Derivation of free boundary problem for tumor growth

Nicolas Vauchelet
vauchelet@math.univ-paris13.fr

collaboration with P. Degond, S. Hecht, B. Perthame,
F. Quiròs, M. Tang, E. Zatorska

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The outline of the lecture is the following

- Lecture 1 : Introduction and Modeling
  - Dynamical system of tumor growth
  - Spatial models of tumor growth
- Lecture 2 : First example
  - Some reminders on parabolic problems
  - Derivation of the Stefan free boundary problem
- Lecture 3 : Derivation of Hele-Shaw problem for tumor growth
  - Derivation of Hele-Shaw model thanks to an incompressible limit of a cell mechanical model
- Lecture 4 : Some extensions
  - Derivation of a free boundary model with viscoelasticity
  - Traveling wave to describe tumor growth

Lecture 1

Introduction and modeling

Outline of lectures 1 and 2

1. Dynamical models
   - A simple model
   - Proliferative and quiescent cells
2. Spatial models of tumor growth
   - Presentation of the cells mechanical model under investigation
   - Free boundary model of Hele-Shaw type
3. Some generalities
   - Parabolic equation in biology
   - BV functions
4. A warm-up example : derivation of Stefan free boundary problems
   - Setting of the problem
   - Proof of the convergence
   - Stefan problem with latent heat
   - Geometric interpretation

Introduction

Tumor is an abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells : cells proliferate or refrain from dying (apoptosis).
When the immune system is unable to detect and eliminate these cells, we talk about malign tumor, which can lead to cancer.

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Some numbers :

- 18.1 M of new cases and 9.6 M of death worldwide in 2018.
- In France, cancer is the first cause of death ($\sim$ 30% of death).
- In France, the number of cases increased of 20% between 1980 and 2000.

In this lecture we will distinguish between several kind of mathematical models

- Time dynamical models, which describe the time the dynamics of the number of tumoral cells, independently of their spatial organization.
- Spatial models, which incorporate the spatial growth. They can be of different nature. For instance in this lecture we will consider :
  - Mechanical models, which describe the dynamics of the density of tumoral cells.
  - Free boundary models, which model the tumor by the dynamic of its domain.

Outline of lecture 1 and 2

Population dynamics

In population dynamics, we are interested to the dynamics of density of populations, for instance density of tumor cells, density of healthy cells, density of nutrients, ...
Let us denote $N(t)$ the density of tumoral cells at time $t > 0$ (we first assume that it does not depend on the spacial variable x). In a simple approach, we only consider that cells grow, divide and die (apoptosis).

$$\frac{dN}{dt} = N(t) \underbrace{R(N(t))}_{\text{growth rate}}, \qquad N(0) = N^0.$$

- If $N^0 \geq 0$, then for all nonnegative time, $N \geq 0$. It is a consequence of uniqueness for this Cauchy problem. (We may also remark that we have the formula $N(t) = e^{\int_0^t R(N(s))\, ds} N^0$).
- If $R(N) > 0$, then N is increasing : The number of tumoral cells increases.
- If $R(N) < 0$, then N is decreasing : The number of tumoral cells decreases.

Equilibria and stability

For a dynamical system autonomous, a stationary solution is an equilibrium. We say that this equilibrium is asymptotically stable if all eigenvalues of the Jacobian taken at the equilibrium have negative real part.

More precisely, consider an autonomous dynamical system

$$y' = f(y).$$

- Equilibria are $\overline{y}$ solution to $f(\overline{y}) = 0$.
- Stability : $\overline{y}$ is asymptotically stable if $\forall\, \lambda \in \mathrm{Sp}(Df(\overline{y}))$, $\mathrm{Re}(\lambda) < 0$.

Simple model

For the simple model

$$\frac{dN(t)}{dt} = N(t)R(N(t)), \qquad N(0) = N_0.$$

The growth function R may have the following expressions :

- $R(N) = r\left(1 - \left(\frac{N}{K}\right)^a\right)$, logistic power growth, $(a > 0)$;
- $R(N) = b\ln(\frac{K}{N})$, Gompertz law.

For both expressions, we have that

Positivity. If $N_0 > 0$ then for any $t > 0$, $N(t) > 0$.

Equilibria. There are two equilibria : 0 and K.
(Indeed, $\overline{N}R(\overline{N}) = 0$ iff $\overline{N} = 0$ or $\overline{N} = K$).

Stability. K is stable, and 0 is unstable.
(Indeed, $(xR(x))' = R(x) + xR'(x)$ and we have $KR'(K) < 0$ and $R(0) > 0$).

Simple model

$$\frac{dN(t)}{dt} = N(t)R(N(t)), \qquad N(0) = N_0.$$

We can draw the following consequence :

Consequence

Let $N_0 > 0$. Solutions are monotonous : if $R(N_0) > 0$, then $\frac{d}{dt}N(t) \geq 0$ for any $t \geq 0$; if $R(N_0) < 0$, then $\frac{d}{dt}N(t) \leq 0$ for any $t \geq 0$.

Proof. Let us denote $u(t) = N'(t)$, then we have

$$u'(t) = u(t)(R(N) + NR'(N)), \qquad u(0) = N_0 R(N_0).$$

By uniqueness, since 0 is a solution to this ODE, the solution does not change sign. □

Simple model : action of a therapy

Mathematical model

Therapy consists in killing tumoral cells. Let us denote $c_{th}(t)$ the effective concentration of a drug killing tumoral cells. It acts as a death term :

$$\frac{dN(t)}{dt} = N(t)R(N(t)) - c_{th}(t)N(t), \qquad N(0) = N_0 > 0.$$

Simple model : action of a therapy

Mathematical model

Therapy consists in killing tumoral cells. Let us denote $c_{th}(t)$ the effective concentration of a drug killing tumoral cells. It acts as a death term :

$$\frac{dN(t)}{dt} = N(t)R(N(t)) - c_{th}(t)N(t), \qquad N(0) = N_0 > 0.$$

If c_{th} is a constant, we can compute the equilibria of the system :

$$r\overline{N}\left(1 - \left(\frac{\overline{N}}{K}\right)^a\right) - c_{th}\overline{N} = 0.$$

It implies

$$\overline{N} = 0 \qquad \text{or} \qquad \overline{N} = K\left(1 - \frac{c_{th}}{r}\right)^{1/a}.$$

Thus, the therapy could be succesful only if $\boxed{c_{th} \geq r}$.

Simple model : action of a therapy

Action of a therapy

Problem : Due to side effects, we can only deliver a maximal dose of the drug during some time (length T) : $\int_0^T c_{th}(t)dt \leq U_m$.
Question : How to optimize the treatment to be as effective as possible ?

Simple model : action of a therapy

Action of a therapy

Problem : Due to side effects, we can only deliver a maximal dose of the drug during some time (length T) : $\int_0^T c_{th}(t)dt \leq U_m$.
Question : How to optimize the treatment to be as effective as possible ?

A possible treatment is to use a *bolus* : maximal dose in one take

$$c_{\text{bolus}}(t) = \sum_{k \geq 0} \delta_0(t - kT)U_m.$$

The mathematical system for this therapy reads

$$\frac{dN_b}{dt} = N_b R(N_b), \text{ on } (0,T), \qquad N_b(T^+) = N_b(T^-)e^{-U_m}$$

Simple model : action of a therapy

To justify this system, we approximate δ_T by $\frac{1}{\varepsilon}\mathbf{1}_{[T-\varepsilon,T]}$ with $\varepsilon \ll 1$. Thus,

$$\frac{dN_b}{dt} = N_b R(N_b) - \frac{U_m}{\varepsilon} N_b, \quad \text{on } (T-\varepsilon, T).$$

Keeping only the dominant term, we get

$$\frac{d}{dt}\ln(N_b) = R(N_b) - \frac{U_m}{\varepsilon} \sim -\frac{U_m}{\varepsilon} \qquad (\varepsilon \ll 1).$$

Integrating on $(T-\varepsilon, T)$ we obtain,

$$\ln(N_b(T)) - \ln(N_b(T-\varepsilon)) \sim -U_m.$$

Letting $\varepsilon \to 0$, we deduce

$$N_b(T^+) = N_b(T^-)e^{-U_m}.$$

Simple model : action of a therapy

Optimal treatment

Assuming that $R'(N) \leq 0$. Then the *bolus* is an optimal therapy.

Proof. On $(0, T)$, the systems read

$$\begin{cases} N' = NR(N) - c_{th}N, \\ N(0) = N_0. \end{cases} \qquad \begin{cases} N_b' = N_b R(N_b), \\ N_b(0) = N_0, \quad N_b(T^+) = N_b(T^-)e^{-U_m}. \end{cases}$$

We use the new variable $U = \ln(N)$ and denote $G(U) = R(N)$.

$$\begin{cases} U' = G(U) - c_{th}, \\ U(0) = U_0 = \ln(N_0). \end{cases} \qquad \begin{cases} U_b' = G(U_b), \\ U_b(0) = U_0, \quad U_b(T^+) = U_b(T^-) - U_m. \end{cases}$$

Clearly, $U(t) \leq U_b(t)$ on $(0, T)$. Since, by assumption G is decreasing, we have $G(U) \geq G(U_b)$. Thus,

$$\frac{d}{dt}(U - U_b) = G(U) - G(U_b) - c_{th} \geq -c_{th}.$$

Simple model : action of a therapy

Integrating on $(0, T)$, we deduce

$$U(T) - U_b(T^-) \geq -\int_0^T c_{th}(t)dt \geq -U_m.$$

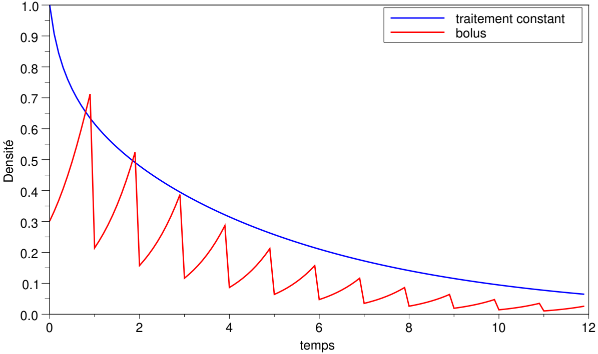
Thus

$$U(T) \geq U_b(T^-) - U_m = U_b(T^+).$$

It ends the proof.

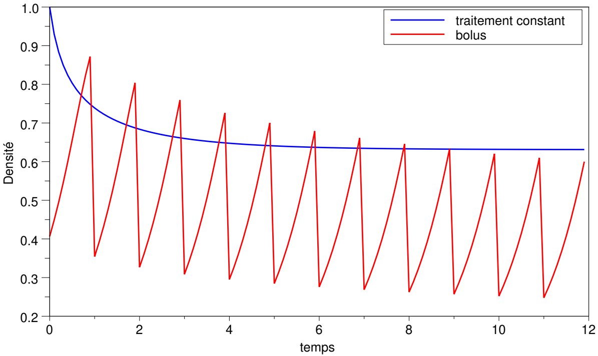
Simple model : numerical illustration

The following graph displays a comparison between the solution for c_{th} constant and the one for the *bolus* case.



Simple model : numerical illustration

Same comparison in the case where the therapy dose is not sufficient to kill the tumor.



Outline of lecture 1 and 2

Proliferative and quiescent cells

It has been observed that not all cells proliferate. Observations show that a big part of cells stay in a quiescent state. To take into account this effect, we should consider at least two states of cells : proliferative cells with density P, quiescent cells with density Q. A simple model reads

$$\begin{cases} \frac{dP}{dt} = F(P) - bP + cQ, \\ \frac{dQ}{dt} = bP - cQ - dQ, \end{cases}$$

with the parameters :

- F growth function (e.g. $F(P) = rP(1 - (\frac{P}{K})^a)$ with $r, a, K > 0$) ;
- $b, c > 0$ transition coefficients ;
- d death rate.

This system is complemented with initial data P_0, Q_0. The density of tumoral cells is given by $N(t) = P(t) + Q(t)$.

Proliferative and quiescent cells

Properties

We have

1. *Preservation of positivity and monotony* :

$$P_0, Q_0 \geq 0 \;\Rightarrow\; P(t), Q(t) \geq 0, \forall\, t \geq 0.$$

$$\begin{cases} u_0 := F(P_0) - bP_0 + cQ_0 \geq 0, \\ v_0 := bP_0 - (c+d)Q_0 \geq 0 \end{cases} \;\Rightarrow\; \frac{dP}{dt} \geq 0, \frac{dQ}{dt} \geq 0.$$

2. *Equilibria :* There are two steady states : $(0,0)$ and $(\overline{P}, \overline{Q})$ with $\overline{P} = K(1 - \frac{bd}{r(c+d)})^{1/a}$, $Q = \frac{b}{c+d}\overline{P}$. And we have
   - For $d \ll 1$, the steady state $(\overline{P}, \overline{Q})$ is asymptotically stable.
   - If $r > b + c + d$, the steady state $(0,0)$ is linearly unstable.

Proliferative and quiescent cells

Proof.

1. *Positivity.* We define $P_- = \min(0, P) \leq 0$ and $Q_- = \min(0, Q) \leq 0$. We recall that we have $P = P_+ + P_-$ and $Q = Q_+ + Q_-$. Multiplying both equation by P_- and Q_-, respectively, and adding, we get

$$\frac{1}{2}\frac{d}{dt}({P_-}^2 + {Q_-}^2) \ = r{P_-}^2(1 - (\frac{P}{K})^a) - b{P_-}^2 + cQP_- + bPQ_- - (c+d){Q_-}^2$$

Using the fact that $QP_- = Q_+P_- + Q_-P_- \leq Q_-P_-$ and $Q_-P = Q_-P_+ + Q_-P_- \leq Q_-P_-$, we deduce

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}({P_-}^2 + {Q_-}^2) \ &\leq r{P_-}^2(1 - (\frac{P}{K})^a) - b{P_-}^2 + (b+c)Q_-P_- - (c+d){Q_-}^2 \\ &\leq ({P_-}^2 + {Q_-}^2)(|r(1 - (\frac{P}{K})^a) - b| + \frac{b+c}{2} + c + d).\end{aligned}$$

Integrating and using the fact that $P_-(0) = 0$ and $Q_-(0) = 0$, we deduce that for all $t \geq 0$, ${P_-}^2(t) + {Q_-}^2(t) = 0$.

Proliferative and quiescent cells

Monotony. By the same token, we define $u = \frac{dP}{dt}$, $v = \frac{dQ}{dt}$. Then

$$u' = F'(P)u - bu + cv, \qquad v' = bu - (c+d)v.$$

Multiplying by u_- and v_- and adding, we get

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt}({u_-}^2 + {v_-}^2) &= (F'(P) - b){u_-}^2 + cvu_- + buv_- - (c+d){v_-}^2 \\
&\leq (F'(P) - b){u_-}^2 + (c+b)u_-v_- - (c+d){v_-}^2 \\
&\leq ({u_-}^2 + {v_-}^2)(|F'(P) - b| + \frac{c+b}{2}).
\end{aligned}$$

We conclude as above using a Gronwall argument.

Proliferative and quiescent cells

2. *Equilibria.* We solve the system

$$F(\overline{P}) - b\overline{P} + C\overline{Q} = 0\ , \qquad b\overline{P} - (c+d)\overline{Q} = 0.$$

It gives

$$\overline{Q} = \frac{b}{c+d}\overline{P}\ , \qquad \overline{P}\left(r(1-(\frac{\overline{P}}{K})^a) - \frac{bd}{c+d}\right) = 0.$$

Thus, we have two equilibria $\overline{P} = \overline{Q} = 0$ or $\overline{P} = K(1-\frac{bd}{r(c+d)})^{1/a}$, $Q = \frac{b}{c+d}\overline{P}$.

Proliferative and quiescent cells

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Stability. The Jacobian is given by

$$J = \begin{pmatrix} F'(\overline{P}) - b & c \\ b & -(c+d) \end{pmatrix} = \begin{pmatrix} r(1-(1+a)(\frac{\overline{P}}{K})^a) - b & c \\ b & -(c+d) \end{pmatrix}.$$

At the equilibrium $(\overline{P}, \overline{Q})$, we have

$$J = \begin{pmatrix} -ra - b + (1+a)\frac{bd}{c+d} & c \\ b & -(c+d) \end{pmatrix}.$$

When $d = 0$, we have $\mathrm{Tr}\, J = -ra - b - c < 0$ and $\mathrm{Det}\, J = rac > 0$. Hence, the real part of eigenvalues is negative. By continuity it is also true for d small.

Proliferative and quiescent cells

At the equilibrium $(0,0)$, then the Jacobian reads

$$J_0 = \begin{pmatrix} r-b & c \\ b & -(c+d) \end{pmatrix}$$

Then $\mathrm{Tr}\, J_0 = r - b - c - d$. Then, if $r > b + c + d$, we deduce that one eigenvalue (at least) has its real part positive. Thus it is linearly unstable.

Proliferative and quiescent cells : action of a therapy

Action of a therapy.
We usually consider that there are two different drugs : cytotoxic drugs kills proliferative cells, cytostatic drugs block the proliferation. We can add these effects in the simple model above :

$$\begin{cases} \dfrac{dP}{dt} = F(P) - (b + c_{\mathrm{stat}})P + cQ - c_{\mathrm{tox}}P, \\ \dfrac{dQ}{dt} = (b + c_{\mathrm{stat}})P - cQ - dQ, \end{cases}$$

where c_{stat} and c_{tox} represent the concentration of cytostatic and cytotoxic drugs, respectively.

- Effect of c_{stat}

We replace b by $b + c_{\mathrm{stat}}$ in the previous equilibrium. Then they are given by $(0, 0)$ and

$$\overline{P} = K\Big(1 - \frac{d(b + c_{\mathrm{stat}})}{r(c + d)}\Big)^{1/a}, \quad \overline{Q} = \frac{b + c_{\mathrm{stat}}}{c + d}\overline{P}.$$

Proliferative and quiescent cells : action of a therapy

In the latter case, we have then,

$$\overline{N} = \overline{P} + \overline{Q} = K\Big(1 + \frac{b + c_{\mathsf{stat}}}{c + d}\Big)\Big(1 - \frac{d(b + c_{\mathsf{stat}})}{r(c + d)}\Big)^{1/a}.$$

Thus $\overline{P}$ diminishes, but $\overline{Q}$ increases. We notice that in the particular case $\frac{d}{r} \ll 1$, $\overline{N}$ increases, i.e. the size of the tumor increases!

Proliferative and quiescent cells : action of a therapy

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- Effect of c_{tox}

The non-zero equilibrium is given by

$$\overline{P} = K\Big(1 - \frac{c_{\mathsf{tox}}}{r} - \frac{bd}{r(c+d)}\Big)^{1/a}, \quad \overline{Q} = \frac{b}{c+d}\overline{P}.$$

and

$$\overline{N} = \overline{P} + \overline{Q} = K\Big(1 + \frac{b}{c+d}\Big)\Big(1 - \frac{c_{\mathsf{tox}}}{r} - \frac{bd}{r(c+d)}\Big)^{1/a}.$$

This is always efficient since $\overline{N}$ decreases.

Competition between healthy and tumor cells

Now, we consider a simple model taking into account competition between healthy and tumor cells. Let H denote the density of healthy cells and T denote the density of tumor cells.

$$\begin{cases} \dfrac{dH}{dt} = R_{\text{in}} + r_H H(1 - \dfrac{H+T}{K_H}) - d_H H, \\ \dfrac{dT}{dt} = r_T(1 - \dfrac{H+T}{K_T}) - d_T T, \end{cases}$$

where $R_{\text{in}} > 0$ is the production rate of healthy cells. We complement with the initial data H_0 and T_0. We can verify with the same techniques as above

Lemma

If $R_{\text{in}} + r_H H_0(1 - \frac{H_0+T_0}{K_H}) - d_H H_0 \leq 0$ and $r_T(1 - \frac{H_0+T_0}{K_T}) - d_T T_0 \geq 0$.
Then, for all $t \geq 0$, $\frac{dH}{dt} \leq 0$, $\frac{dT}{dt} \geq 0$.

In other words if the density of healthy cells starts to diminish and the one of tumor cells starts to increase, then it stay like this for any larger time.

Outline of lecture 1 and 2

Continuum model of tumor growth

Recent models of cancer growth consider tumor cells as elastic materials to describe the cells multiplication within a tissue.

We can distinguish two classes of model :

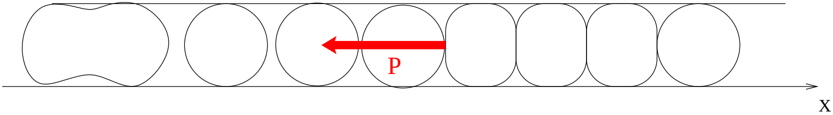
- Individual-based model (IBM) : description of small-scale phenomena
- Continuum model : macroscopic description

IBM : Take into account the mechanical properties of the cells. Very accurate but numerically very expensive.
Continuum model : Less accurate but well adapted for large-scale behaviour and less expensive in a numerical purpose.

In this lecture, we will only focus on the description from a mathematical point of view of the growth of tumor by using macroscopic model of tumor growth.

Cells model

Recent models of cancer growth consider tumor cells as elastic materials to describe the cells multiplication within a tissue.
The invasion ability of tumor cells is mainly driven by cell division which depends on local density and nutrient concentration and on pressure forces.



- In a favorable environment, cells growth by mitosis.
- Cells creates a pressure on their neighbours : they push them, which generates a motion.
- Under mechanical stresses P, cells are compressed and can deform. If P is too large, there is no cells division.
- Influence of the nutrient c.

Continuum model of tumor growth

Unknowns :
$\rho(t,x)$: density of tumor cells at time $t \geq 0$ and position $x \in \mathbb{R}^d$,
$p(t,x)$: elastic pressure, for simplicity we assume that it is given by a law $p = P(\rho)$, [1]
$v(t,x)$: velocity field,
$c(t,x)$: nutrient concentration.

The system governing these quantities reads

$$\partial_t \rho + \underbrace{\text{div}_x(\rho v)}_{\text{mechanical pressure}} = \underbrace{\rho G(p,c)}_{\text{Growth term}} + \underbrace{\epsilon \Delta_x \rho}_{\text{active motion}},$$

$$v = -C_S \nabla_x p, \qquad \text{Darcy law},$$

$$\partial_t c - \Delta_x c + \lambda c \rho = 0, \qquad \text{Nutrient consumption}.$$

1. H. Byrne, D. Drasdo, J. Math. Biol. 58, 2009

Continuum model of tumor growth

- ϵ is a diffusion coefficient, $C_S > 0$ is the mobility (the quotient of permeability and viscosity), $\lambda > 0$.
- The growth function is given by $G(p,c)$ and satisfies $\partial G/\partial p \le 0$, $\partial G/\partial c \ge 0$. In this talk, we will consider G only depending on p or c.
  - If $G = G(p)$, we assume that there exists P_M such that $G(P_M) = 0$. In the physicist litterature (see [Prost et al]), P_M is usually called the homeostatic pressure. In the case $G = G(p)$, we will make the assumptions :

$$G(0) = G_M > 0, \quad G'(\cdot) < 0, \quad G(P_M) = 0.$$

  - If $G = G(c)$, the lack of nutrients leading to cells necrosis is modeled by : $\exists\, \overline{c}$, such that $G(c) < 0$ for $c < \overline{c}$. Then we observe a proliferative rim and a necrotic core. In the case $G = G(c)$, we will make the assumptions :

$$G'(\cdot) \le 0, \quad \exists\, \overline{c} \ge 0, G(\overline{c}) = 0, G'(\overline{c}) > 0.$$

References : Bellomo & Preziosi ['00], Byrne & Drasdo [J Math Bio '09], Byrne & Chaplain [Math Biosc '96], Preziosi & Tosin [J Math Bio '09].

Spatial model with proliferative and quiescent cells

In an extension of this simple spatial model we may consider different states of the cells[2]. We denote
$\rho_P(t,x)$: density of proliferative tumor cells at time $t \geq 0$, position $x \in \mathbb{R}^d$,
$\rho_Q(t,x)$: density of quiescent cells,
$\rho_N(t,x)$: density of necrotic cells,
$p(t,x)$: elastic pressure given by a law $p = P(\rho_P + \rho_Q)$.

The system governing these quantities reads

$$\partial_t \rho_P + \operatorname{div}(\rho_P v_P) = \rho_P G(\rho_P + \rho_Q + \rho_N) - a\rho_P + b\rho_Q,$$
$$\partial_t \rho_Q + \operatorname{div}(\rho_Q v_Q) = a\rho_P - b\rho_Q - d\rho_Q,$$
$$\partial_t \rho_N = d\rho_Q,$$
$$v_P = -\mu_P \nabla_x p, \quad v_Q = -\mu_Q \nabla_x p, \qquad \text{(Darcy law)},$$

where μ_P and μ_Q are the mobilities, b transition rate from proliferative to quiescent state, d death rate.
This model supposes that necrotic cells do not participate to establish a pressure but are present to stop proliferation (taking as above G decreasing and zero at some point).

2. Sheratt & Chaplain (2001), Bertsch, Dal Paso, Mimura (2010), ...

Spatial model with nutrient

In order to model the appearance of a necrotic core for avascularized tumors, we include the effect of the nutrient (dentity $c(t,x)$).

$$\partial_t \rho - \mathrm{div}(\rho \nabla p) = \rho G(p, c),$$
$$\tau \partial_t c - \Delta c + \lambda c \rho + r c = r c_b,$$
$$p = P(\rho) = \rho^k.$$

We complement the model with initial data $\rho(t=0) = \rho^0$ and $c(t=0) = c^0$. In this model, the constant c_b is the fresh nutrient provided by the vasculature with a rate r.

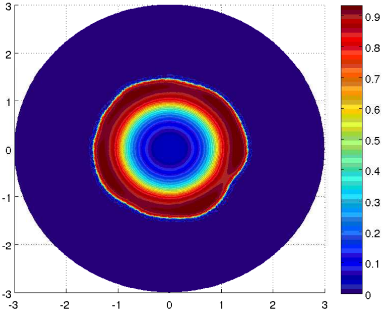
We assume moreover

$$\frac{\partial G(p,c)}{\partial p} < 0, \quad \frac{\partial G(p,c)}{\partial c} < 0, \quad G(p, \overline{c}) = 0, \quad G(P_M, c_b) = 0.$$

Spatial model with nutrient

With this model, the growth of the tumor generates a depletion of nutrient in the center of the tumor, which leads to a necrotic core.

It is illustrated by a numerical simulation of the above model. We clearly distinguish the proliferative rim and the necrotic core.



It induces a lack of control on the growth, then we will mainly consider the case $G = G(p)$ (growth only pressure dependent) in the rest of the lecture.

Spatial model with healthy cells

In some models, we may assume that the response to compression differs between healthy cells (density ρ_H) and tumor cells (density ρ_T)[3].

$$\partial_t \rho_T - \mathrm{div}(\rho_T v) = r_T \rho_T \left(1 - \frac{\rho_H + \rho_T}{K_T}\right), \qquad \rho_T(+\infty) = 0,$$

$$\partial_t \rho_H - \mathrm{div}(\rho_H v) = r_H \rho_H \left(1 - \frac{\rho_H + \rho_T}{K_H}\right), \qquad \rho_H(+\infty) = K_H,$$

$$v = -\mu \nabla p, \qquad p = P(\rho_H + \rho_T).$$

Remark. This system has the segregation property : if $\rho_H^0 \rho_T^0 = 0$, then for all $t \geq 0$, $\rho_H(t)\rho_T(t) = 0$.
It means that the healthy zone and the tumor zone do not overlap.

3. see e.g. Sanchez, Gardino, Maini (1994), Preziosi & Galdani, Sheratt (2003), ...

Multiphase flow approach

It has been also proposed to consider a tumor as a multiphase flow. A simple model is given by the two phases model : tumor cells (local volume ϕ_T) and extracellular fluid (local volume ϕ_L)[4].

$$\partial_t \phi_T + \mathrm{div}(\phi_T v_T) = \Gamma_T,$$
$$\partial_t \phi_L + \mathrm{div}(\phi_L v_L) = \Gamma_L,$$
$$\rho_T \phi_T \big(\partial_t v_T + v_T \cdot \nabla v_T\big) = \mathrm{div}\mathcal{T}_T + m_T,$$
$$\rho_L \phi_L \big(\partial_t v_L + v_L \cdot \nabla v_L\big) = \mathrm{div}\mathcal{T}_L + m_L,$$
$$\phi_T + \phi_L = 1.$$

Γ_L and Γ_T correspond to growth terms.
$\mathcal{T}_T$ and $\mathcal{T}_L$ are the stress tensors.
m_T and m_L account for the interaction forces.
v_T and v_L are the flows, computed with Navier-Stokes equation.
The equation $\phi_T + \phi_L = 1$ expresses the saturation regime.

4. Byrne & Preziosi (2003), Preziosi & Tosin (2009)

Outline of lecture 1 and 2

Free boundary model : Hele-Shaw model

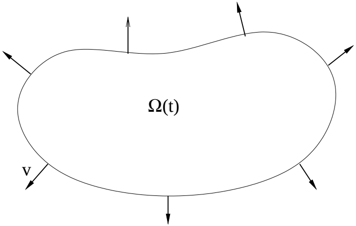
Another class of macroscopic model for tumor growth is geometric model as Hele-Shaw, which describes the tumor by the dynamics of its domain $\Omega(t)$.

The model reads

$$\begin{cases} -\Delta p = G(p), & \text{on } \Omega(t), \\ p = 0, & \text{on } \partial\Omega(t). \end{cases}$$

The velocity of the boundary is given by the Darcy law

$$v = -\nabla_x p.$$



As above, G is the growth function.
One assumes to have constant density in the domain Ω *(incompressibility)*.

References : Lowengrub et al. [Nonlinearity '10], Roose, Chapman & Maini [SIAM '07], Friedman [DCDS B '04], Friedman & Hu [TAMS '08], Greenspan ['72].

Free boundary model : Hele-Shaw model

We may also take into account the surface tension at the interface of the tumor through the boundary condition. The model is changed into

$$\begin{cases} -\Delta p = G(p), & \text{on } \Omega(t), \\ p = \eta\kappa, & \text{on } \partial\Omega(t), \\ v = -\nabla p, \end{cases}$$

where κ is the mean curvature.

When $\Omega = B_{R(t)}$ we talk about *tumor spheroid*. In this case, $\kappa(t,x) = \frac{1}{R(t)}$ for $x \in \partial B_{R(t)}$, and the model reads

$$\begin{cases} -\Delta p = G(p), & \text{on } B_{R(t)}, \\ p = \frac{\eta}{R(t)}, & \text{on } \partial B_{R(t)}, \\ v = -\nabla p. \end{cases}$$

Tumor spheroids growth

Let us consider a *tumor spheroid* $\Omega(t) = B_{R(t)} \subset \mathbb{R}^d$, we denote ν the unit outward normal. We have, applying the Green formula,

$$-\int_{B_{R(t)}} \Delta p \, dx = -\int_{\partial B_{R(t)}} \nabla p \cdot \nu \, dx = \int_{B_{R(t)}} G(p) \, dx.$$

Since we consider radially symmetric solutions, the integrand in the second term is constant. Then

$$-R(t)^{d-1} S_{d-1} \nabla p(t, R(t)) \cdot \nu(t, R(t)) = \int_{B_{R(t)}} G(p) \, dx,$$

where S_{d-1} is the surface of the sphere in dimension d. Thus

$$\frac{d}{dt} R(t) = v(t, R(t)) \cdot \nu(t, R(t)) = \frac{1}{S_{d-1} R(t)^{d-1}} \int_{B_{R(t)}} G(p) \, dx.$$

Tumor growth with nutrient limitation

We incorpore nutrient dependancy by assuming that the nutrient is provided from the boundary of the tumor. Then the nutrient is diffused (instantaneaously) inside the tumor from its boundary :

$$\begin{cases} -\Delta c + \lambda c = 0, & \text{on } \Omega(t), \\ c = c_b, & \text{on } \partial\Omega(t), \end{cases}$$

The Hele-Shaw model reads as above,

$$\begin{cases} -\Delta p = G(c), & \text{on } \Omega(t), \\ p = \eta\kappa, & \text{on } \partial\Omega(t), \\ v = -\nabla p, \end{cases}$$

The growth function G depends on the available nutrient. We may consider that it is an increasing with respect to c and that there exists a maintenance level $\overline{c} > 0$ (cells die if there is not enough nutrient). A simple example is given by

$$G(c) = c - \overline{c}.$$

Tumor spheroids growth with nutrient limitation

Let us consider a *tumor spheroid* $\Omega = B_{R(t)}$. Then

Proposition

The radius $R(t)$ of the tumor spheroid with nutrient limitation and with $G(c) = c - \overline{c}$ verifies
(i) for $c_b \leq \overline{c}$ then $R(t) \to 0$ as $t \to +\infty$;
(ii) for $c_b > \overline{c}$ there is R_∞ such that $R(t) \to R_\infty$ as $t \to +\infty$.

This model is irrealistic in supposing that the dead cells disappear and thus are replaced by other cells moving back from a proliferating rim to the center to maintain a constant density in the ball $B_{R(t)}$. This creates an equilibrium between proliferation and death.

Some generalisations

As in the case of mechanical models, in previous section, one may include more biological ingredients in the modeling. For instance one can consider proliferative, quiescent and dead cells[5]. On $\Omega(t)$,

$$\begin{cases} \partial_t \rho_P + \mathrm{div}(v\rho_P) = G(\rho_P, \rho_Q) - a\rho_P + b\rho_Q, \\ \partial_t \rho_Q + \mathrm{div}(v\rho_Q) = a\rho_P - b\rho_Q - d\rho_Q, \\ \partial_t \rho_D + \mathrm{div}(v\rho_D) = d\rho_Q - \mu\rho_D, \end{cases}$$

coupled with the Darcy law

$$v(t,x) = -\nabla p(t,x).$$

The incompressibility condition, $\rho_P + \rho_Q + \rho_D = constant$ on $\Omega(t)$, allows to determine the pressure (adding the above equations) :

$$-\Delta p = \mathrm{div} v = G(\rho_P, \rho_Q) - \mu\rho_D, \qquad \text{on } \Omega(t),$$

complemented as usual with Dirichlet conditions on p on $\partial\Omega(t)$.

5. A. Friedman, DCDS B, 2004 vol 4 no 1.

Some generalisations

One may also consider tumor and healthy cells [6]

$$\begin{cases} \partial_t \rho_T + \mathrm{div}(v\rho_T) = G(\rho_T, \rho_H), \\ \partial_t \rho_H + \mathrm{div}(v\rho_H) = 0, \end{cases}$$

coupled with the Darcy law

$$v(t,x) = -\nabla p(t,x).$$

The incompressibility condition, $\rho_T + \rho_H = constant$ on $\Omega(t)$, allows to determine the pressure as above.

6. T. Colin, A. Iollo, D. Lombardi, O. Saut, M3AS 2012 Vol 22 no 6.

Continuum model of tumor growth : summary

To simplify, we neglect the influence of the nutrient and we only deal with $G = G(p)$. We have the two following kinds of model

Mechanical model

$$\partial_t \rho + \text{ div }_x(\rho v) = \rho G(p), \qquad \text{on } \mathbb{R}^d$$
$$v = -\nabla_x p, \qquad p = P(\rho).$$

Free boundary model

$$\begin{aligned} -\Delta p &= G(p), && \text{on } \Omega(t), \\ p &= 0, && \text{on } \partial\Omega(t), \end{aligned}$$

where the velocity of the boundary of the domain is given by the Darcy law

$$v = -\nabla_x p.$$

Question

How to link these two models ? How to derive the free boundary model from the cell mechanical model ?

Lecture 2

First example

Outline of lecture 1 and 2

Parabolic equation in biology

Let us denote $n(t, x)$ the density of cells at time t, position $x \in \mathbb{R}^d$. We assume that cells

- move randomly according to Brownian motions,
- are subjected to an external force field $U(t, x) \in \mathbb{R}^d$,
- growth and die ; we denote by $B(t, x)$ and $D(t, x)$ respectively the birth and death term.

The system governing the dynamics of the population n reads

$$\partial_t n \underbrace{- D \, \Delta n}_{\text{active motion}} + \underbrace{\operatorname{div}(U(t, x) n)}_{\text{oriented drift}} = \underbrace{B(t, x) - D(t, x)}_{\text{growth and death}} .$$

The quantity $D > 0$ is the diffusion coefficient.

Such system enters into the class of parabolic equations.

Second order parabolic equations

Let $\Omega \subset \mathbb{R}^d$, $T > 0$, $Q = (0,T) \times \Omega$. We consider the *second order partial differential operator*

$$Pu = \partial_t u - \sum_{i,j=1}^{d} a_{ij}(t,x) \frac{\partial^2 u}{\partial x_i \partial x_j} - \sum_{i=1}^{d} b_i(t,x) \frac{\partial u}{\partial x_i} - c(t,x)u,$$

where a_{ij}, b_i, c are continuous on $\overline{Q}$, bounded, $a_{ij} = a_{ji}$, and such that

Ellipticity

$$\exists\, \nu_0 > 0, \quad \sum_{i,j=1}^{d} a_{ij}\xi_i\xi_j \geq \nu_0 |\xi|^2, \quad \forall\, \xi \in \mathbb{R}^d, (t,x) \in Q.$$

Examples :

- $\partial_t u - \Delta u = f$ (Heat equation).
- $\partial_t u - \Delta u + \mathrm{div}(bu) = 0$ (Drift-diffusion/Fokker-Planck).
- $\partial_t u - \mathrm{div}(A(x)\nabla u) - b(x) \cdot \nabla u - c(x)u = 0$ with A symmetric, positive definite with eigenvalues bounded from below by ν_0.

Second order parabolic equations

From now on, we will always denote by P a parabolic second order partial differential operator

$$Pu = \partial_t u - \sum_{i,j=1}^{d} a_{ij}(t,x) \frac{\partial^2 u}{\partial x_i \partial x_j} - \sum_{i=1}^{d} b_i(t,x) \frac{\partial u}{\partial x_i} - c(t,x)u.$$

For $\Omega \subset \mathbb{R}^d$, we consider the Cauchy problem

$$\begin{aligned} Pu(t,x) &= f(t,x), && \text{in } Q, \\ u(0,x) &= u_0(x), && \forall\, x \in \Omega, \\ u(t,x) &= g(t,x), && \forall\, t \in (0,T), x \in \partial\Omega. \end{aligned}$$

We will not consider the theory of existence of solution and assume that such problem admits a solution. We will review briefly some important properties of such solutions.

Maximum principle for parabolic equations

Weak maximum principle (corollary)

Let $\Omega \subset \mathbb{R}^d$ be bounded and u a function in C^1 in t and C^2 in x on $Q = (0,T) \times \Omega$, continuous on $\overline{Q}$, such that u is a solution to

$$\begin{aligned} Pu \geq 0, \qquad & \text{on } Q, \\ u \geq 0, \qquad & \text{on } \partial_P Q = (\{0\} \times \overline{\Omega}) \cup ([0,T] \times \partial\Omega). \end{aligned}$$

Then $u \geq 0$ on Q.

Idea of the proof (in the case $Pu > 0$). Let (t_0, x_0) such that $u(t_0,x_0) = \min_{\overline{Q}} u$.

- If $(t_0,x_0) \in \partial_P Q$, then by assumption $u(t_0,x_0) \geq 0$.
- If $(t_0,x_0) \notin \partial_P Q$, we have $\nabla u(t_0,x_0) = 0$, $D^2_{xx}u(t_0,x_0) \geq 0$ and $\partial_t u(t_0,x_0) \leq 0$. Thus $0 < Pu(t_0,x_0) \leq -cu(t_0,x_0)$. Then, if $c \leq 0$, $u(t_0,x_0) \geq 0$ and the proof is done. If $c > 0$, we set $u = e^{-\|c\|_\infty t} v$, then we have $Pu = Pv - \|c\|_\infty v = \tilde{P}v$. Since $c - \|c\|_\infty \leq 0$, we may apply the result in the case $c \leq 0$ to the operator $\tilde{P}$. It implies $v \geq 0 \Rightarrow u \geq 0$.

Maximum principle for parabolic equations

Uniqueness for the Cauchy problem

When it exists, the solution to the following problem is unique

$$\begin{aligned} Pu &= f(t,x), && \text{in } Q, \\ u(0,x) &= u_0(x), && \forall\, x \in \Omega, \\ u(t,x) &= g(t,x), && \forall\, t \in (0,T), x \in \partial\Omega. \end{aligned}$$

Proof. It is an easy consequence of the weak maximum principle. Indeed, if we have two solution u_1 and u_2. Using the above result for $u_1 - u_2$ we deduce $u_1 - u_2 \geq 0$. Doing the same with $u_2 - u_1$, we conclude that $u_1 = u_2$.

Comparison principle for parabolic equations

We consider non-linear problem

$$Pu = f(t,x,u), \qquad \text{on } Q = (0,T) \times \Omega,$$

with $f : \overline{Q} \times \mathbb{R} \to \mathbb{R}$ continuous and $u \mapsto f(t,x,u)$ is locally Lipschitz, uniformly with respect to (t,x).

Comparison principle

Let Ω bounded. Let u, v in C^1 in t and C^2 in x on Q, continuous on $\overline{Q}$, and such that

$$\begin{aligned} Pu \geq f(t,x,u), \quad Pv \leq f(t,x,v), & \qquad \text{on } Q \\ u(t,x) \geq v(t,x), & \qquad \forall\, t \in (0,T), x \in \partial\Omega, \\ u(0,x) \geq v(0,x), & \qquad \forall\, x \in \Omega. \end{aligned}$$

Then $u \geq v$ on Q.

Comparison principle for parabolic equations

Idea of the proof (when $f \in C^1$).
Let $w = u - v$. We have

$$Pw \geq f(t,x,u) - f(t,x,v) = \gamma(t,x)w,$$

where

$$\gamma(t,x) = \begin{cases} \dfrac{f(t,x,u(t,x)) - f(t,x,v(t,x))}{u(t,x) - v(t,x)}, & \text{if } u(t,x) \neq v(t,x), \\ \partial_u f(t,x,u(t,x)), & \text{if } u(t,x) = v(t,x). \end{cases}$$

For $f \in C^1$, γ is continuous. Thus,

$$\begin{aligned} (P - \gamma(t,x))w &\geq 0, & \text{on } Q, \\ w &\geq 0, & \text{on } \partial_P Q. \end{aligned}$$

By the weak maximum principle, we deduce $w \geq 0$.

Sub- and super-solutions for parabolic equations

We consider the problem

$$\begin{aligned} Pu &= f(t,x,u), && \text{on } Q, \\ u(0,x) &= u_0(x), && \forall\, x \in \Omega, \\ u(t,x) &= g(t,x), && \forall\, t \in (0,T), x \in \partial\Omega. \end{aligned}$$

From the comparison principle, if $\underline{u}$ verifies

$$\begin{aligned} P\underline{u} &\leq f(t,x,\underline{u}), && \text{on } Q, \\ \underline{u}(0,x) &\leq u_0(x), && \forall\, x \in \Omega, \\ \underline{u}(t,x) &\leq g(t,x), && \forall\, t \in (0,T), x \in \partial\Omega. \end{aligned}$$

Then $\underline{u} \leq u$ on Q. It is called a generalized sub-solution.
By the same token, if $\overline{u}$ verifies

$$\begin{aligned} P\overline{u} &\geq f(t,x,\overline{u}), && \text{on } Q, \\ \overline{u}(0,x) &\geq u_0(x), && \forall\, x \in \Omega, \\ \overline{u}(t,x) &\geq g(t,x), && \forall\, t \in (0,T), x \in \partial\Omega. \end{aligned}$$

Then $u \leq \overline{u}$ on Q. It is called a generalized super-solution.

Outline of lecture 1 and 2

BV functions

For a function $f \in L^1_{loc}(\Omega)$, $\Omega \subset \mathbb{R}^d$, we define its total variation by

$$TV(f) = \sup\left\{ \int_{\mathbb{R}^d} f(x)\mathrm{div}(\phi(x))\,dx, \quad \phi \in C_c^\infty(\Omega), \|\phi\|_\infty \le 1 \right\}.$$

We define the space of functions with bounded variations by

$$BV(\Omega) = \{f \in L^1_{loc}(\Omega),\ TV(f) < +\infty\},$$

endowed with the semi-norm $\|f\|_{BV} = TV(f)$.

Compactness : Helly Theorem

Let $\Omega \subset \mathbb{R}^d$ be an open set. Let $(f_n)_{n\in\mathbb{N}}$ be a sequence of functions in $L^1_{loc}(\Omega)$ such that there exists two nonnegative constants C_1 and C_2 such that for all $n \in \mathbb{N}$

$$\|f_n\|_\infty \le C_1, \qquad \|f_n\|_{BV} \le C_2.$$

Then, there exists a subsequence of $(f_n)_{n\in\mathbb{N}}$ such that $f_n \to f$ strongly in $L^1_{loc}(\Omega)$; moreover the limit f satisfies

$$\|f\|_\infty \le C_1, \qquad \|f\|_{BV} \le C_2.$$

Outline of lecture 1 and 2

Setting of the problem : strong reaction

As a first and simple example, we consider the following system of reaction-diffusion equations

$$\partial_t u_\varepsilon - d_1 \Delta u_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon v_\varepsilon, \qquad t \geq 0, x \in \mathbb{R}^d,$$
$$\partial_t v_\varepsilon - d_2 \Delta v_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon v_\varepsilon,$$
$$(u_\varepsilon, v_\varepsilon)(t=0) = (u_\varepsilon^0, v_\varepsilon^0) \geq 0.$$

We assume that initial data are given in $L^\infty \cap L^1(\mathbb{R}^d)$ and uniformly bounded with respect to ε.

By comparison principle, we have for all $t \geq 0$, $x \in \mathbb{R}^d$,

$$0 \leq u_\varepsilon(t,x) \leq \|u_\varepsilon^0\|_\infty, \qquad 0 \leq v_\varepsilon(t,x) \leq \|v_\varepsilon^0\|_\infty.$$

Indeed $(0,0)$ is a subsolution and $(\|u_\varepsilon^0\|_\infty, \|v_\varepsilon^0\|_\infty)$ is a super-solution for the above system.

Setting of the problem

Integrating both equations on $(0,t)\times\mathbb{R}^d$, for $t>0$, we deduce

$$\int_{\mathbb{R}^d} u_\varepsilon(t)\,dx + \int_0^t\int_{\mathbb{R}^d} \frac{u_\varepsilon(s)v_\varepsilon(s)}{\varepsilon}\,dxds \le \int_{\mathbb{R}^d} u_\varepsilon^0\,dx,$$
$$\int_{\mathbb{R}^d} v_\varepsilon(t)\,dx + \int_0^t\int_{\mathbb{R}^d} \frac{u_\varepsilon(s)v_\varepsilon(s)}{\varepsilon}\,dxds \le \int_{\mathbb{R}^d} v_\varepsilon^0\,dx,$$

- Multiplying by ε and letting $\varepsilon\to 0$, we deduce, using also the nonnegativity that, if the limit (u,v) of $(u_\varepsilon,v_\varepsilon)$ exists, then

  $$uv = 0, \quad \text{a.e.}$$

  It means that the limits u and v have disjoints supports.
- Moreover, if we denote $w=u-v$, we have

  $$w=-v \text{ when } w\le 0, \quad w=u \text{ when } w\ge 0.$$

Setting of the problem

Recalling the system of equation

$$\partial_t u_\varepsilon - d_1 \Delta u_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon v_\varepsilon, \qquad \partial_t v_\varepsilon - d_2 \Delta v_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon v_\varepsilon.$$

Subtracting both equations, we have, with the notation $w_\varepsilon = u_\varepsilon - v_\varepsilon$,

$$\partial_t w_\varepsilon - \Delta(d_1 u_\varepsilon - d_2 v_\varepsilon) = 0.$$

Assuming the convergence of w_ε towards w, we deduce

$$\partial_t w - \Delta A(w) = 0, \qquad A(w) = \begin{cases} d_2 w, & \text{for } w \le 0, \\ d_1 w, & \text{for } w \ge 0. \end{cases}$$

This is the so-called Stefan problem.

Stefan problem without latent heat

Stefan problem

The Stefan problem with latent heat is defined by the system

$$\partial_t w - \Delta A(w) = 0, \qquad t \geq 0, x \in \mathbb{R}^d,$$

with

$$A(w) = \begin{cases} d_2 w, & \text{for } w \leq 0, \\ d_1 w, & \text{for } w \geq 0. \end{cases}$$

We assume to have existence and uniqueness of solutions to this Stefan problem [7]

7. J. A. Carrillo, *Entropy solutions for nonlinear degenerate problems*, Arch. Ration. Mech. Anal. 147 (1999), no. 4, 269–361.

Outline of lecture 1 and 2

Statement of the result

Assumptions

Additionnally to the uniform $L^1 \cap L^\infty$ bound on initial data, we assume also that initial data are 'well-prepared' : there exist constants C^0 and C^1 independent of ε such that

$$\|\nabla u_\varepsilon^0\|_{L^1} + \|\nabla v_\varepsilon^0\|_{L^1} \leq C^0$$

$$\|d_1 \Delta u_\varepsilon^0 - \frac{u_\varepsilon^0 v_\varepsilon^0}{\varepsilon}\|_{L^1} + \|d_1 \Delta v_\varepsilon^0 - \frac{u_\varepsilon^0 v_\varepsilon^0}{\varepsilon}\|_{L^1} \leq C^1$$

Theorem

Under above assumptions, the solution $(u_\varepsilon, v_\varepsilon)$ is uniformly bounded in $BV(\mathbb{R}^+ \times \mathbb{R}^d)$ and we have, for all $t \geq 0$,

$$u_\varepsilon \to u, \quad v_\varepsilon \to v, \qquad \text{strongly in } L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d),$$

$$u, v \in L^\infty(\mathbb{R}^+; L^1 \cap L^\infty(\mathbb{R}^d)), \quad u(t,x)\, v(t,x) = 0, \text{ a.e.}$$

and w is a solution to the Stefan problem.

Idea of the proof

The proof is divided into several steps :

- Prove that the total variation of u_ε and v_ε is uniformly bounded.
- By compactness result (Helly Theorem), we deduce the strong convergence in $L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d)$ of a subsequence.
- Passing to the limit in the system, we show that the limit satisfies the Stefan problem. By uniqueness of solutions for this Stefan problem, the full sequences $(u_\varepsilon)_\varepsilon$ and $(v_\varepsilon)_\varepsilon$ converge.

Proof of Theorem

- *Step 1 : bound on the total variation.*

We first show TV estimates in x. Recalling the system of equation

$$\partial_t u_\varepsilon - d_1 \Delta u_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon v_\varepsilon, \qquad \partial_t v_\varepsilon - d_2 \Delta v_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon v_\varepsilon.$$

We differentiate with respect to x_i for $i = 1, \dots, d$,

$$\partial_t \partial_{x_i} u_\varepsilon - d_1 \Delta \partial_{x_i} u_\varepsilon = -\frac{1}{\varepsilon}(\partial_{x_i} u_\varepsilon v_\varepsilon + u_\varepsilon \partial_{x_i} v_\varepsilon),$$

$$\partial_t \partial_{x_i} v_\varepsilon - d_2 \Delta \partial_{x_i} v_\varepsilon = -\frac{1}{\varepsilon}(\partial_{x_i} u_\varepsilon v_\varepsilon + u_\varepsilon \partial_{x_i} v_\varepsilon).$$

We multiply the first equation by $\mathrm{sign}(\partial_{x_i} u_\varepsilon)$, the second by $\mathrm{sign}(\partial_{x_i} v_\varepsilon)$,

$$\partial_t |\partial_{x_i} u_\varepsilon| - d_1 \Delta |\partial_{x_i} u_\varepsilon| \le -\frac{1}{\varepsilon}(\partial_{x_i} u_\varepsilon v_\varepsilon + u_\varepsilon \partial_{x_i} v_\varepsilon)\mathrm{sign}(\partial_{x_i} u_\varepsilon),$$

$$\partial_t \partial_{x_i} v_\varepsilon - d_2 \Delta |\partial_{x_i} v_\varepsilon| \le -\frac{1}{\varepsilon}(\partial_{x_i} u_\varepsilon v_\varepsilon + u_\varepsilon \partial_{x_i} v_\varepsilon)\mathrm{sign}(\partial_{x_i} v_\varepsilon).$$

Here we use the so-called Kato inequality

$$-\Delta |f| = -\mathrm{div}\,(\mathrm{sign}(f)\nabla f) = -\delta_0(f)|\nabla f|^2 - \mathrm{sign}(f)\Delta f \le -\mathrm{sign}(f)\Delta f.$$

Proof of Theorem

We integrate

$$\frac{d}{dt}\int_{\mathbb{R}^d}\Big(|\partial_{x_i}u_\varepsilon| + |\partial_{x_i}v_\varepsilon|\Big)dx$$
$$\le -\frac{1}{\varepsilon}\int_{\mathbb{R}^d}\big(\partial_{x_i}u_\varepsilon v_\varepsilon + u_\varepsilon\partial_{x_i}v_\varepsilon\big)\Big(\mathsf{sign}(\partial_{x_i}u_\varepsilon) + \mathsf{sign}(\partial_{x_i}v_\varepsilon)\Big)\,dx$$
$$\le -\frac{1}{\varepsilon}\int_{\mathbb{R}^d}\Big(|\partial_{x_i}u_\varepsilon|v_\varepsilon + \partial_{x_i}u_\varepsilon\mathsf{sign}(\partial_{x_i}v_\varepsilon)v_\varepsilon + u_\varepsilon|\partial_{x_i}v_\varepsilon| + \partial_{x_i}v_\varepsilon\mathsf{sign}(\partial_{x_i}u_\varepsilon)u_\varepsilon\Big)\,dx$$

Thus we deduce

$$\frac{d}{dt}\int_{\mathbb{R}^d}\Big(|\partial_{x_i}u_\varepsilon| + |\partial_{x_i}v_\varepsilon|\Big)\,dx \le 0.$$

It implies for all $t \ge 0$, and for any $i \in \{1, \dots, d\}$,

$$\int_{\mathbb{R}^d}\Big(|\partial_{x_i}u_\varepsilon(t,x)| + |\partial_{x_i}v_\varepsilon(t,x)|\Big)\,dx \le \int_{\mathbb{R}^d}\Big(|\partial_{x_i}u_\varepsilon^0(x)| + |\partial_{x_i}v_\varepsilon^0(x)|\Big)\,dx \le C^0,$$

by assumptions on the initial data. It proves the bound on the total variation in x, i.e.

$$\|\nabla_x u_\varepsilon\|_{L^1} + \|\nabla_x v_\varepsilon\|_{L^1} \le C.$$

Proof of Theorem

For the total variation in time, we obtain by the same token,

$$\frac{d}{dt}\int_{\mathbb{R}^d}\Big(|\partial_t u_\varepsilon| + |\partial_t v_\varepsilon|\Big)\,dx \le 0.$$

Integrating in time, we deduce

$$\begin{aligned}\int_{\mathbb{R}^d}\Big(|\partial_t u_\varepsilon(t,x)| + |\partial_t v_\varepsilon(t,x)|\Big)\,dx &\le \int_{\mathbb{R}^d}\Big(|\partial_t u_\varepsilon^0(x)| + |\partial_t v_\varepsilon^0(x)|\Big)\,dx \\ &\le \|d_1\Delta u_\varepsilon^0 - \frac{1}{\varepsilon}u_\varepsilon^0 v_\varepsilon^0\|_{L^1} + \|d_2\Delta v_\varepsilon^0 - \frac{1}{\varepsilon}u_\varepsilon^0 v_\varepsilon^0\|_{L^1} \\ &\le C^1,\end{aligned}$$

thanks to our assumptions on the initial data. It implies the bound on the total variation in time.

Thus u_ε and v_ε are bounded in $BV(\mathbb{R}^+\times\mathbb{R}^d)$ uniformly with respect to ε.

Proof of Theorem

- *Step 2 : local compactness.*

Since the sequences $(u_\varepsilon)_\varepsilon$ and $(v_\varepsilon)_\varepsilon$ are uniformly bounded in $L^\infty \cap BV(\mathbb{R}^+ \times \mathbb{R}^d)$, we deduce from the Helly compactness theorem that

there exist subsequences, still denoted $(u_\varepsilon)_\varepsilon$ and $(v_\varepsilon)_\varepsilon$, and u, v in $L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d)$ such that $u_\varepsilon \to u$ and $v_\varepsilon \to v$ strongly in $L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d)$ and almost everywhere,

i.e. for every $T > 0$ and every compact $K \subset \mathbb{R}^d$, we have $u_\varepsilon \to u$ and $v_\varepsilon \to v$ strongly in $L^1([0, T] \times K)$ and almost everywhere.

Proof of Theorem

- *Step 3 : passing to the limit.*
  - Recalling that by simple integration of the system, we have

$$\int_{\mathbb{R}^d} u_\varepsilon(t)\,dx + \int_0^t \int_{\mathbb{R}^d} \frac{u_\varepsilon(s)v_\varepsilon(s)}{\varepsilon}\,dxds \leq \int_{\mathbb{R}^d} u_\varepsilon^0\,dx,$$
$$\int_{\mathbb{R}^d} v_\varepsilon(t)\,dx + \int_0^t \int_{\mathbb{R}^d} \frac{u_\varepsilon(s)v_\varepsilon(s)}{\varepsilon}\,dxds \leq \int_{\mathbb{R}^d} v_\varepsilon^0\,dx.$$

    We deduce $\boxed{uv = 0 \text{ a.e.}}$
  - We define $w_\varepsilon = u_\varepsilon - v_\varepsilon \underset{\varepsilon\to 0}{\longrightarrow} u - v = w$. It satisfies

$$\partial_t w_\varepsilon - \Delta(d_1 u_\varepsilon - d_2 v_\varepsilon) = 0.$$

    Passing to the limit in the distribution sense, we find,

$$\partial_t w - \Delta A = 0, \qquad A = \lim_{\varepsilon\to 0}(d_1 u_\varepsilon - d_2 v_\varepsilon).$$

  - We identify $A(t,x)$ (using $uv = 0$ a.e.) :
    • For $w > 0$, then $u > 0$, thus $v_\varepsilon \to v = 0$ and $u_\varepsilon \to u > 0$. Then $A(t,x) = d_1 u(t,x) = d_1 w(t,x)$.
    • For $w < 0$, then $v > 0$, thus $u_\varepsilon \to u = 0$ and $v_\varepsilon \to v > 0$. Then $A(t,x) = -d_2 v(t,x) = d_2 w(t,x)$.

Remark for time compactness

In the proof, we require a 'well-prepared' assumptions on initial data. This assumption can be removed by using the Aubin-Lions compactness Lemma. Indeed, we write

$$\partial_t u_\varepsilon = \Delta(d_1 u_\varepsilon) + r_\varepsilon, \qquad \partial_t v_\varepsilon = \Delta(d_2 v_\varepsilon) + r_\varepsilon,$$

where,

- $r_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon v_\varepsilon$ is bounded in $L^1([0,T] \times \mathbb{R}^d)$ from the inequality

$$\int_{\mathbb{R}^d} u_\varepsilon(t)\, dx + \int_0^t \int_{\mathbb{R}^d} \frac{u_\varepsilon(s) v_\varepsilon(s)}{\varepsilon}\, dxds \leq \int_{\mathbb{R}^d} u_\varepsilon^0\, dx.$$

- $(d_1 u_\varepsilon)$ and $(d_2 v_\varepsilon)$ are compact in space, since uniformly bounded in $L^\infty \cap BV(\mathbb{R}^d)$

Outline of lecture 1 and 2

1. Dynamical models
   - A simple model
   - Proliferative and quiescent cells
2. Spatial models of tumor growth
   - Presentation of the cells mechanical model under investigation
   - Free boundary model of Hele-Shaw type
3. Some generalities
   - Parabolic equation in biology
   - BV functions
4. A warm-up example : derivation of Stefan free boundary problems
   - Setting of the problem
   - Proof of the convergence
   - Stefan problem with latent heat
   - Geometric interpretation

Stefan problem with latent heat

We consider the following semi-linear system [a]

$$\partial_t u_\varepsilon - d_1 \Delta u_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon \big(v_\varepsilon + \lambda(1-p_\varepsilon)\big), \qquad t \geq 0, x \in \mathbb{R}^d,$$

$$\partial_t v_\varepsilon - d_2 \Delta v_\varepsilon = -\frac{1}{\varepsilon} v_\varepsilon \big(u_\varepsilon + \lambda p_\varepsilon\big),$$

$$\partial_t p_\varepsilon = \frac{1}{\varepsilon}\big((1-p_\varepsilon)u_\varepsilon - v_\varepsilon p_\varepsilon\big),$$

complemented with nonnegative initial data given in $L^\infty \cap L^1(\mathbb{R}^d)$ and uniformly bounded with respect to ε,

$$0 \leq u_\varepsilon^0 \leq \|u_\varepsilon^0\|_\infty, \qquad 0 \leq v_\varepsilon^0 \leq \|v_\varepsilon^0\|_\infty, \qquad 0 \leq p_\varepsilon^0 \leq 1.$$

The quantity λ is called *the latent heat*.

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a. D. Hilhorst, M. Mimura, R. Schätzle, *Vanishing latent heat limit in a Stefan-like problem arising in biology*, Nonlinear Analysis : Real World Applications, 4(2) (2003) 261–285.

Nonnegativity and *a priori* estimates

Lemma

The weak solution satisfies for all $t \geq 0$, $x \in \mathbb{R}^d$,

$$0 \leq u_\varepsilon(t,x) \leq \|u_\varepsilon^0\|_\infty, \qquad 0 \leq v_\varepsilon(t,x) \leq \|v_\varepsilon^0\|_\infty, \qquad 0 \leq p_\varepsilon(t,x) \leq 1,$$
$$\|u_\varepsilon\|_{L^1} \leq \|u_\varepsilon^0\|_{L^1}, \qquad \|v_\varepsilon\|_{L^1} \leq \|v_\varepsilon^0\|_{L^1}, \qquad \|p_\varepsilon\|_{L^1} \leq \lambda^{-1}\|p_\varepsilon^0\|_{L^1} + \|u_\varepsilon^0\|_{L^1}.$$

Proof.

- The nonnegativity of u_ε and v_ε follows from the nonnegativity principle.
- It follows that

$$\partial_t p_\varepsilon = \frac{1}{\varepsilon}\big((1-p_\varepsilon)u_\varepsilon - v_\varepsilon p_\varepsilon\big) \geq -\frac{1}{\varepsilon}p_\varepsilon(u_\varepsilon + v_\varepsilon).$$

Thus $p_\varepsilon \geq 0$. Similarly,

$$\partial_t(p_\varepsilon - 1) \leq -\frac{1}{\varepsilon}(p_\varepsilon - 1)(u_\varepsilon + v_\varepsilon).$$

Thus $p_\varepsilon \leq 1$.

Nonnegativity and L^∞ estimates

- Finally, from the nonnegativity of u_ε and v_ε and the bound $0 \le p_\varepsilon \le 1$, we deduce that the right hand sides are nonpositive :

$$\partial_t u_\varepsilon - d_1 \Delta u_\varepsilon = -\frac{1}{\varepsilon} u_\varepsilon \big(v_\varepsilon + \lambda(1 - p_\varepsilon) \big), \qquad t \ge 0, x \in \mathbb{R}^d,$$
$$\partial_t v_\varepsilon - d_2 \Delta v_\varepsilon = -\frac{1}{\varepsilon} v_\varepsilon \big(u_\varepsilon + \lambda p_\varepsilon \big).$$

  Thus by comparison principle, we conclude that $u_\varepsilon \le \|u_\varepsilon^0\|_\infty$ and $v_\varepsilon \le \|v_\varepsilon^0\|_\infty$.

A priori L^1 estimates

Then integrating the system, we deduce

$$\int_{\mathbb{R}^d} u_\varepsilon(t)\,dx + \frac{1}{\varepsilon}\int_0^t \int_{\mathbb{R}^d} u_\varepsilon\big(v_\varepsilon + \lambda(1-p_\varepsilon)\big)\,dx \le \int_{\mathbb{R}^d} u_\varepsilon^0 dx,$$
$$\int_{\mathbb{R}^d} v_\varepsilon(t)\,dx + \frac{1}{\varepsilon}\int_0^t \int_{\mathbb{R}^d} v_\varepsilon\big(u_\varepsilon + \lambda p_\varepsilon\big)\,dx \le \int_{\mathbb{R}^d} v_\varepsilon^0 dx,$$
$$\int_{\mathbb{R}^d} p_\varepsilon(t)\,dx - \int_{\mathbb{R}^d} p_\varepsilon^0\,dx \le \frac{1}{\varepsilon}\int_0^t \int_{\mathbb{R}^d} \big((1-p_\varepsilon)u_\varepsilon - v_\varepsilon p_\varepsilon\big)\,dx.$$

- From the first two equations, we deduce an *a priori* estimate on $\|u_\varepsilon\|_{L^1}$ and $\|v_\varepsilon\|_{L^1}$.
- We deduce also that the second term of the left hand side are bounded.
- Then, the right hand side in the 3rd equation is bounded $\Longrightarrow \|p_\varepsilon\|_{L^1}$ is uniformly bounded.

Formal computation

Recalling the system,

$$\begin{aligned}
\partial_t u_\varepsilon - d_1 \Delta u_\varepsilon &= -\frac{1}{\varepsilon} u_\varepsilon \big(v_\varepsilon + \lambda(1-p_\varepsilon)\big), \qquad t \geq 0, x \in \mathbb{R}^d, \\
\partial_t v_\varepsilon - d_2 \Delta v_\varepsilon &= -\frac{1}{\varepsilon} v_\varepsilon \big(u_\varepsilon + \lambda p_\varepsilon\big), \\
\partial_t p_\varepsilon &= \frac{1}{\varepsilon}\big((1-p_\varepsilon) u_\varepsilon - v_\varepsilon p_\varepsilon\big).
\end{aligned}$$

- Let us assume that $(u_\varepsilon)_\varepsilon$, $(v_\varepsilon)_\varepsilon$, and $(p_\varepsilon)_\varepsilon$ converge strongly to $u \geq 0$, $v \geq 0$, and $p \in [0,1]$, respectively. Then

$$u(v + \lambda(1-p)) = 0, \quad v(u + \lambda p) = 0, \quad (1-p)u - vp = 0.$$

(Notice that the last equality is a consequence of the first two ones.)

- Let us define $\boxed{w_\varepsilon = u_\varepsilon - v_\varepsilon + \lambda p_\varepsilon}$. It satisfies

$$\partial_t w_\varepsilon - \Delta(d_1 u_\varepsilon - d_2 v_\varepsilon) = 0.$$

Formal computation

We denote

$$B(w) := d_1 u - d_2 v = \lim_{\varepsilon \to 0} (d_1 u_\varepsilon - d_2 v_\varepsilon).$$

To identify the function B, we make the following observations, due to the algebraic relations at the limit :

$$\begin{cases} u(t,x) > 0 \Longrightarrow v + \lambda(1-p) = 0 \Longrightarrow v = 0, p = 1; \\ v(t,x) > 0 \Longrightarrow u + \lambda p = 0 \Longrightarrow u = 0, p = 0; \end{cases}$$

Then,

$$w = u - v + \lambda p = \begin{cases} -v, & \text{for } v > 0, u = 0, p = 0, \Longleftrightarrow w < 0; \\ \in [0, \lambda], & \text{for } v = 0, u = 0, p \geq 0, \Longleftrightarrow w \in [0, \lambda]; \\ \lambda + u, & \text{for } u > 0, v = 0, p = 1, \Longleftrightarrow w > \lambda. \end{cases}$$

Thus we have

$$B(w) = \begin{cases} d_2 w, & \text{for } w < 0; \\ 0, & \text{for } w \in [0, \lambda]; \\ d_1 (w - \lambda), & \text{for } w > \lambda. \end{cases}$$

Statement of the result

Assumptions

Additionnally to the uniform $L^1 \cap L^\infty$ bound on initial data, we assume also that initial data are 'well-prepared' : there exist constants C^0 and C^1 independent of ε such that, we have the uniform TV bound in space

$$\|\nabla u_\varepsilon^0\|_{L^1} + \|\nabla v_\varepsilon^0\|_{L^1} + \|\nabla p_\varepsilon^0\|_{L^1} \leq C^0,$$

and the uniform TV estimates in time

$$\|d_1 \Delta u_\varepsilon^0 - \frac{1}{\varepsilon} u_\varepsilon^0 \big(v_\varepsilon^0 + \lambda(1 - p_\varepsilon^0)\big)\|_{L^1} \leq C^1,$$

$$\|d_2 \Delta v_\varepsilon^0 - \frac{1}{\varepsilon} v_\varepsilon^0 \big(u_\varepsilon^0 + \lambda p_\varepsilon^0\big)\|_{L^1} \leq C^1,$$

$$\frac{\lambda}{\varepsilon}\|(1 - p_\varepsilon^0) u_\varepsilon^0 - v_\varepsilon^0 p_\varepsilon^0\|_{L^1} \leq C^1.$$

Statement of the result

Theorem

Under above assumptions, the solution $(u_\varepsilon, v_\varepsilon, p_\varepsilon)$ is uniformly bounded in $BV(\mathbb{R}^+ \times \mathbb{R}^d)$ and we have, for all $t \geq 0$,

$$u_\varepsilon \to u, \quad v_\varepsilon \to v, \quad p_\varepsilon \to p, \quad \text{strongly in } L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d),$$

$$u, v, p \in L^\infty(\mathbb{R}^+; L^1 \cap L^\infty(\mathbb{R}^d)),$$

$$u\big(v + \lambda(1-p)\big) = 0, \quad v(u + \lambda p) = 0, \quad u(1-p)vp = 0 \text{ a.e.},$$

and $w = u - v + \lambda p$ is a solution to the Stefan problem with latent heat λ

$$\partial_t w - \Delta B(w) = 0, \qquad B(w) = \begin{cases} d_2 w, & \text{for } w < 0; \\ 0, & \text{for } w \in [0, \lambda]; \\ d_1(w - \lambda), & \text{for } w > \lambda. \end{cases}$$

Proof of the derivation

The proof relies on the same idea as in the previous case, without latent heat.

- *Step 1 : bound on the total variation.*

The TV estimate in x is obtained as before. Denoting $u_i = \partial_{x_i} u_\varepsilon$, $v_i = \partial_{x_i} v_\varepsilon$, and $p_i = \partial_{x_i} p_\varepsilon$, we have by differentiating the system with respect to x_i

$$\partial_t u_i - d_1 \Delta u_i = -\frac{u_i}{\varepsilon}\big(v_\varepsilon + \lambda(1-p_\varepsilon)\big) - \frac{u_\varepsilon}{\varepsilon}\big(v_i - \lambda p_i\big),$$
$$\partial_t v_i - d_2 \Delta v_i = -\frac{v_i}{\varepsilon}\big(u_\varepsilon + \lambda p_\varepsilon\big) - \frac{v_\varepsilon}{\varepsilon}\big(u_i + \lambda p_i\big),$$
$$\partial_t p_i = -\frac{p_i}{\varepsilon}\big(u_i + v_i\big) + \frac{1}{\varepsilon}\big(u_i(1-p_\varepsilon) - v_i p_\varepsilon\big).$$

Multiply the first line by $\mathrm{sign}(u_i)$, the second line by $\mathrm{sign}(v_i)$, the third line by $\mathrm{sign}(p_i)$,

$$\partial_t |u_i| - d_1 \Delta |u_i| \leq -\frac{|u_i|}{\varepsilon}\big(v_\varepsilon + \lambda(1-p_\varepsilon)\big) + \frac{u_\varepsilon}{\varepsilon}\big(|v_i| + \lambda |p_i|\big),$$
$$\partial_t |v_i| - d_2 \Delta |v_i| \leq -\frac{|v_i|}{\varepsilon}\big(u_\varepsilon + \lambda p_\varepsilon\big) + \frac{v_\varepsilon}{\varepsilon}\big(|u_i| + \lambda |p_i|\big),$$
$$\partial_t |p_i| \leq -\frac{|p_i|}{\varepsilon}\big(u_\varepsilon + v_\varepsilon\big) + \frac{1}{\varepsilon}\big(|u_i|(1-p_\varepsilon) + |v_i| p_\varepsilon\big).$$

Proof of the derivation

Then, taking the combination $|u_i| + |v_i| + \lambda |p_i|$ makes that the terms of the right hand sides compensate. We get

$$\partial_t(|u_i| + |v_i| + \lambda |p_i|) - \Delta(d_1|u_i| + d_2|v_i|) \leq 0.$$

Integrating, we deduce that

$$\frac{d}{dt}\int_{\mathbb{R}^d}(|u_i| + |v_i| + \lambda |p_i|)dx \leq 0.$$

Doing this reasoning for any $i = 1, \ldots, d$ and using the TV bound on initial data, we deduce

$$\|\nabla u_\varepsilon(t)\|_{L^1} + \|\nabla v_\varepsilon(t)\|_{L^1} + \lambda \|\nabla p_\varepsilon(t)\|_{L^1} \leq C^0.$$

By the same token for the time derivative, we get

$$\|\partial_t u_\varepsilon(t)\|_{L^1} + \|\partial_t v_\varepsilon(t)\|_{L^1} + \lambda \|\partial_t p_\varepsilon(t)\|_{L^1} \leq 3C^1.$$

Proof of the derivation

- *Step 2 : Compactness*

The TV estimate allows to give compactness in $L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d)$. Thus we can extract subsequences that converge in $L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d)$.

- *Step 3 : Passing to the limit*

It follows the formal derivation explained above. The fact that the full sequences converge is a consequence of the uniqueness of the limit.

Outline of lecture 1 and 2

Nonlinear diffusion

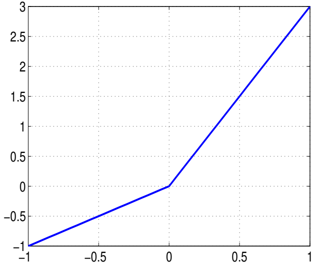

FIGURE – Diffusion coefficient A of the Stefan problem without latent heat.

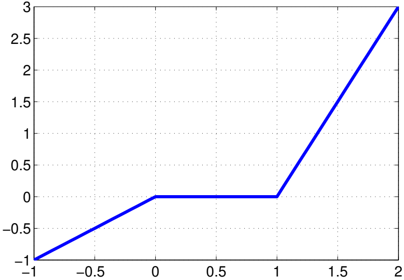

FIGURE – Diffusion coefficient B of the Stefan problem with latent heat $\lambda = 1$.

Geometric interpretation

One can interpret the Stefan problem as a two phases problem with interface :

- The region $\Omega_s = \{x, \text{ s.t. } w(t,x) < 0\}$ is the solid state.
- The region $\Omega_l = \{x, \text{ s.t. } w(t,x) > 0\}$ is the liquid phase.
- The region where $0 \leq w(t,x) \leq \lambda$ is the mushy region. It is a phase where the two phases co-exist