A Dynamic Data-Driven System for Optimized Laser Treatment of Prostate Cancer

J.T. Oden

Institute for Computational Engineering and Sciences
The University of Texas at Austin

DoD/AFOSR-NSF Dynamic Data-Driven Application Systems (DDDAS)-Info Symbiotic Systems Workshop,
Arlington, VA
August 30, 2010
Outline

1. Prostate Cancer, Ablation and Damage Models
2. Mathematical BioHeat Transfer Model
   - Governing Equations
   - Optimality Control
   - Model Calibration
3. CyberInfrastructure
   - FEM Mesh Generation & Prospective 3D Treatment Planning
   - Model Calibration
   - Results
4. Expanded Models of Tumor Growth
The Team

The University of Texas at Austin

J. Tinsley Oden
Ken Diller
Ivo Babuška
Chandra Bajaj
Jon Bass
James C. Browne
Leszek Demkowicz
Andrea Hawkins-Daarud
Sepideh Khoshnevis
Serge Prudhomme
Nichole Rylander
Jessica Zhang

M.D. Anderson Cancer Center
(Houston)

John Hazle
David Fuentes
Andrew Elliott
Anil Shetty
Jason Stafford

The University of Texas at San Antonio
Yusheng Feng

Acknowledgements:
NSF grant CNS-0540033,
NIH K25 Career Grant
NIH T32 Training Grant

J.T. Oden
DDDAS for Laser Treatment of Cancer
The function of the prostate is to store and secrete a slightly alkaline fluid, that usually constitutes 25-50\% of the volume of the semen, to prolong the lifespan of sperm in the vaginal tract.

The latest American Cancer Society estimates for prostate cancer in the United States for 2010 are:

- About 217,730 new cases of prostate cancer will be diagnosed
- About 32,050 men will die of prostate cancer

(The methodology we develop is equally applicable to brain cancer and others.)
A concentrated supply of energy will ionize molecules in biological tissue. Beyond a certain threshold, the absorbed energy is high enough to cause decomposition of the tissue:

- the tissue is then *ablated* (making possible the eradication of cancerous cells)

\[ T \approx \begin{cases} 
42^\circ & \text{hyperthermia} \\
50^\circ & \text{ablation} 
\end{cases} \]

- a laser can be used to deposit photon energy locally to initiate the ablation process.
Goals and Challenges

Goals

- Exploit predictive capabilities of patient specific models of bioheat transfer and tissue damage to optimize the treatment and rapidly deliver highly conformal localized thermal dose
- Routinely deliver a conformal lethal thermal dose to a clinically prescribed target tissue volume
  - reduce morbidity
  - potentially reduce recurrence (1st time kill)
  - treat non-surgical candidates
  - non-ionizing repeatable treatments
  - quality of life

Challenges

- Calibration, validation, verification of the computational model
- Remote imaging, data acquisition and management, parallel adaptive methods
- Real-time control, accurate prediction, minimum damage to healthy tissue, eradication of cancer
Bioheat Transfer Model

The Pennes Model Kernel

\[
\rho c_p \frac{\partial u}{\partial t} - \nabla \cdot (k(u, x) \nabla u) + \omega(u, x) c_{\text{blood}} (u - u_a) = Q_{\text{laser}}(x, t) \quad \text{in } \Omega
\]

\[
Q_{\text{laser}}(x, t) = 3 P(t) \mu_a(u, x) \mu_{tr} \frac{\exp(-\mu_{\text{eff}} \| x - x_0 \|)}{4\pi \| x - x_0 \|}
\]

\[
\mu_{tr} = \mu_a(u, x) + \mu_s(u, x)(1 - g)
\]

\[
\mu_{\text{eff}} = \sqrt{3 \mu_a(u, x) \mu_{tr}}
\]

\[
-k(u, x) \nabla u \cdot n = h(u - u_\infty) \quad \text{on } \partial\Omega_C
\]

\[
-k(u, x) \nabla u \cdot n = g \quad \text{on } \partial\Omega_N
\]

\[
u(x, 0) = u^0 \quad \text{in } \Omega
\]

- \(\rho\) density [\(\frac{kg}{m^3}\)]
- \(\omega(u, x)\) blood perfusion [\(\frac{kg}{s \cdot m^3}\)]
- \(c_p\) specific heat [\(\frac{J}{kg \cdot K}\)]
- \(g\) anisotropy factor
- \(x_0\) laser position [\(m\)]
- \(k(u, x)\) thermal conductivity [\(\frac{W}{m \cdot K}\)]
- \(P(t)\) Power [\(W\)]
- \(\mu_a(u, x), \mu_s(u, x)\) absorb/scattering coeff. [\(\frac{1}{m}\)]
The Mathematical Bio-Heat Transfer Model

Find \( u(x, t) \in \mathcal{V} \equiv L^2([0, \tau]; \mathcal{H}^1(\Omega)) \) such that

\[
B(u, \beta; v) = F(\eta, v) \quad \forall v \in \mathcal{V}
\]

\[
B(u, \beta; v) = \int_0^\tau \int_\Omega \left[ \rho c_p \frac{\partial u}{\partial t} v + k(u, \beta) \nabla u \cdot \nabla v + \omega(u, \beta) c_{blood} (u - u_a) v \right] \, dx \, dt
\]

\[
\quad + \int_0^\tau \int_{\partial \Omega} h u \, v \, dA \, dt + \int_\Omega u(x, 0) \, v(x, 0) \, dx
\]

\[
F(\eta; v) = \int_0^\tau \int_\Omega Q_{laser}(\eta; x) \, dx \, dt + \int_0^\tau \int_{\partial \Omega} h u_\infty \, v \, dA \, dt + \int_\Omega u^0 \, v(x, 0) \, dx
\]
Given a set of model coefficients, $\beta_0$, find the combination of laser power and position, $\eta^* \in \mathbb{P}$, such that

$$Q(u^*(\eta^*, \beta_0), \eta^*) = \inf_{\eta \in \mathbb{P}} Q(u(\eta, \beta_0), \eta)$$

where

$$Q(u(\eta, \beta_0), \eta) = \begin{cases} \frac{1}{2} \left\| u(x, t) - u_{\text{ideal}}(x, t) \right\|^2_{L^2([0, \tau]; L^2(\Omega))} & \text{(Temp. Based)} \\ \frac{1}{2} \left\| D(u) - D_{\text{ideal}}(x) \right\|^2_{L^2(\Omega)} & \text{(Damage Based)} \\ \frac{1}{2} \left\| H(u, t) - H_{\text{ideal}}(x, t) \right\|^2_{L^2([0, \tau]; L^2(\Omega))} & \text{(HSP Based)} \end{cases}$$

and the control space $\mathbb{P}$ is defined as

$$\mathbb{P} = \left\{ \eta \in C^0([0, \tau]) \times \mathbb{R}^5 : \exists! u \text{ s.t. } B(u, \beta_0; v) = F(\eta, v) \quad v \in \mathcal{V} \right\}$$
Objective of Optimization

Red Region: Tumor \((G_T)\)
\[ H_{70,27} \leq 1.0 \]
\[ F_D \geq 0.99 \]

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.

Blue Region: Tissue \((G_H)\)
\[ H_{70,27} > 1.0 \]
\[ F_D \leq 0.01 \]
In Vitro Cell-Damage Model

Results for Human Prostate PC3 Cells

Arrhenius Damage Model

\[ C(T, t) = e^{-A t} e^{-E/RT} \]

New Damage Model*

\[ C(T, t) = \frac{e^{-(\Delta H - T \Delta S)/T}}{1 + e^{-(\Delta H - T \Delta S)/T}} \]

Comparison of Temperature Based and Cell Damage Based Optimization

Temperature $T$ ($°K$)  
Optimized temperature ....................... but insufficient cell damage

Cell Damage $F_D$  
Temperature Profile .........................with optimized cell damage

Note: The optimization was carried out based on the nonlinear steady state solution using ProPhlex.
Heterogeneity

– Local Homogenization –
Inverse Analysis

\[
Q(u(\beta, \mathbf{x}, t)) = \frac{1}{2} \left\| \varphi(u(\beta, \mathbf{x}, t)) - D^{\text{ideal}}(\mathbf{x}) \right\|^2_{L^2(\Omega)} = \frac{1}{2} \left\| D(\mathbf{x}) - D^{\text{ideal}}(\mathbf{x}) \right\|^2_{L^2(\Omega)}.
\]

Find \( \beta^* \in \mathbb{P} \) s.t

\[
Q(u(\beta^*), \beta^*) = \inf_{\beta \in \mathbb{P}} Q(u(\beta), \beta)
\]

\[
\mathbb{P} = \left\{ \beta \in L^\infty(\Omega) \times \mathbb{R}^3 \times L^\infty(\Omega) \times \mathbb{R}^3 \times L^\infty([0, \tau]) \times \mathbb{R}^5 : 0 < k_* < k_0(\mathbf{x}) + k_1 \text{atan}(k_2(u - k_3)) < k^* < \infty, 0 < \omega_* < \omega_0(\mathbf{x}) + \omega_1 \text{atan}(\omega_2(u - \omega_3)) < \omega^* < \infty \right\}
\]
Thermal Image Acquisition

- PRF based thermometry, $\Delta u(x, t)$
  - temperature dependent resonant frequency shift
  - $\Delta u$ increase $\Rightarrow$ protons pulled toward oxygen molecule
- SNR, phase error based MRTI noise estimates, $\sigma(x, t)$
  - difference method for system noise
  - appropriate conversion factors Raleigh/Gaussian

$$
\Delta u(x, t) = \frac{\Delta \phi(x, t)}{2\pi \gamma B_0 \alpha_{TE}} \quad \sigma(x, t) = \max_{\tau \in [0, t] \subseteq \Delta T} \left\{ \frac{\sqrt{2}}{SNR(x, \tau)} \right\} 
$$

$$
f_{res} \sim \gamma B_0 (1 - \sigma_0) \quad f_{res} \sim \gamma B_0 (1 - \sigma_0 - \Delta \sigma)
$$
CyberInfrastructure

- hp adaptive FEM computations
- Compute Server
- Hp3D
- MRTI Data Transfer Feedback Control
- LBIE Mesher
- Image processing and Mesh generation
- Visualization Server
- Volume Rover
- Houston: Surgery/Visualization Client
- MRI & MRTI Scans
- DDDAS for Laser Treatment of Cancer
Workflow: Imaging to Mesh Generation Pipeline

- Data Acquisition
- Geometry Extraction
- Mesh Generation
- Laser Parameter Optimization
- Virtual Treatment
- Registration
- Data Transfer
- Patient Specific Calibration
- Data Filtering
- Predictions
- Visualizations

Animation Linux / Windows
Workflow: Imaging to Mesh Generation Pipeline

- Data Acquisition
- Geometry Extraction
- Mesh Generation
- Laser Parameter Optimization
- Virtual Treatment
- Registration
- Data Transfer
- Patient Specific Calibration
- Data Filtering
- Predictions
- Visualizations

J.T. Oden
DDDAS for Laser Treatment of Cancer
Prostate Cancer, Ablation and Damage Models
Mathematical BioHeat Transfer Model
CyberInfrastructure
Expanded Models of Tumor Growth

Workflow: Virtual Planning

- Data Acquisition
- Geometry Extraction
- Mesh Generation
- Laser Parameter Optimization
- Virtual Treatment
- Registration
- Data Transfer
- Patient Specific Calibration
- Data Filtering
- Predictions
- Visualizations

Animation Linux / Windows

J.T. Oden
DDDAS for Laser Treatment of Cancer
Workflow: Patient Specific Calibration

- Data Acquisition
- Geometry Extraction
- Mesh Generation
- Laser Parameter Optimization
- Virtual Treatment
- Registration
- Data Transfer
- Patient Specific Calibration
- Data Filtering
- Predictions
- Visualizations

J.T. Oden

DDDAS for Laser Treatment of Cancer
Workflow: Real Time Delivery

Data Acquisition
Geometry Extraction
Mesh Generation
Laser Parameter Optimization
Virtual Treatment
Registration
Data Transfer
Patient Specific Calibration
Data Filtering
Predictions
Visualizations

J.T. Oden

DDDAS for Laser Treatment of Cancer
Patient Specific Calibration

Inverse recovery of thermal parameters

Forward Solution with Uncalibrated Parameters

Forward Solution with Patient-Specific Calibrated Parameters

Measured Temperature

Degrees Celsius

Imaging Data

Thermal Conductivity $k$

Prior
Uniform
Distribution of Thermal Conductivity $k$

Laser Applicator

Posterior Heterogeneous Distribution

Predicted Temperature

CALIBRATION PROCESS

J.T. Oden

DDDAS for Laser Treatment of Cancer
Results: Calibration

MRTI Volume
Laser Energy Supply System and Predicted Temperature Field
Laser Energy Supply System and Predicted Temperature Field
Results: Validation
Model Validation

- SNR = Signal to Noise Ratio
- $\sigma = 1/\text{SNR}$
- High $\sigma$ corresponds to high uncertainty in the data

\[
\text{SNR} = \frac{\text{Signal}}{\text{Noise Ratio}}
\]

\[
\sigma = \frac{1}{\text{SNR}}
\]

High $\sigma$ corresponds to high uncertainty in the data.
Future Direction

- Develop Predictive Models of Tumor Growth and Therapies
- Expand Platform to Facilitate Variety of Thermal Therapies
  - Cryo-ablation, Active Cooling, Microwave, Radiofrequency, Photoacoustic, US-RF

J.T. Oden
DDDAS for Laser Treatment of Cancer
Thank you!

oden@ices.utexas.edu
Mixture Theory

- Mixture theory is based on continuum mechanics, but allows multiple constituents to be present at the same point in space.
- Constituents represented with volume fractions.
- Constituent balance laws must be consistent with the balance laws of physics for the entire mixture.

Local Forms of Balance Laws \cite{Oden2010}

For $1 \leq \alpha \leq N$

Mass

$$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha v_\alpha) = \frac{1}{\rho_\alpha} (\gamma_\alpha - \nabla \cdot j_\alpha)$$

Linear Momentum

$$\rho_\alpha \phi_\alpha \frac{dv_\alpha}{dt} = \nabla \cdot T_\alpha + b_\alpha + p_\alpha$$

Angular Momentum

$$M_\alpha = T_\alpha - T_\alpha^T$$

Energy

$$\rho_\alpha \varphi_\alpha \frac{d\alpha e_\alpha}{dt} = \text{tr} T_\alpha^T L_\alpha - \nabla \cdot q_\alpha + \rho_\alpha \varphi_\alpha r_\alpha + \hat{\epsilon}_\alpha$$

$$+ \sum_{\beta=1}^{N} \nabla \cdot \left( \sigma_{\alpha\beta} \frac{d\alpha \varphi_\beta}{dt} \right) + \sum_{\beta=1}^{L} \zeta_{\alpha\beta} \frac{d\alpha m_\beta}{dt}$$

Second Law

$$\sum_{\alpha=1}^{N} \left\{ \frac{1}{\theta_\alpha} \left[ -\rho_\alpha \phi_\alpha \frac{d\psi_\alpha}{dt} + \eta_\alpha \frac{d\theta_\alpha}{dt} + \text{tr} T_\alpha^T L_\alpha - q_\alpha \cdot \frac{g_\alpha}{\theta_\alpha} \right. ight.$$

$$+ \hat{\epsilon}_\alpha - u_\alpha \cdot p_\alpha - \gamma_\alpha \left( \psi_\alpha + \frac{1}{2} u_\alpha \cdot u_\alpha \right) \left. \right\} \geq 0$$

J.T. Oden

DDDAS for Laser Treatment of Cancer
**Example Model Classes**

\[ \mathcal{M}_1: \text{Simple Proliferation Model} \]

\[
\begin{align*}
  u_t &= \nabla \cdot (M \nabla \mu) + Pu & \text{in} \ (0, T) \times \Omega, \\
  \mu &= f'(u) - \epsilon^2 \Delta u & \text{in} \ (0, T) \times \Omega, \\
  \nabla u \cdot n &= \nabla \mu \cdot n = 0 & \text{on} \ (0, T) \times \partial \Omega, \\
  u(0, x) &= u_0 & \text{in} \ \{0\} \times \Omega, \\
  f'(u) &= \gamma \left(4u^3 - 6u^2 + 2u \right). 
\end{align*}
\]

\[ \mathcal{M}_2: \text{Proliferation Model with Oxygen Dependence} \]

\[
\begin{align*}
  u_t &= \nabla \cdot (M \nabla \mu) + Pc u & \text{in} \ (0, T) \times \Omega, \\
  \mu &= f'(u) - \epsilon^2 \Delta u - \epsilon \chi c & \text{in} \ (0, T) \times \Omega, \\
  0 &= \nabla \cdot (D \nabla c) - cu & \text{in} \ (0, T) \times \Omega, \\
  \nabla u \cdot n &= \nabla \mu \cdot n = 0 & c = 1 \quad \text{on} \ (0, T) \times \partial \Omega, \\
  u(0, x) &= u_0 & \text{in} \ \{0\} \times \Omega, \\
  f'(u) &= \gamma \left(4u^3 - 6u^2 + 2u \right). 
\end{align*}
\]
\( M_3: \) Proliferation/Apoptosis Model with Degenerate Mobility and Oxygen Dependence

\[
\begin{align*}
  u_t &= \nabla \cdot (Mu^2 \nabla \mu) + Pcu - Au \\
  \mu &= f'(u) - \epsilon^2 \Delta u - \epsilon \chi c \\
  0 &= \nabla \cdot (D\nabla c) - cu \\
  \nabla u \cdot n &= \nabla \mu \cdot n = 0 \quad c = 1 \\
  u(0, x) &= u_0 \\
  f'(u) &= \gamma (4u^3 - 6u^2 + 2u).
\end{align*}
\]
Example Output from Model 3

Snapshots of simulation at $T=0,3,6, \text{ and } 9$.

This simulation illustrates the effects of the $\chi$ term added in the free energy.
Predictive Computing Within a Bayesian Framework
General Framework

Assume a formulation of a specific mathematical model of the physical events of interest

\[ A(m, S, u(m, S)) = 0 \]  

(2)

representing the system of nonlinear partial differential equations.

- \( m = (m^1, m^2, \ldots, m^n) \) denotes the data defining a specific model (e.g. coefficients, initial data, ...)
- \( S \) denotes scenario parameters, i.e. geometry, initial conditions, etc...

General Framework

- Model Target: Compute specific quantity of interest (QoI)
- QoI characterized by \( Q_S : \mathbb{U}_m \rightarrow \mathbb{R} \)
- Goal: Compute number \( q_S(m) \)

\[
q_S(m) = Q_S(u(m, S))
\]

subject to the requirement that \( A(m, S, u(m, S)) = 0 \).

Figure: Prediction Pyramid of Complexity
A Statistical Validation Framework

Prediction

If the model is found to be “not invalid,”

- QoI random variable $Q(\mathbf{u}(\sigma_M(\mathbf{m}), \mathbf{S}_P))$ characterizes uncertainty.
- Quantify this uncertainty by computing its mean, covariance matrix, moments, etc. i.e.

$$q_P^0 = \langle q_P(\mathbf{m}) \rangle = \int_M q_P(\mathbf{m}) \, d\mathbf{m}$$

$$q_P^r(\mathbf{m}) = \int_M (q_P(\mathbf{m}) - \langle q_P(\mathbf{m}) \rangle)^r \sigma_M(\mathbf{m}) \, d\mathbf{m} \quad r = 1, 2, \ldots$$
Illustrative Preliminary Calculations
Illustrative Example Overview

Goal: Demonstrate the use of Bayesian statistical calibration and validation ideas.

- Generate virtual data using the relatively complicated model $M_3$.
- Use data to calibrate the simple model $M_1$.
- $M_1$ has one parameters: proliferation rate, $P$. Assume a uniform prior probability density:
  \[
  \rho (m) = \rho (P) = U(0, 0.3)
  \]
- Assume the likelihood function takes the form
  \[
  \theta (d|m) = k \exp \left( -\frac{1}{2} (d^{obs} - d(m))^T C^{-1} (d^{obs} - d(m)) \right)
  \]
  Note that this is similar to Gaussian, however, $d(m)$ is not linear so it is not a Gaussian.
Calibration Data

Virtual Data:

1. $L^2$ norm per element

$$d_i := \left( \int_{\text{elem}_i} u(x, T)^2 \, dx \right)^{1/2}$$

2. # of data points = # of elements = 19600

Note:

To calculate $d(m)$, one must solve the model $M_1$ for the given $m$ and then calculate $d_i$ as above with the solution.

Parameters used in $M_3$ to generate virtual data:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M$</td>
<td>200</td>
</tr>
<tr>
<td>$P$</td>
<td>0.1</td>
</tr>
<tr>
<td>$\chi$</td>
<td>10</td>
</tr>
<tr>
<td>$D$</td>
<td>1</td>
</tr>
<tr>
<td>$A$</td>
<td>0</td>
</tr>
</tbody>
</table>
The likelihood covariance for the noise in the observables was set as a diagonal matrix with uniform standard deviation of 0.15. Thus,

$$\sigma_M(m|d^{obs}) = k \exp \left( -\frac{1}{2 \times (0.15)^2} (d^{obs} - d(m))^T(d^{obs} - d(m)) \right)$$
Calibrated PDF

Calibrated PDF visualized by calculating $d(m)$ at many grid points in the region of non-zero probability determined by the prior uniform distribution.

From the grid points tested, the calibrated Maximum Likelihood Estimator (MLE) of the parameters for $\mathcal{M}_1$ is $P = 0.02625$

$\mathcal{M}_1$ simulation at $T = 3$ at MLE  

Data generation simulation at $T = 3$
Validation Data

Virtual Data:

1. $\mathcal{L}^2$ norm per element
   
   $$d_i := \left( \int_{\text{elem}_i} u(x, T)^2 \, dx \right)^{1/2}$$

2. # of data points = # of elements = 19600

We again set the standard deviation to 0.15, so the validation posterior pdf is

$$\sigma_V (m|d_v^{obs}) = k\sigma_M (m|d_c^{obs}) \times \exp \left( -\frac{1}{2 \times (0.15)^2} \left( d_v^{obs} - d(m) \right)^T \left( d_v^{obs} - d(m) \right) \right)$$
Validation PDF

Prior PDF (Calibrated Posterior)

Validation PDF

\[ m = 0.1350, \quad sd = 0.0631 \]

\[ m = 0.0990, \quad sd = 0.0707 \]
Prediction QoI is the tumor volume at $T = 9$.

$$QoI = \int_{\Omega} u(x, t) \, dx$$
Validation Process

Use example metric

\[
D(q_{val}, q_{cal}) = \sup_{y \in [0,1]} \left| F_{val}^{-1}(y) - F_{cal}^{-1}(y) \right| \approx 10.6809
\] (3)

where \( F_{val} \) and \( F_{cal} \) are the CDFs associated with \( q_{val} \) and \( q_{cal} \) respectively.

Validation QoI CDF