Analysis of a mathematical model describing necrotic tumor growth

(joint work with J. Escher and B. Matioc)

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PDE's in Mathematical Biology

Bedlewo, September 12-17, 2010

Outline

Introduction

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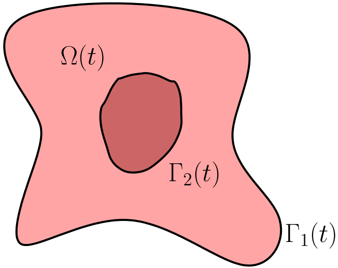
- The blood supply provides the nonnecrotic region with nutrients.
- The concentration of nutrient in the necrotic core is at a constant level which cannot sustain cell proliferation.
- The necrotic region is not vascularised.
- Moreover, no inhibitor chemical species are present

The tumor domain



- $\Omega(t)$-the domain occupied by the nonnecrotic shell
- $\Gamma_1(t)$- outer boundary of the tumor
- $\Gamma_2(t)$- the interior boundary enclosing the necrotic core

The mathematical model

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The evolution of the tumor is described by the coupled problem:

$$\begin{cases} \Delta\psi = \psi & \text{in } \Omega(t), \\ \Delta p = 0 & \text{in } \Omega(t), \\ \psi = G & \text{on } \Gamma_1(t), \\ \psi = G - \psi_0 & \text{on } \Gamma_2(t), \\ p = \kappa_{\Gamma_1(t)} - AG\frac{|\mathbf{x}|^2}{4} & \text{on } \Gamma_1(t), \\ p = \kappa_{\Gamma_2(t)} - AG\frac{|\mathbf{x}|^2}{4} - \psi_0 & \text{on } \Gamma_2(t), \\ V_i = \partial_{\nu_i}\psi - \partial_{\nu_i}p - AG\frac{\nu_i \cdot x}{2} & \text{on } \Gamma_i(t), \\ \Omega(0) = \Omega_0, \end{cases} \tag{1}$$

for $t \geq 0$ and $i = 1, 2$.

Parameter legend

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- G-the rate of mitosis
- A-describes the balance between the rate of mitosis and apoptosis
- $\psi_0 > 0$-corresponds to the nutrient concentration assumed constant within the necrotic region
- Ω_0-the initial tumor domain.

Radially symmetric stationary solutions

Theorem (J. Escher, B. Matioc & A. Matioc '10)

Given $(R_1, R_2) \in (0,\infty)^2$ *with* $R_2 < R_1$*, let* ψ_0^c *be the constant defined by* $\psi_0^c :=$

$$= \frac{(b_1/R_1 - b_2/R_2)\,\frac{1/R_1+1/R_2}{\ln(R_1/R_2)}}{\frac{K_0(R_1)(b_1 I_1(R_2)-b_2 I_1(R_1))+I_0(R_1)(b_1 K_1(R_2)-b_2 K_1(R_1))}{I_0(R_1)K_0(R_2)-I_0(R_2)K_0(R_1)} + \frac{R_1^2-R_2^2}{2R_1R_2\ln(R_1/R_2)}}.$$

There exists $A \in \mathbb{R}$ *and* $G \in \mathbb{R}\setminus\{0\}$*, such that the annulus*

$$A(R_1,R_2) := \{x \in \mathbb{R}^2 \,:\, R_2 < |x| < R_1\},$$

is a **stationary solution** *of problem* (1) *provided* $\psi_0 \neq \psi_0^c$. *Moreover,* A *and* G *are uniquely determined by* R_1, R_2*, and* ψ_0. *If* $G = 0$*, then problem* (1) *has* **no** *radially symmetric stationary solutions.*

The case $G = 0$

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- The annulus $A(R_1, R_2)$ centred in zero with radii $R_1 > R_2$, is a stationary solution of system (1) iff

$$p'(R_i) = \psi'(R_i), \qquad i = 1, 2,$$

where p is the solution of the problem

$$\begin{cases} p'' + \frac{1}{r}p' = 0, & R_2 < r < R_1, \\ p(R_1) = {R_1}^{-1} - AGR_1^2/4, & \\ p(R_2) = -{R_2}^{-1} - AGR_2^2/4 - \psi_0, & \end{cases} \tag{2}$$

when $G = 0$.

$p(r)$

- Given $G \in \mathbb{R}$, the solution of (2) is given by the relation $p(r) = a_{R_1 R_2} \ln(r) + b_{R_1 R_2}$, $R_2 \leq |r| \leq R_1$, with

$$a_{R_1 R_2} = \frac{R_1{}^{-1} + R_2{}^{-1} + AG\left(R_2^2 - R_1^2\right)/4 + \psi_0}{\ln(R_1/R_2)},$$

$$b_{R_1 R_2} = R_1{}^{-1} - AGR_1^2/4 - a_{R_1 R_2} \ln(R_1).$$

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$$b_{R_1R_2} = R_1{}^{-1} - AGR_1^2/4 - a_{R_1R_2}\ln(R_1).$$

- Furthermore, ψ is the solution of the problem

$$\begin{cases} \psi'' + \frac{1}{r}\psi' - \psi = 0, & R_2 < r < R_1, \\ \psi(R_1) = G, & \\ \psi(R_2) = G - \psi_0, & \end{cases} \tag{3}$$

when $G = 0$.

$\psi(r)$

For fixed $G \in \mathbb{R}$, the solution of (3) can be written as linear combination of modified Bessel functions of first and second kind

$$\psi = c^1_{R_1 R_2} I_0 + c^2_{R_1 R_2} K_0,$$

with scalars

$$c^1_{R_1 R_2} = \frac{G K_0(R_2) + (\psi_0 - G) K_0(R_1)}{I_0(R_1) K_0(R_2) - I_0(R_2) K_0(R_1)},$$

$$c^2_{R_1 R_2} = \frac{-G I_0(R_2) - (\psi_0 - G) I_0(R_1)}{I_0(R_1) K_0(R_2) - I_0(R_2) K_0(R_1)}.$$

NO rad. symm. stat. sol. for $G = 0$

- Consequently, $A(R_1, R_2)$ is a steady-state solution of (1) when $G = 0$ if and only if

$$\frac{\frac{1}{R_1} + \frac{1}{R_2} + \psi_0}{\ln(R_1/R_2)} \frac{1}{R_i} = \psi_0 \frac{K_0(R_1)I_1(R_i) + I_0(R_1)K_1(R_i)}{I_0(R_1)K_0(R_2) - I_0(R_2)K_0(R_1)}, \quad i = 1, 2, \tag{4}$$

where we used the relations $I_0' = I_1$ and $K_0' = -K_1$.

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  where we used the relations $I_0' = I_1$ and $K_0' = -K_1$.
- It follows then the system (4) has solutions (R_1, R_2) with $R_1 > R_2$ exactly when

$$\frac{R_2}{R_1} = \frac{K_0(R_1)I_1(R_1) + I_0(R_1)K_1(R_1)}{K_0(R_1)I_1(R_2) + I_0(R_1)K_1(R_2)}. \tag{5}$$

- We shown that equality holds in the relation above only when $R_1 = R_2$ (contradiction).

The case $G \neq 0$

In this case $A(R_1, R_2)$ is a steady-state solution of (1) exactly when

$$\psi'(R_i) - p'(R_i) - AG\frac{R_i}{2} = 0,\ i = 1, 2.$$

$$\Leftrightarrow c^1_{R_1 R_2} I_1(R_i) - c^2_{R_1 R_2} K_1(R_i) - a_{R_1 R_2}\frac{1}{R_i} - AG\frac{R_i}{2} = 0,\ i = 1, 2,$$

$$\Leftrightarrow a_i G + b_i AG = c_i,\ i = 1, 2, \text{with}$$

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$$a_i := \frac{(K_0(R_2) - K_0(R_1))I_1(R_i) - (I_0(R_1) - I_0(R_2))K_1(R_i)}{I_0(R_1)K_0(R_2) - I_0(R_2)K_0(R_1)},$$

$$b_i := \frac{R_1^2 - R_2^2}{4\ln(R_1/R_2)}\frac{1}{R_i} - \frac{R_i}{2},$$

$$c_i := -\psi_0\frac{K_0(R_1)I_1(R_i) + I_0(R_1)K_1(R_i)}{I_0(R_1)K_0(R_2) - I_0(R_2)K_0(R_1)} + \frac{R_1{}^{-1} + R_2{}^{-1} + \psi_0}{\ln(R_1/R_2)}\frac{1}{R_i}.$$

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Lemma

The system $a_i G + b_i AG = c_i$, $i = 1, 2$, has a (unique) solution (A, G) with $G \neq 0$ provided that

$$\begin{aligned} &a_1 b_2 - a_2 b_1 \neq 0, \qquad c_1 b_2 - c_2 b_1 \neq 0, \\ &\text{and} \quad c_1 \neq 0 \quad \text{or} \quad c_2 \neq 0. \end{aligned} \tag{6}$$

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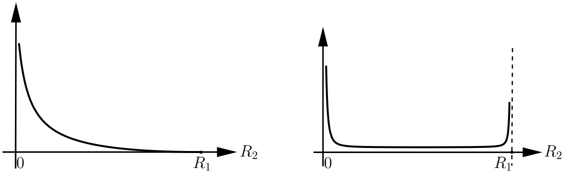
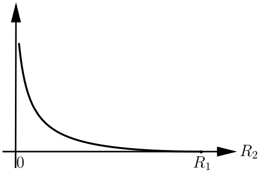
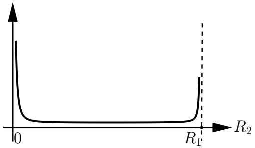
- The computation done for the case $G = 0$ shows that c_1 and c_2 cannot be simultaneously zero when $R_2 < R_1$.
- For fixed $R_1 > 0$ we may see the expression $a_1 b_2 - a_2 b_1$ as a function of $R_2 \in (0, R_1)$. This function is strictly decreasing with respect to R_2, thus $a_1 b_2 = a_2 b_1$ only when $R_1 = R_2$.



- $b_1 c_2 = b_2 c_1$ if and only if $\psi_0 = \psi_0^c$, where

$$\psi_0^c := \frac{(b_1/R_1 - b_2/R_2)\,\frac{1/R_1+1/R_2}{\ln(R_1/R_2)}}{\frac{K_0(R_1)(b_1 I_1(R_2)-b_2 I_1(R_1))+I_0(R_1)(b_1 K_1(R_2)-b_2 K_1(R_1))}{I_0(R_1)K_0(R_2)-I_0(R_2)K_0(R_1)} + \frac{R_1^2-R_2^2}{2R_1R_2\ln(R_1/R_2)}}.$$





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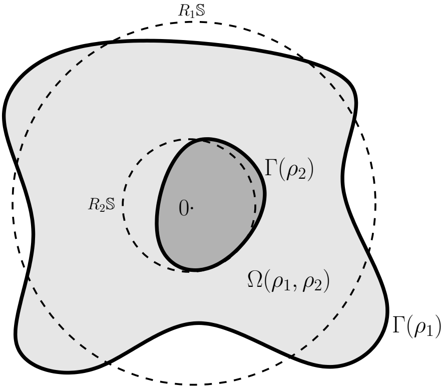
- $A(R_1, R_2)$ is a stationary solution of (1) if and only if $\psi \neq \psi_0^c$ and

$$A = \frac{a_1 c_2 - a_2 c_1}{c_1 b_2 - c_2 b_1}, \qquad G = \frac{c_1 b_2 - c_2 b_1}{a_1 b_2 - a_2 b_1}.$$

The mathematical settings

- We introduce first a parametrisation for the interfaces $\Gamma_1(t)$ and $\Gamma_2(t)$,



The mathematical settings

- Let $0 < R_2 < R_1$ be given and fix $\alpha \in (0, 1)$.
- We set $\mathcal{V} := \{\rho \in h^{4+\alpha}(\mathbb{S}) \,:\, \|\rho\|_{C(\mathbb{S})} < a\}$, where

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- Each pair $(\rho_1, \rho_2) \in \mathcal{V}^2$ parametrises a $C^{4+\alpha}$-domain

$$\Omega(\rho_1, \rho_2) := \left\{ y \in \mathbb{R}^2 \,:\, R_2(1 + \rho_2(y/|y|)) < |y| < R_1(1 + \rho_1(y/|y|)) \right\}$$

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- The condition on a ensures that the boundary portions of $\Omega(\rho_1, \rho_2)$

$$\Gamma(\rho_i) := \{x \,:\, |x| = R_i(1 + \rho_i(x/|x|))\},$$

$i = 1, 2$, are disjoint for any choice of $(\rho_1, \rho_2) \in \mathcal{V}^2$.

The mathematical settings

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- $\Gamma(\rho_i) = N_{\rho_i}{}^{-1}(0)$, where $N_{\rho_i} : \mathbb{R}^2 \setminus \{0\} \to \mathbb{R}, i = 1, 2,$ are defined by

$$N_{\rho_i}(x) = |x| - R_i - R_i\rho_i\,(x/|x|)\,, \qquad x \neq 0.$$

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- The outward unit normal at $\partial\Omega(\rho_1, \rho_2)$ is given by

$$\nu_{\rho_1} = \frac{\nabla N_{\rho_1}}{|\nabla N_{\rho_1}|} \text{ on } \Gamma(\rho_1), \text{ and } \nu_{\rho_2} = -\frac{\nabla N_{\rho_2}}{|\nabla N_{\rho_2}|} \text{ on } \Gamma(\rho_2).$$

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- If the function $(\rho_1, \rho_2) : [0, T] \to \mathcal{V}^2$ describes the motion of the tumor boundaries, then the normal velocity of both boundary components in terms of ρ_i is given by the formula

$$V_1(t) = -\frac{\partial_t N_{\rho_1}}{|\nabla N_{\rho_1}|} \text{ on } \Gamma(\rho_1(t)), \text{ and } V_2(t) = \frac{\partial_t N_{\rho_2}}{|\nabla N_{\rho_2}|} \text{ on } \Gamma(\rho_2(t)).$$

The system of equations

$$
\begin{aligned}
\Delta\psi &= \psi && \text{in } \Omega(\rho_1,\rho_2), && t\geq 0,\\
\Delta p &= 0 && \text{in } \Omega(\rho_1,\rho_2), && t\geq 0,\\
\psi &= G && \text{on } \Gamma(\rho_1), && t\geq 0,\\
\psi &= G-\psi_0 && \text{on } \Gamma(\rho_2), && t\geq 0,\\
p &= \kappa_{\Gamma(\rho_1)} - AG\frac{|x|^2}{4} && \text{on } \Gamma(\rho_1), && t\geq 0,\\
p &= \kappa_{\Gamma(\rho_2)} - AG\frac{|x|^2}{4} - \psi_0 && \text{on } \Gamma(\rho_2), && t\geq 0,\\
\partial_t N_{\rho_i} &= -\langle \nabla\psi - \nabla p - AG\frac{x}{2} | \nabla N_{\rho_i}\rangle && \text{on } \Gamma(\rho_i), && t>0, i=1,2,\\
\rho_1(0) &= \rho_{01},\\
\rho_2(0) &= \rho_{02},
\end{aligned}
\tag{7}
$$

with $(\rho_1(0),\rho_2(0))$ describing the initial shape of the tumor.

The well-posedness result

Classical solution

A pair $(\rho_1, \rho_2, \psi, p)$ is called *classical solution* of (1) on $[0, T]$, $T > 0$, if

$$\rho_i \in C([0,T], \mathcal{V}) \cap C^1([0,T], h^{1+\alpha}(\mathbb{S})), \; i = 1, 2,$$

$$\psi(t,\cdot), p(t,\cdot) \in buc^{2+\alpha}(\Omega(\rho_1(t), \rho_2(t))), \; t \in [0, T],$$

and if $(\rho_1, \rho_2, \psi, p)$ solves (7) pointwise.

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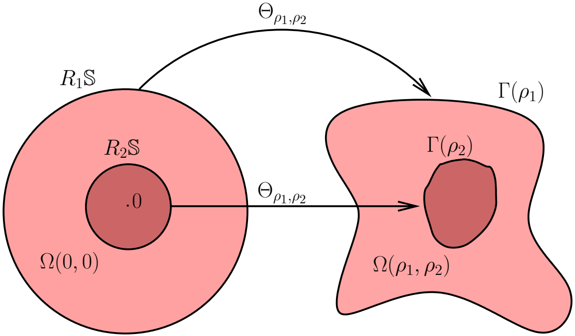
Theorem (J. Escher, B. Matioc & A. Matioc '10)

Let $0 < R_2 < R_1$ and $(A, G, \psi_0) \in \mathbb{R}^3$ be given. There exists an open neighbourhood $\mathcal{O} \subset \mathcal{V}$ such that for all $(\rho_1, \rho_2) \in \mathcal{O}^2$, problem (7) *possesses a unique classical solution defined on a maximal time interval $[0, T(\rho_{01}, \rho_{02}))$ and which satisfies $(\rho_1, \rho_2)(t) \in \mathcal{O}^2$ for all $t \in [0, T(\rho_{01}, \rho_{02}))$.*

The problem on the fixed domain

- We transform the problem on the fixed domain $\Omega := \Omega(0,0)$, with boundary $\Gamma_1 := R_1\mathbb{S}$ and $\Gamma_2 := R_2\mathbb{S}$.



The problem on the fixed domain

- Pick $0 < R_2 < R_1$, $(A, G, \psi_0) \in \mathbb{R}^3$, and $\alpha \in (0, 1)$.
- Given $(\rho_1, \rho_2) \in \mathcal{V}^2$, we define $\Theta_{\rho_1,\rho_2} : \Omega \to \Omega(\rho_1, \rho_2)$ by

$$\Theta_{\rho_1,\rho_2}(x) = \frac{(R_1 - |x|)R_2(1 + \rho_2(x/|x|))}{R_1 - R_2} \frac{x}{|x|} + \\ + \frac{(|x| - R_2)R_1(1 + \rho_1(x/|x|))}{R_1 - R_2} \frac{x}{|x|}$$

for $x \in \Omega$.

- $\Theta_{\rho_1,\rho_2} \in Diff^{4+\alpha}(\Omega, \Omega(\rho_1, \rho_2))$

The transformed operators

- $\mathcal{A}(\rho_1, \rho_2) : buc^{2+\alpha}(\Omega) \to buc^{\alpha}(\Omega)$

$$\mathcal{A}(\rho_1, \rho_2)v := \Delta(v \circ \Theta^{-1}_{\rho_1,\rho_2}) \circ \Theta_{\rho_1,\rho_2}.$$

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- $\mathcal{B}_i : \mathcal{V}^2 \times (buc^{2+\alpha}(\Omega))^2 \to h^{1+\alpha}(\mathbb{S})$

$$\mathcal{B}_i(\rho_1,\rho_2,v,q) := \frac{1}{R_i}\mathcal{C}_i(\rho_1,\rho_2)v - \frac{1}{R_i}\mathcal{C}_i(\rho_1,\rho_2)q - \mathcal{D}_i(\rho_1,\rho_2),$$

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where for $(\rho_1, \rho_2) \in \mathcal{V}^2$ the linear operators $\mathcal{C}_i(\rho_1, \rho_2) \in \mathcal{L}(buc^{2+\alpha}(\Omega), h^{1+\alpha}(\mathbb{S}))$, $i = 1, 2$, are given by

$$\mathcal{C}_i(\rho_1, \rho_2)v(y) := \langle \nabla(v \circ \Theta^{-1}_{\rho_1,\rho_2}) | \nabla N_{\rho_i} \rangle \circ \Theta_{\rho_1,\rho_2}(R_i y)$$

for $v \in buc^{2+\alpha}(\Omega)$ and $y \in \mathbb{S}$.

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for $v \in buc^{2+\alpha}(\Omega)$ and $y \in \mathbb{S}$. Moreover,

$$\mathcal{D}_i(\rho_1, \rho_2) := -\frac{AG}{R_i}\langle \frac{x}{2} | \nabla N_{\rho_i} \rangle \circ \Theta_{\rho_1,\rho_2}(R_i y).$$

The transformed problem

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$$
\left\{
\begin{array}{rcll}
\mathcal{A}(\rho_1,\rho_2)v &=& v & \text{in } \Omega, \quad t \geq 0,\\
\mathcal{A}(\rho_1,\rho_2)q &=& 0 & \text{in } \Omega, \quad t \geq 0,\\
v &=& G & \text{on } \Gamma_1, \quad t \geq 0,\\
v &=& G-\psi_0 & \text{on } \Gamma_2, \quad t \geq 0,\\
q &=& \frac{1}{R_1}\kappa(\rho_1)-\frac{AGR_1^2}{4}(1+\rho_1)^2 & \text{on } \Gamma_1, \quad t \geq 0,\\
q &=& -\frac{1}{R_2}\kappa(\rho_2)-\frac{AGR_2^2}{4}(1+\rho_2)^2-\psi_0 & \text{on } \Gamma_2, \quad t \geq 0,\\
\partial_t\rho_i &=& \mathcal{B}_i(\rho_1,\rho_2,v,q) & \text{on } \mathbb{S}, \quad t > 0,\\
\rho_1(0) &=& \rho_{01}, & \\
\rho_2(0) &=& \rho_{02}, &
\end{array}
\right. \tag{8}
$$

where $v := \psi \circ \Theta_{\rho_1,\rho_2}$, and $q := p \circ \Theta_{\rho_1,\rho_2}$,

Solution operators

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Lemma

Given $(\rho_1, \rho_2) \in \mathcal{V}^2$, we let $\mathcal{T}(\rho_1, \rho_2)$, $\mathcal{S}(\rho_1, \rho_2) \in buc^{2+\alpha}(\Omega)$ denote the unique solution of the Dirichlet problem

$$\left\{\begin{array}{rcll} \mathcal{A}(\rho_1, \rho_2)v &=& v & \text{in } \Omega, \\ v &=& G & \text{on } \Gamma_1, \\ v &=& G - \psi_0 & \text{on } \Gamma_2, \end{array}\right.$$

and

$$\left\{\begin{array}{rcll} \mathcal{A}(\rho_1, \rho_2)q &=& 0 & \text{in } \Omega, \\ q &=& \frac{1}{R_1}\kappa(\rho_1) - \frac{AGR_1^2}{4}(1+\rho_1)^2 & \text{on } \Gamma_1, \\ q &=& -\frac{1}{R_2}\kappa(\rho_2) - \frac{AGR_2^2}{4}(1+\rho_2)^2 - \psi_0 & \text{on } \Gamma_2, \end{array}\right.$$

respectively. The operators $\mathcal{T}$ and $\mathcal{S}$ depend analytically on (ρ_1, ρ_2).

The evolution equation

- The system (8) reduces to the following evolution equation

$$\partial_t X = \Phi(X) \qquad X(0) = X_0, \tag{9}$$

where $X := (\rho_1, \rho_2)$, $X_0 := (\rho_{01}, \rho_{02})$, and $\Phi := (\Phi_1, \Phi_2)$.

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- The components of the nonlocal and nonlinear operator Φ are defined as follows

$$\Phi_i(\rho_1, \rho_2) := \mathcal{B}_i(\rho_i, \mathcal{T}(\rho_1, \rho_2), \mathcal{S}(\rho_1, \rho_2)), \qquad i = 1, 2.$$

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- In order to prove well-posedness of problem (9) it suffices to show that

$$\partial\Phi(0) = \begin{bmatrix} \partial_{\rho_1}\Phi_1(0) & \partial_{\rho_2}\Phi_1(0) \\ \partial_{\rho_1}\Phi_2(0) & \partial_{\rho_2}\Phi_2(0) \end{bmatrix}$$

generates a strongly continuous and analytic semigroup.

Theorem

The operator Φ *is analytic, i.e.* $\Phi \in C^\omega(\mathcal{V}^2, (h^{1+\alpha}(\mathbb{S}))^2)$. *The Fréchet derivative* $\partial\Phi(0)$, *seen as an unbounded operator in* $(h^{1+\alpha}(\mathbb{S}))^2$ *with domain* $(h^{4+\alpha}(\mathbb{S}))^2$ *generates a strongly continuous and analytic semigroup in* $\mathcal{L}((h^{1+\alpha}(\mathbb{S}))^2)$, *i.e.*

$$-\partial\Phi(0) \in \mathcal{H}((h^{4+\alpha}(\mathbb{S}))^2, (h^{1+\alpha}(\mathbb{S}))^2).$$

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$$-\partial\Phi(0) \in \mathcal{H}((h^{4+\alpha}(\mathbb{S}))^2, (h^{1+\alpha}(\mathbb{S}))^2).$$

Proof

- $\partial_{\rho_1}\Phi_1(0)[\rho_1] = A_{11} + B_{11}$, where

$$B_{11} \in \mathcal{L}(h^{2+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S}))$$

$$A_{11}\rho_1 := \frac{1}{R_1^2} C_1(0)(\Delta, \mathrm{tr}_1, \mathrm{tr}_2)^{-1}(0, \rho_1'', 0), \quad \forall \rho_1 \in h^{4+\alpha}(\mathbb{S})$$

$$A_{11}\rho_1(y) = -\frac{1}{R_1^3} \sum_{m\in\mathbb{Z}\setminus\{0\}} \frac{R_1^{|m|}R_2^{-|m|} + R_1^{-|m|}R_2^{|m|}}{R_1^{|m|}R_2^{-|m|} - R_1^{-|m|}R_2^{|m|}} |m|^3 \widehat{\rho}_1(m) y^m,$$

for $\rho_1(y) = \sum_m \widehat{\rho}_1(m) y^m$.

- $\partial_{\rho_2}\Phi_1(0) = A_{12} + B_{12}$, where

$$B_{12} \in \mathcal{L}(h^{2+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S}))$$

$$A_{12}\rho_2 := -\frac{1}{R_1 R_2} C_1(0)(\Delta, \mathrm{tr}_1, \mathrm{tr}_2)^{-1}(0, 0, \rho_2'') \quad \forall \rho_2 \in h^{4+\alpha}(\mathbb{S})$$

$$A_{12}\rho_2(y) = -\frac{1}{R_1^2 R_2} \sum_{m\in\mathbb{Z}\setminus\{0\}} \frac{2}{R_1^{|m|} R_2^{-|m|} - R_1^{-|m|} R_2^{|m|}} |m|^3 \widehat{\rho}_2(m) y^m,$$

provided that $\rho_2 = \sum_{m\in\mathbb{Z}} \widehat{\rho}_2(m) y^m$.

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provided that $\rho_2 = \sum_{m\in\mathbb{Z}} \widehat{\rho}_2(m) y^m$.

- $\partial_{\rho_2}\Phi_2(0) = A_{22} + B_{22}$, with

$$B_{22} \in \mathcal{L}(h^{2+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S}))$$

$$A_{22}\rho_2 := -\frac{1}{R_2^2} C_2(0)(\Delta, \mathrm{tr}_1, \mathrm{tr}_2)^{-1}(0, 0, \rho_2'') \quad \forall \rho_2 \in h^{4+\alpha}(\mathbb{S})$$

$$A_{22}\rho_2(y) = -\frac{1}{R_2^3} \sum_{m\in\mathbb{Z}\setminus\{0\}} \frac{R_1^{|m|} R_2^{-|m|} + R_1^{-|m|} R_2^{|m|}}{R_1^{|m|} R_2^{-|m|} - R_1^{-|m|} R_2^{|m|}} |m|^3 \widehat{\rho}_2(m) y^m,$$

- $\partial_{\rho_1}\Phi_2(0) = A_{21} + B_{21}$, where

$$B_{21} \in \mathcal{L}(h^{2+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S}))$$

$$A_{21}\rho_1 := \frac{1}{R_1 R_2} C_2(0)(\Delta, \mathrm{tr}_1, \mathrm{tr}_2)^{-1}(0, \rho_1'', 0) \quad \forall \rho_2 \in h^{4+\alpha}(\mathbb{S})$$

$$A_{21}\rho_1(y) = -\frac{1}{R_1 R_2^2} \sum_{m\in\mathbb{Z}\setminus\{0\}} \frac{2}{R_1^{|m|}R_2^{-|m|} - R_1^{-|m|}R_2^{|m|}} |m|^3 \widehat{\rho}_1(m) y^m,$$

for all functions $\rho_1 = \sum_{m\in\mathbb{Z}} \widehat{\rho}_1(m) y^m$ in $h^{4+\alpha}(\mathbb{S})$.

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- The operators $A_{ij}, 1 \leq i,j \leq 2$, found above are all **Fourier multipliers**, since they are of the form

$$\sum_{m\in\mathbb{Z}} \widehat{\rho}(m)y^m \mapsto \sum_{m\in\mathbb{Z}} M_k \widehat{\rho}(m)y^m$$

with symbol $(M_k)_{k\in\mathbb{Z}} \subset \mathbb{C}$.

The matrix $\partial\Phi(0)$ is a generator

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- $-A_{ii} \in \mathcal{H}(h^{4+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S})), i = 1, 2.$

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- $-\partial_{\rho_i}\Phi_i(0) \in \mathcal{H}(h^{4+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S})), i = 1, 2,$

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- Thus the matrix

$$\partial\Phi(0) = \begin{bmatrix} \partial_{\rho_1}\Phi_1(0) & \partial_{\rho_2}\Phi_1(0) \\ \partial_{\rho_1}\Phi_2(0) & \partial_{\rho_2}\Phi_2(0) \end{bmatrix}$$

generates a strongly continuous and analytic semigroup, which completes the proof.

Conclusions

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Conclusions

- We study a model describing the growth of necrotic tumors in different regimes of vascularisation.
- We determine all radially symmetric stationary solutions and reduce the moving boundary problem into a nonlinear evolution equation for the functions parameterising the boundaries of the shell.
- Parabolic theory provides a suitable context for proving local well-posedness of the problem for small initial data.

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Thank you for your attention!