The Cahn-Hilliard equation with a proliferation term

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The Cahn–Hilliard equation : recent advances and applications

Equation :

$$\frac{\partial u}{\partial t} - \frac{\partial^2}{\partial x^2}[\ln(1-q)\frac{\partial^2 u}{\partial x^2} + F'(u)] + \lambda u(u-1) = 0,\ \lambda > 0$$

Proposed to model cells which move, proliferate and interact via diffusion and adhesion in wound healing and tumor growth (propagation front)

2D extension : clustering of malignant brain tumor cells

u : local density of cells
q : adhesion parameter

$$q = 1 - \exp(-\frac{J}{k_B T}),$$

J : interatomic interactions (coupling strength in the Ising model)
k_B : Boltzmann's constant
T : absolute temperature (assumed constant)
λ : proliferation rate

F : local free energy

$$F(s) = \frac{1}{4}a(s - \frac{1}{2})^4 + \frac{1}{2}b(s - \frac{1}{2})^2,$$

$$a = (\frac{q - q_{\rm cr}}{1 - 16\frac{(1-q)^2}{q^4}})^{\frac{1}{4}} \frac{c(q)}{{q_{\rm cr}}^{\frac{1}{4}}}, \ b = -\frac{q - q_{\rm cr}}{|q - q_{\rm cr}|^{\frac{3}{4}}} \frac{c(q)}{{q_{\rm cr}}^{\frac{1}{4}}}$$

$q_{\rm cr} > 0$, $q > q_{\rm cr}$: unstable region

Note that, even in the case $q < q_{\rm cr}$, when the proliferation term is switched on, the initially homogeneous state can become inhomogeneous, leading also to phase separation and clustering

$c(q)$:

$$\lim_{q \to 0} a = 0, \ \lim_{q \to 0} b = \frac{1}{4},$$

$$\lim_{q \to 0} c(q) = \frac{1}{4}$$

The cubic nonlinear term :

Equations :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + g(u) = 0$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma$$

$$u|_{t=0} = u_0$$

$g(s) = s(s-1), f(s) = s^3 - s$

Equation for the spatial average :

$$\frac{d\langle u\rangle}{dt} + \langle g(u)\rangle = 0$$

Set $u = \langle u \rangle + \overline{u}$ $(\langle \overline{u} \rangle = 0)$:

$$\begin{aligned}\langle g(u) \rangle &= \langle \overline{u}^2 + 2\langle u \rangle \overline{u} + \langle u \rangle^2 - \langle u \rangle - \overline{u} \rangle \\ &= g(\langle u \rangle) + \langle \overline{u}^2 \rangle + 2\langle u \rangle \langle \overline{u} \rangle - \langle \overline{u} \rangle \\ &= g(\langle u \rangle) + \langle \overline{u}^2 \rangle\end{aligned}$$

Thus :

$$\frac{d\langle u \rangle}{dt} + g(\langle u \rangle) = -\langle \overline{u}^2 \rangle$$

Local in time well-posedness :

Proposition : For every $u_0 \in L^2(\Omega)$, there exists $T_0 = T_0(\|u_0\|) > 0$ and a unique solution u such that
$u \in \mathcal{C}([0,T_0); L^2(\Omega)_w) \cap L^4(\Omega \times (0,T)) \cap L^2(0,T; H^2(\Omega)), \forall T < T_0$.

Uniqueness :

Let u_1, u_2 be two solutions with initial data $u_{1,0}$, $u_{2,0}$

Set $u = u_1 - u_2$, $u_0 = u_{1,0} - u_{2,0}$ ($u = \overline{u} + \langle u \rangle$) :

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - \Delta\overline{u} + f(u_1) - f(u_2) - \langle f(u_1) - f(u_2)\rangle$$
$$+(-\Delta)^{-1}(g(u_1) - g(u_2) - \langle g(u_1) - g(u_2)\rangle) = 0$$
$$\frac{d\langle u\rangle}{dt} + \langle g(u_1) - g(u_2)\rangle = 0$$
$$\frac{\partial \overline{u}}{\partial \nu} = 0 \text{ on } \Gamma$$
$$u(0) = u_0$$

Multiply the second equation by $\langle u\rangle$ $(g(u_i) = g(\overline{u}_i + \langle u_i\rangle) = g(\langle u_1\rangle) + \langle \overline{u}_i^2\rangle)$:

$$\frac{1}{2}\frac{d\langle u\rangle^2}{dt} + (g(\langle u_1\rangle) - g(\langle u_2\rangle))\langle u\rangle = -\langle \overline{u}_1^2 - \overline{u}_2^2\rangle\langle u\rangle$$

Note that

$$g(\langle u_1\rangle) - g(\langle u_2\rangle) = (\langle u_1 + u_2\rangle - 1)\langle u\rangle$$
$$\langle \overline{u}_1^2 - \overline{u}_2^2\rangle = \langle(\overline{u}_1 + \overline{u}_2)\overline{u}\rangle$$

Thus :

$$\frac{d\langle u\rangle^2}{dt} \leq c(\|u_1\| + \|u_2\| + 1)\langle u\rangle^2 + c'(\|\overline{u}_1\| + \|\overline{u}_2\|)\|\overline{u}\||\langle u\rangle|$$

$\rightarrow$ If $T < T_0$:

$$\frac{d\langle u\rangle^2}{dt} \leq Q(t)(\langle u\rangle^2 + \|\overline{u}\|^2),\ 0 \leq t \leq T$$

$Q \in L^\infty(0,T)$

Multiply the first equation by $\overline{u}$:

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\overline{u}\|_V^2 + ((f(u_1) - f(u_2), \overline{u})) + ((g(u_1) - g(u_2), (-\Delta)^{-1}\overline{u})) = 0$$

We have $(H^2(\Omega) \subset L^\infty(\Omega))$:

$$\begin{aligned} |((g(u_1) - g(u_2), (-\Delta)^{-1}\overline{u}))| &= |(((u_1 + u_2)u, (-\Delta)^{-1}\overline{u})) + \|\overline{u}\|_{-1}^2| \\ &\leq (\|u_1\|_{L^\infty(\Omega)} + \|u_2\|_{L^\infty(\Omega)})\|u\|\|(-\Delta)^{-1}\overline{u}\| + \|\overline{u}\|^2 \\ &\leq c(\|u_1\|_{H^2(\Omega)} + \|u_2\|_{H^2(\Omega)})\|u\|^2 + \|\overline{u}\|^2 \\ &\leq Q(t)(\|\overline{u}\|^2 + \langle u \rangle^2) \end{aligned}$$

$Q \in L^2(0, T)$

Furthermore ($f' \geq -1$) :

$$((f(u_1)-f(u_2),\overline{u})) = ((f(u_1)-f(u_2),u)) - \mathrm{Vol}(\Omega)\langle f(u_1)-f(u_2)\rangle\langle u\rangle$$

$$= ((f(u_1)-f(u_2),u)) - \mathrm{Vol}(\Omega)\langle u_1^3 - u_2^3\rangle\langle u\rangle + \mathrm{Vol}(\Omega)\langle u\rangle^2$$

$$\geq -\|u\|^2 - \mathrm{Vol}(\Omega)\langle u_1^3 - u_2^3\rangle\langle u\rangle$$

Hölder's inequality :

$$|\langle u_1^3 - u_2^3\rangle| = |\int_\Omega (u_1^2 + u_1 u_2 + u_2^2)u\,dx|$$

$$\leq c(\|u_1\|_{L^4(\Omega)}^2 + \|u_2\|_{L^4(\Omega)}^2)\|u\|$$

$$\leq Q(t)\|u\|$$

$Q \in L^2(0,T)$

Thus :

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\overline{u}\|_V^2 \leq Q(t)(\|\overline{u}\|^2 + \langle u \rangle^2),$$

Interpolation inequality $\|\overline{u}\|^2 \leq \|\overline{u}\|{-1}\|\overline{u}\|_V$:

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 \leq Q(t)(\|\overline{u}\|_{-1}^2 + \langle u \rangle^2),\ 0 \leq t \leq T$$

$Q \in L^1(0,T)$

Finally :

$$\frac{d}{dt}(\|\overline{u}\|_{-1}^2 + \langle u \rangle^2) \leq Q(t)(\|\overline{u}\|_{-1}^2 + \langle u \rangle^2),\ 0 \leq t \leq T$$

$Q \in L^1(0,T)$

$\rightarrow$ Continuous dependence with respect to the initial data with respect to the $H^{-1}(\Omega)$-norm, uniqueness

Blow up in finite time :

Spatially homogeneous solutions ($u(x,t) = y(t)$) : Riccati ODE

$$y' + y^2 - y = 0, \ y(0) = y_0$$

Solution ($y_0 \neq 0$) as long as it exists :

$$y(t) = \frac{1}{(\frac{1}{y_0} - 1)e^{-t} + 1}$$

$\rightarrow y_0 < 0$: blow up in finite time

Of course, $y_0 < 0$ is not biologically relevant

We can be more precise

Integrate over Ω :

$$\frac{d}{dt}\int_\Omega u\,dx + \int_\Omega g(u)\,dx = 0$$

$2s \leq s^2 + 1$:

$$\int_\Omega g(u)\,dx \geq \int_\Omega u\,dx - \mathrm{Vol}(\Omega)$$

Thus :

$$\frac{d\langle u\rangle}{dt} + \langle u\rangle \leq 1$$

Gronwall's lemma :

$$\langle u(t)\rangle \leq (\langle u_0\rangle - 1)e^{-t} + 1,\ t \geq 0$$

$\langle u \rangle$ is bounded from above : $\langle u \rangle \leq 1$ if $\langle u_0 \rangle \in [0, 1]$, as long as it exists

Next :

$$\frac{d\langle u \rangle}{dt} \leq \langle u \rangle$$

Gronwall's lemma :

$$\langle u(t) \rangle \leq e^t \langle u_0 \rangle$$

$\rightarrow$ If $\langle u_0 \rangle \leq 0$, then $\langle u(t) \rangle \leq 0, \; t \geq 0$

Furthermore : if $\langle u_0 \rangle < 0$, then $|\langle u(t) \rangle|$ grows at least exponentially fast, as long as it exists

Remark : We have a similar result if there exists $t_0 \geq 0$ such that $\langle u(t_0) \rangle \leq 0$

$\to$ Either $\langle u\rangle$ is nonnegative (and is uniformly bounded) or $\langle u\rangle$ tends to $-\infty$ as time goes to $+\infty$ at least exponentially fast

In the second case : $\langle u\rangle$ (and u) blows up in finite time

$\overline{u} = u - \langle u\rangle$ satisfies :

$$\frac{\partial \overline{u}}{\partial t} + \Delta^2 \overline{u} - \Delta f(\overline{u} + \langle u\rangle) + g(\overline{u} + \langle u\rangle) - \langle g(\overline{u} + \langle u\rangle)\rangle = 0$$

$$\frac{\partial \overline{u}}{\partial \nu} = \frac{\partial \Delta \overline{u}}{\partial \nu} = 0 \text{ on } \Gamma$$

$$\overline{u}|_{t=0} = \overline{u}_0 = u_0 - \langle u_0\rangle$$

Multiply by $(-\Delta)^{-1}\overline{u}$:

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\overline{u}\|_V^2 + ((f(\overline{u} + \langle u\rangle) - f(\langle u\rangle), \overline{u}))$$

$$+((g(\overline{u} + \langle u\rangle) - g(\langle u\rangle), (-\Delta)^{-1}\overline{u})) = 0$$

We have :

$$((f(\overline{u}+\langle u\rangle)-f(\langle u\rangle),\overline{u})) = \int_\Omega (\overline{u}^4 + 3\overline{u}^3\langle u\rangle + 3\overline{u}^2\langle u\rangle^2)\,dx - \|\overline{u}\|^2$$

$$\geq \int_\Omega (\overline{u}^4 + 3\overline{u}^2\langle u\rangle^2)\,dx - 3\int_\Omega |\overline{u}^3\langle u\rangle|\,dx - \|\overline{u}\|^2$$

$$\geq c_0 \int_\Omega (\overline{u}^4 + \overline{u}^2\langle u\rangle^2)\,dx - \|\overline{u}\|^2,\ c_0 > 0$$

$$|((g(\overline{u}+\langle u\rangle)-g(\langle u\rangle),(-\Delta)^{-1}\overline{u}))| = |((\overline{u}^2 + 2\overline{u}\langle u\rangle - \overline{u},(-\Delta)^{-1}\overline{u}))|$$

$$\leq \frac{3c_0}{8}\int_\Omega (\overline{u}^4 + \overline{u}^2\langle u\rangle^2)\,dx + c\|\overline{u}\|^2 + c'$$

Thus :

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\overline{u}\|_V^2 + \frac{5c_0}{4}\int_\Omega (\overline{u}^4 + \overline{u}^2\langle u\rangle^2)\,dx \le c\|\overline{u}\|^2 + c'$$

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\overline{u}\|_V^2 + c_0\int_\Omega (\overline{u}^4 + \overline{u}^2\langle u\rangle^2)\,dx \le c$$

Furthermore :

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + c\|\overline{u}\|_{-1}^2 \le c',\ c > 0$$

Gronwall's lemma :

$$\|\overline{u}(t)\|_{-1}^2 \le e^{-ct}\|\overline{u}_0\|_{-1}^2 + c',\ c > 0,\ t \ge 0$$

Let B be a bounded subset of V' and t_0 be such that $\overline{u}_0 \in B$ and $t \geq t_0$ imply $\overline{u}(t) \in \mathcal{B}_0$, where $\mathcal{B}_0 = \{\varphi \in V,\ \|\varphi\|_{-1}^2 \leq 2c'\}$

Furthermore :

$$\int_t^{t+r} \|\overline{u}\|_V^2\, ds \leq c(r),\ \int_t^{t+r} ds \int_\Omega (\overline{u}^4 + \overline{u}^2 \langle u \rangle^2)\, dx \leq c(r)$$

$$\int_t^{t+r} \|\overline{u}\|_V^2\, ds \leq c(r),\ \int_t^{t+r} ds \int_\Omega (\overline{u}^4 + \overline{u}^2 \langle u \rangle^2)\, dx \leq c(r)$$

Multiply by $\overline{u}$ ($f' \geq -1$) :

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|^2 + \|\Delta \overline{u}\|^2 + ((g(\overline{u} + \langle u \rangle) - g(\langle u \rangle), \overline{u})) \leq \|\overline{u}\|_V^2$$

We have :

$$|((g(\overline{u}+\langle u\rangle)-g(\langle u\rangle),\overline{u}))| \leq \int_\Omega (|\overline{u}|^3+2\overline{u}^2|\langle u\rangle|)\,dx+\|\overline{u}\|^2$$
$$\leq c(\int_\Omega (\overline{u}^4+\overline{u}^2\langle u\rangle^2)\,dx+\|\overline{u}\|^2+1)$$

Thus :

$$\frac{d}{dt}\|\overline{u}\|^2+\|\Delta\overline{u}\|^2 \leq c(\int_\Omega (\overline{u}^4+\overline{u}^2\langle u\rangle^2)\,dx+\|\overline{u}\|_V^2+1)$$

Uniform Gronwall's lemma :

$$\|\overline{u}(t)\|^2 \leq c,\ t\geq t_0+r$$
$$\|\overline{u}(t)\|^2 \leq Q(\|\overline{u}_0\|),\ t\geq 0$$

Assume that $\langle u(T)\rangle < 0$, for some $T \geq 0$

Equation for the spatial average :

$$\frac{d\langle u\rangle}{dt} + g(\langle u\rangle) = g(\langle u\rangle) - \langle g(u)\rangle$$

$$g(\langle u\rangle) - \langle g(u)\rangle = -\langle \overline{u}^2\rangle$$

$\rightarrow$ We have the ODE

$$y' + y^2 - y = c(t)$$

$y = \langle u\rangle$ and $c = -\langle \overline{u}^2\rangle$

Riccati ODE $y' + y^2 - y = 0$:

$$y(t) = \frac{1}{\frac{y(T)}{y(T)-1}e^{t-T} - 1} + 1,\ t \geq T$$

Theorem : If $\langle u(T)\rangle < 0$, for some $T \geq 0$ (and, in particular, if $\langle u_0\rangle < 0$), then the solution blows up in finite time. Furthermore, the blow up time T^+ satisfies

$$T^+ \leq T + \ln \frac{\langle u(T)\rangle - 1}{\langle u(T)\rangle}.$$

$\|\overline{u}\|$: uniformly bounded

Set $z = \langle u\rangle - y$ (y : solution to the Riccati ODE $y' + y^2 - y = 0$ such that $y(T) = \langle u(T)\rangle$) :

$$z' + g(\langle u\rangle) - g(y) = -\langle \overline{u}^2\rangle$$

$$z(T) = 0$$

Multiply by $z^+ = \max(z, 0)$ ($z^+ \geq 0$) :

$$\frac{1}{2}\frac{d}{dt}|z^+|^2 + (g(\langle u\rangle) - g(y))z^+ = -\langle\overline{u}\rangle^2 z^+ \leq 0$$

Furthermore ($z^+ = 0$ if $z \leq 0$) :

$$\begin{aligned}(g(\langle u\rangle) - g(y))z^+ &= (\langle u\rangle^2 - y^2 - (\langle u\rangle - y))z^+ \\ &= (\langle u\rangle + y - 1)zz^+ \\ &= (\langle u\rangle + y - 1)|z^+|^2\end{aligned}$$

Thus :

$$\frac{d}{dt}|z^+|^2 + 2(\langle u\rangle + y - 1)|z^+|^2 \leq 0$$

Gronwall's lemma ($z^+(T) = 0$) :

$$|z^+(t)|^2 \leq e^{-2\int_T^t (\langle u\rangle + y - 1)\, ds} |z^+(T)|^2 = 0$$

$\rightarrow z^+ = 0$, so that $z \leq 0$:

$$\langle u(t)\rangle \leq y(t),\ t \geq T$$

as long as it exists

Corollary : Let u be a solution. Then, either u blows up in finite time or it exists globally in time and $0 \leq \langle u(t)\rangle \leq 1$, $\forall t \geq 0$.

Corollary : Let u be a global in time solution. Then, u is dissipative in $L^2(\Omega)$.

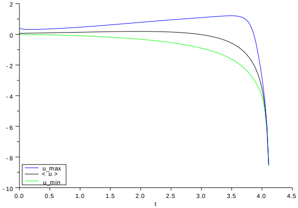
Natural question : does u remain in the biologically relevant interval if the same holds for u_0 ?

Answer : no (cf. the original Cahn-Hilliard equation)

Numerical simulations show that $\langle u \rangle$ (and u) can blow up even if $\langle u_0 \rangle$ is positive for $f(s) = (s - \frac{1}{2})^3 - (s - \frac{1}{2})$

$\rightarrow$ One has to be careful when employing this model in biology

We will see that logarithmic nonlinear terms prevent the blow up



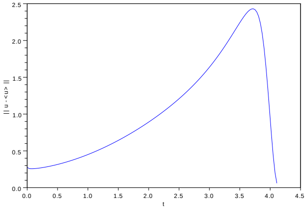


FIGURE – Blow up, $u_0 \in [0, 1]$ and $\langle u_0 \rangle = 0.069$; $u - \langle u \rangle$ tends to 0.

Theorem : Let u be a nonvanishing solution such that $u(t) \in [0, 1], \forall t \geq 0$. Then, $u(t)$ tends to 1 in $H^1(\Omega)$ as $t \to +\infty$.

Remark :

Wound healing : the wound heals completely

Tumor growth : the tumor spreads completely

Idea of the proof :

The ω-limit set of any nonvanishing u_0 is nonempty and compact in $H^1(\Omega)$

If $\tilde{u}$ belongs to this set, necessarily, $\langle \tilde{u} \rangle = 1$ and $\tilde{u} \equiv 1$

$u(t)$ tends to 1 in $H^2(\Omega)$

Logarithmic nonlinear terms :

We make the rescaling $u \mapsto 2u - 1$, mapping $[0, 1]$ onto $[-1, 1]$

$\to g(s) = \lambda(s^2 - 1)$

Equations :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + g(u) = 0$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma$$

$$u|_{t=0} = u_0$$

f : logarithmic, $g(s) = s^2 - 1$

$$f' \geq -c_0, \; c_0 = \theta_c$$

Write $F(s) = \frac{\theta_c}{2}(1 - s^2) + F_1(s)$ and set $f_1 = F_1'$

Approximated functions $F_{1,N} \in C^4(\mathbb{R})$:

$$F_{1,N}^{(4)}(s) = F_1^{(4)}(1 - \frac{1}{N}),\ s \geq 1 - \frac{1}{N}$$

$$F_{1,N}^{(4)}(s) = F_1^{(4)}(s),\ |s| \leq 1 - \frac{1}{N}$$

$$F_{1,N}^{(4)}(s) = F_1^{(4)}(-1 + \frac{1}{N}),\ s \leq -1 + \frac{1}{N}$$

$$F_{1,N}^{(k)}(0) = F_1^{(k)}(0),\ k = 0,\ 1,\ 2,\ 3$$

$$F_{1,N}(s)=\sum_{k=0}^{4}\frac{1}{k!}F_1^{(k)}(1-\frac{1}{N})(s-1+\frac{1}{N})^k,\ s\geq 1-\frac{1}{N}$$

$$F_{1,N}(s)=F_1(s),\ |s|\leq 1-\frac{1}{N}$$

$$F_{1,N}(s)=\sum_{k=0}^{4}\frac{1}{k!}F_1^{(k)}(-1+\frac{1}{N})(s+1-\frac{1}{N})^k,\ s\leq -1+\frac{1}{N}$$

Set $F_N(s)=\frac{\theta_c}{2}(1-s^2)+F_{1,N}(s), f_{1,N}=F'_{1,N}, f_N=F'_N$

$$f'_{1,N}\geq 0,\ f'_N\geq -c_0$$

$$F_N\geq -c_1,\ c_1\geq 0$$

$$f_N(s)s\geq c_2(F_N(s)+|f_N(s)|)-c_3,\ c_2>0,\ c_3\geq 0,\ s\in\mathbb{R}$$

$$(f_N(s+a)-f_N(a))s\geq c_4(s^4+a^2s^2)-c_5,\ c_4>0,\ c_5\geq 0,\ s,\ a\in\mathbb{R}$$

More generally :

$$f_N(s)(s-m) \geq c_{6,m}(F_N(s) + |f_N(s)|) - c_{7,m}$$

$$c_{6,m} > 0,\ c_{7,m} \geq 0,\ s \in \mathbb{R},\ m \in (-1,1)$$

Young's inequality :

$$|g(s+a) - g(a)| \leq c_8(s^2 + |as|)$$

$$|g(s+a) - g(a)|^2 \leq c_9(s^4 + a^2 s^2)$$

$s, a \in \mathbb{R}$

Approximated problems :

$$\frac{\partial u_N}{\partial t} + \Delta^2 u_N - \Delta f_N(u_N) + g(u_N) = 0$$

$$\frac{\partial u_N}{\partial \nu} = \frac{\partial \Delta u_N}{\partial \nu} = 0 \text{ on } \Gamma$$

$$u_N|_{t=0} = u_0$$

A priori estimates :

Main aims :

Uniform (with respect to N) estimate on $f_N(u_N)$ in some $L^2(\Omega \times (0,T))$, $T > 0$ independent of N

Uniform (with respect to N) strict separation property of $\langle u_N \rangle$ from the singular points -1 and 1

Assume that $u_0 \in H^1(\Omega) \cap L^\infty(\Omega)$, $|u_0(x)| < 1$, a.e. $x \in \Omega$, and

$$|\langle u_0 \rangle| \leq 1 - 2\delta,\ \delta \in (0, \frac{1}{2}] \text{ given}$$

Integrate over Ω :

$$\frac{d\langle u_N \rangle}{dt} + \langle g(u_N) \rangle = 0$$

Set :

$$u_N = \langle u_N \rangle + \overline{u}_N,\ \langle \overline{u}_N \rangle = 0$$

Thus :

$$\frac{d\langle u_N \rangle}{dt} + \langle \langle u_N \rangle^2 - 1 + \overline{u}_N^2 + 2\langle u_N \rangle \overline{u}_N \rangle = 0$$

and ($\langle \overline{u}_N \rangle = 0$)

$$\frac{d\langle u_N \rangle}{dt} + g(\langle u_N \rangle) = -\langle \overline{u}_N^2 \rangle$$

$\overline{u}_N$ is solution to

$$\frac{\partial \overline{u}_N}{\partial t} + \Delta^2 \overline{u}_N - \Delta f_N(u_N) + g(u_N) - \langle g(u_N) \rangle = 0,\ u_N = \langle u_N \rangle + \overline{u}_N$$

$$\frac{\partial \overline{u}_N}{\partial \nu} = \frac{\partial \Delta \overline{u}_N}{\partial \nu} = 0 \text{ on } \Gamma$$

$$\overline{u}_N|_{t=0} = v_0 (= u_0 - \langle u_0 \rangle)$$

Equivalent formulation :

$$(-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t} - \Delta \overline{u}_N + \overline{f_N(u_N)} + (-\Delta)^{-1}\overline{g(u_N)} = 0$$

$$\frac{\partial \overline{u}_N}{\partial \nu} = 0 \text{ on } \Gamma$$

$$\overline{u}_N|_{t=0} = v_0$$

Multiply by $\overline{u}_N$:

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + \|\overline{u}_N\|_V^2 + ((\overline{f_N(u_N)}, \overline{u}_N)) + ((\overline{g(u_N)}, (-\Delta)^{-1}\overline{u}_N)) = 0$$

Note that

$$((\overline{f_N(u_N)}, \overline{u}_N)) = ((f_N(u_N) - f_N(\langle u_N \rangle), \overline{u}_N))$$

$$((\overline{f_N(u_N)}, \overline{u}_N)) \geq c_4 \int_\Omega (\overline{u}_N^4 + \langle u_N \rangle^2 \overline{u}_N^2)\, dx - c$$

Furthermore :

$$
\begin{aligned}
|((\overline{g(u_N)}, (-\Delta)^{-1}\overline{u}_N))| &= |((g(u_N) - g(\langle u_N \rangle), (-\Delta)^{-1}\overline{u}_N))| \\
&\leq c\|\overline{u}_N\|\|g(u_N) - g(\langle u_N \rangle)\|
\end{aligned}
$$

Thus :

$$
\begin{aligned}
|((\overline{g(u_N)}, (-\Delta)^{-1}\overline{u}_N))| &\leq \frac{c_4}{4}\int_\Omega (\overline{u}_N^4 + \langle u_N \rangle^2 \overline{u}_N^2)\, dx + c\|\overline{u}_N\|^2 \\
&\leq \frac{c_4}{2}\int_\Omega (\overline{u}_N^4 + \langle u_N \rangle^2 \overline{u}_N^2)\, dx + c
\end{aligned}
$$

Finally :

$$
\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + c(\|\overline{u}_N\|_{H^1(\Omega)}^2 + \int_\Omega (\overline{u}_N^4 + \langle u_N \rangle^2 \overline{u}_N^2)\, dx) \leq c',\ c > 0
$$

Multiply by $-\Delta\overline{u}_N$:

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}_N\|^2 + \|\Delta\overline{u}_N\|^2 + ((\overline{f_N(u_N)}, -\Delta\overline{u}_N)) + ((\overline{g(u_N)}, \overline{u}_N)) = 0$$

Furthermore :

$$\begin{aligned} ((\overline{f_N(u_N)}, -\Delta\overline{u}_N)) = ((f_N(u_N), -\Delta\overline{u}_N)) = ((f_N'(u_N)\nabla\overline{u}_N, \nabla\overline{u}_N)) \\ \geq -c_0\|\overline{u}_N\|_V^2 \end{aligned}$$

$$\begin{aligned} |((\overline{g(u_N)}, \overline{u}_N))| &= |((g(u_N) - g(\langle u_N\rangle), \overline{u}_N))| \\ &\leq \frac{1}{2}\|\Delta\overline{u}_N\|^2 + c\int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2\overline{u}_N^2)\,dx \end{aligned}$$

Thus :

$$\frac{d}{dt}\|\overline{u}_N\|^2 + \|\Delta\overline{u}_N\|^2 \leq c(\|\overline{u}_N\|_{H^1(\Omega)}^2 + \int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2\overline{u}_N^2)\,dx)$$

Combine the two estimates :

$$\frac{d}{dt}(\|\overline{u}_N\|_{-1}^2 + \gamma_1\|\overline{u}_N\|^2)$$

$$+c(\|\overline{u}_N\|_{H^2(\Omega)}^2 + \int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2\overline{u}_N^2)\,dx) \leq c',\ c > 0$$

Note that ($g(s) \geq 2s - 2$)

$$\frac{d\langle u_N\rangle}{dt} + 2\langle u_N\rangle \leq 2$$

Thus :

$$\langle u_N(t)\rangle \leq (\langle u_0\rangle - 1)e^{-2t} + 1$$

as long as it exists

$\to \langle u_N(t)\rangle < 1$ as long as it exists

Furthermore $(g(s) \geq -2s-2)$:

$$\frac{d\langle u_N\rangle}{dt} \leq 2\langle u_N\rangle + 2$$

as long as it exists

Thus :

$$\langle u_N(t)\rangle \leq (\langle u_0\rangle + 1)e^{2t} - 1$$

as long as it exists

For $t_0 \geq 0$:

$$\langle u_N(t)\rangle \leq (\langle u(t_0)\rangle + 1)e^{2(t-t_0)} - 1,\ t \geq t_0,$$

as long as it exists

$\rightarrow$ If $\langle u(t_0)\rangle < -1$, then $\langle u_N(t)\rangle$ goes to $-\infty$, at least exponentially fast

We can again have blow up in finite time

Note that

$$\frac{d}{dt}(\|\overline{u}_N\|_{-1}^2 + \gamma_1\|\overline{u}_N\|^2) + c(\|\overline{u}_N\|_{-1}^2 + \gamma_1\|\overline{u}_N\|^2) \leq c',\ c > 0$$

Thus :

$$\|\overline{u}_N(t)\|^2 \leq ce^{-c't}\|v_0\|^2 + c'',\ c' > 0$$

as long as it exists

$\rightarrow \langle \overline{u}_N^2(t) \rangle \leq c(u_0, \delta)(= c\|v_0\|^2 + c')$ as long as it exists

Consider the Riccati ODE's

$$y_+' + g(y_+) = 0, \ y_+(0) = \langle u_0 \rangle$$
$$y_-' + g(y_-) = -c(u_0, \delta), \ y_-(0) = \langle u_0 \rangle$$

Comparison principle (as long as this makes sense) :

$$y_-(t) \leq \langle u_N(t) \rangle \leq y_+(t)$$

(Consider the equations satisfied by $z_+ = \langle u \rangle - y_+$ and $z_- = y_- - \langle u \rangle$ multiplied by z_+^+ and z_-^+)

$\rightarrow$ Local in time solution on some $[0, T]$, $T > 0$ is independent of N

Note that

$$y_+(t) = \frac{2}{1 - \frac{\langle u_0\rangle - 1}{\langle u_0\rangle + 1} e^{2t}} - 1$$

$\rightarrow$ If $\langle u_0\rangle < -1$ (similar situation if, for $t_0 \in (0, T)$, $\langle u_N(t_0)\rangle < -1$), then $\langle u_N\rangle$ blows up in finite time

$\rightarrow$ Blow up in finite time : the blow up time $T_\star$ belongs to $[T_{-,\star}, T_{+,\star}]$, where $T_{-,\star}$ and $T_{+,\star}$ are the blow up times for y_- and y_+ (independent of N)

We can choose $T > 0$ (independent of N ; $T = T(u_0, \delta)$) such that

$$|\langle u_N(t)\rangle| \leq 1 - \delta, \ t \in [0, T]$$

Take $t \in [0, T]$

Multiply

$$(-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t} - \Delta \overline{u}_N + \overline{f_N(u_N)} + (-\Delta)^{-1}\overline{g(u_N)} = 0$$

by $\overline{u}_N$:

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + \|\overline{u}_N\|_V^2 + ((f_N(u_N), \overline{u}_N)) \leq c\int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2 \overline{u}_N^2)\, dx + c'$$

Thus :

$$\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + c_\delta(\|f_N(u_N)\|_{L^1(\Omega)} + \int_\Omega F_N(u_N)\, dx)$$

$$\leq c' \int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2 \overline{u}_N^2)\, dx + c''_\delta,\ c_\delta > 0$$

Combine the estimates :

$$\frac{dE_{1,N}}{dt} + c_\delta(E_{1,N} + \|\overline{u}_N\|^2_{H^2(\Omega)} + \int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2 \overline{u}_N^2)\, dx$$

$$+\|f_N(u_N)\|_{L^1(\Omega)} + \int_\Omega F_N(u_N)\, dx) \le c'_\delta,\ c_\delta > 0$$

$$E_{1,N} = (1+\gamma_2)\|\overline{u}_N\|^2_{-1} + \gamma_1\|\overline{u}_N\|^2.$$

Note that ($|\langle u_N\rangle| \le 1$)

$$\frac{d\langle u_N\rangle^2}{dt} = 2\langle u_N\rangle(-\langle \overline{u}_N^2\rangle - \langle u_N\rangle^2 + 1) \le c\|\overline{u}_N\|^2 + 4$$

Thus :

$$\frac{d\langle u_N\rangle^2}{dt} + \langle u_N\rangle^2 \le c\|\overline{u}_N\|^2 + 5$$

Combine the estimates :

$$\frac{dE_{2,N}}{dt} + c_\delta(E_{2,N} + \|u_N\|^2_{H^2(\Omega)} + \int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2 \overline{u}_N^2)\, dx$$
$$+\|f_N(u_N)\|_{L^1(\Omega)} + \int_\Omega F_N(u_N)\, dx) \leq c'_\delta,\ c_\delta > 0$$
$$E_{2,N} = E_{1,N} + \gamma_3 \langle u_N\rangle^2$$
$$c\|u_N\|^2 \leq E_{2,N} \leq c'\|u_N\|^2,\ c,\ c' > 0.$$

Multiply

$$(-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t} - \Delta \overline{u}_N + \overline{f_N(u_N)} + (-\Delta)^{-1}\overline{g(u_N)} = 0$$

by $\frac{\partial \overline{u}_N}{\partial t}$:

$$\|\frac{\partial \overline{u}_N}{\partial t}\|^2_{-1} + \frac{1}{2}\frac{d}{dt}\|\nabla u_N\|^2 + ((f_N(u_N), \frac{\partial \overline{u}_N}{\partial t}))$$
$$+((u_N^2 - 1, (-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t})) = 0$$

Note that

$$
\begin{aligned}
((f_N(u_N), \frac{\partial \overline{u}_N}{\partial t})) &= ((f_N(u_N), \frac{\partial u_N}{\partial t})) - ((f_N(u_N), \frac{\partial \langle u_N \rangle}{\partial t})) \\
&= \frac{d}{dt} \int_\Omega F_N(u_N)\, dx + ((f_N(u_N), \langle \overline{u}_N^2 \rangle + \langle u_N \rangle^2 - 1)) \\
&= \frac{d}{dt} \int_\Omega F_N(u_N)\, dx + \mathrm{Vol}(\Omega) \langle f_N(u_N) \rangle (\langle \overline{u}_N^2 \rangle + \langle u_N \rangle^2 - 1) \\
&\geq \frac{d}{dt} \int_\Omega F_N(u_N)\, dx - c \| f_N(u_N) \|_{L^1(\Omega)} (\| \overline{u}_N \|^2 + 1),\ c > 0
\end{aligned}
$$

$$
\begin{aligned}
|((u_N^2 - 1, (-\Delta)^{-1} \frac{\partial \overline{u}_N}{\partial t}))| &= |((u_N^2 - \langle u_N \rangle^2, (-\Delta)^{-1} \frac{\partial \overline{u}_N}{\partial t}))| \\
&\leq \frac{1}{2} \| \frac{\partial \overline{u}_N}{\partial t} \|_{-1}^2 + c \int_\Omega (\overline{u}_N^4 + \langle u_N \rangle^2 \overline{u}_N^2)\, dx
\end{aligned}
$$

Thus :

$$\frac{d}{dt}(\|\nabla u_N\|^2 + 2\int_\Omega F_N(u_N)\,dx) + \|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2$$

$$\leq c(\|f_N(u_N)\|_{L^1(\Omega)}(\|\overline{u}_N\|^2 + 1) + \int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2 \overline{u}_N^2)\,dx)$$

Multiply by $\overline{f_N(u_N)}$:

$$\|\overline{f_N(u_N)}\|^2 - ((\Delta\overline{u}_N, \overline{f_N(u_N)})) + ((-\Delta)^{-1}\frac{\partial \overline{u}_N}{dt}, \overline{f_N(u_N)}))$$

$$+(((-\Delta)^{-1}\overline{g(u_N)}, \overline{f_N(u_N)})) = 0$$

Note that

$$((\Delta\overline{u}_N, \overline{f_N(u_N)})) = ((\Delta u_N, f_N(u_N)))$$

$$= -((f_N'(u_N)\nabla u_N, \nabla u_N)) \geq -c_0\|\nabla u_N\|^2$$

Thus :

$$\|\overline{f_N(u_N)}\|^2 \leq c(\|u_N\|^2_{H^1(\Omega)} + \int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^2 \overline{u}_N^2)\,dx + \|\frac{\partial \overline{u}_N}{\partial t}\|^2_{-1})$$

Finally :

$$|\langle f_N(u_N)\rangle| \leq c_\delta \|\overline{u}_N\| \|\overline{f_N(u_N)}\| + c'_\delta$$

$\rightarrow$ Uniform (with respect to N) estimate on $f_N(u_N)$ in $L^2(\Omega \times (0,T))$

Existence of solutions :

Theorem : We assume that $u_0 \in H^1(\Omega)$, $|\langle u_0 \rangle| < 1$ and $-1 < u_0(x) < 1,$ a.e. $x \in \Omega$. Then, there exists $T = T(u_0) > 0$ and a solution u on $[0,T]$ such that $u \in \mathcal{C}([0,T]; H^1(\Omega)_w) \cap L^2(0,T; H^2(\Omega)) \cap L^4(\Omega \times (0,T))$ and $\frac{\partial u}{\partial t} \in L^2(0,T; H^{-1}(\Omega))$. Furthermore, $-1 < u(x,t) < 1$, a.e. $(x,t) \in \Omega \times (0,T)$.

Theorem : The solution u is global in time.

Uniqueness, further regularity : open problems

$[0, T_\star)$, $T_\star > 0$: maximal interval of existence

$$|u(x,t)| \leq 1, \text{ a.e. } (x,t) \in [0, T_\star)$$

$\langle u \rangle$ satisfies

$$\frac{d\langle u \rangle}{dt} + \langle u^2 - 1 \rangle = 0$$

Note that

$$\frac{d\langle u \rangle}{dt} + 2\langle u \rangle = -\langle u^2 - 2u - 1 \rangle$$

Thus :

$$\langle u(t) \rangle = e^{-2t}\langle u_0 \rangle - e^{-2t} \int_0^t e^{2s} \langle u^2 - 2u - 1 \rangle \, ds$$

Note that

$$|\langle u^2 - 2u - 1 \rangle| \leq 2$$

Thus :

$$|\langle u(t) \rangle| \leq e^{-2t} |\langle u_0 \rangle| + 1 - e^{-2t}, \ t \in [0, T_\star)$$

Finally :

$$|\langle u(t) \rangle| < 1, \ t \in [0, T_\star)$$

$\rightarrow \langle u \rangle$ (and u) cannot blow up in finite time (if $T_\star < +\infty$, then $|\langle u(t) \rangle| \leq 1 - \delta$, $\delta = \delta(u_0, T_\star) \in (0,1)$)

$\rightarrow$ The solution is global

Further comments :

a) Reaction-diffusion equation :

$$\frac{\partial u}{\partial t} - \Delta u + g(u) = 0$$

Also useful for biological applications

Blow up in finite time

$u_0 \in L^\infty(\Omega)$: consider the ODE's

$$y'_\pm + g(y_\pm) = 0, \; y_\pm(0) = y_{\pm,0}$$
$$y_{-,0} \le u_0(x) \le y_{+,0}$$

Comparison principle :

$$y_-(t) \le u(x,t) \le y_+(t)$$

$\rightarrow$ Global (in time) existence of a biologically relevant solution when $u_0 \in [0,1]$

b) Other function g in tumor growth :

$$g(s) = \frac{\lambda_d}{2}(1+s) - \lambda_g(1+s)^2(1-s)^2,\ \lambda_d,\ \lambda_g > 0,$$

λ_d, λ_g : death and growth coefficients

Numerical simulations : no blow up if $u_0 \in [0, 1]$

Source term :

$$g = g(x,t,s) = \frac{\lambda_d}{2}(1+s) - \lambda_g(1+s)^2(1-s)^2 - h(x,t)$$

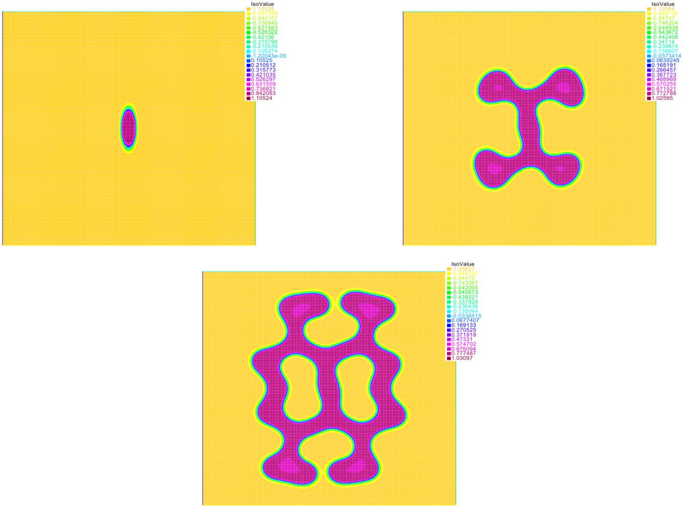


FIGURE – Tumor growth, $g(s) = 46(s+1) - 280(s-1)^2(s+1)^2$.

c) Cahn-Hilliard model in tumor growth :

$$\frac{\partial u}{\partial t} - \Delta\mu - (P\sigma - A)h(u) = 0$$

$$\mu = -\Delta u + f(u)$$

$$\frac{\partial \sigma}{\partial t} - \Delta\sigma + C\sigma h(u) + B(\sigma_s - \sigma) = 0$$

u : tumor phase concentration

σ : concentration of a nutrient for the tumor cells (oxygen, glucose)

μ : chemical potential of the "phase transition" from healthy to tumor cells

P, A, B, C : positive constants, $\sigma_s \in (0, 1)$

P : proliferation rate

A : apoptosis rate

C : nutrient consumption rate

B : nutrient supply rate

$P\sigma h(u)$: models the proliferation of tumor cells which is proportional to the concentration of the nutrient

$Ah(u)$: describes the apoptosis of tumor cells
$C\sigma h(u)$ models the consumption of the nutrient by the tumor cells.
σ_s : nutrient concentration in a pre-existing vasculature
$B(\sigma_s - \sigma)$: models the supply of nutrient from the blood vessels if $\sigma_s > \sigma$, transport of nutrient away from the domain Ω if $\sigma_s < \sigma$
Possible choice for h : $h(s) = \frac{1}{2}(s+1)$

Well-posedness, asymptotic behavior (A. Miranville-E. Rocca-G. Schimperna)

Cahn-Hilliard systems are also relevant : describe the different phases of a tumor (proliferative, quiescent, necrotic cells)