# On a parabolic-hyperbolic system for contact inhibition of cell growth

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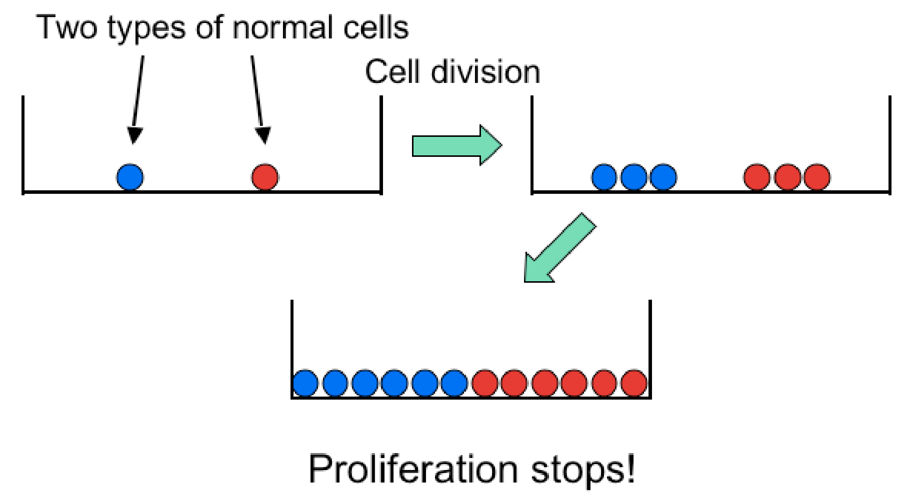
# The biological context

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.

Today we prove this property in higher space dimension.

We study associated travelling wave solutions, which can be segregated or overlapping.

# Proliferation of cells



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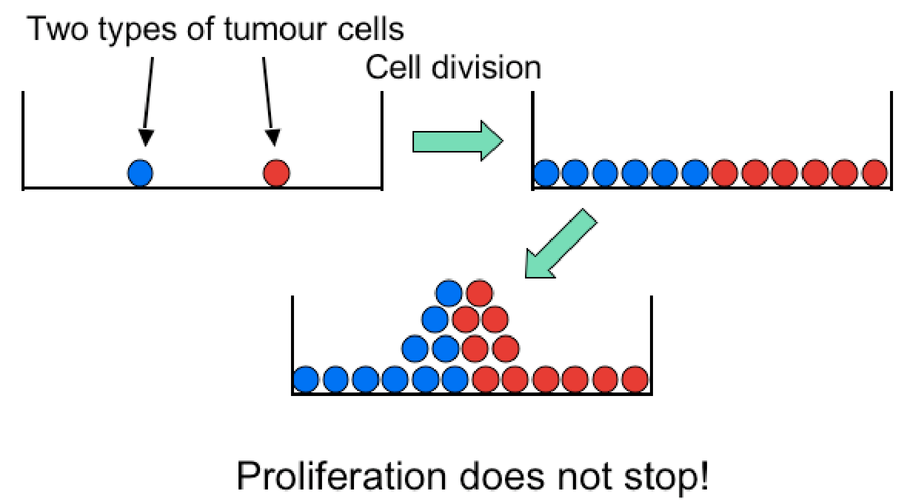
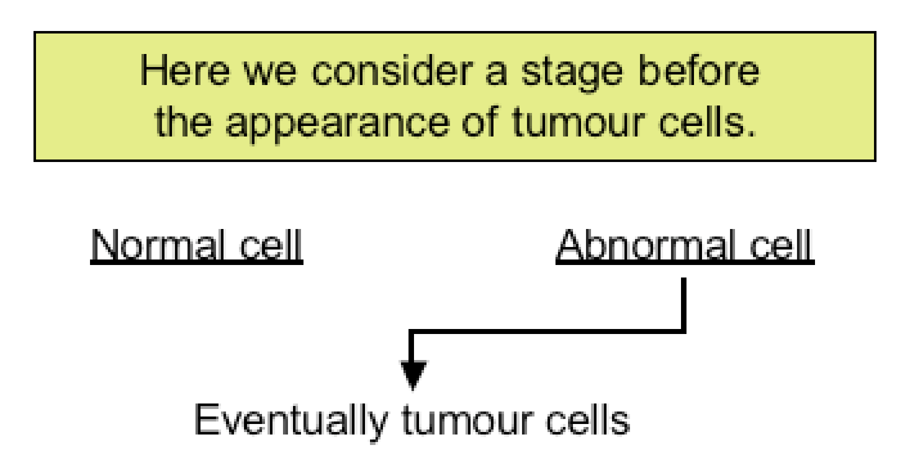


# Contact inhibition



# 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;
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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 $\chi = Id$

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

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

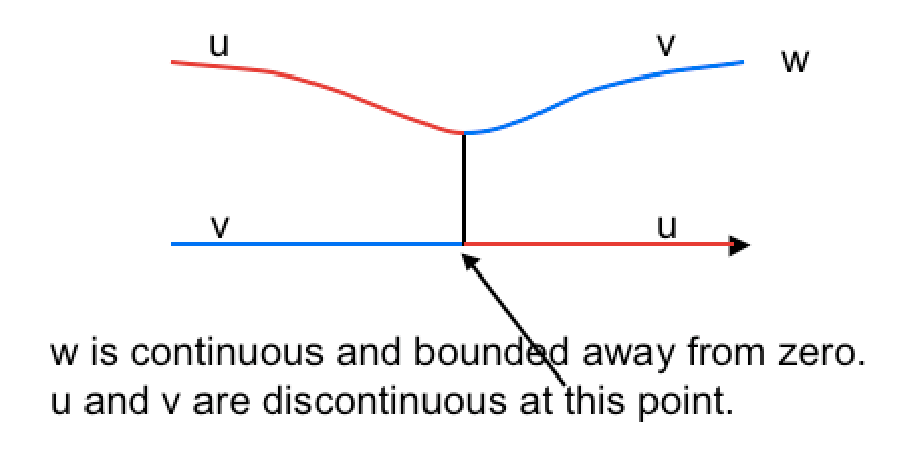
The equation for $w$ has the form of a nonlinear diffusion equation

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

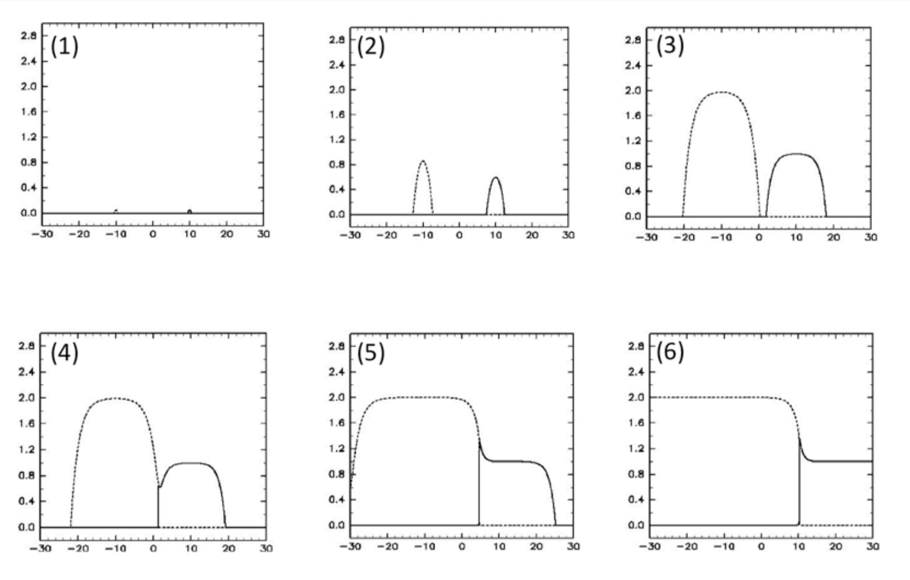
This equation is uniformly parabolic since $w$ is bounded away from zero, and therefore $w$ is smooth. But now, suppose that $u$ and $v$ have disjoint supports. Then both $u$ and $v$ have to be discontinuous across the interface between their supports.

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

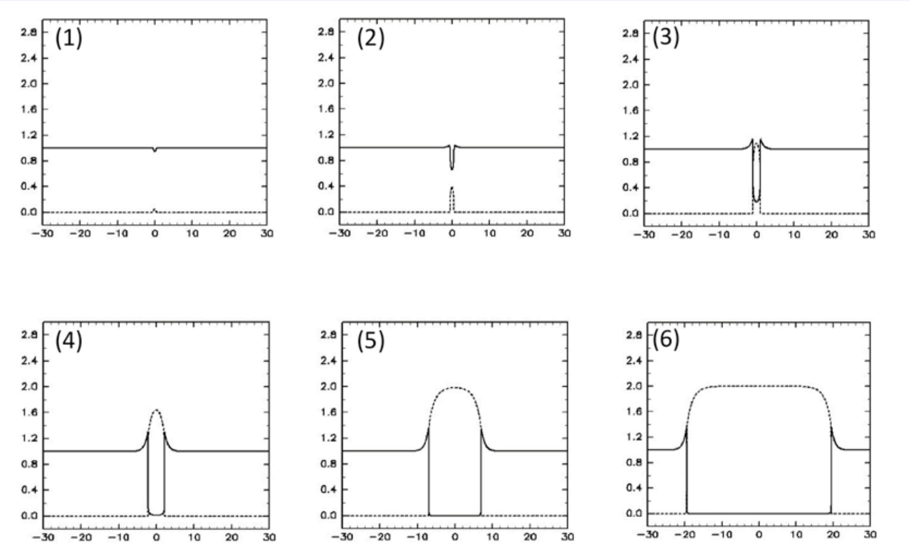
# A typical (u,v,w) profile



# 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

$$0 \leq r \leq 1.$$

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 $\nabla w$ 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 $b = -\nabla w$. De Lellis also introduces such concepts as

- regular Lagrangian flow;
- a nearly incompressible vector field;
- a concept of renormalized solutions, which satisfy the chain rule even though they are not very smooth weak solutions.

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# Regularization method

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

# Existence of smooth overlapping solutions

Theorem. Let $\mathcal{B}_n \subset \mathbb{R}^N$ be a ball of radius $\mathcal{R}_n$, $\alpha$, $\beta$, $\gamma$ 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 $\Omega$. 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

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

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

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

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 $W^{2,1}_p(\mathcal{B}_n \times (0, T))$. Therefore there exist a function $w \in W^{2,1}_{p,\text{loc}}(\mathbb{R}^N \times [0,\infty))$ and a subsequence of $\{w_n\}$ which we denote again by $\{w_n\}$ such that

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

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

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

At this point, we also know that there exists a bounded function $\chi$ such that

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

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

# Strong convergence of $r_n$ to $r$

It follows from a result 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

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

where $\nu$ 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

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

This problem is much 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

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

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

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

This theorem connects the solutions of a rather complicated system with the unique solution of an initial value problem with a Fisher type nonlinear parabolic equation.

# Ideas of proof

From maximum principle arguments

$$0 \leq v^k \leq w^k \leq 1.$$

Moreover

$$\int_0^T \int_\Omega w^k v^k \leq Ck.$$

Therefore

$$v^k w^k \to 0$$

as $k \to 0$, and since $v^k \leq w^k$, it follows that

$$v^k \to 0.$$

Formally setting $v = 0$ in the equation for $u$ gives the limit equation.

# Travelling wave solutions

We would now like to study travelling wave solutions of our system. Before doing so, we recall results about travelling wave solutions of the nonlinear diffusion Fisher equation

$$u_t = \frac{1}{m}(u^m)_{xx} + u(1-u), \ (x,t) \in \mathbb{R} \times \mathbb{R}_+$$

There exist travelling wave solutions of the nonlinear diffusion Fisher equation, namely functions of the form $u(x,t) = U(x-ct)$ which are weak solutions of the problem

$$\begin{cases} \frac{1}{m}(U^m)'' + cU' + U(1-U) = 0, \ x \in \mathbb{R} \\ U(-\infty) = 1, \quad U(+\infty) = 0. \end{cases}$$

# Travelling wave solutions for degenerate Fisher equation

**Theorem** (Gilding and Kersner) Assume that $m > 1$. Then there exists $c_m > 0$ such that

- For $0 < c < c_m$, there is no weak solution of the nonlinear diffusion Fisher equation
- For any $c \geq c_m$, there exists a weak solution $U_c$ to the nonlinear Fisher equation which is unique up to translation. Moreover, $U_c$ is nonincreasing. More precisely, for $c > c_m$, $U_c$ is strictly positive and stricly decreasing on $\mathbb{R}$; for $c = c_m$, $U_{c_m}$ is compactly supported from the right.

The main difference with the linear case $m = 1$ is the fact that the travelling wave of minimal velocity is compactly supported from one side.

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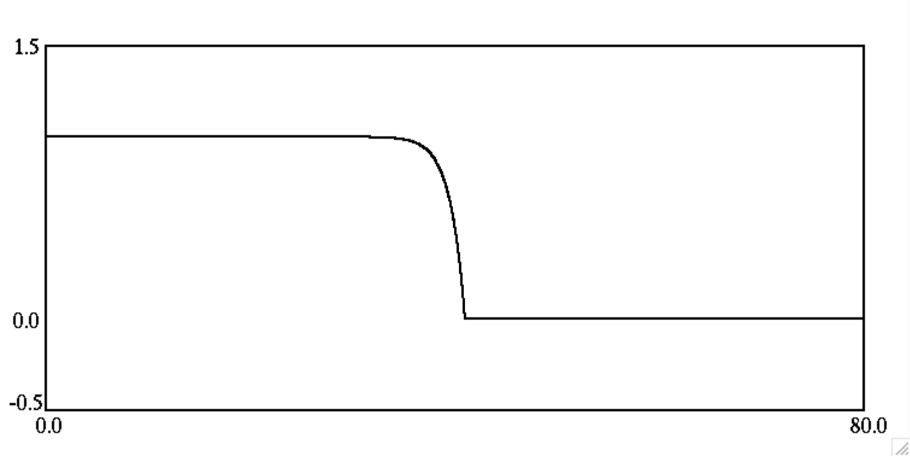
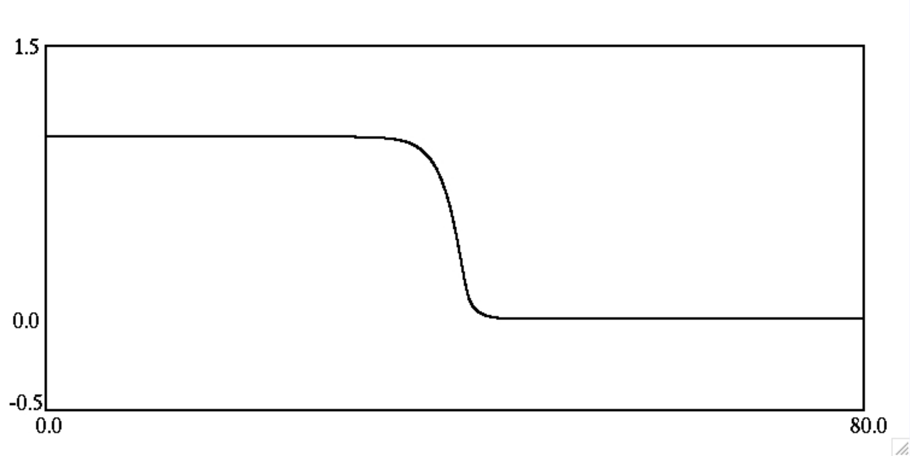
# Travelling wave solutions with compact support



# Positive travelling wave solutions



# Travelling wave solutions of the original problem

We now consider travelling wave solutions, namely solutions of the problem (TW)

$$\begin{cases} (uw')' + cu' + u(1-u-v) = 0 \\ (vw')' + cv' + \gamma v(1 - \dfrac{u-v}{k}) = 0 \\ w = u + v \\ v(-\infty) = k,\ u(\infty) = 1,\ u(-\infty) = v(\infty) = 0. \end{cases}$$

Bertsch, Mimura et Wakasa show that for any $k > 1$ and $\gamma > 0$ there exists a unique (up to translation) segregated travelling wave, $(u_{\overline{c}}(z), v_{\overline{c}}(z))$, for a unique wave speed $\overline{c} > 0$, which satisfies

$$u_{\overline{c}}(z) \begin{cases} = 0 & \text{if } z < 0 \\ > 0 & \text{if } z > 0, \end{cases} \qquad v_{\overline{c}}(z) \begin{cases} > 0 & \text{if } z < 0 \\ = 0 & \text{if } z > 0, \end{cases}$$

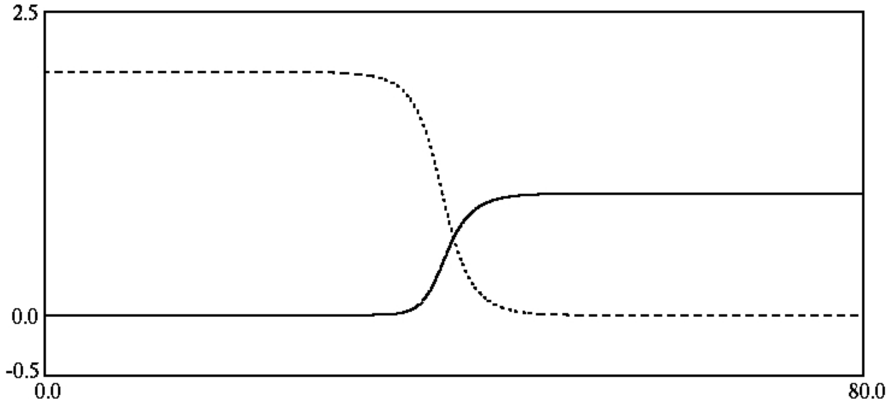
and

$$u_{\overline{c}}(0^+) = v_{\overline{c}}(0^-) > 0.$$

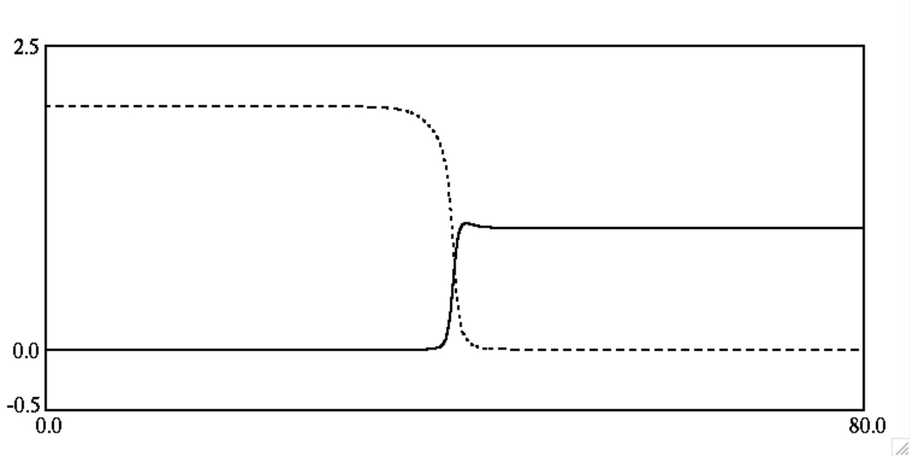
**Theorem 1** Let $\overline{c} > 0$ be the speed of the segregated travelling wave. Then for any $c > \overline{c}$ Problem (TW) has a solution satisfying

$$u_c(z) > 0, \ v_c(z) > 0, \ w_c'(z) < 0 \quad \text{for all } z.$$

# Numerical graph



# Numerical graph



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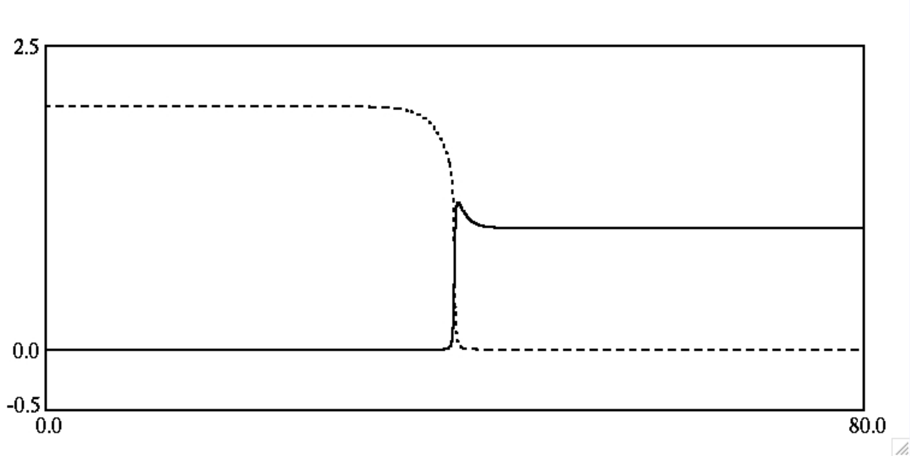

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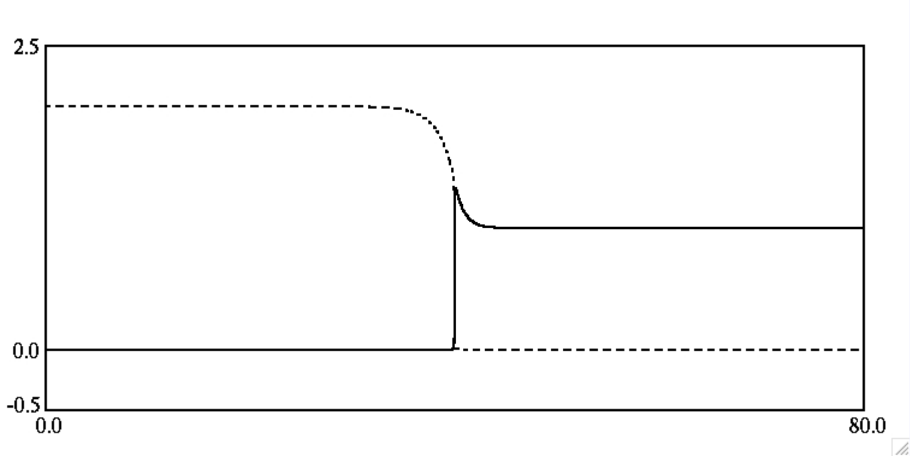
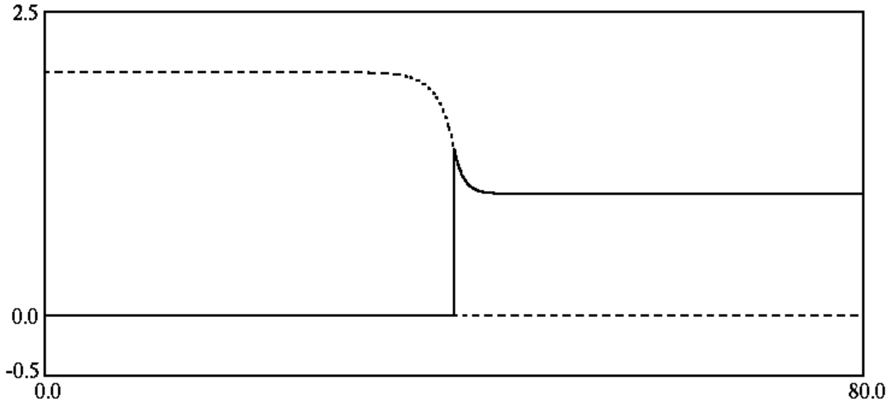


# Numerical graph



# Travelling wave solutions

Theorem 2 Let $c > 0$ and let $u_c(z)$ and $v_c(z)$ be nonnegative and bounded functions on $\mathbb{R}$ which satisfy

$$\begin{cases} (u(u+v)')' + cu' + u(1-u-v) = 0 \\ (v(u+v)')' + cv' + \gamma v(1-(u+v)/k) = 0 \\ v(-\infty) = k, \ u(\infty) = 1, \end{cases}$$

such that $w_c' := (u_c + v_c)' < 0 \quad \text{in } \mathbb{R}$. If

$$u(z+ct,t) \to u_c(z) \text{ and } v(z+ct,t) \to v_c(z) \text{ in } L^1_{\text{loc}}(\mathbb{R}) \text{ as } t \to \infty,$$

$$\begin{cases} w(z+ct,t) \to w_c(z) \\ w_x(z+ct,t) \to w_c'(z) \end{cases} \quad \text{uniformly with respect to } z > a \text{ as } t \to \infty$$

and

$$v_0(x) = 0 \text{ and } u_0(x) \geq \delta_0 > 0 \text{ for a.e. } x > x_0$$

for some constants $x_0 \in \mathbb{R}$ and $\delta_0 > 0$, then $(u_c, v_c)$ is a segregated travelling wave.