A DYNAMIC DATA-DRIVEN SYSTEM FOR LASER TREATMENT OF CANCER

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Department of Biomedical Engineering
The University of Texas at Austin

In collaboration with
Department of Imaging Physics
M.D. Anderson Cancer Center
The University of Texas, Houston

DYNAMIC DATA DRIVEN APPLICATION SYSTEMS WORKSHOP
National Science Foundation
Washington D.C.
January 19-20, 2006
TEAM AND OUTLINE

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Outline:

1. Motivations and objectives
2. Treatment planning model:
   A Dynamic Data Driven System
   2.1. Measurements
   2.2. Modeling
3. Optimization and Calibration
4. Team

http://www.ices.utexas.edu/~feng/dddas/
MOTIVATION

Prostate cancer is responsible for 33% of the cancer deaths of male patients in the United States and 1 in 6 men are expected to contract the disease in their lifetime.

Treatments:

Conventional surgery for removal of cancerous tissue. Not effective when tumor is small and spread.

Laser thermal therapy is minimally invasive, is simpler to perform, requires shorter hospitalization time.
Laser thermal therapy can be compromised by Heat Shock Protein (HSP) expression. HSPs are critical components of a cell’s defense mechanism under adverse environmental conditions (heat stress for example).

Increased HSP expression is implicated in multidrug resistance, regulation of apoptosis.

Thermal initiation of HSP 27 and 70 is shown to provide cellular resistance to radiation and chemotherapy.

Elevation of HSP 27, 60, 70 are markers signaling poor prognosis in prostatic carcinoma.
OBJECTIVES

1. Develop HSP expression and damage predictive models.

2. Develop finite element models to predict temperature, HSP expression, and damage due to laser heating.

3. Develop an adaptive control system that operates over a computational grid connecting a Treatment/Measurement Arena in Houston at the M.D. Anderson Cancer Center and a Computational/Simulation Arena in Austin at The University of Texas.
Need to develop new algorithms, laboratory and modeling protocols to enable the development of the control systems, including adaptive modeling and meshing procedures, calibration procedures, verification and validation procedures, inverse modeling and sensitivity analysis algorithms, and laboratory procedures for measuring tissue damage and HSP expressions.
MRTI Specifications:
Spatio-temporal temperature distribution is measured during the laser treatment with update times less than 5 seconds per image. Thickness of planes is 2.0 mm.
Prostate tumor cells are inoculated in the hind legs of mouse and grown to a tumor burden of less than 1.0 cc.

(left) Courtesy of M.N. Rylander et al.  (right) Courtesy of J. Zhang and C. Bajaj

Hexahedral mesh of tumor (blue) and tissue (yellow). A semi-automatic segmentation method is adapted to find the interface boundaries of tumor and tissue. Cubic spline and lofting methods are applied to obtain smooth boundaries from the segmented MRI data.
MESH GENERATION

[Images of medical images related to mesh generation]
MESH GENERATION: FILTERING
MRTI FOLLOWING LASER IRRADIATION
TEMUERATURE MODEL

Pennes’ equations for bio-heat transfer (1948):

\[ c_p \rho \frac{\partial T}{\partial t} = -\nabla \cdot k(T) \nabla T - \omega(T) c_b (T - T_a) + Q(x) \quad + \text{BCs and IC} \]

Constitutive relations

**Thermal conductivity** \( k(T) \):

\[ k(T) = 0.419(0.133 - 1.36\lambda_k w) \]
\[ \lambda_k = 1.0 + 1.78^{-3}(T - 293) \]

**Blood perfusion** \( \omega(T) \):

\[ \omega(T) = \begin{cases} 
0.833, & T < 37^\circ C \\
f(T), & 37 \leq T \leq 42^\circ C \\
0.416, & T > 42^\circ C 
\end{cases} \]
\[ f(T) = 0.833 - (T - 37)^{4.8}/5.438 \times 10^3 \]

Laser source

**Energy absorbed by tissue:**

\[ Q(x) = \mu_a \phi(x) \]

**Energy fluence rate**

\[ \phi(x) = 3P \mu_{tr} \frac{e^{-\mu_{eff} ||x-x_0||}}{4\pi ||x-x_0||} \]

with

\[ P = \text{power} \]
\[ x_0 = \text{position of laser tip} \]
Pennes assumed in his model that the **arterial blood** acts as an isotropic heat source and that blood is isothermal until it reaches the capillaries that perfuse the tissue averaging 600 capillaries per cubic millimeter.

This means that there exists a capillary at every point in tissue at $T_a$ that supplies or takes away heat from the tissue.
Comparison Between Model Predicted and MRTI Measured Temperature

 Courtesy of M.N. Rylander et al.
HSP expression $H(T, t)$ can be predicted by:

$$\frac{\partial H}{\partial t}(T, t) = f(T, t)H(T, t), \quad H(T, 0) = H_0$$

where $f(T, t)$ is a general rate function which captures the HSP kinetics characteristics and is empirically determined as:

$$f(T, t) = \alpha - \beta \gamma t^{\gamma - 1}$$

Thus,

$$H(T, t) = H_0 e^{\alpha t - \beta t^\gamma}$$

where $\alpha$, $\beta$, and $\gamma$ are time independent parameters that may depend on temperature, with $\gamma > 1$. 
The damage fraction $F_D$ is predicted by means of the Arrhenius integral formulation, i.e.

$$F_D(t) = 1 - e^{-\Omega(t)}$$

$$\Omega(t) = \ln\left(\frac{C_0}{C_t}\right) = A \int_0^t e^{E_a/RT(\tau)} d\tau$$

where

- $C_0$ = initial concentration of healthy cells
- $C_t$ = concentration of healthy cells after heating at time $t$
- $A$ = pre-exponential scaling factor
- $E_a$ = activation energy of the injury process
- $R$ = universal gas constant
- $T$ = absolute temperature
## DATA IN PENNES’ MODEL FOR BIO-HEAT TRANSFER

<table>
<thead>
<tr>
<th>Parameter Set</th>
<th>Definition</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Omega$</td>
<td>computational domain</td>
<td>no</td>
</tr>
<tr>
<td>$\Omega_0$</td>
<td>tumor region</td>
<td>no</td>
</tr>
<tr>
<td>$T_0 (= T(x, t))$</td>
<td>Dirichlet BC on the outer domain</td>
<td>no</td>
</tr>
<tr>
<td>$\sigma (= \partial_n T(x, t))$</td>
<td>Neumann BC on the outer domain</td>
<td>no</td>
</tr>
<tr>
<td>$\rho$</td>
<td>mass density of the tissue</td>
<td>no</td>
</tr>
<tr>
<td>$c$</td>
<td>specific heat of the tissue</td>
<td>no</td>
</tr>
<tr>
<td>$k$</td>
<td>thermal conductivity of the tissue</td>
<td>yes</td>
</tr>
<tr>
<td>$\omega_b$</td>
<td>perfusion coefficient</td>
<td>yes</td>
</tr>
<tr>
<td>$\mu_a$</td>
<td>absorption coefficient of the tissue</td>
<td>no</td>
</tr>
<tr>
<td>$\mu_s$</td>
<td>scattering coefficient of the tissue</td>
<td>no</td>
</tr>
<tr>
<td>$T_a$</td>
<td>temperature of blood</td>
<td>yes</td>
</tr>
<tr>
<td>$x_0$</td>
<td>location of the laser tip</td>
<td>yes</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>laser frequency</td>
<td>yes</td>
</tr>
<tr>
<td>$\nu_0$</td>
<td>laser orientation</td>
<td>yes</td>
</tr>
<tr>
<td>$P$</td>
<td>laser power intensity</td>
<td>yes</td>
</tr>
<tr>
<td>$N$</td>
<td>number of laser applicators</td>
<td>yes</td>
</tr>
</tbody>
</table>
1. Define some objective functions with respect to damage fraction, HSP expression, or temperature, i.e.

\[ J_T = \int_{\Omega} (T(x, t_f) - T_{opt})^2 dx \]

2. Determine set of parameters \((P_i, \mu_a, \mu_s, x_i), i = 1, \ldots, M\) \((M\) is number of laser sources\) that minimize the objective function (done in preliminary study using the steepest descent method).
**Preliminary Results**

<table>
<thead>
<tr>
<th>Red Region: Tumor ($G_T$)</th>
<th>Blue Region: Tissue ($G_H$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_{70,27} \leq 1.0$</td>
<td>$H_{70,27} &gt; 1.0$</td>
</tr>
<tr>
<td>$F_D \geq 0.99$</td>
<td>$F_D \leq 0.01$</td>
</tr>
</tbody>
</table>

Goal here is to optimize laser parameters ($P, \mu_a, \mu_s, x$) based on objective functions defined w.r.t. damage, HSP$_{70,27}$, or temperature.

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Courtesy of M.N. Rylander et al.
INSUFFICIENT THERMAL DOSE - $P_1 = 0.5$ W, $P_2 = 0.15$ W
THERMAL OVERDOSE - $P_1 = 1.6$ W, $P_2 = 1.1$ W

Temperatures

Cell damage

HSP 70

HSP 27
DAMAGE BASED OPTIMIZED - $P_1 = 1.0 \text{ W, } P_2 = 0.5 \text{ W}$
HSP 70, 27 BASED OPTIMIZED - $P_1 = 1.0\ W, P_2 = 0.5\ W$
TEMPERATURE BASED OPTIMIZED - $P_1 = 0.5 \, \text{W}, \, P_2 = 0.3 \, \text{W}$

Temperature

Cell damage

HSP 70

HSP 27
## TEAM AT UT AUSTIN

<table>
<thead>
<tr>
<th>Participant</th>
<th>Position</th>
<th>Roles/Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. T. Oden</td>
<td>PI</td>
<td>Overall program coordination and management. Research on modeling, V&amp;V, simulation, calibration components.</td>
</tr>
<tr>
<td>C. Bajaj</td>
<td>Co-PI</td>
<td>Coordination/Research on visualization, geometry reconstruction, meshing.</td>
</tr>
<tr>
<td>J. C. Browne</td>
<td>Co-PI</td>
<td>Coordination/Research on development and testing of parallel algorithms/solvers, database construction and management, and grid computing.</td>
</tr>
<tr>
<td>K. R. Diller</td>
<td>Co-PI</td>
<td>Coordination/Research on case studies with MDA. Management of the pre-treatment arena of the surgical procedure at UT Austin.</td>
</tr>
<tr>
<td>J. M. Bass</td>
<td>Sr Pers.</td>
<td>Oversight of system component development, software development, dynamic controls, integration and testing.</td>
</tr>
<tr>
<td>S. Prudhomme</td>
<td>Sr Pers.</td>
<td>Mathematical modeling, error analysis, system integration and testing.</td>
</tr>
</tbody>
</table>
## TEAM AT MD ANDERSON

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<tr>
<td>J. Hazle</td>
<td>Co-PI</td>
<td>Coordination and oversight of all Houston TMA activities. Research on MR image acquisition and analysis process.</td>
</tr>
<tr>
<td>L. Bidaut</td>
<td>Sr Pers.</td>
<td>Data processing and graphics visualization at MDA for MRI and MRTI procedures.</td>
</tr>
<tr>
<td>R. J. Stafford</td>
<td>Sr Pers.</td>
<td>Direct Supervision of all imaging experiments.</td>
</tr>
</tbody>
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