \begin{cases} 37.0^\circ C & x \in \Omega_H \\ 50.0^\circ C & x \in \Omega_C \end{cases}$$

where $\Omega_H$ and $\Omega_C$ are the domains of the healthy and cancerous tissue respectively, find the best combination of laser position and power, $\eta^* = (x_0, y_0, z_0, P) \in \mathbb{R}^4$, that produces the temperature field, $T^* \in \mathcal{V}$, such that

$$Q(T^*(\eta^*, \beta_0)) = \int_0^T \int_{\Omega} (T^*(x, t) - \phi(x))^2 \, dx \, dt$$

satisfies

$$Q(T^*(\eta^*, \beta_0)) = \inf_{\eta \in \mathcal{M}} Q(T(\eta, \beta_0))$$

$$\mathcal{M} = \left\{ \eta \in \mathbb{R}^4 : \exists T \text{ s.t. } B(T, \beta_0; v) = F(\eta; v) \quad v \in \mathcal{V} \right\}$$

where $\mathcal{V}$ is the appropriate space for the bioheat transfer model.
Control Loop: Pre-Treatment

Given a set of model coefficients, $\beta_0$, and laser parameters, $\eta_0$, Find the temperature field $T^*(\eta_0, \beta_0)$ such that

$$Q(T^*(\eta_0, \beta_0)) = \int_0^T \int_\Omega w(x)T^*(x, t) \, dxdt$$

satisfies

$$Q(T^*) = \inf_{T \in \mathcal{M}} Q(T)$$

$$\mathcal{M} = \{T \in \mathcal{V} : B(T, \beta_0; v) = F(\eta_0; v) \quad v \in \mathcal{V}\}$$

where $w(x)$ is a weighting function and $\mathcal{V}$ is the appropriate space for the bioheat transfer model.
Given a set of laser parameters, \( \eta_0 \), and an experimentally determined temperature field

\[
T_{\text{exp}}(x, t)
\]

Find the best combination of model coefficients, \( \beta^* \in \mathbb{R}^m \), that produces the temperature field, \( T^* \in \mathcal{V} \), such that

\[
Q(T^*(\eta_0, \beta^*)) = \int_0^\tau \int_{\Omega} (T^*(x, t_n) - T_{\text{exp}}(x, t))^2 \, dx \, dt
\]

satisfies

\[
Q(T^*(\eta_0, \beta^*)) = \inf_{\beta \in \mathcal{M}} Q(T(\eta_0, \beta))
\]

\[
\mathcal{M} = \{ \beta \in \mathbb{R}^m : \exists T \, \text{s.t.} \, B(T, \beta; \nu) = F(\eta_0, \nu) \quad \forall \nu \in \mathcal{V} \}.
\]
Mathematical Framework for Optimal Control

Find $u^* \in \mathcal{W} : Q(u^*) = \inf_{u \in \mathcal{M}} Q(u)$

$\mathcal{M} = \{u \in \mathcal{W} : B(u; v) = F(v) \quad v \in \mathcal{V}\}$

\[\Downarrow\]

Find $(u, p) \in \mathcal{W} \times \mathcal{V} :$

$B(u; v) = F(v) \quad v \in \mathcal{V}$

$B'(u, \hat{u}; p) = Q'(u; \hat{u}) \quad \hat{u} \in \mathcal{W}$

The similarities in the mathematical structure will be exploited when programming.
The Adjoint(Dual) Problems

Solving for the Lagrange multiplier, \( p \in \mathcal{V} \), such that

\[
B'(T, \beta; q, p) = \begin{cases} 
Q'_{\text{laser}}(T; q) \\
Q'_{\text{mesh}}(T; q) \\
Q'_{\text{calib}}(T; q)
\end{cases} \quad \forall q \in \mathcal{V}
\]

Leads to a solution method for each of the problems posed in the computational grid.

Optimal Control:

\[
\frac{\partial Q}{\partial \eta_i} = \frac{\partial F(\eta; p)}{\partial \eta_i}
\]

Mesh Refinement:

\[
Q(T) - Q(T^h) \approx R(T^h, p)
\]

Calibration:

\[
\frac{\partial Q}{\partial \beta_i} = -\frac{\partial B(T, \beta; p)}{\partial \beta_i}
\]
Computational Feasibility (5 sec simulation)

- Size of Dicom File $= 140$KB, Bandwidth of Internet Connection $= 800$kB/s
  $\approx 1.22$sec to transfer data
- 5 time steps per data transmission, 4 linear solves per time step, 5 gradient computations
  $\Rightarrow$ 100 linear system solves per data transmission
- $N_{dof} = 10,000$
- Direct Solver, $\hat{b}(p = 2) \approx 500$
  $$100 \cdot N_{flop} \approx 100 \cdot (2 \cdot \hat{b}^2(p) \cdot N_{dof} + 4 \cdot \hat{b}(p) \cdot N_{dof}) \approx 500 \text{ Gflop}$$
  92 processors at TACC running at 90% theoretical peak for 1 sec
- Iterative Solver, $b(p = 2) \approx 250$
  $$100 \cdot N_{flops} \approx 100 \cdot 40 \cdot b \cdot N_{dof} \approx 10 \text{ Gflop}$$
  8 processors at TACC running at 25% theoretical peak for 1 sec
- Leaves more than half the time (2.78s) for matrix assembly and additional latencies
Code Structure

- GMP / Matlab / LBIE for Mesh generation

- hp3D for parallel data structures and mesh refinement

- Petsc for parallel robust nonlinear equation solvers

- TAO for optimization

- GMV for visualization
Preliminary Calculations

Find \( T(x, t) \) such that

\[
- \nabla \cdot (k(T) \nabla T) = q_0 \text{ in } \Omega
\]

where

\[
k(T) = k_0 + k_1 T
\]

given the boundary condition

\[
k(T) \nabla T \cdot n = h(T - T_\infty) \quad \text{on } \partial \Omega_c
\]

Exact solution

\[
T = \frac{q_0}{2k_1} r^2 - \frac{k_0}{k_1}
\]
Preliminary Calculations
Preliminary Calculations

![Graph showing temperature vs radius for different numerical simulations.](image-url)
Preliminary Calculations

The strong form of the adjoint formulation is as follows

Given the spatially and temporally varying temperature field \( T(x, t) \) find the Lagrange multiplier \( p(x, t) \) such that

\[
-\rho c_p \frac{\partial p}{\partial t} - \nabla \cdot (k(T) \nabla p) + \frac{\partial k}{\partial T}(T, \beta) \nabla T \cdot \nabla p + \omega(T, \beta) p + \frac{\partial \omega}{\partial T}(T, \beta) p (T - T_a) = 2(T - T_{exp}) \quad \text{in } \Omega
\]

given the Cauchy boundary condition

\[
k(T) \nabla p \cdot n + h p = 0 \quad \text{on } \partial \Omega
\]

and the terminal condition

\[
p(x, \tau) = 0 \quad \text{in } \Omega
\]

in the classical sense
Preliminary Calculations
Summary of Target Contributions

Area A:
- Well posedness of bioheat equations
- Well posedness of corresponding adjoint equations
- A Priori and A Posteriori Error Estimates

Area B:
- Development and efficient parallel implementation of algorithms for adaptive 3D hp-FEM models of inverse analysis, calibration, and optimal control
- Development of a computational system that interacts with laboratory treatments at remote sites

Area C:
- Model validation of the equations of bioheat transfer and laser source terms through the comparison of computational prediction to experiment
Pennes Model: Derivation

\( \rho = \text{mass density} \)
\( e = \text{internal energy/unit mass} \)
\( q = \text{heat flux} \)
\( Q_{\text{laser}}, Q_{\text{blood}} = \text{vol. heat source} \)

Conservation of Energy (\( \dot{\mathcal{K}} = 0, \dot{\mathcal{E}} = 0 \))

\[
\frac{d}{dt} \int_{\hat{\omega} \subset \Omega} \rho e \, dx = - \int_{\partial \hat{\omega}} q \cdot n \, dA + \int_{\hat{\omega}} Q_{\text{blood}} + Q_{\text{laser}} \, dx
\]
Pennes Model: Derivation

For the constitutive equations take

- $e = c_p \ T(x, t)$, where $c_p$ is the specific heat and $T(x, t)$ denotes the temperature of the homogenized tissue.

  since no deformation the material may be considered incompressible and the specific heat at constant pressure is the same as the specific heat at constant volume. The constitutive equation follows from the definition of the specific heat $c_p = \frac{\partial e}{\partial T}_v$

- $q = -k(T) \nabla T$, where $k(T)$ is the scalar coefficient of thermal conductivity.