Convergence to Equilibria in mutation selection model

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Experiment realised by Frederic Fabre, Josselin Montarry, Vincent Simon and Benoit Moury (INRA, UR407 Pathologie Végétale)

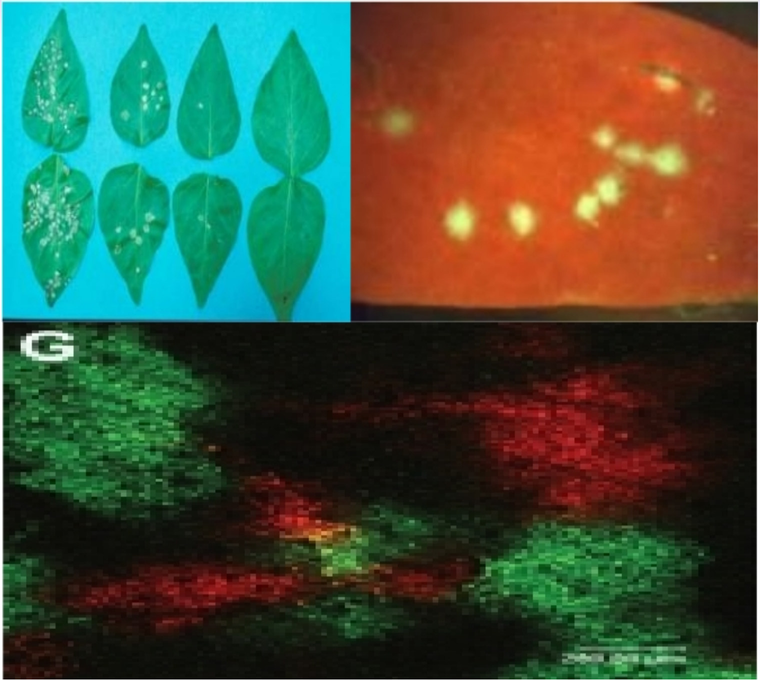
Host Plant : Pepper (*capsicum annuum*)

1. **Virus** : Potato Virus Y (PVY)–Potyviridae –ARNss(+)

2. **4 PYV Variant** (DH, NH, DN, NN) differing only by 1 or 2 substitutions involving their **pathogenicity properties**

	AA Position in the VPg gene	
	119	121
NN	N	N
NH	N	H
DN	D	N
DH	D	H

3. **Analysis of the within-host population dynamics** of these 4 variants in a susceptible host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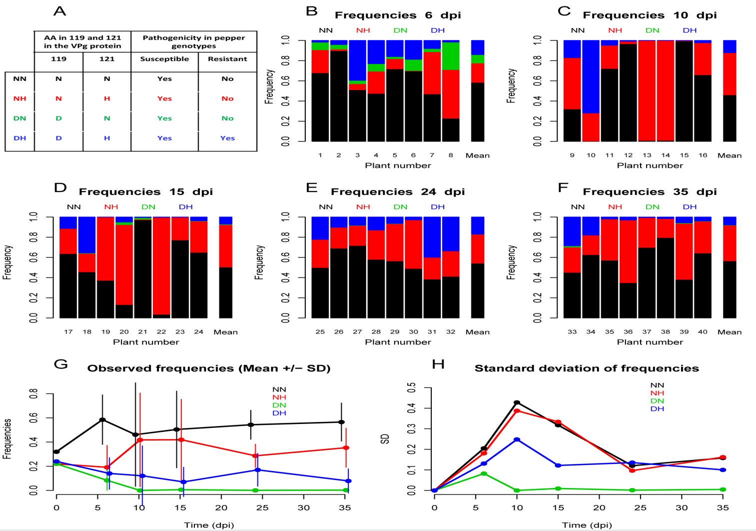
Experimentation protocol and Data set

Presentation of the experiment and the data

- **Protocol :** 5 rows of 8 plants inoculated at the same time and 5 sampling date



	AA in 119 and 121 in the VPg protein		Pathogenicity in pepper genotypes	
	119	121	Susceptible	Resistant
NN	N	N	Yes	No
NH	N	H	Yes	No
DN	D	N	Yes	No
DH	D	H	Yes	Yes

The best model which fit the Data is a Lotka-Volterra system with mutation (Fabre,C et al. 12)

$$\frac{dv_i}{dt} = r_i v_i \left(1 - \frac{1}{K}(1 + \sum_{j\neq i, j=1}^{4} \frac{r_j}{r_i} v_j)\right) + \sum_{j=1}^{4} \mu_{ij}(v_j - v_i)$$

Assumption on the Problems and Questions

1. The reproduction rate is very high for virus and it is admitted that mutation occurs in small quantity
2. What is the dynamics of

$$\frac{dv_i}{dt} = v_i \left(r_i - \frac{1}{K} \sum_{j=1}^{4} r_j v_j\right) + \sum_{j=1}^{4} \mu_{ij}(v_j - v_i)$$

3. Numerics suggest that the (v_i) converges to a steady states which is independent of the initial data
4. **How to prove that v converges to a unique steady state ?**
5. **How fast it converge to the equilibria ?**
6. **How is affected the dynamics for a small perturbation of the competition ?**

Similar question can be address for the Mutation-Selection Model

The mutation-selection model

$$\frac{\partial u}{\partial t} = u\left(r(x) - \int_\Omega \mathcal{K}(x,x')u(x')\,dx'\right) + \mathcal{M}[u] \quad \text{in} \quad \mathbb{R}^+ \times \Omega \tag{1}$$

$$u(x,0) = u_0(x) \tag{2}$$

where $\Omega \subset \mathbb{R}^d$ is bounded, $\mathcal{M}$ is a diffusion operator and for each x, $\mathcal{K} : \Omega^2 \to \mathbb{R}$ is locally Lipschitz, non negative.

Biological interpretation

- $u(x,t)$ is a density of population structured by a phenotypical trait
- $\mathcal{M}$ is a modelling the process of mutation
- $(r(x) - \Psi(x,u))$ nonlocal Logistic control of the population

Connection with the Lotka-Volterra Equation with mutation

Nice Observation of Champagnat :

$$\frac{\partial u}{\partial t} = u\left(r(x) - \int_{\Omega} k(x,y)u(y)\,dy\right) + \int_{\Omega} m(x,y)(u(y,t) - u(x,t))\,dy \quad \text{in} \quad \mathbb{R}^+ \times \Omega \tag{3}$$

$$u(x,0) = u_0(x) \tag{4}$$

Plugg $v(t) = \sum_{i=1}^{N} v_i(t)\delta_{x_i}$ and set $r_i = r(x_i), k_{ij} = k(x_i, x_j)$ and $\mu_{ij} = m(x_i, x_j)$ then

$$\frac{dv_i}{dt} = v_i(r(x_i) - \sum_{j=1}^{N} k_{ij} v_i) + \sum_{j=1}^{N} \mu_{ij}(v_j - v_i) \quad \text{in} \quad \mathbb{R}^+ \tag{5}$$

$$v_i(0) = v_0(x_i) \tag{6}$$

Statement

The mutation-selection model

$$\frac{\partial u}{\partial t} = u(r(x) - \Psi(x,u)) + \mathcal{M}[u] \quad \text{in} \quad \mathbb{R}^+ \times \Omega \tag{7}$$

$$u(x,0) = u_0(x) \tag{8}$$

where $\Omega \subset \mathbb{R}^d$ is bounded, $\mathcal{M}$ is a diffusion operator, $r \geq 0$ and for each x, $\Psi(x,\cdot) : \mathcal{L}^p(\Omega) \to \mathbb{R}$ is locally Lipschitz, monotone increasing, $\Psi(x,0) = 0$.

Assumption

$\exists R > 0, k \geq 1, c_0 > 0$ so that $\forall x \in \Omega, \forall\, v \in \{f \in L^p(\Omega) \,|\, f \geq 0, \|f\|_p > R\}$,

$$c_0 \left(\int_\Omega f(y)\, dy\right)^k \leq \Psi(x,f).$$

Example

- $\Psi(x,u) = \int_\Omega \mathcal{K}(x,y,u(y))\, dy$ with $k \in C^{0,1}(\Omega^2 \times \mathbb{R})$, $k(x,y,0) = 0$ for all x, y and for all $s \geq 0$ $k(x,y,s) \geq 0$ and is increasing with respect to s.

Known Results

Pure Competition $\mathcal{M} \equiv 0$

- For the ODE System

$$\frac{dv}{dt} = Rv - \Psi(v)v$$

  Crow (1970), Akin (1979), Hadeler (1981),Hirsch (1982,1985,1988), Hofbauer (1987), Burger (90,2000), Champagnat (2010), Diekmann (2005), Jabin-Raoul (2011), Li (1999), Perthame (2007).

  - *Existence of global solution, steady states , stability, global asymptotic . . ..*

- For the PDE Equation :

$$\frac{\partial u}{\partial t} = u(r(x) - \Psi(x,u)) \quad \text{in} \quad \mathbb{R}^+ \times \Omega$$

  Barles (2008) , Calsina (2005,07.09), Canizo-Carrillo (2007), Champagnat (2011,2012), Arnold-Desvillettes (2003,2008), Diekmann 2005, Mishler-Perthame (2007), Jabin-Raoul (2011), Mirahimi (2011,2012), Prevost (2004).

  - *Existence of global solution, steady states , local stability, some asymptotic behaviour*
  - *Blow-up solution .*

Competition with mutation

- For the ODE System

$$\frac{dv}{dt} = (R + \epsilon M)v - \Psi(v)v$$

  - *For particular interaction functions Ψ or for small ϵ : Existence of steady states, local/global stability are investigated Crow (1970), Hadeler (1981), Hofbauer (1985), Bates-Chen (2011), Eigen (90'), Burger (1994), Calsina (2005), Calsina (2007),. . .*

- For the PDE

$$\frac{\partial u}{\partial t} = u(r(x) - \Psi(x,u)) + \epsilon\mathcal{M}[u] \quad \text{in} \quad \mathbb{R}^+ \times \Omega$$

  - *Barles (2008) , Calsina-Cuadrado (2005,07.09), Canizo-Carrillo (2007), Champagnat (2011,2012), Arnold-Desvillettes (2003,2008), Diekmann 2005, Mishler-Perthame (2007), Jabin-Raoul (2011), Mirahimi (2011,2012), Prevost (2004) . . . : Existence of a global time solution (not clear always), Steady states, local stability, convergence as $\epsilon \to 0$*

Remarks

- Pertubative techniques, no control on how small ϵ should be
- Results on the global dynamics for a particular case.
- Use of Constrained Hamilton Jacobi Approach to analyse the Dynamics as $\epsilon \to 0$
- No information at the asymptotic for fixed ϵ and $t \to \infty$.

$$\frac{\partial u}{\partial t} = u(r(x) - \Psi(x,u)) + div(A(x)\nabla u) \quad \text{in} \quad \mathbb{R}^+ \times \Omega \tag{9}$$
$$u(x,0) = u_0(x), \quad u(x,t) = 0 \quad \text{in } \partial\Omega \tag{10}$$

Theorem 1

Assume, A is elliptic and smooth, $\Psi(x,u) = \alpha(u)$ is independent of x and Lipschitz continuous with respect to the L^p with $p \geq 2$. Then for any initial data $u_0 \in L^p$ there exists a global time solution $u(t,x) \in C^1(\mathbb{R}^+, C^2(\Omega))$. Moreover, let $\lambda_1(div(A(x)\nabla\cdot) + r(x))$ be first eigenvalue then

- *if $\lambda_1 \geq 0$, there is no positive stationary solution and $u(t,x) \to 0$ as $t \to \infty$*
- *if $\lambda_1 < 0$, there exists a unique positive stationary solution $\bar{u}$ and $u(x,t) \to \bar{u}$*

Theorem 2

Assume, A is elliptic and smooth, $\Psi(x,u) = \int_\Omega \mathcal{K}(y,u(y))\,dy + \epsilon\psi(x,u)$ with $\mathcal{K}$ smooth and ψ smooth uniformly bounded. Ψ is Lipschitz continuous with respect to an L^p norm with $p \geq 2$. Then there exists a ϵ_0, so that for all $0 \leq \epsilon \leq \epsilon_0$ there exists a unique stationary solution $\bar{u}_\epsilon$ and for any initial data $u_0 \in L^p$ there exists a global time solution $u(t,x) \in C^1(\mathbb{R}^+, C^2(\Omega))$. Moreover, as above

- *if $\lambda_1 \geq 0$, there is no positive stationary solution and $u(t,x) \to 0$ as $t \to \infty$*
- *if $\lambda_1 < 0$, there exists a unique positive stationary solution $\bar{u}$ and $u(x,t) \to \bar{u}_\epsilon$*

$$\frac{\partial u}{\partial t} = u(r(x) - \Psi(x,u)) + \int_\Omega m(x,y)[u(y,t) - u(x,t)]\,dy \quad \text{in} \quad \mathbb{R}^+ \times \Omega \tag{11}$$

$$u(x,0) = u_0(x), \quad u(x,t) = 0 \quad \text{in } \partial\Omega \tag{12}$$

Theorem 3

Assume, m is continuous, nonnegative irreducible, $\Psi(x,u) = \alpha(u)$ and Lipschitz continuous with respect to the L^p with $p \geq 2$. Then $\forall\, u_0 \in L^p, \exists! u(t,x) \in C^1(\mathbb{R}^+, C(\Omega))$. Moreover, let $\lambda_p(\mathcal{M} + r(x))$ be generalized principal eigenvalue then

- *if $\lambda_p \geq 0$, then $u(t,x) \to 0$ as $t \to \infty$*
- *if $\lambda_p < 0$ and is an eigenvalue then exists a unique positive stationary solution $\bar{u}$ and $u(x,t) \to \bar{u}$*

Theorem 4

Assume, m is continuous, nonnegative irreducible, $\Psi(x,u)$ as in Theorem 2. Then there exists a ϵ_0, so that for all $0 \leq \epsilon \leq \epsilon_0, \exists\,!\bar{u}_\epsilon$ stationary solution and $\forall\, u_0 \in \mathcal{L}^p,\ \exists!,\ u(t,x) \in C^1(\mathbb{R}^+, C(\Omega))$. Moreover, as above

- *if $\lambda_p \geq 0$, then $u(t,x) \to 0$ as $t \to \infty$*
- *if $\lambda_p < 0$ and is an eigenvalue then exists a unique positive stationary solution $\bar{u}$ and $u(x,t) \to \bar{u}$*

Global Facts

Existence of a solution of 9

- Positivity principle : if $u(0) \geq 0$ then
$$0 < u(t, x)$$
- Parabolic Regularity $\Longrightarrow$
$$u(x, t) \leq Ce^{\lambda_1 t}\phi_1$$
where λ_1 is the first eigenvalue of the matrix $div(A(x)\nabla) + r(x)$ and ϕ_1 is a positive eigenfunction associated to λ_1
- Existence via standard scheme.

For the nonlocal case :

- No parabolic regularity, so construction is a bit more difficult ! ! !
- A particular case : $\Psi(u) := \int_\Omega \mathcal{K}(y)u(y)\,dy$, by adapting an idea in the book of Perthame (2007), we see that
$$u(x, t) = \frac{e^{\mathcal{L}t}u_0(x)}{1 + \int_\Omega \mathcal{K}(y)\int_0^t \left(e^{\mathcal{L}s}u_0(y)\right)\,dsdy}. \qquad (13)$$
where $\mathcal{L}[u] := r(x)u + \int_\Omega m(x, y)(u(y) - u(x))\,dy$

Theorem 5 (General Identities)

Let H be a smooth (at least C^2) function. Let $u, \bar{u}$ be two positive solution (9) *then we have*

$$\frac{d\mathcal{H}(t)}{dt} = -\mathcal{D}(u) + \int_\Omega \bar{u}^2(x) H'\left(\frac{u}{\bar{u}}(x)\right) \Gamma(x) u(x)\, dx \qquad (14)$$

where $\mathcal{H}$, $\mathcal{D}$ are the following quantity :

$$\mathcal{H}(u(t)) := \int_\Omega \bar{u}^2(x) H\left(\frac{u(x)}{\bar{u}(x)}\right) dx$$

$$\mathcal{D}(u) := \int_\Omega \bar{u}^2(x) A(x) H''\left(\frac{u(x)}{\bar{u}(x)}\right) \left|\nabla\left(\frac{u}{\bar{u}}\right)\right|^2 dx$$

Comments

- This identity works whatever the problem is ! ! ! ! !
- When $\Gamma \equiv 0$, it is the well known General Relative Entropy of Mischler-Michel-Perthame (2005)
- Similar identities holds for the Competition system and for the non local problem.
- Choosing the right function H gives access to all possible useful norm

Sketch of the proof of Theorem 1 : $\forall x, \Psi(x,u) = \alpha(u)$

Stationary Solution

Let ϕ_1 be the positive eigenvector of $div(A(x)\nabla + r(x))$ associated to λ_1 normalized by $\|\phi_1\|_2 = 1$ Then $\exists!\ \mu_0$ so that $\mu_0\phi_1$ is a stationary solution of (9). Moreover, this is the unique stationary solution of the problem.

A priori Estimate

- Let u be a positive solution of (9), then there exists $C_1(u_0)$ so that

$$\|u\|_2 + \|u\phi_1\|_1 \leq C_1,$$

- There exists $c_0 > 0$ so that for all times $t \geq 0$, $\|u\phi_1\|_1 > c_0(u_0)$

- Decomposition : $u(t) = \lambda(t)\mu_0\phi_1 + h(t)$ with $h(t) \in \phi_1^\perp$
- Miraculous identities + Decomposition $\Longrightarrow$

$$\frac{d\beta(v(t))}{dt} = (\alpha(\bar{u}) - \alpha(u))\beta(u) \tag{15}$$

$$\frac{d\mathcal{E}(h(t))}{dt} = -2\int_\Omega \bar{u}^2(x)A(x)\left|\nabla\left(\frac{u}{\bar{u}}\right)\right|^2 dx + 2(\alpha(\bar{u}) - \alpha(u))\mathcal{E}(h) \tag{16}$$

where $\mathcal{E}(h(t)) = \|h\|_2^2$ and $\beta(u) := \|u\bar{u}\|_1$ with $\bar{u} = \mu_0\phi_1$ the unique steady state.

- Decomposition+ (15)+Lipschitz continuity of $\alpha \Longrightarrow$

$$\lambda'(t) = (\alpha(\bar{u}) - \tilde{\alpha}(\lambda(t)))\lambda(t) + \lambda(t)o(1)$$

where $|o(1)| = |\tilde{\alpha}(\lambda(t)\bar{u}) - \alpha(\lambda(t)\bar{u} + h(t))| \le C\sqrt{\mathcal{E}(h)}$ as $t \to \infty$ and

$$\tilde{\alpha}(s) := \alpha(s\bar{u}).$$

- (15) +(16) $\Longrightarrow$ for $\mathcal{F}(t) := \log\left[\frac{\|h\|_2^2}{(\beta(u))^2}\right]$,

$$\frac{d}{dt}\mathcal{F}(t) = -\frac{2}{\mathcal{E}(h)}\int_\Omega \bar{u}^2(x)A(x)\left|\nabla\left(\frac{u}{\bar{u}}\right)\right|^2 dx < 0.$$

Ideas for the convergence when $\Psi(x,u) := \alpha(u) + \epsilon\psi(x,u)$

Lemma 6

There exists $\bar{\omega}^- < \bar{\omega}^+ \in \mathbb{R}^+, \bar{c}_1 < \bar{C}_1, \bar{c}_2(u_0) < \bar{C}_2(u_0)$ *and* ϵ_1 *so that for all* $0 \leq \epsilon \leq \epsilon_1$ *and for any positive stationary solution* $\bar{u}_\epsilon$, *we have*

$$\bar{c}_1 \leq \|\bar{u}_\epsilon\|_1 < \bar{C}_1, \quad \bar{c}_2 \leq \beta(u_\epsilon(t)) := \|\bar{u}_\epsilon u_\epsilon\|_1 \leq \bar{C}_2.$$

Moreover, $\bar{u}_\epsilon$ *satisfies* $\bar{\omega}^-\phi_1 \leq \bar{u}_\epsilon \leq \bar{\omega}^+\phi_1$.

Need information on homeomorphism :

$$\tilde{\Psi}_{\bar{u}_\epsilon}(s) := \int_\Omega \Psi(x, s\bar{u}_\epsilon)\bar{u}_\epsilon^2\, dx.$$

Lemma 7

There exists ϵ_2 *and* $\tau_0 > 0$ *so that* $\forall\, \epsilon \leq \epsilon_2, \forall\, \bar{v}_\epsilon$ *stationary solution :*

$$\bar{c}_3 \leq \tilde{\Psi}_{\bar{u}_\epsilon}(1) \leq \bar{C}_3 \leq 2\bar{C}_3 \leq \tilde{\Psi}_{\bar{u}_\epsilon}(1+\tau_0).$$

Moreover $\exists \epsilon_3, k > 0$ *so that* $\forall\, \epsilon \leq \epsilon_3$ *and* $\forall\, \bar{u}_\epsilon$ *and* $\forall,\ t, s \in (0, 1+\tau_0)$

$$|t-s| \leq k|\tilde{\Psi}_{\bar{u}_\epsilon}(t) - \tilde{\Psi}_{\bar{u}_\epsilon}(s)|.$$

- Decomposition : $v(t) = \lambda(t)\bar{u} + h(t)$ with $h(t) \in \bar{u}^{\perp}$
- Miraculous identities + Decomposition +estimates $\Longrightarrow$

$$\lambda'(t)\mathcal{E}(\bar{u}) = \lambda(t)(\tilde{\Psi}_{\bar{u}}(1) - \tilde{\Psi}_{\bar{u}}(\lambda(t))) + o(1), \tag{17}$$

$$\frac{d\mathcal{E}(h)}{dt} - \mathcal{E}(h)\frac{d}{dt}\log(\beta^2(u(t))) \leq -\frac{C_1(\bar{\omega}^+\phi_1)}{4}\mathcal{E}(h) + \epsilon C_4|1-\lambda(t)|\sqrt{\mathcal{E}(h)}. \tag{18}$$

where

$$|o(1)| \leq C(1+\epsilon)\sqrt{\mathcal{E}(h)}$$

and C_1, C_4 are positive constants.

- $\mathcal{E}(h) \to 0 \Longrightarrow \lambda(t) \to 1$
- $\mathcal{E}(h) \to 0$: Iterative Scheme using (18) and (17)

Remark

- The proof rely on the Hilbert structure of $L^2 \Longrightarrow$ with the Parabolic regularity we can extend the proof to $p \geq 1$ as soon as the coefficient are regular enough.
- This will not be the case for nonlocal equation ! ! ! New ideas are needed.
- No blow up in these cases

Blow-up phenomena :

A particular case

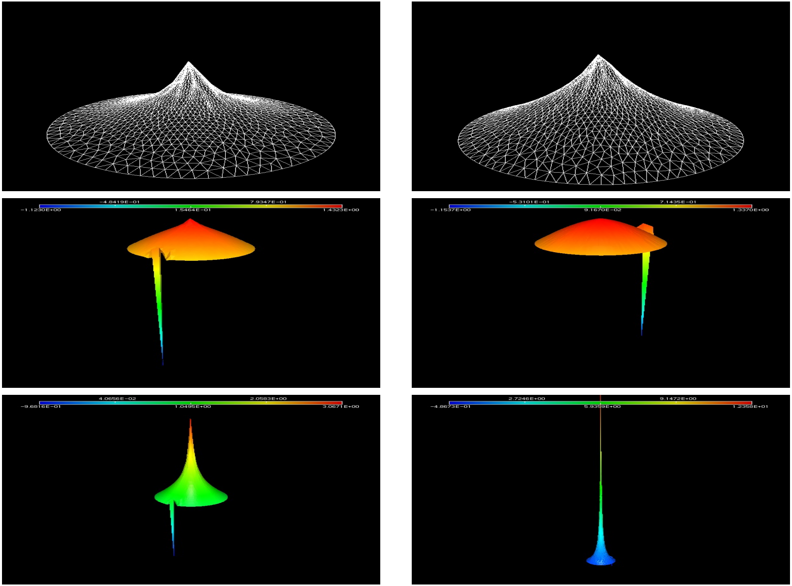
$$\frac{\partial u}{\partial t} = u\left(r(x) - \int_\Omega u\right) + \rho\left(\int_\Omega u(y)\,dy - |\Omega| u(x)\right) \quad \text{in} \quad \mathbb{R}^+ \times \Omega \tag{19}$$

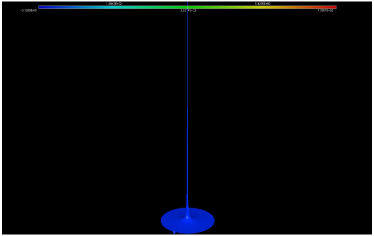
$$u(x,0) = u_0(x) \tag{20}$$

Theorem 8

Assume r achieve a single maximum in x_0 and so that $\|\frac{1}{r(x_0)-r(x)}\|_1 < 1$. Assume that $\lambda_p < 0$, then there exists ρ_0 so that for all $\rho \leq \rho_0$ and for any initial data $u_0 \in L^1$ the global time solution $u(t,x) \in C^1(\mathbb{R}^+, C(\Omega))$ blow up in infinite time. Moreover, $u(x,t) \to \alpha\delta_{x_0} + f$ where $f \in L^1$.

Some numerics to convince you (Run by Freefem++ with the Help of O. Bonnefon, G. Legendre)

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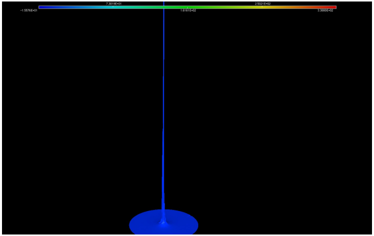
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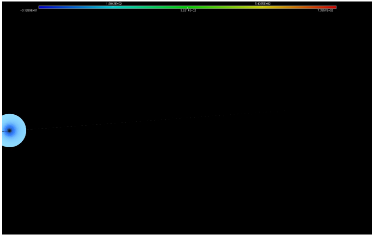
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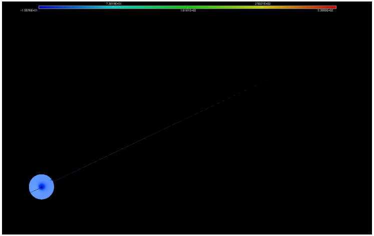
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2.5021E+02
-1.5576E+01
1.6161E+02
3.3880E+02

III. Perspective and Open Problems

Summary

- Provided a way to analyse the asymptotic of some competition model with mutation via the construction of a relative entropy.
- This analysis apply both for PDE mutation- selection model and for ODE system, even lattice system. It give new perspective on the analysis of the spectral property of nonlocal operator.

Things to do

- Better understanding of the PDE/ODE system for more general interaction
- Remove the symmetry condition.
- Better understanding of the blow up solution
- Mixing space and trait, curve front
- Have better numerics

Thank you for your attention