

Gradient Flows Face-to-Face 5, Granada, September 16-19, 2025



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On a chemotaxis system with nonlinear diffusion modelling Multiple Sclerosis

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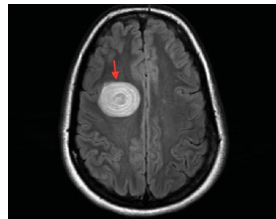
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Multiple Sclerosis pathology is a central nervous system (brain and spinal cord) chronic inflammatory disease, that can induces progressive disability. It is caused by an abnormal response of the immune system that produces inflammation and damages myelin and neurons. (ISS)

- ▶ **Myelin** is a lipid-rich sheath that surrounds neurons axons and facilitates the transmission of nerve impulses. Is produced by **oligodendrocytes**.
- ▶ Immune system (**macrophages**) **attacks and destroys the oligodendrocytes** and the myelin sheath around the nerves.
- ▶ **Demyelination** process produces lesions (plaques in 2D sections) of the white matter of the brain.

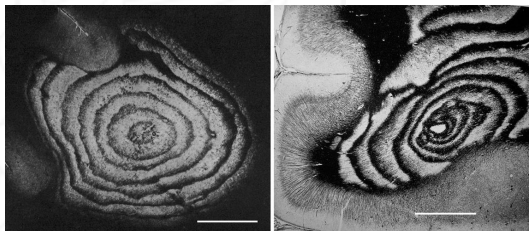
Examples of $2d$ plaques.



Macrophages



- ▶ Heterogeneity of demyelination in different MS patients: **different types of lesions (Type I - IV)** and different types of clinical variants **Lucchinetti et al. '00.**
- ▶ Stage-dependent pathology: the pathological heterogeneity is due to evolution of lesional pathology. **Type III lesions are typical of the first stages**, followed by type I and II lesions **Barnett and Prineas, '04.**
- ▶ **Baló MS** present an acute fulminant disease that progresses rapidly to death within months. It manifests large demyelinated lesions showing a peculiar pattern of alternating layers of preserved and destroyed myelin. The plaques are classified as Type III lesions.



The model proposed by Calvez, Khonsari '08 consider

- ▶ **Activated macrophages** are attracted by the signalling molecules taking into account the volume-filling effect. Antibody travels in the white matter, driving macrophages into their active state:

$$\partial_t m = D\Delta m - \chi \nabla \cdot \left(\frac{m}{1 + \delta m} \nabla c \right) + \mu m (1 - m)$$

- ▶ **Pro-inflammatory cytokines** are produced by activated macrophages and destroyed oligodendrocytes:

$$\tau \partial_t c = \bar{\alpha} \Delta c - c + \lambda d + \beta m$$

- ▶ **Destroyed oligodendrocytes** are destroyed by neurotoxic agents (oxidative stress) produced by activated macrophages.

$$\partial_t d = rm \frac{m}{1 + \delta m} (1 - d)$$

Let $\Omega \subset \mathbb{R}^n$ be a bounded domain with smooth boundary $\partial\Omega$. We will consider the following **chemotaxis-haptotaxis** system with **nonlinear diffusion**

$$\begin{cases} \partial_t m = \nabla \cdot (D(m) \nabla m - \chi f(m) \nabla c) + M(m), \\ \tau \partial_t c = \alpha \Delta c - c + \lambda d + \beta m, \\ \partial_t d = rh(m) (1 - d), \end{cases} \quad x \in \Omega, t > 0, \text{ (MainSys)}$$

endowed with the Neumann boundary conditions

$$\left. \frac{\partial m}{\partial n} \right|_{\partial\Omega} = \left. \frac{\partial c}{\partial n} \right|_{\partial\Omega} = \left. \frac{\partial d}{\partial n} \right|_{\partial\Omega} = 0,$$

and subject to the initial conditions

$$m(x, 0) = m_0(x), c(x, 0) = c_0(x), d(x, 0) = d_0(x),$$

- On the model with linear diffusion:
Desvillettes, Giunta '21 and Desvillettes, Giunta, Morgan, Tang '21 global well-posedness of strong solutions.
Asymptotic behaviour is studied in Lombardo, Barresi, Bilotta, Gargano, Pantano, Sammartino, '17; Bilotta, Gargano, Giunta, Lombardo, Pantano, Sammartino, '18
- Other models and approaches in Hu, Fu, Ai '20 and Moise, Friedman '21.
- Chemotaxis-haptotaxis system with nonlinear diffusion was introduced in Chaplain, Lolas '06

$$\begin{cases} \partial_t u = \nabla \cdot (D(u) \nabla u - \chi u \nabla v - \xi u \nabla w) + \mu u(1 - u), \\ \epsilon \partial_t v = \Delta v - v + \beta u, \\ \partial_t w = vw, \end{cases} \quad x \in \Omega, t > 0,$$

- Several results concerning existence and boundedness of solutions Tao, Winkler '11, Tao, Winkler '12, Li, Lankeit '16 and Liu, Zheng, Li, Yan '20

- (AD) $D \in C^2([0, \infty))$, $D(s) \geq 0$, for all $s \geq 0$ and there exist some constants $\gamma > 1$ and $k_d > 0$ such that $D(s) > k_d s^{\gamma-1}$ for all $s \geq 0$ there exist a function Φ such that $\Phi(u) = \int_0^u D(s) ds$,
- (AM) $M \in C^1([0, \infty))$, and exists $\mu > 1$ such that $\frac{M(s)}{s} \leq \mu(1-s)$, for all $s > 0$.
- (Ah) $h \in C^1([0, \infty))$, and exists $k_h > 0$ such that $h'(s) \leq k_h s$, for all $s \geq 0$.
- (Af) $f \in C^1([0, \infty))$, and exists $k_f > 0$ such that $f(s) \leq k_f s$, for all $s \geq 0$.
- (InCo) the functions m_0 , c_0 and d_0 are non-negative in Ω , $m_0 \neq 0$, $0 \leq d_0 \leq 1$ and satisfy

$$\begin{cases} m_0 \in L^\infty(\Omega), \nabla m_0 \in L^2(\Omega) \text{ with } m_0 \geq 0 \text{ in } \Omega \text{ and } m_0 \neq 0, \\ c_0 \in W^{1,\infty}(\Omega) \text{ with } c_0 \geq 0 \text{ in } \Omega, \\ d_0 \in C^2(\bar{\Omega}) \text{ with } 0 \leq d_0 \leq 1 \text{ in } \bar{\Omega}. \end{cases}$$

The diffusion exponent γ satisfies the following restrictions

$$\gamma > \max \left\{ 2 - \frac{2}{n}, 1 \right\} \text{ for } n = 1, 2, 3. \quad (\text{cond-}\gamma)$$

Theorem (F, Radici, Romagnoli '25)

Let $\Omega \subset \mathbb{R}^n$ be a bounded domain with smooth boundary $\partial\Omega$ and $\chi, \mu > 0$. Assume that D satisfies (AD), M, f and h are under assumptions (AM), (Af) and (Ah) respectively. Consider a triple (m_0, c_0, d_0) satisfying (InCo). Then, for any $\gamma > 1$ that satisfies (cond- γ), there is $C > 0$ such that system (PEsys) endowed with the Neumann boundary conditions has a weak solution

$$(m, c, d) \in L^2_{loc}([0, T]; L^2(\Omega)) \times L^2_{loc}([0, T]; W^{1,2}(\Omega)) \times L^2_{loc}([0, T]; L^\infty(\Omega)),$$

$$D(m)\nabla m \in L^2_{loc}([0, T]; L^2(\Omega)),$$

that exists globally in time and satisfies

$$\|m(\cdot, t)\|_{L^\infty(\Omega)} + \|c(\cdot, t)\|_{W^{1,\infty}(\Omega)} + \|d(\cdot, t)\|_{L^\infty(\Omega)} \leq C,$$

for all $t \in (0, \infty)$.

- For $\epsilon \in (0, 1)$, we introduce the function D_ϵ is defined by

$$D_\epsilon(s) = D(s + \epsilon). \quad (\text{RegDif})$$

Note that, $D_\epsilon(s) \geq k_D(s + \epsilon)^{\gamma-1}$ and $D_\epsilon(0) > 0$.

- For $T > 0$, we consider the following regularised system

$$\begin{aligned} \partial_t m_\epsilon &= \nabla \cdot (D_\epsilon(m_\epsilon) \nabla m_\epsilon) - \chi \nabla \cdot (f(m_\epsilon) \nabla c_\epsilon) + M(m_\epsilon), \\ \partial_t c_\epsilon &= \Delta c_\epsilon + d_\epsilon - c_\epsilon + m_\epsilon, \\ \partial_t d_\epsilon &= h(m_\epsilon) (1 - d_\epsilon), \end{aligned} \quad (\text{RegSys})$$

endowed with Neumann boundary conditions.

- By a standard **fixed point argument and classical parabolic regularity** we have that there exists a maximal existence time $T_{\max} \in (0, \infty]$ and a triple of nonnegative solutions that solves (RegSys) classically on $\Omega \times (0, T_{\max})$ and satisfies $0 \leq d_\epsilon \leq 1$, $m_\epsilon \geq 0$ and $c_\epsilon \geq 0$ in $\Omega \times (0, T_{\max})$.

- For any $p \geq 1$ the first equation of (RegSys) gives us

$$\begin{aligned} \frac{1}{p} \frac{d}{dt} \int_{\Omega} m_{\epsilon}^p dx + \frac{p-1}{2} \int_{\Omega} D_{\epsilon}(m_{\epsilon}) m_{\epsilon}^{p-2} |\nabla m_{\epsilon}|^2 dx + \frac{k_D(p-1)}{(p+\gamma-1)^2} \int_{\Omega} |\nabla m_{\epsilon}^{\frac{p+\gamma-1}{2}}|^2 dx \\ \leq \frac{k_f^2}{k_D} \chi^2 (p-1) \int_{\Omega} m_{\epsilon}^{p-\gamma+1} |\nabla c_{\epsilon}|^2 dx + \mu \int_{\Omega} m_{\epsilon}^p dx - \mu \int_{\Omega} m_{\epsilon}^{p+1} dx \end{aligned}$$

- Recalling the properties of the (Neumann-)heat semigroup and using the Duhamel formula we get

$$\begin{aligned} \frac{1}{q} \frac{d}{dt} \int_{\Omega} |\nabla c_{\epsilon}|^{2q} dx + 2 \int_{\Omega} |\nabla c_{\epsilon}|^{2q} dx + \frac{q-1}{q^2} \int_{\Omega} |\nabla |\nabla c_{\epsilon}|^q|^2 dx \\ \leq \left(2(q-1) + \frac{n}{2} \right) \int_{\Omega} (d_{\epsilon} + m_{\epsilon})^2 |\nabla c_{\epsilon}|^{2q-2} dx + C_1, \end{aligned}$$

- Intensive use of Gagliardo-Nirenberg and Young inequalities shows that for any $\eta > 0$

$$\begin{aligned} \int_{\Omega} m_{\epsilon}^{p-\gamma+1} |\nabla c_{\epsilon}|^2 dx \leq \eta \int_{\Omega} |\nabla m_{\epsilon}^{\frac{p+\gamma-1}{2}}|^2 dx + \eta \int_{\Omega} |\nabla |\nabla c_{\epsilon}|^q|^2 dx + C, \\ \int_{\Omega} (d_{\epsilon} + m_{\epsilon})^2 |\nabla c_{\epsilon}|^{2q-2} dx \leq \eta \|\nabla m_{\epsilon}^{\frac{p+\gamma-1}{2}}\|_{L^2(\Omega)}^2 + \eta \|\nabla |\nabla c_{\epsilon}|^q\|_{L^2(\Omega)}^2 + C, \end{aligned}$$

for all $t \in (0, T_{\max})$, under some conditions on $p, q > 1$, see [Li, Lankeit '16](#).
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- Using an **iteration procedure** as in **Tao, Winkler '12** we get that there exists a constant $C > 0$ independent from ϵ such that

$$\|m_\epsilon(\cdot, t)\|_{L^\infty(\Omega)} \leq C, \quad \|c_\epsilon(\cdot, t)\|_{W^{1,\infty}(\Omega)} \leq C \quad \text{and} \quad \|d_\epsilon(\cdot, t)\|_{L^\infty(\Omega)} \leq C$$

and classical solution **exists globally in time**.

- There exists a constant $C > 0$ independent from ϵ such that

$$\int_0^t \int_\Omega D_\epsilon(m_\epsilon) m_\epsilon^{p-2} |\nabla m_\epsilon|^2 dx \leq C(1+t), \quad \text{and} \quad \int_0^t \int_\Omega |\nabla m_\epsilon|^{\frac{p+\gamma-1}{2}} dx \leq C(1+t).$$

- Let $\theta > \max\{1, \frac{\gamma}{2}\}$. Then for $r > 1$ and for any $T > 0$ there exists a constant $C > 0$ such that

$$\|\partial_t m_\epsilon^\theta\|_{L^1(0,T;(W_0^{2,r}(\Omega))^*)} \leq C,$$

for any $\epsilon > 0$.

- Aubin-Lions for strong convergence in m_ϵ

Multiplying each equation of (RegSys) by ϕ and integrating by parts we get

$$\begin{aligned} - \int_0^T \int_{\Omega} m_{\epsilon} \phi_t \, dx dt - \int_{\Omega} m_{\epsilon,0}(x, 0) \phi(x, 0) \, dx &= - \int_0^T \int_{\Omega} D_{\epsilon}(m_{\epsilon}) \nabla m_{\epsilon} \nabla \phi \, dx dt \\ &\quad + \chi \int_0^T \int_{\Omega} m_{\epsilon} \nabla c_{\epsilon} \nabla \phi \, dx dt + \int_0^T \int_{\Omega} M(m_{\epsilon}) \phi \, dx dt, \\ - \int_0^T \int_{\Omega} c_{\epsilon} \phi_t \, dx dt - \int_{\Omega} c_{\epsilon,0}(x, 0) \phi(x, 0) \, dx &= - \int_0^T \int_{\Omega} \nabla c_{\epsilon} \nabla \phi \, dx dt + \int_0^T \int_{\Omega} (m_{\epsilon} + d_{\epsilon} - c_{\epsilon}) \phi \, dx dt, \\ - \int_0^T \int_{\Omega} d_{\epsilon} \phi_t \, dx dt - \int_{\Omega} d_{\epsilon,0}(x, 0) \phi(x, 0) \, dx &= \int_0^T \int_{\Omega} h(m_{\epsilon}) (1 - d_{\epsilon}) \phi \, dx dt. \end{aligned}$$

The convergences obtained allow to pass to the limit in all the terms in the above equalities. Then we can conclude that the limiting triple (m, c, d) is a weak solution to (PEsys). Finally, the boundedness of the convergences above together with the boundedness of the regularised solution.

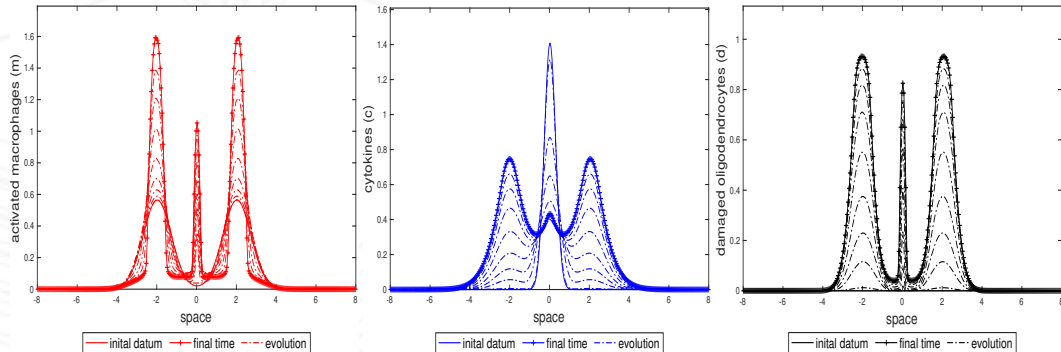


Figure: $\chi = 4$

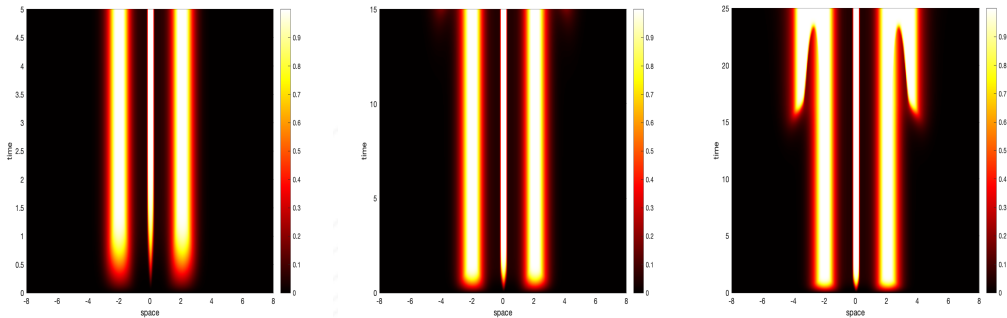


Figure: Demyelination plaques for $\chi = 4$

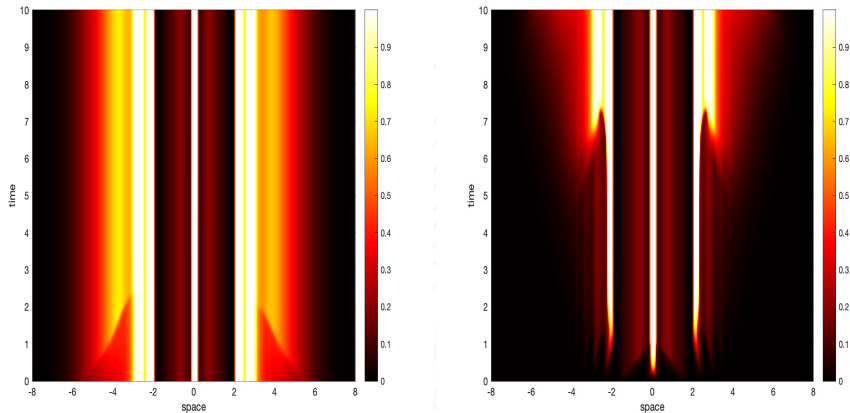


Figure: Linear vs Nonlinear diffusion for $\chi = 10$

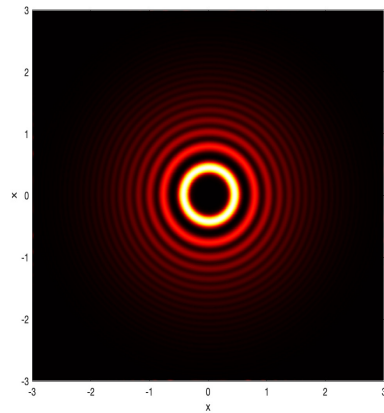
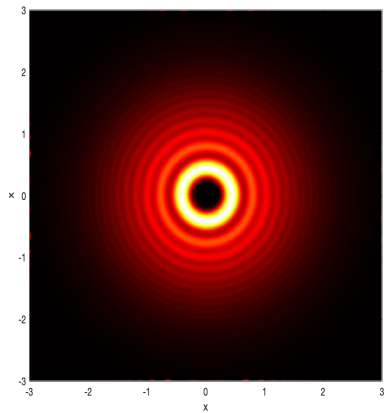
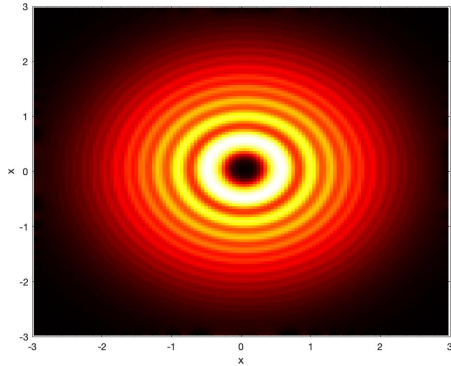


Figure: $\chi = 4$ vs $\chi = 5$



- ▶ Spatially homogeneous steady states for the system are $(\bar{m}, \bar{c}, \bar{d}) = (1, 2, 1)$. For small perturbations $(\tilde{m}, \tilde{c}, \tilde{d})$ we have the system:

$$\begin{cases} \partial_t \tilde{m} = \mu \gamma \Delta \tilde{m} - \chi \Delta \tilde{c} - \tilde{m} \\ \partial_t \tilde{c} = \epsilon \Delta \tilde{c} - \tilde{c} + \tilde{m} + \tilde{d} \\ \partial_t \tilde{d} = -\tilde{d} \end{cases} \quad (1)$$

- ▶ The stability of the linearized system depends on the eigenvalues of the matrix

$$A_k := \begin{pmatrix} -\mu \gamma \nu_k - 1 & \chi \nu_k & 0 \\ 1 & -\epsilon - \alpha & 1 \\ 0 & 0 & -1 \end{pmatrix},$$

$\{\nu_k\}_k$ be a set of eigenvalues of the Laplacian operator. Stability condition

$$\chi > \mu \gamma \epsilon \nu_k + \mu \gamma \alpha + \epsilon + \frac{\alpha}{\nu_k} \quad (2)$$

- ▶ Under the above condition, an H^1 stability argument can be performed.

- Consider the following *Parabolic-Elliptic* problem

$$\begin{cases} \partial_t m = \nabla \cdot (D(m) \nabla m - \chi m \nabla c) + M(m), \\ 0 = \Delta c - c + d + m, \\ \partial_t d = h(m)(1 - d), \end{cases} \quad x \in \mathbb{R}^2, \quad t > 0, \quad (\text{PEsys})$$

- Second equation can be explicitly solved

$$c(t, x) = K * (m + d),$$

with K being the d -dimensional Bessel kernel,

- Stationary solution for the third equation is $\bar{d}(x) = 1_{\text{supp}(m)}(x)$.
- Chemotaxis term becomes

$$\chi m \nabla c = \chi m (\nabla K * m + \nabla K * 1_{\text{supp}(m)}(x))$$

Then we consider the equation

$$\partial_t \rho = \nabla \cdot (\rho \nabla D'(\rho) - \chi \rho (\nabla K * \rho + \nabla K * \mathbf{1}_{S_\rho})) + M(\rho), \quad x \in \mathbb{R}^n, t > 0,$$

Properties of Bessel kernel

1. for $d = 1$, $K(x) = \frac{1}{2}e^{-|x|}$
2. For $d \geq 2$, $K \in L^1(\mathbb{R}) \cap L^p(\mathbb{R})$ for each $p \in [1, \frac{d}{d-2})$ and $\nabla K \in L^1(\mathbb{R}) \cap L^q(\mathbb{R})$ for each $q \in [1, \frac{d}{d-1})$.
3. K is radially symmetric and decreasing in $|x|$.

see [Cygan, Karch, Krawczyk and Wakui '21](#).

$$\partial_t \rho = \underbrace{\nabla \cdot (\rho \nabla D'(\rho) - \chi \rho (\nabla K * \rho + \nabla K * \mathbf{1}_\rho))}_{\text{wannabe Gradient Flow}} + \underbrace{M(\rho)}_{\text{Reaction}}$$

In the spirit of Carrillo, F, Santambrogio, Schmidtchen '18 we construct an iterative scheme

- Reaction Step: Given $\rho^n \in L^\gamma(\mathbb{R}^d) \cap \mathcal{P}_2(\mathbb{R}^d)$, we solve the "ODE" in $[t^n, t^{n+1}]$

$$\begin{cases} \partial_t \rho = M(\rho), \\ \rho(t^n) = \rho^n \end{cases} \quad (3)$$

Set $\rho^{n+\frac{1}{2}} = \rho|_{t=t^{n+1}}$.

- Aggregation-diffusion step: Given $\rho^{n+\frac{1}{2}}$ from the reaction step, solve the minimization problem:

$$\rho^{n+1} \in \operatorname{argmin}_{m \in \mathcal{P}_2^M(\mathbb{R}^2) \cap L^\infty(\mathbb{R}^2)} \left\{ \frac{1}{2\tau} W_2^2(\rho, \rho^{n+\frac{1}{2}}) + \mathcal{F}[\rho|\rho^{n+1/2}] \right\} \quad (4)$$

where $M = \|\rho^{n+\frac{1}{2}}\|_{L^1(\mathbb{R}^d)}$ and $\mathcal{P}_2^M(\mathbb{R}^n) := \{\varphi \mid m_2[\varphi] < +\infty; \|\varphi\|_{L^1(\mathbb{R}^d)} = m\}$ and the associated implicit-explicit energy functional

$$\mathcal{F}[\rho|\nu] = \mathcal{A}[\rho] + \mathcal{K}[\rho] + \mathcal{S}[\rho|\nu] = \frac{1}{\gamma-1} \int_{\mathbb{R}^2} \rho^\gamma dx - \frac{\chi}{2} \int_{\mathbb{R}^2} \rho K * \rho dx - \chi \int_{\mathbb{R}^2} \rho K * 1_{S_\nu} dx, \quad (5)$$

- combining steps with Bounded-Lipschitz distance

- Lower bound on the functional:

$$\begin{aligned} \int_{\mathbb{R}^2} \rho(x) K * 1_{S_\nu}(x) dx &\leq \left| \int_{\mathbb{R}^2} \rho(x) K * 1_{S_\nu}(x)(x) dx \right| \\ &\leq \|\rho\|_{L^1(\mathbb{R}^2)} \|K * 1_{S_\nu}\|_{L^\infty(\mathbb{R}^2)} \\ &\leq \|\rho\|_{L^1(\mathbb{R}^2)} \|K\|_{L^1(\mathbb{R}^2)} = 1. \end{aligned}$$

- Existence of absolutely continuous limiting curve ρ for the piecewise constant interpolation ρ_τ is standard. In particular

$$\begin{aligned} \mathcal{S} \left[\rho_\tau^{k-1} | \rho_\tau^{k-1} \right] - \mathcal{S} \left[\rho_\tau^k | \rho_\tau^{k-1} \right] &\leq \chi \|K\|_{L^1(\mathbb{R}^2)} \int_{\mathbb{R}^2} |\rho_\tau^k(t, x) - \rho_\tau^{k-1}(t, x)| dx \\ &\leq \chi \int_{\mathbb{R}^2 \times \mathbb{R}^2} |x - y| d\gamma_\tau^n(x, y) \\ &\leq \chi W_2(\rho_\tau^k, \rho_\tau^{k-1}) \leq \frac{1}{4\tau} W_2^2(\rho_\tau^k, \rho_\tau^{k-1}) + C\tau, \end{aligned}$$

implies

$$W_2(\rho_\tau(s), \rho_\tau(t)) \leq C(t-s)^{\frac{1}{2}} + o(\tau).$$

- Flow interchange techniques with the heat flow η gives

$$\begin{aligned} \int \nabla \eta \cdot \nabla K * 1_{S^{k-1}} &= - \int \eta \Delta K * 1_{S^{k-1}} = \int \eta (\delta_0 - K) * 1_{S^{k-1}} \\ &= \int \eta 1_{S^{k-1}} - \int \eta K * 1_{S^{k-1}} \\ &\leq 1 + \|\eta\|_{L^1} \|K * 1_{S^{k-1}}\|_{L^\infty} \leq 2. \\ \left\| \rho_{\tau}^{\frac{\gamma}{2}} \right\|_{L^2(0, T; H^1(\mathbb{R}^d))} &\leq C(1 + T), \end{aligned}$$

The estimates above are independent on S_ν .

- Extended Aubin-Lions Lemma provides strong converges to a limit function ρ in $L^\gamma([0, T] \times \mathbb{R}^n)$ for every $T > 0$.

- ▶ We have the following optimality conditions

$$\frac{\varphi}{\tau} + f'(\rho_\tau^k) - \chi K * (\rho_\tau^k + 1_{S_{\rho_\tau^{k-1}}}) \geq C \quad \text{a.e.} \quad (6)$$

$$\frac{\varphi}{\tau} + f'(\rho_\tau^k) - \chi K * (\rho_\tau^k + 1_{S_{\rho_\tau^{k-1}}}) = C \quad \text{a.e. } S_{\rho_\tau^k} \quad (7)$$

- ▶ Define $u = K * (\rho_\tau^k + 1_{S_{\rho_\tau^{k-1}}})$ and let $x_0 \in S_{\rho_\tau^{k-1}}$ be the minimum point of $\varphi - \chi u$. Then x_0 is the maximum point for $f'(\rho_\tau^k)$ and hence for ρ_τ^k .
- ▶ The Monge-Ampere equation provides

$$\begin{aligned} \rho_\tau^k(x_0) &= \rho_\tau^{k-1}(T(x_0)) \det(\mathbb{I} - D^2\varphi(x_0)) \\ &\leq \rho_\tau^{k-1}(T(x_0)) \left(1 - \frac{1}{2}\Delta\varphi(x_0)\right)^2 \\ &\leq \rho_\tau^{k-1}(T(x_0)) \left(1 + \frac{\chi\tau}{2}(\rho_\tau^k(x_0) + 1)\right)^2 \end{aligned}$$

$$\|\rho_\tau^{k-1}\|_{L^\infty} \geq \rho_\tau^{k-1}(T(x_0)) \geq \frac{\rho_\tau^k(x_0)}{\left(1 + \frac{\chi\tau}{2}(\rho_\tau^k(x_0) + 1)\right)^2}$$

- ▶ Uniform bound w.r.t. τ of the L^∞ norm.
- ▶ Passing to the limit $1_{S_{\rho_\tau^k}}$. Uniform bound w.r.t. τ .
- ▶ Numerical comparison between the solutions to (PEsys) and the reduced one.
- ▶ Complete characterization of non-constant stationary solutions.



Thank you for your attention!