A nonlinear cross-diffusion system for contact inhibition of cell growth

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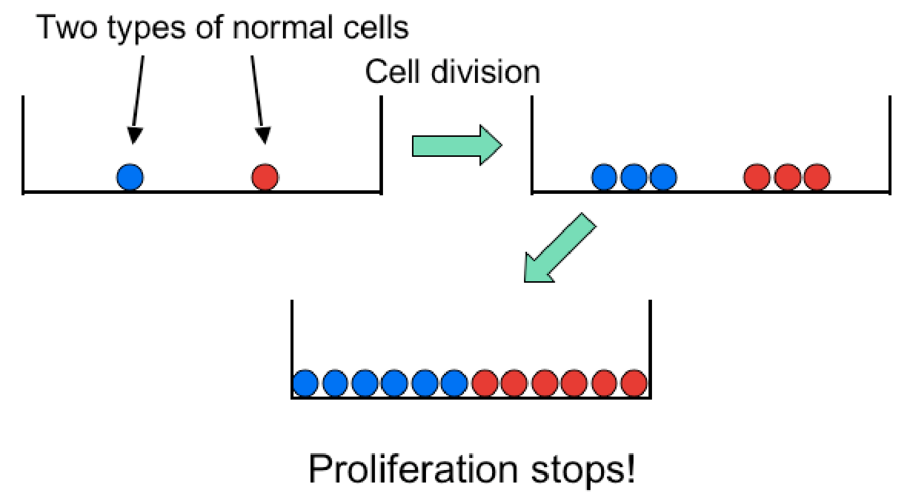
The biological context

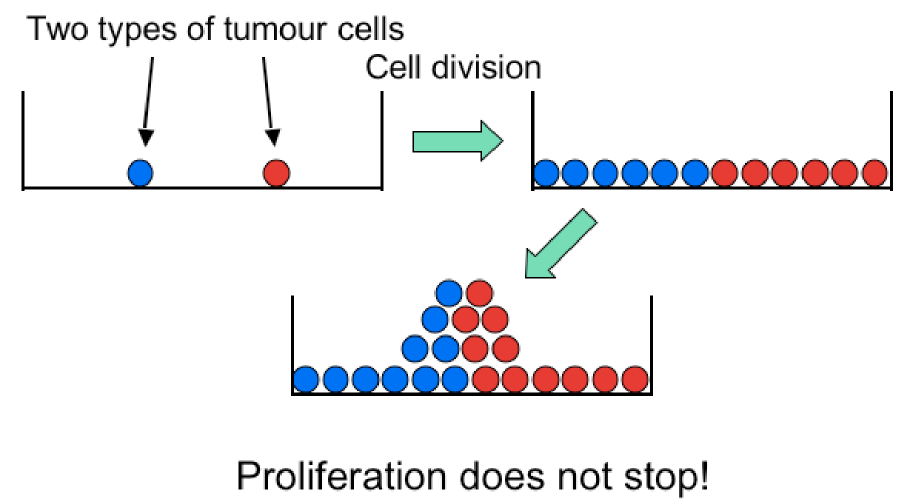
We consider a cross-diffusion system which describes a simplified model for contact inhibition of growth of two cell populations. In one space dimension it is known that the solutions satisfy a segregation property: if two populations initially have disjoint habitats, this property remains true at all later times.

Our purpose today : Extend this result to higher space dimension.

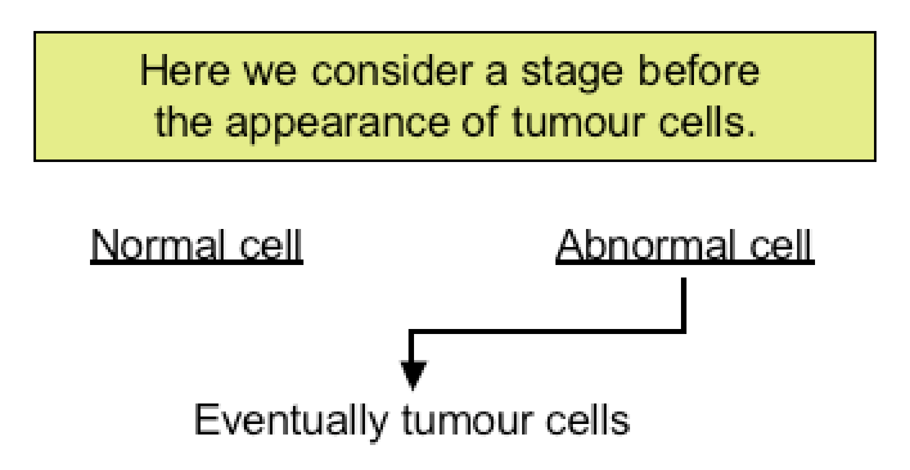
Proliferation of cells



Proliferation of cancer cells



Contact inhibition



The model equations

This tumor growth model has been proposed by Chaplain, Graziano and Preziosi

$$\begin{cases} n_t = div(n\nabla V(N)) + G_n(N)n & \text{in } \mathbb{R}^N \times \mathbb{R}^+ \\ a_t = div(a\nabla V(N)) + G_a(N)a & \text{in } \mathbb{R}^N \times \mathbb{R}^+ \end{cases}$$

- n: density of normal cells;
- a: density of abnormal cells;
- N: total density of cells;
- V: monotone increasing function;
- G_n: growth rate of normal cells;
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The model studied by Bertsch, Dal Passo and Mimura

Bertsch, Dal Passo and Mimura have proved the existence of a segregated solution of the system

$$\begin{cases} u_t = div(u \nabla \chi(u+v)) + u(1-u-\alpha v) \\ v_t = D\, div(v \nabla \chi(u+v)) + \gamma v(1-\beta u - v/k) \end{cases}$$

- u: density of normal cells;
- v: density of abnormal cells;
- the function χ is a monotone increasing function;
- D, α, β, γ are positive constants.

in the one dimensional case. The growth terms are Lotka-Volterra competition terms.

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The Bertsch, Dal Passo and Mimura result

More precisely, Bertsch, Dal Passo and Mimura have proved the existence of a segregated solution of the system

$$\begin{cases} u_t = (u(\chi(u+v))_x)_x + u(1-u-\alpha v) & -L < x < L, t > 0 \\ v_t = D\,(v(\chi(u+v))_x)_x + \gamma v(1-\beta u - v/k) & -L < x < L, t > 0 \\ u(\chi(u+v))_x) = v(\chi(u+v))_x = 0 & x = -L, L, t > 0 \\ u(x,0) = u_0(x), v(x,0) = v_0(x), -L < x < L. \end{cases}$$

The habitats of the two cell populations remain disjoint. Mathematically we express this property as follows
If $u_0 v_0 = 0$, then $u(t)v(t) = 0$ for all $t > 0$.

This system has the form of a nonlinear cross-diffusion system.

The nonlinear cross-diffusion system

We suppose that $\chi = Id$ and $D = 1$

$$\begin{cases} u_t = \frac{1}{2}\triangle u^2 + u\triangle v + \nabla u.\nabla v + u(1 - u - \alpha v), \\ v_t = \frac{D}{2}\triangle v^2 + D\, v\triangle u + D\, \nabla u.\nabla v + \gamma v(1 - \beta u - v/k), \end{cases}$$

so that it is a hard system. This motivated Bertsch et al to look for other unknown functions. One of them is quite natural. We set

$$w = u + v, \;\; w_0 := u_0 + v_0$$

and suppose that

$$u_0 \geq 0, v_0 \geq 0, w_0 \geq B_0 > 0.$$

Maximum principle type arguments successively tell that

$$u(t) \geq 0, v(t) \geq 0, w(t) \geq B_1 > 0 \qquad \text{for all } t > 0.$$

Regularity considerations

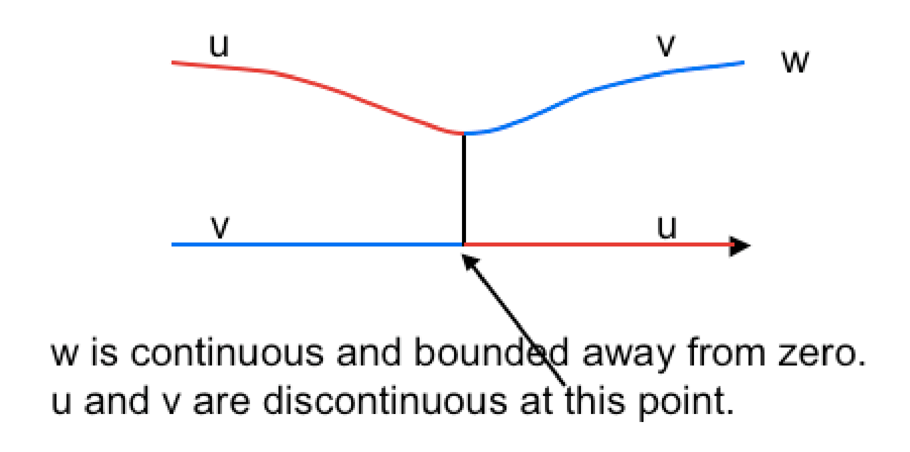
The equation for w has the form of a nonlinear diffusion equation

$$w_t = div(w\nabla w) + w\mathcal{F}(u, v, w).$$

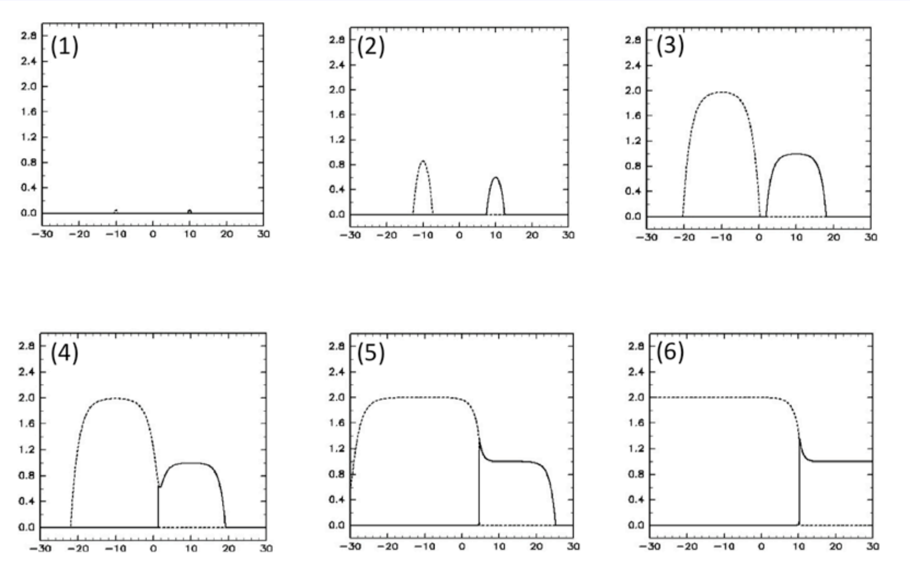
This equation is uniformly parabolic since w is bounded away from zero, and therefore w is smooth. But now, suppose that u and v have disjoint supports. Then both u and v have to be discontinuous across the interface between their supports.

We are searching for discontinuous solutions u and v of the original system. This makes our problem very hard.

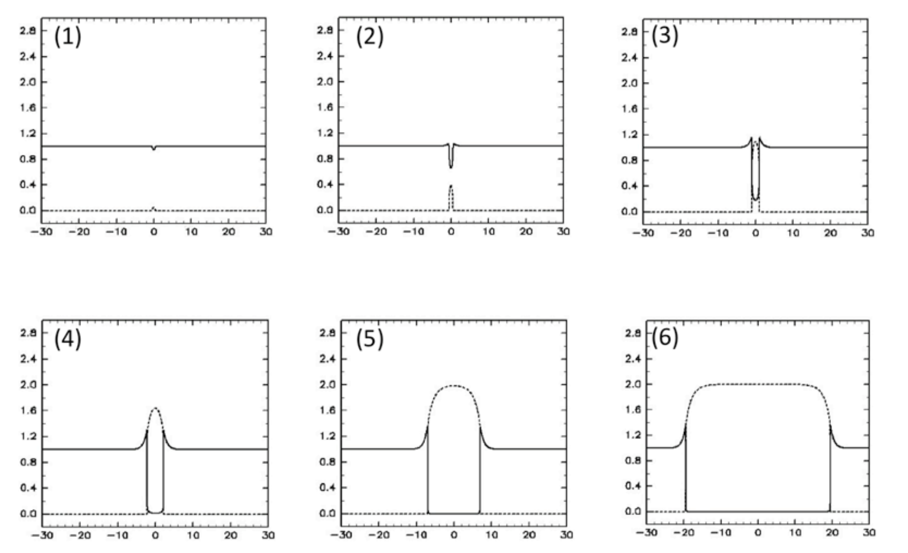
A typical (u,v,w) profile



Disjoint supports



Overlapping supports



New set of unknown functions

We set

$$w := u + v, r := \frac{u}{u+v}$$

and remark that in the case of disjoint supports, r can only take the values 0 and 1, and that

$$uv = 0 \ \text{ is equivalent to } r(1-r) = 0.$$

The system for w and r is given by

$$\begin{cases} w_t = div(w\nabla w) + wF(r,w) & \text{in } \mathbb{R}^N \times \mathbb{R}^+ \\ r_t = \nabla w \cdot \nabla r + r(1-r)G(r,w) & \text{in } \mathbb{R}^N \times \mathbb{R}^+ \\ w(x,0) = w_0(x) \text{ and } r(x,0) = r_0(x) & \text{for } x \in \mathbb{R}^N, \end{cases}$$

where

$$F(r,w) := r(1 - rw - \alpha(1-r)w) + \gamma(1-r)(1 - \beta rw - (1-r)w/k)$$
$$G(r,w) := (1 - rw - \alpha(1-r)w) - \gamma(1 - \beta rw - (1-r)w/k).$$

Regularity again

We deal with a coupled system with a parabolic equation for w coupled to a transport equation for r. Now what can we expect for regularity? First consider the equation for w; applying again the maximum principle, we will have that w is bounded from below by a positive constant whereas $0 \leq r \leq 1$. Therefore we can apply a very handy result of the book of Lieberman; this result is based upon regularity considerations such as in the elliptic articles of Agmon, Douglis, and Nirenberg. We obtain that w is bounded in

$$W_p^{2,1}(B_L \times (0, T)) \text{ and in } C^{1+\mu,(1+\mu)/2}(\overline{B}_L \times [0, T]),$$

for all positive constants L, where $B_L \subset \mathbb{R}^N$ is the ball of radius L. In particular

$$\nabla w \in C^{\mu,\mu/2}(\overline{B}_L \times [0, T]).$$

The function r

We recall that it satisfies the first order hyperbolic equation

$$r_t = \nabla w \cdot \nabla r + r(1-r)G(r,w) \text{ in } \mathbb{R}^N \times \mathbb{R}^+$$

so that in particular

$$0 \le r \le 1.$$

A possibility is to first solve the equations for the characteristics

$$\begin{cases} X_t(y,t) = -\nabla w(X(y,t),t) \ \text{ for } \ t > 0 \\ X(y,0) = y \text{ for } y \text{ in } \mathbb{R}^N \end{cases}$$

and then solve for $R(y,t) = r(X(y,t),t)$ along the characteristics:

$$\begin{cases} R_t = R(1-R)G(R, w(X(y,t),t)) & \text{in } \mathbb{R}^N \times \mathbb{R}^+, \\ R(\cdot,0) = r_0 & \text{in } \mathbb{R}^N. \end{cases}$$

A regularity problem

However, since ∇w is not Lipschitz continuous, but only Hölder continuous, the characteristics are not well-defined in the classical sense. This is why we work with a recent concept of characteristics developed by DiPerna and Lions, De Lellis and Ambrosio.

More precisely, it permits to work with a velocity field $b = -\nabla w$ which only possess the "Sobolev regularity", namely

$$b \in L^\infty_{\text{loc}}(\mathbb{R}^N \times [0,\infty)) \cap L^1_{\text{loc}}([0,\infty); W^{1,1}_{\text{loc}}(\mathbb{R}^N)).$$

The main concepts of the survey paper by De Lellis

The starting point is a velocity field b with the Sobolev regularity, namely

$$b \in L^\infty_{\text{loc}}(\mathbb{R}^N \times [0,\infty)) \cap L^1_{\text{loc}}([0,\infty); W^{1,1}_{\text{loc}}(\mathbb{R}^N)).$$

We have here $b = -\nabla w$. Another new concept is that of a regular Lagrangian flow Φ satisfying

$$\begin{cases} \Phi_t(y,t) = -\nabla w(\Phi(y,t),t) \ \text{ for } \ t > 0 \\ \Phi(y,0) = y \text{ for } y \text{ in } \mathbb{R}^N \end{cases}$$

We have here $\Phi = X$.

Nearly incompressible vector field

A velocity field b is said to be nearly incompressible if there exists a function $\eta \in L^\infty(\mathbb{R}^N \times [0,\infty))$ and a positive constant C such that $C \le \eta \le C^{-1}$ and

$$\eta_t + \text{ div } (\eta b) = 0$$

in the sense of distributions. Here we will have $\eta = \rho$, with $\rho(x,t) = |det(J^{-1}(x,t)|$ and $J(y,t)$ the Jacobian matrix $\{(X_i)_{y_j}\}$.

Concept of renormalized solutions

We say that the bounded nearly incompressible velocity field b with density η has the renormalization property if for all $c \in L^1_{\text{loc}}(\mathbb{R}^N \times [0,\infty))$ and $q \in L^\infty_{\text{loc}}(\mathbb{R}^N \times [0,\infty))$ such that

$$(q\eta)_t + \operatorname{div}(b\eta q) = c\eta$$

in the sense of distributions, $\beta(q)$ satisfies

$$(\beta(q)\eta)_t + \operatorname{div}(b\eta\beta(q)) = c\eta\beta'(q)$$

in the sense of distributions for all $\beta \in C^1(\mathbb{R})$. This property, which is trivially satisfied if c and q are smooth functions, is nontrivial because of the regularity which is assumed here.
Any velocity field b which possesses the "Sobolev regularity" satisfies the renormalization property.

Regularization method

Our general approach is to work with smooth solutions, which are easy to work with, and then study their limit as the regularization parameter n tends to infinity.

Existence of smooth solutions on a bounded domain

Theorem. Let $\mathcal{B}_n \subset \mathbb{R}^N$ be a ball of radius $\mathcal{R}_n$, α, β, γ and k positive constants, and $u_0, v_0 \in C^3(\overline{\Omega})$ such that $u_0, v_0 \geq 0$ and $u_0 + v_0 \geq B_0 > 0$ in Ω. Then there exists a pair of smooth nonnegative solutions (u, v), with $u, v \in C^{2,1}(\overline{\Omega} \times [0, T])$, of the problem

$$(P_n) \begin{cases} u_t = div(u\nabla(u+v)) + u(1-u-\alpha v) & \text{in } \mathcal{B}_n \times \mathbb{R}^+ \\ v_t = div(v\nabla(u+v)) + \gamma v(1-\beta u - v/k) & \text{in } \mathcal{B}_n \times \mathbb{R}^+ \\ u\dfrac{\partial(u+v)}{\partial \nu} = v\dfrac{\partial(u+v)}{\partial \nu} = 0 & \text{on } \partial\mathcal{B}_n \times \mathbb{R}^+ \\ u(\cdot,0) = u_0,\ v(\cdot,0) = v_0 & \text{in } \mathcal{B}_n, \end{cases}$$

where $\nu(x)$ denotes the outward normal at $x \in \mathcal{B}_n$.

A remark

Note that u and v can be smooth since they are overlapping, first at the time $t = 0$ and then at all later times.

The corresponding approximating problem in w and r

We recall that $w = u + v$ and that $r = u/(u+v)$.The problem then reads as

$$(\mathcal{P}_n) \quad \begin{cases} w_t = div(w\nabla w) + wF(r,w) & \text{in } \mathcal{B}_n \times (0,T] \\ r_t = \nabla w \cdot \nabla r + r(1-r)G(r,w) & \text{in } \mathcal{B}_n \times (0,T] \\ w\dfrac{\partial w}{\partial \nu} = 0 & \text{on } \partial\mathcal{B}_n \times (0,T] \\ w(\cdot,0) = w_0 := u_0 + v_0, \; r(\cdot,0) = r_0 := u_0/w_0 & \text{in } \mathcal{B}_n. \end{cases}$$

Existence of solution for the approximate problems

We define

$$\mathcal{A} = \{r \in C^{\mu,\mu/2}(\overline{\mathcal{B}}_n \times [0,T]), \quad 0 \le r \le 1\}$$

For given $r \in C^{\mu,\mu/2}(\overline{\mathcal{B}_n} \times [0,T])$, let $w \in C^{2+\mu,1+\mu/2}(\overline{\mathcal{B}_n} \times [0,T])$ be the unique solution of

$$\begin{cases} w_t = div(w\nabla w) + wF(r,w) & \text{in } \mathcal{B}_n \times (0,T] \\ w\dfrac{\partial w}{\partial \nu} = 0 & \text{on } \partial\mathcal{B}_n \times (0,T] \\ w(\cdot,0) = w_0 := u_0 + v_0 & \text{in } \mathcal{B}_n. \end{cases}$$

An priori estimate of the form $0 < B_1 \le w \le B_2$ follows from the maximum principle.

The equation on the characteristics

For given w, we consider the ODE for the characteristics

$$\begin{cases} X_t(y,t) = -\nabla w(X(y,t),t) \text{ for } 0 < t \leq T \\ X(y,0) = y. \end{cases}$$

Then X is continuously differentiable and one to one from $\overline{\mathcal{B}}_n \times [0,T]$ into itself.
On the characteristics the transport equation reduces to the ODE

$$\begin{cases} R_t = R(1-R)G(R, w(X(y,t),t)) & \text{in } \mathcal{B}_n \times (0,T] \\ R(\cdot,0) = r_0 & \text{in } \mathcal{B}_n. \end{cases}$$

The bounds on $w(x,t)$ and $X(y,t)$ imply that $R \in C^{1,1}(\overline{\mathcal{B}}_n \times [0,T])$.

Existence of a smooth solution

We transform $R(y,t)$ to the original variables:

$$\tilde{r}(x,t) := R(X^{-1}(x,t),t) \quad \text{for } (x,t) \in \overline{\mathcal{B}}_n \times [0,T].$$

and we find that $\tilde{r} \in C^{1,1}(\overline{\mathcal{B}}_n \times [0,T])$.
We finally apply Schauder's fixed point theorem to the map $r \mapsto w \mapsto \tilde{r} =: \mathcal{T}(r)$ from the closed convex set $\mathcal{A}$ into itself and conclude that there exists a solution (w_n, r_n) of Problem $(\mathcal{P}_n)$.

Existence of solution of the original system

We then return to the system

$$\begin{cases} w_t = div(w\nabla w) + wF(r, w) & \text{in } \mathbb{R}^N \times \mathbb{R}^+ \\ r_t = \nabla w \cdot \nabla r + r(1-r)G(r, w) & \text{in } \mathbb{R}^N \times \mathbb{R}^+ \\ w(x, 0) = w_0(x) \text{ and } r(x, 0) = r_0(x) & \text{for } x \in \mathbb{R}^N, \end{cases}$$

and would like to prove that it possesses a solution. The main idea is to find a (weak) solution (w, r) as a limit of a sequence of solutions (w_n, r_n) of the problems $(\mathcal{P}_n)$.

Technical difficulties

We have already seen that $\{w_n\}$ is bounded in $W_p^{2,1}(\mathcal{B}_n \times (0, T))$. Therefore there exist a function $w \in W_{p,\text{loc}}^{2,1}(\mathbb{R}^N \times [0, \infty))$ and a subsequence of $\{w_n\}$ which we denote again by $\{w_n\}$ such that

$$w_n \to w \text{ in } C_{\text{loc}}^{1+\mu,(1+\mu)/2}(\mathbb{R}^N \times [0, \infty)) \text{ as } n \to \infty.$$

On the other hand, we only know that

$$0 \le r_n \le 1$$

but nothing more; thus there exist $r \in [0, 1]$ and a subsequence of $\{r_n\}$ which we denote again by $\{r_n\}$ such that

$$r_n \rightharpoonup r \text{ in } L_{loc}^2(\mathbb{R}^N \times [0, \infty)) \text{ as } n \to \infty.$$

At this point, we also know that there exists a bounded function χ such that

$$F(r_n, w_n) \rightharpoonup \chi \text{ as } n \to \infty,$$

but we do not know yet that $\chi = F(r, w)$.

The essential result of Camillo De Lellis

Let b a bounded nearly incompressible velocity field with the renormalization property. Then there exists a unique regular Lagrangian flow Φ for b. Moreover, let b_n be a sequence of bounded nearly incompressible velocity fields with renormalization property such that

(i) $\{b_n\}$ is uniformly bounded in $L^\infty(\mathbb{R}^N \times (0,\infty);\mathbb{R}^N)$ and $b_n \to b$ strongly in $L^1_{\mathrm{loc}}(\mathbb{R}^N \times (0,\infty);\mathbb{R}^N)$.

(ii) The densities η_n generated by b_n satisfy $\limsup_n(\|\eta_n\|_\infty + \|\eta_n^{-1}\|_\infty) < \infty$.

Then the regular Lagrangian flows Φ_n generated by b_n converge to Φ in $L^1_{\mathrm{loc}}(\mathbb{R}^N \times (0,\infty);\mathbb{R}^N)$.

We recall that here $b = -\nabla w, \Phi = X$ and $\eta = \rho = |det(J^{-1})|$.

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Strong convergence of r_n to r

It follows from the theorem of De Lellis that

$$X_n \to X \text{ in } L^1_{loc}(\mathbb{R}^N \times [0,\infty)) \text{ as } n \to \infty.$$

Defining

$$R_n(y,t) = r_n(X_n(y,t),t),$$

we prove that

$$R_n \to R \text{ in } L^1_{loc}(\mathbb{R}^N \times [0,\infty)),$$

and also deduce that

$$r_n \to r \text{ in } L^1_{loc}(\mathbb{R}^N \times [0,\infty)).$$

Segregation property

We consider again the equation for $R(y,t) = r(X(y,t),t)$. We recall that r satisfies

$$r_t = \nabla w \cdot \nabla r + r(1-r)G(r,w) \ \text{ in } \mathbb{R}^N \times \mathbb{R}^+$$

so that R is a solution of the problem

$$\begin{cases} R_t = R(1-R)G(R, w(X(y,t),t)) & \text{in } \mathbb{R}^N \times \mathbb{R}^+ \\ R(y,0) = r_0(y) & \text{for } y \in \mathbb{R}^N. \end{cases}$$

In turn this implies that

$$\begin{cases} (R(1-R))_t = R(1-R)(1-2R)G(R, w(X(y,t),t)) & \text{in } \mathbb{R}^N \times \mathbb{R}^+ \\ (R(1-R))(y,0) = 0 & \text{for } y \in \mathbb{R}^N, \end{cases}$$

so that

$$R(1-R) = 0 \text{ or else } uv = 0 \in \mathbb{R}^N \times \mathbb{R}^+.$$

Singular limit in a special case

We consider the special case that $\alpha = 1$ and that $\beta = \frac{1}{k}$ and consider the corresponding problem on a bounded domain with natural boundary conditions. This gives

$$\begin{cases} u_t = \mathrm{div}(u\nabla(u+v)) + (1-u-v)u, & \\ v_t = \mathrm{div}(v\nabla(u+v)) + \gamma(1-\frac{u+v}{k})v, & x\in\Omega,\ t\in(0,T], \\ u\nabla(u+v)\cdot\nu = 0, & \\ v\nabla(u+v)\cdot\nu = 0, & x\in\partial\Omega,\ t\in(0,T], \\ u(x,0) = u_0(x), & \\ v(x,0) = v_0(x), & x\in\Omega, \end{cases}$$

where ν is a outward normal unit vector, and we we set $w = u + v$.

Singular limit in a special case

The system for w and v is given by

$$\begin{cases} w_t = \mathrm{div}(w\nabla w) + (1-w)w + (\gamma(1-\kappa w) - 1 - w)v & \text{in } \Omega \times (0,T], \\ v_t = \mathrm{div}(v\nabla w) + \gamma(1-\kappa w)v & \text{in } \Omega \times (0,T], \\ w\nabla w \cdot \nu = v\nabla w \cdot \nu = 0 & \text{on } \partial\Omega \times (0,T], \\ w(x,0) = w_0(x),\ v(x,0) = v_0(x), & x \in \Omega \end{cases}$$

where $\kappa = k^{-1}$. This problem is easier to study since the reaction terms are linear in v.

The uniformly parabolic approximating problem

In order to prove the existence of a solution, we can approximate it by a uniformly parabolic system, say

$$\begin{cases} w_t = \varepsilon \triangle w + \mathrm{div}(w \nabla w) + (1-w)w + (\gamma(1-\kappa w) - 1 - w)v & \text{in } Q_T, \\ v_t = \varepsilon \triangle v + \mathrm{div}(v \nabla w) + \gamma(1-\kappa w)v & \text{in } Q_T, \\ w \nabla w \cdot \nu = v \nabla w \cdot \nu = 0 & \text{on } \partial\Omega \times (0, T], \\ w(x,0) = w_0(x), \ v(x,0) = v_0(x), & x \in \Omega \end{cases}$$

where $Q_T = \Omega \times (0, T]$, and find that along a subsequence as $\varepsilon \to 0$

$$\begin{aligned} w^\varepsilon &\to w \ \text{ strongly in } \ L^2(Q_T), \\ \nabla w^\varepsilon &\rightharpoonup \nabla w \ \text{ weakly in } \ L^2(Q_T), \\ v^\varepsilon &\rightharpoonup v \ \text{ weakly in } \ L^2(Q_T), \end{aligned}$$

where (w, v) is a solution of the original problem.

The convergence result

Theorem. As k tends to zero, v^k converges to zero weakly in $L^2(Q_T)$, and w^k converges strongly in $L^2(Q_T)$ to the unique weak solution u of the problem

$$\begin{cases} u_t = \mathrm{div}(u\nabla u) + (1-u)u & \text{in } Q_T, \\ u\nabla u \cdot \nu = 0 & \text{on } \partial\Omega \times (0,T], \\ u(x,0) = u_0(x) & x \in \Omega. \end{cases}$$