Mathematical modeling and analysis of tumor-immune interactions

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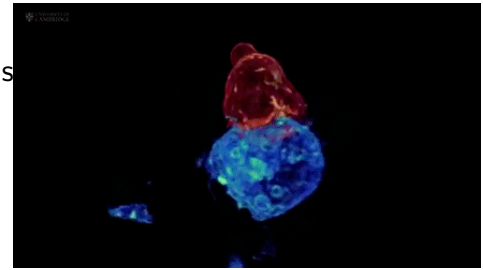
6 août 2019

Summary

The Immune system Attacks Tumor cells

- **Immunotherapy** starts in 1891 with W. Coley (Coley's toxins) ;
- Immunotherapy restarted seriously With the appearance of AIDS ;
- **immunodeficient** patients often develop cancer
- **Immune cells** play an important role in the control or in the development of tumors



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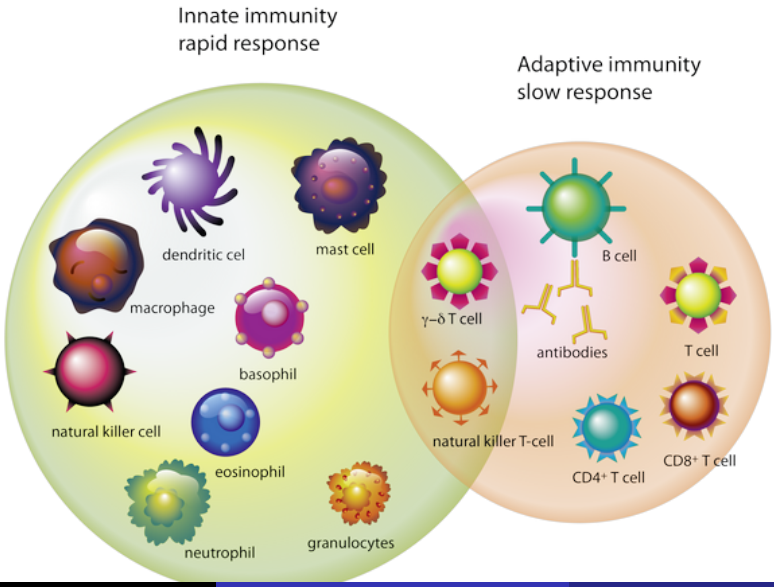
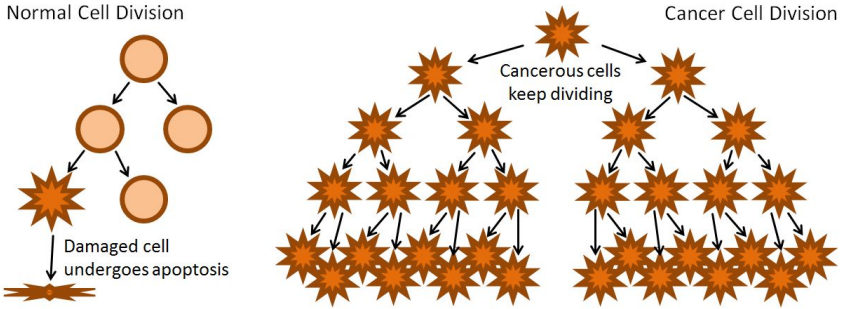
1. source : https ://gifer.com/en/7ftZ

Two types of Immune system



Tumor cells cycle

- Genes involved in cell cycle control are subject to the **genetic alterations** $\Longrightarrow$ **cancer** $\Longrightarrow$ **Uncontrolled Cell division**



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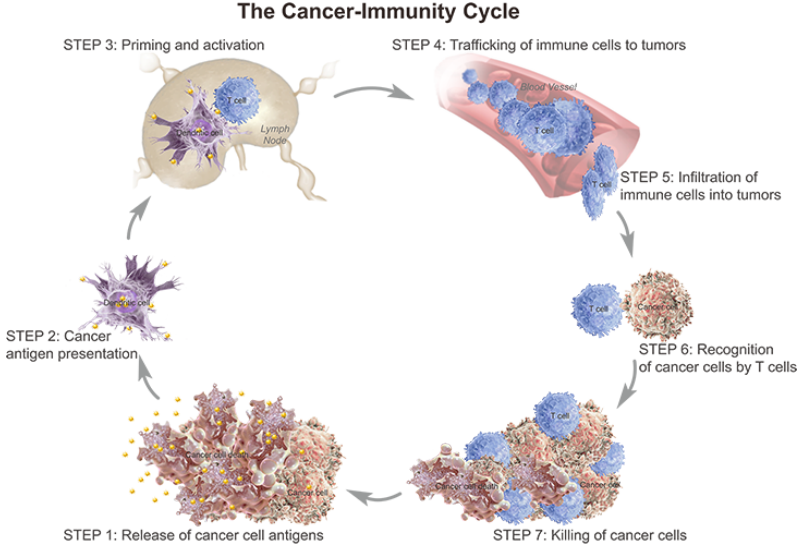
3. source : https ://curioussciencewriters.org/

Tumor Immunity Cycle



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4. source : http ://biocc.hrbmu.edu.cn/TIP/

K.Atsou - Impediments of the tumor immunity cycle

Tumor has many suppressive influences

The prevalence of cancer indicates that the immune system does not have a strong enough effect on Tumors.

- high levels of **suppressive cytokines** ;
- **T regulatory cells** (Tregs produce TGF-β and IL-10) ;
- high expression of **PD-L1** (Programmed death-ligand 1) by tumors ;
- Production of **VEGF** (Vascular Endothelial Growth Factor) for **angiogenesis** ;

Summary

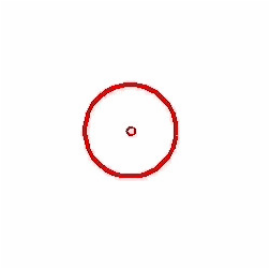
A growth-fragmentation modeling approach : Tumor

- $(t, z) \mapsto n(t, z)$ (in $cell_n \cdot \mu m^{-3}$) the size-structured tumor cells distribution
- $(t, x) \mapsto c(t, x)$ (in $cell_c \cdot mm^{-3}$) the concentration of Effector T cells

Tumor growth main processes

Tumor growth is splitted into two main processes :

- natural (microscopic) growth of the cells,
- cell division.



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A growth-fragmentation modeling approach : Tumor

We model the tumor growth by the following equation :

$$\frac{\partial}{\partial t} n(t,z) = \underbrace{-\frac{\partial}{\partial z}(V(z)n(t,z))}_{\text{the cell's volume growth}} + \underbrace{Q(n(t,z))}_{\text{Cellular division operator}} .$$

We can complete the equation by the **initial data**,

$$n(t=0,z) = n_0$$

and the **boundary condition**,

$$n(t,0) = 0$$

The cellular division

$$\frac{\partial}{\partial t} n(t,z) = \underbrace{-\frac{\partial}{\partial z}(V(z)n(t,z))}_{\text{the cell's volume growth}} + \underbrace{Q(n(t,z))}_{\text{Cellular division operator}} .$$

$Q(n(t,z))$?

- $a(z)$, the **rate at which cells of size z process division**.
- $k(z'|z)$ **the distribution of products from a cells of size z dividing**.

The cellular division

$k(z'|z)$ must be normalized so that mass is conserved :

$$\int_0^z z' k(z'|z) dz' = z. \tag{1}$$

Consequently,

$$Q(n) = \underbrace{-a(z)n(t,z)}_{\text{The loss of cells of size } z} + \underbrace{\int_z^\infty a(z')k(z|z')n(t,z')dz'}_{\text{gain of cells with size } z}. \tag{2}$$

Binary and symmetric The cellular division

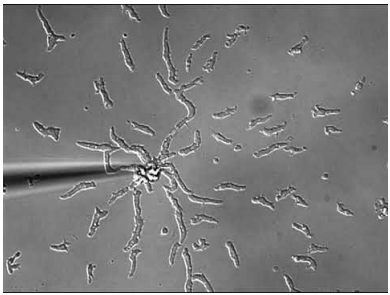
$$Q(n) = \underbrace{-a(z)n(t,z)}_{\text{The loss of cells of size } z} + \underbrace{\int_z^\infty a(z')k(z|z')n(t,z')dz'}_{\text{gain of cells with size } z}. \tag{3}$$

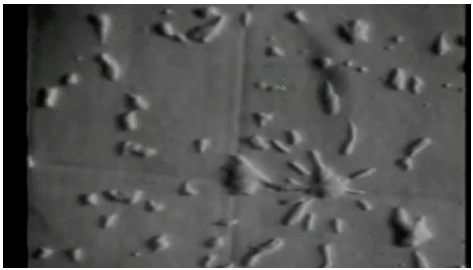
We assume binary and symmetric division process. Therefore cells of size $2z$ give birth to cells of size z. $k(z|2z) = 2\delta_{z'=2z}$

$$Q(n(t,z)) = -a(z)n(t,z) + 2a(2z)n(t,2z)d(2z) \tag{4}$$

$$Q(n(t,z)) = \underbrace{4a(2z)n(t,2z)}_{\text{gain of cells with size } z} - \underbrace{a(z)n(t,z)}_{\text{The loss of cells of size } z} \tag{5}$$

Chemotaxis phenomenon





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T cells displacement towards the tumor microenvironment is model by **chemotaxis**.

K.A - The antigen-specific CD8+ effector T cells displacement

the activated T cells follows the gradient of the chemical signal

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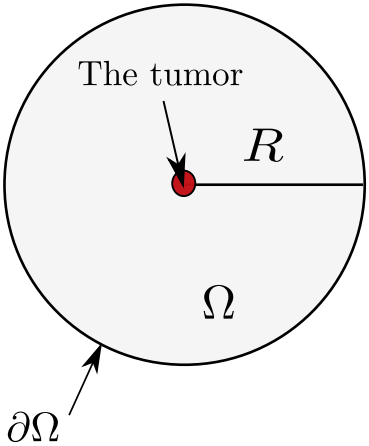
the activated T cells follows the gradient of the chemical signal

Let's denote by

$$\Omega = \{x \in \mathbb{R}^N, |x| \leq R\},$$

$c_\omega(t)$ the time dependent concentration of immune cells in a volume $\omega \subset \Omega$:

$$c_\omega(t) = \int_\omega c(t,x)dx \qquad (6)$$



The tumor mass : kth order moments

- Let's denote by $\mu_0(t)$ (the zeroth order moment) **the total number of tumor cells** in the tumor ;

$$\mu_0(t) = \int_0^\infty n(t,z)dz \tag{7}$$

- Let's denote by $\mu_1(t)$ (the first order moment) **the total volume of the tumor** ;

$$\mu_1(t) = \int_0^\infty zn(t,z)dz \tag{8}$$

The Chemotaxis model

$$\frac{\partial c}{\partial t}(t,x) + \overbrace{\nabla \cdot (\chi_\Phi(\nabla_x \Phi) c)}^{\text{Convection term}} - \overbrace{D(\nabla_x c)}^{\text{Diffusion term}} = \overbrace{p_f g(\mu_1) S}^{\text{Conversion of Im. cells}} - \overbrace{\gamma c}^{\text{Natural Death}} \tag{9}$$

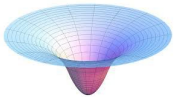
$$c|_{\partial\Omega} = 0$$

Typical conversion law of Naive T cells (*Saturated conversion*).

$$g(\mu_1) = \frac{\mu_1}{\delta + \mu_1} \tag{10}$$

Tumor antigen-induced potential

The attractive potential Φ satisfies a **Poisson equation** :



$$-\nabla \cdot (k(x)\nabla\Phi) = \langle\sigma\rangle \int_0^\infty zn(t,z)\,dz,$$

$$-\nabla \cdot (k(x)\nabla\Phi) = \mu_1(t)\langle\sigma\rangle,$$

With **Neumann homogeneous boundary condition**.

$$k(x)\nabla_x\Phi(x)\cdot n_{\partial\Omega} = 0$$

where $\langle\sigma\rangle = \sigma - \frac{1}{|\Omega|}\int_\Omega \sigma \,\mathrm{d}x$

A chemotaxis model : Immune cells

The resulting Chemotaxis model

$$\begin{cases} \partial_t c(t,x) + \nabla \cdot (\chi(\phi)(\nabla_x \phi)c - (D(x)\nabla_x c)) = pg(\mu_1)S - \gamma c, & \forall t > 0, x \in \Omega \\ -\nabla \cdot (k(x)\nabla\phi) = \displaystyle\int_0^\infty zn(t,z)\sigma(x,z)dz, & \forall t, z > 0, x \in \Omega \\ c = 0, & \forall x \in \partial\Omega, \\ c(t=0,x) = c_0(x), & \forall x \in \Omega, \\ k(x)\nabla\phi \cdot n_{\partial\Omega} = 0 & \forall x \in \partial\Omega. \end{cases}$$

Tumor vs Immune cells : the interactions term

Let's denote by $m(c, n)$ the death term describing the immune response The tumor growth model becomes :

$$\frac{\partial}{\partial t} n(t,z) = -\frac{\partial}{\partial z}(Vn(t,z)) + Q(n(t,z)) - \underbrace{m(c,n)}_{\text{The interaction Tumor-Im. Cells}} .$$

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$$m(c,n)(t) = \int_\Omega \delta(y) c(t,y)\, dy \times \frac{n(t,z)}{\alpha + n(t,z)}.$$

where δ is an **interaction kernel**

Asymptotic behavior : Tumor growth

We turn back to the tumor growth equation without immune response :

$$\begin{cases} \partial_t n(t,z) = -\partial_z(V(z)n(t,z)) - a(z)n(t,z) + 4a(z)n(t,2z), & \forall (t,z) \in \mathbb{R}_+^\star \times \mathbb{R}_+ \\ n(t,0) = 0, & \forall t \geq 0, \\ n(t=0,z) = n_0(z) \in L^1(\mathbb{R}_+), & \forall z \geq 0, \end{cases}$$

The solution behaves like : $(t,z) \mapsto \rho e^{\lambda t} N(z)$ with $\rho = \int_{\mathbb{R}_+} n_0(z)$

Asymptotic behavior : Tumor growth

The long time behavior of n is directly linked with **the existence of a solution** λ, N, ϕ**, in** L^1 **sense, of the associated eigenproblem**,

$$\begin{cases} \partial_z(V(z)N(z)) + (\lambda + a(z))N(z) = 4a(z)N(2z), \quad z \geq 0 \\ N(0) = 0, \quad N(z) > 0 \text{ for } z > 0, \quad \int_0^\infty N(z)dz = 1 \\ V(z)\partial_z\psi(z) - (\lambda + a(z))\psi(z) = -2a(z)\psi(\frac{z}{2}), \quad x \geq 0 \\ \psi(z) > 0 \text{ for } x \geq 0, \int_0^\infty N(z)\psi(z)dz = 1 \end{cases}$$

Asymptotic behavior : Tumor growth

The solution of the dual equation allows to define a conservation law on $n(t,z)$:

Mass Conservation

$$\int_0^\infty n(t,z)e^{-\lambda t}\psi(z)dz = \int_0^\infty n_0(z)\psi(z)dz$$

Existence and uniqueness of the eigenelements

Theorem, B. Perthame et al., 2005

if **the division rate** a **is lower bounded and upper bounded**, then **there is a unique solution** (λ, N, ψ) to the eigenproblem with ψ, N in $C^1(\mathbb{R}_+)$ and moreover, **all the moments of the asymptotic state** N **are bounded**.

The existence of the eigenelements is based on the **Krein-Rutman Theorem**

Asymptotic behavior : Tumor growth

Exponential decay to the leading eigenpair of the growth-fragmentation operator :

Theorem, B. Perthame et al., 2004

If the **division rate and the growth rate of the tumor are constant**, there is a **unique solution** to **the first eigenvalue problem**. This solution belongs to the Schwartz space and furthermore, **all the solutions to the tumor growth equation converges exponentially to the first eigenvector** with a rate equal to the tumor division rate.

Asymptotic behavior : Tumor growth

There is a semi-explicit formula for the leading eigenfunction N (F. Baccelli, 2002, B. Perthame et al., 2004) given by a series that **converges absolutely and uniformly**

Lemma, F.Baccelli, 2002

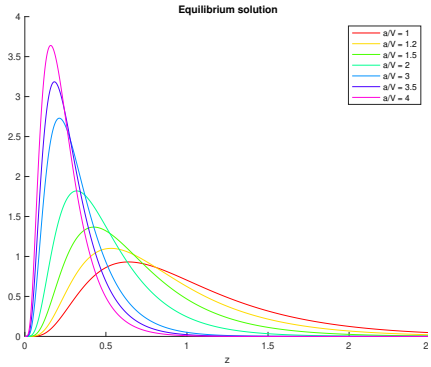
Let $\alpha_0 = 1$, $\alpha_n = \dfrac{2}{2^n - 1}\alpha_{n-1}$, then the function

$$N(z) = \langle N \rangle \sum_{n=0}^{\infty} (-1)^n \alpha_n \exp\left(-2^{n+1}\frac{a}{V}z\right),$$

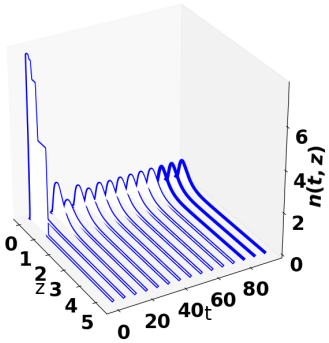
belongs to $\mathcal{S}(\mathbb{R}^+)$ and is unique.

Asymptotic behavior : Tumor growth

different profiles :



An example of time evolution :



Asymptotic behavior : Tumor growth

Existence and uniqueness of eigenelements has been proved

Residual distribution

- the system reaches a certain **equilibrium state**, with a non zero tumor cells distribution
- In which cases the immune system can control the tumor progression ?

Asymptotic behavior : Immune cells taking control

An attempt which clarifies this issue is provided by the following statement for small division rates (non-aggressive tumors)

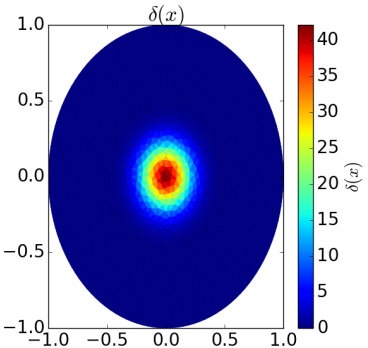
Proposition, Kevin ATSOU & Thierry Goudon

If the tumor is **non-aggressive**, there exist a **unique tumor mass** which depends on the tumor division rate at which the tumor is always **controlled by the immune cells**.

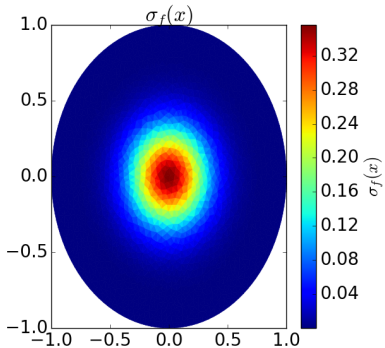
Summary

model parameters

- **Variable parameters** :



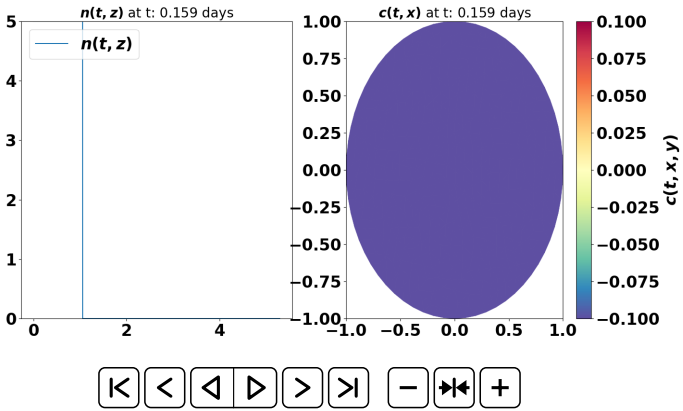
(a) The T cells Strength δ



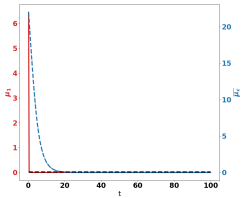
(b) The chemical signal σ_f

Homogeneous distribution of Naive cells : $a = 1$

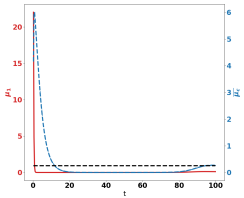
Tumor vs Homogeneous distribution of Immune cells :



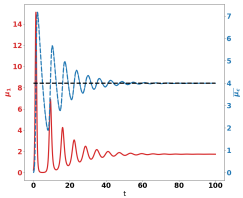
Homogeneous distribution of Naive cells : a



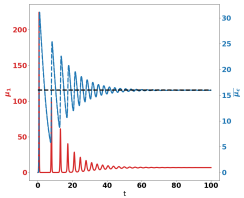
(c) $a = 0.0625$



(d) $a = 0.25$



(e) $a = 4$

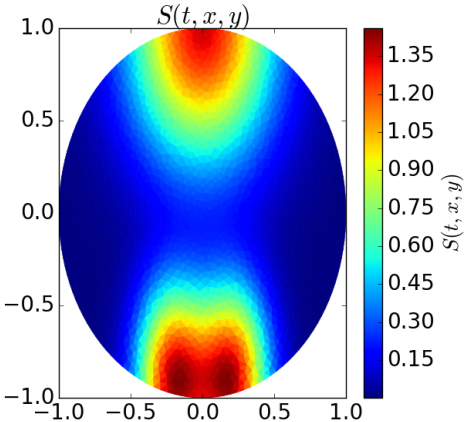


(f) $a = 16$

FIGURE – behavior of the solutions. (μ_1 in red, μ_c in blue, a in black)

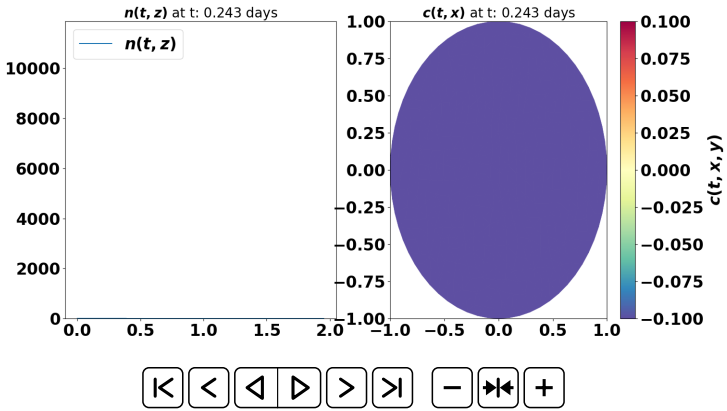
Heterogeneous distribution of Naive cells

Tumor vs Heterogeneous distribution of Immune cells :

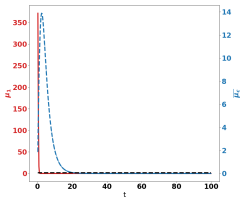


Heterogeneous distribution of Naive cells : $a = 4$

Tumor vs Heterogeneous distribution of Immune cells :



Heterogeneous distribution of Naive cells



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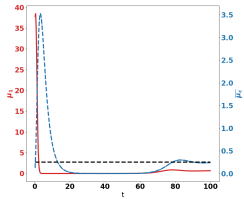
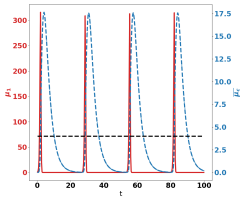
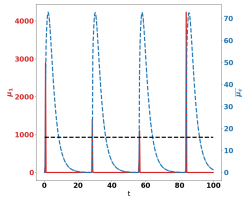


(b) $a = 0.25$



(c) $a = 4$



(d) $a = 16$

FIGURE – Evolution of the tumor mass μ_1 (red curves, left axis), and of

Thank you for your attention...