Anti-angiogenic therapy based on the receptors

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September 10, 2010

1. The model

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2. Evolution problem

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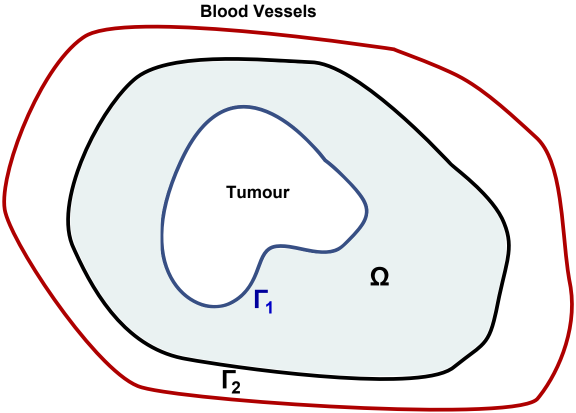
2. Evolution problem
3. Stationary problem


Blood Vessels
Tumour
Ω
Γ1
Γ2

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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$$\frac{\partial u}{\partial n} = \underbrace{-\gamma_1 u}_{ECs\ out} \quad on \;\; \Gamma_1 \times (0, T),$$

Equation and boundary conditions for TAF

- u: Endothelial Cells.
- v: TAF.

$$v_t = \underbrace{\Delta v}_{Diffusion} \underbrace{-v}_{Decay} \quad in \;\; \Omega \times (0, T),$$

$$\frac{\partial v}{\partial n} = \underbrace{-\tau_3 v}_{TAF\ out} \quad on \;\; \Gamma_2 \times (0, T),$$

$$\frac{\partial v}{\partial n} = \underbrace{\widetilde{\gamma}(oxigen)}_{TAF\ enter} \quad on \;\; \Gamma_1 \times (0, T),$$

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

Equation and boundary conditions for TAF

- u: Endothelial Cells.
- v: TAF.

$$v_t = \underbrace{\Delta v}_{Diffusion} \underbrace{-v}_{Decay} \quad in \;\; \Omega \times (0, T),$$

$$\frac{\partial v}{\partial n} = \underbrace{-\tau_3 v}_{TAF\ out} \quad on \;\; \Gamma_2 \times (0, T),$$

$$\frac{\partial v}{\partial n} = \underbrace{\widetilde{\gamma}(oxigen) = \widetilde{\gamma}(s(u))}_{TAF\ enter} \quad on \;\; \Gamma_1 \times (0, T),$$

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

1. Target receptors
2. Target TAF

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Effect of the Therapy in EC

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

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

Equation and boundary conditions for Anti-TAF

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

$$z_t = \underbrace{\Delta z}_{Diffusion} \underbrace{-z}_{Decay} + \underbrace{I_0}_{Input} \quad in \;\; \Omega \times (0,T),$$

$$\frac{\partial z}{\partial n} = \underbrace{-\gamma_2 z}_{Anti-TAF\, out} \quad on \;\; \Gamma_2 \times (0,T),$$

$$\frac{\partial z}{\partial n} = \underbrace{-\tau_2 z}_{Anti-TAF\, out} \quad on \;\; \Gamma_1 \times (0,T),$$

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

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

Theorem

Moreover, there exists $C > 0$ such that

$$\|\mathbf{u}(\mathbf{u_0}) - \mathbf{u}(\overline{\mathbf{u}}_0)\|_{\mathbf{X}_\tau} \leq C\|\mathbf{u_0} - \overline{\mathbf{u}}_0\|_{\mathbf{X}}$$

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

$$\|\mathbf{u}(I_0) - \mathbf{u}(\overline{I}_0)\|_{\mathbf{X}_\tau} \leq C\|I_0 - \overline{I}_0\|_{X_\tau}$$

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.

Let us observe that

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

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

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

$$\int_{\Gamma_2} w^2 \leq \epsilon \int_\Omega |\nabla w|^2 + C(\epsilon^{-\theta} + 1) \int_\Omega w^2 .$$

$l_0 \geq 0$ is a constant.

$$-\Delta u = -\nabla \cdot (\alpha(v,z)u\nabla v) + \lambda\beta(v,z)u - u^2 \ \ in \ \ \Omega$$

$$-\Delta v + v = 0 \ , \quad -\Delta z + z = l_0 \ \ in \ \ \Omega$$

$$\frac{\partial u}{\partial n} = (-\gamma_1 u, \tau_1 u) \ \ on \ \ \partial\Omega$$

$$\frac{\partial v}{\partial n} = (\gamma(u), -\tau_3 v) \ \ on \ \ \partial\Omega$$

$$\frac{\partial z}{\partial n} = (-\gamma_2 z, -\tau_2 z) \ \ on \ \ \partial\Omega$$

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

$$-\Delta v + v = 0\,, \quad \frac{\partial v}{\partial n} = (\gamma(0), -\tau_3 v)\,,$$

$$-\Delta z + z = l_0\,, \quad \frac{\partial z}{\partial n} = (-\gamma_2 z, -\tau_2 z)\,.$$

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

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

$$-\Delta\xi = -\nabla \cdot (\alpha(v_0, z_0)\nabla v_0\xi) + \lambda\beta(v_0, z_0)\xi \quad in \quad \Omega$$

$$\frac{\partial\xi}{\partial n} = (-\gamma_1\xi, \tau_1\xi) \quad on \quad \partial\Omega$$

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.

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

$$X_1 := \{u \in C^{2+\gamma}(\overline{\Omega}) \, : \, \frac{\partial u}{\partial n} = (-\gamma_1 u, \tau_1 u) \;\; on \;\; \partial\Omega\}$$

$$X_2 := \{v \in C^{2+\gamma}(\overline{\Omega}) \, : \, \frac{\partial v}{\partial n} + \tau_3 v = 0 \;\; on \;\; \Gamma_2\}$$

We define the map

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

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 $\mathcal{C}^+ \subset \mathbf{R} \times X_1 \times X_2$ of positive solutions emanating at $(\lambda_1(u_0, v_0), 0, v_0)$.

We consider the mapping

$$l_0 \in [0, +\infty) \mapsto \lambda_1(v_0, z_0) = \lambda_1(v_0, l_0 e) = \lambda_1(l_0)$$

where e is the unique positive solution of

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

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

$$\lambda_1'(0) = -\frac{\lambda_1(0)\int_\Omega \beta_z(v_0,0)e\varphi_1\varphi_1^* + \int_\Omega \alpha_z(v_0,0)e\varphi_1\nabla v_0 \cdot \nabla\varphi_1^* + (*)}{\int_\Omega \beta(v_0,0)\varphi_1\varphi_1^*}$$

where

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

$$\lim_{l_0 \to +\infty} \lambda_1(l_0) = \begin{cases} +\infty & \text{if } \lambda_\infty > 0, \\ -\infty & \text{if } \lambda_\infty < 0, \end{cases}$$

where λ_∞ is the principal eigenvalue of

$$-\Delta\xi + \alpha(v_0, +\infty)\nabla v_0 \cdot \nabla\xi + \alpha(v_0, +\infty)\xi = \lambda\xi \quad in \quad \Omega$$

$$\frac{\partial\xi}{\partial n} = (-\gamma_1\xi, \tau_1\xi) \quad on \quad \partial\Omega.$$