Analysis and modeling of metastatic growth including angiogenesis

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The model

Why a model?

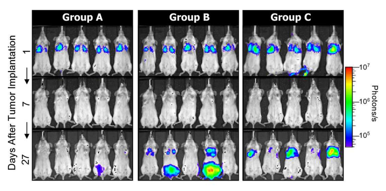


Fig. : Experiments on mice from [Eb09]. Group A received the vehicle while group B and C received short-term treatment either before or after tumor inoculation

Since the 70's, we know with J. Folkman's work, that **tumoral angiogenesis** is a key process in tumor growth as well as in the formation of metastases. Although there exists more than ten anti-angiogenic drugs, the **optimal administration protocol** is still a challenge (see [Eb05] where they show that metastatic acceleration can occur after an anti-angiogenic treatment in some cases).

In [HA99], Folkman et al. proposed an interesting ODE model to deal with endostatin and angiostatin administration in order to control the growth of the primitive tumor. Beside, in [BBHV09] Barbolosi et al. studied a model from [KIS00], based on a transport-type PDE to describe the **metastatic** evolution. The aim of this work is to build a model able to describe the impact of the anti-angiogenic drugs both on the primitive tumor and on the metastatic process in order to optimize the treatments. Our model is based on two-dimensional transport equation coupled with an ODE system build on ideas from [HA99] and [BBHV09].

▶ **We hope with this model to obtain in silico predictions for therapeutic windows for angiogenic drugs.**

Flow of the ODE system

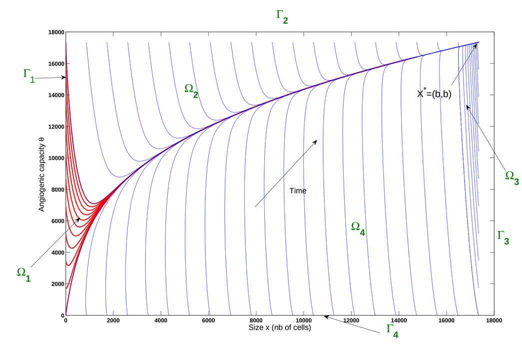


Fig. : Phase plan

$$(1)\quad \begin{cases} \frac{dx}{dt} = ax\ln\left(\frac{\theta}{x}\right) \\ \frac{d\theta}{dt} = cx - d\theta x^{\frac{2}{3}} \end{cases}$$

x = size of the tumor
θ = angiogenic capacity

$$\Omega = (1,b)\times(1,b),\ \Gamma = \partial\Omega$$

$$\Lambda : \begin{array}{ccc}]0,\infty[\times\Gamma\setminus(b,b) & \to & \Omega \\ (\tau,\sigma) & \mapsto & \underbrace{\Phi_\tau(\sigma)}_{Flow} \end{array}$$

$$G(x,\theta) = \left(ax\ln\left(\frac{\theta}{x}\right), cx - d\theta x^{\frac{2}{3}}\right)$$

$\Omega \simeq$ Time $\times$ Boundary

Proposition. *Λ is a diffeomorphism $]0,+\infty[\times\Gamma_i \to \Omega_i$ and for all $\tau\geq 0$ and almost every $\sigma\in\Gamma$*

$$J_\Lambda(\tau,\sigma) = G\cdot\overrightarrow{\nu}(\sigma)e^{\int_0^\tau \mathrm{div}(G(\Phi_s(\sigma)))ds}$$

where $J_\Lambda(\tau,\sigma)$ is the Jacobian of Λ. Globally, Λ is an homeomorphism $]0,\infty[\times\Gamma^* := \Gamma\setminus(b,b)\to\Omega$ wich locally bilipschitz.

A renewal equation for the density of metastasis

We adapt the model studied in [BBHV09], concerning the **density of metastasis** to take into account the angiogenesis process.

$$(2)\quad \begin{cases} \partial_t\rho + \mathrm{div}(G\rho) = 0 & \mathbb{R}^+\times\Omega \\ -G\cdot\overrightarrow{\nu}\rho(t,\sigma) = \underbrace{N(\sigma)\int_\Omega\beta\rho(t)}_{\text{Secondary metastasis}} + \underbrace{f(t,\sigma)}_{\text{Primary tumor}} & \mathbb{R}^+\times\Gamma \\ \rho(0) = \rho^0 & \Omega \end{cases}$$

$$(3)\quad \beta(x,\theta) = mx^\alpha,\ f(t,\sigma) = \beta(x_p(t),\theta_p(t))$$

where $(x_p(t),\theta_p(t))$ represents the primary tumor and solves system (1).

$$(4)\quad \int_0^\infty\int_\Gamma \beta(\Phi_\tau(\sigma))N(\sigma)d\tau d\sigma > 1,\ N\in Lip_c(\Gamma)\ N\geq 0,\ \int_\Gamma N = 1$$

Homogeneous problem

$$(5)\begin{cases} \partial_t\rho_h + \mathrm{div}(G\rho_h) = 0 \\ -G\cdot\overrightarrow{\nu}\rho_h = N\int\beta\rho_h \\ \rho_h(0) = \rho^0 \end{cases}$$

Non-homogeneous problem

$$(6)\begin{cases} \partial_t\rho_s + \mathrm{div}(G\rho_s) = 0 \\ -G\cdot\overrightarrow{\nu}\rho_s = N\int\beta\rho_s + f(t,\sigma) \\ \rho_s(0,x,\theta) = 0 \end{cases}$$

$$\boxed{\rho = \rho_{\mathbf{h}} + \rho_{\mathbf{s}}}$$

Functional space and properties of the operator

Semigroup approach for the homogeneous problem

▶ The domain of the operator

$$D(A) = \left\{V\in W_{\mathrm{div}}(\Omega);\ -G.\overrightarrow{\nu}\cdot\gamma(V)(\sigma) = N(\sigma)\int_\Omega\beta V,\ \forall\sigma\in\Gamma\right\}$$

▶ The operator

$$A : \begin{array}{ccc} D(A)\subset L^1(\Omega) & \to & L^1(\Omega) \\ V & \mapsto & -\mathrm{div}(GV) \end{array}$$

Definitions.

▶*A function $\rho : [0,+\infty[\to L^1(\Omega)$ is called a* **classical solution** *of* (5) *if*

$$\rho\in\mathcal{C}^1([0,+\infty[;L^1(\Omega)),\ \rho(t)\in D(A),\ \forall t\geq 0 \text{ and } \rho \text{ solves } (5)$$

▶*A continuous function $\rho : [0,+\infty[\to L^1(\Omega)$ is called a* **mild solution** *of* (2) *if*

$$\int_0^t\rho(s)ds\in D(A),\ \forall t\geq 0,\ \text{and } \rho(t) = A\int_0^t\rho(s)ds + \rho^0$$

Proposition. *Consider the homogeneous problem (5) and let ρ be in $\mathcal{C}([0,\infty[;L^1(\Omega))$, then*

$$(\rho \text{ is a mild solution}) \Leftrightarrow (\rho \text{ is a distributional solution})$$

The space Wdiv

$$\mathbf{W}_{\mathrm{div}}(\boldsymbol{\Omega}) := \{\mathbf{V}\in\mathbf{L}^1(\boldsymbol{\Omega})\mid\mathrm{div}(\mathbf{GV})\in\mathbf{L}^1(\boldsymbol{\Omega})\}$$

Theorem : Conjugation
The spaces $W_{\mathrm{div}}(\Omega)$ and $W^{1,1}((0,+\infty);L^1(\Gamma))$ are conjugated

$$V\in W_{\mathrm{div}}(\Omega)\Leftrightarrow V(\Phi_\tau(\sigma))|J_\Lambda|\in W^{1,1}((0,+\infty);L^1(\Gamma))$$

$$\partial_\tau V(\Phi_\tau(\sigma)) = \mathrm{div}(GV)|J_\Lambda|$$

▶ Define the **trace** of V : $\gamma(V)(\sigma) = V(\Phi_0(\sigma))\in L^1(\Gamma,|G\cdot\overrightarrow{\nu}|d\sigma)$

▶ **Integration by part** formula

$$\int\int_\Omega U\mathrm{div}(GV) + \int\int_\Omega VG\cdot\nabla U = -\int_\Gamma\gamma(V)\gamma(U)G\cdot\overrightarrow{\nu}$$

▶ For all Lipschitz function $H : \mathbb{R}\to\mathbb{R}$

$$H(V)\in W_{\mathrm{div}}(\Omega),\ \mathrm{div}(H(V)) = H'(V)G\cdot\nabla V + H(V)\mathrm{div}(G)$$

Properties of the operator

Proposition. *The operator $(A,D(A))$ is closed and* **densely defined**. *Its adjoint is given by*

$$D(A^*) = \{U\in L^\infty;\ G\cdot\nabla U\in L^\infty\},\ A^*U = G\cdot\nabla U + \beta\int_\Gamma\gamma(U)N$$

Spectral problem

$$(7)\quad\begin{cases} (\lambda,V,\Psi)\in\mathbb{R}_+^*\times D(A)\times D(A^*) \\ AV = \lambda V,\quad A^*\Psi = \lambda\Psi \\ \int_\Omega V\Psi dxd\theta = 1,\quad \int_\Gamma\Psi N = 1,\ \Psi\geq 0 \end{cases}$$

Theorem : Spectral properties
Under asumption (4), there exists a unique triplet (λ_0,V,Ψ) in $(]0,+\infty[\times D(A)\times D(A^*))$ solution to the eigenproblem (7). Moreover, we have the following **spectral equation** *on λ_0 :*

$$\boxed{\int_0^{+\infty}\int_\Gamma\beta(\Phi_\tau(\sigma))N(\sigma)e^{-\lambda_0\tau}d\tau d\sigma = 1}$$

Proposition. *The operator $(A,D(A))$ generates a* **semigroup** *on $L^1(\Omega)$ denoted by e^{tA} and we have*

$$|||e^{tA}|||\leq e^{t||\beta||_{L^\infty}}$$

Existence and asymptotic behavior

Definition. *A function $\rho\in\mathcal{C}([0,\infty[;L^1(\Omega))$ is called a* **weak solution** *of (2) if it verifies for each function $\phi\in\mathcal{C}_c^1([0,+\infty[\times\overline{\Omega}\setminus(b,b))$*

$$\int_0^\infty\int_\Omega\rho[\partial_t\phi + G\cdot\nabla\phi]dtdxd\theta + \int_\Omega\rho^0(x,\theta)\phi(0,x,\theta)dxd\theta$$
$$-\int_0^\infty\int_\Gamma\left\{N(\sigma)\left(\int_\Omega\beta(x,\theta)\rho(t,x,\theta)dxd\theta\right) + f(t,\sigma)\right\}\phi(t,\sigma)d\sigma dt = 0$$

Theorem : Existence and uniqueness of solutions
- *For each initial condition $\rho^0\in L^1(\Omega)$ and source term $f\in\mathcal{C}([0,+\infty[;L^1(\Omega))$, there is a unique weak solution to the equation (2) given by*

$$\rho = e^{tA}\rho^0 + \mathcal{T}f$$

with $\mathcal{T}f$ being a weak solution of the equation (6).
- *If $\rho^0\in D(A)$ and f(0)=0, then $\rho\in\mathcal{C}^1([0,\infty[;D(A))$*

▶ We use a fixed point argument for the existence of solutions of the non-homogeneous problem (6).

Proposition. *Let $\rho\in\mathcal{C}([0,+\infty[;L^1(\Omega))$ be a weak solution of (2). We have :*
(i) $\int_\Omega\rho(t)\Psi = e^{\lambda_0 t}\left\{\int_\Omega\rho^0\Psi + \int_0^t\int_\Gamma\Psi(\sigma)e^{-\lambda_0 s}f(s,\sigma)d\sigma ds\right\},\quad\forall t\geq 0$
(ii) (Comparison principle)

$$\rho_1^0\leq\rho_2^0\quad\Rightarrow\quad\rho_1(t)\leq\rho_2(t)\quad\forall t\geq 0$$

Theorem : Asymptotic behavior
In the particular case of the problem (3) there exists $\mu>0$ such that $\beta-\mu\Psi\geq 0$ and we have

$$||\rho(t)e^{-\lambda_0 t} - m_0V||_{L^1_\Psi}\leq e^{-\mu t}||\rho^0 - m_0V||_{L^1_\Psi} + \int_\Gamma\Psi(\sigma)\int_0^t e^{-\lambda_0 s}|f(s,\sigma)|dsd\sigma,$$

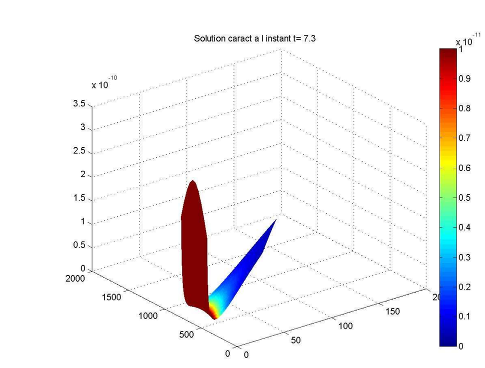
where $||f||_{L^1_\Psi} = \int_\Omega|f|\Psi$, and $m_0 = \int_\Omega\rho^0\Psi$.

Numerical results and perspectives

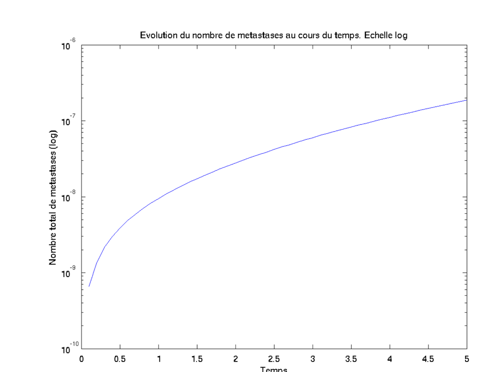
Metastatic progression on mice

▶ Parameters are taken from Folkman [HA99].

▶ Numerical simulations of the equation via a characteristic scheme



Density ρ



Total number of metastases

Perspectives

▶ Include the effect of an anti-angiogenic drug in the numerical model

▶ Use the model to optimize the administration protocols of cytostatic drugs in combination with chimiotherapies.

▶ Take into account the toxicities of drugs.

▶ Investigate therapeutic windows for anti-angiogenic drugs.

References

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