# Analysis of a Coupled Reaction-Diffusion Model for Tumour-Induced Angiogenesis in Breast Cancer Tissue

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## Introduction

- Breast cancer is a chronic disease which affects women with high rates of mortality and morbidity in any country (every 3 in 6 deaths)
- Occurs when abnormal cells divide in an uncontrolled way causing metastases.
- Angiogenesis is the formation of new blood vessels from a parent vasculature.
- Occurs when an avascular tumour releases a growth factor protein called VEGF (Vascular Endothelial Growth Factor) to stimulate cellular growth of new vessels.

## Objective

- Model avascular tumour growth based on nutrient diffusion from tissues using a **multicellular spheroid** which has 3 layers: **proliferating(p), quiescent(q)** and **necrotic (n)**
- Observe the possibility of **tumour-induced angiogenesis** by observing the movement of blood vessel cell sprouts towards the avascular tumour in response to the secreted VEGF

## Model Formulation 1 - Tumour Spheroid

- The tumour cell has densities $p(x,t)$, $q(x,t)$, and $n(x,t)$ and by Fick's Diffusive Law, viable population flux will be:

$$J = -\nabla(p+q) \tag{1}$$

- By mass conservation we have:

$$\frac{\partial p}{\partial t} = \nabla(p+q) + g(c)p(1-p-q-n) - f(c)p \tag{2}$$

$$\frac{\partial q}{\partial t} = \nabla(p+q) + f(c)p - h(c)q \tag{3}$$

$$\frac{\partial n}{\partial t} = h(c)q \tag{4}$$

$$c = \frac{c_0\gamma}{\gamma+p}(1-\alpha(p+q+n)) : \text{nutrient} \tag{5}$$

- Assume a zero-flux at the boundaries
- Initial conditions: $q(x,0) = n(x,0) = 0$ and $p(x,0) = e^{(-0.1x)}$
- Assume the tumour cell to be radially symmetric, and the nutrients will diffuse through it radially

## Model Formulation 2 - Tumour-Induced Angiogenesis

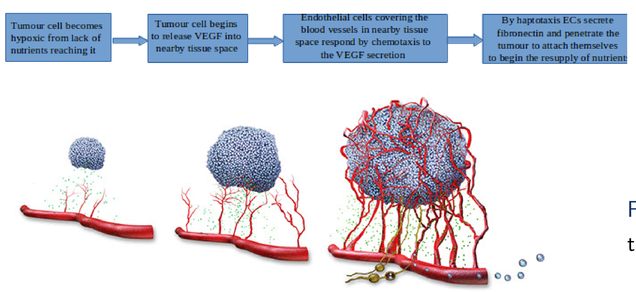


Figure 1: Tumour-Induced Angiogenesis Process

- Consider the endothelial cells, the VEGF and the fibronectin for angiogenesis to take place:

$$\frac{\partial n}{\partial t} = \overbrace{D_n\nabla^2 n}^{\text{random motility}} - \overbrace{\nabla\cdot(\chi(c)n\nabla c)}^{\text{chemotaxis}} - \overbrace{\nabla\cdot(\rho n\nabla f)}^{\text{haptotaxis}}$$

$$\frac{\partial c}{\partial t} = \overbrace{-\lambda nc}^{\text{uptake}} \tag{7}$$

$$\frac{\partial f}{\partial t} = \overbrace{\omega n}^{\text{generation}} - \overbrace{\mu n f}^{\text{uptake}} \tag{8}$$

on $\Omega(x,y), \quad (x,y) \in [0,1]\times[0,1]$

- **Boundary Cond**:
$\underline{\zeta}\cdot(-D_n\nabla n + n(\chi(c)\nabla c + \rho\nabla f)) = 0$
- **Initial Cond**: $c = e^{-\frac{(1-x)^2}{\epsilon_1}}$, $f = ke^{-\frac{x^2}{\epsilon_2}}$, and $n = e^{-\frac{x^2}{\epsilon_3}}\sin^2(6\pi y)$
- The system is non-dimensionalized and solved with forward and central FDM

## Result 1

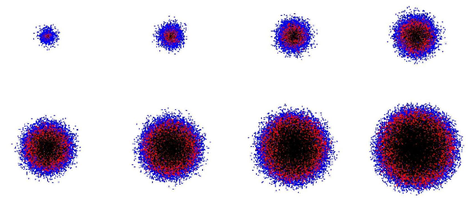

Figure 2: 2D behaviour of the tumour spheroid progression from t=2 to t=16

- With the tissue nutrient supply, a measure of proliferating cells (blue) is closely followed steadily by the layer of quiescent and necrotic cells as diffusion decreases across the radius of the tumour cell

**Initial Concentration Profile for VEGF and Fibronectin**

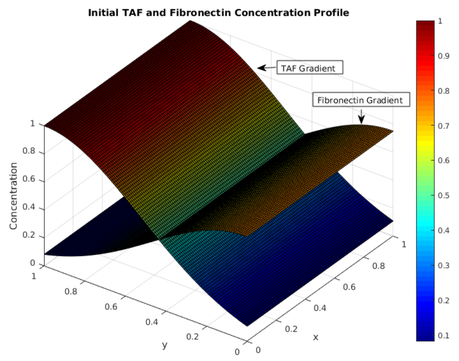


Figure 3: Conc. of TAF (VEGF) and Fibronectin

- The VEGF concentration estimates a gradient created by the tumour which lies at $x = 1$ and the initial gradient of the fibronectin is towering at the mother blood vessel at $x = 0$.

## Result 2

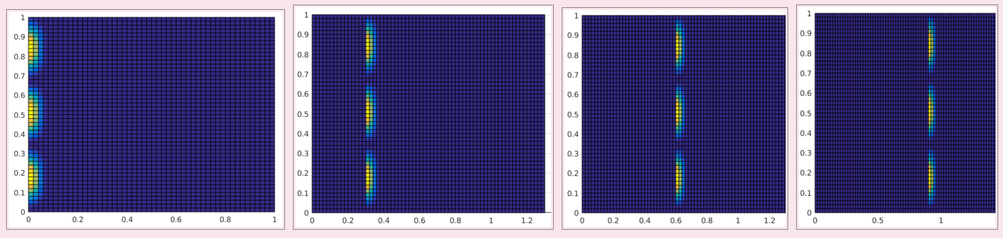

Figure 4: Progression of the endothelial cell with chemotaxis in response to the secretion of the VEGF gradient from the tumour cell, with the parent blood vessel at $x = 0$ and the tumour cell at $x = 1$. [L-R]: ECs at $x = 0, x = 0.3, 0.6$ and $0.9$

## Discussion

- The ECs have sprouted from the mother capillary vessel and are stationed at $x = 0$. This shows the initial EC distribution in response to the secretion of the VEGF from the tumour
- Approximately, 1.6 **day**, the ECs move to about one-quarter into the domain to about $x = 0.3$
- At 3.2 **days**, the ECs have moved more than halfway through the domain to about $x = 0.6$.
- At approximately 4.8 **days** into the migration, the ECs have moved almost completely covering the entire domain to reach the tumour at $x = 1$. The is some **lateral movement** towards the y-axis due to **haptotaxis**.
- On reaching the tumour line, fibronectin gradient increases as the ECs prepare to attach themselves to the tumour
- It can be seen that the movement is largely governed by the process of the chemotactic factor with very little sideways motion. This maintain the shape of the cells until they reach the tumour line where they begin to stretch out
- Chemotaxis and Haptotaxis play a major role in angiogenesis which in turns leads to metastases

## References

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