Anti-angiogenic therapy based on the receptors

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Outline

The model Evolution Problem Stationary problem

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Cristian Morales Rodrigo Anti-angiogenic therapy, 17th September 2010, Bedlewo

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Outline

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Outline

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- Stationary problem

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Angiogenesis model Angiogenesis model with therapy



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Angiogenesis model Angiogenesis model with therapy

Equation and boundary conditions for EC

- u: Endothelial Cells.
- v: TAF.

$$u_{t} = \underbrace{\Delta u}_{Diffusion} - \underbrace{\nabla \cdot (\alpha(v)u\nabla v)}_{Chemotaxis} + \underbrace{\lambda\beta(v)u - u^{2}}_{Reaction} \quad in \; \Omega \times (0, T),$$

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Angiogenesis model Angiogenesis model with therapy

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$$\frac{\partial u}{\partial n} = \underbrace{\tau_{1}u}_{ECs \text{ enter}} \text{ on } \Gamma_{2} \times (0, T),$$

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Angiogenesis model Angiogenesis model with therapy

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$$\frac{\partial u}{\partial n} = \underbrace{\tau_{1}u}_{ECs \text{ enter}} \text{ on } \Gamma_{2} \times (0, T),$$
$$\frac{\partial u}{\partial n} = \underbrace{-\gamma_{1}u}_{ECs \text{ out}} \text{ on } \Gamma_{1} \times (0, T),$$

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Angiogenesis model Angiogenesis model with therapy

Equation and boundary conditions for TAF

• u: Endothelial Cells.

• v: TAF.

 $v_{t} = \underbrace{\Delta v}_{Diffusion \ Decay} \quad in \ \Omega \times (0, T),$ $\frac{\partial v}{\partial n} = \underbrace{-\tau_{3} v}_{TAF \ out} \quad on \ \Gamma_{2} \times (0, T),$ $\frac{\partial v}{\partial n} = \underbrace{\widetilde{\gamma}(oxigen)}_{TAF \ enter} \quad on \ \Gamma_{1} \times (0, T),$

 $\widetilde{\gamma}$ is a decreasing function.

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Angiogenesis model Angiogenesis model with therapy

Equation and boundary conditions for TAF

- u: Endothelial Cells.
- v: TAF.

 $v_{t} = \underbrace{\Delta v}_{Diffusion} \underbrace{-v}_{Decay} \text{ in } \Omega \times (0, T),$ $\frac{\partial v}{\partial n} = \underbrace{-\tau_{3} v}_{TAF \text{ out}} \text{ on } \Gamma_{2} \times (0, T),$ $\frac{\partial v}{\partial n} = \underbrace{\widetilde{\gamma}(\text{oxigen}) = \widetilde{\gamma}(s(u))}_{TAF \text{ enter}} \text{ on } \Gamma_{1} \times (0, T),$

 $\widetilde{\gamma}$ is a positive decreasing function. *oxigen* = s(u) with s a positive increasing function. Therefore $\widetilde{\gamma} \cdot s = \gamma$ is decreasing.

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Angiogenesis model Angiogenesis model with therapy

- Target receptors
- 2 Target TAF

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Angiogenesis model Angiogenesis model with therapy

- Target receptors
 Target TAF
- 2 Target TAF





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Angiogenesis model Angiogenesis model with therapy

Effect of the Therapy in EC

- u: Endothelial Cells.
- v: TAF.
- z: Anti-TAF (receptors)

$$u_{t} = \underbrace{\Delta u}_{\text{Diffusion}} - \underbrace{\nabla \cdot (\alpha(v, z)u\nabla v)}_{\text{Chemotaxis}} + \underbrace{\lambda\beta(v, z)u - u^{2}}_{\text{Reaction}} \text{ in } \Omega \times (0, T),$$

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Angiogenesis model Angiogenesis model with therapy

Equation and boundary conditions for Anti-TAF

- u: Endothelial Cells.
- v: TAF.
- z: Anti-TAF (receptors)

$$z_{t} = \underbrace{\Delta z}_{Diffusion} \underbrace{-z}_{Decay} + \underbrace{l_{0}}_{Input} \quad in \; \Omega \times (0, T),$$
$$\frac{\partial z}{\partial n} = \underbrace{-\gamma_{2} z}_{Anti-TAF \; out} \quad on \; \Gamma_{2} \times (0, T),$$
$$\frac{\partial z}{\partial n} = \underbrace{-\tau_{2} z}_{Anti-TAF \; out} \quad on \; \Gamma_{1} \times (0, T),$$

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Local and continuity Global existence

Theorem

Let p > N,

$$X_T := C([0,T]; C^0(\overline{\Omega})), \quad Y_T := C([0,T]; W^{1,p}(\Omega))$$

and the initial data

$$\mathbf{u_0} := (u_0, v_0, z_0) \in \mathbf{X} := C^0(\overline{\Omega}) \times W^{1,p}(\Omega) \times C^0(\overline{\Omega}).$$

Then there exists $\tau(\|\mathbf{u}_0\|_{\mathbf{X}})$ such that the evolution problem admits a unique solution

$$\mathbf{u} := (u, v, z) \in \mathbf{X}_{\tau} := X_{\tau} \times Y_{\tau} \times X_{\tau}.$$

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Local and continuity Global existence

Theorem

Moreover, there exists C > 0 such that

$$\| \mathsf{u}(\mathsf{u}_0) - \mathsf{u}(\overline{\mathsf{u}}_0) \|_{\mathsf{X}_ au} \leq C \| \mathsf{u}_0 - \overline{\mathsf{u}}_0 \|_\mathsf{X}$$

where $\mathbf{u}(\mathbf{u_0})$ and $\mathbf{u}(\overline{\mathbf{u}_0})$ stand for the solutions to the evolution problem with initial data $\mathbf{u_0}$ and $\overline{\mathbf{u}_0}$ respectively. Furthermore, there exists C > 0 such that

$$\|\mathbf{u}(\mathbf{I}_0) - \mathbf{u}(\overline{\mathbf{I}}_0)\|_{\mathbf{X}_{\tau}} \leq C \|\mathbf{I}_0 - \overline{\mathbf{I}}_0\|_{\mathbf{X}_{\tau}}$$

where $\mathbf{u}(I_0)$ and $\mathbf{u}(\overline{I}_0)$ stand for the solutions to the evolution problem with coefficients I_0 and \overline{I}_0 respectively.

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Local and continuity Global existence

Let us observe that

$$v_t = \Delta v - v$$
 in $\Omega \times (0, T)$,

$$\frac{\partial \mathbf{v}}{\partial n} = (\gamma(u), -\tau_3 \mathbf{v}) \text{ on } \partial \Omega \times (0, T).$$

The boundary term belong to L^{∞} therefore $v(t) \in W^{1,p}(\Omega)$ for every $t < T_{max}$ and $p \in (1, \infty)$. Now, we can combine well-known estimates that are known for the Keller-Segel with the Sobolev-Trace inequality to get rid of the boundary terms

Lemma

(Sobolev-Trace inequality) For every $w \in W^{1,2}(\Omega)$, $\theta > 1$ and $\epsilon > 0$ we have

$$\int_{\mathsf{\Gamma}_2} \mathsf{w}^2 \leq \epsilon \int_\Omega |
abla \mathsf{w}|^2 + \mathit{C}(\epsilon^{- heta}+1) \int_\Omega \mathsf{w}^2 \, .$$

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Outline	Semi-trivial states
The model	stability (linear) of $(0, v_0, z_0)$
Evolution Problem	coexistence for $\lambda > \lambda_1(v_0, z_0)$
Stationary problem	The mapping $l_0 \mapsto \lambda_1(l_0)$

$I_0 \ge 0$ is a constant.

$$-\Delta u = -\nabla \cdot (\alpha(v, z)u\nabla v) + \lambda\beta(v, z)u - u^{2} \text{ in } \Omega$$
$$-\Delta v + v = 0, \quad -\Delta z + z = l_{0} \text{ in } \Omega$$
$$\frac{\partial u}{\partial n} = (-\gamma_{1}u, \tau_{1}u) \text{ on } \partial\Omega$$
$$\frac{\partial v}{\partial n} = (\gamma(u), -\tau_{3}v) \text{ on } \partial\Omega$$
$$\frac{\partial z}{\partial n} = (-\gamma_{2}z, -\tau_{2}z) \text{ on } \partial\Omega$$

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 $\begin{array}{lll} & \mbox{Semi-trivial states} \\ & \mbox{The model} \\ & \mbox{stability (linear) of } (0, v_0, z_0) \\ & \mbox{Evolution Problem} \\ & \mbox{Stationary problem} \\ \end{array}$

 $(0, v_0, z_0)$ is the unique semi-trivial state. v_0, z_0 are the unique solution to the linear problems

$$-\Delta v + v = 0, \quad \frac{\partial v}{\partial n} = (\gamma(0), -\tau_3 v),$$
$$-\Delta z + z = I_0, \quad \frac{\partial z}{\partial n} = (-\gamma_2 z, -\tau_2 z).$$

 $(0, v_0, z_0)$ (no angiogenesis state) $(0, v_0, z_0)$ stability ? (linear stability)

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Outline	Semi-trivial states
The model	stability (linear) of $(0, v_0, z_0)$
Evolution Problem	coexistence for $\lambda > \lambda_1(v_0, z_0)$
stationary problem	The mapping $I_0 \mapsto \lambda_1(I_0)$

Let $\lambda_1(v_0, z_0)$ the principal eigenvalue of

$$-\Delta \xi = -
abla \cdot (lpha(v_0, z_0)
abla v_0 \xi) + \lambda eta(v_0, z_0) \xi$$
 in Ω

$$rac{\partial \xi}{\partial n} = (-\gamma_1 \xi, au_1 \xi)$$
 on $\partial \Omega$

If $\lambda < \lambda_1(v_0, z_0)$ then the solution $(0, v_0, z_0)$ is stable If $\lambda > \lambda_1(v_0, z_0)$ then the solution $(0, v_0, z_0)$ is unstable.

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Outline	Semi-trivial states
The model	stability (linear) of $(0, v_0, z_0)$
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The idea is to apply the Crandall-Rabinowitz theorem in order to find a continuum emanating from the semi-trivial solution $(0, v_0)$. Let

$$X_{1} := \{ u \in C^{2+\gamma}(\overline{\Omega}) : \frac{\partial u}{\partial n} = (-\gamma_{1}u, \tau_{1}u) \text{ on } \partial\Omega \}$$
$$X_{2} := \{ v \in C^{2+\gamma}(\overline{\Omega}) : \frac{\partial v}{\partial n} + \tau_{3}v = 0 \text{ on } \Gamma_{2} \}$$

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Outline	Semi-trivial states
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We define the map

$$\mathcal{F}: \mathbf{R} imes X_1 imes X_2 \mapsto C^\gamma(\overline{\Omega}) imes C^\gamma(\overline{\Omega}) imes C^\gamma(\Gamma_1)$$

where

$$\mathcal{F}(\lambda, u, v) := (f_1(\lambda, u, v), f_2(v), f_3(u, v))$$
$$f_1(\lambda, u, v) := -\Delta u + \nabla \cdot (\alpha(v, z_0)u\nabla v) - \lambda\beta(v, z_0)u + u^2$$
$$f_2(v) := -\Delta v + v$$
$$f_3(u, v) := \frac{\partial v}{\partial n} - \gamma(u)$$

By the Crandall-Rabinowitz Theorem there exists a continuum $C^+ \subset \mathbf{R} \times X_1 \times X_2$ of positive solutions emanating at $(\lambda_1(u_0, v_0), 0, v_0)$.

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We consider the mapping

$$I_0 \in [0,+\infty) \mapsto \lambda_1(v_0,z_0) = \lambda_1(v_0,I_0e) = \lambda_1(I_0)$$

where e is the unique positive solution of

$$-\Delta e + e = 1$$
 in Ω $\frac{\partial e}{\partial n} = (-\gamma_2 e, -\tau_2 e)$ on $\partial \Omega$

we want to know the behaviour of $\lambda_1(l_0)$ around zero and around $+\infty$.

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$$\lambda_{1}^{\prime}(0) = -\frac{\lambda_{1}(0)\int_{\Omega}\beta_{z}(v_{0},0)e\varphi_{1}\varphi_{1}^{*} + \int_{\Omega}\alpha_{z}(v_{0},0)e\varphi_{1}\nabla v_{0}\cdot\nabla\varphi_{1}^{*} + (*)}{\int_{\Omega}\beta(v_{0},0)\varphi_{1}\varphi_{1}^{*}}$$

where

$$(*) = \int_{\partial\Omega} \alpha_z(v_0, 0) e\varphi_1 \varphi_1^* \frac{\partial v_0}{\partial n}$$

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$$\lim_{I_0 \to +\infty} \lambda_1(I_0) = \begin{cases} +\infty & \text{if } \lambda_\infty > 0, \\ -\infty & \text{if } \lambda_\infty < 0, \end{cases}$$

where λ_∞ is the principal eigenvalue of

$$-\Delta\xi + \alpha(\mathbf{v}_0, +\infty)\nabla\mathbf{v}_0 \cdot \nabla\xi + \alpha(\mathbf{v}_0, +\infty)\xi = \lambda\xi \text{ in } \Omega$$
$$\frac{\partial\xi}{\partial n} = (-\gamma_1\xi, \tau_1\xi) \text{ on } \partial\Omega.$$

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