Design of Optimal Laser Protocols for Prostate Cancer by Controlling Heat Shock Protein Expression

M. Nichole Rylander
Outline

- Introduction
- Cellular Studies
  - HSP Expression Kinetics and cell viability profiles
  - HSP and cell injury Predictive Model
- Tissue Studies
  - Thermal treatment and monitoring with MRTI
  - Tissue immunostaining and HSP expression
- Treatment Planning Model
  - Tissue Response prediction model
  - Optimization Algorithm
- Conclusions
- Future Work
Motivation

- Prostate cancer is the second leading cause of cancer death for males in the United States with one in six men expected to contract the disease in their lifetime.
- Laser thermal therapy can be compromised by Heat Shock Protein (HSP) expression.
Study Objectives

- Characterize thermally induced HSP expression kinetics and cell viability in prostate in vitro and in vivo
- Develop HSP expression and damage predictive models based on measured data
- Create a finite element model to predict temperature, HSP expression, and damage due to laser heating
- Utilize models to design optimal laser treatments to maximize tumor destruction
Heat Shock Protein Stimuli

CELLULAR STRESS RESPONSE

1. ENVIRONMENTAL STRESS
   - AMINO ACID ANALOGUES
   - TRANSITION HEAVY METALS
   - INHIBITORS OF ENERGY METABOLISM
   - HEAT SHOCK

2. PATHOPHYSIOLOGICAL STATE
   - FEVER
   - HYPERTROPHY
   - OXIDANT INJURY
   - INFLAMMATION
   - ISCHEMIA
   - ANTI-NEOPLASTIC CHEMICALS
   - VIRAL INFECTION
   - ONCOGENES AND PROTO-ONCOGENES
   - DEVELOPMENT AND DIFFERENTIATION

3. NON-STRESSFUL CONDITIONS
   - CELL CYCLE
   - GROWTH FACTORS
HSP Molecular Functions

- HSP function as molecular chaperones
  - inhibit improper protein aggregation
  - direct newly formed proteins to target organelles for final packaging degradation or repair
- In the presence of stress HSP assist in:
  - refolding and repair of denatured proteins
  - facilitate synthesis of new proteins in response to damage

<table>
<thead>
<tr>
<th>Stimulus</th>
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<th>Protective Effects</th>
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<tbody>
<tr>
<td>Stress (Heat, ischaemia)</td>
<td>HSF-1</td>
<td>Enhanced protein folding</td>
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<tr>
<td></td>
<td></td>
<td>Degradation of abnormal proteins</td>
</tr>
<tr>
<td>Cytokines</td>
<td>NF-IL6 STAT</td>
<td>Inhibition of apoptosis</td>
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<tr>
<td></td>
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<td>Protection of cytoskeleton</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhanced NO synthesis</td>
</tr>
</tbody>
</table>
HSP Response to Stress

Environmental stresses:
- radiation
- oxidants
- chemicals
- heat

Antioxidant enzymes

DNA damage
- mutation

DNA repair system

Molecular chaperones
- refolding
- degradation

Normal function

Abnormal cells
- disabled protein

Hereditary disease
Aging
Cancer
HSP and Prostate Cancer

- Increased HSP expression has been implicated in multidrug resistance, regulation of apoptosis, and modulation of p53 functions
- Elevation of HSP 27, 60, 70 are markers signaling poor prognosis in prostatic carcinoma
- Thermal initiation of HSP 27 and 70 have been shown to provide cellular resistance to radiation or chemotherapy

HSP60 (top view)
Cellular Studies
HSP Kinetics Characterization

- HSP 27, 60, 70 expression kinetics and cell viability were determined for prostate cancer (PC3) cells and normal prostate cells (RWPE-1) cells
- Water bath heating was employed to simulate hyperthermic conditions for \( T=44-60^\circ C \) and \( t=1-30 \) minutes
- Western Blot determined HSP27,60, and 70 expression levels following 16-18 hrs post-heating
- Propidium Iodide staining and flow cytometry was employed to determine cell viability
### Western Blot T=46°C

#### Heating Time (min)

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</table>
Cell Immunostaining T=48°C for 2 min

Green Fluorescence HSP27
Red Fluorescence HSP70
Duration of HSP Phenomenon

Cells heated at T=44°C and HSP measured for several post-heating durations.
Duration of HSP Phenomenon T=44°C
Histograms for Cell Viability

Control

Propidium Iodide Staining

Events

Extreme Heat Shock

Propidium Iodide Staining

Events

Mild Heat Shock

Propidium Iodide Staining

Events
Cell Viability
PC3 (a) and RWPE-1 (b) cells

(a)
- T=44°C
- T=46°C
- T=48°C
- T=50°C
- T=52°C
- T=54°C
- T=56°C
- T=58°C
- T=60°C

(b)
- T=44°C
- T=46°C
- T=48°C
- T=50°C
- T=52°C
- T=54°C
- T=56°C
- T=58°C
- T=60°C

Cell Viability (%) vs. Heating Time (min)
Damage

- Damage was determined from the experimental data by means of the Arrhenius integral formulation

\[
\Omega(\tau) = \ln\left(\frac{C_0}{C_\tau}\right) = A \int_0^\tau e^{-\frac{E_a}{RT(t)}} dt
\]

- \(C_0\) initial concentration of healthy cells
- \(C_\tau\) remaining fraction of healthy cells after heating at time \(\tau\), from cell adhesion studies.
- \(A\) (1/s) is a pre-exponential scaling factor
- \(\tau\) (s) is the time of thermal stress
- \(E_a\) (J/mol) is the activation energy of the injury process
- \(R\) (J/mol-K) is the universal gas constant
- \(T\) (K) is the absolute temperature
In the case of isothermal conditions when $\Omega = 1$ the damage equation simplifies to the logarithmic form,

$$\ln(\tau) = \frac{E_a}{R} \left( \frac{1}{T} \right) - \ln(A)$$
# Measured Damage Parameters

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>$E_a$ (kcal/mole) $T \leq 54^\circ C$</th>
<th>$A$ (s$^{-1}$) $T \leq 54^\circ C$</th>
<th>$E_a$ (kcal/mole) $T &gt; 54^\circ C$</th>
<th>$A$ (s$^{-1}$) $T &gt; 54^\circ C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC3</td>
<td>$2.38 \times 10^5$</td>
<td>$1.80 \times 10^{36}$</td>
<td>$1.24 \times 10^5$</td>
<td>$7.00 \times 10^{17}$</td>
</tr>
<tr>
<td>RWPE-1</td>
<td>$2.49 \times 10^5$</td>
<td>$1.03 \times 10^{38}$</td>
<td>$5.88 \times 10^4$</td>
<td>$5.65 \times 10^7$</td>
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</table>
Optimal Hyperthermia Protocols

- Required heating protocols to diminish HSP expression below basal level and corresponding cell viability.
- The conditions which elicit HSP70 expression decline are more severe than necessary for HSP27 degradation.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>HSP70 Duration minimum (min)</th>
<th>Cell Viability (%)</th>
<th>HSP27 Duration minimum (min)</th>
<th>Cell Viability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>25</td>
<td>21</td>
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<tr>
<td>60</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
<td>0.7</td>
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</table>
Tissue Studies
Prostate Cancer *In Vivo* Studies

- Prostate tumors cells were inoculated in the hind legs of female SCID mice and grown to a tumor burden of < 1.0 cc
- Tissue was heated with a 810-nm diode laser. Fluence=5 W/cm² and pulse duration=3 min to generate a temperature differential to enable HSP expression and damage to be measured.
Magnetic Resonance Imaging (MRI)

Nuclei possess a tiny magnetic moment called spin
Human body primarily composed of fat and water which contain many hydrogen atoms
Hydrogen atoms contain a single proton which has a ±1/2 spin denoting different energy states

Absence of Magnetic Field

Hydrogen atoms in random alignment.

\[ E = \frac{1}{2} \gamma h B_0 \]

\[ E = \frac{1}{2} \gamma h B_0 \]

\[ E = -\frac{1}{2} \gamma h B_0 \]
Hydrogen Nuclei Precession

Static magnetic field causes the magnetic moment to precess in the direction of the field.
This movement is called the Larmor precession and the frequency of this precession around the z-axis is called the Larmor frequency, which is 42,57 MHz for protons.
Electromagnetic waves in this frequency range are called radio frequent or RF waves.
MR Imaging

Hydrogen atoms aligned to magnetic field

Applied Magnetic Field
Relaxation and Measurement

- **T1 relaxation (spin lattice relaxation)** - Longitudinal component of the net magnetization vector and involves the exchange of energy between the spin system and the surrounding thermal system.

- **T2 relaxation (spin-spin relaxation)** - Transverse magnetisation, pointing in the x/y-direction and is an entropy process.
Magnetic Resonance Temperature Imaging

- Spatiotemporal temperature distribution was measured during laser treatment using magnetic resonance temperature imaging (MRTI) sequence with 1.5 Tesla, 40 cm bore Bruker Biospec system
- Image update times less than 5 seconds per image
- A 3D fast spoiled gradient echo sequence was employed which acquired 4 planes every 6.5 seconds
- Pulse repetition time (TR) = 12.3 ms, Echo time (TE) = 5.3 ms and Planes=2.0 mm thick
The measured phase $\Delta \phi$ can be employed in calculating temperature differences $\Delta T$ in the following equation

$$\Delta \phi = \gamma \alpha B_o \Delta T \cdot TE$$

- where $\gamma$ is the gyromagnetic ratio
- $\nu$ is the photon frequency
- $\alpha$ is proton resonance frequency shift thermal coefficient (slope of shift vs. temperature plot)
- $B_o$ is the main magnetic field
- TE is the echo time (time between start of RF pulse and maximum signal)
MRT Image Following Laser Irradiation
**Tissue Analysis**

<table>
<thead>
<tr>
<th>HSP</th>
<th>Primary Antibody Type</th>
<th>Fluorescent Conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>mouse monoclonal IgG(_2)</td>
<td>Rhodamine Red-X</td>
</tr>
<tr>
<td>27</td>
<td>mouse monoclonal IgG(_1) conjugated to biotin</td>
<td>Cy2-conjugated to streptavidin</td>
</tr>
</tbody>
</table>
What is an antibody?

- An immunoglobulin that is capable of combining with specificity to the antigen that elicited its production.
- An antigen is any substance that elicits an immune response and is then capable of binding to the subsequently produced antibodies.
- Antigens are generally proteins or polysaccharides, but other substances such as nucleic acids can also be antigens.
How does antibody staining work?

- Antibody-antigen reaction is highly specific for a given antibody-antigen pair.
- Immunostaining techniques rely on the extreme specificity of an antibody for its antigen.
Fluorescence
## Statistics

<table>
<thead>
<tr>
<th>Position (mm)</th>
<th>HSP27 Mean Fluorescence</th>
<th>HSP70 Mean Fluorescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>47.25</td>
<td>68.15</td>
</tr>
<tr>
<td>1</td>
<td>24.12</td>
<td>36.04</td>
</tr>
<tr>
<td>2</td>
<td>14.66</td>
<td>25.33</td>
</tr>
</tbody>
</table>
HSP Concentration Calculations

\[
HSP_{\text{Norm}} = \frac{HSP_{\text{Final}}}{HSP_{\text{Control}}} = \frac{FI_{Fm}}{FI_{Cm}}
\]

- \(HSP_{\text{Norm}}\) is the normalized HSP concentration
- \(HSP_{\text{Final}}\): HSP concentration of tumor following heating with or without nanoshells
- \(HSP_{\text{Control}}\): HSP concentration for unheated tumor
- \(FI_{Fm}\): Mean fluorescence intensity following heating with or without nanoshells
- \(FI_{Cm}\): Mean fluorescence intensity for uneated tumor
Modeling
Modeling Strategy Diagram

- $\lambda$=wavelength of the laser source
- $P$=power
- $O_F$=optical fiber orientation
- $t$=duration of thermal exposure
- $\phi(r,t,T)$, HSP($r,t,T$), and $\Omega(r,t,T)$ are the spatiotemporal temperature dependent distributions of fluence, HSP, and damage respectively
- $T(r,t)$=spatiotemporal temperature distribution
Model Equations

\[ c \rho \frac{\partial T}{\partial t} = \nabla (k(T) \nabla T) + \omega_b(T)c_b(T - T_a) + Q(x, y, z) \]

where \( Q(x, y, z) = \mu_a \phi(x, y, z) \)

\[ \phi = 3P\mu_{tr} \exp^{-\mu_{eff} \| \vec{r} - \vec{r}_0 \|} / 4\pi \| \vec{r} - \vec{r}_0 \| \]

- \( c \)-specific heat of tissue
- \( \rho \)-density of tissue
- \( c_b \)-specific heat of blood
- \( k(T) \)-temperature dependent thermal conductivity of the tissue
- \( \omega(T) \)-temperature dependent perfusion rate
- \( T_a \)-temperature of blood
- \( Q(x, y, z) \)-amount of photon energy absorbed in the tissue
- \( \mu_a \)-absorption coefficient of tissue
- \( \phi \)-energy fluence rate (radiant power incident on a small sphere divided by the cross-sectional area of the sphere)
Constitutive Relations

Temperature Dependent Blood Perfusion

\[
\omega_{\text{tumor}} = \begin{cases} 
0.833 & T < 37.0 \\
0.833 - (T - 37.0)^{4.8} / 5.44 \times 10^3, & 37.0 \leq T \leq 42.0 \\
0.416 & T > 42.0 
\end{cases} \text{ Kg/s/m}^3
\]


Temperature Dependent Thermal Conductivity

\[
K(T) = 4.19(0.133 + 1.36\lambda_k \text{ w}) \times 10^{-1} \text{ W/mk}
\]

where \( \lambda_k = 1 + 1.78 \times 10^{-3}(T - 20^\circ\text{C}) \)

HSP Expression Model

\[ \frac{\partial H(t,T)}{\partial t} = f(t,T) \cdot H(t,T) \]

where \( H(T,t) \) represents HSP expression and \( f(t,T) \) is a general rate function which both capture HSP kinetics characteristics and are defined as

\[ f(t,T) = (\alpha - \beta_1 t^{\gamma-1}) \quad \text{and} \quad H(t,T) = A e^{\alpha - \beta t^\gamma} \]

where \( \alpha, \beta_1=\beta \gamma, \text{ and } \gamma \) are parameters which are independent of time, but may be dependent on temperature, with \( \gamma > 1 \)
Measured and Model Predicted HSP70 Expression Comparison
<table>
<thead>
<tr>
<th>Temperature °C</th>
<th>PC3 Cells</th>
<th>RWPE-1 Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HSP27 Expression Parameters</td>
<td>HSP70 Expression Parameters</td>
</tr>
<tr>
<td></td>
<td>$\alpha$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>44</td>
<td>0.91</td>
<td>0.23</td>
</tr>
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<td>46</td>
<td>6.89</td>
<td>5.83</td>
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<td>22.01</td>
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## Correlation Coefficients for Model Predicted HSP Expression

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>PC3 Cells</th>
<th>RWPE-1 Cells</th>
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<td></td>
<td>HSP70 model</td>
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<td>56</td>
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<tr>
<td>60</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Hypoxia Induced p53 activation
\[ \Omega(\tau) = \ln \left( \frac{C_0}{C_\tau} \right) = A \int_0^\tau e^{\left(-\frac{E_a}{RT(t)}\right)} dt \]

\[ F_D = 1 - \exp^{-\Omega} \]

- \( C_0 \) initial concentration of healthy cells
- \( C_\tau \) remaining fraction of healthy cells after heating at time \( \tau \), from cell adhesion studies.
- \( A \) (1/s) is a pre-exponential scaling factor
- \( \tau \) (s) is the time of thermal stress
- \( E_a \) (J/mol) is the activation energy of the injury process
- \( R \) (J/mol-K) is the universal gas constant
- \( T \) (K) is the absolute temperature
- \( F_D \)-damage fraction of damaged to undamaged tissue
- Native tissue is represented by \( F_D=0 \) (\( \Omega=0 \)) and while fully denatured tissue is given by \( F_D=1 \) (\( \Omega=\infty \))
## Measured Damage Parameters

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Ea (kcal/mole) T≤54°C</th>
<th>A (s⁻¹) T≤54°C</th>
<th>Ea (kcal/mole) T&gt;54°C</th>
<th>A (s⁻¹) T&gt;54°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC3</td>
<td>2.38x10⁵</td>
<td>1.80x10³⁶</td>
<td>1.24x10⁵</td>
<td>7.00x10¹⁷</td>
</tr>
<tr>
<td>RWPE-1</td>
<td>2.49x10⁵</td>
<td>1.03x10³⁸</td>
<td>5.88x10⁴</td>
<td>5.65x10⁷</td>
</tr>
</tbody>
</table>
Current Model

- Using Hypermesh, the system geometries were generated which included a quarter sphere, MRI based tumore, and prostate with interior tumors and a hexahedron 3D finite element mesh and boundary conditions were imposed.
- Model was imported into PHLEX, an hp adaptive finite element package.
- Using a posteriori error estimation in PHLEX, the tumor model was adaptively refined by 1-irregular meshing technique with highest polynomial order up to six.
External Heating
Temperature Distribution Pulse Length 3 min

Q=3W

Q=6W
HSP27 Distribution Pulse Length 3 min

Q=3W

mg/ml

Q=6W

mg/ml
HSP70 Distribution Pulse Length 3 min

Q=3W

Q=6W
Comparison Between Model Predicted and MRTI measured Temperature

Accuracy of Model Prediction
Intra-tumoral Heating
Tumor Model $Q=3W$ Pulse Duration=3 min

- Temperature
- HSP70
- HSP27
- Damage
HSP27 Distribution
MRI Based Mouse Model

- A hexahedral mesh was developed for the tumor and the tissue from the MR images.

- A semi-automatic segmentation method was adapted to find the boundaries of the tumor and the tissue from each imaging slice.

- Then the cubic spline and lofting methods were applied to obtain smooth boundary surfaces from which hexahedral meshes were extracted from the segmented MRI data.

Hexahedral mesh of the tumor (blue) and the tissue (yellow)
MRI-Derived Tumor Model

Temperature

HSP70

HSP27

Damage
Intratumoral Heating of Prostate with Interior Tumor

<table>
<thead>
<tr>
<th></th>
<th>T(K)</th>
<th>mg/ml</th>
</tr>
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<tbody>
<tr>
<td>Temperature</td>
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<tr>
<td>HSP70</td>
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<tr>
<td>HSP27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Damage</td>
<td></td>
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</tbody>
</table>
Laser Therapy Optimization
-where G is the computational domain, the criteria specified above for HSP and damage fraction $F_D$ are typical values and can be chosen differently by users.
Objective Functions

Damage Fraction Based Objective Function

\[ J_{F_D} = \int_{x,y,z \in G_T} (F_{DT}(x, y, z, t) - \delta_T)^2 dV + \int_{x,y,z \in G_H} (F_{DH}(x, y, z, t) - \delta_H)^2 dV \]

HSP\textsubscript{27,70} Expression Based Objective Function

\[ J_{HSP_{27,70}} = \int_{x,y,a \in G_T} (HSP_{27,70}^T(x, y, z, t) - \sigma_T)^2 dV + \int_{x,y,z \in G_H} (HSP_{27,70}^H(x, y, z, t) - \sigma_H)^2 dV \]

Temperature Based Objective Function

\[ J_{Temp} = \int_{x \in G_T} (T - \beta_T)^2 dV + \int_{x \in G_H} (T_H - \beta_H) dV \]

where \( \delta_T \) and \( \delta_H \) represent desired damage fractions, \( \sigma_T \) and \( \sigma_H \) represent desired HSP\textsubscript{27,70} expression, and \( \beta_T \) and \( \beta_H \) represent the desired temperature values.
Temperature Based Optimization

\[ J_{Temp} = \int_{x \in G_T} (T_T - \beta_T)^2 dV + \int_{x \in G_H} (T_H - \beta_H) dV \]

Equivalent Thermal Dose

\[
(t_{43})_N = \sum_{i=1}^{N} R^{(43°C - T_i)} \cdot \Delta t, \quad \text{with } R = \begin{cases} 
0.25, & T_i < 43°C \\
0.50, & T_i \geq 43°C 
\end{cases}
\]

where \( \Delta t \) is the time between measurements (1 sec) and, \( T_i \) is the temperature in degrees Celsius for the ith measurement, and \( R \) is a constant empirically derived from hyperthermia experiments in living tissue.

The selected \( T_i \) value was chosen as 48°C which yielded an equivalent thermal dose of 1 minute.
Optimization Strategy

- Determine set of parameters $X_i=(P_i, \mu_a, \mu_s, x_i, y_i, z_i)$ for $i=1,...,M$ ($M$ is number of laser sources) that minimizes the objective function is minimized.

1) Damage-Based Optimization Problem: Find $X$ such that

$$J^*_{FD} = \min J_{FD}(X)$$

2) HSP Expression-Based Optimization Problem: Find $X$ such that

$$J^*_{HSP_{27,70}} = \min J_{HSP_{27,70}}(X)$$

3) Temperature-Based Optimization Problem: Find $X$ such that

$$J^*_{Temp} = \min J_{Temp}(X)$$
Steepest Descent Method

- An **algorithm** for finding the nearest **local minimum** of a function which presupposes that the **gradient** of the function can be computed. The method of steepest descent, also called the gradient descent method, starts at a point $P_0$ and, as many times as needed, moves from $P_i$ to $P_{i+1}$ by minimizing along the line extending from $P_i$ in the direction of $-\nabla P_i$ the local downhill gradient.

- The direction of steepest descent $-\nabla J_i$ points in the direction in which $J_i$ is decreasing most rapidly. As a result, minimization is along the steepest direction, $-\nabla J_i$. 

![Graph of function and steepest descent](image)
Optimization Algorithm

Solution Method: Steepest Descent

- Specify initial values of $P_o$, $\mu_a$, $\mu_{so}$, $x_o$, $y_o$, $z_o$ and $t$
  calculate $T(x,y,z,t)$, $F_D(x,y,z,t)$, and $HSP_{27,70}(x,y,z,t)$
- Compute $J_o$ ($J_{Temp}$, $J_{FD}$, and $J_{HSP27,70}$)
- Parameters are perturbed according to:
  - $P_1 = P_o + \Delta P$, $\mu_{a1} = \mu_a + \Delta \mu_a$, $\mu_{s1} = \mu_{so} + \Delta \mu_s$, $x_1 = x_o + \Delta x$
  - $y_1 = y_o + \Delta y$, $z_1 = z_o + \Delta z$
- Compute new objective functions $J_1$ ($J_{Temp}$, $J_{FD}$, and $J_{HSP27,70}$)
- Compute gradient for all parameters

\[
\frac{\partial J}{\partial P} = \frac{J_1 - J_o}{\Delta P}, \quad \frac{\partial J}{\partial \mu_a} = \frac{J_1 - J_o}{\Delta \mu_a}, \quad \frac{\partial J}{\partial \mu_s} = \frac{J_1 - J_o}{\Delta \mu_s}, \quad \frac{\partial J}{\partial x} = \frac{J_1 - J_o}{\Delta x}, \quad \frac{\partial J}{\partial y} = \frac{J_1 - J_o}{\Delta y}, \quad \frac{\partial J}{\partial z} = \frac{J_1 - J_o}{\Delta z}
\]
Optimization Steps

- Update the value of all parameters $P$, $\mu_a$, $\mu_s$, $x$, $y$, $z$
  - A new value of $X_i$ is determined according to the following equation:
    $$X(i) = X(i) + k \frac{\partial J}{\|\nabla J\|}$$
    where
    $$\begin{pmatrix}
    X(1) \\
    X(2) \\
    X(3) \\
    X(4) \\
    X(5) \\
    X(6)
    \end{pmatrix} =
    \begin{pmatrix}
    P \\
    \mu_a \\
    \mu_s \\
    x \\
    y \\
    z
    \end{pmatrix}$$

  and $k$ is the step size

- Compute $J_2$ and Compare all computed $Y(i) = J_i$ ($i = 0,1,2,3$)
  - if $\|Y(1) - Y(0)\| < \varepsilon$, $\frac{Y(2) - Y(1)}{Y(1) - Y(0)} > 0$ and $Y(2) < Y(1)$
    - update $Y(0) = Y(1)$ and $Y(1) = Y(2)$

  - Verify difference is within convergence tolerance, $\varepsilon$
    $$\|Y(2) - Y(1)\| < \varepsilon$$

  - However, if $Y(2) > Y(1)$ than decelerate and value is reset and step size is halved

- Initial steps are repeated until the objective function is minimized according to specified criteria

- Process is repeated until objective function is minimized
Insufficient Thermal Dose: 
$Q_1 = 0.5W$, $Q_2 = 0.15W$
Thermal Overdose:
\[ Q_1 = 1.6W, \quad Q_2 = 1.1W \]
$F_D$ Based Optimized Thermal Dose: $Q_1 = 1\text{W}, \ Q_2 = 0.5\text{W}$

Temperature

Cell Damage

HSP 70

HSP 27
HSP\textsubscript{27,70} Based Optimized Thermal Dose: 
Q_1 = 1W, \ Q_2 = 0.5W
Temperature Based Optimized Thermal Dose: $Q_1 = 0.5W$, $Q_2 = 0.3W$
## Computational Characteristics

<table>
<thead>
<tr>
<th>Metric for Optimization</th>
<th>J (initial)</th>
<th>J (optimum)</th>
<th>Convergence Steps</th>
<th>CPU Time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damage Fraction</td>
<td>.1806</td>
<td>.0075</td>
<td>18</td>
<td>71</td>
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<tr>
<td>HSP Expression</td>
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<tr>
<td>Temperature</td>
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<td>78</td>
</tr>
</tbody>
</table>
Conclusions

- Thermally induced HSP expression and injury were characterized in both prostate cells and tissue
- Cellular and Tissue HSP expression and cell viability data permitted development of HSP expression and Arrhenius damage models
- Integration of HSP expression and damage models into a finite element thermal model enables prediction of the tissue response to laser heating
- Coupling the computational model with an optimization algorithm enabled determination of the most optimal laser parameters
- Utilization of the treatment planning model in design of laser therapies will yield more optimal post-therapy outcomes consisting of complete tumor eradication and minimization of tumor recurrence
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Questions?