Diffusion Models for Tissues and Tumor Growth

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Introduction

- Researchers have studied cancer and tumor growth patterns for thousands of years
- First models: described tumors based on color and sensitivity to touch.
- Application of mathematical models to tumor growth gained traction in the 20th century
- Paper discusses an overview of two influential diffusion papers: Hill (1928) and Greenspan (1972)

Hill's Paper on Diffusion

- Discussed the diffusion constant, k. This constant is usually very small when discussing processes in the body.
- Modeled diffusion of oxygen and lactic acid through tissues. Conclusion: Not all oxygen can be absorbed.
- Derived equations for steady-state diffusion of oxygen and lactic acid

Diffusion of Oxygen Within a Steady State

- Fick's first and second laws of diffusion (next slide)
- Derived differential equation for oxygen concentration, y
- Maximum absorption of oxygen in a tissue of thickness x'

Fick's First and Second Laws of Diffusion

First law:

$$J = -k\frac{dy}{dx} \tag{1}$$

J = the rate of diffusion (diffusion flux), k = diffusion rate (also known of diffusivity), $\frac{dy}{dx}$ = concentration gradient.

- Particles move from high to low concentration.

Second law:

$$\frac{dJ}{dx} = k\nabla^2 J \tag{2}$$

- If one dimension, can simplify Laplacian

Deriving Oxygen Concentration

Using Fick's second law (one dimension, assumption of constant concentration):

$$\underbrace{a}_{\text{Usage Rate}} = k\frac{d^2y}{dx^2} \tag{3}$$

Solution:

$$y = \frac{ax^2}{2k} + bx + y_0 \tag{4}$$

After finding b and maximum penetration distance, we get

$$Y = \int_0^{\sqrt{\frac{2ky_0}{a}}} \frac{ax^2}{2k} + bx + y_0 dx = y_0\frac{x'}{3} \tag{5}$$

- Conclusion: Not all oxygen absorbed by tissue

Combining Oxygen and Lactic Acid Diffusion

- Combining 2 diffusion equations in the same tissue
- Modeled the interaction of oxygen and lactic acid in a muscle
- Derived the ratio of oxygen consumed to lactic acid removed: $\frac{a}{\alpha}$

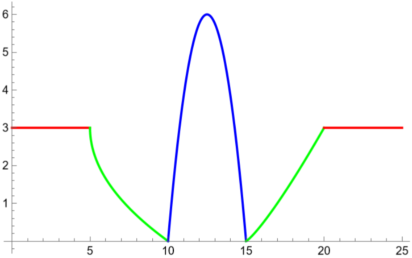

Figure: Red: Steady state condition y_0. Green: y decreases as you go further into the tissue. Blue: y', lactic acid increases towards center of tissue.

Greenspan's Paper: Models for the Growth of a Solid Tumor by Diffusion

- Aimed to find what changes the outer radius of the tumor. Proposition: chemical substance.
- Modeled the tumor as a sphere with a necrotic core, middle layer, and outer layer
- Utilized the same diffusion model as Hill (1928); referenced Burton (1966), a famous paper on diffusion with tumors.

Illustration of a Tumor Model

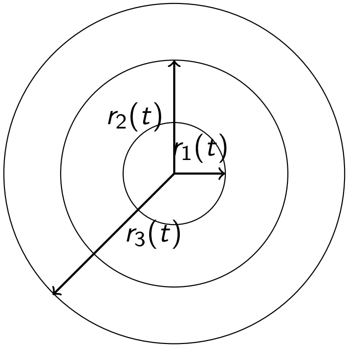

Figure: A cross-section of the sphere that represents the tumor. The necrotic core is situated between $0 < r < r_1$, the middle layer is situated between $r_1 < r < r_2$, and the healthy outer layer is located between $r_2 < r < r_3$.

Conservation of Mass and Volume Equation

- Derived the conservation of volume equation (3.1 in Greenspan)

$$r_3^3(t) = r_3^3(0) + 3\int_0^t dt \int_{\max(r_1(t),r_2(t))}^{r_3(t)} S(\sigma,\beta) r^2 dr - \int_0^t 3\lambda r_1^3(t) dt \tag{6}$$

- Modeled the inward movement of live tumor cells towards the necrotic center (push volume towards center)
- Time partial derivative: how tumor grows with time

Diffusion Equations for Tumor Growth

- Derived diffusion equations for β (inhibitor) and σ (nutrients) using Fick's second law
- Diffusion equations for each of these two derived:

$$\frac{1}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial}{\partial r}\beta(r,t) = \frac{-P}{k'} \tag{7}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial}{\partial r}\sigma(r,t) = \frac{a}{k} \tag{8}$$

Solving the Diffusion Equations

- Solving the equations directly turns out to be very hard
- Assuming r is in the correct region, many simplifications can be applied.
- Verified the solutions, which are:

$$\beta = \frac{Pr_1^3}{3k'}(\frac{1}{r} - \frac{1}{r_3}) \tag{9}$$

$$\sigma = [\sigma_\infty - \frac{a}{6k}(r_3^2 - r^2) + \frac{ar_1^3}{3k}(\frac{1}{r} - \frac{1}{r_3})] \tag{10}$$

Present day models

- Diffusion is applied to model many common problems (biology, emissions, air pollution)
- A recent paper by Stepien et al. (2015) included a diffusion model for in vitro glioblastoma growth:

$$\frac{\partial u_i(r,t)}{\partial t} = \underbrace{k\nabla^2 u_i}_{\text{Diffusion}} + \underbrace{g u_i \left(1 - \frac{u_i}{u_{\max}}\right)}_{\text{Logistic growth}} - \underbrace{\nu_i \nabla_r \cdot u_i}_{\text{Taxis}} + \underbrace{s\delta(r - R(t))}_{\text{Shed cells from core}} \tag{11}$$

Conclusion

- Hill and Greenspan proposed similar diffusion models for their respective problems
- Many modern diffusion models build upon these foundational works
- Diffusion models are versatile and somewhat simple to work with

Thanks!