**The Thermodynamics of Solid Tumor Growth: A Continuum Mechanics Approach**

Student: Sarah Verner
2009 Summer Mathematics REU
Advisor: Professor Krishna Garikipati

**Abstract:** Using data available from Helmlinger et al. (1997), West et al. (2001, 2002), Guiot et al. (2003) and other experimental literature, as well as from previous theoretical work of Garikipati et al. (2004, 2006), this project aims to study the efficiency of energy usage (metabolism) of tumors. As a preliminary step in this direction we will consider the experiments in which tumor growth was demonstrated to be inhibited in the presence of mechanical stresses. However, there remains a gap in the data, in that the mechanical properties of the cells, fluid and composite tumor (composed of cells, ECM and fluid), various energies and metabolic rates are not readily available. It is to bridge this gap that we will use our computations. With the other data gathered from the literature, we will vary the above experimentally unavailable mechanical properties in our computational model to seek a good match with the tumor spheroid growth data published in Helmlinger et al. (1997). The attainment of such a match (chosen by a least squares fit) will indicate that we have a good model for the missing mechanical properties and that the entire computational model is then an accurate representation of the physics and mechanics of the growing tumor spheroid. All physical parameters of relevance will then be readily available to us from the computations. From the laws of thermodynamics, which govern all macroscopic physical processes, we are able to obtain highly rigorous bounds (Garikipati et al., 2004, 2006; Narayanan, 2007) for the energy consumed by the growing tumor. In conjunction with computational studies, our collaborators at the Max Planck Institut fur Metallforschung, Germany, will perform experiments to reproduce the results of stress-inhibited tumor and cancer cell growth of Helmlinger et al. (1997) and Chang et al., (2008) while measuring the full range of data that we need for our study. By both these means, computational and experimental, we expect to demonstrate that by using the methods of physics, mathematics, and computation, in conjunction with lab data, we can obtain insight into the chemical energy consumption within cells. Thereby we will be able to form a complete series of studies on the energy usage of tumor growth.

Casciari, J., Stratis, V., Sutherland, R., Variations in tumor cell growth rates and metabolism with oxygen concentration, glucose concentration, and extracellular pH.


Introduction and Background:

Past research by the Computational Physics Lab has established a basic framework model of solid spheroid tumor growth. Based upon this prior work, the model has been refined in order to more reasonably model the findings of research in the literature and the documented behavior of tumor spheroid metabolism and growth. The goal of this research is to determine a lower bound for the energy requirements of tumor growth by use of the Second Law of Thermodynamics and the mechanics of tumor growth. Before energy considerations can be made, it is first necessary to ensure that the governing system of Partial Differential Equations (PDEs) accurately model tumor growth as seen by various research groups and published in the literature. The purpose of this report is to provide a description of the research conducted over the duration of the 2009 REU Mathematics Fellowship.
Mathematical Modeling:

In order to solve the coupled PDEs, it was necessary to use the multiphysics software, COMSOL. Within such, it is possible to combine various “modules” such as diffusion, plane strain, and convection diffusion. A characteristic equation is associated with each “module” and the user may specify constants and functions within the given expression. On the reference frame, we have defined a plane strain module which dictates the physical properties of the spheroid as well as the diffusion module associated with the Extracellular Matrix (ECM) which provides a structural lattice on which the cells may grow. On a moving mesh (which allows for PDEs to be defined on the deformed shape of the tumor as time progresses), we have defined the diffusion equations for glucose and oxygen (critical metabolites to tumor growth) as well as the convection diffusion equation for the cells themselves. This section discusses the governing equations which have been specified for each module. It is to be noted that the initial geometry which has been selected is a semicircle (radius 50 nm) due to the symmetry of the problem. For clarity, a table of constants and units from the included equations is provided below.

<table>
<thead>
<tr>
<th>Constant</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>8.26x10^-10 [1/s]</td>
</tr>
<tr>
<td>b</td>
<td>-10^-10 [m^2/s]</td>
</tr>
<tr>
<td>c</td>
<td>6.8x10^7 [s/(kg/m^3)^0.46]</td>
</tr>
<tr>
<td>d</td>
<td>0.46 [unitless]</td>
</tr>
<tr>
<td>E</td>
<td>2.3x10^-4 [kg/m^3]</td>
</tr>
<tr>
<td>f</td>
<td>3.2x10^-3 [kg/m^3]</td>
</tr>
<tr>
<td>g</td>
<td>-10^-10 [m^2/s]</td>
</tr>
<tr>
<td>h</td>
<td>-4.73x10^-2 [1/s]</td>
</tr>
<tr>
<td>k</td>
<td>9.98x10^-5 [kg/(m^3s)]</td>
</tr>
<tr>
<td>l</td>
<td>9.0078x10^-4 [kg/m^3]</td>
</tr>
<tr>
<td>m</td>
<td>-3.2x10^-9 [m^2/s]</td>
</tr>
<tr>
<td>n</td>
<td>-7.99x10^-7 [1/s]</td>
</tr>
<tr>
<td>p</td>
<td>3.36x10^-6 [kg/m^3/s]</td>
</tr>
<tr>
<td>q</td>
<td>1.47x10^-4 [kg/m^3]</td>
</tr>
</tbody>
</table>

Material Properties and Plane Strain:

It is reasonable to use a Hyper-elastic model for the tissue in the tumor, specifically a Mooney-Rivlin model, and the appropriate constants are $C_{10}=3.75$ kPa and $C_{01}=1.1$ kPa and an initial bulk modulus of 100 kPa. A symmetry boundary condition was imposed on the flat edge of the tumor and the outer boundaries are allowed to deform freely. No initial stress, strain, or displacement was instated.

In order to allow for growth of the tumor, the deformation tensor, $F$ needed to be chosen carefully such that $F = FeFg$. Where $Fe$ is the elastic part of the deformation tensor and $Fg$ is the growth portion of the deformation tensor. The deformation and growth tensors are given below. Here, $u$ and $v$ represent the deformations in the x and y directions respectively.
Diffusion of the Extracellular Matrix:

Although the ECM does not actually diffuse, the diffusion module made it possible to specify a production (or reaction) rate of ECM. It is well established in biology that cells produce collagen which they lay down as they migrate thereby producing ECM. Thus, the source term in 2 was approximated using a typical amount of collagen produced by cells over a day in an experimental setting. As this value was specified by the unofficial observations of a fellow lab member, some amount of flexibility was allowed. The \( \det(\mathbf{F}^e) \) term signifies the transformation to reference coordinates as the ECM expression are entirely in the reference configuration and the cells are in the current configuration.

\[
\frac{\partial (\rho^{ ECM})}{\partial t} = \pi^{ ECM} \\
\pi^{ ECM} = a \cdot \rho^{ cell} \cdot \det (\mathbf{F}^e)
\]

**Figure 1:** Extracellular Matrix (ECM) concentration \( (\rho^{ ECM}) \) initial distribution. Color indicates concentration of ECM in kg/m\(^3\), arrows indicate cell flux.
Convection and Diffusion of Cells:

The two dominant mechanisms relating to cells in tumor growth are diffusion and haptotaxis, or the drawing in effect that the ECM has on the cells. Due to both of these effects, it is appropriate to use the convection-diffusion module, since the cells diffuse as well as exhibit convection toward areas of high ECM. The governing equations are shown in (3)-(6) below. The proliferation term (\( \pi_{\text{cell}} \)) was taken from the time derivative of an expression developed by Casciari et al. (1992) for cell number as a function of hydrogen ion, glucose, and oxygen concentration, as well as time. This expression for cell number used ambient conditions for metabolite concentrations, thus we have assumed that this relationship holds down to a continuum level and replaced the variables for ambient concentrations with field variables for concentration (spatially variable).

\[
\frac{\partial (\rho_{\text{cell}})}{\partial t} + \nabla \cdot (b \cdot \nabla \rho_{\text{cell}}) = \pi_{\text{cell}} - \text{hap} \tag{3}
\]

\[
\pi_{\text{cell}} = \rho_0 \cdot \log \left( \frac{2}{t_d} \cdot \frac{t}{t_d} \cdot \rho^d \right) \tag{4}
\]

\[
\rho^d = c \cdot (\rho^h)^d \cdot \left[ \frac{\rho^{O_2+E}}{\rho^{O_2}} \right] \cdot \left[ \frac{\rho^{f}}{\rho^f} \right] \tag{5}
\]

\[
\text{hap} = 10^{11} \left( \frac{\partial \rho_{\text{cell}}}{\partial x} \cdot \frac{\partial (\rho_{\text{ECM}})}{\partial (\det(F))} + \frac{\partial \rho_{\text{cell}}}{\partial y} \cdot \frac{\partial (\rho_{\text{ECM}})}{\partial (\det(F))} + \rho_{\text{cell}} \nabla^2 \left( \frac{\rho_{\text{ECM}}}{\det(F)} \right) \right) \tag{6}
\]

Shown in Fig.2 (p.5) are five growth progression plots for cell concentration over the period of 5 days. It is interesting to note the strong effect of the ECM distribution (see Figure 1, above), or haptotaxis, on cell distribution.
Diffusion of Glucose and Oxygen

The expressions used for the consumption of glucose and oxygen are variants of the expressions discussed in Casciari et al. (1992). The changes which were made to each expression are discussed below.

Glucose: The original expression introduced by Casciari et al (1992) was of the form

\[ \pi_g = (a+b/\rho_{O2})(\rho_g/\rho_{H2})(1/\rho_{H2})^d, \]

where \( a, b, c, \) and \( d \) are all constants determined by data fitting. From this expression, it is clear to see that in the limit when oxygen concentration approaches zero, the consumption rate of glucose approaches infinity. This is obviously nonphysical. While the biology does indicate that glucose consumption will increase in the absence of oxygen (upregulation of glycolysis), it does not make sense that this value should become
unboundedly large. Thus the first term in the expression was assumed to be in the form \((b' - a'\rho^{O_2})\). This still follows that glycolysis will be upregulated in the absence of oxygen (increased glucose consumption) but has a milder form which the computational software is capable of handling. The constants \(b'\) and \(a'\) were determined by fitting the expression to the data presented in Casciari et al (1992). The diffusion equation and the modified glucose consumption equation are shown below.

\[
\frac{\partial (\rho^g)}{\partial t} + \nabla \cdot (g \cdot \nabla \rho^g) = -\pi^g \tag{7}
\]
\[
\pi^g = \rho^{\text{cell}} \cdot (h \cdot \rho^{O_2} + k) \cdot \left[\frac{\rho^g}{\rho^{g+1}}\right] \tag{8}
\]

**Figure 3:** Glucose concentration \((\rho^g)\) over 5 days of growth. Color indicates concentration of glucose in kg/m\(^3\), arrows indicate cell flux. Initial Condition: Constant value of 0.991 kg/m\(^3\).
**Oxygen**: For the same arguments discussed above, the original form of the oxygen consumption rate equation from Casciari et al. (1992) was modified in order to prevent oxygen consumption rate from becoming unboundedly large when glucose concentration became close to zero. Again, a negative linear form was used for the first term and the associated constants were chosen based upon fits to the experimental data.

\[
\frac{\partial (\rho^{O_2})}{\partial t} + \nabla \cdot (m \cdot \nabla \rho^{O_2}) = -\pi^{O_2} \\
\pi^{O_2} = \rho^{\text{cell}} \cdot (n \cdot \rho^g + p) \cdot \left[ \frac{\rho^{O_2}}{\rho^{O_2 + q}} \right]
\]  

(9)  

(10)

**Figure 4**: Oxygen concentration \((\rho^{O_2})\) over 5 days of growth. Color indicates concentration of oxygen in kg/m\(^3\), arrows indicate cell flux. Initial Condition: Constant value of 7.424x10\(^{-4}\) kg/m\(^3\).
Conclusions and Future Research:

In the future, it is anticipated that more refinements to the model will be made with the findings of our colleagues in Germany (such as more specific values for the mechanical properties of the tumor as well as agarose gel). Additionally, more complexities within the problem of tumor growth will be introduced, such as the development of a necrotic core (a spherical volume within the tumor where cells have died due to lack of nutrient supply) and metastasis.

Currently, we are working to determine the mathematics behind a phenomenon which is observed in the computations. In the initial time steps of growth, the deformed shape of the tumor is very amorphous and misshapen, however, as time progresses, valleys in the contour begin to bulge to form protrusions. This has a smoothing effect on the deformed shape of the tumor, thus making it appear more spheroid-like as time progresses. It appears that this is somehow connected to the current ECM concentration, however more research is being implemented in order to better understand the mechanism and mathematics behind the phenomenon.

Figure 5: Smoothing phenomenon. Surface is cell concentration, images taken from Figure 2.