Level Set Tumor Growth Model

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Level Set vs Mixture Theory

- The Level Set model is based on Mixture Theory.
- While Mixture Theory has the concept of Volume Fractions,

$$\sum_{\alpha=1}^{\kappa} n^{\alpha} = \sum_{\alpha=1}^{\kappa} \frac{\rho^{\alpha}}{\rho^{\alpha R}} = 1, \tag{1}$$

- Level Set says, "We have volume fractions, two solids and one liquid-dissolved nutrient. The two solids do not mix. The nutrient is consumed by one of the two solids."
- One solid is Tumor tissue, the other is Host (or normal) tissue. Yes, host tissue consumes nutrient, but at a much lower rate than tumor tissue. Thus, we ignore homeostasis for this model.

Level Set departure from Mixture Theory

- Mixture Theory concerns itself with Balance of Mass and Momentum equations of Continuum Mechanics:
- Balance of Mass - constituent's mass rate $\hat{\rho}^\alpha$, and velocity $\mathbf{v}^\alpha$

$$\frac{\partial n^\alpha}{\partial t} + \nabla \cdot (n^\alpha \mathbf{v}^\alpha) = \hat{\rho}^\alpha \rho^{\alpha R} \tag{2}$$

- Balance of Momentum - Cauchy stress tensor $\mathbf{T}^\alpha$, body force $\mathbf{b}^\alpha$

$$\nabla \cdot \mathbf{T}^\alpha + \rho^{\alpha R} n^\alpha \left(\mathbf{b}^\alpha - \frac{\mathrm{d}\mathbf{v}^\alpha}{dt} \right) + \hat{\mathbf{p}}^\alpha - \hat{\rho}^\alpha \mathbf{v}^\alpha = 0 \tag{3}$$

- Balance of Energy (1st Law of Thermo) is combined with Entropy Inequality (2nd Law of Thermo) to help construct constitutive equations to go with above equations.

Level Set departure from Mixture Theory, *(continued)*

- We temporarily shift to 2 dimensions, without loss of generality.
- Assume the two solid tissues act as fluids, with only one volume fraction ($n \in [0, 1]$), and incompressible Navier-Stokes behavior:

$$\frac{\partial v_x}{\partial x} + \frac{\partial v_y}{\partial y} = 0 \tag{4}$$

- Here is x-component of momentum balance equations,

$$\frac{\partial v_x}{\partial t} + v_x \frac{\partial v_x}{\partial x} + v_y \frac{\partial v_x}{\partial y} + \boldsymbol{\nu} \left(\frac{\partial^2 v_x}{\partial x^2} + \frac{\partial^2 v_x}{\partial y^2} \right) = -\frac{\partial P}{\partial x} + \rho g_x + kcn \tag{5}$$

- and y-component of momentum balance equations,

$$\frac{\partial v_y}{\partial t} + v_x \frac{\partial v_y}{\partial x} + v_y \frac{\partial v_y}{\partial y} + \boldsymbol{\nu} \left(\frac{\partial^2 v_y}{\partial x^2} + \frac{\partial^2 v_y}{\partial y^2} \right) = -\frac{\partial P}{\partial y} + \rho g_y + kcn \tag{6}$$

Level Set Methodology: Governing Equations for Nutrient and Interface

- The Interface is defined by the volume fraction of tumor tissue, n (AKA "level set"). Where $n = 1$, we have tumor tissue, and where $n = 0$ we have normal host tissue. Equation to move the interface with velocity field $\mathbf{v}$:

$$\frac{\partial n}{\partial t} + \mathbf{v} \cdot \nabla n = \gamma \left[\nabla \cdot \left(\epsilon \nabla n - n(1-n) \frac{\nabla n}{|\nabla n|} \right) \right] \quad (7)$$

- Evolution equation for nutrient as a dissolved species

$$\frac{\partial c}{\partial t} + v_x \frac{\partial c}{\partial x} + v_y \frac{\partial c}{\partial y} - \mathbf{D} \left(\frac{\partial^2 v_x}{\partial x^2} + \frac{\partial^2 v_y}{\partial y^2} \right) = \dot{r}_c(c, n) \quad (8)$$

Level Set Methodology: Description of Symbols

- n – if $n = 1$, tumor tissue; if $n = 0$, host tissue
- v_x, v_y – x- and y- components of tumor tissue velocity field $\mathbf{v}$
- P – pressure
- $\boldsymbol{\nu}$ – the viscosity tensor
- ρ – the (tumor) tissue density
- g_x, g_y – x- and y- components of the gravitational field $\mathbf{g}$ (negligible)
- c – concentration of a dissolved nutrient species, such as oxygen
- k – rate of consumption of the nutrient
- $\mathbf{D}$ – the diffusivity tensor
- ϵ – thickness of the interface region
- γ – amount of reinitialization or stabilization of the level set function

- Phase initialization step - GI is reciprocal of initial interface distance

$$\nabla GI \cdot \nabla GI + \sigma_w GI(\nabla \cdot \nabla GI) = (1 + 2\sigma_w) GI^4 \tag{9}$$

$$l_w = \frac{1}{GI} - \frac{l_{ret}}{1} \tag{10}$$

- Time Dependent step

$$\rho \frac{\partial \mathbf{v}}{\partial t} + \rho(\mathbf{v} \cdot \nabla)\mathbf{v} = \nabla \cdot \left[-\rho \mathbf{I} + \mu(\nabla \mathbf{v} + (\nabla \mathbf{v})^T) \right] + \rho \mathbf{g} + \mathbf{f} \tag{11}$$

$$\nabla \cdot \mathbf{v} = 0, \qquad \frac{\partial n}{\partial t} + \mathbf{v} \cdot \nabla n = \gamma \nabla \cdot \left[\epsilon_{ls} \nabla n - n(1-n) \frac{\nabla n}{|n|} \right] \tag{12}$$

Level Set - COMSOL Model Setup

- Length scale factor: 1 meter in model is 10 microns ($10^{-5} m$) in reality
- Time scale factor: 1 second in model is 1 day (86400 s) in reality
- Model is $100\mu m$ on each side
- capillary structure is $20\mu m$ in diameter, $10\mu m$ away from tumor
- tumor starts out at $20\mu m$ in diameter
- intent is to see tumor grow, and prefer to grow around capillary, forming a "tumor cord"

(... Show Pictures Now ...)

What needs to happen now to the Level Set model?

- Calculate scaling parameters for: density, viscosity, velocity, etc.
- Find a transform to convert viscosity to some kind of tissue hardness unit
- Make model more realistic by converting real parameters to scaled parameters
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That's all, Folks!

Thank You!

Any Questions?

Thermodynamics: First Law

- Consider our mixture in a 3D volume Ω, and an increment of that volume, $\mathrm{d}v$. Ω's surface is $\partial\Omega$.
- This is a widely accepted mathematical form for the First Law of Thermodynamics, applicable to each constituent (α) in our mixture:

$$\rho \frac{\partial \varepsilon^\alpha}{\partial t} - \mathbf{T}_{\boldsymbol{\alpha}} : \mathbf{L}_{\boldsymbol{\alpha}} - \rho^\alpha \hat{\rho}^c + \nabla \cdot \mathbf{q}^\alpha = 0 \tag{13}$$

- ρ^α – the density of the constituent
- ε^α – internal energy of the constituent
- $\mathbf{T}_{\boldsymbol{\alpha}} : \mathbf{L}_{\boldsymbol{\alpha}}$ – stress power of the constituent
- $\hat{\rho}^c$ – reduction of energy due to consumption of c internal to $\mathrm{d}v$
- $\mathbf{q}^\alpha$ – heat flux through $\mathrm{d}v$
- $\mathbf{T}_{\boldsymbol{\alpha}}$ – Cauchy stress tensor
- $\mathbf{L}_{\boldsymbol{\alpha}}$ – velocity gradient $= \mathbf{D}_\alpha$(symmetric) $+ \mathbf{W}_\alpha$(skew symmetric)

First law of thermodynamics, continued

- Since the Cauchy stress tensor is symmetric, the stress power simplifies to

$$\mathbf{T} : \mathbf{L} = \mathbf{T} : \mathbf{D} = \mathrm{tr}(\mathbf{TD}) \tag{14}$$

- So the First Law simplifies to

$$\rho \frac{\partial \varepsilon}{\partial t} - \mathrm{tr}(\mathbf{TD}) - \rho \hat{\rho}^{c} + \nabla \cdot \mathbf{q} = 0 \tag{15}$$

Thermodynamics: Second Law

- The mathematical form for the Second Law of Thermodynamics, (AKA Entropy Inequality) is:

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_{\Omega}\rho\eta\,\mathrm{d}v \geq \int_{\Omega}\rho\frac{\hat{\rho}^{c}}{\theta}\,\mathrm{d}v - \int_{\partial\Omega}\frac{\mathbf{q}\cdot\hat{\mathbf{n}}}{\theta}\,\mathrm{d}a, \text{ where} \tag{16}$$

- η – the specific entropy of the constituent
- $\hat{\mathbf{n}}$ – the unit vector normal to S.
- The divergence theorem changes our surface integral to a volume integral. Due to the arbitrary nature of the volumes under consideration, we may then discard the volume integrals after converting the surface integral, leaving the integrands:

$$\rho\dot{\eta} - \frac{\rho\hat{\rho}_c}{\theta} + \frac{\nabla\cdot\mathbf{q}}{\theta} - \frac{\mathbf{q}\cdot\nabla\theta}{\theta^2} \geq 0 \tag{17}$$

Second law of thermodynamics, continued

- After multiplying Equation (17) through by θ, we subtract Equation (13) from it to get:

$$\rho\dot{\eta}\theta - \rho\frac{\partial \varepsilon}{\partial t} - \frac{\mathbf{q}\cdot\nabla\theta}{\theta} + \mathbf{T}:\mathbf{D} \geq 0 \tag{18}$$

- We now introduce the Helmholtz Free Energy, defined as

$$\psi = \varepsilon - \eta\theta \tag{19}$$

- Differentiate with respect to time and rearrange to get,

$$\dot{\eta}\theta = \frac{\partial \varepsilon}{\partial t} - \eta\dot{\theta} - \frac{\partial \psi}{\partial t} \tag{20}$$

The Entropy Inequality

- Replace the $\dot{\eta}\theta$ term in Equation (18) by the right-hand side of the last Equation, and we get:

$$\rho\frac{\partial\varepsilon}{\partial t} - \rho\eta\dot{\theta} - \rho\frac{\partial\psi}{\partial t} - \rho\frac{\partial\varepsilon}{\partial t} - \frac{\mathbf{q}\cdot\nabla\theta}{\theta} + \mathbf{T}:\mathbf{D} \geq 0 \tag{21}$$

- The terms involving ε cancel each other, and this equation simplifies to

$$\mathbf{T}:\mathbf{D} - \rho\eta\dot{\theta} - \rho\frac{\partial\psi}{\partial t} - \frac{\mathbf{q}\cdot\nabla\theta}{\theta} \geq 0 \tag{22}$$

- This is known as the modified Clausius-Duhem inequality.