

Some non-local elliptic problems. Applications to population dynamics and cancer stem-cells models

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Local models

There are several biological and physical phenomena that can be modeled by PDEs

$$u_t(x, t) - Lu(x, t) = f(x, t, u(x, t))$$

$x \in \Omega$, bounded domain of \mathbb{R}^N , $t > 0$, L a linear second order elliptic operator.

In this problem, the relation between the unknown u and its derivatives are local in space.

Non-Local models: examples

There are, however, where a global spatial coupling is present in the phenomena and has to be incorporated in the model.

Some examples....

Liouville (1837) published a study of the equation

$$u_t = u_{xx} - b^2 x \int_0^1 x u_t dx$$

in connection with models in thermo-mechanics.

Non-Local models: examples

A turbulence model proposed by Burgers (1939)

$$\begin{cases} u_t = P - \frac{1}{R}u - \int_0^1 v^2 dx \\ v_t + 2v_x v = \frac{1}{R}v_{xx} + uv \end{cases}$$

Here u denotes the velocity in a channel due to some applied force P , while v stands for the turbulent perturbation of the motion and R is the Reynolds number associated with the viscosity of the fluid.

Non-Local models: examples

Burgers equation with non-local term

$$u_t = u_{xx} + \varepsilon u_x u + \frac{1}{2}(a\bar{u} + b)u$$

where \bar{u} is a power of the L^p norm of u , that is,

$$\bar{u} = \left(\int_{\Omega} u^p \right)^q.$$

Non-Local models: examples

Plasma physics

$$u_t = \Delta u + \alpha \frac{e^{-u}}{\left(\int_{\Omega} e^{-u} dx \right)^p}$$

(when $p = 1$ Poisson-Boltzmann equation)

Non-Local models: examples

The distribution $u(x)$ of the phytoplankton species at water depth x is modeled by the following reduced model

$$-[d u' - g(x) u]' = \left[f \left(e^{-k_0 x - \int_0^x u(\eta) d\eta} \right) - m \right] u$$

where

$$f(s) = \frac{s}{\delta_1 + s},$$

Population dynamics and non-local terms

Furter and Grinfeld (1989) incorporated non-local effects in some population dynamics models:

"In ecological context, there is no real justification for assuming that the interactions are local. There are many (hypothetical) examples where such an assumption is clearly untenable, such as: (1) a population in which individua compete for a shared rapidly equilibrated (e.g. by convection) resource; (2) a population in which individua communicate either visually or by chemical means."

Population dynamics and non-local terms

And they proposed, for example,

$$u_t - \Delta u = u \left(\lambda - a \int_{\Omega} u \right),$$

or even in a non-local diffusion:

$$u_t - A \left(\int_{\Omega} u \right) \Delta u = u(\lambda - au),$$

where A is a positive and regular function, see also Chipot (1996), Chipot & Lovat (1997), Chipot & Correa (2009), etc.....

Population dynamics and non-local terms

Or even systems

$$\begin{cases} u_t - D_1 \Delta u = u \left(\lambda - \int_{\Omega} K_{11}(x, y) u(y, t) dy - \int_{\Omega} K_{12}(x, y) v(y, t) dy \right) \\ v_t - D_2 \Delta v = v \left(\mu - \int_{\Omega} K_{21}(x, y) u(y, t) dy - \int_{\Omega} K_{22}(x, y) v(y, t) dy \right) \end{cases}$$

Population dynamics and non-local terms: a more realistic model

It seems more realistic (see for instance Chipot, 2006) to consider that the crowding effect depends also on the value of the population around of x , that is, the crowding effect depends on the value of u in a neighborhood of x , $B_r(x)$, the centered ball at x of radius $r > 0$. So, we consider the equation

$$\begin{cases} u_t - \Delta u = u \left(\lambda - \int_{\Omega \cap B_r(x)} b(y) u^p(y) dy \right) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega. \end{cases} \quad (1)$$

We can write

$$\int_{\Omega \cap B_r(x)} b(y) u^p(y) dy = \int_{\Omega} K(x, y) u^p(y) dy,$$

for some $K \in L^\infty(\Omega \times \Omega)$.

Population dynamics and non-local terms: a more realistic model

Or even in the diffusion

$$u_t - \operatorname{div} \left(A \left(\int_{\Omega \cap B_r(x)} b(y) u^p(y) dy \right) \nabla u \right) = f(x, u)$$

Ovono, Rougirel (2010), Alves, Chipot, Correa (2016)

Population dynamics and non-local terms: birth-jump processes

Hillen et al. (2015) proposed the following general model

$$\begin{aligned}
 -d\Delta u = & \underbrace{\int_{\Omega} K(x, y, u(x, t)) \alpha(u(y, t)) u(y, t) dy - \alpha(u(x, t)) u(x, t)}_{\text{position-jump process}} \\
 & + \underbrace{\int_{\Omega} S(x, y, u(x, t)) \beta(u(y, t)) u(y, t) dy}_{\text{birth-jump process}} - \underbrace{\delta(u(x, t)) u(x, t)}_{\text{death}}
 \end{aligned}$$

Population dynamics and non-local terms: birth-jump processes

- 1 The first two terms describe a nonlinear position-jump process, where $\alpha(u)$ is the rate for an individual to leave location x . The kernel K is a redistribution kernel representing the probability density of an individual to jump from y to x , conditioned on the local occupancy at x given by $u(x, t)$.
- 2 The third term describes the proper birth-jump process. The function $\beta(u)$ is a proliferation rate at location y , and S is the redistribution kernel for newly generated individuals at y to jump to x .

Non-local models of Stem Cells and Cancer

Hillen, Enderling and Hahnfeldt (2013) proposed the following model to explain “tumor growth paradox”:

$$\begin{cases} u_t = D_1 \Delta u + \delta \gamma \int_{\Omega} K(x, y, p(x, t)) u(y, t) dy \\ v_t = D_2 \Delta v - \alpha v + \rho \int_{\Omega} K(x, y, p(x, t)) v(y, t) dy \\ \quad + (1 - \delta) \gamma \int_{\Omega} K(x, y, p(x, t)) u(y, t) dy, \end{cases}$$

where u , v denote cancer stem cells (CSCs) and nonstem tumor cells (TCs), and $p = u + v$.

Non-local models: pure nonlocal diffusion

$$u_t = \int_{\Omega} S(x, y, u(x, t)) \beta(u(y, t)) u(y, t) dy - \delta(u(x, t)) u(x, t)$$

Hutson, Martínez, Mischaikow and Vickers (2003), Coville (2004..), García-Melián, Rossi (2008...)

Non-local models: Kirchhoff equation

$$-M(x, \|u\|^2)\Delta u = f(x, u),$$

where

$$\|u\|^2 = \int_{\Omega} |\nabla u|^2.$$

(Alves, Correa, Ma (2005), G. Figueiredo....)

Non-local models: chemotaxis models

In tumors growth models, it appears the equation

$$u_t = d_1 \Delta u - \underbrace{\nabla \cdot (u \nabla v)}_{\text{chemotaxis}} + f(u, v)$$

where u and v denote (CE), and TAF.

Consider

$$u_t = d_1 \Delta u - \nabla \cdot (u K \star v) + f(u, v)$$

where

$$K \star v = \int_{\Omega} K(x, y) v(y) dy.$$

Population dynamics and non-local terms

Our first problem is to analyse

$$\begin{cases} u_t - \Delta u = u \left(\lambda - \int_{\Omega} K(x, y) u^p(y) dy \right) & \text{in } \Omega \times (0, \infty), \\ u = 0 & \text{on } \partial\Omega \times (0, \infty), \\ u(x, 0) = u_0 & \text{in } \Omega, \end{cases} \quad (2)$$

and the corresponding stationary problem

$$\begin{cases} -\Delta u = u \left(\lambda - \int_{\Omega} K(x, y) u^p(y) dy \right) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases} \quad (3)$$

where $p > 0$, $\lambda \in \mathbb{R}$ and K is a continuous function.

Population dynamics and non-local terms

$$\begin{cases} u_t - \Delta u = u \left(\lambda - \int_{\Omega} K(x, y) u^p(y) dy \right) & \text{in } \Omega \times (0, \infty), \\ u = 0 & \text{on } \partial\Omega \times (0, \infty), \\ u(x, 0) = u_0 & \text{in } \Omega. \end{cases} \quad (4)$$

We can prove:

- If $K \geq 0$, there exists a unique positive solution of (4) for all $t > 0$.
- If $K < 0$, the unique positive solution of (4) blows up in finite time.

Stationary non-local problem

Consider

$$\begin{cases} -\Delta u = u \left(\lambda - \int_{\Omega} K(x, y) u^p(y) dy \right) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases} \quad (5)$$

with $K(x, y) > 0$ or $K(x, y) < 0$.

Main difficulties:

- ① (5) has not a variational structure and so we can not apply the powerful tool of “variational methods” to attack (5).
- ② The linearized operator of (5) at a stationary solution is an integral-differential operator and it will not be self-adjoint.

The lack of these properties does not necessarily imply a change on the behaviour of the equation, but it makes the study harder.

Variational structure

In the local case

$$-\Delta u = f(x, u)$$

we have a variational problem associated

$$J(v) = \frac{1}{2} \int_{\Omega} |\nabla v|^2 - \int_{\Omega} F(x, v), \quad F(x, s) = \int_0^s f(x, s) ds.$$

In the non-local case: this is not true in general.

We can apply it for particular case, for example

$$-\Delta u = f(u) \left[\int_{\Omega} F(u) \right]^p$$

with

$$J(v) = \frac{1}{2} \int_{\Omega} |\nabla v|^2 - \frac{1}{p+1} \left[\int_{\Omega} F(v) \right]^{p+1},$$

Linearization:

Let u_0 a positive solution of the local problem

$$-\Delta u_0 = f(x, u_0),$$

then the linearization around u_0 is:

$$-\Delta v - f_u(x, u_0)v = \lambda v.$$

Then, there exists a sequence of eigenvalues $\{\lambda_i\}_i \subset \mathbb{R}$ and the principal eigenvalue λ_1 is simple and it is the unique eigenvalue with positive eigenfunction associated φ_1 .

Linearization:

Let u_0 a positive solution of the non-local problem

$$-\Delta u_0 = f(x, u_0, B(u_0)), \quad B(u_0) = \int_{\Omega} u_0^p,$$

then the linearization around u_0 is:

$$-\Delta v - f_u(x, u_0, B(u_0))v - f_v(x, u_0, B(u_0))p \int_{\Omega} u_0^{p-1} v = \lambda v.$$

What can we say about this eigenvalue problem (non self-adjoint)?

The eigenvalue problem:

Consider $K \leq 0$ and $m \in L^\infty(\Omega)$,

$$(EP) \quad \begin{cases} -\Delta v + m(x)v + \int_{\Omega} K(x,y)v(y)dy = \lambda v & \text{in } \Omega, \\ v = 0 & \text{on } \partial\Omega. \end{cases}$$

Take $R > 0$ large, then this problem is equivalent to

$$-\Delta v + (m(x) + R)v + \int_{\Omega} K(x,y)v(y)dy = (\lambda + R)v.$$

Krein-Rutmann Theorem: Given f , and consider the solution v of the linear integro-differential problem

$$-\Delta v + (m(x) + R)v + \int_{\Omega} K(x, y)v(y)dy = f(x).$$

We can prove:

- 1 For each f , there exists a unique v solution of the linear equation.
- 2 The map $f \mapsto v$ is compact.
- 3 If $f \geq 0$, $f \neq 0$, then $v > 0$.

Then, there exists $\lambda_1 \in \mathbb{R}$ the principal eigenvalue.

Multiplying by v^- , we get

$$\int_{\Omega} |\nabla v^-|^2 + \int_{\Omega} (m(x) + R)(v^-)^2 + \int_{\Omega} \left(\int_{\Omega} K(x, y) v(y) dy \right) v^-(x) dx \leq 0.$$

On the other hand,

$$\begin{aligned} \int_{\Omega} \left(\int_{\Omega} K(x, y) v(y) dy \right) v^-(x) dx &= \\ \int_{\Omega} \left(\int_{\Omega} K(x, y) (v^+ + v^-)(y) dy \right) v^-(x) dx & \\ \geq \int_{\Omega} \left(\int_{\Omega} K(x, y) v^-(y) dy \right) v^-(x) dx. \end{aligned}$$

Thus,

$$\int_{\Omega} \left(\int_{\Omega} K(x, y) v(y) dy \right) v^-(x) dx \geq -C_3 |K|_{\infty} |v^-|_2^2.$$

Combining the above expression, we have

$$\|v^-\|^2 + (m_L + R - C_3 |K|_{\infty}) |v^-|_2^2 \leq \int_{\Omega} f v^- \leq 0.$$

Taking R large, we have that $v^- = 0$, that is, $v \geq 0$.

Now, by the strong maximum principle,

$$-\Delta v + (m(x) + R)v = f(x) - \int_{\Omega} K(x, y) v(y) dy > 0$$

we conclude that $v > 0$.

Theorem

Assume that $m \in L^\infty(\Omega)$ and $K \in L^\infty(\Omega \times \Omega)$, $K \leq 0$, $K \neq 0$. Then, there exists a principal eigenvalue of (EL),

$$\lambda_1 = \lambda_1(m, K),$$

which is real, simple, it has an associated positive eigenfunction and it is the unique eigenvalue of (EL) having an associated eigenfunction without change of sign. Moreover,

- *Any other eigenvalue λ of (EL) satisfies*

$$\lambda_1 < \operatorname{Re}(\lambda).$$

- ① $m \in L^\infty(\Omega) \mapsto \lambda_1$ is continuous and increasing.
- ② $K \in L^\infty_-(\Omega \times \Omega) \mapsto \lambda_1$ is continuous and increasing.
- ③ $\Omega \mapsto \lambda_1^\Omega$ is continuous and decreasing.
- ④ It holds

$$\lambda_1 > 0 \iff \text{Maximum principle,}$$

that is, given $f > 0$ and the solution v of

$$-\Delta v + m(x)v + \int_{\Omega} K(x, y)v(y)dy = f(x),$$

then $v > 0 \iff \lambda_1 > 0$.

- 1 The same result holds if $\|K\|_\infty \in (0, a_0)$, for small a_0 .
- 2 Given $f \geq 0$, $f \neq 0$ there exists $K > 0$ such that the solution v of the linear problem becomes negative in some part of Ω .
OPEN PROBLEM!!!!

This implies:

- Maximum principle does not hold in general.
 - The sub-supersolution method can not applied.
- 3 What happens if $\|K\|_\infty$ large? OPEN PROBLEM!!!!
 - 4 Allegretto-Barabanova (96) showed an example, with homogeneous Neumann boundary conditions, in which for $\|K\|_\infty$ large there are several eigenvalues less than an eigenvalue having a positive eigenfunction associated.

(Freitas-Sweers (94, 97), Allegretto-Barabanova (96)...)

Our first main goal is to study:

$$\begin{cases} u_t - \Delta u = u \left(\lambda - \int_{\Omega \cap B_r(x)} b(y) u^p(y) dy \right) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

where $\lambda \in \mathbb{R}$, $b > 0$ and $p > 0$.

Writing

$$K(x, y) = \chi_{\Omega \cap B_r(x)}(y)b(y) = \begin{cases} b(y) & y \in \Omega \cap B_r(x), \\ 0 & y \notin \Omega \cap B_r(x), \end{cases}$$

then, the equation can be written as

$$(LP) \quad \begin{cases} -\Delta u = u \left(\lambda - \int_{\Omega} K(x, y) u^p(y) dy \right) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

where $K(x, y) \geq 0$, $K \neq 0$, $\lambda \in \mathbb{R}$ and $p > 0$.

Local model

Consider

$$\begin{cases} u_t - \Delta u = u(\lambda - a(x)u^p) & \text{in } \Omega \times (0, \infty), \\ u = 0 & \text{on } \partial\Omega \times (0, \infty), \\ u(x, 0) = u_0(x) & \text{in } \Omega, \end{cases}$$

with $\lambda \in \mathbb{R}$, $p > 0$ and $u_0 > 0$.

Then:

- Case $\underline{a(x) \geq 0}$: There exists a unique positive solution $u(x, t)$ for all $t > 0$.
- Case $\underline{a(x) < 0}$: the unique positive solution $u(x, t)$ blows up in finite time.

Stationary local model

Consider the stationary problem

$$\begin{cases} -\Delta u = u(\lambda - a(x)u^p) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

with $\lambda \in \mathbb{R}$, $\underline{a(x)} > 0$ and $p > 0$.

Then:

- $u \equiv 0$ is solution for all $\lambda \in \mathbb{R}$.
- There exists a positive solution if and only if $\lambda > \lambda_1$.
Moreover, the positive solution is unique, denoted by $u^* > 0$.

Furthermore, it is globally stable, that is,

- 1 If $\lambda < \lambda_1$ we have that $u(x, t) \rightarrow 0$ as $t \rightarrow \infty$,
- 2 If $\lambda > \lambda_1$ we have that $u(x, t) \rightarrow u^*(x)$ as $t \rightarrow \infty$.

A Remark

Consequence (with respect to the spatial dependence): fixed a growth rate of the species, the species coexist if the domain Ω is large, and goes to the extinction if Ω is small.

Larger islands should be easier to find and colonize, and they should support larger populations which are less susceptible to extinction.

Problem: calculate λ_1 .

- 1 When $\Omega = (0, L)$, then $\lambda_1 = (\pi/L)^2$;
- 2 When $\Omega = B(0, R)$, then $\lambda_1 = \mu_1/R^2$, where μ_1 is the eigenvalue of $B(0, 1)$.

For other domains..... only estimates and numerical approximations.

Stationary local model

$$\begin{cases} -\Delta u = u(\lambda - a(x)u^p) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

with $\lambda \in \mathbb{R}$, $p > 0$, $\underline{a(x)} \geq 0$ and $\Omega_0 = \text{int}\{x \in \Omega : a(x) = 0\} \neq \emptyset$.

Then:

- $u \equiv 0$ is solution for all $\lambda \in \mathbb{R}$.
- There exists a positive solution if and only if $\lambda_1 < \lambda < \lambda_1^{\Omega_0}$.
Moreover, the positive solution is unique, denoted by $u^* > 0$.

Furthermore, it is globally stable, that is,

- 1 If $\lambda < \lambda_1$ we have that $u(x, t) \rightarrow 0$ as $t \rightarrow \infty$,
- 2 If $\lambda_1 < \lambda < \lambda_1^{\Omega_0}$ we have that $u(x, t) \rightarrow u^*(x)$ as $t \rightarrow \infty$.
- 3 If $\lambda > \lambda_1^{\Omega_0}$ we have that $u(x, t) \rightarrow \infty$ as $t \rightarrow \infty$.

Stationary local model: $a(x) < 0$

$$\begin{cases} -\Delta u = u(\lambda - a(x)u^p) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

Then:

- 1 $u \equiv 0$ is solution for all $\lambda \in \mathbb{R}$.
- 2 If there exists a positive solution, then $\lambda < \lambda_1$.
- 3 Assume $p < 4/(N-2)$, then if $\lambda < \lambda_1$ there exists positive solution. Moreover, it is unstable (multiplicity!!!)
- 4 If $p \geq 4/(N-2)$, non-existence of positive classical solution.

For general $K(x, y) \geq 0$, consider

$$(LP) \quad \begin{cases} -\Delta u = u \left(\lambda - \int_{\Omega} K(x, y) u^p(y) dy \right) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

where $\lambda \in \mathbb{R}$ and $p > 0$.

General results:

- 1 $(\lambda_1, 0)$ is a bifurcation point from the trivial solution.
- 2 There exists an unbounded continuum \mathcal{C} of positive solutions emanating from $(\lambda_1, 0)$.
- 3 There does not exist positive solution for $\lambda \leq \lambda_1$.
- 4 For any $\Lambda > 0$, there exists $r > 0$ such that: if $(\lambda, \mathbf{u}) \in \mathcal{C}$ and $\lambda \leq \Lambda$, we should have $\|\mathbf{u}\| \leq r??$

Previous results for K general and $N = 1$:

1

$$K(x, x) \geq K_0 > 0 \text{ for all } x \in \Omega,$$

see Leman, Méléard and Mirrahimi (2014).

2

$K(x, y) = K_1(|x - y|)$, where $K_1 : [0, 2] \mapsto (0, \infty)$ is a nondecreasing and piecewise continuous map with

$$\int_0^2 K_1(y) dy > 0.$$

see Sun, Shi and Wang (2013).

then, a priori bounds.

Previous results for K general and $N > 1$:

- 1 $K(x, y) \geq K_0 > 0$, see Coville (2014), Leman, Méléard and Mirrahimi (2014).
- 2 $K(x, y) = K_\delta(|x - y|)$ is a mollifier in \mathbb{R}^N , i. e.,
 $K_\delta(|x - y|) \in C_0^\infty$, $\int_{\mathbb{R}^N} K_\delta(|x - y|) dy = 1$ for any x with

$$K_\delta(|x - y|) = 0 \text{ if } |x - y| \geq \delta$$

and

$$K_\delta(|x - y|) \text{ bounded away from zero is } |x - y| < \mu < \delta,$$

Allegretto and Nistri (97).

then, a priori bounds.

Let $x_M \in \Omega$ such that $\|u\|_\infty = u(x_M)$, then

$$K_0 \int_{\Omega} u^p \leq \int_{\Omega} K(x_M, y) u^p(y) \leq \lambda.$$

On the other hand, (Gilbarg, Trudinger, 1983), if $u \in W^{1,2}(\Omega)$ such that $Lu \leq f(x)$, then for any $B_{2R}(y) \subset \Omega$ and $\beta > 1$,

$$\sup_{B_R(y)} u \leq C(\|u^+\|_{\beta, B_{2R}(y)} + \|f\|_q), \quad \beta > 1, q > N/2.$$

Hence,

$$\|u\|_\infty \leq C \left(\int_B u^\beta \right)^{1/\beta} \leq C \|u\|_\infty^{(\beta-p)/\beta} \left(\int_B u^p \right)^{1/\beta},$$

and then

$$\|u\|_\infty \leq C.$$

We introduce the class \mathcal{K} , which is formed by functions $K : \Omega \times \Omega \rightarrow \mathbb{R}$ verifying:

- i) $K \in L^\infty(\Omega \times \Omega)$ and $K(x, y) \geq 0$ for all $x, y \in \Omega$
- ii) If w is measurable and

$$\int_{\Omega \times \Omega} K(x, y) |w(y)|^p w(x)^2 dx dy = 0,$$

then $w = 0$ a.e in Ω .

Theorem

Suppose that $K \in \mathcal{K}$. Then problem (P) has a positive solution if, and only if, $\lambda > \lambda_1$.

(C. Alves, M. Delgado, M. A. Souto, A. Suárez, 2015)

Arguing by contradiction, assume that there exist a sequence of solutions (λ_n, u_n) such that

$$\|u_n\| \rightarrow \infty \quad \text{and} \quad \lambda_n \rightarrow \lambda^*.$$

Considering $w_n = u_n / \|u_n\|$, it follows that

$$\int_{\Omega} \nabla w_n \cdot \nabla v dx + \int_{\Omega} \phi_{u_n} w_n v dx = \lambda_n \int_{\Omega} w_n v dx, \quad \forall v \in H_0^1(\Omega),$$

where

$$\phi_w(x) := \int_{\Omega} K(x, y) |w(y)|^p dy.$$

Hence (w_n) is bounded in $H_0^1(\Omega)$, and there is $w \in H_0^1(\Omega)$ verifying

$$\begin{aligned} w_n &\rightharpoonup w \text{ in } H_0^1(\Omega), \\ w_n &\rightarrow w \text{ in } L^2(\Omega) \text{ and} \\ w_n(x) &\rightarrow w(x) \text{ a.e. in } \Omega. \end{aligned}$$

Taking $v = \frac{u_n}{||u_n||^{p+1}}$ as a test function, we obtain

$$\frac{1}{||u_n||^p} + \int_{\Omega} \phi_{w_n} w_n^2 dx = \frac{\lambda_n}{||u_n||^p} \int_{\Omega} w_n^2 dx, \quad \forall n.$$

Passing to the limit in the above equality, we derive

$$\lim_n \int_{\Omega} \phi_{w_n} w_n^2 dx = 0.$$

From Fatou Lemma

$$\int_{\Omega} \phi_w w^2 dx \leq \lim_n \int_{\Omega} \phi_{w_n} w_n^2 dx = 0,$$

and so,

$$\int_{\Omega \times \Omega} K(x, y) |w(y)|^p |w(x)|^2 dx dy = 0.$$

Since $K \in \mathcal{K}$, we should have $w \equiv 0$.

Thereby, (w_n) converges to 0 in $L^2(\Omega)$. Taking $v = w_n$ as test function, we see that

$$\int_{\Omega} |\nabla w_n|^2 dx + \int_{\Omega} \phi_{u_n} w_n^2 dx = \lambda_n \int_{\Omega} w_n^2 dx.$$

Since (λ_n) is bounded from above by Λ and $\int_{\Omega} \phi_{u_n} w_n^2 dx \geq 0$, we have

$$\int_{\Omega} |\nabla w_n|^2 dx \leq \Lambda \int_{\Omega} w_n^2 dx.$$

Taking the limit, we conclude that $\|w_n\| \rightarrow 0$, which is an absurd, because $\|w_n\| = 1$ for all n , proving the claim.

Since (u_n) is bounded in $H_0^1(\Omega)$, iterations arguments imply that (u_n) is bounded in $L^\infty(\Omega)$, and the proof is done.

Remark:

If kernel K does not belong to \mathcal{K} , then there exists a measurable function $w : \Omega \rightarrow \mathbb{R}$ such that

$$\int_{\Omega \times \Omega} K(x, y) |w(y)|^p w(x)^2 dx dy = 0 \quad \text{but} \quad w \neq 0.$$

Thus, there exists $a > 0$ such that $A = \{x \in \Omega : |w(x)| \geq a\}$ has positive measure.

Observe that

$$a^{p+2} \int_{A \times A} K(x, y) dx dy \leq \int_{\Omega \times \Omega} K(x, y) |w(y)|^p w(x)^2 dx dy = 0,$$

i.e, $K = 0$ a.e. in $A \times A$.

If K belongs to a class \mathcal{K}' , which is formed by functions K verifying the following condition:

There exists a connected open set U such that

$$K(x, y) > 0, \text{ such that } x \notin U \text{ and } |x - y| < r.$$

Theorem

Suppose that $K \in \mathcal{K}'$. Then, for any $\lambda_1 < \lambda < \lambda_1^U$, problem (P) has a positive solution.

As a by product, we have the following corollary

Corollary

*Suppose that $K \in \mathcal{K}'$ and $K(x, y) = 0$ in U for any $y \in \Omega$.
Suppose that ∂U is C^1 . For any $\lambda_1 < \lambda < \lambda_1(U)$, there exists a positive solution u for the problem (P). Moreover, (P) does not have any positive solution for $\lambda \geq \lambda_1(U)$.*

We finish with two examples in $N = 1$, $\Omega = (0, \pi)$, in which K vanishes in the diagonal and there exists positive solution for all $\lambda > 1$. Consider

$$K(x, y) = \begin{cases} 1 & \text{if } (x, y) \in (0, \pi/2) \times (\pi/2, \pi) \cup (\pi/2, \pi) \times (0, \pi/2), \\ 0 & \text{in other cases.} \end{cases}$$

Observe that

$$A = \int_{\pi/2}^{\pi} \sin^p(y) dy = \int_0^{\pi/2} \sin^p(y) dy,$$

and then a solution for (LP) is

$$u(x) = \left(\frac{\lambda - 1}{A} \right)^{1/p} \sin(x).$$

Consider

$$K(x, y) = \begin{cases} 1 & \text{if } y > a_0, \\ 0 & \text{in other cases.} \end{cases}$$

Observe that

$$A = \int_{a_0}^{\pi} \sin^p(y) dy,$$

and then a solution for (LP) is

$$u(x) = \left(\frac{\lambda - 1}{A} \right)^{1/p} \sin(x).$$

Stability and uniqueness results:

- 1 Assume $K(x, y) > 0$. If $\lambda < \lambda_1$, then $u(x, t) \rightarrow 0$ as $t \rightarrow \infty$.
- 2 Assume $K(x, y) = b(y) > 0$, $p = 1$, then $u(x, t) \rightarrow u^*$ as $t \rightarrow \infty$, u^* is the unique positive solution of (LP), (see Coville (2014), Leman, Méléard and Mirrahimi (2014)).
- 3 Assume $K(x, y) = K(y, x) > 0$, $p = 2$, then $u(x, t) \rightarrow u^*$ as $t \rightarrow \infty$, u^* is the unique positive solution of (LP).
- 4 In any case, OPEN PROBLEM: UNIQUENESS AND STABILITY?????

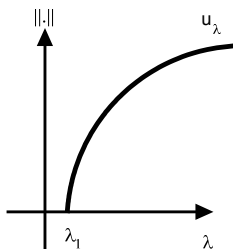
Assume that K is variable separable, $K(x, y) = a(x)b(y)$, $b > 0$, and consider

$$\begin{cases} -\Delta u = u \left(\lambda - a(x) \int_{\Omega} b(y) u^p \right) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

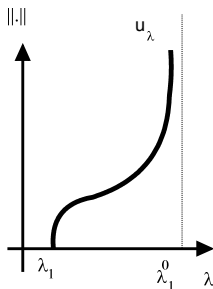
- 1 If $a > 0$. There exists a positive solution if and only if $\lambda > \lambda_1$. Moreover, the positive solution is unique.
- 2 If $a \geq 0$, $a \neq 0$, $a = 0$ in $\Omega_0 \subset \Omega$. There exists a positive solution if and only if $\lambda \in (\lambda_1, \lambda_1^0)$. Moreover, the positive solution is unique.
- 3 If $a < 0$. There exists a positive solution if and only if $\lambda < \lambda_1$. Moreover, the positive solution is unique and unstable.

REMARK: we don't need to impose any condition on the size of $p!!!$

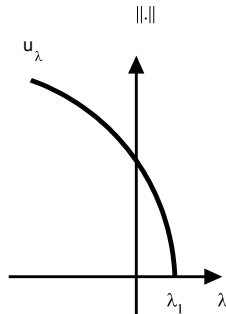
Population dynamics and non-local terms



Case 1



Case 2



Case 3

Eigenvalue method:

Assume that $a > 0$. Then, consider

$$\lambda_1(t) := \lambda_1(-\Delta + a(x)t).$$

Then, $\lambda_1(0) = \lambda_1$, is an increasing function and $\lambda_1(t) \rightarrow +\infty$ as $t \rightarrow \infty$.

Take $\lambda > \lambda_1$, there exists a unique $t_0 > 0$ such that

$$\lambda = \lambda_1(t_0).$$

Then, $u = K_0 \varphi_0$ is a solution (and the unique) of the problem, where φ_0 is a positive eigenfunction associated to $\lambda_1(t_0)$ and

$$K_0 = \left(\int_{\Omega} b(y) \varphi_0(y) dy \right)^{1/(p-1)}.$$

Comments:

1. *The non-local logistic equation with non-linear diffusion:*

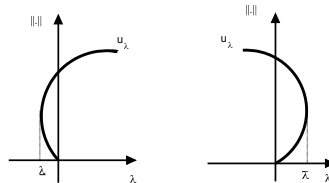
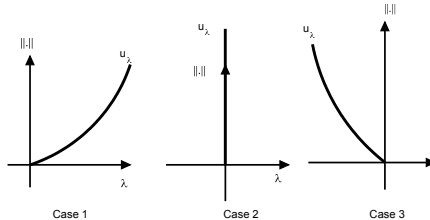
$$\begin{cases} -\Delta u^m = u \left(\lambda - a(x) \int_{\Omega} u^p \right) & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases}$$

with

$$1 < m, \quad p > 0,$$

works with F. J. Correa and M. Delgado.

The non-local logistic equation with non-linear diffusion:



Case 4

Case 5

Comments::

2. *Non-local boundary conditions:*

$$\begin{cases} -\Delta u = \lambda u - u^p & \text{in } \Omega, \\ \mathcal{B}u = \int_{\Omega} K(x)u(x)dx & \text{on } \partial\Omega, \end{cases} \quad (6)$$

where $\lambda \in \mathbb{R}$, $p > 1$, $K \in C(\overline{\Omega})$, $K \geq 0$, $K \neq 0$.

Comments:

3. In the local case,

$$-\Delta u = \lambda u^\beta + u^p$$

it is well known that we have a priori bounds (and so existence of positive solution for $\lambda < \lambda_1$) if for instance $\beta = 1$ and

$$1 < p < \frac{N+2}{N-2};$$

and no existence of solution for $p \geq (N+2)/(N-2)$.

However, in the non-local case

$$-\Delta u = \lambda u^\beta + \int_{\Omega} u^p$$

we have obtained a priori-bounds (Correa & Suárez (2012)) if:

- $\beta = 1$ and for all $p > 1$; or,
- $1 < \beta < \frac{N+2}{N-2}$ and for all $p > 0$; or
- $\beta \geq \frac{N+2}{N-2}$ and $p > (N/2)(\beta - 1)$.

Cancer stems models

Cancer has been characterized as a collection (complex) of diseases described by uncontrolled growth of cells and development of a tumor that invades the tissue of origin and distant organs.

Once a cancer cell has successfully developed, will it inevitably form a frank tumor?.

Furthermore, it is increasingly argued that only a small subset of cancer cells is intrinsically able to initiate and repopulate the tumor.

Table 1

Diverse markers have been used for the identification of cancer stem cells in solid tumors.

Tumor entity	Markers	Citation
Breast cancer	CD44 ⁺ CD24 ^{-/low} CD133 ⁺ CD133 ⁺ CXCR4 ⁺ ALDH-1 ⁺ CD49F ⁺ DLL1 ^{high} DNER ^{high}	Al-Hajj et al. (2003) Wright et al. (2008) Hwang-Versluis et al. (2009) Ginestier et al. (2007) Pece et al.
Glioblastoma	CD133 ⁺ SSEA-1 ⁺	Singh et al. (2004) Son et al. (2009)
Prostate cancer	CD44 ⁺ alpha2beta1 ^{high} CD133 ⁺ CD133 ⁺ CXCR4 ⁺	Collins et al. (2005) Miki et al. (2007)
Melanoma	CD20 ⁺ ABC85 ⁺	Fang et al. (2005) Schatten et al. (2008)
Lung cancer	Sca-1 ⁺ , CD45 ⁻ , PECAM ⁻ , CD34 ⁺ CD133 ⁺ CXCR4 ⁺	Kim et al. (2005) Bertolini et al. (2009)
Colon cancer	CD133 ⁺ EpCAM ⁺ CD44 ⁺ CD166 ⁺	O'Brien et al. (2007), Ricci-Vitiani et al. (2007) Dalerba et al. (2007)
Pancreatic cancer	EpCAM ⁺ CD44 ⁺ CD24 ⁺ CD133 ⁺ CD133 ⁺ CXCR4 ⁺ ALDH-1 ⁺	Li et al. (2007) Hermann et al. (2007) Hermann et al. (2007) Feldmann et al. (2007), Jimeno et al. (2009), Rasheed et al.
Head and neck cancer	CD44 ⁺ BMI-1	Prince et al. (2007)
Liver cancer	CD133 ⁺ CD90 ⁺	Ma et al. (2007) Yang et al. (2008)

Cancer stem cells in solid tumors.

Tumor type	Cells expressing CSC marker (%)	Minimal number of cells expressing marker for tumor formation	Calculated cancer stem cell ratio
Breast	11–35	200	1.1×10^{-3}
	ND	2000	
	3–10	500	
Brain	19–29	100	3.3×10^{-4}
	6–21	100	
Colon	1.8–25	200	5.4×10^{-4}
	0.7–6	3000	
	0.03–38	200	
Head and neck	0.1–42	5000	4.2×10^{-5}
Pancreas	0.2–0.8	100	3.5×10^{-5}
	1–3	500	
Lung	0.32–22	10,000	1.1×10^{-4}
Liver	0.03–6	5000	6×10^{-6}

Distinct properties of these so-called cancer stem cells (CSCs) are:

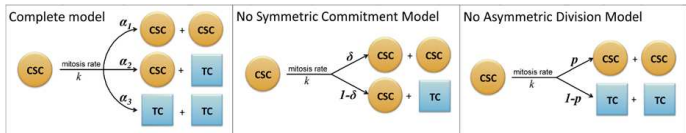
- longevity or even immortality,
- self-renewal,
- unlimited proliferation and
- the ability to produce more such cancer stem cells as well as non-stem cancer cells (or tumor cells, TCs).

Cancer stems models

In Hillen, Enderling and Hahnfeldt (2013), a mathematical model of a heterogeneous population of CSCs and TCs is proposed to investigate the “tumor growth paradox”:

“an increasing rate of spontaneous cell death in TC shortens the waiting time for CSC proliferation and migration, and thus facilitates tumor progression”.

Cancer stems models



Cancer stems models

- 1 CSCs are immortal (rate of cell death 0) and have an infinite proliferation capacity. A CSC can give rise to one CSC and one TC (asymmetric division).
- 2 TC proliferation always results in two TCs, and TCs have a positive probability of cell death reflecting exhaustion of proliferation potential as well as spontaneous death due to genomic instability ($\alpha > 0$).

Non-local models of Stem Cells and Cancer

$$\begin{cases} u_t = D_1 \Delta u + \delta \gamma \int_{\Omega} K(x, y, p(x, t)) u(y, t) dy \\ v_t = D_2 \Delta v - \alpha v + \rho \int_{\Omega} K(x, y, p(x, t)) v(y, t) dy \\ \quad + (1 - \delta) \gamma \int_{\Omega} K(x, y, p(x, t)) u(y, t) dy, \end{cases}$$

where u , v denote cancer stem cells (CSCs) and nonstem tumor cells (TCs), and $p = u + v$.

- 1 The number of cell cycle times per unit time of CSCs and TCs are denoted by $\gamma > 0$ and $\rho > 0$, respectively.
- 2 The parameter δ with $0 \leq \delta \leq 1$ denotes the fraction of CSC divisions that are symmetric, and $\alpha > 0$ denotes the TC death rate.
- 3 Cell motility for CSCs and TCs is described by diffusion with coefficients $D_u, D_v > 0$

- The spatial distribution kernel $K(x, y, p)$ describes the rate of progeny contribution to location x from a cell at location y , per “cell cycle time”.
- K is decreasing in p .

Previous works

- Hillen, Enderling and Hahnfeldt (2013).
- Forsi, Fasano, Primicerio, Hillen (2016).
- Fasano, Mancini, Primicerio (2016).
- Maddalena (2014).

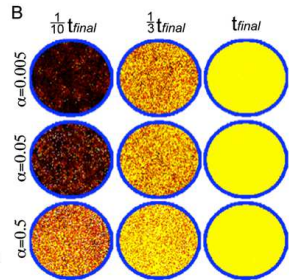
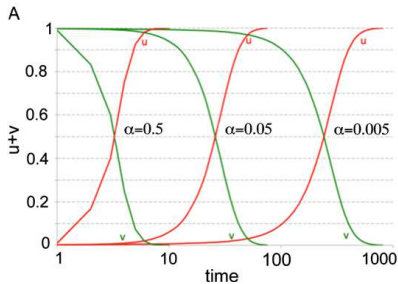
In Hillen, Enderling and Hahnfeldt (2013), they assume:

- 1 The species do not diffuse ($D_u = D_v = 0$).
- 2 The kernel

$$K(x, y, p) = K(p) = (1 - p^\sigma)_+, \quad \sigma \geq 1.$$

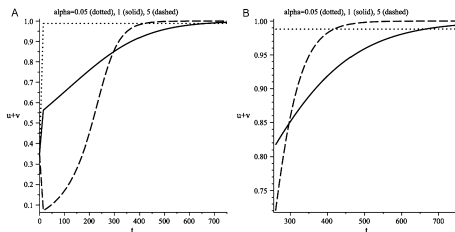
and prove:

- 1 If $\alpha/\rho > K(0)$, the steady states are $(0, 0)$ and $(1, 0)$.
- 2 If $\alpha/\rho < K(0)$, the steady states are $(0, 0)$, $(0, v_0)$ and $(1, 0)$.
- 3 In both cases, $(0, 0)$ and $(0, v_0)$ are unstable, and $(1, 0)$ is globally stable.



They compare different sizes of the tumor changing α , and they show that the tumor increases as α increases: these results confirm the observations of the tumor growth paradox.

Conclusion: *Successful therapy must eradicate cancer stem cells.*



Non-local models of Stem Cells and Cancer

Assume that

$$K(x, y, p) = K(x, y)g(p),$$

where g is a positive and decreasing function, for instance,

$$g(p) = (A(x) - p^r)^+,$$

and the system is

$$(S) \quad \begin{cases} -D_1 \Delta u = \delta \gamma g(p(x)) \int_{\Omega} K(x, y) u(y, t) dy \\ -D_2 \Delta v = -\alpha v + \rho g(p(x)) \int_{\Omega} K(x, y) v(y, t) dy \\ \quad + (1 - \delta) \gamma g(p(x)) \int_{\Omega} K(x, y) u(y, t) dy, \end{cases}$$

Non-local models of Stem Cells and Cancer

We have three kinds of solutions:

- 1 The trivial solution $(u, v) = (0, 0)$.
- 2 The semi-trivial solutions $(u, v) = (0, v^*)$ or $(u, v) = (u^*, 0)$.
- 3 The coexistence states (u, v) , with $u > 0$ and $v > 0$.

Non-local models of Stem Cells and Cancer

To study the semi-trivial solutions, we have to analyse the following nonlocal logistic equation:

$$\begin{cases} -d\Delta u = \sigma g(u) \int_{\Omega} K(x, y) u(y) dy & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega, \end{cases} \quad (7)$$

where $K \in C(\overline{\Omega} \times \overline{\Omega})$ is a non-negative and non-identically zero function and

$$g(u) := (A(x) - u^p)^+,$$

with $p \geq 1$, $d > 0$, $\sigma > 0$ and $A \in C(\overline{\Omega})$, with $A^+ \neq 0$.

Non-local models of Stem Cells and Cancer

Theorem

There exists a positive solution if and only if $\sigma > \sigma_1$. If the positive solution exists, this is unique.

In this result, σ_1 is the principal eigenvalue of

$$\begin{cases} -d\Delta u = \sigma A^+(x) \int_{\Omega} K(x,y) u(y) dy & \text{in } \Omega, \\ u = 0 & \text{on } \partial\Omega. \end{cases} \quad (8)$$

Non-local models of Stem Cells and Cancer

With respect to the system, there exist:

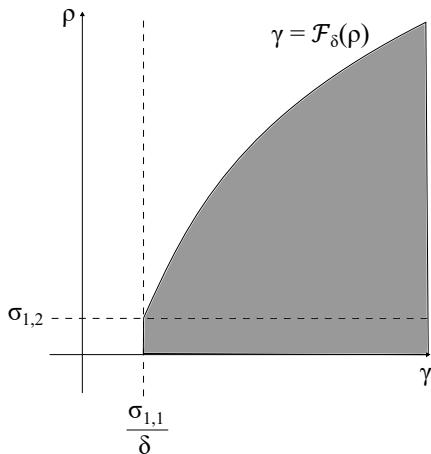
- 1 The trivial solution $(u, v) = (0, 0)$ for all values of the parameter.
- 2 The semi-trivial solution $(u, v) = (0, v^*)$ exists if $\rho > \sigma_{1,2}$.
- 3 The semi-trivial solution $(u, v) = (u^*, 0)$ exists if $\gamma > \sigma_{1,1}$ if $\delta = 1$ and not exist if $\delta \neq 1$.

Case $\delta \neq 1$:

- 1 The trivial solution $(u, v) = (0, 0)$ for all values of the parameter.
- 2 The semi-trivial solution $(u, v) = (0, v^*)$ exists if $\rho > \sigma_{1,2}$.
- 3 The semi-trivial solution $(u, v) = (u^*, 0)$ does not exist.
- 4 If $\gamma \leq \sigma_{1,1}/\delta$, then (S) does not have coexistence states.
- 5 There exists a curve $\mathcal{F}_\delta(\rho)$ such that there exists at least a coexistence state if

$$\gamma > \mathcal{F}_\delta(\rho) \quad \text{and} \quad \rho > 0.$$

Cancer stems models



Coexistence region for $\delta \neq 1$.

Cancer stems models

Conclusions:

Fixed the growth rate of CSCs and TC, then:

- 1 **If we attack the TC, then the size of the tumour does not go to zero, the tumor persists...and both populations coexist.**
- 2 However, if δ is small, the unique that persists is TC.

Case $\delta \neq 1$:

- 1 The trivial solution $(u, v) = (0, 0)$ for all values of the parameter.
- 2 The semi-trivial solution $(u, v) = (0, v^*)$ exists if $\rho > \sigma_{1,2}$.
- 3 The semi-trivial solution $(u, v) = (u^*, 0)$ exist if $\gamma > \sigma_{1,1}$.
- 4 If $\gamma < \sigma_{1,1}$ or $\rho < \sigma_{1,2}$, (S) does not have coexistence states.
- 5 If $\gamma > \sigma_{1,1}$ and $\rho > \sigma_{1,2}$, there exist two curves $\mathcal{F}_1(\rho)$ and $\mathcal{G}(\gamma)$ such that there exists at least a coexistence state if

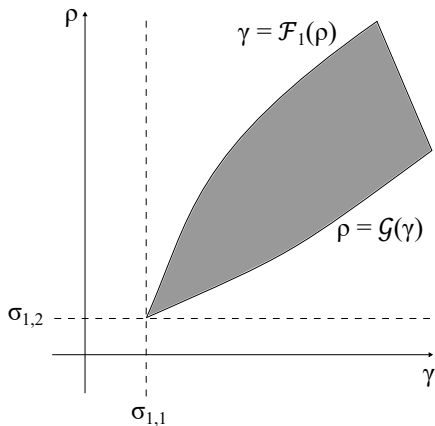
$$(\gamma - \mathcal{F}_1(\rho)) \cdot (\rho - \mathcal{G}(\gamma)) > 0.$$

Theorem

Assume that $\gamma > \sigma_{1,1}$ and $\rho > \sigma_{1,2}$, then the following claims are verified:

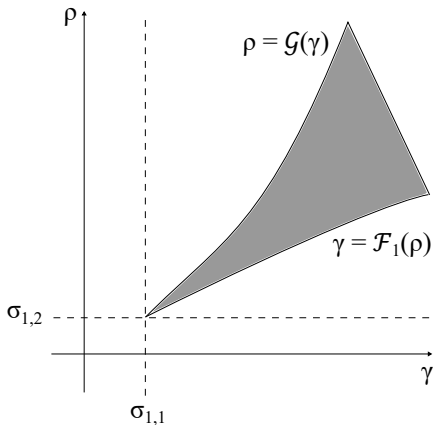
- (i) $i_W(H(1, \cdot, \cdot), N) = 1$;
- (ii) $i_W(H(1, \cdot, \cdot), (0, 0)) = 0$;
- (iii) $i_W(H(1, \cdot, \cdot), (0, v^*)) = 0$, if $\gamma > \mathcal{F}_1(\rho)$;
- (iv) $i_W(H(1, \cdot, \cdot), (0, v^*)) = 1$, if $\gamma < \mathcal{F}_1(\rho)$;
- (v) $i_W(H(1, \cdot, \cdot), (u^*, 0)) = 0$, if $\rho > \mathcal{G}(\gamma)$;
- (vi) $i_W(H(1, \cdot, \cdot), (u^*, 0)) = 1$, if $\rho < \mathcal{G}(\gamma)$.

Cancer stems models



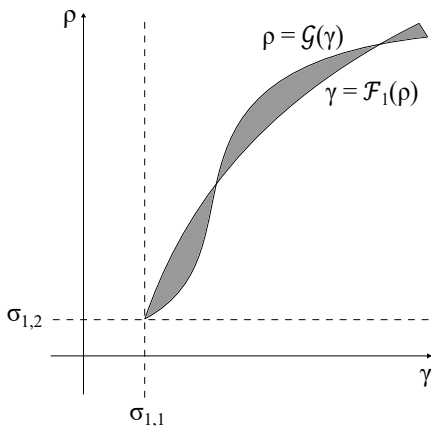
Coexistence region for $\delta = 1$.

Cancer stems models



Coexistence region for $\delta = 1$.

Cancer stems models



Coexistence region for $\delta = 1$.

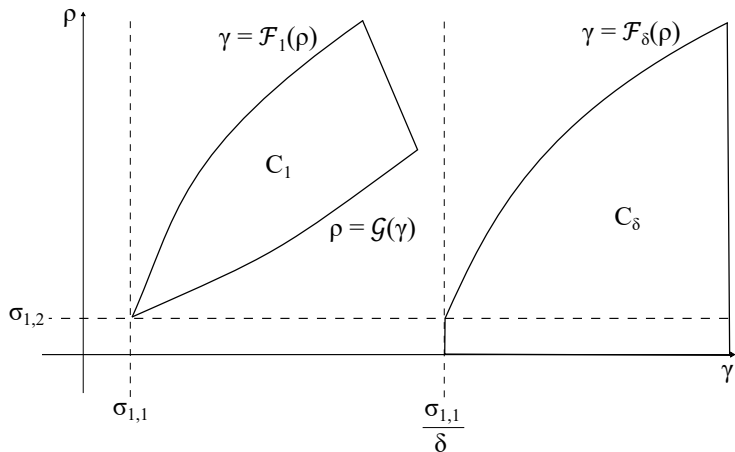
Cancer stems models

Conclusions (recall $\delta = 1$):

Fixed the growth rate of CSCs and TC, then:

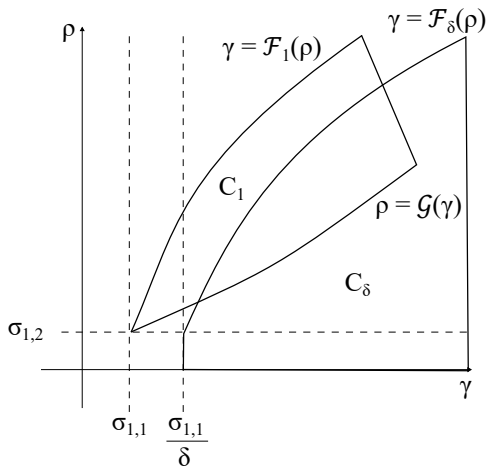
- ❶ If we attack the TC, then the size of the tumour does not go to zero, the tumor persists...but the CSCs drives to TC to extinction.

Cancer stems models



Comparison coexistence regions for δ small.

Cancer stems models



Comparison coexistence regions for δ close 1.