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Secteur de recherche : Mathématiques et applications

Présentée par :
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The PDE type models for the growth of glial cells

Directeur(s) de Thèse :
Alain Miranville, Rémy Guillevin

Soutenue le 10 mars 2023 devant le jury

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THESE

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Modèles de type EDP pour la croissance de tumeurs gliales

Directeur de Thèse :

Alain MIRANVILLE
Rémy GUILLEVIN

Soutenue le 10 Mars 2023

Devant la Commission d'Examen

JURY

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	Shubin Wang	Professeur, Zhengzhou University

Dedicated to my beloved family : my mother Chunmei, my father Kuangshan,
and my elder brother Wenxuan.
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Chapitre 1

Introduction générale

1.1 Modèles de séparation de phase

En tant que représentant des équations aux dérivées partielles non linéaires, les modèles de séparation de phase qui ont été initialement proposés en science des matériaux puis ont été largement utilisés dans de nombreux domaines différents au cours des dernières décennies, par exemple la biologie, l'écologie, l'astronomie ou encore le traitement d'images. De plus, l'équation de Cahn-Hilliard, proposée par J.W. Cahn et J.E. Hilliard en 1958 (voir [12]), est une équation de physique mathématique qui décrit le processus de séparation de phase, par lequel les deux composants d'un fluide binaire se séparent spontanément et forment des domaines purs dans chaque composant.

1.1.1 Les équations de Cahn-Hilliard

Le système de Cahn-Hilliard

$$\begin{cases} \dfrac{\partial u}{\partial t} = \kappa \Delta \mu, \ \kappa > 0, \\ \mu = -\alpha \Delta u + f(u), \ \alpha > 0, \end{cases} \tag{1.1}$$

est généralement réécrit, de manière équivalente, sous la forme d'une équation parabolique du quatrième ordre en espace

$$\frac{\partial u}{\partial t} + \alpha \kappa \Delta^2 u - \kappa \Delta f(u) = 0, \tag{1.2}$$

qui est précisément l'équation connue sous le nom d'équation de Cahn-Hilliard. Ces équations jouent un rôle essentiel dans la science des matériaux et décrivent des caractéristiques qualitatives importantes des systèmes à deux phases liées aux processus de séparation de phase, en supposant une isotropie et une température constante. Cela peut être observé, par exemple, lorsqu'un alliage binaire (par exemple, Aluminium/Zinc (voir [112]) ou Fer/Chrome (voir [80, 81, 82]) est suffisamment refroidi . Dans la première étape, dite de décomposition spinodale : le matériau initialement homogène devient rapidement inhomogène, d'où une microstructure très finement dispersée. La deuxième étape, appelée grossissement, se produit à une échelle de temps plus lente. De tels phénomènes jouent un rôle essentiel dans les propriétés mécaniques du matériau, par exemple la résistance, la dureté, la rupture, la ténacité et la ductilité. Nous renvoyons le lecteur, par exemple, à [11, 12, 65, 67, 76, 77, 102, 103] pour plus de détails.

Ici, u est le paramètre d'ordre (nous considérerons une densité d'atomes redimensionnée ou concentration d'un des composants du matériau qui prend des valeurs comprises entre -1 et 1, les valeurs -1 et 1 correspondant aux états purs. La densité du deuxième composant est $-u$, ce qui signifie que la densité totale est une quantité conservée) et μ est le potentiel chimique (plus précisément, la différence de potentiels chimiques entre les deux composants). De plus, f est la dérivée d'un potentiel de double

puits F. Un potentiel thermodynamiquement pertinent F est la fonction logarithmique suivante qui découle d'un modèle de champ moyen :

$$F(s) = \frac{\theta_c}{2}(1-s^2)+\frac{\theta}{2}[(1-s)\ln(\frac{1-s}{2})+(1+s)\ln(\frac{1+s}{2})],\ s \in (-1,1),\ 0<\theta<\theta_c, \quad (1.3)$$

c'est-à-dire,

$$f(s) = -\theta_c s + \frac{\theta}{2}\ln\frac{1+s}{1-s}, \quad (1.4)$$

bien que cette fonction soit très souvent approximée par des fonctions régulières (voir [25, 26, 37, 38]), typiquement,

$$F(s) = \frac{1}{4}(s^2-1)^2, \quad (1.5)$$

c'est-à-dire,

$$f(s) = s^3 - s, \quad (1.6)$$

plus généralement, on peut prendre $F(s) = \frac{1}{4}(s^2-\beta^2)^2$, $\beta \in \mathbb{R}$. Dans ce cas, si un terme source non linéaire est ajouté dans l'équation (1.2), on n'a plus la conservation de la moyenne spatiale du paramètre d'ordre u, l'existence d'une solution globale en temps devient un problème. Pire encore, on peut avoir une explosion en temps fini lorsque l'on considère des termes non linéaires réguliers (voir [28, 36]), ce qui est problématique au vu des applications. Néanmoins, il a été prouvé dans [73, 89, 96] que, dans certains cas particuliers, l'existence de solutions globales en temps peut être prouvée lorsque l'on considère plutôt un terme non linéaire logarithmique. Voir Figure 1.1 pour une comparaison entre les deux potentiels.

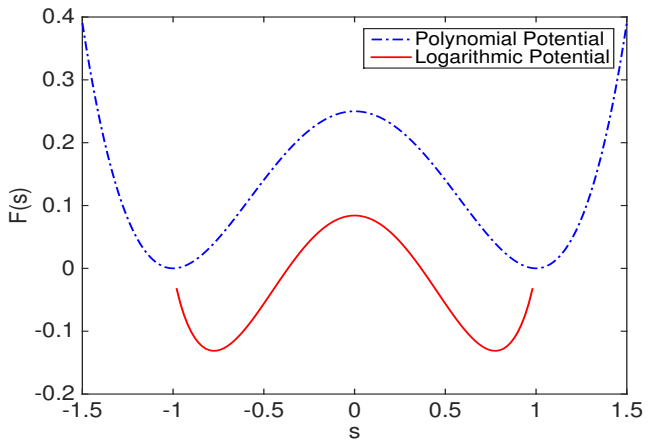

FIGURE 1.1 – Le potentiel logarithmique et le potentiel polynomial.

Les termes logarithmiques dans (1.3) correspondent à l'entropie du mélange, et θ et θ_c sont respectivement proportionnels à la température absolue (supposée constante pendant le processus) et à une température critique ; la condition $\theta < \theta_c$ garantit que F a une forme à double puits et qu'une séparation de phase peut se produire. Notez également que l'approximation polynomiale est raisonnable lorsque la trempe est peu profonde, c'est-à-dire lorsque la température absolue est proche de la température critique. Enfin, κ est la mobilité et α est lié à la tension superficielle à l'interface. Nous renvoyons le lecteur à [15, 16, 46, 91, 92, 94, 99] pour plus de détails.

D'un point de vue phénoménologique, le système de Cahn-Hilliard peut être dérivé comme suit.

On considère l'énergie libre (totale) suivante, appelée énergie libre de Ginzburg-Landau :

$$\Psi_\Omega(u, \nabla u) = \int_\Omega (\frac{\alpha}{2}|\nabla u|^2 + F(u))dx, \ \alpha > 0, \tag{1.7}$$

où $\Omega \subset \mathbb{R}^n$, $n = 1, 2$ ou 3, est le domaine occupé par le matériau. Le terme de gradient dans (1.7) a été proposé dans [12] afin de modéliser l'énergie de surface de l'interface (c'est-à-dire la capillarité ; notez que ces gradients remontent à J.D. van der Waals (voir [115]) ; F est aussi appelée énergie libre homogène.

On a alors le bilan de masse

$$\frac{\partial u}{\partial t} = -\operatorname{div} h,$$

où h est le flux massique qui est lié au potentiel chimique μ par l'équation constitutive suivante (postulée) qui ressemble à la loi de Fick :

$$h = -\kappa \nabla \mu.$$

La définition habituelle du potentiel chimique est qu'il s'agit de la dérivée de l'énergie libre par rapport au paramètre d'ordre. Ici, une telle définition est incompatible avec la présence de ∇u dans l'énergie libre. Au lieu de cela, μ est défini comme une dérivée variationnelle de l'énergie libre par rapport à u, ce qui donne (en supposant des conditions aux limites appropriées)

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

le système de Cahn-Hilliard s'ensuit alors. Cette dérivée variationnelle peut être (formellement) vue en écrivant que, pour une petite variation,

$$\delta \Psi_\Omega = \int_\Omega (\alpha \nabla u \cdot \nabla \delta u + f(u)\delta u)dx,$$

où $\cdot$ désigne le produit scalaire euclidien habituel. En supposant des conditions aux limites compatibles et en intégrant par parties, cela donne

$$\delta \Psi_\Omega = \int_\Omega (-\alpha \Delta u + f(u))\delta u dx,$$

d'où découle la définition.

Le système de Cahn-Hilliard, dans un domaine borné et régulier Ω, est généralement associé à des conditions aux limites de Neumann, à savoir,

$$\frac{\partial \mu}{\partial \nu} = 0 \text{ sur } \Gamma,$$

ce qui signifie qu'il n'y a pas de flux de masse aux bords du domaine (notez que $h \cdot \nu = -\kappa \frac{\partial \mu}{\partial \nu}$), et

$$\frac{\partial u}{\partial \nu} = 0 \text{ sur } \Gamma,$$

qui est une condition aux limites variationnelle naturelle (par naturelle, nous entendons qu'elle permet d'écrire une formulation variationnelle/faible convenable en vue de l'analyse mathématique du problème ; cette condition aux limites entraîne également que l'interface est orthogonale aux bords). Ici, $\Gamma = \partial\Omega$ et ν est la normale unitaire extérieure des bords du domaine. En particulier, il découle de la première condition aux limites que l'on a la conservation de la masse, c'est-à-dire de la moyenne spatiale du paramètre d'ordre, obtenue en intégrant (formellement) la première équation de (1.1) sur Ω,

$$\langle u(t) \rangle \equiv \frac{1}{\text{Vol}(\Omega)} \int_\Omega u(x,t) dx = \langle u(0) \rangle, \ \forall t \leq 0. \tag{1.8}$$

Si nous avons à l'esprit l'équation de Cahn-Hilliard du quatrième ordre en espace, nous pouvons réécrire ces conditions aux limites, de manière équivalente, comme

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ sur } \Gamma. \tag{1.9}$$

Notez que nous ne considérons généralement pas les conditions aux limites de Dirichlet, en raison précisément du fait qu'elles ne donnent pas la conservation de la masse, bien que de telles conditions aux limites simplifient certainement l'analyse mathématique. Par ailleurs, on peut aussi considérer des conditions aux limites périodiques (auquel cas $\Omega = \prod_{i=1}^n (0, L_i),\ L_i > 0,\ i = 1, \cdots, n$) ; dans ce cas, on a toujours la conservation de la masse. De plus, dans le cas de l'hydromécanique, par exemple pour les mélanges de deux fluides non miscibles, l'angle de contact est dynamique, en raison des mouvements des fluides. L'étude de l'équation de Cahn-Hilliard munie de conditions aux limites dynamiques se trouve dans [29, 62, 83, 101, 119].

1.1.2 Les variantes de l'équation de Cahn-Hilliard

Notez que l'équation de Cahn-Hilliard et certaines de ses variantes sont également pertinentes pour d'autres phénomènes que la séparation de phase, par exemple le désalliage (ceci peut être observé dans les processus de corrosion (voir [34])) ; dynamique

des populations (voir [13]) ; croissance tumorale (voir [6, 63]) ; films bactériens (voir [64]) ; couches minces (voir [106, 113]) ; chimie (voir [116]) ; traitement d'images (voir [8, 9, 18, 23, 33]) ; l'astronomie, avec même les anneaux de Saturne (voir [114]) ; et l'écologie (par exemple, le regroupement des moules peut être parfaitement décrit par l'équation de Cahn-Hilliard (voir [75]).

En particulier, plusieurs de ces phénomènes peuvent être modélisés par l'équation généralisée de Cahn-Hilliard :

$$\frac{\partial u}{\partial t} + \alpha\kappa\Delta^2 u - \kappa\Delta f(u) + g(x,u) = 0,\ \alpha,\kappa > 0 \tag{1.10}$$

(ici, α et κ n'ont pas nécessairement la même signification physique que dans l'équation originale de Cahn-Hilliard). Nous renvoyons le lecteur à [84, 87, 95] (voir aussi [6, 24, 28, 35, 108]) pour plus d'études sur l'équation (1.10). En particulier, l'équation générale contient les modèles suivants.

(i) Système mixte Allen-Cahn/Cahn-Hilliard. Dans ce cas, on considère le système d'équations

$$\begin{cases} \dfrac{\partial u}{\partial t} = \varepsilon^2 D\Delta\mu - \mu,\ D,\varepsilon > 0, \\ \mu = -\Delta u + \dfrac{f(u)}{\varepsilon^2}, \end{cases}$$

qui peut s'écrire, de façon équivalente, comme

$$\frac{\partial u}{\partial t} + \varepsilon^2 D\Delta^2 u - \Delta(Df(u) + u) + \frac{f(u)}{\varepsilon^2} = 0,$$

et est bien de la forme ci-dessus. En particulier, sans le terme $\varepsilon^2 D\Delta\mu$ dans la première équation, nous avons l'équation d'Allen-Cahn (qui décrit l'ordre des atomes pendant le processus de séparation de phases ; voir [4]), et, sans le terme $-\mu$, nous avons l'équation de Cahn-Hilliard. Ces équations sont proposées pour tenir compte des mécanismes microscopiques tels que la diffusion de surface et l'adsorption/désorption, c'est-à-dire l'adhésion d'atomes à une surface/la libération d'une substance depuis ou à travers une surface (voir [57, 59, 60, 79]) et sont étudiés dans [53, 54, 55, 56, 58].

(ii) Équation de Cahn-Hilliard-Oono. Dans ce cas,

$$g(x,s) = g(s) = \beta s,\ \beta > 0.$$

Cette fonction a été proposée dans [105] pour tenir compte des interactions à longue portée (c'est-à-dire non locales) dans la séparation de phase et également pour simplifier les simulations numériques, car nous n'avons pas à tenir compte de la conservation de la masse, bien qu'il semble que cette équation n'est pas considérée dans les simulations.

Une variante de ce modèle, proposée dans [31] pour modéliser la séparation de microphases des copolymères diblocs, consiste à prendre

$$g(x,s) = g(s) = \beta(s - \frac{1}{\mathrm{Vol}(\Omega)}\int_\Omega u_0(x)dx),\ \beta > 0,$$

où u_0 est la condition initiale. Dans ce cas, nous avons la conservation de la masse ; des simulations efficaces sont effectuées dans [5, 20]. Cette variante de l'équation de Cahn-Hilliard-Oono peut également être couplée aux équations incompressibles de Navier-Stokes pour modéliser un fluide binaire réagissant chimiquement (voir [51, 52] ; voir aussi [10] pour l'analyse mathématique). Nous renvoyons le lecteur à [30, 88, 118] pour plus d'études sur l'équation de Cahn-Hilliard-Oono.
(iii) Terme de prolifération. Dans ce cas,

$$g(x, s) = g(s) = \beta s(s - 1),\ \beta > 0.$$

Cette fonction a été proposée dans [63] en vue d'applications biologiques et, plus précisément, pour modéliser la cicatrisation et la croissance tumorale (dans une dimension spatiale) et le regroupement des cellules tumorales cérébrales malignes (dans deux dimensions spatiales) ; voir aussi [116] pour d'autres fonctions quadratiques avec des applications chimiques et [6, 28, 89] pour d'autres polynômes avec des applications biologiques.
(iv) Terme de fidélité. Dans ce cas,

$$g(x, s) = \lambda_0 \chi_{\Omega\setminus D}(x)(s - h(x)),\ \lambda_0 > 0,\ D \subset \Omega,\ h \in L^2(\Omega),$$

où χ désigne la fonction indicatrice, et on considère l'équation

$$\frac{\partial u}{\partial t} + \varepsilon\Delta^2 u - \frac{1}{\varepsilon}\Delta f(u) + g(x, t) = 0,\ \varepsilon > 0.$$

Ainsi écrit, ε correspond à l'épaisseur de l'interface. Cette fonction g est proposée dans [8, 9] en vue d'applications à l'inpainting d'images binaires (c'est-à-dire des images en noir et blanc). Ici, h est une image donnée (endommagée) et D est la région d'inpainting (c'est-à-dire endommagée). De plus, le terme de fidélité $g(x, u)$ est ajouté pour garder la solution proche de l'image en dehors de la région d'inpainting. L'idée de ce modèle est de résoudre l'équation jusqu'à l'état stationnaire pour obtenir une version peinte (c'est-à-dire restaurée) $u(x)$ de $h(x)$. Nous renvoyons le lecteur à [23, 24] pour plus d'études.

Dans cette thèse, nous étudions quelques autres variantes de l'équation de Cahn-Hilliard, qui sont pratiquement appliquées en biologie et en segmentation d'images.

1.2 Problèmes et cadre

Les cellules gliales sont des cellules non neuronales du système nerveux central (cerveau et moelle épinière) et du système nerveux périphérique, qui comprennent différents types de cellules (voir Figure 1.2). En plus de maintenir l'homéostasie et de fournir un soutien et une protection aux neurones, ils ont également de nombreuses autres fonctions, par exemple, fournir des nutriments et de l'oxygène aux neurones, détruire les agents pathogènes et éliminer les neurones morts, etc.

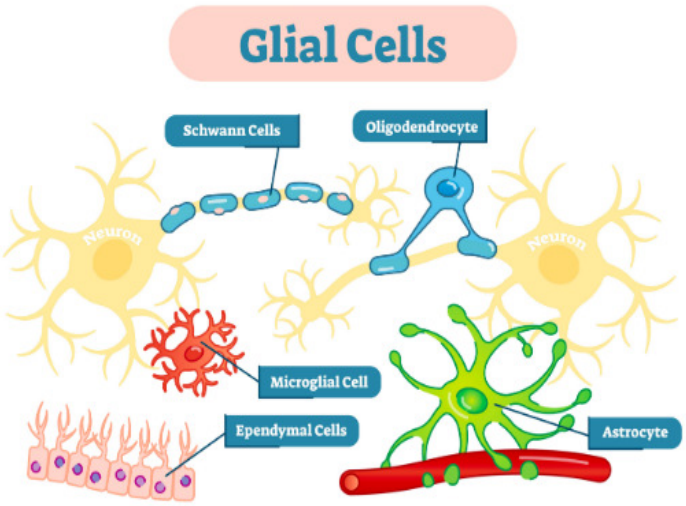

FIGURE 1.2 – Cellules gliales.

Un gliome est un type de tumeur qui prend naissance dans les cellules gliales du cerveau ou de la colonne vertébrale. Les gliomes représentent environ 30 pour cent de toutes les tumeurs cérébrales et du système nerveux central, et 80 pour cent de toutes les tumeurs cérébrales malignes. Comme expliqué dans [45], l'hypoxie est une caractéristique des gliomes et une faible concentration en oxygène déclenche une transition proliférative à invasive. Il est important d'étudier la biologie du point de vue des modèles mathématiques. Dans la première partie de cette thèse, nous appliquons plusieurs modèles différentiels partiels non linéaires pour analyser les problèmes ci-dessus.

De plus, dans la deuxième partie de cette thèse, nous étudions des modèles de type Cahn-Hilliard pour la segmentation d'image, qui vise à partitionner une image donnée en régions afin de reconnaître et d'analyser différents objets. La segmentation d'image joue un rôle important dans le traitement d'image et la vision par ordinateur, plus précisément, les applications pratiques de la segmentation d'image incluent l'imagerie médicale, la vision artificielle, la détection d'objets, la vidéosurveillance, etc.

1.2.1 Modèles de Cahn-Hilliard pour les cellules gliales

Nous considérons tout d'abord dans le chapitre 3 un modèle de Cahn-Hilliard avec un terme symport, qui est proposé pour modéliser certains mécanismes énergétiques dans les cellules gliales, et

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \frac{ku}{k' + u} = J,\ k,\ k' > 0, \tag{1.11}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{1.12}$$

$$u|_{t=0} = u_0, \tag{1.13}$$

où u correspond à une concentration, $\frac{kx}{k'+x}$ est appelé terme symport et prend en compte les échanges, par exemple, d'une cellule vers son environnement. Une difficulté cruciale ici est de prouver l'existence d'une solution biologiquement pertinente, pour surmonter cela, nous prenons f logarithmique plutôt qu'un terme non linéaire régulier (typiquement cubique), qui peut rendre u négatif et le terme symport singulier. On obtient l'existence d'une solution faible locale en temps, à savoir,

Théorème 1.2.1. Nous supposons que u_0 est donné tel que $u_0 \in H^1(\Omega)$, $0 < \langle u_0 \rangle < 1$ et $0 < u_0(x) < 1$, a.e. $x \in \Omega$. Alors, il existe $T_0 = T_0(u_0) > 0$ et une solution faible u de (1.11)-(1.13) sur $[0, T_0]$ telle que u dans $C([0, \mathrm{T}_0]; \mathrm{H}^1(\Omega)_{\mathrm{w}}) \cap \mathrm{L}^\infty(0, \mathrm{T}_0; \mathrm{H}^1(\Omega)) \cap \mathrm{L}^2(0, \mathrm{T}_0; \mathrm{H}^2(\Omega))$ et $\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega))$, où w désigne la topologie faible. De plus, $0 < u(x,t) < 1$, a.e. $(x,t) \in \Omega \times (0, T_0)$.

De plus, sous l'hypothèse de $0 \leq J\frac{k'+1}{k} \leq 1$, la solution faible locale en temps obtenue dans le Théorème 1.2.1 peut être globale en temps, c'est-à-dire, défini sur $[0, T]$, $\forall T > 0$. On en déduit alors la régularité des solutions, qui est cruciale pour prouver une séparation stricte du paramètre d'ordre u (et pas seulement sa moyenne spatiale) des états purs 0 et 1 (voir [96]) . Plus précisément, nous avons ce qui suit.

Théorème 1.2.2. On suppose que $n = 1$ ou 2, Alors, il existe $\delta \in (0, 1)$ dépendant de la norme $H^1(\Omega)$ de u_0 tel que

$$\delta \leq u(x,t) \leq 1 - \delta, \text{ pour presque tout } (x,t),\ x \in \Omega,\ t \geq r,$$

$r > 0$ donné.

De plus, nous travaillons sur l'équation de Cahn-Hilliard-Oono avec les termes logarithmiques non linéaires :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \alpha u + \frac{ku}{k' + u} = J,\ \alpha,\ k,\ k' > 0, \tag{1.14}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ sur } \Gamma, \tag{1.15}$$

$$u|_{t=0} = u_0, \tag{1.16}$$

et nous avons le

Théorème 1.2.3. Nous supposons que u_0 est donné tel que $u_0 \in H^1(\Omega)$, $0 < \langle u_0 \rangle < 1$ et $0 < u_0(x) < 1$, a.e. $x \in \Omega$. Alors, il existe $T_0 = T_0(u_0) > 0$ et une solution faible u de (1.14)-(1.16) sur $[0, T_0]$ telle que u dans $C([0, \mathrm{T}_0]; \mathrm{H}^1(\Omega)_{\mathrm{w}}) \cap \mathrm{L}^\infty(0, \mathrm{T}_0; \mathrm{H}^1(\Omega)) \cap \mathrm{L}^2(0, \mathrm{T}_0; \mathrm{H}^2(\Omega))$ et $\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega))$. De plus, $0 < u(x,t) < 1$, a.e. $(x,t) \in \Omega \times (0, T_0)$.

De même, sous l'hypothèse de $0 \leq J \leq \alpha$, la solution faible locale en temps obtenue dans le Théorème 1.2.3 peut être globale en temps. Nous avons enfin ce qui suit.

Théorème 1.2.4. On suppose que $n = 1$ ou 2, Alors, il existe $\delta \in (0, 1)$ dépendant de la norme $H^1(\Omega)$ de u_0 tel que

$$\delta \leq u(x,t) \leq 1 - \delta, \text{ pour presque tout } (x,t),\ x \in \Omega,\ t \geq r,$$

$r > 0$ donné.

1.2.2 Un modèle de Cahn-Hilliard couplé pour les cellules de gliome hypoxiques

Nous étudions ensuite un modèle couplé pour la transition proliférative à invasive des cellules de gliome hypoxique, qui est comme suit

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u), \tag{1.17}$$

$$\frac{\partial \sigma}{\partial t} - \Delta \sigma + \frac{u\sigma}{1+\sigma} = \gamma(\beta - \sigma), \tag{1.18}$$

où u représente la densité des cellules tumorales, σ représente la concentration en oxygène et h est le taux de prolifération défini comme

$$h(s) = a[\frac{s}{\beta} + b(1 - \frac{s}{\beta})].$$

Le terme $h(\sigma)u(\alpha - u)$ dans l'équation (1.17) représente la croissance dite logistique qui suppose que les cellules tumorales prolifèrent jusqu'à atteindre la densité cellulaire α. La constante α est appelée capacité de charge, β représente la concentration en oxygène dans les vaisseaux sanguins, γ, a, b sont des paramètres biologiques positifs et $b \sim 0,6 < 1$ (ici, on a fixé plusieurs autres paramètres biologiques égaux à un et se référer à [45] pour plus de détails). De plus, le terme $\Delta\sigma$ dans l'équation (1.18) représente la diffusion isotrope de l'oxygène, le terme non linéaire $\frac{u\sigma}{1+\sigma}$ représente la consommation d'oxygène par les cellules tumorales, en supposant une cinétique de Michaelis-Menten, et le terme $\gamma(\beta - \sigma)$ considère le fait que l'oxygène est libéré des vaisseaux sanguins à une vitesse linéaire.

Nous travaillons dans un premier temps sur une équation de type Cahn-Hilliard pour l'oxygène dans le modèle couplé dans le chapitre 4, plus précisément,

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u), \tag{1.19}$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2\sigma - \Delta f(\sigma) + \frac{u\sigma}{1+\sigma} + \gamma\sigma = \gamma\beta, \tag{1.20}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = \frac{\partial \Delta \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{1.21}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{1.22}$$

Ici, nous prenons f logarithmique pour la même raison que dans la section 1.2.1. Nous déduisons ensuite les estimations a priori pour le problème et la régularité d'une unique solution faible, à savoir,

Théorème 1.2.5. Nous supposons que $(u_0, \sigma_0) \in L^2(\Omega) \times H^1(\Omega)$, $u_0 \geq 0$ a.e., $0 < \sigma_0 < \beta$ a.e. et $0 < \langle \sigma_0 \rangle < \beta$. Alors (1.19)-(1.22) possède au moins une solution faible locale en temps (u, σ) tel que, pour un certain $T_0 > 0$,

$$u \in L^\infty(0, T_0; L^2(\Omega)) \cap L^2(0, T_0; H^1(\Omega)),\ \frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)),$$

$$\sigma \in L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)),\ \frac{\partial \sigma}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)).$$

En outre,

$$u \geq 0,\ 0 < \sigma < \beta \text{ pour presque tout } (x, t) \in \Omega \times [0, T_0].$$

Nous prouvons en outre que la solution locale en temps donnée ci-dessus est globale en temps.

Nous travaillons ensuite sur une équation de type Cahn-Hilliard pour la cellule tumorale dans le modèle couplé dans le chapitre 5, plus précisément,

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) = h(\sigma) u(\alpha - u),\ \alpha > 0, \tag{1.23}$$

$$\frac{\partial \sigma}{\partial t} - \Delta \sigma + \gamma \sigma + \frac{u\sigma}{1 + \sigma} = \gamma \beta,\ \gamma,\ \beta > 0, \tag{1.24}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = 0 \text{ sur } \Gamma, \tag{1.25}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{1.26}$$

Ici, le terme non linéaire f est de type logarithmique. Nous avons alors

Théorème 1.2.6. On suppose que $(u_0, \sigma_0) \in H^1(\Omega) \times L^2(\Omega)$ satisfait $u_0 \in (0, \alpha)$, $\sigma_0 \in [0, \beta]$ a.e., et le terme non linéaire $h(s) \geq 0,\ s \geq 0$ est borné et Lipschitz continu sur $\mathbb{R}$. Alors, (1.23)-(1.26) possède une solution faible locale en temps (u, σ), définie sur $[0, T_0]$, $T_0 > 0$, telle que

$$u \in L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)),$$

$$\sigma \in L^\infty(0,T_0;L^2(\Omega)) \cap L^2(0,T_0;H^1(\Omega)),$$

$$\frac{\partial \sigma}{\partial t} \in L^2(0,T_0;H^{-1}(\Omega)),$$

$$u(t) \in (0,\alpha),\ \sigma(t) \in [0,\beta] \text{ pour presque tout } t \in [0,T_0]$$

et il existe une constante $\delta \in (0,\alpha)$ telle que

$$\delta \leq \langle u(t) \rangle \leq \alpha - \delta \text{ pour presque tout } t \in [0,T_0].$$

Nous prouvons en outre que la solution locale en temps donnée par le Théorème 1.2.6 est globale en temps. Nous étudions également la permanence de la tumeur, et donnons éventuellement des simulations numériques.

On considère enfin des équations de type Cahn-Hilliard à la fois pour la densité tumorale et la concentration en oxygène dans le Chapitre 6, le modèle se réécrit alors comme suit :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f_1(u) = h(\sigma)u(\alpha - u), \tag{1.27}$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2 \sigma - \Delta f_2(\sigma) + \frac{u\sigma}{1+\sigma} + \gamma\sigma = \gamma\beta, \tag{1.28}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = \frac{\partial \Delta \sigma}{\partial \nu} = 0 \text{ sur } \Gamma, \tag{1.29}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{1.30}$$

Ici, les termes non linéaires $f_i(s),\ i = 1,2$ sont tous deux de type logarithmique. Nous avons alors

Théorème 1.2.7. Nous supposons que $(u_0,\sigma_0) \in H^1(\Omega) \times H^1(\Omega)$, et $u_0 \in (0,\alpha)$, $\sigma_0 \in (0,\beta)$ a.e. Alors (1.27)-(1.30) possède au moins une solution faible locale en temps (u,σ) définie sur $[0,T_0]$, pour un certain $T_0 > 0$, telle que

$$u \in L^\infty(0,T_0;H^1(\Omega)) \cap L^2(0,T_0;H^2(\Omega)),\ \frac{\partial u}{\partial t} \in L^2(0,T_0;H^{-1}(\Omega)),$$
$$\sigma \in L^\infty(0,T_0;H^1(\Omega)) \cap L^2(0,T_0;H^2(\Omega)),\ \frac{\partial \sigma}{\partial t} \in L^2(0,T_0;H^{-1}(\Omega)).$$

De plus,

$$0 < u < \alpha,\ 0 < \sigma < \beta \text{ pour presque tout} (x,t) \in \Omega \times [0,T_0].$$

De plus, sous l'hypothèse de $\gamma \geq \frac{\alpha}{\beta+1}$, la solution faible locale en temps donnée par le Théorème 1.2.7 est globale en temps.

1.2.3 Sur un modèle de type Cahn-Hilliard pour la segmentation d'images

Nous considérons dans le chapitre 7 un modèle de Cahn-Hilliard pour la segmentation d'images, qui est comme suit

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \frac{h(x)}{1 + (u - \frac{1}{2})^2} = 0, \tag{1.31}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ sur } \Gamma, \tag{1.32}$$

$$u|_{t=0} = u_0, \tag{1.33}$$

Ici, nous prenons f un terme cubique non linéaire. Nous avons alors ce qui suit.

Théorème 1.2.8. Nous supposons que $u_0 \in H^1(\Omega)$. Alors, (1.31)-(1.33) possède une unique solution faible u telle que

$$u \in L^\infty(0, T; H^1(\Omega)) \cap L^2(0, T; H^2(\Omega))$$

et

$$\frac{\partial u}{\partial t} \in L^2(0, T; H^{-1}(\Omega)),$$

$\forall T > 0$.

Nous prouvons également qu'il existe des solutions qui ne sont pas bornées lorsque le temps tend vers l'infini. Pour pallier cela, nous proposons une variante du modèle, basée sur le modèle de Cahn-Hilliard-Oono, qui assure la bornitude globale dans le temps des solutions. Plus précisément,

$$\frac{\partial u}{\partial t} + \alpha u + \Delta^2 u - \Delta f(u) + \frac{h(x)}{1 + (u - \frac{1}{2})^2} = 0, \tag{1.34}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ sur } \Gamma, \tag{1.35}$$

$$u|_{t=0} = u_0. \tag{1.36}$$

Ce qui nous permet de réaliser des simulations numériques qui illustrent les résultats théoriques.

Dans le chapitre 8, nous étudions en profondeur le modèle de Cahn-Hilliard-Oono ci-dessus pour la segmentation d'images. Dans le cas où f est un polynôme cubique, nous prouvons tout d'abord que le problème est bien posé, à savoir,

Théorème 1.2.9. Pour tout $u_0 \in H^1(\Omega)$ et tout $T > 0$, (1.34)-(1.36) possède une unique solution faible u telle que

$$u \in L^\infty(0,T;H^1(\Omega)) \cap L^2(0,T;H^2(\Omega)) \cap L^4(0,T;L^4(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0,T;H^{-1}(\Omega)).$$

Nous définissons ensuite le semi-groupe et prouvons l'existence de l'attracteur exponentiel, qui garantit que le semi-groupe possède l'attracteur global de dimension finie.

Dans le cas où f est logarithmique, on prouve d'abord l'existence d'une solution faible, à savoir

Théorème 1.2.10. Nous supposons que u_0 est donné tel que $u_0 \in H^1(\Omega)$, $0 < u_0(x) < 1$ et $0 < \langle u_0 \rangle < 1$, a.e. $x \in \Omega$. Alors il existe $T_0 = T_0(u_0) > 0$, (1.34)-(1.36) possède une solution faible u sur $[0,T_0]$ telle que

$$u \in C([0,T_0];H^1(\Omega)_W) \cap L^\infty(0,T_0;H^1(\Omega)) \cap L^2(0,T_0;H^2(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0,T_0;H^{-1}(\Omega)).$$

Par ailleurs, $0 < u(x,t) < 1$, a.e $(x,t) \in \Omega \times (0,T_0)$.

Nous prouvons ensuite la régularité supplémentaire des solutions et la séparation des états purs dans les dimensions 1 et 2, et enfin nous prouvons l'existence d'un attracteur exponentiel et la dimensionnalité fractale finie de l'attracteur global.

Enfin, le contenu et les conclusions du chapitre 3 au chapitre 8 ont été publiées dans des revues, plus d'informations peuvent être trouvées dans [68, 69, 70, 71, 72, 73].

Chapitre 2

General introduction

2.1 Phase separation models

As a representative of nonlinear partial differential equations, phase separation models which were originally proposed in materials science, and have been extensively used in many different areas, e.g., biology, ecology, astronomy and image processing in the past decades. Furthermore, the Cahn-Hilliard equation, proposed by J.W. Cahn and J.E. Hilliard in 1958 (see [12]), is an equation of mathematical physics which describes the process of phase separation, by which the two components of a binary fluid spontaneously separate and form domains pure in each component.

2.1.1 The Cahn-Hilliard equations

The Cahn-Hilliard system

$$\begin{cases} \dfrac{\partial u}{\partial t} = \kappa \Delta \mu, \ \kappa > 0, \\ \mu = -\alpha \Delta u + f(u), \ \alpha > 0, \end{cases} \tag{2.1}$$

is usually rewritten, equivalently, as the forth-order-in-space parabolic equation

$$\frac{\partial u}{\partial t} + \alpha \kappa \Delta^2 u - \kappa \Delta f(u) = 0, \tag{2.2}$$

which is precisely the equation known as the Cahn-Hilliard equation. Theses equations play an essential role in materials science and describe important qualitative features of two-phase systems related to phase separation processes, assuming isotropy and a constant temperature. This can be observed, e.g., when a binary alloy (e.g., Aluminium/Zinc (see [112]) or Iron/Chromium (see [80, 81, 82]) is cooled down sufficiently. In the first stage, which is known as spinodal decomposition : the initially homogeneous material quickly becomes inhomogeneous, resulting in a very finely dispersed microstructure. In the second stage, which is called coarsening and occurs at a slower time scale. Such phenomena play an essential role in the mechanical properties of the material, e.g., strength, hardness, fracture, toughness and ductility. We refer the reader to, e.g., [11, 12, 65, 67, 76, 77, 102, 103] for more details.

Here, u is the order parameter (we will consider a rescaled density of atoms or concentration of one of the material's components which takes values between -1 and 1, with the values -1 and 1 corresponding to the pure states. The density of the second component is $-u$, meaning that the total density is a conserved quantity) and μ is the chemical potential (more precisely, the difference of chemical potentials between the two components). Furthermore, f is the derivative of a double-well potential F. A thermodynamically relevant potential F is the following logarithmic function which follows from a mean-field model :

$$F(s) = \frac{\theta_c}{2}(1-s^2) + \frac{\theta}{2}[(1-s)\ln(\frac{1-s}{2}) + (1+s)\ln(\frac{1+s}{2})], \ s \in (-1,1), \ 0 < \theta < \theta_c, \tag{2.3}$$

i.e.,

$$f(s) = -\theta_c s + \frac{\theta}{2} \ln \frac{1+s}{1-s}, \tag{2.4}$$

although this function is very often approximated by regular ones (see [25, 26, 37, 38]), typically,

$$F(s) = \frac{1}{4}(s^2 - 1)^2, \tag{2.5}$$

i.e.,

$$f(s) = s^3 - s, \tag{2.6}$$

more generally, we can take $F(s) = \frac{1}{4}(s^2 - \beta^2)^2$, $\beta \in \mathbb{R}$. In that case, if a nonlinear source term is added in equation (2.2), one no longer has the conservation of the spatial average of the order parameter u, the existence of a global in time solutions becomes a challenging problem. Even worse, one can have blow up in finite time when considering regular nonlinear terms (see [28, 36]), which is problematic in view of applications. Nevertheless, it was proved in [73, 89, 96] that, in some particular cases, the existence of global in time solutions can be proved when we consider instead a logarithmic nonlinear term. See Figure 2.1 for a comparison between the two potentials.

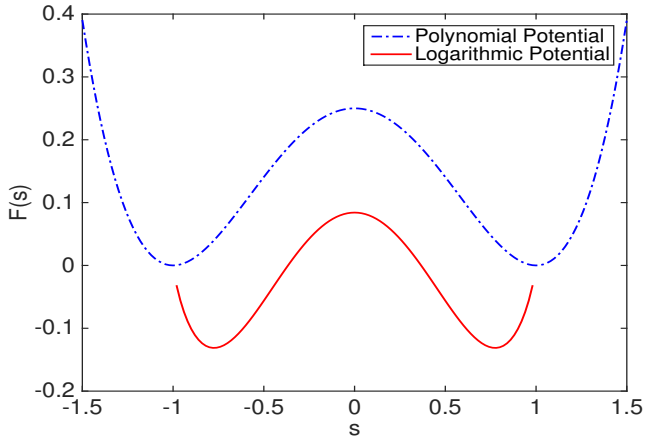

FIGURE 2.1 – The logarithmic potential and the polynomial potential.

The logarithmic terms in (2.3) correspond to the entropy of mixing, and θ and θ_c are proportional to the absolute temperature (assumed constant during the process) and a critical temperature, respectively ; the condition $\theta < \theta_c$ ensures that F has a double-well form and that phase separation can occur. Also note that the polynomial approximation is reasonable when the quench is shallow, i.e., when the absolute temperature is close to the critical one. Finally, κ is the mobility and α is related to the surface tension at the interface. We refer the reader to [15, 16, 46, 91, 92, 94, 99] for more details.

From a phenomenological point of view, the Cahn-Hilliard system can be derived as follows.

One considers the following (total) free energy, called Ginzburg-Landau free energy :

$$\Psi_\Omega(u, \nabla u) = \int_\Omega (\frac{\alpha}{2}|\nabla u|^2 + F(u))dx, \ \alpha > 0, \tag{2.7}$$

where $\Omega \subset \mathbb{R}^n$, $n = 1, 2$ or 3, is the domain occupied by the material. The gradient term in (2.7) has been proposed in [12] in order to model the surface energy of the interface (i.e., capillarity ; note that such gradients go back to J.D. van der Waals (see [115]) ; F is also called homogeneous free energy.

One then has the mass balance

$$\frac{\partial u}{\partial t} = -\operatorname{div} h,$$

where h is the mass flux which is related to the chemical potential μ by the following (postulated) constitutive equation which resembles the Fick's law :

$$h = -\kappa \nabla \mu.$$

The usual definition of the chemical potential is that it is the derivative of the free energy with respect to the order parameter. Here, such a definition is incompatible with the presence of ∇u in the free energy. Instead, μ is defined as a variational derivative of the free energy with respect to u, which yields (assuming proper boundary conditions)

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

the Cahn-Hilliard system then follows. This variational derivative can be (formally) seen by writing that, for a small variation,

$$\delta \Psi_\Omega = \int_\Omega (\alpha \nabla u \cdot \nabla \delta u + f(u)\delta u)dx,$$

where $\cdot$ denotes the usual Euclidean scalar product. Assuming compatible boundary conditions and integrating by parts, this yields

$$\delta \Psi_\Omega = \int_\Omega (-\alpha \Delta u + f(u))\delta u dx,$$

from which the definition follows.

The Cahn-Hilliard system, in a bounded and regular domain Ω, usually is associated with Neumann boundary conditions, namely,

$$\frac{\partial \mu}{\partial \nu} = 0 \text{ on } \Gamma,$$

meaning that there is no mass flux at the boundary (note that $h \cdot \nu = -\kappa \frac{\partial \mu}{\partial \nu}$), and

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

which is a natural variational boundary condition (by natural, we mean that it allows to write down a convenient variational/weak formulation in view of the mathematical analysis of the problem ; this boundary condition also yields that the interface is orthogonal to the boundary). Here, $\Gamma = \partial\Omega$ and ν is the unit outer normal to the boundary. In particular, it follows from the first boundary condition that we have the conservation of mass, i.e., of the spatial average of the order parameter, obtained by (formally) integrating the first equation of (2.1) over Ω,

$$\langle u(t) \rangle \equiv \frac{1}{\text{Vol}(\Omega)} \int_\Omega u(x,t)dx = \langle u(0) \rangle, \ \forall t \leq 0. \tag{2.8}$$

If we have in mind the fourth-order in space Cahn-Hilliard equation, we can rewrite these boundary conditions, equivalently, as

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma. \tag{2.9}$$

Note that we generally do not consider Dirichlet boundary conditions, due precisely to the fact that they do not yield the conservation of mass, although such boundary conditions certainly simplify the mathematical analysis. Besides, We can also consider periodic boundary conditions (in which case $\Omega = \prod_{i=1}^n (0, L_i), \ L_i > 0, \ i = 1, \cdots, n$) ; in that case, we still have the conservation of mass. Furthermore, in the case of hydromechanics, e.g., for mixtures of two immiscible fluids, the contact angle is dynamic, due to the movements of the fluids. The study of the Cahn-Hilliard equation endowed with dynamic boundary conditions can be found in [29, 62, 83, 101, 119].

2.1.2 The variants of the Cahn-Hilliard equation

Note that the Cahn-Hilliard equation and some of its variants are also relevant to other phenomena other than phase separation, for instance, dealloying (this can be observed in corrosion processes (see [34])) ; population dynamics (see [13]) ; tumor growth (see [6, 63]) ; bacterial films (see [64]) ; thin films (see [106, 113]) ; chemistry (see [116]) ; image processing (see [8, 9, 18, 23, 33]) ; astronomy, with even the rings of Saturn (see [114]) ; and ecology (for instance, the clustering of mussels can be perfectly well described by the Cahn-Hilliard equation (see [75]).

In particular, several such phenomena can be modeled by the generalized Cahn-Hilliard equation :

$$\frac{\partial u}{\partial t} + \alpha\kappa\Delta^2 u - \kappa\Delta f(u) + g(x,u) = 0, \ \alpha, \kappa > 0 \tag{2.10}$$

(here, α and κ do not necessarily have the same physical meaning as in the original Cahn-Hilliard equation). We refer the reader to [84, 87, 95] (see also [6, 24, 28, 35, 108]) for more studies on equation (2.10). In particular, the general equation contains the following models.

(i) Mixed Allen-Cahn/Cahn-Hilliard system. In this case, we consider the system of equations

$$\begin{cases} \dfrac{\partial u}{\partial t} = \varepsilon^2 D\Delta\mu - \mu, \ D, \varepsilon > 0, \\ \mu = -\Delta u + \dfrac{f(u)}{\varepsilon^2}, \end{cases}$$

which can be written, equivalently, as

$$\frac{\partial u}{\partial t} + \varepsilon^2 D\Delta^2 u - \Delta(Df(u) + u) + \frac{f(u)}{\varepsilon^2} = 0,$$

and is indeed of the form above. In particular, without the term $\varepsilon^2 D\Delta\mu$ in the first equation, we have the Allen-Cahn equation (which describes the ordering of atoms during the phase separation process; see [4]), and, without the term $-\mu$, we have the Cahn-Hilliard equation. These equations are proposed to account for microscopic mechanisms such as surface diffusion and adsorption/desorption, i.e., adhesion of atoms to a surface/release of a substance from or through a surface (see [57, 59, 60, 79]) and are studied in [53, 54, 55, 56, 58].

(ii) Cahn-Hilliard-Oono equation. In this case,

$$g(x, s) = g(s) = \beta s, \ \beta > 0.$$

This function is proposed in [105] to account for long-ranged (i.e., nonlocal) interactions in phase separation and also to simplify numerical simulations, because we do not have to account for the conservation of mass, although it seems that this equation is not considered in simulations.

A variant of this model, proposed in [31] to model microphase separation of diblock copolymers, consists of taking

$$g(x, s) = g(s) = \beta(s - \frac{1}{\mathrm{Vol}(\Omega)} \int_\Omega u_0(x)dx), \ \beta > 0,$$

where u_0 is the initial condition. In this case, we have the conservation of mass; efficient simulations are performed in [5, 20]. This variant of the Cahn-Hilliard-Oono equation can also be coupled with the incompressible Navier-Stokes equations to model a chemically reacting binary fluid (see [51, 52]; see also [10] for the mathematical analysis). We refer the reader to [30, 88, 118] for more studies on Cahn-Hilliard-Oono equation.

(iii) Proliferation term. In this case,

$$g(x, s) = g(s) = \beta s(s-1),\ \beta > 0.$$

This function was proposed in [63] in view of biological applications and, more precisely, to model wound healing and tumor growth (in one space dimension) and the clustering of malignant brain tumor cells (in two space dimensions); see also [116] for other quadratic functions with chemical applications and [6, 28, 89] for other polynomials with biological applications.
(iv) Fidelity term. In this case,

$$g(x, s) = \lambda_0 \chi_{\Omega\setminus D}(x)(s - h(x)),\ \lambda_0 > 0,\ D \subset \Omega,\ h \in L^2(\Omega),$$

where χ denotes the indicator function, and we consider the equation

$$\frac{\partial u}{\partial t} + \varepsilon\Delta^2 u - \frac{1}{\varepsilon}\Delta f(u) + g(x,t) = 0,\ \varepsilon > 0.$$

Written in this way, ε corresponds to the interface thickness. This function g is proposed in [8, 9] in view of applications to binary image inpainting (i.e., black and white images). Here, h is a given (damaged) image and D is the inpainting (i.e., damaged) region. Furthermore, the fidelity term $g(x, u)$ is added to keep the solution close to the image outside the inpainting region. The idea in this model is to solve the equation up to steady state to obtain an inpainted (i.e., restored) version $u(x)$ of $h(x)$. We refer the reader to [23, 24] for more studies.

In this thesis, we study some other variants of Cahn-Hilliard equation, which are practically applied in biology and image segmentation.

2.2 Problems and framework

Glial cells are non-neuronal cells in the central nervous system (brain and spinal cord) and the peripheral nervous system, which include different types of cells (see Figure 2.2). In addition to maintain homeostasis, and provide support and protection for neurons, they also have many other functions, for instance, to supply nutrients and oxygen to neurons, to destroy pathogens and remove dead neurons, etc.

A glioma is a type of tumor that starts in the glial cells of the brain or the spine. Gliomas comprise about 30 percent of all brain tumors and central nervous system tumors, and 80 percent of all malignant brain tumors. As explained in [45], hypoxia is a hallmark of gliomas and low oxygen concentration triggers a proliferative-to-invasive transition. It is significant to study biology from the perspective of mathematical models. In the first part of this thesis, we apply several nonlinear partial differential models to analyze the above issues.

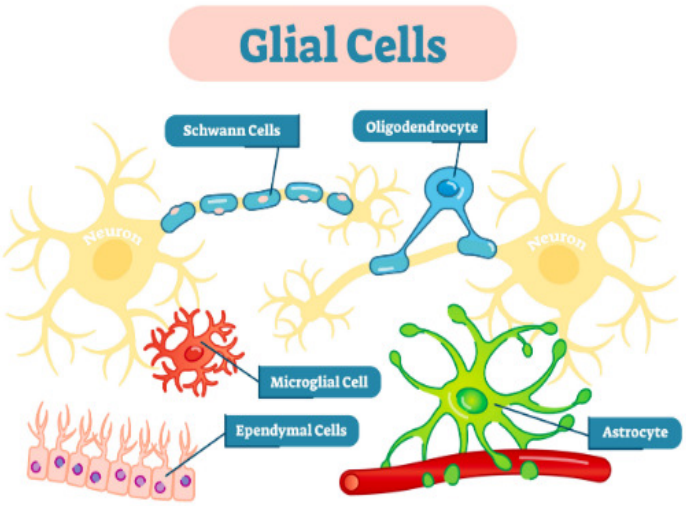

FIGURE 2.2 – Glial cells.

Moreover, in the second part of this thesis, we study Cahn-Hilliard type models for image segmentation, which aims to partition a given image into regions in order to recognize and analyze different objects. Image segmentation plays an important role in image processing and computer vision, more precisely, the practical applications of image segmentation include medical imaging, machine vision, object detection, video surveillance and so on.

2.2.1 Cahn-Hilliard models for glial cells

We consider firstly in Chapter 3 a Cahn-Hilliard model with a symport term, which is proposed to model some energy mechanisms in glial cells, and reads

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \frac{ku}{k' + u} = J,\ k,\ k' > 0, \tag{2.11}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{2.12}$$

$$u|_{t=0} = u_0, \tag{2.13}$$

where u corresponds to a concentration, $\frac{kx}{k'+x}$ is known as symport term and accounts for exchanges, e.g., from a cell to its environment. One crucial difficulty here is to prove the existence of a biologically relevant solution, to overcome this, we take f logarithmic rather than a regular (typically, cubic) nonlinear term, which can drive u to become negative and the symport term become singular. We obtain the existence of a local in time weak solution, namely,

Theorem 2.2.1. *We assume that u_0 is given such that $u_0 \in H^1(\Omega)$, $0 < \langle u_0 \rangle < 1$ and $0 < u_0(x) < 1$, a.e. $x \in \Omega$. Then, there exists $T_0 = T_0(u_0) > 0$ and a weak solution u to (2.11)-(2.13) on $[0, T_0]$ such that $u \in C([0, T_0]; H^1(\Omega)_{\mathrm{w}}) \cap L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega))$ and $\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega))$, where w denotes the weak topology. Furthermore, $0 < u(x, t) < 1$, a.e. $(x, t) \in \Omega \times (0, T_0)$.*

Additionally, under the assumption of $0 \leq J\frac{k'+1}{k} \leq 1$, the local in time weak solution obtained in Theorem 2.2.1 can be global in time, i.e., defined on $[0, T]$, $\forall T > 0$. We then deduce the regularity of the solutions, which is the key to prove a strict separation of the order parameter u (and not just its spatial average) from the pure states 0 and 1 (see [96]). More precisely, we have the following.

Theorem 2.2.2. *We assume that $n = 1$ or 2, Then, there exists $\delta \in (0, 1)$ depending on the $H^1(\Omega)$-norm of u_0 such that*

$$\delta \leq u(x, t) \leq 1 - \delta, \ \textit{for almost all } (x, t), \ x \in \Omega, \ t \geq r,$$

$r > 0$ given.

Moreover, we work on the Cahn-Hilliard-Oono equation with the logarithmic nonlinear terms :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \alpha u + \frac{ku}{k' + u} = J, \ \alpha, \ k, \ k' > 0, \tag{2.14}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{2.15}$$

$$u|_{t=0} = u_0, \tag{2.16}$$

and have the

Theorem 2.2.3. *We assume that u_0 is given such that $u_0 \in H^1(\Omega)$, $0 < \langle u_0 \rangle < 1$ and $0 < u_0(x) < 1$, a.e. $x \in \Omega$. Then, there exists $T_0 = T_0(u_0) > 0$ and a weak solution u to (2.14)-(2.16) on $[0, T_0]$ such that $u \in C([0, T_0]; H^1(\Omega)_{\mathrm{w}}) \cap L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega))$ and $\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega))$. Furthermore, $0 < u(x, t) < 1$, a.e. $(x, t) \in \Omega \times (0, T_0)$.*

Similarly, under the assumption of $0 \leq J \leq \alpha$, the local in time weak solution obtained in Theorem 2.2.3 can be global in time. We finally have the following.

Theorem 2.2.4. *We assume that $n = 1$ or 2, Then, there exists $\delta \in (0, 1)$ depending on the $H^1(\Omega)$-norm of u_0 such that*

$$\delta \leq u(x, t) \leq 1 - \delta, \ \textit{for almost all } (x, t), \ x \in \Omega, \ t \geq r,$$

$r > 0$ given.

2.2.2 A coupled Cahn-Hilliard model for hypoxic glioma cells

We then study a coupled model for the proliferative-to-invasive transition of hypoxic glioma cells, which reads

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u), \tag{2.17}$$

$$\frac{\partial \sigma}{\partial t} - \Delta \sigma + \frac{u\sigma}{1+\sigma} = \gamma(\beta - \sigma), \tag{2.18}$$

where u accounts for the tumor cell density, σ accounts for the oxygen concentration and h is proliferation rate defined as

$$h(s) = a[\frac{s}{\beta} + b(1 - \frac{s}{\beta})].$$

The term $h(\sigma)u(\alpha - u)$ in equation (2.17) represents the so-called logistic growth which assumes that tumor cells proliferate until they reach the cell density α. The constant α is known as carrying capacity, β represents the oxygen concentration in blood vessels, γ, a, b are positive biological parameters and $b \sim 0.6 < 1$ (here, we have set several other biological parameters equal to one and refer to [45] for more details). Furthermore, the term $\Delta\sigma$ in equation (2.18) accounts for the isotropic diffusion of oxygen, the nonlinear term $\frac{u\sigma}{1+\sigma}$ accounts for the oxygen uptake by tumor cells, assuming a Michaelis-Menten kinetics, and the term $\gamma(\beta - \sigma)$ considers that oxygen is released from blood vessels at a linear rate.

We firstly work on a Cahn-Hilliard type equation for the oxygen in the coupled model in Chapter 4, more precisely,

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u), \tag{2.19}$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2\sigma - \Delta f(\sigma) + \frac{u\sigma}{1+\sigma} + \gamma\sigma = \gamma\beta, \tag{2.20}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = \frac{\partial \Delta\sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{2.21}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{2.22}$$

Here, we take f logarithmic with the same reason in Section 2.2.1. We then derive the a priori estimates for the problem and the regularity of a unique weak solution, namely,

Theorem 2.2.5. *We assume that* $(u_0, \sigma_0) \in L^2(\Omega) \times H^1(\Omega)$, $u_0 \geq 0$ *a.e.,* $0 < \sigma_0 < \beta$ *a.e. and* $0 < \langle \sigma_0 \rangle < \beta$. *Then* (2.19)-(2.22) *possesses at least one local in time weak solution* (u, σ) *such that, for some* $T_0 > 0$,

$$u \in L^\infty(0, T_0; L^2(\Omega)) \cap L^2(0, T_0; H^1(\Omega)),\ \frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)),$$

$$\sigma \in L^\infty(0,T_0;H^1(\Omega)) \cap L^2(0,T_0;H^2(\Omega)),\ \frac{\partial \sigma}{\partial t} \in L^2(0,T_0;H^{-1}(\Omega)).$$

Furthermore,

$$u \geq 0,\ 0 < \sigma < \beta \ for\ almost\ all\ (x,t) \in \Omega \times [0,T_0].$$

We further prove the local in time solution as given above is global in time.

We next work on a Cahn-Hilliard type equation for the tumor cell in the coupled model in Chapter 5, more precisely,

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) = h(\sigma)u(\alpha - u),\ \alpha > 0, \tag{2.23}$$

$$\frac{\partial \sigma}{\partial t} - \Delta \sigma + \gamma\sigma + \frac{u\sigma}{1+\sigma} = \gamma\beta,\ \gamma,\ \beta > 0, \tag{2.24}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{2.25}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{2.26}$$

Here, the nonlinear term f is of logarithmic type. We then have

Theorem 2.2.6. *We assume that* $(u_0,\sigma_0) \in H^1(\Omega) \times L^2(\Omega)$ *satisfies* $u_0 \in (0,\alpha)$, $\sigma_0 \in [0,\beta]$ a.e., *and the nonlinear term* $h(s) \geq 0,\ s \geq 0$ *is bounded and Lipschitz continuous on* $\mathbb{R}$. *Then,* (2.23)-(2.26) *possesses a local in time weak solution* (u,σ), *defined on* $[0,T_0]$, $T_0 > 0$, *such that*

$$u \in L^\infty(0,T_0;H^1(\Omega)) \cap L^2(0,T_0;H^2(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0,T_0;H^{-1}(\Omega)),$$

$$\sigma \in L^\infty(0,T_0;L^2(\Omega)) \cap L^2(0,T_0;H^1(\Omega)),$$

$$\frac{\partial \sigma}{\partial t} \in L^2(0,T_0;H^{-1}(\Omega)),$$

$$u(t) \in (0,\alpha),\ \sigma(t) \in [0,\beta]\ for\ almost\ all\ t \in [0,T_0]$$

and there exists a constant $\delta \in (0,\alpha)$ *such that*

$$\delta \leq \langle u(t) \rangle \leq \alpha - \delta\ for\ almost\ all\ t \in [0,T_0].$$

We further prove the local in time solution given by Theorem 2.2.6 is global in time. We also study permanence of the tumor, and eventually give some numerical simulations.

We finally consider Cahn-Hilliard type equations for both the tumor density and the oxygen concentration in Chapiter 6, the model then rewrite as following :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f_1(u) = h(\sigma)u(\alpha - u), \tag{2.27}$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2 \sigma - \Delta f_2(\sigma) + \frac{u\sigma}{1+\sigma} + \gamma\sigma = \gamma\beta, \tag{2.28}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = \frac{\partial \Delta \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{2.29}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{2.30}$$

Here, the nonlinear terms $f_i(s),\ i = 1, 2$ are both of logarithmic type. We then have

Theorem 2.2.7. *We assume that* $(u_0, \sigma_0) \in H^1(\Omega) \times H^1(\Omega)$*, and* $u_0 \in (0, \alpha)$*,* $\sigma_0 \in (0, \beta)$ *a.e. Then* (2.27)-(2.30) *possesses at least one local in time weak solution* (u, σ) *defined on* $[0, T_0]$ *, for some* $T_0 > 0$*, such that*

$$u \in L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)),\ \frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)),$$
$$\sigma \in L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)),\ \frac{\partial \sigma}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)).$$

Furthermore,

$$0 < u < \alpha,\ 0 < \sigma < \beta \text{ for almost all } (x, t) \in \Omega \times [0, T_0].$$

Additionally, under the assumption of $\gamma \geq \frac{\alpha}{\beta+1}$, then the local in time weak solution given by Theorem 2.2.7 is global in time.

2.2.3 On a Cahn-Hilliard type model for image segmentation

We consider in Chapter 7 a Cahn-Hilliard model for image segmentation, which reads

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \frac{h(x)}{1 + (u - \frac{1}{2})^2} = 0, \tag{2.31}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{2.32}$$

$$u|_{t=0} = u_0, \tag{2.33}$$

Here, we take f a cubic nonlinear term. We then have the following.

Theorem 2.2.8. *We assume that* $u_0 \in H^1(\Omega)$*. Then,* (2.31)-(2.33) *possesses a unique weak solution u such that*

$$u \in L^\infty(0, T; H^1(\Omega)) \cap L^2(0, T; H^2(\Omega))$$

and

$$\frac{\partial u}{\partial t} \in L^2(0, T; H^{-1}(\Omega)),$$

$\forall T > 0$.

We also prove that there exist solutions which are unbounded as time goes to infinity. To overcome this, we propose a variant of the model, based on the Cahn-Hilliard-Oono model, which ensures the global in time boundedness of the solutions. More precisely,

$$\frac{\partial u}{\partial t} + \alpha u + \Delta^2 u - \Delta f(u) + \frac{h(x)}{1 + (u - \frac{1}{2})^2} = 0, \tag{2.34}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{2.35}$$

$$u|_{t=0} = u_0. \tag{2.36}$$

Which allows us to performe numerical simulations which illustrate the theoretical results.

In Chapter 8, we deeply study the above Cahn-Hilliard-Oono model for image segmentation. In the case of f is cubic polynomial, we firstly prove the well-posedness, namely,

Theorem 2.2.9. *For everty $u_0 \in H^1(\Omega)$ and every $T > 0$, (2.34)-(2.36) possesses a unique weak solution u such that*

$$u \in L^\infty(0, T; H^1(\Omega)) \cap L^2(0, T; H^2(\Omega)) \cap L^4(0, T; L^4(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0, T; H^{-1}(\Omega)).$$

We then define the semigroup and prove the existence of the exponential attractor, which ensures that the semigroup possesses the finite-dimensional global attractor.

In the case of f is logarithmic, we firstly prove the existence of a weak solution, namely

Theorem 2.2.10. *We assume that u_0 is given such that $u_0 \in H^1(\Omega)$, $0 < u_0(x) < 1$ and $0 < \langle u_0 \rangle < 1$, a.e. $x \in \Omega$. Then there exists $T_0 = T_0(u_0) > 0$, (2.34)-(2.36) possesses a weak solution u on $[0, T_0]$ such that*

$$u \in C([0, T_0]; H^1(\Omega)_W) \cap L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)).$$

Furthermore, $0 < u(x, t) < 1$, a.e $(x, t) \in \Omega \times (0, T_0)$.

We next prove the further regularity of solutions and separation from the pure states in 1 and 2 dimensions, and finally prove the existence of an exponential attractor and the finite fractal dimensionality of the global attractor.

Last but not least, the content and conclusions from Chapter 3 to Chapter 8 have been published in journals, more information can be found in [68, 69, 70, 71, 72, 73].

Première partie

Problèmes non linéaires en séparation de phase

Chapitre 3

Cahn-Hilliard Models for Glial Cells

Modèles de Cahn-Hilliard pour les cellules gliales

Cahn-Hilliard Models for Glial Cells

3.1 Introduction

We are interested in this paper in the analysis of PDEs models for energy mechanisms in the brain.

ODEs of the form

$$x' + \frac{kx}{k' + x} = J(x,t),\ k,\ k' > 0,\ J \geq 0,$$

are often relevant in such situations. We can mention, e.g., lactate or oxygen exchanges in glial cells (see [7, 17, 107]). Such ODEs were also proposed in [49] to model brain metabolites concentrations in the circadian rhythm. Here, $\frac{kx}{k'+x}$ is known as symport term and accounts for exchanges, e.g., from a cell to its environment (see [61]).

Now, in all these mechanisms, one should also account for spatial diffusion, having in mind different zones in the brain or in cells. In particular, we studied in [85] (see also [48]) a reaction-diffusion equation of the form

$$\frac{\partial u}{\partial t} - \Delta u + \frac{ku}{k' + u} = J(x,t)$$

(we can more generally consider a source term of the form $J = J(u,x,t)$). Such an equation also appears in models in [16, 45, 78].

In this paper, we consider instead a Cahn-Hilliard type fourth-order equation, namely,

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \frac{ku}{k' + u} = J(x,t).$$

The original Cahn-Hilliard equation,

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

was initially proposed to model phase separation processes in binary alloys (see [11, 12]). Since then, this equation, or some of its variants, were successfully applied to many other applications than just phase separation in alloys. We can mention, for instance, dealloying (this can be observed in corrosion processes ; see [34]), population dynamics (see [13]), tumor growth (see [6, 39, 40, 63, 98]), bacterial films (see [64]), thin films (see [106]), chemistry (see [34]), image processing (see [9, 18, 33]) and even astronomy, with the rings of Saturn (see [114]), and ecology (for instance, the clustering of mussels can be perfectly well described by the Cahn-Hilliard equation ; see [75]). We refer the

interested reader to [96, 103] for reviews on the Cahn-Hilliard equation and some of its variants, as well as their mathematical analysis.

In view of the energy metabolism in the brain and in glial cells, one interest in considering a Cahn-Hilliard type model is that, in addition to spatial diffusion, we can also account for the phase separation process (having again in mind different zones in the brain or in cells in which, typically, the concentration of a metabolite may be high or very low) and clustering effects.

Compared to the reaction-diffusion model, one essential difficulty is to prove that the order parameter u remains nonnegative; recall indeed that u generally corresponds to a concentration (of a metabolite) and should belong to $[0, 1]$. This is due to the fact that we no longer have the maximum principle/comparison principle. Also note that the symport term $\frac{ku}{k'+u}$ can become singular when u is negative.

The original Cahn-Hilliard equation usually is associated with a regular (typically, cubic) nonlinear term. However, as we will see below, the order parameter can indeed become negative in that case, preventing us from proving a global in time existence result. To overcome this, we instead consider a logarithmic nonlinear term f. Actually, as far as the original Cahn-Hilliard equation is concerned, a logarithmic nonlinear term is the one which is thermodynamically relevant; it is thus natural to also consider such a nonlinear term for our model. In addition, we consider a modified problem to avoid the symport term to become singular. A second major difficulty is to prove a strict separation property of the order parameter from the singular points of f. This necessitates further regularity on the time derivative of u which is in general not known for variants of the Cahn-Hilliard equation of the form

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + h(x, u) = 0.$$

Surprisingly, this is already challenging for the simple linear term $h(x, s) = \alpha s$, $\alpha > 0$, when considering logarithmic nonlinear terms f (see [44]); in that case, one has the Cahn-Hilliard-Oono equation, proposed in [105] to account for nonlocal effects in phase separation processes. In our case, we are able to prove such a regularity under conditions on the parameters.

This paper is organized as follows. We first define the mathematical setting for our problem. We then prove the existence of a local in time biologically relevant solution which is global under (unfortunately rather restrictive) conditions on the parameters. We next prove further regularity on the solutions, allowing us to prove the strict separation in one and two space dimensions. We finally consider a second model, based on the Cahn-Hilliard-Oono equation, and obtain similar results, this time under more realistic conditions on the parameters.

3.2 Setting of the problem

We assume in what follows that J is a constant. We will however discuss the extension of some our results to more general functions $J = J(x, t)$.

We consider the following initial and boundary value problem, in a bounded and regular domain Ω of $\mathbb{R}^n$, $n = 1$, 2 or 3, with boundary Γ :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \frac{ku}{k' + u} = J,\ k,\ k' > 0, \tag{3.1}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.2}$$

$$u|_{t=0} = u_0. \tag{3.3}$$

Remark 3.2.1. *As mentioned in the introduction, u corresponds to a concentration. It is thus important to ensure that this quantity takes values between* 0 *and* 1. *Furthermore, as mentioned in the introduction, one usually takes regular (typically, cubic) nonlinear terms with Cahn-Hilliard type models. Unfortunately, such nonlinear terms do not ensure biologically relevant solutions. Let us indeed take* $J = 0$, $f(s) = (s - \frac{1}{2})^3 - (s - \frac{1}{2})$ *and consider the one-dimentional equation*

$$u_t + u_{xxxx} - (f(u))_{xx} + \frac{ku}{k' + u} = 0,$$

with obvious notation. Let us now take u_0 *smooth enough satisfying the Neumann boundary conditions and such that* $u_0 \in [0, 1]$ *and* $u_0(x) = (x - \frac{1}{2})^4$ *in a neighborhood of* $\frac{1}{2}$. *Thus, we easily see that* $u_0(\frac{1}{2}) = u_0'(\frac{1}{2}) = u_0''(\frac{1}{2}) = 0$, *so that* $(f(u))_{xx}(\frac{1}{2}, 0) = 0$, *and* $u_0^{(iv)}(\frac{1}{2}) = 24$. *It thus follows that* $u_t(\frac{1}{2}, 0) = -24$ *and*

$$u(\frac{1}{2}, t) = -24t + o(t),$$

for t close to 0. *This yields that u can indeed become negative, which is problematic here, as the equation may become singular if u approaches* $-k'$.

In view of the above remark, we take f logarithmic, namely,

$$f(s) = -c_0(s - \frac{1}{2}) + \theta \ln \frac{s}{1 - s},\ c_0,\ \theta > 0,\ s \in (0, 1).$$

Remark 3.2.2. *In the case of the original Cahn-Hilliard equation, one further takes* $\theta < \frac{c_0}{4}$ *to ensure that f is the derivative of a double-well potential F and that phase separation can occur.*

We can note that f is of class C^∞ and satisfies

$$f' \geq -c_0. \tag{3.4}$$

Furthermore, the following holds, for $s, m \in (0,1)$:

$$f(s)(s-m) \geq c_m(|f(s)| + F(s)) - c'_m,\ c_m > 0,\ c'_m \geq 0, \tag{3.5}$$

where $F(s) = \int_{\frac{1}{2}}^{s} F(\xi)\, d\xi$ and c_m and c'_m depend continuously on m. We refer the reader to, e.g., [96] for the proof. Note that, there, the order parameter u takes values in $(-1,1)$; we can come back to $(0,1)$ by a proper rescaling.

In order to prove the existence of solutions, we consider the following modified problem :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + g(u) = J, \tag{3.6}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.7}$$

$$u|_{t=0} = u_0, \tag{3.8}$$

where $g(s) = \frac{ks}{k'+|s|}$. Note that g is of class C^1, with $g'(s) = \frac{kk'}{(k'+|s|)^2}$, so that g is (strictly) monotone increasing and maps $\mathbb{R}$ onto $[-k,k]$. Here, the only difficulty occurs at $s=0$ and note that

$$\frac{g(s)-g(0)}{s} = \frac{k}{k'+|s|} \to \frac{k}{k'} \text{ as } s \to 0.$$

Furthermore, if $s > 0$, then

$$g'(s) = \frac{kk'}{(k'+s)^2} = \frac{kk'}{(k'+|s|)^2} \to \frac{k}{k'} \text{ as } s \to 0^+,$$

while, if $s < 0$,

$$g'(s) = \frac{kk'}{(k'-s)^2} = \frac{kk'}{(k'+|s|)^2} \to \frac{k}{k'} \text{ as } s \to 0^-.$$

Notation

We denote by $((\cdot,\cdot))$ the usual L^2-scalar product, with associated norm $\|\cdot\|$. We also set $\|\cdot\|_{-1} = \|(-\Delta)^{-\frac{1}{2}}\cdot\|$, where $(-\Delta)^{-1}$ denotes the inverse of the minus Laplace operator associated with Neumann boundary conditions and acting on functions with null spatial average. More generally, we denote by $\|\cdot\|_X$ the norm on the Banach space X.

We set $\langle\cdot\rangle = \frac{1}{\mathrm{Vol}(\Omega)}\int_\Omega \cdot\, dx$, being understood that, if $v \in H^{-1}(\Omega) = H^1(\Omega)'$, then $\langle v\rangle = \frac{1}{\mathrm{Vol}(\Omega)}\langle v, 1\rangle_{H^{-1}(\Omega),H^1(\Omega)}$. We also set, whenever this makes sense, $\overline{v} = v - \langle v\rangle$.

We note that

$$v \mapsto (\|\overline{v}\|_{-1}^2 + \langle v\rangle^2)^{\frac{1}{2}},\ v \mapsto (\|\overline{v}\|^2 + \langle v\rangle^2)^{\frac{1}{2}},$$

$$v \mapsto (\|\nabla v\|^2 + \langle v\rangle^2)^{\frac{1}{2}} \text{ and } v \mapsto (\|\Delta v\|^2 + \langle v\rangle^2)^{\frac{1}{2}}$$

are norms on $H^{-1}(\Omega)$, $L^2(\Omega)$, $H^1(\Omega)$ and $H^2(\Omega)$, respectively, which are equivalent to the usual norms on these spaces ; furthermore, $\|\cdot\|_{-1}$ is a norm on $\{v \in H^{-1}(\Omega),\ \langle v\rangle = 0\}$ which is equivalent to the usual H^{-1}-norm.

Throughout this paper, the same letters c and c' denote (generally positive) constants which may vary from line to line, or even in a same line.

3.3 Existence of solutions

We first prove a local in time existence result.

Theorem 3.3.1. *We assume that u_0 is given such that $u_0 \in H^1(\Omega)$, $0 < \langle u_0\rangle < 1$ and $0 < u_0(x) < 1$, a.e. $x \in \Omega$. Then, there exists $T_0 = T_0(u_0) > 0$ and a weak solution u to (3.1)-(3.3) on $[0, T_0]$ such that $u \in C([0, T_0]; H^1(\Omega)_{\mathrm{w}}) \cap L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega))$ and $\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega))$, where w denotes the weak topology. Furthermore, $0 < u(x, t) < 1$, a.e. $(x, t) \in \Omega \times (0, T_0)$.*

Proof.

We actually prove the existence of a local in time solution to the auxiliary problem (3.6)-(3.8) satisfying the regularity and weak separation property stated in the theorem. Then, since $u > 0$ almost everywhere, it immediately follows that it is solution to the original problem.

The idea, to prove existence, is to approximate the singular nonlinear term f by regularized ones defined on the whole real line and then pass to the limit in the approximated problems. For instance, one can consider the following C^1-functions defined on the real line and having a linear growth at infinity, $N \in \mathbb{N}$:

$$f_N(s) = \begin{cases} f(1 - \frac{1}{N}) + f'(1 - \frac{1}{N})(s - 1 + \frac{1}{N}), & s > 1 - \frac{1}{N}, \\ f(s), \ s \in [\frac{1}{N}, 1 - \frac{1}{N}], \\ f(\frac{1}{N}) + f'(\frac{1}{N})(s - \frac{1}{N}), & s < \frac{1}{N}, \end{cases}$$

and replace f by f_N in the equations. As this procedure is now standard for the Cahn–Hilliard equation, we will not detail it here and will instead work directly on the original equation (3.6) and refer the interested reader to [96]. Note that the approximated functions satisfy (3.4), as well as a property similar to (3.5), with constants which are independent of the approximation parameter N, at least when N is large enough (see [96]). Therefore, the constants which appear below are independent of the approximation parameter when considering approximated solutions. Also note that, as the approximated functions go to infinity as s goes to infinity, the solutions to the approximated problems may also exit $[0, 1]$ and may, in particular, become negative, as mentioned above. This

explains why one only has a local in time existence result when considering this scheme. We finally mention that the crucial step is to prove that $f(u)$ belongs to $L^2(\Omega \times (0, T_0))$, for some $T_0 > 0$ (this allows to pass to the limit in the nonlinear term in the approximated problems).

That said, we rewrite (3.6) in the following equivalent weaker form :

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - \Delta \overline{u} + \overline{f(u)} + (-\Delta)^{-1}\overline{g(u)} = 0, \tag{3.9}$$

$$\frac{d\langle u \rangle}{dt} + \langle g(u) \rangle = J, \tag{3.10}$$

$$\frac{\partial \overline{u}}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.11}$$

$$\overline{u}|_{t=0} = \overline{u}_0, \ \langle u \rangle|_{t=0} = \langle u_0 \rangle. \tag{3.12}$$

Note that (3.10) is obtained by formally integrating (3.6) over Ω and integrating by parts.

The a priori estimates derived below will be formal. Note that, on the approximated problems level, they can easily be justified by a standard Galerkin scheme.

First, note that

$$-k \leq \langle g(u) \rangle \leq k$$

(note indeed that g is bounded, so that so is $\langle g(u) \rangle$), so that

$$\langle u_0 \rangle + (J - k)t \leq \langle u(t) \rangle \leq \langle u_0 \rangle + (J + k)t,$$

as long as it exists. Assume that

$$2\delta \leq \langle u_0 \rangle \leq 1 - 2\delta, \ \delta \in (0, \frac{1}{2}).$$

It then follows from the above that there exists $T_0 = T_0(\delta, u_0) > 0$ such that

$$\delta \leq u(t) \leq 1 - \delta, \ t \in [0, T_0]. \tag{3.13}$$

Let us emphasize that, when working with the approximated problems, T_0 can be chosen independent of the approximation parameter, which is essential to pass to the limit. Indeed, the equation for the spatial average of the approximated solutions (i.e., the equivalent of (3.10)) would be the same, so that the constants in the corresponding estimates would also be the same.

We assume from now on that $t \in [0, T_0]$.

Let us multiply (3.9) by $\overline{u}$ and integrate over Ω and by parts. This gives

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 + (\overline{f(u)}, \overline{u})) + (((-\Delta)^{-1}\overline{g(u)}, \overline{u})) = 0. \tag{3.14}$$

Note that it follows from (3.5) and (3.13) that

$$((\overline{f(u)},\overline{u})) = ((f(u),\overline{u})) \geq c(\|f(u)\|_{L^1(\Omega)} + \int_\Omega F(u)\,dx) - c',\ c>0, \tag{3.15}$$

where the above constants depend on δ. Furthermore, we have

$$|(((-\Delta)^{-1}\overline{g(u)},\overline{u}))| \leq c\|\overline{g(u)}\|\|\overline{u}\| \leq c\|\nabla u\|. \tag{3.16}$$

We deduce from (3.14)-(3.16) that

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + c(\|\nabla u\|^2 + \|f(u)\|_{L^1(\Omega)} + \int_\Omega F(u)\,dx) \leq c',\ c>0. \tag{3.17}$$

Let us next multiply (3.9) by $\frac{\partial\overline{u}}{\partial t}$ to obtain

$$\frac{1}{2}\frac{d}{dt}\|\nabla u\|^2 + \|\frac{\partial\overline{u}}{\partial t}\|_{-1}^2 + ((\overline{f(u)},\frac{\partial\overline{u}}{\partial t})) + (((-\Delta)^{-1}\overline{g(u)},\frac{\partial\overline{u}}{\partial t})) = 0. \tag{3.18}$$

Note that

$$\begin{aligned}((\overline{f(u)},\frac{\partial\overline{u}}{\partial t})) &= ((f(u),\frac{\partial\overline{u}}{\partial t}))\\ &= \frac{d}{dt}\int_\Omega F(u)\,dx - ((f(u),\frac{d\langle u\rangle}{dt}))\\ &= \frac{d}{dt}\int_\Omega F(u)\,dx + \mathrm{Vol}(\Omega)(\langle g(u)\rangle - J)\langle f(u)\rangle\\ &\geq \frac{d}{dt}\int_\Omega F(u)\,dx - c\|f(u)\|_{L^1(\Omega)},\end{aligned} \tag{3.19}$$

recalling that g is bounded. Furthermore,

$$\begin{aligned}|(((-\Delta)^{-1}\overline{g(u)},\frac{\partial\overline{u}}{\partial t}))| &= ((\overline{g(u)},(-\Delta)^{-1}\frac{\partial\overline{u}}{\partial t}))|\\ &\leq c\|\overline{g(u)}\|\|\frac{\partial\overline{u}}{\partial t}\|_{-1}\\ &\leq c\|\frac{\partial\overline{u}}{\partial t}\|_{-1}.\end{aligned} \tag{3.20}$$

It thus follows from (3.18)-(3.20) that

$$\frac{d}{dt}(\|\nabla u\|^2 + 2\int_\Omega F(u)\,dx) + \|\frac{\partial\overline{u}}{\partial t}\|_{-1}^2 \leq c\|f(u)\|_{L^1(\Omega)} + c'. \tag{3.21}$$

Let us now add (3.17) and (3.21), multiplied by $\delta_1 > 0$ small enough, to find a differential inequality of the form

$$\frac{dE_1}{dt} + c(E_1 + \|f(u)\|_{L^1(\Omega)} + \|\frac{\partial\overline{u}}{\partial t}\|_{-1}^2) \leq c',\ c>0, \tag{3.22}$$

where

$$E_1 = \|\overline{u}\|_{-1}^2 + \delta_1(\|\nabla u\|^2 + 2\int_\Omega F(u)\,dx)$$

satisfies

$$E_1 \geq c\|\nabla u\|^2 - c',\ c > 0.$$

Multiplying (3.9) by $-\Delta\overline{u}$, we find, employing (3.4),

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|^2 + \|\Delta u\|^2 \leq c_0\|\nabla u\|^2 - ((g(u), \overline{u})), \tag{3.23}$$

which yields, noting that

$$|((g(u), \overline{u}))| \leq c\|\overline{u}\|^2 + c',$$

the differential inequality

$$\frac{d}{dt}\|\overline{u}\|^2 + \|\Delta u\|^2 \leq c\|\overline{u}\|^2 + c'. \tag{3.24}$$

Here, we have also used the fact that

$$\|\nabla u\|^2 \leq \frac{1}{2}\|\Delta u\|^2 + c\|\overline{u}\|^2,$$

which follows from standard elliptic regularity results and a proper interpolation inequality.

Next, we deduce from (3.10) and (3.13) that

$$\frac{d}{dt}\langle u\rangle^2 + \langle u\rangle^2 \leq c. \tag{3.25}$$

Furthermore, it follows from (3.24) that

$$\frac{d}{dt}\|\overline{u}\|^2 + c\|\overline{u}\|_{H^2(\Omega)}^2 \leq c'(\|\overline{u}\|^2 + \langle u\rangle^2) + c'',\ c > 0. \tag{3.26}$$

Summing finally (3.22), (3.25) and (3.26), multiplied by $\delta_2 > 0$ small enough, we have a differential inequality of the form

$$\frac{dE_2}{dt} + c(E_2 + \|\overline{u}\|_{H^2(\Omega)}^2 + \|\frac{\partial u}{\partial t}\|_{H^{-1}(\Omega)}^2 + \|f(u)\|_{L^1(\Omega)}) \leq c',\ c > 0, \tag{3.27}$$

where

$$E_2 = E_1 + \langle u\rangle^2 + \delta_2\|\overline{u}\|^2$$

satisfies

$$E_2 \geq c\|u\|_{H^1(\Omega)}^2 - c',\ c > 0.$$

Note indeed that it follows from (3.10) and the boundedness of g that $\frac{d\langle u\rangle}{dt}$ is bounded.

Having this, we note that (3.9) yields

$$\overline{f(u)} = \Delta u - (-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - (-\Delta)^{-1}\overline{g(u)},$$

so that

$$\|\overline{f(u)}\| \leq c(\|\Delta u\| + \|\frac{\partial \overline{u}}{\partial t}\|_{-1} + 1) \tag{3.28}$$

and

$$\|\overline{f(u)}\|^2_{L^2(0,T_0;L^2(\Omega))} \leq cE_2(0). \tag{3.29}$$

Next, taking $s = u$ and $m = \langle u\rangle$ in (3.5), it follows from (3.13) that

$$\begin{aligned} |\langle f(u)\rangle| &\leq c((f(u), \overline{u})) + c' \\ &= c((\overline{f(u)}, u)) + c' \\ &\leq c\|\overline{f(u)}\|\|u\| + c', \end{aligned}$$

where the above constants depend on δ. Therefore,

$$\begin{aligned} Vert f(u)\|^2_{L^2(0,T_0;L^2(\Omega))} &\leq c(\|\overline{f(u)}\|^2_{L^2(0,T_0;L^2(\Omega))} + \int_0^{T_0}\langle f(u)\rangle^2\, dt) \\ &\leq cE_2(0) + c'E_2(0)\|u\|^2_{L^\infty(0,T_0;L^2(\Omega))} + c'' \\ &\leq cE_2^2(0) + c' \end{aligned}$$

and

$$\|f(u)\|_{L^2(0,T_0;L^2(\Omega))} \leq c(E_2(0) + 1). \tag{3.30}$$

As mentioned above, (3.30) is the crucial estimate to pass to the limit in the nonlinear term and prove the existence of a local in time solution. The rest of the proof is standard and we omit the details.

□

Remark 3.3.1. *The separation property from the singular points* 0 *and* 1 *given in the above theorem says that there will be no zone where the metabolite under study is totally absent ; there will always be at least some trace of it.*

Remark 3.3.2. *For a regular, in particular, cubic, nonlinear term f, we can similarly prove the existence, and also the uniqueness, of the local in time solution. Note however that, as already mentioned, the solution may become negative (or strictly larger than one), in which case, the equation may become singular. Consequently, we are not able to prove a global in time existence result in that case.*

Theorem 3.3.1 can be extended to more general functions $J = J(x, t)$ as follows.

Theorem 3.3.2. *We assume that the assumptions of Theorem 3.3.1 hold and that* $J \in L^\infty(\Omega \times (0,T))$, $T > 0$. *Then, the assertions of Theorem 3.3.1 still hold.*

Proof.

Note that the weaker formulation of the problem now reads

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - \Delta \overline{u} + \overline{f(u)} + (-\Delta)^{-1}\overline{g(u)} = (-\Delta)^{-1}\overline{J}, \tag{3.31}$$

$$\frac{d\langle u\rangle}{dt} + \langle g(u)\rangle = \langle J\rangle, \tag{3.32}$$

$$\frac{\partial \overline{u}}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.33}$$

$$\overline{u}|_{t=0} = \overline{u}_0,\ \langle u\rangle|_{t=0} = \langle u_0\rangle. \tag{3.34}$$

We can then repeat the estimates made above, with minor changes. In particular, when estimating the spatial average of u, we obtain

$$\langle u_0\rangle - (\|J\|_{L^\infty(\Omega\times(0,T))} + k)t \le \langle u(t)\rangle \le \langle u_0\rangle + (\|J\|_{L^\infty(\Omega\times(0,T))} + k)t.$$

Also note that, e.g., when multiplying (3.31) by $\frac{\partial \overline{u}}{\partial t}$, we have to estimate the term $(((-\Delta)^{-1}\overline{J}, \frac{\partial \overline{u}}{\partial t}))$. To do so, we write

$$\begin{aligned}(((-\Delta)^{-1}\overline{J}, \frac{\partial \overline{u}}{\partial t})) &= (((-\Delta)^{-\frac{1}{2}}\overline{J}, (-\Delta)^{-\frac{1}{2}}\frac{\partial \overline{u}}{\partial t})) \\ &\le c\|J\|\|\frac{\partial \overline{u}}{\partial t}\|_{-1} \\ &\le \varepsilon\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + c_\varepsilon,\ \forall \varepsilon > 0.\end{aligned}$$

□

We then have the following.

Theorem 3.3.3. *Let us assume that* $0 \le J^{\frac{k'+1}{k}} \le 1$ *and let* u *be a local in time weak solution as in Theorem 3.3.1. Then, it is global in time, i.e., defined on* $[0,T]$, $\forall T > 0$.

Proof.

Let u be a local in time weak solution on $[0,T]$, $T > 0$ given, and $T^\star$ be its maximal time of existence. Let us assume that $T^\star < T$. Then, necessarily, u belongs to $[0,1]$ for $t \in [0,T^\star)$. In particular, this yields

$$\frac{ku}{k'+1} \le g(u) \le \frac{ku}{k'}$$

and

$$J - \frac{k}{k'}\langle u\rangle \le J - \langle g(u)\rangle \le J - \frac{k}{k'+1}\langle u\rangle.$$

Therefore, noting that J is nonnegative and recalling that $J\frac{k'+1}{k} \leq 1$,

$$\langle u_0\rangle e^{-\frac{k}{k'}t} \leq \langle u(t)\rangle \leq \langle u_0\rangle e^{-\frac{k}{k'+1}t} + J\frac{k'+1}{k}(1-e^{-\frac{k}{k'+1}t})$$
$$\leq \langle u_0\rangle e^{-\frac{k}{k'+1}t} + 1 - e^{-\frac{k}{k'+1}t},\ t \in [0, T^\star). \tag{3.35}$$

Finally, it follows from (3.35) that there exists $\delta \in (0,1)$ (which can be taken independent of $T^\star$) such that

$$\delta < \langle u(t)\rangle < 1-\delta,\ \forall t \in [0, T^\star).$$

Note indeed that, setting

$$\varphi(t) = \langle u_0\rangle e^{-\frac{k}{k'+1}t} + 1 - e^{-\frac{k}{k'+1}t},$$

then

$$\varphi'(t) = \frac{k}{k'+1}(1-\langle u_0\rangle)e^{-\frac{k}{k'+1}t} \geq 0.$$

Therefore, φ is monotone increasing and takes values in $[\varphi(0), \varphi(T)] = [\langle u_0\rangle, (\langle u_0\rangle - 1)e^{-\frac{k}{k'+1}T} + 1] \subset (0,1)$. The lower bound is straightforward. This yields that, necessarily, the solution is global in time, since, otherwise, owing to continuity, it can be extended (recall that $T^\star < T$).

□

Remark 3.3.3. *(i) Note that the above argument does not work for the approximated problems (and regular nonlinear terms f).*
(ii) In the case of lactate exchanges in glial cells, possible biologically relevant values are (see, e.g., [47] and the references therein)

$$k = 0.01\text{mM.s}^{-1},\ k' = 3.5\text{mM},$$
$$J = 5.7.10^{-3}\text{mM.s}^{-1},$$

so that the condition $J\frac{k'+1}{k} \leq 1$ is a restrictive one. It is however satisfied if one considers a sufficiently small external flux J. Note nevertheless that our equation should be regarded as only a very simplified model in this situation. More concrete models should account for different energy mechanisms (e.g., glucose and glutamate/glutamine) or for the tumor growth in case of cancerous cells. Such more elaborate models will be studied elsewhere.
(iii) Note that, since g is monotone increasing,

$$\frac{d\langle u\rangle}{dt} \in [J - \frac{k}{k'+1}, J].$$

Therefore, if $J = 0$, then $\langle u\rangle$ is monotone decreasing and, since it belongs to $[0,1]$, it converges to some limit. A similar situation arises when $J - \frac{k}{k'+1} \geq 0$, in which case $\langle u\rangle$ is monotone increasing. Also note that it follows from (3.35) that, when $J = 0$, then $\langle u\rangle$ converges to 0 as time goes to $+\infty$, as expected.

We also have the following result, for nonconstant functions $J = J(x,t)$.

Theorem 3.3.4. *We assume that the assumptions of Theorem 3.3.2 hold and that* $J \in [0, J^\star]$, *where* $J^\star \frac{k'+1}{k} \leq 1$. *Then, a solution as in Theorem 3.3.2 is global in time, i.e., defined on* $[0,T]$.

Proof.

The proof is similar to that of Theorem 3.3.3, noting that we now have

$$-\frac{k}{k'}\langle u\rangle \leq J - \langle g(u)\rangle \leq J^\star - \frac{k}{k'+1}\langle u\rangle,$$

so that

$$\begin{aligned}\langle u_0\rangle e^{-\frac{k}{k'}t} \leq \langle u(t)\rangle &\leq \langle u_0\rangle e^{-\frac{k}{k'+1}t} + J^\star \frac{k'+1}{k}(1 - e^{-\frac{k}{k'+1}t}) \\ &\leq \langle u_0\rangle e^{-\frac{k}{k'+1}t} + 1 - e^{-\frac{k}{k'+1}t}.\end{aligned}$$

□

Remark 3.3.4. *In the study of brain metabolites concentrations in the circadian rhythm, one considers in [49] functions J of the form*

$$J = a\sin^2(bt + c),\ a,\ b,\ c > 0.$$

The condition in Theorem 3.3.4 on the parameters is again restrictive when compared to the numerical values taken in [49].

Remark 3.3.5. *In the case of a logarithmic nonlinear term f, uniqueness is an open problem (see however the next section below for a partial uniqueness result).*

3.4 Regularity of solutions

We assume in this section that J is a constant.

We have the following.

Theorem 3.4.1. *We assume that the assumptions of Theorem 3.3.3 hold and that* $0 < J\frac{k'+1}{k} < 1$. *Then, any weak solution u to (3.1)-(3.3) satisfies*

$$\frac{\partial u}{\partial t} \in L^\infty(r, +\infty; H^{-1}(\Omega)) \cap L^2(r, T; H^1(\Omega)),$$

$\forall r < T,\ r > 0$ *and* $T > 0$ *given.*

Proof.

The estimates below are again formal, but they can also be justified within a Galerkin scheme for the approximated problems.

Rewrite the equations in the equivalent form

$$\frac{\partial u}{\partial t} + g(u) - J = \Delta\mu, \tag{3.36}$$

$$\mu = -\Delta u + f(u), \tag{3.37}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \mu}{\partial \nu} = 0 \text{ on } \Gamma. \tag{3.38}$$

First, note that it follows from (3.37) that

$$\langle \mu \rangle = \langle f(u) \rangle,$$

so that, owing to the regularity obtained in the previous section, $\mu \in L^2(0,T;H^1(\Omega))$, since

$$\overline{\mu} = -(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - (-\Delta)^{-1}\overline{g(u)}. \tag{3.39}$$

Next, let us multiply (3.36) by $\frac{\partial \mu}{\partial t}$ to have

$$((\frac{\partial u}{\partial t}, \frac{\partial \mu}{\partial t})) = -\frac{1}{2}\frac{d}{dt}\|\nabla\mu\|^2 - ((g(u) - J, \frac{\partial \mu}{\partial t})). \tag{3.40}$$

Let us then differentiate (3.37) with respect to time to obtain

$$\frac{\partial \mu}{\partial t} = -\Delta\frac{\partial u}{\partial t} + f'(u)\frac{\partial u}{\partial t}. \tag{3.41}$$

Multiply (3.41) by $\frac{\partial u}{\partial t}$ to find

$$\begin{aligned}((\frac{\partial u}{\partial t}, \frac{\partial \mu}{\partial t})) &= \|\nabla\frac{\partial u}{\partial t}\|^2 + ((f'(u)\frac{\partial u}{\partial t}, \frac{\partial u}{\partial t})) \\ &\geq \|\nabla\frac{\partial u}{\partial t}\|^2 - c_0\|\frac{\partial u}{\partial t}\|^2,\end{aligned} \tag{3.42}$$

owing to (3.4). Combine (3.40) and (3.42) to have

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\nabla\mu\|^2 + \|\nabla\frac{\partial u}{\partial t}\|^2 + ((g(u) - J, \frac{\partial \mu}{\partial t})) &\leq c_0\|\frac{\partial u}{\partial t}\|^2 \\ &\leq \frac{1}{2}\|\nabla\frac{\partial u}{\partial t}\|^2 + c(\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + \langle\frac{\partial u}{\partial t}\rangle^2),\end{aligned} \tag{3.43}$$

owing to a proper interpolation inequality. Now, note that

$$((g(u) - J, \frac{\partial \mu}{\partial t})) = \frac{d}{dt}((g(u) - J, \mu)) - ((g'(u)\frac{\partial u}{\partial t}, \mu)). \tag{3.44}$$

Let us then combine (3.43) and (3.44) to obtain

$$\frac{d}{dt}(\|\nabla\mu\|^2 + ((g(u) - J, \mu))) + \|\nabla\frac{\partial u}{\partial t}\|^2 \leq c\|\frac{\partial u}{\partial t}\|^2_{H^{-1}(\Omega)} + c'\|\frac{\partial u}{\partial t}\|\|\mu\| \\ \leq \frac{1}{2}\|\nabla\frac{\partial u}{\partial t}\|^2 + c(\|\frac{\partial u}{\partial t}\|^2_{H^{-1}(\Omega)} + \|\mu\|^2),$$

noting that g' is bounded, so that

$$\frac{d}{dt}(\|\nabla\mu\|^2 + ((g(u) - J, \mu))) + \frac{1}{2}\|\nabla\frac{\partial u}{\partial t}\|^2 \leq c(\|\frac{\partial u}{\partial t}\|^2_{H^{-1}(\Omega)} + \|\mu\|^2). \tag{3.45}$$

Set finally

$$\Lambda = \|\nabla\mu\|^2 + ((g(u) - J, \mu)).$$

Note that, since $g' \geq 0$,

$$\begin{aligned}((g(u) - J, \mu)) &= ((g(u) - J, -\Delta u + f(u))) \\ &= ((g'(u)\nabla u, \nabla u)) + ((g(u) - J, f(u)) \\ &\geq ((g(u) - J, f(u))).\end{aligned}$$

Also note that

$$g(u) - J = \frac{k - J}{k' + u}(u - \frac{Jk'}{k - J}),$$

so that it follows from (3.5) (indeed, $0 < J\frac{k'+1}{k} < 1$ implies that $k > J$ and $0 < \frac{Jk'}{k-J} < 1$) that

$$((g(u) - J, f(u))) \geq c\int_\Omega F(u)\,dx - c',\ c > 0.$$

Therefore,

$$\Lambda \geq \|\nabla\mu\|^2 - c,\ c \geq 0,$$

and an application of the uniform Gronwall's lemma yields that

$$\overline{\mu} \in L^\infty(r, +\infty; H^1(\Omega)),$$

$r > 0$ given, owing also to (3.27) and (3.39) which allow to see that the assumptions of this lemma indeed hold.

The result finally follows from (3.39), recalling that $\frac{d\langle u\rangle}{dt}$ is uniformly bounded.

□

The regularity obtained in Theorem 3.4.1 is the key regularity for proving a strict separation of the order parameter u (and not just its spatial average) from the pure states 0 and 1 (see [96]). More precisely, we have the following.

Theorem 3.4.2. *We assume that $n = 1$ or 2 and that the assumptions of theorems 3.3.3 and 3.4.1 hold. Then, there exists $\delta \in (0,1)$ depending on the $H^1(\Omega)$-norm of u_0 such that*

$$\delta \le u(x,t) \le 1-\delta, \text{ for almost all } (x,t),\ x \in \Omega,\ t \ge r,$$

$r > 0$ given.

The proof of this theorem is very similar to those given in [96], Chapter 4 (see also [44, 99]), and we omit the details.

Remark 3.4.1. *(i) This result says that, as soon as time is positive, the nonlinear term becomes regular (and also bounded). Note that this then allows to prove additional regularity on u and, in particular, that the solution is strong as soon as time is positive. (ii) The strict separation is not known in three space dimensions, already for the original Cahn–Hilliard equation, unless we make some growth assumptions on the singular nonlinear term f which are not satisfied by the relevant logarithmic ones (see [99]).*

Remark 3.4.2. *From a biological point of view, the strict separation property says that, in the phase separation process, there is always some amount (and not just some trace) of the metabolite in, say, all regions of the cell.*

A consequence of the above results is the following.

Corollary 1. We assume that $n = 1$ or 2 and that $u_0 \in H^3(\Omega)$, with $\frac{\partial u_0}{\partial \nu} = 0$ on Γ and $\delta \le u_0(x) \le 1-\delta$, a.e. $x \in \Omega$, $\delta \in (0,1)$. Then, a solution as given in Theorem 3.4.1 is unique.

Proof.

We first note that the regularity on u_0 implies that $\frac{\partial u}{\partial t}(0) \in H^{-1}(\Omega)$ and, thus, $\mu(0) \in H^1(\Omega)$, allowing us to take $r = 0$ in the above results.

Next, having the strict separation property, we can essentially proceed as for the original Cahn-Hilliard equation with a regular nonlinear term to prove uniqueness, as well as the continuous dependence with respect to the initial data (say, with respect to the $H^{-1}(\Omega)$-norm). Let us just mention that the difference, when compared to the original Cahn-Hilliard equation, is that we have to handle a term of the form

$$((f(u_1) - f(u_2), \langle u_1 - u_2 \rangle)),$$

where u_1 and u_2 are two solutions which satisfy the strict separation property (in the case of the original Cahn-Hilliard equation, this term does not appear, due to the conservation of the spatial average of the order parameter; see [96], also for several other variants of the Cahn-Hilliard equation). Without the strict separation property, we would not know how to estimate this term, whereas, here, noting that the nonlinear term f is globally

Lipschitz continuous when considering two solutions which are strictly separated from the pure states, we can write

$$|f(u_1) - f(u_2)| \leq c|u_1 - u_2|.$$

□

Remark 3.4.3. *(i) Having the strict separation property and uniqueness, we can study the asymptotic behavior of the associated dynamical system. In particular, we can prove the existence of finite dimensional attractors, meaning, roughly speaking, that the limit dynamics can be described by a finite number of degrees of freedom. We refer the interested reader to, e.g., [96, 100, 111] for discussions on this.*
(ii) Another interesting problem is the convergence of single trajectories to steady states. Not that, already for the original Cahn-Hilliard equation, such a question is not a trivial one, since one may have a continuum of steady states (see [109]). Here, due to the additional symport term, the problem is particularly challenging and we cannot proceed as in [109].
(iii) When $k > J$, one has a unique spatially homogeneous equilibrium given by

$$u_e = \frac{k'J}{k - J}.$$

In particular, when $J = 0$, $u_e = 0$ and we already saw that $\langle u(t)\rangle$ tends to 0 as t goes to $+\infty$. Proving a full stability result is however challenging and will be studied elsewhere.

3.5 A second model

We consider in this section the following initial and boundary value problem :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \alpha u + \frac{ku}{k' + u} = J,\ \alpha,\ k,\ k' > 0, \tag{3.46}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.47}$$

$$u|_{t=0} = u_0. \tag{3.48}$$

We again assume that J is a constant. When the symport term does not appear and $J = 0$, we recover the Cahn-Hilliard-Oono equation.

Considering again a modified problem, namely,

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \alpha u + g(u) = J, \tag{3.49}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.50}$$

$$u|_{t=0} = u_0, \tag{3.51}$$

we can prove the following.

Theorem 3.5.1. *We assume that u_0 is given such that $u_0 \in H^1(\Omega)$, $0 < \langle u_0 \rangle < 1$ and $0 < u_0(x) < 1$, a.e. $x \in \Omega$. Then, there exists $T_0 = T_0(u_0) > 0$ and a weak solution u to (3.46)-(3.48) on $[0, T_0]$ such that $u \in C([0, T_0]; H^1(\Omega)_w) \cap L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega))$ and $\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega))$. Furthermore, $0 < u(x, t) < 1$, a.e. $(x, t) \in \Omega \times (0, T_0)$.*

Proof.

We first note that the equation for the spatial average of the order parameter now reads

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

which yields

$$\langle u_0 \rangle e^{-\alpha t} + \frac{J-k}{\alpha}(1 - e^{-\alpha t}) \le \langle u(t) \rangle \le \langle u_0 \rangle e^{-\alpha t} + \frac{J+k}{\alpha}(1 - e^{-\alpha t}), \tag{3.52}$$

allowing us to deduce the existence of $T_0 > 0$ such that, for $t \in [0, T_0]$,

$$\delta \le \langle u(t) \rangle \le 1 - \delta, \ \delta \in (0, \frac{1}{2}).$$

Here, we again assume that $2\delta \le \langle u_0 \rangle \le 1 - 2\delta$.

We then consider the weaker formulation

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - \Delta \overline{u} + \overline{f(u)} + \alpha(-\Delta)^{-1}\overline{u} + (-\Delta)^{-1}\overline{g(u)} = 0, \tag{3.53}$$

$$\frac{\partial \overline{u}}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.54}$$

$$u|_{t=0} = u_0. \tag{3.55}$$

Let us multiply (3.53) by $\frac{\partial \overline{u}}{\partial t}$ to obtain, for $t \in [0, T_0]$,

$$\frac{1}{2}\frac{d}{dt}\|\nabla u\|^2 + \|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + ((\overline{f(u)}, \frac{\partial \overline{u}}{\partial t})) + \frac{\alpha}{2}\frac{d}{dt}\|\overline{u}\|_{-1}^2 + (((-\Delta)^{-1}\overline{g(u)}, \frac{\partial \overline{u}}{\partial t})) = 0. \tag{3.56}$$

Note that

$$\begin{aligned}
((\overline{f(u)}, \frac{\partial \overline{u}}{\partial t})) &= ((f(u), \frac{\partial \overline{u}}{\partial t})) \\
&= \frac{d}{dt}\int_\Omega F(u)\,dx - ((f(u), \frac{d\langle u \rangle}{dt})) \\
&= \frac{d}{dt}\int_\Omega F(u)\,dx + \mathrm{Vol}(\Omega)(\langle g(u) \rangle + \alpha\langle u \rangle - J)\langle f(u) \rangle \\
&\ge \frac{d}{dt}\int_\Omega F(u)\,dx - c\|f(u)\|_{L^1(\Omega)},
\end{aligned} \tag{3.57}$$

since $\langle u \rangle$ belongs to $[0, 1]$. It thus follows from (3.56)-(3.57) that, for $t \in [0, T_0]$,

$$\frac{d}{dt}(\|\nabla u\|^2 + \alpha\|\overline{u}\|^2_{-1} + 2\int_\Omega F(u)\,dx) + \|\frac{\partial \overline{u}}{\partial t}\|^2_{-1} \leq c\|f(u)\|_{L^1(\Omega)} + c'. \tag{3.58}$$

The rest of the proof is similar to that of Theorem 3.3.1 and we omit the details.

□

Remark 3.5.1. *(i) Note that if $J \geq k$ and $J + k \leq \alpha$, then it follows from (3.52) that $\delta \leq \langle u(t) \rangle \leq 1 - \delta$ for all times (in a finite time interval), so that the solution is actually global in time.*
(ii) When $k = J = 0$, it follows from (3.52) that $\langle u \rangle \in (0, 1)$ for all times and we recover the global in time existence for the Cahn-Hilliard-Oono equation. This slightly simplifies the proof given in [96].

We then have the following theorem which improves the global existence result mentioned in the above remark.

Theorem 3.5.2. *Let us assume that $0 \leq J \leq \alpha$ and let u be a local in time weak solution as in Theorem 3.5.1. Then, it is global in time.*

Proof.
We proceed as in the proof of Theorem 3.3.3.

Let again u be a local in time weak solution on $[0, T]$, $T > 0$ given, and $T^\star$ be its maximal time of existence. Assume that $T^\star < T$. Noting once more that u belongs to $[0, 1]$ for $t \in [0, T^\star)$, it follows that

$$0 \leq g(u) \leq \frac{k}{k' + 1},$$

so that, proceeding as above,

$$\langle u_0 \rangle e^{-\alpha t} + \frac{1}{\alpha}(J - \frac{k}{k' + 1})(1 - e^{-\alpha t}) \leq \langle u(t) \rangle \leq \langle u_0 \rangle e^{-\alpha t} + \frac{J}{\alpha}(1 - e^{-\alpha t}),$$

which allows us to conclude when $J^{\frac{k'+1}{k}} \geq 1$, i.e., $J \geq \frac{k}{k'+1}$. When $J^{\frac{k'+1}{k}} \leq 1$, we can write

$$-(\frac{k}{k'} + \alpha)\langle u \rangle \leq J - \alpha\langle u \rangle - \langle g(u) \rangle \leq J - \frac{k}{k' + 1}\langle u \rangle,$$

yielding

$$\langle u_0 \rangle e^{-(\frac{k}{k'} + \alpha)t} \leq \langle u(t) \rangle \leq \langle u_0 \rangle e^{-\frac{k}{k'+1}t} + J\frac{k' + 1}{k}(1 - e^{-\frac{k}{k'+1}t}).$$

We can again conclude as in the proof of Theorem 3.3.3.

□

Remark 3.5.2. *Note that the value of J given in Remark 3.3.3, (ii), is compatible with the condition $J \leq \alpha$, for a rather small value of α. This is no longer the case for the values considered in [49], with a proper extension of the results when J is nonconstant, as in Section 3. In that case, indeed, α should be large, i.e., less but close to 1. It is interesting to note here that, as far as the original Cahn-Hilliard theory is concerned, the dynamics of the Cahn-Hilliard-Oono equation is close, in a proper sense, to that of the Cahn-Hilliard equation when α is small (see [96]).*

We next have the following.

Theorem 3.5.3. *We assume that the assumptions of Theorem 3.5.2 hold and that $k > \varepsilon J$, $0 < \frac{\varepsilon J k'}{k - \varepsilon J} < 1$ and $(1 - \varepsilon)J < \alpha$, $\varepsilon \in (0, 1)$. Then, any weak solution u to (3.46)-(3.48) satisfies*

$$\frac{\partial u}{\partial t} \in L^\infty(r, +\infty; H^{-1}(\Omega)) \cap L^2(r, T; H^1(\Omega)),$$

$\forall r < T$, $r > 0$ and $T > 0$ given.

Proof.

We proceed as in the proof of theorem 3.4.1. The only difference here is that

$$\Lambda = \|\nabla \mu\|^2 + ((g(u) + \alpha u - J, \mu))$$

and we have to estimate

$$((g(u) + \alpha u - J, f(u)))$$

from below. Writing

$$g(u) + \alpha u - J = g(u) - \varepsilon J + \alpha(u - (1 - \varepsilon)\frac{J}{\alpha}),$$

it follows that

$$((g(u) + \alpha u - J, f(u))) \geq c \int_\Omega F(u)\, dx - c', \ c > 0,$$

which finishes the proof.

□

We finally have the following.

Theorem 3.5.4. *We assume that $n = 1$ or 2 and that the assumptions of theorems 3.5.2 and 3.5.3 hold. Then, there exists $\delta \in (0, 1)$ depending on the $H^1(\Omega)$-norm of u_0 such that*

$$\delta \leq u(x, t) \leq 1 - \delta, \text{ for almost all } (x, t), \ x \in \Omega, \ t \geq r,$$

$r > 0$ given.

Remark 3.5.3. *Let us assume that $J = 0$ and let us consider the spatially homogeneous equilibrium $u_e = 0$. Then, multiplying (3.46) by u, we obtain*

$$\frac{1}{2}\frac{d}{dt}\|u\|^2 + \|\Delta u\|^2 + \alpha\|u\|^2 \leq c_0\|\nabla u\|^2 + \frac{k}{k'}\|u\|^2.$$

Let λ_1 be the first eigenvalue of the operator $-\Delta$ associated with Neumann boundary conditions and acting on functions with null spatial average. Writing (see, e.g., [96, 111])

$$\|\Delta u\|^2 = \|(-\Delta)\overline{u}\|^2 \geq \lambda_1\|(-\Delta)^{\frac{1}{2}}\overline{u}\|^2 = \lambda_1\|\nabla u\|^2,$$

we find

$$\frac{1}{2}\frac{d}{dt}\|u\|^2 + (\lambda_1 - c_0)\|\nabla u\|^2 + (\alpha - \frac{k}{k'})\|u\|^2 \leq 0.$$

Therefore, if $c_0 \leq \lambda_1$ and $\frac{k}{k'} \leq \alpha$, then 0 is stable. Furthermore, if $\frac{k}{k'} < \alpha$, then we have a differential inequality of the form

$$\frac{d}{dt}\|u\|^2 + c\|u\|^2 \leq 0,\ c > 0,$$

and it follows from Gronwall's lemma that 0 is asymptotically stable. Note however that the condition $c_0 \leq \lambda_1$ is a restrictive one.

Chapitre 4

A coupled Cahn-Hilliard model for the proliferative-to-invasive transition of hypoxic glioma cells

Un modèle couplé de Cahn-Hilliard pour la transition proliférative à invasive des cellules de gliome hypoxique

A coupled Cahn-Hilliard model for the proliferative-to-invasive transition of hypoxic glioma cells

4.1 Introduction

We consider in this article a Cahn-Hilliard type model for the proliferative-to-invasive transition of hypoxic glioma cells.

Gliomas are highly invasive brain tumors and constitute the most prevalent malignant brain tumors. In particular, low-grade gliomas are diffuse tumors and have an uncommon growth. More precisely, one observes an inexorable slow growth without any symptom, followed by a changeover to high-grade gliomas [66]. Studying and curing such tumors involve several difficulties. On the one hand, as it is hidden in the brain, having an idea of the glioma stage and size requires the use of imaging techniques such as MRI (magnetic resonance imaging) or PET-scan (positron-emission tomography scan). On the other hand, a glioma is highly diffusive, so that it is difficult to define it with certainty or to remove all of it with a simple resection without affecting normal tissues.

In [45], H. Gomez proposed a model for the proliferative-to-invasive transition of hypoxic glioma cells. As explained in [45], hypoxia is a hallmark of gliomas that is often associated with poor prognosis and resistance to therapies. Furthermore, an insufficient oxygen supply reduces the proliferation rate of tumor cells, which contributes to a slower progression of the lesion, but also increases the invasiveness of the tumor, making it more aggressive. The model reads

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u),$$

$$\frac{\partial \sigma}{\partial t} - \Delta \sigma + \frac{u\sigma}{1+\sigma} = \gamma(\beta - \sigma),$$

where α, β and γ are positive biological parameters (here, we have set several other biological parameters equal to one and refer to [45] for more details) and

$$h(s) = a[\frac{s}{\beta} + b(1 - \frac{s}{\beta})],$$

with $a, b > 0$ and $b \sim 0.6 < 1$; note that, in our analysis, we will actually take h bounded, as in [16] (see also [98]). These equations account for the tumor and oxygen dynamics and assume that the rate of change of the tumor cells density is given by the net migration of the tumor cells plus the proliferation of the cancerous cells. In

particular, u is the tumor cells density and σ is the oxygen concentration. The nonlinear term in the first equation represents the so-called logistic growth which assumes that tumor cells proliferate until they reach the cell density α. The constant α is known as carrying capacity. Furthermore, the nonlinear term $\frac{u\sigma}{1+\sigma}$ in the second equation accounts for the oxygen uptake by tumor cells, assuming a Michaelis-Menten kinetics.

In this paper, we consider instead a Cahn-Hilliard type equation for the oxygen, namely,

$$\frac{\partial \sigma}{\partial t} + \Delta^2 \sigma - \Delta f(\sigma) + \frac{u\sigma}{1+\sigma} + \gamma\sigma = \gamma\beta.$$

Actually, more precisely, in view of the term $\gamma\sigma$, $\gamma > 0$, one has here a Cahn-Hilliard-Oono type equation; the Cahn-Hilliard-Oono equation was proposed in [105] to also account for long-ranged effects.

The original Cahn-Hilliard equation,

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

was initially proposed to model phase separation processes in binary alloys (see [11, 12]). Since then, this equation, or some of its variants, were successfully applied to many other applications than just phase separation in alloys. We refer the interested reader to [96, 103] for reviews on the Cahn-Hilliard equation and some of its variants, as well as their mathematical analysis.

In particular, Cahn-Hilliard type models in the context of tumor growth and energy metabolism in the brain can be found in, e.g., [6, 28, 39, 40, 63, 73, 89, 98].

One interest in considering a Cahn-Hilliard type model here is that, in addition to spatial diffusion, we can also account for the phase separation process, having in mind different zones in the cells in which, typically, the concentration of oxygen may be high or very low.

Our aim in this paper is to prove the existence of weak solutions. Compared to the reaction-diffusion model, one essential difficulty is to prove that the order parameter σ remains nonnegative; recall indeed that σ corresponds to the concentration of oxygen. This is due to the fact that we no longer have the maximum principle/comparison principle for Cahn-Hilliard type equations. Also note that the term $\frac{u\sigma}{1+\sigma}$ can become singular when σ is negative. To overcome this, we consider a logarithmic nonlinear term f in the above system. Actually, as far as the original Cahn-Hilliard equation is concerned, a logarithmic nonlinear term is the one which is thermodynamically relevant; it is thus natural to also consider such a nonlinear term in our model. In addition, we consider a modified problem to avoid the second nonlinear term $\frac{u\sigma}{1+\sigma}$ to become singular.

4.2 Setting of the problem

We consider the following initial and boundary value problem, in a bounded and regular domain $\Omega \subset \mathbb{R}^n$, $n = 1, 2$ or 3, with boundary Γ :

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u), \tag{4.1}$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2 \sigma - \Delta f(\sigma) + \frac{u\sigma}{1+\sigma} + \gamma\sigma = \gamma\beta, \tag{4.2}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = \frac{\partial \Delta\sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{4.3}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{4.4}$$

Here, α, β and γ are positive (biological) parameters and $h : \mathbb{R} \to \mathbb{R}$ is a bounded and globally Lipschitz continuous function such that

$$h(s) \geq 0,\ s \geq 0.$$

Furthermore, f is of logarithmic type,

$$f(s) = -c_0(s - \frac{\beta}{2}) + \theta \ln \frac{s}{\beta - s},\ s \in (0,\beta),\ 0 < \theta < \frac{\beta c_0}{4}$$

(the condition $0 < \theta < \frac{\beta c_0}{4}$ is made to ensure that we indeed have a double-well form for the corresponding potential and that phase separation can occur when considering the original Cahn-Hilliard equation). Note that

$$f' \geq -c_0. \tag{4.5}$$

Besides, there holds, for $s, m \in (0,\beta)$,

$$f(s)(s - m) \geq c_m(|f(s)| + F(s)) - c'_m,\ c_m > 0,\ c'_m \geq 0, \tag{4.6}$$

where

$$F(s) = \int_{\frac{\beta}{2}}^{s} f(\xi)\, d\xi$$

corresponds to the potential and c_m and c'_m depend continuously on m (see [96] ; actually, there, f is defined on $(-1, 1)$, but we can make a rescaling).

Remark 4.2.1. *The original Cahn-Hilliard equation is often associated with a cubic nonlinear term, typically, $f(s) = s^3 - s$. However, in that case, the order parameter may not remain in the relevant interval. In particular, it can become negative. In our case, this may be problematic, as the nonlinear term $\frac{u\sigma}{1+\sigma}$ may become singular. On the contrary, as we will see below, logarithmic nonlinear terms ensure that σ remains in the relevant interval.*

In order to study the existence of solutions, we introduce the following auxiliary problem :

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u), \tag{4.7}$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2\sigma - \Delta f(\sigma) + \frac{u\sigma}{1+|\sigma|} + \gamma\sigma = \gamma\beta, \tag{4.8}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = \frac{\partial \Delta\sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{4.9}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{4.10}$$

Note that the nonlinear term $\frac{u\sigma}{1+|\sigma|}$ can not become singular. However, taking f cubic may still lead to a negative σ.

Next, we approximate the singular function f by the following C^1-functions defined on the real line, $N \in \mathbb{N}$:

$$f_N(s) = \begin{cases} f(\beta - \frac{1}{N}) + f'(\beta - \frac{1}{N})(s - \beta + \frac{1}{N}),\ s > \beta - \frac{1}{N}, \\ f(s),\ s \in [\frac{1}{N}, \beta - \frac{1}{N}], \\ f(\frac{1}{N}) + f'(\frac{1}{N})(s - \frac{1}{N}),\ s < \frac{1}{N}. \end{cases}$$

Note that, for every $N \in \mathbb{N}$,

$$f_N' \geq -c_0 \tag{4.11}$$

and, for $s \in \mathbb{R}$, $m \in (0, \beta)$ and N large enough,

$$f_N(s)(s - m) \geq c_m(|f_N(s)| + F_N(s)) - c_m',\ c_m > 0,\ c_m' \geq 0, \tag{4.12}$$

where

$$F_N(s) = \int_{\frac{\beta}{2}}^{s} f_N(\xi)\, d\xi$$

and c_m and c_m' depend continuously on m and are independent of N (see [96]).

We then consider the following approximated problems, for $N \in \mathbb{N}$:

$$\frac{\partial u_N}{\partial t} - \Delta u_N = h(\sigma_N)u_N(\alpha - u_N), \tag{4.13}$$

$$\frac{\partial \sigma_N}{\partial t} + \Delta^2\sigma_N - \Delta f_N(\sigma_N) + \frac{u_N\sigma_N}{1+|\sigma_N|} + \gamma\sigma_N = \gamma\beta, \tag{4.14}$$

$$\frac{\partial u_N}{\partial \nu} = \frac{\partial \sigma_N}{\partial \nu} = \frac{\partial \Delta\sigma_N}{\partial \nu} = 0 \text{ on } \Gamma, \tag{4.15}$$

$$u_N|_{t=0} = u_0,\ \sigma_N|_{t=0} = \sigma_0. \tag{4.16}$$

Note that, for a given $N \in \mathbb{N}$, we can prove, via a standard Galerkin scheme, the local in time existence (as well as the uniqueness) of a solution (u_N, σ_N), on some interval

$[0, T_N)$, $T_N > 0$ (see also the estimates in the next section below). Note indeed that $s \mapsto \frac{s}{1+|s|}$ is globally Lipschitz continuous on $\mathbb{R}$, with derivative $s \mapsto \frac{1}{(1+|s|)^2}$.

We set, for $v \in L^1(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \int_\Omega v \, dx$$

and, for $v \in H^{-1}(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \langle v, 1 \rangle_{H^{-1}(\Omega), H^1(\Omega)}.$$

We finally set, whenever it makes sense,

$$\overline{v} = v - \langle v \rangle.$$

We denote by $((\cdot, \cdot))$ the usual L^2-scalar product, with associated norm $\| \cdot \|$. We also set $\| \cdot \|_{-1} = \|(-\Delta)^{-\frac{1}{2}} \cdot \|$, where $(-\Delta)^{-1}$ denotes the inverse of the minus Laplace operator associated with Neumann boundary conditions and acting on functions with null spatial average. More generally, we denote by $\| \cdot \|_X$ the norm on the Banach space X.

We note that

$$v \mapsto (\|\overline{v}\|_{-1}^2 + \langle v \rangle^2)^{\frac{1}{2}}, \; v \mapsto (\|\overline{v}\|^2 + \langle v \rangle^2)^{\frac{1}{2}},$$

$$v \mapsto (\|\nabla v\|^2 + \langle v \rangle^2)^{\frac{1}{2}} \text{ and } v \mapsto (\|\Delta v\|^2 + \langle v \rangle^2)^{\frac{1}{2}}$$

are norms on $H^{-1}(\Omega)$, $L^2(\Omega)$, $H^1(\Omega)$ and $H^2(\Omega)$, respectively, which are equivalent to the usual norms on these spaces. Furthermore, $\| \cdot \|_{-1}$ is a norm on $\{v \in H^{-1}(\Omega), \; \langle v \rangle = 0\}$ which is equivalent to the usual H^{-1}-norm.

Throughout this paper, the same letters c and c' denote (generally positive) constants which may vary from line to line, or even in a same line.

4.3 A priori estimates

We assume that there exists $\delta \in (0, \frac{\beta}{2})$ such that

$$2\delta \leq \langle \sigma_0 \rangle \leq \beta - 2\delta. \tag{4.17}$$

The estimates below are formal, but they can be justified within a standard Galerkin scheme. Furthermore, all constants below are independent of the approximation parameter N.

That said, we rewrite the problem in the following equivalent weak form :

$$\frac{\partial u_N}{\partial t} - \Delta u_N = h(\sigma_N) u_N (\alpha - u_N), \tag{4.18}$$

$$(-\Delta)^{-1} \frac{\partial \overline{\sigma}_N}{\partial t} - \Delta \overline{\sigma}_N + \overline{f_N(\sigma_N)} + (-\Delta)^{-1} \overline{\frac{u_N \sigma_N}{1 + |\sigma_N|}} + \gamma (-\Delta)^{-1} \overline{\sigma}_N = 0, \tag{4.19}$$

$$\frac{d\langle\sigma_N\rangle}{dt} + \langle\frac{u_N\sigma_N}{1+|\sigma_N|}\rangle = \gamma\beta, \tag{4.20}$$

$$\frac{\partial u_N}{\partial \nu} = \frac{\partial \sigma_N}{\partial \nu} = 0 \text{ on } \Gamma, \tag{4.21}$$

$$u_N|_{t=0} = u_0,\ \sigma_N|_{t=0} = \sigma_0, \tag{4.22}$$

with

$$\sigma_N = \overline{\sigma}_N + \langle\sigma_N\rangle.$$

We multiply (4.18) by u_N and have, integrating over Ω and by parts and recalling that h is bounded,

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|u_N\|^2 + \|\nabla u_N\|^2 &= \int_\Omega h(\sigma_N)u_N^2(\alpha - u_N)dx \\ &\leq c\int_\Omega |u_N|^2(\alpha + |u_N|)dx \\ &\leq c(\|u_N\|^2 + \|u_N\|^3_{L^3(\Omega)}),\end{aligned}$$

which yields, noting that it follows from interpolation that (see [16])

$$\|u_N\|^3_{L^3(\Omega)} \leq \frac{1}{2}(\|\nabla u_N\|^2 + \|u_N\|^2) + c\|u_N\|^6,$$

the differential inequality

$$\frac{d}{dt}\|u_N\|^2 + \|\nabla u_N\|^2 \leq c(1 + \|u_N\|^6), \tag{4.23}$$

where we have also employed Young's inequality.

In particular, it follows from (4.23) that

$$\frac{d}{dt}\|u_N\|^2 \leq c(1 + \|u_N\|^6), \tag{4.24}$$

which yields, owing to the comparison principle, that there exists $T_1 > 0$ independent of N such that

$$\|u_N\| \leq c_1,\ t \in [0, T_1], \tag{4.25}$$

where we emphasize that the constant c_1 is independent of N. Note indeed that the constant in (4.24) is independent of N. Moreover, within a Galerkin scheme, we would have the same constants and time T_1.

Having this, it follows from (4.20) that

$$\langle\sigma_N(t)\rangle = e^{-\gamma t}\langle\sigma_0\rangle + e^{-\gamma t}\int_0^t e^{\gamma t}(\gamma\beta - \langle\frac{u_N\sigma_N}{1+|\sigma_N|}\rangle)ds$$

and, for $t \in [0, T_1]$ and owing to (4.25),

$$|e^{-\gamma t} \int_0^t e^{\gamma t}(\gamma\beta - \langle \frac{u_N \sigma_N}{1+|\sigma_N|} \rangle) ds| \le e^{-\gamma t} \int_0^t e^{\gamma t}(\gamma\beta + c_2) ds$$
$$\le (\beta + \frac{c_2}{\gamma})(1 - e^{-\gamma t}),$$

where c_2 is independent of N. We thus deduce that

$$e^{-\gamma t}\langle \sigma_0 \rangle - c_3(1 - e^{-\gamma t}) \le \langle \sigma_N(t) \rangle \le e^{-\gamma t}\langle \sigma_0 \rangle + c_3(1 - e^{-\gamma t}),\ t \in [0, T_1], \tag{4.26}$$

where c_3 is independent of N. It follows from (4.17) and (4.26) that there exists $T_2 > 0$, $T_2 \le T_1$, independent of N (but depending on δ) such that

$$\delta \le \langle \sigma_N(t) \rangle \le \beta - \delta,\ t \in [0, T_2]. \tag{4.27}$$

We assume from now on that $t \in [0, T_2]$.
We multiply (4.19) by $\overline{\sigma}_N$ and obtain

$$\frac{1}{2}\frac{d}{dt}\|\overline{\sigma}_N\|_{-1}^2 + \|\nabla \sigma_N\|^2 + \gamma \|\overline{\sigma}_N\|_{-1}^2 + ((f_N(\sigma_N), \overline{\sigma}_N)) + (((-\Delta)^{-1} \overline{\frac{u_N \sigma_N}{1+|\sigma_N|}}, \overline{\sigma}_N)) = 0.$$

Note that, owing to (4.12) and (4.27) and for N large enough,

$$((f_N(\sigma_N), \overline{\sigma}_N)) \ge c(\|f_N(\sigma_N)\|_{L^1(\Omega)} + \int_\Omega F_N(\sigma_N)\, dx) - c',\ c > 0,$$

where c and c' depend on δ. Furthermore, owing to (4.25),

$$|(((-\Delta)^{-1} \overline{\frac{u_N \sigma_N}{1+|\sigma_N|}}, \overline{\sigma}_N))| = |((\frac{u_N \sigma_N}{1+|\sigma_N|}, (-\Delta)^{-1}\overline{\sigma}_N))$$
$$\le c\|u_N\|\|\overline{\sigma}_N\|_{-1}$$
$$\le \gamma \|\overline{\sigma}_N\|_{-1}^2 + c\|u_N\|^2$$
$$\le \gamma \|\overline{\sigma}_N\|_{-1}^2 + c.$$

We thus deduce from the above the differential inequality

$$\frac{d}{dt}\|\overline{\sigma}_N\|_{-1}^2 + c(\|\nabla \sigma_N\|^2 + \|f_N(\sigma_N)\|_{L^1(\Omega)} + \int_\Omega F_N(\sigma_N)\, dx) \le c',\ c > 0. \tag{4.28}$$

We now multiply (4.19) by $\frac{\partial \overline{\sigma}_N}{\partial t}$ and find

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

Note that

$$|((\frac{u_N\sigma_N}{1+|\sigma_N|},(-\Delta)^{-1}\frac{\partial\overline{\sigma}_N}{\partial t}))| \le c\|u_N\|\|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}$$
$$\le c\|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}$$

and

$$((f_N(\sigma_N),\frac{\partial\overline{\sigma}_N}{\partial t})) = \frac{d}{dt}\int_\Omega F_N(\sigma_N)\,dx - \mathrm{Vol}(\Omega)\langle f_N(\sigma_N)\rangle\langle\frac{\partial\sigma_N}{\partial t}\rangle.$$

Furthermore, it follows from (4.20) and (4.25) that

$$|\langle\frac{\partial\sigma_N}{\partial t}\rangle| \le c(1+\|u_N\|) \le c,$$

which yields

$$((f_N(\sigma_N),\frac{\partial\overline{\sigma}_N}{\partial t})) \ge \frac{d}{dt}\int_\Omega F_N(\sigma_N)\,dx - c\|f_N(\sigma_N)\|_{L^1(\Omega)}.$$

It follows from the above that we have the following differential inequality :

$$\frac{d}{dt}(\|\nabla\sigma_N\|^2+\gamma\|\overline{\sigma}_N\|_{-1}^2+2\int_\Omega F_N(\sigma_N)\,dx)+\|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}^2 \le c\|f_N(\sigma_N)\|_{L^1(\Omega)}+c'. \quad (4.29)$$

We finally multiply (4.19) by $-\Delta\sigma_N$ and have

$$\frac{1}{2}\frac{d}{dt}\|\overline{\sigma}_N\|^2+\|\Delta\sigma_N\|^2+\gamma\|\overline{\sigma}_N\|^2+((f_N'(\sigma_N)\nabla\sigma_N,\nabla\sigma_N))+((\frac{u_N\sigma_N}{1+|\sigma_N|},\overline{\sigma}_N))=0,$$

which yields, owing to (4.11) and noting that

$$|((\frac{u_N\sigma_N}{1+|\sigma_N|},\overline{\sigma}_N))| \le c\|\overline{\sigma}_N\|,$$

the differential inequality

$$\frac{d}{dt}\|\overline{\sigma}_N\|^2+\|\Delta\sigma_N\|^2+\gamma\|\overline{\sigma}_N\|^2 \le c(1+\|\nabla\sigma_N\|^2). \quad (4.30)$$

Summing (4.28), η_1 times (4.29) and η_2 times (4.30), η_1, $\eta_2 > 0$ small enough, we obtain a differential inequality of the form

$$\frac{dE}{dt}+c(E+\|\Delta\sigma_N\|^2+\|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}^2+\|f_N(\sigma_N)\|_{L^1(\Omega)}) \le c',\ c>0, \quad (4.31)$$

where

$$E=\|\overline{\sigma}_N\|_{-1}^2+\eta_1(\|\nabla\sigma_N\|^2+\gamma\|\overline{\sigma}_N\|_{-1}^2+2\int_\Omega F_N(\sigma_N)\,dx)+\eta_2\|\overline{\sigma}_N\|^2$$

satisfies

$$E \geq c\|\nabla\sigma_N\|^2 - c',\ c > 0. \tag{4.32}$$

It now follows from (4.19) that

$$\overline{f_N(\sigma_N)} = -(-\Delta)^{-1}\frac{\partial\overline{\sigma}_N}{\partial t} + \Delta\sigma_N - \gamma(-\Delta)^{-1}\overline{\sigma}_N - (-\Delta)^{-1}\overline{\frac{u_N\sigma_N}{1+|\sigma_N}},$$

so that

$$\|\overline{f_N(\sigma_N)}\| \leq c(\|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1} + \|\Delta\sigma_N\| + 1). \tag{4.33}$$

Combining (4.31) and (4.33) gives the differential inequality

$$\frac{dE}{dt} + c(E + \|\Delta\sigma_N\|^2 + \|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}^2 + \|f_N(\sigma_N)\|_{L^1(\Omega)} + \|\overline{f_N(\sigma_N)}\|^2) \leq c',\ c > 0. \tag{4.34}$$

In particular, it follows from (4.34) that

$$\|\overline{f_N(\sigma_N)}\|^2_{L^2(0,T_2;L^2(\Omega)} \leq c(E(0) + 1). \tag{4.35}$$

Then, taking $s = \sigma_N$ and $m = \langle\sigma_N\rangle$ in (4.12), we find

$$\begin{aligned}
|\langle f_N(\sigma_N)\rangle| &\leq c((f_N(\sigma_N), \overline{\sigma}_N)) + c' \\
&= c((\overline{f_N(\sigma_N)}, \sigma_N)) + c' \\
&\leq c\|\overline{f_N(\sigma_N)}\|\|\sigma_N\| + c' \\
&\leq c\|\overline{f_N(\sigma_N)}\|(E(0)+1)^{\frac{1}{2}} + c',
\end{aligned}$$

so that

$$\|f_N(\sigma_N)\|_{L^2(0,T_2;L^2(\Omega)} \leq c(E(0) + 1). \tag{4.36}$$

4.4 Existence of solutions

We have the following.

Theorem 4.4.1. *We assume that $(u_0, \sigma_0) \in L^2(\Omega) \times H^1(\Omega)$, $u_0 \geq 0$ a.e., $0 < \sigma_0 < \beta$ a.e. and $0 < \langle\sigma_0\rangle < \beta$. Then (4.1)-(4.4) possesses at least one local in time weak solution (u, σ) such that, for some $T_0 > 0$,*

$$u \in L^\infty(0, T_0; L^2(\Omega)) \cap L^2(0, T_0; H^1(\Omega)),\ \frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)),$$

$$\sigma \in L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)),\ \frac{\partial \sigma}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)).$$

Furthermore,

$$u \geq 0,\ 0 < \sigma < \beta \text{ for almost all } (x, t) \in \Omega \times [0, T_0].$$

Proof. The passage to the limit in the approximated problems, as well as the separation property for σ from the singular values 0 and β, are based on the a priori estimates derived in the previous section and standard techniques (see, e.g., [16] and [96] for details). This yields in particular a local in time weak solution to the auxiliary problem (4.7)-(4.10). Noting then that $\sigma > 0$ a.e., this solution actually is a local in time weak solution to the original problem (4.1)-(4.4).

There only remains to prove that $u \geq 0$ a.e.. This can be proved, as in [16], by multiplying (4.1) by $-u^-$, where

$$u = u^+ - u^-,\ u^+ = \max(u, 0),\ u^- = -\min(0, u),$$

noting that h is nonnegative for $s \geq 0$ (recall indeed that $\sigma > 0$ a.e.). Note that such a multiplication is compatible with a Galerkin scheme.

□

Remark 4.4.1. *Considering logarithmic nonlinear terms allows to directly ensure that σ satisfies the biologically relevant condition*

$$0 < \sigma < \beta \text{ a.e..}$$

Furthermore, assuming that u_0 further satisfies

$$u_0 \leq \alpha \text{ a.e.}$$

allows to have the further biologically relevant condition

$$0 \leq u \leq \alpha \text{ a.e.,}$$

as long as the solution exists. Indeed, this immediately follows by multiplying (4.1) by $(u - \alpha)^+$ (see also [16]).

Let $T_* > 0$ be the maximal time of existence of a local in time weak solution as given in Theorem 4.4.1.

We then have the following.

Theorem 4.4.2. *We further assume that $u_0 \in [0, \alpha]$ a.e.,*

$$h(s) \geq H,\ H > 0,\ s \geq 0,$$

and

$$\gamma \geq \frac{\alpha}{\beta + 1}.$$

Then, for any $T > 0$, a local in time solution as given above is global in time, i.e., defined on $[0, T]$.

Proof. First, multiply (4.1) by u to obtain

$$\frac{1}{2}\frac{d}{dt}\|u\|^2 + \|\nabla u\|^2 = \alpha \int_\Omega h(\sigma)u^2\,dx - \int_\Omega h(\sigma)u^3\,dx.$$

Note that, since $u \geq 0$ and $\sigma > 0$ a.e.,

$$\int_\Omega h(\sigma)u^3\,dx \geq H\|u\|^3_{L^3(\Omega)}.$$

Furthermore, owing to interpolation and Young's inequality,

$$\begin{aligned}
|\alpha \int_\Omega h(\sigma)u^2\,dx| \leq c\|u\|^2 &\leq c\|u\|\|u\|_{H^1(\Omega)} \\
&\leq \frac{1}{2}\|\nabla u\|^2 + c(\|u\|^2 + \langle u\rangle^2) \\
&\leq \frac{1}{2}\|\nabla u\|^2 + c\|u\|^2 \\
&\leq \frac{1}{2}\|\nabla u\|^2 + \frac{H}{2}\|u\|^3_{L^3(\Omega)} + c.
\end{aligned}$$

We thus deduce from the above the differential inequality

$$\frac{d}{dt}\|u\|^2 + \|\nabla u\|^2 + H\|u\|^3_{L^3(\Omega)} \leq c. \tag{4.37}$$

In particular, it follows from (4.37) and Young's inequality that

$$\frac{d}{dt}\|u\|^2 + c\|u\|^2 \leq c',\ c > 0,$$

which yields, employing Gronwall's lemma, the global in time estimate (compare with (4.25))

$$\|u\| \leq c, \tag{4.38}$$

as long as the solution exists, where the constant c only depends on u_0. Therefore, owing to continuity, we can extend u.

Now, in order to extend σ, we note that the crucial point is to prove that $\langle\sigma\rangle$ remains in $(0,\beta)$ for all times.

Note that σ satisfies

$$\frac{d\langle\sigma\rangle}{dt} + \gamma\langle\sigma\rangle + \langle\frac{u\sigma}{1+\sigma}\rangle = \gamma\beta,$$

so that, since $u \in [0,\alpha]$ a.e. and $\sigma \in [0,\beta]$ a.e. and as long as the solution exists (note that here we need to work on the original equations, not on the approximated ones),

$$\gamma\beta - \frac{\alpha\beta}{1+\beta} \leq \frac{d\langle\sigma\rangle}{dt} + \gamma\langle\sigma\rangle \leq \gamma\beta.$$

It thus follows from Gronwall's lemma that

$$\langle\sigma_0\rangle e^{-\gamma t} + \frac{\beta}{\gamma}(\gamma - \frac{\alpha}{1+\beta})(1 - e^{-\gamma t}) \leq \langle\sigma(t)\rangle \leq \langle\sigma_0\rangle e^{-\gamma t} + \beta(1 - e^{-\gamma t}), \tag{4.39}$$

as long as it exists.

Let us consider the function

$$\varphi(t) = \langle\sigma_0\rangle e^{-\gamma t} + \beta(1 - e^{-\gamma t}).$$

Noting that $\varphi(0) = \langle\sigma_0\rangle \in (0,\beta)$ and $\lim_{t\to+\infty} \varphi(t) = \beta$, we easily see that

$$\langle\varphi(t)\rangle \in (\delta, \beta - \delta),\ \delta \in (0,\beta),\ t \in [0,T],$$

since φ is monotone. Proceeding similarly for the left-hand side of (4.39), we deduce that there exists $\delta \in (0,\beta)$ depending only on T, such that

$$\langle\varphi(t)\rangle \in (\delta, \beta - \delta),\ \delta \in (0,\beta),\ t \in [0,T].$$

Therefore, we can also extend σ, owing again to continuity, which finishes the proof of the theorem.

□

Remark 4.4.2. *(i) Actually, when $u_0 \in [0,\alpha]$, the condition $H > 0$ is not necessary, since we immediately have*

$$\|u\| \leq \alpha\sqrt{\mathrm{Vol}(\Omega)},$$

as long as it exists, and can extend u. Also note that we actually have a solution defined on $\mathbb{R}^+$.
(ii) If we do not assume that $u \leq \alpha$ a.e., we have, owing to (4.38),

$$|\langle\frac{u\sigma}{1+\sigma}\rangle| \leq c\|u\| \leq c',$$

where the constant c' only depends on the initial datum u_0, the biological parameters of the problem and the domain Ω. Therefore,

$$\langle\sigma_0\rangle e^{-\gamma t} + (\beta - \frac{c'}{\gamma})(1 - e^{-\gamma t}) \leq \langle\sigma(t)\rangle \leq \langle\sigma_0\rangle e^{-\gamma t} + \beta(1 - e^{-\gamma t}),$$

and we deduce that the solution is global in time, provided that

$$\beta \geq \frac{c'}{\gamma} \iff \gamma \geq \frac{c'}{\beta}.$$

This condition is however stronger than the one in Theorem 4.4.2 in general. Also note that, if we again take $H = 0$, then we obtain a differential inequality of the form

$$\frac{d}{dt}\|u\|^2 \leq c\|u\|^2,$$

yielding, owing to Gronwall's lemma,

$$\|u\|^2 \leq e^{cT},$$

as long as it exists. We thus find an estimate of the form

$$|\langle \frac{u\sigma}{1+\sigma} \rangle| \leq c\|u\| \leq ce^{c'T},$$

which does not allow to extend σ when T is large.

Remark 4.4.3. *Uniqueness and further regularity (in particular, the existence of strong solutions) are open problems. The difficulty here comes from the Cahn-Hilliard type equation and already appears without any coupling (see [96]).*

Chapitre 5

A Cahn-Hilliard model with a proliferation term for the proliferative-to-invasive transition of hypoxic glioma cells

Un modèle de Cahn-Hilliard avec un terme de prolifération pour la transition prolifératives à invasive des cellules de gliome hypoxique

A Cahn-Hilliard model with a proliferation term for the proliferative-to-invasive transition of hypoxic glioma cells

5.1 Introduction

Our aim in this paper is to prove the existence of solutions for the following problem :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) = h(\sigma)u(\alpha - u),$$

$$\frac{\partial \sigma}{\partial t} - \Delta\sigma + \gamma\sigma + \frac{u\sigma}{1+\sigma} = \gamma\beta.$$

This system of equations is a variant of the following one :

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u),$$

$$\frac{\partial \sigma}{\partial t} - \Delta\sigma + \frac{u\sigma}{1+\sigma} = \gamma(\beta - \sigma),$$

proposed in [45] to model the proliferative-to-invasive transition of hypoxic glioma cells.

Gliomas are highly invasive brain tumors and constitute the most prevalent malignant brain tumors. In particular, low-grade gliomas are diffuse tumors and have an uncommon growth. More precisely, one observes an inexorable slow growth without any symptom, followed by a changeover to high-grade gliomas (see [66]). Studying and curing such tumors involve several difficulties. On the one hand, as it is hidden in the brain, having an idea of the glioma stage and size requires the use of imaging techniques such as MRI (magnetic resonance imaging) or PET-scan (positron-emission tomography scan). On the other hand, a glioma is highly diffusive, so that it is difficult to define it with certainty or to remove all of it with a simple resection without affecting normal tissues. Furthermore, as explained in [45], hypoxia is a hallmark of gliomas that is often associated with poor prognosis and resistance to therapies. An insufficient oxygen supply reduces the proliferation rate of tumor cells, which contributes to a slower progression of the lesion, but also increases the invasiveness of the tumor, making it more aggressive.

In the above equations, α, β and γ are positive biological parameters (here, we have set several other biological parameters equal to one and refer to [45] for more details) and

$$h(s) = a[\frac{s}{\beta} + b(1 - \frac{s}{\beta})], \tag{5.1}$$

with $a, b > 0$ such that $h(s) > 0$ for $s \in [0, \beta]$. Note that, in our analysis, we will actually take h bounded, as in [16] (see also [98]). These equations account for the tumor and oxygen dynamics and assume that the rate of change of the tumor cells density is given by the net migration of the tumor cells plus the proliferation of the cancerous cells. In particular, u is the tumor cells density and σ is the oxygen concentration. The nonlinear term in the right-hand side of the first equation of each system represents the so-called logistic growth which assumes that tumor cells proliferate until they reach the cell density α. The constant α is known as carrying capacity. Furthermore, the nonlinear term $\frac{u\sigma}{1+\sigma}$ accounts for the oxygen uptake by tumor cells, assuming a Michaelis-Menten kinetics. Finally, the nonlinear term f in the equation for the tumor cells density considered in this paper, which is of Cahn-Hilliard type, is the derivative of a double-well potential F. Such a nonlinear term, which is already present in the original Cahn-Hilliard equation, allows to account for phase separation and clustering processes, which are processes that we also wish to model here (see below).

The original Cahn-Hilliard equation,

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

was initially proposed to model phase separation processes in binary alloys (see [11, 12]). Since then, this equation, or some of its variants, were successfully applied to many other applications than just phase separation in alloys. We refer the interested reader to [96, 103] for reviews on the Cahn-Hilliard equation and some of its variants, as well as their mathematical analysis.

In particular, Cahn-Hilliard type models in the context of tumor growth can be found in, e.g., [6, 28, 39, 40, 63, 73, 72, 89, 98]. One interest in considering a Cahn-Hilliard type model is that, in addition to spatial diffusion, we can also account for the phase separation process. Indeed, in the phase separation of binary alloys, one ends up with zones (separated by a diffuse interface) in which one of the alloys is dominant. By analogy, Cahn-Hilliard type equations in tumor growth were proposed to separate, e.g., different zones in the tumor such as quiescent and proliferative cells. In particular, this allows to have the same equation in both zones. Furthermore, Cahn-Hilliard type equations also model clustering effects which are indeed observed in tumors (we can think for instance of the clustering of brain tumor cells; see, e.g., the concluding section in [63]). Note that such effects cannot be modeled by a reaction-diffusion equation.

The reaction-diffusion system proposed in [45] was studied in [16] in which, in particular, existence and uniqueness of biologically relevant solutions are obtained, i.e., solutions such that $u \in [0, \alpha]$ and $\sigma \in [0, \beta]$ almost everywhere.

Taking a Cahn-Hilliard type model for the tumor growth is more challenging, due to the nonlinear term $h(\sigma)u(\alpha - u)$, called proliferation term in [63] (for a constant h). Indeed, as observed in [28], for a constant h, one can have blow up in finite time when considering a cubic nonlinear term f; this blow up can be avoided by considering a

logarithmic nonlinear term f (see [89]). Furthermore, again for a cubic nonlinear term and a constant h, an example of a solution which instantaneously becomes negative was constructed in [96] in one space dimension, meaning that the solution cannot be biologically relevant.

In this paper, in order to prove the existence of global in time biologically relevant solutions, we take a logarithmic nonlinear term and consider an auxiliary system in which the nonlinear term $\frac{u\sigma}{1+\sigma}$ is replaced by $\frac{u\sigma}{1+|\sigma|}$. In this way, this nonlinear term cannot be singular when approximating the logarithmic nonlinear term by regular ones. We then prove the existence of a local in time solution to the approximated problems. We are next able to pass to the limit in the approximated problems and prove the existence of a local in time biologically relevant solution to the original problem. We finally prove that this solution is global in time.

We can note that, contrary to the reaction-diffusion system proposed in [45], we no longer have a maximum principle which allows us to immediately deduce that both the tumor cells density and the oxygen concentration are bounded and that local in time solutions are global (see [16]). This, together with the possibility of blow up in finite time for approximated solutions, makes the proof of existence of a solution more complicated. Furthermore, even though we still have the boundedness of the oxygen concentration (indeed, we still have a reaction-diffusion equation for the oxygen), proving the boundedness of the tumor cells density and, thus, the existence of a global in time solution, requires a more involved analysis. On the other hand, we studied in [**?**] a model in which the oxygen concentration is modeled by a Cahn-Hilliard equation, while the equation for the tumor is of reaction-diffusion type. In that case, the analysis is simpler, since the maximum principle allows to have the boundedness of the tumor cells density. Consequently, the additional nonlinear source term in the Cahn-Hilliard equation is bounded, contrary to what we have here in the equation for the tumor. Note that having such a bounded source term allows, e.g., to avoid blow up in finite time. It is also interesting to note that considering the sole Cahn-Hilliard equation with such a bounded source term allows to prove additional regularity and uniqueness results in two space dimensions (see [72]) ; this seems much more involved with an unbounded one.

Another important question is to predict the tumor evolution. We give a sufficient condition ensuring permanence of the solutions, meaning that the tumor cannot disappear.

We finally give some numerical simulations.

5.2 Setting of the problem

We consider the following initial and boundary value problem, in a bounded and regular domain $\Omega \subset \mathbb{R}^n$, $n = 1, 2$ or 3, with boundary Γ :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) = h(\sigma)u(\alpha - u),\ \alpha > 0, \tag{5.2}$$

$$\frac{\partial \sigma}{\partial t} - \Delta\sigma + \gamma\sigma + \frac{u\sigma}{1+\sigma} = \gamma\beta,\ \gamma,\ \beta > 0, \tag{5.3}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{5.4}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{5.5}$$

We make the following assumptions.
(H1) The initial datum (u_0, σ_0) belongs to $H^1(\Omega) \times L^2(\Omega)$ and satisfies

$$u_0 \in (0, \alpha),\ \sigma_0 \in [0, \beta] \text{ a.e..}$$

(H2) The nonlinear term h is bounded and Lipschitz continuous on $\mathbb{R}$ and satisfies

$$h(s) \geq 0,\ s \geq 0.$$

We set $h^\star = \max_{[0,\beta]} h$.

Remark 5.2.1. *Since we are interested in biologically relevant (and thus bounded) solutions, taking h bounded is reasonable. For instance, we can take h as in* (**??**) *in* $[0, \beta]$ *and truncate outside this interval.*

(H3) The nonlinear term f is of logarithmic type,

$$f(s) = -\theta_0(s - \frac{\alpha}{2}) + \theta_1 \ln \frac{s}{\alpha - s},\ s \in (0, \alpha),\ 0 < \theta_1 < \frac{\alpha\theta_0}{4}.$$

In particular, there holds

$$f' \geq -\theta_0 \tag{5.6}$$

and there exist constants $c_m > 0$ and $c'_m \geq 0$ which depend continuously on m such that

$$f(s)(s - m) \geq c_m(|f(s)| + F(s)) - c'_m,\ s,\ m \in (0, \alpha), \tag{5.7}$$

where

$$\begin{aligned} F(s) &:= \int_{\frac{\alpha}{2}}^{s} f(\xi)\, d\xi \\ &= -\frac{\theta_0}{2}(s - \frac{\alpha}{2})^2 + \theta_1((\alpha - s)\ln(\frac{2(\alpha - s)}{\alpha}) + s\ln(\frac{2s}{\alpha})),\ s \in (0, \alpha). \end{aligned}$$

Note that there exists a constant $c_1 \geq 0$ such that

$$F \geq -c_1. \tag{5.8}$$

Furthermore, the condition $0 < \theta_1 < \frac{\alpha\theta_0}{4}$ is made to ensure that F has a double-well form and that phase separation can occur. Note however that it was observed in [63] that, when h is a positive constant, then phase separation can also occur even if F does not have a double-well structure.

In order to avoid the nonlinear term $\frac{u\sigma}{1+\sigma}$ to become singular, we introduce the following auxiliary problem :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) = h(\sigma)u(\alpha - u), \tag{5.9}$$

$$\frac{\partial \sigma}{\partial t} - \Delta\sigma + \gamma\sigma + \frac{u\sigma}{1+|\sigma|} = \gamma\beta, \tag{5.10}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{5.11}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{5.12}$$

Next, we approximate the singular function f by smooth functions f_N defined on the whole real line. Actually, we also need to approximate the potential F and, more precisely, its convex part F_1, defined by

$$F_1(s) := \theta_1((\alpha - s)\ln(\frac{2(\alpha - s)}{\alpha}) + s\ln(\frac{2s}{\alpha})).$$

We thus have

$$F(s) = -\frac{\theta_0}{2}(s - \frac{\alpha}{2})^2 + F_1(s)$$

and we can write, similarly,

$$f(s) = -\theta_0(s - \frac{\alpha}{2}) + f_1(s),$$

where

$$f_1(s) := F_1'(s) = \theta_1 \ln\frac{s}{\alpha - s}.$$

We then approximate, for $N \in \mathbb{N}$ large enough, the function F_1 by the functions $F_{1,N}$ of class C^4 defined by

$$F_{1,N}^{(4)}(s) := \begin{cases} F_1^{(4)}(\alpha - \frac{1}{N}), & s > \alpha - \frac{1}{N}, \\ F_1^{(4)}(s), & s \in [\frac{1}{N}, \alpha - \frac{1}{N}], \\ F_1^{(4)}(\frac{1}{N}), & s < \frac{1}{N}, \end{cases}$$

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

This yields that

$$F_{1,N}(s) = \begin{cases} \sum_{k=0}^{4} \frac{1}{k!} F_1^{(k)}(\alpha - \frac{1}{N})(s - \alpha + \frac{1}{N})^k,\ s > \alpha - \frac{1}{N}, \\ F_1(s),\ s \in [\frac{1}{N}, \alpha - \frac{1}{N}], \\ \sum_{k=0}^{4} \frac{1}{k!} F_1^{(k)}(\frac{1}{N})(s - \frac{1}{N})^k,\ s < \frac{1}{N}, \end{cases}$$

and we can introduce the functions $f_{1,N}$ defined as follows :

$$f_{1,N}(s) := F'_{1,N}(s) = \begin{cases} \sum_{k=0}^{3} \frac{1}{k!} f_1^{(k)}(\alpha - \frac{1}{N})(s - \alpha + \frac{1}{N})^k,\ s > \alpha - \frac{1}{N}, \\ f_1(s),\ s \in [\frac{1}{N}, \alpha - \frac{1}{N}], \\ \sum_{k=0}^{3} \frac{1}{k!} f_1^{(k)}(\frac{1}{N})(s - \frac{1}{N})^k,\ s < \frac{1}{N}. \end{cases}$$

Note in particular that $f_{1,N}$ has a cubic growth at infinity and is of class C^3. We finally define the approximated potentials and nonlinear terms as follows :

$$F_N(s) := -\frac{\theta_0}{2}(s - \frac{\alpha}{2})^2 + F_{1,N}(s),$$

$$f_N(s) := F'_N(s) = -\theta_0(s - \frac{\alpha}{2}) + f_{1,N}(s),$$

respectively.

Adapting the proofs given in [96], we can prove that these approximated functions satisfy, for N large enough,

$$f'_N \geq -\theta_0,\ F_N \geq -c_1, \tag{5.13}$$

there exist constants $c_m > 0$ and $c'_m \geq 0$ which depend continuously on m such that

$$f_N(s)(s - m) \geq c_m(|f_N(s)| + F_N(s)) - c'_m,\ s \in \mathbb{R},\ m \in (0, \alpha), \tag{5.14}$$

and there exist constants $c_2 > 0$ and $c_3 \geq 0$ which are independent of s and m such that

$$(f_N(s + m) - f_N(m))s \geq c_2(s^4 + m^2 s^2) - c_3,\ s,\ m \in \mathbb{R}. \tag{5.15}$$

Furthermore, all constants are independent of N.

We finally introduce the following approximated problems, for $N \in \mathbb{N}$ large enough :

$$\frac{\partial u_N}{\partial t} + \Delta^2 u_N - \Delta f_N(u_N) = h(\sigma_N)u_N(\alpha - u_N), \tag{5.16}$$

$$\frac{\partial \sigma_N}{\partial t} - \Delta \sigma_N + \gamma \sigma_N + \frac{u_N \sigma_N}{1 + |\sigma_N|} = \gamma \beta, \tag{5.17}$$

$$\frac{\partial u_N}{\partial \nu} = \frac{\partial \Delta u_N}{\partial \nu} = \frac{\partial \sigma_N}{\partial \nu} = 0 \text{ on } \Gamma, \tag{5.18}$$

$$u_N|_{t=0} = u_0,\ \sigma_N|_{t=0} = \sigma_0. \tag{5.19}$$

We set, for $v \in L^1(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \int_\Omega v \, dx$$

and, for $v \in H^{-1}(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \langle v, 1 \rangle_{H^{-1}(\Omega), H^1(\Omega)}.$$

We finally set, whenever it makes sense,

$$\overline{v} = v - \langle v \rangle.$$

We denote by $((\cdot, \cdot))$ the usual L^2-scalar product, with associated norm $\| \cdot \|$. We also set $\| \cdot \|_{-1} = \| (-\Delta)^{-\frac{1}{2}} \cdot \|$, where $(-\Delta)^{-1}$ denotes the inverse of the minus Laplace operator associated with Neumann boundary conditions and acting on functions with null spatial average. More generally, we denote by $\| \cdot \|_X$ the norm on the Banach space X.

We note that

$$v \mapsto (\|\overline{v}\|_{-1}^2 + \langle v \rangle^2)^{\frac{1}{2}},\ v \mapsto (\|\overline{v}\|^2 + \langle v \rangle^2)^{\frac{1}{2}},$$

$$v \mapsto (\|\nabla v\|^2 + \langle v \rangle^2)^{\frac{1}{2}} \text{ and } v \mapsto (\|\Delta v\|^2 + \langle v \rangle^2)^{\frac{1}{2}}$$

are norms on $H^{-1}(\Omega)$, $L^2(\Omega)$, $H^1(\Omega)$ and $H^2(\Omega)$, respectively, which are equivalent to the usual norms on these spaces. Furthermore, $\| \cdot \|_{-1}$ is a norm on $\{v \in H^{-1}(\Omega),\ \langle v \rangle = 0\}$ which is equivalent to the usual H^{-1}-norm.

Throughout this paper, the same letters c and c' denote (generally positive) constants which may vary from line to line, or even in a same line.

5.3 Local well-posedness of the approximated problems

We can note that (5.16)-(5.19) is associated with the following weak (variational) formulation :

Given $(u_0, \sigma_0) \in H^2(\Omega) \times H^1(\Omega)$, find $(u_N, \sigma_N) : [0, T] \to H^2(\Omega) \times H^1(\Omega)$ such that

$$\frac{d}{dt}((u_N, v)) + ((\Delta u_N, \Delta v)) - ((f_N(u_N), \Delta v)) = ((h(\sigma_N) u_N (\alpha - u_N), v))$$

$$\text{in } \mathcal{D}'(0, T),\ \forall v \in H^2(\Omega),$$

$$\frac{d}{dt}((\sigma_N, w)) + ((\nabla\sigma_N, \nabla w)) + \gamma((\sigma_N, w)) + ((\frac{u_N\sigma_N}{1+|\sigma_N|}, w)) = ((\gamma\beta, w))$$
$$\text{in } \mathcal{D}'(0,T),\ \forall w \in H^1(\Omega),$$
$$u_N|_{t=0} = u_0,\ \sigma_N|_{t=0} = \sigma_0,$$

for a given $T > 0$, where $\mathcal{D}'$ denotes the space of distributions.

We will actually work with the following equivalent formulation of (5.16)-(5.19) :

$$(-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t} - \Delta\overline{u}_N + \overline{f_N(u_N)} = (-\Delta)^{-1}\overline{h(\sigma_N)u_N(\alpha - u_N)}, \tag{5.20}$$

$$\frac{d\langle u_N\rangle}{dt} = \langle h(\sigma_N)u_N(\alpha - u_N)\rangle, \tag{5.21}$$

$$\frac{\partial\sigma_N}{\partial t} - \Delta\sigma_N + \gamma\sigma_N + \frac{u_N\sigma_N}{1+|\sigma_N|} = \gamma\beta, \tag{5.22}$$

$$\frac{\partial u_N}{\partial \nu} = \frac{\partial\sigma_N}{\partial\nu} = 0 \text{ on } \Gamma, \tag{5.23}$$

$$u_N|_{t=0} = u_0,\ \sigma_N|_{t=0} = \sigma_0, \tag{5.24}$$

where $u_N = \overline{u}_N + \langle u_N\rangle$. These equations are associated with the following weak formulation :

Given $(u_0, \sigma_0) \in H^1(\Omega)\times H^1(\Omega)$, find $(u_N, \sigma_N) : [0,T] \to H^1(\Omega)\times H^1(\Omega)$ such that

$$\frac{d}{dt}(((-\Delta)^{-\frac{1}{2}}\overline{u}_N, (-\Delta)^{-\frac{1}{2}}v)) + ((\nabla\overline{u}_N, \nabla v)) + ((f_N(u_N), v)) = (((-\Delta)^{-1}\overline{h(\sigma_N)u_N(\alpha - u_N)}, v))$$
$$\text{in } \mathcal{D}'(0,T),\ \forall v \in H^1(\Omega),\ \langle v\rangle = 0,$$
$$\frac{d\langle u_N\rangle}{dt} = \langle h(\sigma_N)u_N(\alpha - u_N)\rangle \text{ in } \mathcal{D}'(0,T),$$
$$\frac{d}{dt}((\sigma_N, w)) + ((\nabla\sigma_N, \nabla w)) + \gamma((\sigma_N, w)) + ((\frac{u_N\sigma_N}{1+|\sigma_N|}, w)) = ((\gamma\beta, w))$$
$$\text{in } \mathcal{D}'(0,T),\ \forall w \in H^1(\Omega),$$
$$u_N|_{t=0} = u_0,\ \sigma_N|_{t=0} = \sigma_0,$$

for a given $T > 0$, where $u_N = \overline{u}_N + \langle u_N\rangle$. We can note that this second variational formulation is weaker than the first one, in the sense that it is defined under weaker regularity on u_N. However, they are equivalent for regular enough solutions and a solution to (5.20)-(5.24) will be considered as a weak solution to (5.16)-(5.19) (being understood that we consider here solutions to the associated variational formulations).

We have the following.

Theorem 5.3.1. *We assume that* **(H1)**-**(H3)** *hold. Then, there exists* $T_0 > 0$ *and a unique weak solution* (u_N, σ_N) *to* (5.16)-(5.19) *such that*

$$\begin{aligned} u_N &\in L^\infty(0,T_0;H^1(\Omega)) \cap L^2(0,T_0;H^2(\Omega)),\\ \frac{\partial u_N}{\partial t} &\in L^2(0,T_0;H^{-1}(\Omega)),\\ \sigma_N &\in L^\infty(0,T_0;L^2(\Omega)) \cap L^2(0,T_0;H^1(\Omega)),\\ \frac{\partial \sigma_N}{\partial t} &\in L^2(0,T_0;H^{-1}(\Omega)). \end{aligned}$$

Remark 5.3.1. *Actually, here, the conditions* $u_0 \in (0,\alpha)$ *and* $\sigma_0 \in [0,\beta]$ *a.e. are not necessary. When* h *is constant, as mentioned in the introduction, we can observe blow up in finite time, so that we do not expect a global in time existence result. Furthermore, again when* h *is constant, we can construct solutions to* (5.16) *which instantaneously exit the relevant interval* $[0,\alpha]$*, even if* $u_0 \in [0,\alpha]$.

Proof.

Existence : The proof of existence can be carried out via a standard Galerkin scheme associated with (5.20)-(5.24) and appropriate a priori estimates. In what follows, we only give formal estimates.

We multiply (5.20) by $-\Delta\overline{u}_N$, integrate over Ω and by parts and multiply (5.21) by $\mathrm{Vol}(\Omega)\langle u_N\rangle$. Summing then the resulting differential equalities, we obtain, noting that $\|\cdot\|^2 = \|\dot{-}\|^2 + \mathrm{Vol}(\Omega)\langle\cdot\rangle^2$ (also note that this amounts to multiplying (5.16) by u_N),

$$\frac{1}{2}\frac{d}{dt}\|u_N\|^2 + \|\Delta u_N\|^2 + ((f_N'(u_N)\nabla u_N, \nabla u_N)) = \int_\Omega h(\sigma_N)u_N^2(\alpha - u_N)\,dx. \tag{5.25}$$

Note that it follows from (5.13) that

$$\begin{aligned} ((f_N'(u_N)\nabla u_N, \nabla u_N)) &\geq -\theta_0\|\nabla u_N\|^2\\ &\geq -\frac{1}{4}\|\Delta u_N\|^2 - c\|u_N\|^2, \end{aligned} \tag{5.26}$$

since, owing to interpolation and standard elliptic regularity results,

$$\begin{aligned} \|\nabla u_N\|^2 &\leq c\|u_N\|\|u_N\|_{H^2(\Omega)}\\ &\leq c\|u_N\|(\|\Delta u_N\| + \|u_N\|). \end{aligned}$$

Furthermore, since h is bounded,

$$\begin{aligned} \Big|\int_\Omega h(\sigma_N)u_N^2(\alpha - u_N)dx\Big| &\leq c(\|u_N\|^2 + \|u_N\|^3_{L^3(\Omega)})\\ &\leq c(\|u_N\|^2 + \|u_N\|^3_{H^1(\Omega)})\\ &\leq c(\|u_N\|^2 + \|u_N\|^{\frac{3}{2}}\|u_N\|^{\frac{3}{2}}_{H^2(\Omega)})\\ &\leq c(1 + \|u_N\|^6) + \frac{1}{4}\|\Delta u_N\|^2, \end{aligned} \tag{5.27}$$

where we have employed Young's inequality and interpolation again. It follows from (5.25)-(5.27) that

$$\frac{d}{dt}\|u_N\|^2 + \|\Delta u_N\|^2 \le c(1 + \|u_N\|^6). \tag{5.28}$$

In particular,

$$\frac{d}{dt}\|u_N\|^2 \le c(1 + \|u_N\|^6). \tag{5.29}$$

We deduce from (5.29) and the comparison principle that there exists $T_0 > 0$ such that

$$\|u_N(t)\| \le c, \ t \in [0, T_0]. \tag{5.30}$$

We assume from now on that $t \in [0, T_0]$.
First, note that

$$|\langle \frac{\partial u_N}{\partial t} \rangle| \le c(1 + \|u_N\|^2) \le c. \tag{5.31}$$

We multiply (5.20) by $\frac{\partial \overline{u}_N}{\partial t}$ and have, noting that $\langle \frac{\partial \overline{u}_N}{\partial t} \rangle = 0$,

$$\frac{1}{2}\frac{d}{dt}\|\nabla u_N\|^2 + \|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 + ((f_N(u_N), \frac{\partial \overline{u}_N}{\partial t})) = ((h(\sigma_N)u_N(\alpha - u_N), (-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t})). \tag{5.32}$$

Note that

$$((f_N(u_N), \frac{\partial \overline{u}_N}{\partial t})) = \frac{d}{dt}\int_\Omega F_N(u_N)\,dx - ((f_N(u_N), \frac{d\langle u_N \rangle}{dt})).$$

Furthermore, owing to the expression of f_N (recall that f_N has a cubic growth at infinity), Young's inequality, (5.21) and (5.30)-(5.31),

$$\begin{aligned} |((f_N(u_N), \frac{d\langle u_N \rangle}{dt}))| &= |\int_\Omega f_N(u_N)\,dx \frac{d\langle u_N \rangle}{dt}| \\ &\le c(1 + \|u_N\|_{L^3(\Omega)}^3) \end{aligned}$$

and, owing to the continuous embedding $H^{\frac{1}{2}}(\Omega) \subset L^3(\Omega)$ and the interpolation inequality

$$\|u_N\|_{H^{\frac{1}{2}}(\Omega)} \le c\|u_N\|^{\frac{1}{2}}\|u_N\|_{H^1(\Omega)}^{\frac{1}{2}}$$

(we consider the most complicated case $n = 3$),

$$\|u_N\|_{L^3(\Omega)}^3 \le c\|u_N\|^{\frac{3}{2}}\|u_N\|_{H^1(\Omega)}^{\frac{3}{2}} \le c\|u_N\|_{H^1(\Omega)}^{\frac{3}{2}},$$

so that, owing to (5.30),

$$|((f_N(u_N), \frac{d\langle u_N \rangle}{dt}))| \le c(1 + \|u_N\|_{H^1(\Omega)}^{\frac{3}{2}}) \le c(1 + \|\nabla u_N\|^2). \tag{5.33}$$

Finally,

$$\begin{aligned}|((h(\sigma_N)u_N(\alpha-u_N),(-\Delta)^{-1}\frac{\partial\overline{u}_N}{\partial t}))| &\le c\|(-\Delta)^{-1}\frac{\partial\overline{u}_N}{\partial t}\|_{L^3(\Omega)}(\int_\Omega(|u_N|^3+1)\,dx)^{\frac{2}{3}}\\ &\le c\|\frac{\partial\overline{u}_N}{\partial t}\|_{-1}(\int_\Omega(|u_N|^3+1)\,dx)^{\frac{2}{3}}\\ &\le \frac{1}{2}\|\frac{\partial\overline{u}_N}{\partial t}\|^2_{-1}+c(1+\|\nabla u_N\|^2),\end{aligned}\tag{5.34}$$

proceeding as above and noting that the embedding $H^1(\Omega)\subset L^3(\Omega)$ is continuous. It thus follows from (5.32)-(5.34) that

$$\frac{d}{dt}(\|\nabla u_N\|^2+2\int_\Omega F_N(u_N)\,dx)+\|\frac{\partial\overline{u}_N}{\partial t}\|^2_{-1}\le c(1+\|\nabla u_N\|^2).\tag{5.35}$$

We now multiply (5.22) by σ_N and obtain, owing to (5.30) and noting that $|\frac{s}{1+|s|}|\le 1$,

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\sigma_N\|^2+\|\nabla\sigma_N\|^2+\gamma\|\sigma_N\|^2 &\le ((\gamma\beta,\sigma_N))+\int_\Omega|\frac{u_N\sigma_N^2}{1+|\sigma_N|}|\,dx\\ &\le \frac{\gamma}{2}\|\sigma_N\|^2+c(1+\|u_N\|^2)\\ &\le \frac{\gamma}{2}\|\sigma_N\|^2+c,\end{aligned}$$

so that

$$\frac{d}{dt}\|\sigma_N\|^2+\|\nabla\sigma_N\|^2+\gamma\|\sigma_N\|^2\le c.\tag{5.36}$$

The regularity stated in the theorem follows from the second of (5.13), (5.28)-(5.30) and (5.35)-(5.36) (the regularity on $\frac{\partial\sigma_N}{\partial t}$ can be read from (5.22)). Furthermore, the passage to the limit in the Galerkin scheme follows from the above estimates and classical Aubin–Lions compactness results (see also [16]).

Uniqueness : Let (u_1,σ_1) and (u_2,σ_2) (for simplicity, we drop the index N) be two local in time solutions with initial data $(u_{1,0},\sigma_{1,0})$ and $(u_{2,0},\sigma_{2,0})$, respectively, and assume that they are defined on a common time interval $[0,T_0]$. Then, $(u,\sigma)=(u_1,\sigma_1)-(u_2,\sigma_2)$ and $(u_0,\sigma_0)=(u_{1,0},\sigma_{1,0})-(u_{2,0},\sigma_{2,0})$ satisfy

$$(-\Delta)^{-1}\frac{\partial\overline{u}}{\partial t}-\Delta\overline{u}+\overline{f_N(u_1)-f_N(u_2)}=(-\Delta)^{-1}\overline{(h(\sigma_1)u_1(\alpha-u_1)-h(\sigma_2)u_2(\alpha-u_2))},\tag{5.37}$$

$$\frac{d\langle u\rangle}{dt}=\langle h(\sigma_1)u_1(\alpha-u_1)-h(\sigma_2)u_2(\alpha-u_2)\rangle,\tag{5.38}$$

$$\frac{\partial\sigma}{\partial t}-\Delta\sigma+\gamma\sigma+\frac{u_1\sigma_1}{1+|\sigma_1|}-\frac{u_2\sigma_2}{1+|\sigma_2|}=0,\tag{5.39}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{5.40}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{5.41}$$

We multiply (5.37) by $\overline{u}$ and obtain

$$\begin{aligned} &\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 + ((f_N(u_1) - f_N(u_2), \overline{u})) \\ &= ((h(\sigma_1)u_1(\alpha - u_1) - h(\sigma_2)u_2(\alpha - u_2), (-\Delta)^{-1}\overline{u})). \end{aligned} \tag{5.42}$$

Note that, owing to (5.13),

$$\begin{aligned} ((f_N(u_1) - f_N(u_2), \overline{u})) &= ((f_N(u_1) - f_N(u_2), u)) - ((f_N(u_1) - f_N(u_2), \langle u \rangle)) \\ &\geq -\theta_0\|u\|^2 - ((f_N(u_1) - f_N(u_2), \langle u \rangle)). \end{aligned}$$

Furthermore, owing to the continuous embedding $H^1(\Omega) \subset L^4(\Omega)$ and recalling that f_N has a cubic growth at infinity,

$$\begin{aligned} |((f_N(u_1) - f_N(u_2), \langle u \rangle))| &\leq c|\langle u \rangle| \int_\Omega (|u_1^3 - u_2^3| + |u_1^2 - u_2^2| + |u|)\, dx \\ &\leq c|\langle u \rangle| \int_\Omega (u_1^2 + u_2^2 + 1)|u|\, dx \\ &\leq c(\|u_1\|_{L^4(\Omega)}^2 + \|u_2\|_{L^4(\Omega)}^2 + 1)\|u\|\langle u \rangle| \\ &\leq c(\|u_1\|_{H^1(\Omega)}^2 + \|u_2\|_{H^1(\Omega)}^2 + 1)\|u\|\langle u \rangle| \\ &\leq c_{T_0}\|u\|\langle u \rangle|. \end{aligned}$$

Note that all constants above depend on N. It thus follows that

$$((f_N(u_1) - f_N(u_2), \overline{u})) \geq -c_{T_0}(\|\overline{u}\|^2 + \langle u \rangle^2). \tag{5.43}$$

We also note that, since h is bounded and globally Lipschitz continuous,

$$\begin{aligned} &|((h(\sigma_1)u_1(\alpha - u_1) - h(\sigma_2)u_2(\alpha - u_2), (-\Delta)^{-1}\overline{u}))| \\ &\leq |(((h(\sigma_1) - h(\sigma_2))u_1(\alpha - u_1), (-\Delta)^{-1}\overline{u}))| \\ &\quad + |((h(\sigma_2)(u_1(\alpha - u_1) - u_2(\alpha - u_2)), (-\Delta)^{-1}\overline{u}))| \\ &\leq c\Big(\int_\Omega |\sigma|(u_1^2 + 1)|(-\Delta)^{-1}\overline{u}|\, dx + \int_\Omega (u_1^2 + u_2^2 + 1)|u||(-\Delta)^{-1}\overline{u}|\, dx\Big) \\ &\leq c(\|u_1\|_{L^6(\Omega)}^2 + \|u_2\|_{L^6(\Omega)}^2 + 1)(\|u\| + \|\sigma\|)\|(-\Delta)^{-1}\overline{u}\|_{L^6(\Omega)} \\ &\leq c(\|u_1\|_{H^1(\Omega)}^2 + \|u_2\|_{H^1(\Omega)}^2 + 1)(\|u\| + \|\sigma\|)\|\overline{u}\|_{-1} \\ &\leq c_{T_0}(\|u\| + \|\sigma\|)\|\overline{u}\|_{-1} \\ &\leq c_{T_0}(\|u\|^2 + \|\sigma\|^2), \end{aligned} \tag{5.44}$$

where we have used the continuous embedding $H^1(\Omega) \subset L^6(\Omega)$. It thus follows from (5.42)-(5.44) that

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 \leq c_{T_0}(\|\overline{u}\|^2 + \langle u\rangle^2 + \|\sigma\|^2),$$

which yields, employing the interpolation inequality $\|\overline{u}\|^2 \leq c\|\overline{u}\|_{-1}\|\nabla u\|$,

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 \leq c_{T_0}(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2 + \|\sigma\|^2). \tag{5.45}$$

Multiplying then (5.38) by $\langle u\rangle$ and proceeding in a similar way, we find

$$\frac{d\langle u\rangle^2}{dt} \leq c_{T_0}(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2 + \|\sigma\|^2) + \frac{1}{2}\|\nabla u\|^2. \tag{5.46}$$

We now multiply (5.39) by σ and have

$$\frac{1}{2}\frac{d}{dt}\|\sigma\|^2 + \|\nabla\sigma\|^2 + \gamma\|\sigma\|^2 + ((\frac{u_1\sigma_1}{1+|\sigma_1|} - \frac{u_2\sigma_2}{1+|\sigma_2|}, \sigma)) = 0. \tag{5.47}$$

We note that, since $s \mapsto \frac{s}{1+|s|}$ is globally Lipschitz continuous,

$$\begin{aligned}
|((\frac{u_1\sigma_1}{1+|\sigma_1|} - \frac{u_2\sigma_2}{1+|\sigma_2|}, \sigma))| &\leq |((\frac{u\sigma_1}{1+|\sigma_1|}, \sigma))| + |((u_2(\frac{\sigma_1}{1+|\sigma_1|} - \frac{\sigma_2}{1+|\sigma_2|}), \sigma))| \\
&\leq \|u\|\|\sigma\| + c\int_\Omega |u_2||\sigma|^2\,dx \\
&\leq \|u\|\|\sigma\| + c\|u_2\|_{L^3(\Omega)}\|\sigma\|_{L^3(\Omega)}^2 \\
&\leq \|u\|\|\sigma\| + c_{T_0}\|\sigma\|_{L^3(\Omega)}^2.
\end{aligned}$$

Let us again consider the most difficult case $n = 3$. Recall that we have the continuous embedding $H^{\frac{1}{2}}(\Omega) \subset L^3(\Omega)$, as well as the interpolation inequality

$$\|\sigma\|_{H^{\frac{1}{2}}(\Omega)} \leq c\|\sigma\|^{\frac{1}{2}}\|\sigma\|_{H^1(\Omega)}^{\frac{1}{2}}.$$

Therefore,

$$\begin{aligned}
&|((\frac{u_1\sigma_1}{1+|\sigma_1|} - \frac{u_2\sigma_2}{1+|\sigma_2|}, \sigma))| \\
&\leq \|u\|\|\sigma\| + c_{T_0}\|\sigma\|\|\sigma\|_{H^1(\Omega)} \\
&\leq (\|\nabla\sigma\|^2 + \gamma\|\sigma\|^2) + \frac{1}{2}\|\nabla u\|^2 + c_{T_0}(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2 + \|\sigma\|^2),
\end{aligned}$$

which yields

$$\frac{d}{dt}\|\sigma\|^2 \leq c_{T_0}(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2 + \|\sigma\|^2) + \frac{1}{2}\|\nabla u\|^2. \tag{5.48}$$

Summing finally (5.45)-(5.46) and (5.48), we find a differential inequality of the form

$$\frac{dE_1}{dt} \leq c_{T_0} E_1, \tag{5.49}$$

where

$$E_1 = \|\overline{u}\|_{-1}^2 + \langle u \rangle^2 + \|\sigma\|^2.$$

This yields, employing Gronwall's lemma,

$$E_1(t) \leq e^{c_{T_0} t} E_1(0), \ t \in [0, T_0], \tag{5.50}$$

and the uniqueness, as well as the continuous dependence with respect to the initial data in the $H^{-1}(\Omega) \times L^2(\Omega)$-norm, follow.

□

Remark 5.3.2. *(i) In general, the Cahn–Hilliard equation is considered with a cubic nonlinear term, typically, $f(s) = s^3 - s$. The estimates above also yield a local in time well-posedness result in that case, for the auxiliary problem. However, we again mention that we cannot rule out the possibility of blow up in finite time, nor the fact that u can instantaneously become negative. Therefore, we cannot ensure that σ remains nonnegative, so that this does not yield a local in time solution to the original problem.*

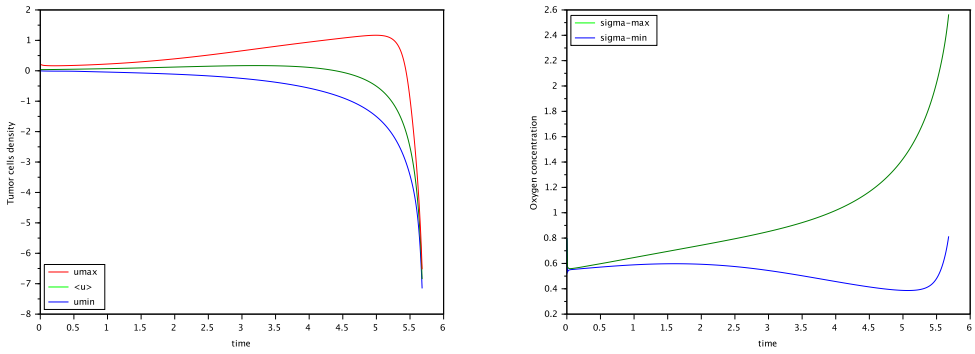

FIGURE 5.1 – Unbounded function h.

(ii) Numerical simulations show that we can have blow up in finite time in the original problem (5.2)-(5.5) with a cubic nonlinear term (see Figures 5.1-5.2). In these simulations, we take $\Omega = (0,5) \times (0,1)$, $\alpha = 1$, $\beta = 1.5$, $\gamma = 0.1$, $f(s) = (s - 0.5)^3 - (s - 0.5)$, $u_0(x_1, x_2) = \frac{0.2}{(x_1^6+1)(x_2^5+0.5)}$ and σ_0 randomly distributed between 0.3 and 0.8. In Figure 5.1, h is as given as in [45], $h(s) = \frac{s}{\beta} + 0.6(1 - \frac{s}{\beta})$, while, in Figure 5.2, $h(s) = 0.6$ if $s < 0$, $h(s) = \frac{s}{\beta} + 0.6(1 - \frac{s}{\beta})$ if $0 \leq s \leq \beta$ and $h(s) = 1$ if $s > 1$, so that **(H1)** *is satisfied. In both cases, we observe blow up at $t_{max} = 5.68$. Also note that σ remains positive, while u becomes negative. In the figures, umax (resp., umin) and sigma-max (resp., sigma-min) denote the maximal (resp., minimal) values of u and σ, respectively.*

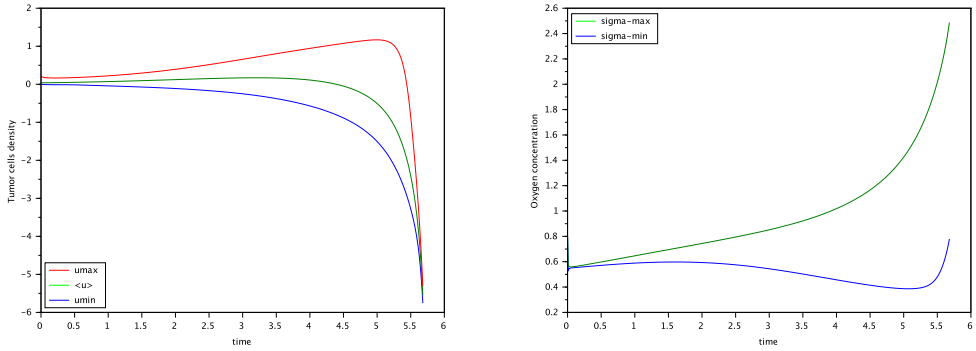

FIGURE 5.2 – Truncated function h.

Remark 5.3.3. *Note that the constants in* (5.26)-(5.30) *and* (5.36) *are independent of* N*, so that the same holds for* T_0 *which only depends on the initial data* u_0 *and* σ_0*. However, the estimates on the time derivative of* u_N *depend on* N*. In the next section, we will derive estimates which are independent of* N*, allowing us to pass to the limit in the approximated problems.*

5.4 Existence of solutions to the original problem

We can note that (5.2)-(5.5) is associated with the following weak formulation :
Given $(u_0, \sigma_0) \in H^2(\Omega) \times H^1(\Omega)$, find $(u, \sigma) : [0, T] \to H^2(\Omega) \times H^1(\Omega)$ such that

$$\frac{d}{dt}((u, v)) + ((\Delta u, \Delta v)) - ((f(u), \Delta v)) = ((h(\sigma)u(\alpha - u), v))$$

$$\text{in } \mathcal{D}'(0, T), \ \forall v \in H^2(\Omega),$$

$$\frac{d}{dt}((\sigma, w)) + ((\nabla\sigma, \nabla w)) + \gamma((\sigma, w)) + ((\frac{u\sigma}{1+\sigma}, w)) = ((\gamma\beta, w))$$

$$\text{in } \mathcal{D}'(0, T), \ \forall w \in H^1(\Omega),$$

$$u|_{t=0} = u_0, \ \sigma|_{t=0} = \sigma_0,$$

for a given $T > 0$.

We also consider the following equivalent formulation of (5.2)-(5.5) :

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - \Delta\overline{u} + \overline{f(u)} = (-\Delta)^{-1}\overline{h(\sigma)u(\alpha - u)}, \tag{5.51}$$

$$\frac{d\langle u\rangle}{dt} = \langle h(\sigma)u(\alpha - u)\rangle, \tag{5.52}$$

$$\frac{\partial \sigma}{\partial t} - \Delta \sigma + \gamma \sigma + \frac{u\sigma}{1+\sigma} = \gamma\beta, \tag{5.53}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{5.54}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0, \tag{5.55}$$

where $u = \overline{u} + \langle u \rangle$. These equations are associated with the following weak formulation :

Given $(u_0, \sigma_0) \in H^1(\Omega) \times H^1(\Omega)$, find $(u, \sigma) : [0, T] \to H^1(\Omega) \times H^1(\Omega)$ such that

$$\frac{d}{dt}(((-\Delta)^{-\frac{1}{2}}\overline{u}, (-\Delta)^{-\frac{1}{2}}v)) + ((\nabla \overline{u}, \nabla v)) + ((f(u), v))$$

$$= (((-\Delta)^{-1}\overline{h(\sigma)u(\alpha - u)}, v)) \text{ in } \mathcal{D}'(0,T),\ \forall v \in H^1(\Omega),\ \langle v \rangle = 0,$$

$$\frac{d\langle u \rangle}{dt} = \langle h(\sigma)u(\alpha - u) \rangle \text{ in } \mathcal{D}'(0,T),$$

$$\frac{d}{dt}((\sigma, w)) + ((\nabla \sigma, \nabla w)) + \gamma((\sigma, w)) + ((\frac{u\sigma}{1+\sigma}, w)) = ((\gamma\beta, w))$$

$$\text{in } \mathcal{D}'(0,T),\ \forall w \in H^1(\Omega),$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0,$$

for a given $T > 0$, where $u = \overline{u} + \langle u \rangle$.

As in the previous section, a solution to (5.51)-(5.55) will be called a weak solution to (5.2)-(5.5) (by solution, we again mean a solution to the corresponding variational formulation).

We have the following.

Theorem 5.4.1. *We assume that* **(H1)**-**(H3)** *hold. Then,* (5.2)-(5.5) *possesses a local in time weak solution* (u, σ)*, defined on* $[0, T_0]$*,* $T_0 > 0$*, such that*

$$u \in L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)),$$

$$\sigma \in L^\infty(0, T_0; L^2(\Omega)) \cap L^2(0, T_0; H^1(\Omega)),$$

$$\frac{\partial \sigma}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)),$$

$$u(t) \in (0, \alpha),\ \sigma(t) \in [0, \beta] \text{ for a.a. } t \in [0, T_0]$$

and there exists a constant $\delta \in (0, \alpha)$ *such that*

$$\delta \leq \langle u(t) \rangle \leq \alpha - \delta \text{ for a.a. } t \in [0, T_0].$$

Proof.

All constants below are independent of N.

First, note that it follows from **(H1)** that there exists $\delta \in (0, \frac{\alpha}{2})$ such that

$$2\delta \le \langle u_0 \rangle \le \alpha - 2\delta. \tag{5.56}$$

Then, considering again the equivalent formulation (5.20)-(5.24), recall that

$$\|u_N(t)\| \le c, \ t \in [0, T_0], \tag{5.57}$$

for $T_0 > 0$ independent of N.

Noting that it follows from (5.21) that

$$\begin{aligned} |\frac{d\langle u_N \rangle}{dt}| &\le |\langle h(\sigma_N) u_N(\alpha - u_N) \rangle| \\ &\le c(1 + \|u_N\|^2) \\ &\le c, \end{aligned} \tag{5.58}$$

we can assume, taking if necessary T_0 smaller and still independent of N, that

$$\delta \le \langle u_N(t) \rangle \le \alpha - \delta, \ t \in [0, T_0]. \tag{5.59}$$

We assume from now on that $t \in [0, T_0]$.

We next multiply (5.20) by $\overline{u}_N$ to obtain

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + \|\nabla u_N\|^2 + ((f_N(u_N), \overline{u}_N)) = ((h(\sigma_N) u_N(\alpha - u_N), (-\Delta)^{-1}\overline{u}_N)). \tag{5.60}$$

We write

$$((f_N(u_N), \overline{u}_N)) = \frac{1}{2}((f_N(u_N), \overline{u}_N)) + \frac{1}{2}((f_N(u_N) - f(\langle u_N \rangle), \overline{u}_N)),$$

so that, employing (5.14) (with $s = u_N$ and $m = \langle u_N \rangle$; also recall (5.59)) and (5.15) (with $s = \overline{u}_N$ and $m = \langle u_N \rangle$), we find

$$\begin{aligned} ((f_N(u_N), \overline{u}_N)) \ge c(\|f_N(u_N)\|_{L^1(\Omega)} &+ \int_\Omega F_N(u_N)\, dx \\ &+ \int_\Omega (\overline{u}_N^4 + \overline{u}_N^2 \langle u_N \rangle^2)\, dx) - c', \ c > 0. \end{aligned} \tag{5.61}$$

Furthermore,

$$\begin{aligned} |((h(\sigma_N) u_N(\alpha - u_N), (-\Delta)^{-1}\overline{u}_N))| &\le c(\int_\Omega (u_N^4 + 1) dx)^{\frac{1}{2}} \|\overline{u}_N\|_{-1} \\ &\le c(\int_\Omega (\overline{u}_N^4 + \langle u_N \rangle^4 + 1)\, dx)^{\frac{1}{2}} \|u_N\| \\ &\le \varepsilon \int_\Omega \overline{u}_N^4\, dx + c_\varepsilon(1 + \|u_N\|^4) \\ &\le \varepsilon \int_\Omega \overline{u}_N^4\, dx + c_\varepsilon, \ \forall \varepsilon > 0, \end{aligned} \tag{5.62}$$

owing to (5.57) and Young's inequality. It thus follows from (5.60)-(5.62) that there exist constants $c > 0$ and $c' \geq 0$ such that

$$\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + c(\|\nabla u_N\|^2 + \|f_N(u_N)\|_{L^1(\Omega)} + \int_\Omega F_N(u_N)\,dx + \int_\Omega (\overline{u}_N^4 + \overline{u}_N^2\langle u_N\rangle^2)\,dx) \leq c'. \quad (5.63)$$

We now multiply (5.20) by $\frac{\partial \overline{u}_N}{\partial t}$ and obtain

$$\frac{1}{2}\frac{d}{dt}\|\nabla u_N\|^2 + \|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 + ((f_N(u_N), \frac{\partial \overline{u}_N}{\partial t})) = ((h(\sigma_N)u_N(\alpha - u_N), (-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t})). \quad (5.64)$$

We note that

$$\begin{aligned}((f_N(u_N), \frac{\partial \overline{u}_N}{\partial t})) &= \frac{d}{dt}\int_\Omega F_N(u_N)\,dx - \mathrm{Vol}(\Omega)\langle f_N(u_N)\rangle\langle\frac{\partial u_N}{\partial t}\rangle \\ &\geq \frac{d}{dt}\int_\Omega F_N(u_N)\,dx - c\|f_N(u_N)\|_{L^1(\Omega)}, \end{aligned} \quad (5.65)$$

owing to (5.58). Furthermore,

$$\begin{aligned}|((h(\sigma_N)u_N(\alpha - u_N), (-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t}))| &\leq c(\int_\Omega (u_N^4 + 1)\,dx)^{\frac{1}{2}}\|\frac{\partial \overline{u}_N}{\partial t}\|_{-1} \\ &\leq \frac{1}{2}\|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 + c\int_\Omega (\overline{u}_N^4 + \langle u_N\rangle^4 + 1)\,dx \\ &\leq \frac{1}{2}\|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 + c(\int_\Omega \overline{u}_N^4\,dx + 1). \end{aligned} \quad (5.66)$$

It thus follows from (5.64)-(5.66) that

$$\frac{d}{dt}(\|\nabla u_N\|^2 + 2\int_\Omega F_N(u_N)\,dx) + \|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 \leq c(\|f_N(u_N)\|_{L^1(\Omega)} + \int_\Omega \overline{u}_N^4\,dx + 1). \quad (5.67)$$

We sum the differential inequality

$$\frac{d}{dt}\|u_N\|^2 + \|\Delta u_N\|^2 \leq c$$

which holds here (see (5.28) and recall (5.57)), (5.63) and δ times (5.67), $\delta > 0$ small enough. This yields, taking ε small enough, that there exist constants $c > 0$ and $c' \geq 0$ such that we have a differential inequality of the form

$$\frac{dE_2}{dt} + c(E_2 + \|u_N\|_{H^2(\Omega)}^2 + \|f_N(u_N)\|_{L^1(\Omega)} + \|\frac{\partial u_N}{\partial t}\|_{H^{-1}(\Omega)}^2) \leq c',\ t \in [0, T_0], \quad (5.68)$$

where

$$E_2 = \|u_N\|^2 + \|\overline{u}_N\|_{-1}^2 + \delta(\|\nabla u_N\|^2 + 2\int_\Omega F_N(u_N)\,dx)$$

satisfies

$$E_2 \geq c\|u_N\|^2_{H^1(\Omega)} - c', \ c > 0.$$

Here we have also used the fact that

$$\langle u_N \rangle^2 \leq c, \ \langle \frac{\partial u_N}{\partial t} \rangle^2 \leq c, \ t \in [0, T_0].$$

Having this, we note that

$$\overline{f_N(u_N)} = -(-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t} + \Delta u_N + (-\Delta)^{-1}\overline{h(\sigma_N)u_N(\alpha - u_N)},$$

which yields

$$\|\overline{f_N(u_N)}\| \leq c(\|\frac{\partial u_N}{\partial t}\|_{H^{-1}(\Omega)} + \|u_N\|_{H^2(\Omega)} + 1). \tag{5.69}$$

Note indeed that

$$\begin{aligned}\|(-\Delta)^{-1}\overline{h(\sigma_N)u_N(\alpha - u_N)}\| &\leq c(\|u_N\|^2_{L^4(\Omega)} + \|u_N\|) \\ &\leq c(\|u_N\|^2_{H^1(\Omega)} + 1) \\ &\leq c(\|u_N\|\|u_N\|_{H^2(\Omega)} + 1) \\ &\leq c(\|u_N\|_{H^2(\Omega)} + 1).\end{aligned}$$

Combining (5.68) and (5.69) and also summing with (5.36) (which holds here), we find a differential inequality of the form

$$\frac{dE_3}{dt} + c(E_3 + \|u_N\|^2_{H^2(\Omega)} + \|\sigma_N\|^2_{H^1(\Omega)} + \|f_N(u_N)\|_{L^1(\Omega)} + \|\overline{f_N(u_N)}\|^2 \tag{5.70}$$

$$+\|\frac{\partial u_N}{\partial t}\|^2_{H^{-1}(\Omega)}) \leq c', \ t \in [0, T_0],$$

for proper constants $c > 0$ and $c' \geq 0$, where

$$E_3 = E_2 + \|\sigma_N\|^2$$

satisfies

$$E_3 \geq c(\|u_N\|^2_{H^1(\Omega)} + \|\sigma_N\|^2) - c', \ c > 0.$$

In particular, it follows from (5.70) that

$$\|\overline{f_N(u_N)}\|^2_{L^2(0,T_0;L^2(\Omega)} \leq c(E_3(0) + 1). \tag{5.71}$$

Next, employing once more (5.14), with $s = u_N$ and $m = \langle u_N \rangle$, we see that

$$\begin{aligned}|\langle f_N(u_N)\rangle| &\leq c|((f_N(u_N), \overline{u}_N))| + c' \\ &= c|((\overline{f_N(u_N)}, u_N))| + c' \\ &\leq c\|\overline{f_N(u_N)}\|\|u_N\| + c',\end{aligned}$$

so that

$$|\langle f_N(u_N)\rangle| \leq c\|\overline{f_N(u_N)}\|(E_3(0)+1)^{\frac{1}{2}} + c'$$

and

$$\|f_N(u_N)\|_{L^2(0,T_0;L^2(\Omega)} \leq c(E_3(0)+1). \tag{5.72}$$

The regularity stated in the theorem follows from (5.70) and (5.72). Furthermore, these estimates allow to pass to the limit and have a weak solution (u,σ) to (5.9)-(5.12) in a standard way (see [16, 96] for details) satisfying

$$0 < u(x,t) < \alpha \text{ for almost all } (x,t) \in \Omega \times (0,T_0).$$

Finally, since $u \geq 0$ a.e., we easily prove that

$$0 \leq \sigma(x,t) \leq \beta \text{ for almost all } (x,t) \in \Omega \times (0,T_0),$$

multiplying (5.10) by $-\sigma^-$ and $(\sigma-\beta)^+$, respectively, where

$$x = x^+ - x^-,\ x^+ = \max(x,0),\ x^- = -\min(0,x).$$

Indeed, multiplying (5.10) by $-\sigma^-$, we obtain

$$\frac{1}{2}\frac{d}{dt}\|\sigma^-\|^2 + \|\nabla\sigma^-\|^2 + \gamma\|\sigma^-\|^2 + \int_\Omega \frac{u|\sigma^-|^2}{1+|\sigma|}\,dx = -\gamma\beta\int_\Omega \sigma^-\,dx \leq 0,$$

so that

$$\frac{d}{dt}\|\sigma^-\|^2 \leq 0 \text{ and } \|\sigma^-(t)\|^2 \leq \|\sigma_0^-\|^2 \text{ for a.a. } t \in [0,T_0].$$

Note that, since $\sigma_0 \in [0,\beta]$ a.e., then $\sigma_0^- = 0$ a.e. and $\sigma^- = 0$ for almost all $(x,t) \in \Omega \times (0,T_0)$. Therefore, $\sigma \geq 0$ for almost all $(x,t) \in \Omega \times (0,T_0)$. We proceed in a similar way for the upper bound on σ. In particular, this yields that (u,σ) actually is a solution to the original problem (5.2)-(5.5).

□

We then have the following.

Theorem 5.4.2. *Under the assumptions of Theorem 5.4.1, the local in time weak solution (u,σ) is global in time.*

Proof.

Let $T^\star$ be the maximal existence time of a local in time solution given by Theorem 5.4.1 and assume that $T^\star < +\infty$.

Then, one has, immediately,

$$\|u(t)\| \leq \|\alpha\| = \mathrm{Vol}(\Omega)^{\frac{1}{2}}\alpha,\ t \in [0,T^\star), \tag{5.73}$$

meaning that the upper bound on $\|u\|$ is now independent of $T^\star$.

However, in order to extend the solution, we need to make sure that

$$\langle u(t)\rangle \in [\delta, \alpha - \delta],\ t \in [0, T^\star),$$

holds for some $\delta \in (0, \alpha)$ (having this, we can repeat all estimates in the proof of Theorem 5.4.1, for the limit solution, and see that they hold for $t \in [0, T^\star)$).

To do so, note that

$$\frac{d\langle u\rangle}{dt} = \langle h(\sigma)u(\alpha - u)\rangle,$$

which yields, since $u \in [0, \alpha]$ and $\sigma \in [0, \beta]$, as long as the solution exists,

$$0 \le \frac{d\langle u\rangle}{dt} \le h^\star \langle u(\alpha - u)\rangle.$$

Therefore,

$$0 \le \frac{d\langle u\rangle}{dt} + h^\star \alpha \langle u\rangle \le h^\star \langle -u^2 + 2\alpha u\rangle \le h^\star \alpha^2,$$

so that

$$\langle u_0\rangle e^{-h^\star \alpha t} \le \langle u(t)\rangle \le \langle u_0\rangle e^{-h^\star \alpha t} + \alpha(1 - e^{-h^\star \alpha t}). \tag{5.74}$$

It immediately follows from (5.74) that

$$\langle u(t)\rangle \in [\delta, \alpha - \delta],\ t \in [0, T^\star),$$

where $\delta \in (0, \alpha)$. Indeed, setting

$$\varphi(s) = \langle u_0\rangle e^{-h^\star \alpha s} + \alpha(1 - e^{-h^\star \alpha s}),$$

it is easy to see that φ takes values in such an interval, noting that φ is monotone increasing.

Having this, we can extend the solution by continuity, which finishes the proof.

□

Remark 5.4.1. *Further regularity, in particular the existence of a strong solution, and uniqueness are open problems. Actually, multiplying (5.3) by $-\Delta\sigma$, we obtain*

$$\frac{1}{2}\frac{d}{dt}\|\nabla\sigma\|^2 + \|\Delta\sigma\|^2 + \gamma\|\nabla\sigma\|^2 \le \int_\Omega |u||\Delta\sigma|\, dx,$$

which yields

$$\frac{d}{dt}\|\nabla\sigma\|^2 + \|\Delta\sigma\|^2 + \gamma\|\nabla\sigma\|^2 \le \|u\|^2.$$

We can thus have more regularity on σ. The difficulty is to derive additional regularity on u. Note that this is already an open problem for (5.2) with h constant.

5.5 Permanence of the solutions

We have the following.

Theorem 5.5.1. *We assume that* $\|u_0 - \alpha\| < \|\alpha\|$ *and* $\theta_0 \leq \lambda_1$*, where* λ_1 *is the first eigenvalue of the minus Laplace operator associated with Neumann boundary conditions and acting on functions with vanishing average. Then, for any solution to* (5.2)-(5.5) *as given in Theorem 5.4.2, there exists a constant* $c > 0$ *such that*

$$\|u(t)\| \geq c, \ t \geq 0,$$

meaning that there cannot be extinction of the tumor, even as time goes to $+\infty$*.*

Proof.

Set $v = u - \alpha$. Then, v solves

$$\frac{\partial v}{\partial t} + \Delta^2 v - \Delta f(u) = -h(\sigma)uv, \tag{5.75}$$

$$\frac{\partial v}{\partial \nu} = \frac{\partial \Delta v}{\partial \nu} = 0 \text{ on } \Gamma, \tag{5.76}$$

$$v|_{t=0} = v_0 := u_0 - \alpha. \tag{5.77}$$

Multiplying (5.75) by v, we obtain, owing to (5.6) and noting that $h(\sigma) \geq 0$ and $u \geq 0$,

$$\frac{1}{2}\frac{d}{dt}\|v\|^2 + \|\Delta v\|^2 \leq \theta_0 \|\nabla v\|^2.$$

Writing

$$\|\Delta v\|^2 = \|(-\Delta)\overline{v}\|^2 \geq \lambda_1 \|(-\Delta)^{\frac{1}{2}}\overline{v}\|^2 = \lambda_1 \|\nabla v\|^2,$$

we find

$$\frac{1}{2}\frac{d}{dt}\|v\|^2 + (\lambda_1 - \theta_0)\|\nabla v\|^2 \leq 0,$$

so that

$$\|v(t)\| \leq \|u_0 - \alpha\|, \ t \geq 0.$$

Finally,

$$\|u(t)\| \geq \|\alpha\| - \|v(t)\| \geq \|\alpha\| - \|u_0 - \alpha\| > 0, \ t \geq 0,$$

which finishes the proof.

□

Remark 5.5.1. *We can also take* $\theta_0 = 0$*, meaning that* f *is convex. In that case, one always has permanence of the solutions given by Theorem 5.4.2. Note that, when* h *is a positive constant, then one can also observe phase separation in that case (see [63]).*

Remark 5.5.2. *Let us consider the spatially homogeneous solutions $u = u(t)$, $\sigma = \sigma(t)$ to (5.2)-(5.5), i.e., the system of ODEs*

$$u' = h(\sigma)u(\alpha - u), \tag{5.78}$$

$$\sigma' + \gamma\sigma + \frac{u\sigma}{1+\sigma} = \gamma\beta, \tag{5.79}$$

$$u(0) = u_0 \in [0, \alpha],\ \sigma(0) = \sigma_0 \in [0, \beta]. \tag{5.80}$$

Then, when **(H3)** *holds, this system is a particular instance of the reaction-diffusion system considered in [16] and one has the global in time existence and uniqueness of biologically relevant solutions. Let us now take h as in (5.1) and assume that $u_0 \in (0, \alpha)$ (the cases $u_0 = 0$ and $u_0 = \alpha$ are straightforward). Then, h is no longer bounded and only locally Lipschitz continuous. However, the Cauchy–Lipschitz theorem yields the existence and uniqueness of the maximal solution (u, σ) on $[0, t^\star)$, $t^\star > 0$. Note that if, for $t \in [0, t^\star)$, $\sigma(t) = 0$, then it follows from (5.79) that*

$$\sigma'(t) = \gamma\beta > 0.$$

Therefore, σ cannot become negative and $\sigma(t) \geq 0$, $t \in [0, t^\star)$. Let now $0 < t_\star \leq t^\star$ be the maximal time such that $u(t) \in (0, \alpha)$, $t \in [0, t_\star)$. Then, for $t \in [0, t_\star)$,

$$\frac{u'}{u(\alpha - u)} = h(\sigma). \tag{5.81}$$

Note that h is monotone increasing and invertible, with

$$h^{-1}(s) = \frac{\beta}{1-b}\left(\frac{s}{a} - b\right).$$

Furthermore, for $t \in [0, t_\star)$,

$$\frac{u'}{u(\alpha - u)} = \varphi(t),\ h(\sigma) = \varphi(t),$$

for some continuous function φ, which yields

$$\frac{u(t)}{\alpha - u(t)} = \frac{u_0}{\alpha - u_0} e^{\alpha \int_0^t \varphi(s)\, ds},\ \sigma(t) = h^{-1}(\varphi(t)),\ t \in [0, t_\star). \tag{5.82}$$

Recall that $\sigma(t) \geq 0$, which is equivalent to

$$\varphi(t) \geq ab,\ t \in (0, t_\star). \tag{5.83}$$

Therefore, it follows from (5.82) that

$$\frac{u(t)}{\alpha - u(t)} \geq \frac{u_0}{\alpha - u_0} e^{\alpha abt},\ t \in [0, t_\star). \tag{5.84}$$

In particular, this yields that there is no blow up in finite time and that u remains in $(0,\alpha)$. Consequently, if, for some $t \in [0, t_\star)$, $\sigma(t) = \beta$, then it follows from (5.79) that

$$\sigma'(t) = -\frac{u(t)\beta}{1+\beta} < 0.$$

We thus conclude that $t_\star = t^\star = +\infty$ and that the solution is global in time, with $(u(t), \sigma(t)) \in (0,\alpha) \times [0,\beta]$, $t \in [0, +\infty)$. It is also interesting to note that it follows from (5.84) that

$$\lim_{t\to+\infty} u(t) = \alpha$$

and that this convergence is exponentially fast (this also holds, for h bounded, if $h(s) \geq h_\star > 0$, $s \geq 0$). This is in agreement with the results obtained in [16] and above, i.e., permanence of the tumor. However, here, we can be more precise, since the tumor reaches its maximal size exponentially fast.

5.6 Numerical simulations

As far as the numerical simulations are concerned, we slightly modify the equations, following [45], and consider the following system of equations :

$$\frac{\partial u}{\partial t} + \Delta(\mathrm{div}(D(\sigma)\nabla u)) - \Delta f(u) = \frac{1}{\alpha} h(\sigma) u(\alpha - u),$$

$$\frac{\partial \sigma}{\partial t} - D_0 \Delta \sigma + \frac{A_0 u \sigma}{k_0 + \alpha\sigma} = \gamma(\beta - \sigma),$$

where $D(\sigma) = 0.02(\frac{\sigma}{\beta} + 0.9(1 - \frac{\sigma}{\beta}))$ and $h(\sigma) = 2(\frac{\sigma}{\beta} + 0.6(1 - \frac{\sigma}{\beta}))$. Note in particular that, contrary to the analysis performed in the previous sections, the function h is no longer bounded. However, as mentioned in Remark 5.2.1, since the relevant solutions are expected to be bounded, this will not affect the simulations. We also consider, as in [45] for the reaction-diffusion model, a more general nonconstant diffusion coefficient D for the tumor growth and note that, since σ is expected to take values in $[0,\beta]$, D is bounded and positive. These modifications will allow us to compare some of our simulations with those in [45].

Then, we write the above system in the following equivalent way :

$$\begin{cases} \dfrac{\partial u}{\partial t} - \Delta w = \dfrac{1}{\alpha} h(\sigma) u(\alpha - u), \\ w = -\mathrm{div}(D(\sigma)\nabla u) + f(u), \\ \dfrac{\partial \sigma}{\partial t} - D_0 \Delta \sigma + \dfrac{A_0 u \sigma}{k_0 + \alpha\sigma} = \gamma(\beta - \sigma), \end{cases}$$

which has the advantage of splitting the fourth-order (in space) equation into a system of two second-order ones. This allows us to consider a P_1 finite element approach for the space discretization, together with an implicit but linearized Euler time discretization. More precisely, let $\mathcal{T}_h$ be the triangulation of $\bar{\Omega}$ and $V_h = \{v^h \in C^0(\bar{\Omega}),\ v^h_{|K} \in P_1,\ \forall K \in \mathcal{T}_h\}$. The discrete variational formulation reads :

Let $u_h^i,\ \sigma_h^i \in V_h$, for $i = 0, 1, ..., n$. Find $(u_h^{n+1}, w_h^{n+1}, \sigma_h^{n+1}) \in (V_h)^3$ such that

$$\begin{cases} \frac{1}{\delta t}((u_h^{n+1}, \phi)) + ((\nabla w_h^{n+1}, \nabla\phi)) - \frac{1}{\alpha}((h(\sigma_h^n)u_h^{n+1}(\alpha - u_h^{n+1}), \phi)) = \frac{1}{\delta t}((u_h^n, \phi)), \\ ((w_h^{n+1}, \varphi)) - ((D(\sigma_h^n)\nabla u_h^{n+1}, \nabla\varphi)) - ((f(u_h^{n+1}), \varphi)) = 0, \\ \frac{1}{\delta t}((\sigma_h^{n+1}, \zeta)) + D_0((\nabla\sigma_h^{n+1}, \nabla\zeta)) + ((\frac{A_0 u_h^{n+1}\sigma_h^{n+1}}{k_0 + \alpha\sigma_h^{n+1}}, \zeta)) = \gamma(((\beta - \sigma_h^{n+1}), \zeta)), \end{cases}$$

for all $\varphi,\ \phi,\ \zeta \in V_h$.

For simplicity and in order to reduce the computation times, the scheme is linearized, except for the computations in Figure 5.4, in the sense that each nonlinear implicit term $G(u_h^{n+1})$, where G is a nonlinear function, is approximated by :

$$G(u_h^{n+1}) \sim G(u_h^n) + (u_h^{n+1} - u_h^n)G'(u_h^n).$$

We make the following choices :

$$\Omega = (0, 2) \times (0, 1.5),\ \alpha = 2,\ \beta = 0.5,\ f(s) = -2(s - \frac{\alpha}{2}) + 0.25 \ln\frac{s}{\alpha - s},$$

$$D_0 = 0.01,\ A_0 = 5,\ k_0 = 1,\ \gamma = 1.3,\ \delta h = 0.02,$$

where δh is the meshsize.

5.6.1 The initial conditions are constants or small perturbations of constants

We first take constant (spatially homogeneous) initial conditions, namely, $u_0 \equiv 1.3$ and $\sigma_0 \equiv 0.25$. The stepsize δt is taken as 0.002. The solutions u and σ remain spatially homogeneous for every $t > 0$, as expected, and their behavior is given in Figure 5.3. The tumor concentration increases and tends to $\alpha = 2$, while the oxygen concentration σ decreases and tends to σ^*, solution to the equilibrium problem $\frac{A_0 u\sigma}{k_0+\alpha\sigma} = \gamma(\beta - \sigma)$. Our choices of parameters lead to σ^* approximately equal to 0.0639.

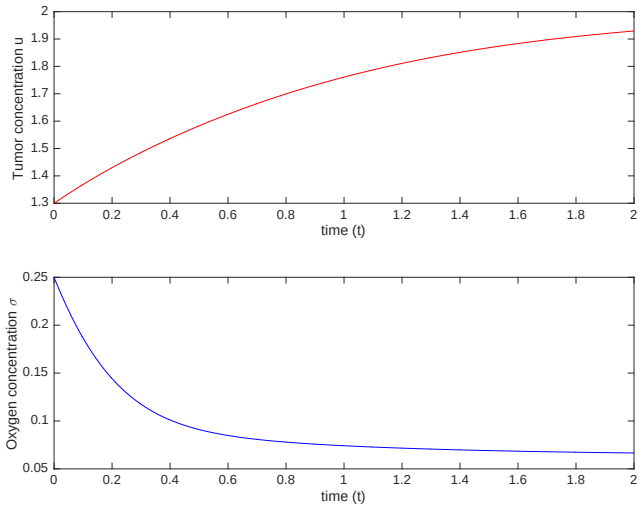

FIGURE 5.3 – Constant initial conditions : $u_0 \equiv 1.3$ and $\sigma_0 \equiv 0.25$.

Next, we take u_0 randomly distributed between 1.3 and 1.5 and σ_0 randomly distributed between 0.25 and 0.35. We use the non-linearized scheme in that case, since the minimal value of the tumor cells density comes very close to 0 and the linearized scheme is not satisfactory. The stepsize δt is taken as 0.0005. We can note that this is a rather small stepsize. Actually, one often takes a small stepsize in simulations for Cahn-Hilliard type models ; here and also below, since we do not have any information on the stability of our scheme (also note that the scheme should be at best of order one in time and we consider a P_1 finite element), we voluntarily took an even smaller one. The oxygen concentration still decreases, but the behavior of the tumor concentration changes drastically (see Figure 5.4). Note that we observe a phase separation here, similar to what is obtained with the original Cahn-Hilliard equation. As mentioned in the introduction, this cannot be observed with the reaction-diffusion model.

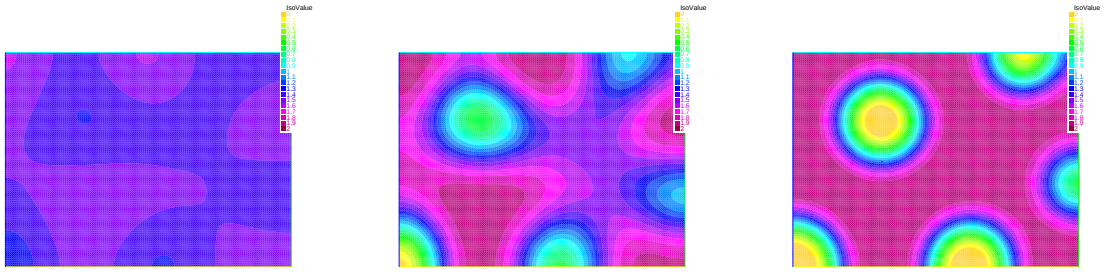

FIGURE 5.4 – Tumor concentration at $t = 0.15$ (left), $t = 0.25$ (middle) and $t = 0.35$ (right), u_0 = randomly distributed between 1.3 et 1.5 and σ_0 randomly distributed between 0.25 et 0.35.

5.6.2 Modeling of tumor growth and hypoxia

In our last test, we take $u_0 = 0.85\alpha e^{(-20((x-2)^2+y^2))} + 0.05$ and $\sigma_0 = \beta(1 - 0.9\frac{u_0}{\alpha})$, as displayed in Figure 5.5. The stepsize δt is taken as 0.0005.

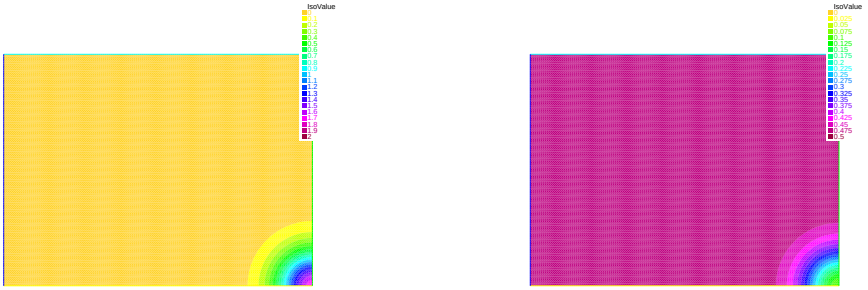

FIGURE 5.5 – Tumor at $t = 0$ (left), Oxygen at $t = 0$ (right).

The tumor and oxygen concentrations corresponding to $t = 0.15$ and 0.4 are displayed in Figures 5.6 and 5.7, respectively. We can note that the tumor spreads and proliferates, with the area under acute hypoxia increasing. The behavior of the tumor and the oxygen is consistent with what is observed in [45].

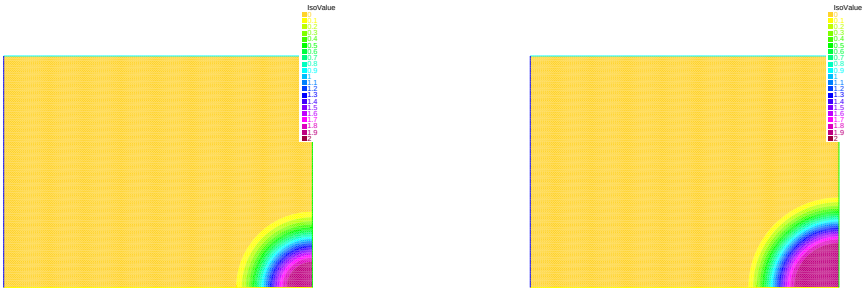

FIGURE 5.6 – Tumor at $t = 0.15$ (left) and at $t = 0.4$ (right).

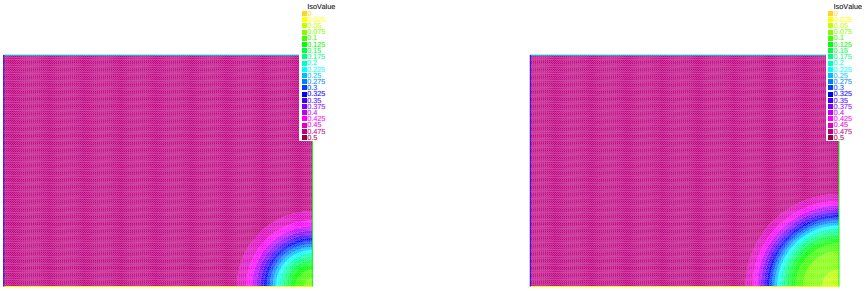

FIGURE 5.7 – Oxygen at $t = 0.15$ (left) and at $t = 0.4$ (right).

Chapitre 6

On a coupled Cahn-Hilliard/Cahn-Hilliard model for the proliferative-to-invasive transition of hypoxic glioma cells

Sur un modèle couplé de Cahn-Hilliard/Cahn-Hilliard pour la transition proliférative à invasive des cellules de gliome hypoxique

On a coupled Cahn–Hilliard/Cahn–Hilliard model for the proliferative-to-invasive transition of hypoxic glioma cells

6.1 Introduction

Glioma is a common malignant primary brain tumor, which is used to describe cancerous tumors that stem from glial cells. In particular, compared with low-grade glioma, high-grade glioma is characterized by high-rate proliferation and diffuse invasion. Based on the Fisher-Kolmogorov theory, H. Gomes extended the classical proliferation-invasion mathematical model by introducing an equation that governs the oxygen dynamics (see [45]). Since hypoxia is a hallmark of gliomas and low oxygen concentration triggers a proliferative-to-invasive transition, this model accounts for the dependence on the proliferation rate and the diffusion coefficient of tumor cells on oxygen concentration. The model reads

$$\frac{\partial u}{\partial t} - \Delta u = h(\sigma)u(\alpha - u),$$

$$\frac{\partial \sigma}{\partial t} - \Delta \sigma + \frac{u\sigma}{1+\sigma} = \gamma(\beta - \sigma),$$

where u is the tumor cell density, σ is the oxygen concentration and h is proliferation rate defined as

$$h(s) = a[\frac{s}{\beta} + b(1 - \frac{s}{\beta})].$$

The term $h(\sigma)u(\alpha-u)$ in the first equation represents the so-called logistic growth which assumes that tumor cells proliferate until they reach the cell density α. The constant α is known as carrying capacity, β represents the oxygen concentration in blood vessels, γ, a, b are positive biological parameters and $b \sim 0.6 < 1$ (here, we have set several other biological parameters equal to one and refer to [45] for more details). Furthermore, the term $\Delta\sigma$ in the second equation accounts for the isotropic diffusion of oxygen, the nonlinear term $\frac{u\sigma}{1+\sigma}$ accounts for the oxygen uptake by tumor cells, assuming a Michaelis-Menten kinetics, and the term $\gamma(\beta - \sigma)$ considers that oxygen is released from blood vessels at a linear rate.

Note that, we will actually take h bounded, as in [16] (see also [98]). The model accounts for the tumor and oxygen dynamics and assume that the rate of change of tumor cells density is given by the net migration of the tumor cells plus the proliferation of the cancerous cells.

The model above is modeled by standard reaction-diffusion equations. In this paper, we consider instead Cahn-Hilliard type equations for both the tumor density and the

oxygen concentration, i.e.

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f_1(u) = h(\sigma)u(\alpha - u),$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2 \sigma - \Delta f_2(\sigma) + \frac{u\sigma}{1+\sigma} + \gamma\sigma = \gamma\beta.$$

In view of the term $\gamma\sigma$, $\gamma > 0$ in the second equation, we actually have a Cahn-Hilliard-Oono type equation. The Cahn-Hilliard-Oono equation was proposed in [105] to also account for long-ranged effects.

The original Cahn-Hilliard equation,

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

was initially proposed to model phase separation processes in binary alloys (see [11, 12]). Since then, this equation, or some of its variants, were successfully applied to many other applications than just phase separation in alloys. We refer the interested reader to [96, 103] for reviews on the Cahn-Hilliard equation and some of its variants, as well as their mathematical analysis.

In particular, Cahn-Hilliard type models in the context of tumor growth and energy metabolism in the brain can be found in, e.g., [6, 28, 39, 40, 63, 73, 89, 98]. For the study of the model for proliferative-to-invasive transition of hypoxic glioma cells, actually, there are two special cases have already been addressed. In [72], we consider the equations that consist of the coupling of a reaction-diffusion equation for the tumor density and a Cahn-Hilliard type equation for the oxygen concentration. For the Cahn-Hilliard type equation one accounts for the phase separation process (e.g. different zones in the cells in which, typically, the concentration of oxygen may be high or very low). In this case, we have proved the existence of weak solutions. In [70], we take into account the equations that consist of the coupling of a Cahn-Hilliard type equation for the tumor density and of a reaction-diffusion equation for the oxygen concentration. For the Cahn-Hilliard type equation one accounts for phase separation processes (e.g. different zones in the tumor) and clustering effects in tumor growth. In this case, we have proved the existence of weak solutions, studied permanence of the tumor and given some numerical simulations.

In this paper, we consider two Cahn-Hilliard type equations in the model for the proliferative-to-invasive transition of hypoxic glioma cells. Our aim is to prove the existence of a local in time biologically relevant solution, which means we need to ensure the solution won't blow up or go to negative. Note that the nonlinear term $h(\sigma)u(\alpha - u)$ is one of the challenges to conquer. For a constant h, blow up could occur in finite time when we consider a cubic nonlinear term f (see [28]). To avoid this, we consider a logarithmic nonlinear term f_1 (see [89]) for the first equation. Another challenge is to

prove the order parameter σ remains nonnegative. This is due to the fact that we no longer have the maximum principle/comparison principle for Cahn-Hilliard type equations. Also note that the term $\frac{u\sigma}{1+\sigma}$ can become singular when σ is negative. To overcome this, we also consider a logarithmic nonlinear term f_2 for the second equation. Actually, as far as the original Cahn-Hilliard equation is concerned, the logarithmic nonlinear term is the one which is thermodynamically relevant; it is thus natural to also consider these nonlinear terms in our model. In addition, we consider a modified problem to avoid the second nonlinear term $\frac{u\sigma}{1+\sigma}$ to become singular. Otherwise, we prove the existence of a local in time biologically relevant solution which is conditionally global in time.

6.2 Setting of the problem

We consider the following initial and boundary value problem, in a bounded and regular domain $\Omega \subset \mathbb{R}^n$, $n = 1$, 2 or 3, with boundary Γ :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f_1(u) = h(\sigma)u(\alpha - u), \tag{6.1}$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2 \sigma - \Delta f_2(\sigma) + \frac{u\sigma}{1+\sigma} + \gamma\sigma = \gamma\beta, \tag{6.2}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = \frac{\partial \Delta \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{6.3}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{6.4}$$

Here, α, β and γ are positive (biological) parameters and $h : \mathbb{R} \to \mathbb{R}$ is a bounded and globally Lipschitz continuous function such that

$$h(s) \geq 0,\ s \geq 0.$$

Furthermore, the nonlinear terms f_1 and f_2 are of logarithmic type, precisely

$$f_1(s) = -\theta_0(s - \frac{\alpha}{2}) + \theta_1 \ln \frac{s}{\alpha - s},\ s \in (0, \alpha),\ 0 < \theta_1 < \frac{\alpha\theta_0}{4},$$
$$f_2(s) = -\kappa_0(s - \frac{\beta}{2}) + \kappa_1 \ln \frac{s}{\beta - s},\ s \in (0, \beta),\ 0 < \kappa_1 < \frac{\beta\kappa_0}{4},$$

where the conditions $0 < \theta_1 < \frac{\alpha\theta_0}{4}$ and $0 < \kappa_1 < \frac{\beta\kappa_0}{4}$ are made to ensure that we indeed have the double-well forms for the corresponding potentials and that phase separation can occur when considering the original Cahn-Hilliard equation.

Note that

$$f_1' \geq -\theta_0, \tag{6.5}$$
$$f_2' \geq -\kappa_0 \tag{6.6}$$

respectively. Furthermore, there hold, for $s, m \in (0, \alpha)$,

$$f_1(s)(s-m) \geq c_{1m}(|f_1(s)| + F_1(s)) - c'_{1m},\ c_{1m} > 0,\ c'_{1m} \geq 0, \tag{6.7}$$

while for $s, m \in (0, \beta)$,

$$f_2(s)(s-m) \geq c_{2m}(|f_2(s)| + F_2(s)) - c'_{2m},\ c_{2m} > 0,\ c'_{2m} \geq 0, \tag{6.8}$$

where c_{1m}, c'_{1m}, c_{2m} and c'_{2m} depend continuously on m (see [96]) and

$$F_1(s) = \int_{\frac{\alpha}{2}}^{s} f_1(\xi)\, d\xi, \quad F_2(s) = \int_{\frac{\beta}{2}}^{s} f_2(\xi)\, d\xi.$$

Remark 6.2.1. *The original Cahn-Hilliard equation is often associated with a cubic nonlinear term, typically, $f(s) = s^3 - s$. However, in that case, the order parameter may not remain in the relevant interval. In particular, it can become negative. In our case, u could blow up in finite time, and the nonlinear term $\frac{u\sigma}{1+\sigma}$ may become singular when σ becomes negative. In fact, as we will see below, these problems can be avoided by taking logarithmic nonlinear terms.*

We consider the following auxiliary problem :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f_1(u) = h(\sigma)u(\alpha - u), \tag{6.9}$$

$$\frac{\partial \sigma}{\partial t} + \Delta^2 \sigma - \Delta f_2(\sigma) + \frac{u\sigma}{1+|\sigma|} + \gamma\sigma = \gamma\beta, \tag{6.10}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = \frac{\partial \Delta \sigma}{\partial \nu} = 0 \text{ on } \Gamma, \tag{6.11}$$

$$u|_{t=0} = u_0,\ \sigma|_{t=0} = \sigma_0. \tag{6.12}$$

Next, we approximate the singular function f_1 by the following approximated functions of class C^4 and C^3 defined on the whole real line :

$$F_{1,N} = -\frac{\theta_0}{2}(s - \frac{\alpha}{2})^2 + F_{11,N}(s),$$
$$f_{1,N} = F'_{1,N} = -\theta_0(s - \frac{\alpha}{2}) + f_{11,N}(s),$$

where $F_{1,N}(s) = \int_{\frac{\beta}{2}}^{s} f_{1,N}(\xi)\, d\xi$ and $f_{11,N} = F'_{11,N}$ is the approximated function of $f_{11} = \theta_1 \ln \frac{s}{\alpha - s}$. We have

$$F^{(4)}_{11,N}(s) = \begin{cases} F^{(4)}_{11}(\alpha - \frac{1}{N}),\ s > \alpha - \frac{1}{N}, \\ F^{(4)}_{11}(s),\ s \in [\frac{1}{N}, \alpha - \frac{1}{N}], \\ F^{(4)}_{11}(\frac{1}{N}),\ s < \frac{1}{N}, \end{cases}$$
$$F^{(k)}_{11,N}(\frac{\alpha}{2}) = F^{(k)}_{11}(\frac{\alpha}{2}),\ k = 0, ..., 3.$$

This yields that

$$F_{11,N}(s) = \begin{cases} \Sigma_{k=0}^{4} \frac{1}{k!} F_{11}^{(k)}(\alpha - \frac{1}{N})(s - \alpha + \frac{1}{N})^k, \ s > \alpha - \frac{1}{N}, \\ F_{11}(s), \ s \in [\frac{1}{N}, \alpha - \frac{1}{N}], \\ \Sigma_{k=0}^{4} \frac{1}{k!} F_{11}^{(k)}(\frac{1}{N})(s - \frac{1}{N})^k, \ s < \frac{1}{N}, \end{cases}$$

and

$$f_{11,N}(s) = \begin{cases} \Sigma_{k=0}^{3} \frac{1}{k!} f_{11}^{(k)}(\alpha - \frac{1}{N})(s - \alpha + \frac{1}{N})^k, \ s > \alpha - \frac{1}{N}, \\ f_{11}(s), \ s \in [\frac{1}{N}, \alpha - \frac{1}{N}], \\ \Sigma_{k=0}^{3} \frac{1}{k!} f_{11}^{(k)}(\frac{1}{N})(s - \frac{1}{N})^k, \ s < \frac{1}{N}. \end{cases}$$

Note in particular that $f_{11,N}$ has a cubic growth at infinity. And for N large enough, these approximated functions satisfy

$$f'_{1,N} \geq -\theta_0, \tag{6.13}$$

$$f_{1,N}(s)(s-m) \geq c_1(|f_{1,N}(s)| + F_{1,N}(s)) - c'_1, \ s \in \mathbb{R}, \ m \in (0, \alpha), \tag{6.14}$$

where $c_1 > 0$ and $c'_1 \geq 0$ depend continuously on m, and

$$(f_{1,N}(s)(s+m) - f_{1,N}(m))s \geq c_2(s^4 + m^2 s^2) - c'_2, s, m \in \mathbb{R}, \tag{6.15}$$

where $c_2 > 0$ and $c'_2 \geq 0$ are independent of s and m. Moreover, all constants are independent of N. We refer the reader to [96] for the proof.

The singular function f_2 can be approximated in a similar way by the following C^1-functions defined on the real line, $N \in \mathbb{N}$:

$$f_{2,N}(s) = \begin{cases} f_2(\beta - \frac{1}{N}) + f'_2(\beta - \frac{1}{N})(s - \beta + \frac{1}{N}), \ s > \beta - \frac{1}{N}, \\ f_2(s), \ s \in [\frac{1}{N}, \beta - \frac{1}{N}], \\ f_2(\frac{1}{N}) + f'_2(\frac{1}{N})(s - \frac{1}{N}), \ s < \frac{1}{N}. \end{cases}$$

Note that, for every $N \in \mathbb{N}$,

$$f'_{2,N} \geq -\kappa_0 \tag{6.16}$$

and for N large enough,

$$f_{2,N}(s)(s-m) \geq c_3(|f_{2,N}(s)| + F_{2,N}(s)) - c'_3, \ s \in \mathbb{R}, m \in (0, \beta), \tag{6.17}$$

where $F_{2,N}(s) = \int_{\frac{\beta}{2}}^{s} f_{2,N}(\xi)\, d\xi$, $c_3 > 0$ and $c'_3 \geq 0$ depend continuously on m and are independent of N (see [96]).

We then consider the following approximated problems, for $N \in \mathbb{N}$:

$$\frac{\partial u_N}{\partial t} + \Delta^2 u_N - \Delta f_{1,N}(u_N) = h(\sigma_N) u_N(\alpha - u_N), \tag{6.18}$$

$$\frac{\partial \sigma_N}{\partial t} + \Delta^2 \sigma_N - \Delta f_{2,N}(\sigma_N) + \frac{u_N \sigma_N}{1 + |\sigma_N|} + \gamma \sigma_N = \gamma \beta, \tag{6.19}$$

$$\frac{\partial u_N}{\partial \nu} = \frac{\partial \Delta u_N}{\partial \nu} = \frac{\partial \sigma_N}{\partial \nu} = \frac{\partial \Delta \sigma_N}{\partial \nu} = 0 \text{ on } \Gamma, \tag{6.20}$$

$$u_N|_{t=0} = u_0,\ \sigma_N|_{t=0} = \sigma_0. \tag{6.21}$$

Note that, for a given $N \in \mathbb{N}$, we can prove, via a standard Galerkin scheme, the local in time existence (as well as the uniqueness) of a solution (u_N, σ_N), on some interval $[0, T_N)$, $T_N > 0$ (see also the estimates in the next section below). Note indeed that $s \mapsto \frac{s}{1+|s|}$ is globally Lipschitz continuous on $\mathbb{R}$, with derivative $s \mapsto \frac{1}{(1+|s|)^2}$.

We set, for $v \in L^1(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \int_\Omega v \, dx$$

and, for $v \in H^{-1}(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \langle v, 1 \rangle_{H^{-1}(\Omega), H^1(\Omega)}.$$

We finally set, whenever it makes sense,

$$\overline{v} = v - \langle v \rangle.$$

We denote by $((\cdot, \cdot))$ the usual L^2-scalar product, with associated norm $\| \cdot \|$. We also set $\| \cdot \|_{-1} = \| (-\Delta)^{-\frac{1}{2}} \cdot \|$, where $(-\Delta)^{-1}$ denotes the inverse of the minus Laplace operator associated with Neumann boundary conditions and acting on functions with null spatial average. More generally, we denote by $\| \cdot \|_X$ the norm on the Banach space X.

We note that

$$v \mapsto (\|\overline{v}\|_{-1}^2 + \langle v \rangle^2)^{\frac{1}{2}},\ v \mapsto (\|\overline{v}\|^2 + \langle v \rangle^2)^{\frac{1}{2}},$$
$$v \mapsto (\|\nabla v\|^2 + \langle v \rangle^2)^{\frac{1}{2}},\ v \mapsto (\|\Delta v\|^2 + \langle v \rangle^2)^{\frac{1}{2}}$$

are norms on $H^{-1}(\Omega)$, $L^2(\Omega)$, $H^1(\Omega)$ and $H^2(\Omega)$, respectively, which are equivalent to the usual norms on these spaces. Furthermore, $\| \cdot \|_{-1}$ is a norm on $\{v \in H^{-1}(\Omega),\ \langle v \rangle = 0\}$ which is equivalent to the usual H^{-1}-norm.

Throughout this paper, the same letters c and c' denote (generally positive) constants which may vary from line to line, or even in a same line.

6.3 Existence of a local weak solution

Theorem 6.3.1. *We assume that* $(u_0, \sigma_0) \in H^1(\Omega) \times H^1(\Omega)$, *and* $u_0 \in (0, \alpha)$, $\sigma_0 \in (0, \beta)$ *a.e. Then* (6.1)-(6.4) *possesses at least one local in time weak solution* (u, σ) *defined on*

$[0, T_0]$, *for some* $T_0 > 0$, *such that*

$$u \in L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)), \ \frac{\partial u}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)),$$
$$\sigma \in L^\infty(0, T_0; H^1(\Omega)) \cap L^2(0, T_0; H^2(\Omega)), \ \frac{\partial \sigma}{\partial t} \in L^2(0, T_0; H^{-1}(\Omega)).$$

Furthermore,

$$0 < u < \alpha, \ 0 < \sigma < \beta \text{ for almost all } (x, t) \in \Omega \times [0, T_0].$$

Proof. The proof of existence can be carried out via a standard Galerkin method and appropriate priori estimates. In what follows, we only give formal estimates. Furthermore, all constants below are independent of the approximation parameter N.

We first multiply (6.18) by u_N and have, integrating over Ω and by parts

$$\frac{1}{2}\frac{d}{dt}\|u_N\|^2 + \|\Delta u_N\|^2 + ((f'_{1,N}(u_N)\nabla u_N, \nabla u_N)) = \int_\Omega h(\sigma_N)u_N^2(\alpha - u_N)dx. \tag{6.22}$$

Note that it follows from (6.13) that

$$((f'_{1,N}(u_N)\nabla u_N, \nabla u_N)) \geq -\theta_0\|\nabla u_N\|^2 \geq -\frac{1}{4}\|\Delta u_N\|^2 - c\|u_N\|^2, \tag{6.23}$$

since proper interpolation and standard elliptic regularity results that

$$\|\nabla u_N\|^2 \leq c\|u_N\|\|u_N\|_{H^2(\Omega)} \leq c\|u_N\|(\|\Delta u_N\| + \|u_N\|).$$

Furthermore, since h is bounded, we have

$$\begin{aligned} |\int_\Omega h(\sigma_N)u_N^2(\alpha - u_N)dx| &\leq c(\|u_N\|^2 + \|u_N\|^3_{L^3(\Omega)}) \\ &\leq c(\|u_N\|^2 + \|u_N\|^3_{H^1(\Omega)}) \\ &\leq c(\|u_N\|^2 + \|u_N\|^{\frac{3}{2}}\|u_N\|^{\frac{3}{2}}_{H^2(\Omega)}) \\ &\leq c(1 + \|u_N\|^6) + \frac{1}{4}\|\Delta u_N\|^2, \end{aligned} \tag{6.24}$$

owing to the continuous embedding $H^1(\Omega) \subset L^3(\Omega)$, interpolation inequality and young's inequality. It follows from (6.22)-(6.24) that

$$\frac{d}{dt}\|u_N\|^2 + \|\Delta u_N\|^2 \leq c(1 + \|u_N\|^6). \tag{6.25}$$

In particular,

$$\frac{d}{dt}\|u_N\|^2 + \leq c(1 + \|u_N\|^6). \tag{6.26}$$

We deduce from (6.26) and the comparison principle that there exists $T_1 > 0$, which is independent of N, such that

$$\|u_N(t)\|^2 \leq c, \ t \in [0, T_1]. \tag{6.27}$$

We assume from now on that $t \in [0, T_1]$.

Now we rewrite the problem in the following equivalent weak form :

$$(-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t} - \Delta \overline{u}_N + \overline{f_{1,N}(u_N)} = (-\Delta)^{-1}\overline{h(\sigma_N)u_N(\alpha - u_N)}, \tag{6.28}$$

$$(-\Delta)^{-1}\frac{\partial \overline{\sigma}_N}{\partial t} - \Delta \overline{\sigma}_N + \overline{f_{2,N}(\sigma_N)} + (-\Delta)^{-1}\frac{\overline{u_N\sigma_N}}{1+|\sigma_N|} + \gamma(-\Delta)^{-1}\overline{\sigma}_N = 0, \tag{6.29}$$

$$\frac{d\langle u_N\rangle}{dt} = \langle h(\sigma_N)u_N(\alpha - u_N)\rangle, \tag{6.30}$$

$$\frac{d\langle \sigma_N\rangle}{dt} + \langle \frac{u_N\sigma_N}{1+|\sigma_N|}\rangle = \gamma\beta, \tag{6.31}$$

$$\frac{\partial u_N}{\partial \nu} = \frac{\partial \sigma_N}{\partial \nu} = 0 \text{ on } \Gamma, \tag{6.32}$$

$$u_N|_{t=0} = u_0, \ \sigma_N|_{t=0} = \sigma_0, \tag{6.33}$$

where $u_N = \overline{u}_N + \langle u_N\rangle$ and $\sigma_N = \overline{\sigma}_N + \langle \sigma_N\rangle$.

We assume that there exist $\delta_1 \in (0, \frac{\alpha}{2})$ and $\delta_2 \in (0, \frac{\beta}{2})$ such that

$$2\delta_1 \leq \langle u_0\rangle \leq \alpha - 2\delta_1, \tag{6.34}$$

$$2\delta_2 \leq \langle \sigma_0\rangle \leq \beta - 2\delta_2. \tag{6.35}$$

Then, we recall (6.27) and it follows from (6.30) that

$$|\frac{d\langle u_N\rangle}{dt}| \leq |\langle h(\sigma_N)u_N(\alpha - u_N)\rangle| \leq c(1 + \|u_N\|^2) \leq c. \tag{6.36}$$

We can deduce that, for $t \in [0, T_1]$

$$\delta_1 \leq \langle u_N(t)\rangle \leq \alpha - \delta_1, \ t \in [0, T_1]. \tag{6.37}$$

Similarly, it follows from (6.31) that

$$\langle \sigma_N(t)\rangle = e^{-\gamma t}\langle \sigma_0\rangle + e^{-\gamma t}\int_0^t e^{\gamma t}(\gamma\beta - \langle \frac{u_N\sigma_N}{1+|\sigma_N|}\rangle)ds,$$

owing to (6.27) again,

$$|e^{-\gamma t}\int_0^t e^{\gamma t}(\gamma\beta - \langle \frac{u_N\sigma_N}{1+|\sigma_N|}\rangle)ds| \leq e^{-\gamma t}\int_0^t e^{\gamma t}(\gamma\beta + c_2)ds \leq (\beta + \frac{c_2}{\gamma})(1 - e^{-\gamma t}),$$

where c_2 is independent of N. We thus deduce that

$$e^{-\gamma t}\langle\sigma_0\rangle - c_3(1-e^{-\gamma t}) \le \langle\sigma_N(t)\rangle \le e^{-\gamma t}\langle\sigma_0\rangle + c_3(1-e^{-\gamma t}),\ t\in[0,T_1], \tag{6.38}$$

where c_3 is independent of N. It follows from (6.35) and (6.38) that there exists $0 < T_2 \le T_1$, which is independent of N (but depending on δ_2), such that

$$\delta_2 \le \langle\sigma_N(t)\rangle \le \beta - \delta_2,\ t\in[0,T_2]. \tag{6.39}$$

We assume from now on that $t\in[0,T_2]$.

We multiply (6.28) by $\overline{u}_N$ and have

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + \|\nabla u\|^2 + ((f_{1,N}(u_N),\overline{u}_N)) = ((h(\sigma_N)u_N(\alpha-u_N),(-\Delta)^{-1}\overline{u}_N)).$$

We write

$$((f_{1,N}(u_N),\overline{u}_N)) = \frac{1}{2}((f_{1,N}(u_N),\overline{u}_N)) + \frac{1}{2}((f_{1,N}(u_N)-f_1(\langle u_N\rangle),\overline{u}_N)),$$

so that, employing (6.14) (with $s=u_N$ and $m=\langle u_N\rangle$, also recall (6.37)) and (6.15) (with $s=\overline{u}_N$ and $m=\langle u_N\rangle$), we have

$$((f_{1,N}(u_N),\overline{u}_N)) \ge c(\|f_{1,N}(u_N)\|_{L^1(\Omega)} + \int_\Omega F_{1,N}(u_N)dx + \int_\Omega(\overline{u}_N^4 + \overline{u}_N^2\langle u_N\rangle^2)dx) - c',\ c>0.$$

Furthermore,

$$\begin{aligned}
|((h(\sigma_N)u_N(\alpha-u_N),(-\Delta)^{-1}\overline{u}_N))| &\le c(\int_\Omega(u_N^4+1)dx)^{\frac{1}{2}}\|\overline{u}_N\|_{-1}\\
&\le c(\int_\Omega(\overline{u}_N^4+\langle u_N\rangle^4+1)dx)^{\frac{1}{2}}\|u_N\|\\
&\le \varepsilon\int_\Omega\overline{u}_N^4dx + c_\varepsilon(1+\|u_N\|^2)\\
&\le \varepsilon\int_\Omega\overline{u}_N^4dx + c_\varepsilon,\ \forall\varepsilon>0,
\end{aligned}$$

since (6.27) and Young's inequality. It thus deduces from above that

$$\begin{aligned}
&\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + c(\|\nabla u\|^2 + \|f_{1,N}(u_N)\|_{L^1(\Omega)} + \int_\Omega F_{1,N}(u_N)dx\\
&+ \int_\Omega(\overline{u}_N^4 + \overline{u}_N^2\langle u_N\rangle^2)dx) \le c', c>0.
\end{aligned} \tag{6.40}$$

We now multiply (6.28) by $\frac{\partial \overline{u}_N}{\partial t}$ and obtain

$$\frac{1}{2}\frac{d}{dt}\|\nabla u_N\|^2 + \|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 + ((f_{1,N}(u_N), \frac{\partial \overline{u}_N}{\partial t})) = ((h(\sigma_N)u_N(\alpha - u_N), (-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t})). \quad (6.41)$$

Note that

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

owing to (6.36). Furthermore,

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

It thus follows from above that

$$\begin{aligned}&\frac{d}{dt}(\|\nabla u_N\|^2 + 2\int_\Omega F_{1,N}(u_N)dx) + \|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 \\ &\leq c(\|f_{1,N}(u_N)\|_{L^1(\Omega)} + \int_\Omega \overline{u}_N^4 dx + 1).\end{aligned} \quad (6.42)$$

Summing (6.25), (6.40) and (6.42) times η_1, η_1 small enough, we have, taking ε small enough, a differential inequality of the form

$$\frac{dE_1}{dt} + c(E_1 + \|u_N\|_{H^2(\Omega)}^2 + \|f_{1,N}(u_N)\|_{L^1(\Omega)} + \|\frac{\partial u_N}{\partial t}\|_{-1}^2) \leq c', \quad (6.43)$$

where $c > 0, t \in [0, T_1]$ and

$$E_1 = \|u_N\|^2 + \|\overline{u}_N\|_{-1}^2 + \eta_1(\|\nabla u_N\|^2 + 2\int_\Omega F_{1,N}(u_N)dx)$$

satisfies

$$E_1 \geq c\|u_N\|_{H^1(\Omega)}^2 - c',\ c > 0.$$

Here we have also used the fact that

$$\langle u_N\rangle^2 \leq c,\ \langle\frac{\partial u_N}{\partial t}\rangle^2 \leq c,\ t \in [0, T_1].$$

Having this, we note that

$$\overline{f_{1,N}(u_N)} = -(-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t} + \Delta u_N + (-\Delta)^{-1}\overline{h(\sigma_N)u_N(\alpha - u_N)},$$

which yields

$$\|\overline{f_{1,N}(u_N)}\| \leq c(\|\frac{\partial u_N}{\partial t}\|_{-1}^2 + \|u_N\|_{H^2(\Omega)}^2 + 1). \tag{6.44}$$

Note indeed that

$$\begin{aligned}\|(-\Delta)^{-1}\overline{h(\sigma_N)u_N(\alpha - u_N)}\| &\leq c(\|u_N\|_{L^4(\Omega)}^2 + \|u_N\|)\\ &\leq c(\|u_N\|_{H^1(\Omega)}^2 + 1)\\ &\leq c(\|u_N\|\|u_N\|_{H^2(\Omega)} + 1)\\ &\leq c(\|u_N\|_{H^2(\Omega)} + 1).\end{aligned}$$

Combining (6.43) and (6.44), we obtain a differential inequality of the form

$$\frac{dE_1}{dt} + c(E_1 + \|u_N\|_{H^2(\Omega)}^2 + \|f_{1,N}(u_N)\|_{L^1(\Omega)} + \|\overline{f_{1,N}(u_N)}\|^2 + \|\frac{\partial u_N}{\partial t}\|_{-1}^2) \leq c'. \tag{6.45}$$

It follows from (6.45) that

$$\|\overline{f_{1,N}(u_N)}\|_{L^2(0,T_1;L^2(\Omega))}^2 \leq c(E_1(0) + 1),$$

using (6.14) again, with $s = u_N$ and $m = \langle u_N \rangle$, we have

$$\begin{aligned}|\langle f_{1,N}(u_N)\rangle| &\leq c|((f_{1,N}(u_N), \overline{u}_N))| + c'\\ &= c|((\overline{f_{1,N}(u_N)}, u_N))| + c'\\ &\leq c\|\overline{f_{1,N}(u_N)}\|\|u_N\| + c'\\ &\leq c\|\overline{f_{1,N}(u_N)}\|(E_1(0) + 1)^{\frac{1}{2}} + c',\end{aligned}$$

so that

$$\|f_{1,N}(u_N)\|_{L^2(0,T_1;L^2(\Omega))}^2 \leq c(E_1(0) + 1). \tag{6.46}$$

These estimates allow to pass to the limit of (6.28) to have a weak solution.

We next multiply (6.29) by $\overline{\sigma_N}$ and obtain

$$\frac{1}{2}\frac{d}{dt}\|\overline{\sigma}_N\|_{-1}^2 + \|\nabla\sigma_N\|^2 + \gamma\|\overline{\sigma}_N\|_{-1}^2 + ((f_{2,N}(\sigma_N), \overline{\sigma}_N)) + (((-\Delta)^{-1}\frac{\overline{u_N\sigma_N}}{1 + |\sigma_N|}, \overline{\sigma}_N)) = 0.$$

Note that, owing to (6.17) and (6.35) and for N large enough,

$$((f_{2,N}(\sigma_N), \overline{\sigma}_N)) \geq c(\|f_{2,N}(\sigma_N)\|_{L^1(\Omega)} + \int_\Omega F_{2,N}(\sigma_N)dx) - c',\ c > 0,$$

where c and c' depend on δ. Furthermore, owing to (6.27),

$$\begin{aligned}|((-\Delta)^{-1}\frac{\overline{u_N\sigma_N}}{1+|\sigma_N|},\overline{\sigma}_N))| &= |((\frac{u_N\sigma_N}{1+|\sigma_N|},(-\Delta)^{-1}\overline{\sigma}_N))|\\ &\le c\|u_N\|\|\overline{\sigma}_N\|_{-1}\\ &\le \gamma\|\overline{\sigma}_N\|_{-1}^2 + c\|u_N\|^2\\ &\le \gamma\|\overline{\sigma}_N\|_{-1}^2 + c.\end{aligned}$$

We thus deduce from the above that

$$\frac{d}{dt}\|\overline{\sigma}_N\|_{-1}^2 + c(\|\nabla\sigma_N\|^2 + \|f_{2,N}(\sigma_N)\|_{L^1(\Omega)} + \int_\Omega F_{2,N}(\sigma_N)dx) \le c',\ c>0. \tag{6.47}$$

We then multiply (6.29) by $\frac{\partial\overline{\sigma}_N}{\partial t}$ and have

$$\frac{1}{2}\frac{d}{dt}(\|\nabla\sigma_N\|^2 + \gamma\|\overline{\sigma}_N\|_{-1}^2) + \|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}^2 + ((f_{2,N}(\sigma_N),\frac{\partial\overline{\sigma}_N}{\partial t})) + ((\frac{u_N\sigma_N}{1+|\sigma_N|},(-\Delta)^{-1}\frac{\partial\overline{\sigma}_N}{\partial t})) = 0.$$

Note that

$$|((\frac{u_N\sigma_N}{1+|\sigma_N|},(-\Delta)^{-1}\frac{\partial\overline{\sigma}_N}{\partial t}))| \le c\|u_N\|\|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1} \le c\|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}$$

and

$$((f_{2,N}(\sigma_N),\frac{\partial\overline{\sigma}_N}{\partial t})) = \frac{d}{dt}\int_\Omega F_{2,N}(\sigma_N)dx - \mathrm{Vol}(\Omega)\langle f_{2,N}(\sigma_N)\rangle\langle\frac{\partial\sigma_N}{\partial t}\rangle.$$

Furthermore, it follows from (6.27) and (6.30) that

$$|\langle\frac{\partial\sigma_N}{\partial t}\rangle| \le c(1+\|u_N\|) \le c,$$

which yields

$$((f_{2,N}(\sigma_N),\frac{\partial\overline{\sigma}_N}{\partial t})) \ge \frac{d}{dt}\int_\Omega F_{2,N}(\sigma_N)dx - c\|f_{2,N}(\sigma_N)\|_{L^1(\Omega)}.$$

It deduces from the above that

$$\frac{d}{dt}(\|\nabla\sigma_N\|^2 + \gamma\|\overline{\sigma}_N\|_{-1}^2 + 2\int_\Omega F_{2,N}(\sigma_N)dx) + \|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}^2 \le c\|f_{2,N}(\sigma_N)\|_{L^1(\Omega)} + c'. \tag{6.48}$$

We finally multiply (6.29) by $-\Delta\sigma_N$ and have

$$\frac{1}{2}\frac{d}{dt}\|\overline{\sigma}_N\|^2 + \|\Delta\sigma_N\|^2 + \gamma\|\overline{\sigma}_N\|^2 + ((f'_{2,N}(\sigma_N)\nabla\sigma_N,\nabla\sigma_N)) + ((\frac{u_N\sigma_N}{1+|\sigma_N|},\overline{\sigma}_N)) = 0,$$

which yields, owing to (6.16) and noting that

$$|((\frac{u_N\sigma_N}{1+|\sigma_N|},\overline{\sigma}_N))| \le c\|\overline{\sigma}_N\|,$$

the differential inequality

$$\frac{d}{dt}\|\overline{\sigma}_N\|^2 + \|\Delta\sigma_N\|^2 + \gamma\|\overline{\sigma}_N\|^2 \leq c(1 + \|\nabla\sigma_N\|^2). \tag{6.49}$$

Summing (6.47), η_2 times (6.48) and η_3 times (6.49), $\eta_2, \eta_3 > 0$ small enough, we obtain a differential inequality of the form

$$\frac{dE_2}{dt} + c(E_2 + \|\Delta\sigma_N\|^2 + \|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}^2 + \|f_{2,N}(\sigma_N)\|_{L^1(\Omega)}) \leq c',\ c > 0, \tag{6.50}$$

where

$$E_2 = \|\overline{\sigma}_N\|_{-1}^2 + \eta_2(\|\nabla\sigma_N\|^2 + \gamma\|\overline{\sigma}_N\|_{-1}^2 + 2\int_\Omega F_{2,N}(\sigma_N)dx) + \eta_3\|\overline{\sigma}_N\|^2$$

satisfies

$$E_2 \geq c\|\nabla\sigma_N\|^2 - c',\ c > 0.$$

It now follows from (6.29) that

$$\overline{f_{2,N}(\sigma_N)} = -(-\Delta)^{-1}\frac{\partial\overline{\sigma}_N}{\partial t} + \Delta\sigma_N - \gamma(-\Delta)^{-1}\overline{\sigma}_N - (-\Delta)^{-1}\frac{\overline{u_N\sigma_N}}{1 + |\sigma_N|},$$

so that

$$\|\overline{f_{2,N}(\sigma_N)}\| \leq c(\|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1} + \|\Delta\sigma_N\| + 1). \tag{6.51}$$

Combining (6.50) and (6.51) gives the differential inequality

$$\frac{dE_2}{dt} + c(E_2 + \|\Delta\sigma_N\|^2 + \|\frac{\partial\overline{\sigma}_N}{\partial t}\|_{-1}^2 + \|f_{2,N}(\sigma_N)\|_{L^1(\Omega)} + \|\overline{f_{2,N}(\sigma_N)}\|^2) \leq c',\ c > 0. \tag{6.52}$$

It follows from (6.52) that

$$\|\overline{f_{2,N}(\sigma_N)}\|_{L^2(0,T_2;L^2(\Omega)}^2 \leq c(E_2(0) + 1).$$

Then, taking $s = \sigma_N$ and $m = \langle\sigma_N\rangle$ in (6.17), we have

$$\begin{aligned}
|\langle f_{2,N}(\sigma_N)\rangle| &\leq c((f_{2,N}(\sigma_N), \overline{\sigma}_N)) + c' \\
&= c((\overline{f_{2,N}(\sigma_N)}, \sigma_N)) + c' \\
&\leq c\|\overline{f_{2,N}(\sigma_N)}\|\|\sigma_N\| + c' \\
&\leq c\|\overline{f_{2,N}(\sigma_N)}\|(E_2(0) + 1)^{\frac{1}{2}} + c',
\end{aligned}$$

so that

$$\|f_{2,N}(\sigma_N)\|_{L^2(0,T_2;L^2(\Omega)} \leq c(E_2(0) + 1). \tag{6.53}$$

The estimates above allow us to pass to the limit of (6.29) to obtain a weak solution. The regularity stated in the theorem follows from (6.45), (6.46), (6.52) and (6.53). Furthermore, we have a local in time weak solution (u, σ) to the auxiliary problem (6.9)-(6.12) in a standard way (see [16, 96] for details) satisfying

$$0 < u(x,t) < \alpha,\ 0 < \sigma(x,t) < \beta \text{ for almost all } (\mathrm{x}, \mathrm{t}) \in \Omega \times (0, \mathrm{T}_0),$$

where $T_0 = \min\{T_1, T_2\}$. Noting that $u \geq 0$ and $\sigma > 0$ a.e., which yields that (u, σ) is also a local in time weak solution to the original problem (6.1)-(6.4). □

Remark 6.3.1. *When we consider logarithmic nonlinear terms with the Chan-Hilliard type equations, which allows to directly ensure that u, σ satisfy the biologically relevant conditions*

$$0 < u < \alpha,\ 0 < \sigma < \beta \ a.e.$$

These are crucial to make sure that (u, σ) actually is a solution to the original problem.

We then show that a local in time weak solution is conditionally global in time.

Theorem 6.3.2. *Under the assumptions of Theorem 6.3.1, for $h(s) \geq 0$, $s \geq 0$, if we set*

$$h^* = \max_{[0,\beta]} h,$$

and assume that

$$\gamma \geq \frac{\alpha}{\beta + 1}.$$

Then a local in time weak solution (u, σ) is global in time.

Proof. Let T^* be the maximal time of existence of a local in time weak solution as given in Theorem 6.3.1 and assume that $T^* < \infty$.

Then, we have

$$\|u(t)\| \leq \|\alpha\| = \mathrm{Vol}(\Omega)^{\frac{1}{2}}\alpha,\ \mathrm{t} \in [0, \mathrm{T}^*),$$

which means the upper bound on $\|u\|$ is now independent of T^*.

In order to extend the local in time weak solution (u, σ), it's critical that proving $\langle u \rangle$ and $\langle \sigma \rangle$ remain in $(0, \alpha)$ and $(0, \beta)$, respectively, for all times. Note that the following estimates are working on the original equations rather than the approximated ones, but we can repeat all preceding estimates for the limit solution, which hold for $t \in [0, T^*)$.

Then we have

$$\frac{d\langle u \rangle}{dt} = \langle h(\sigma)u(\alpha - u) \rangle,$$

which yields, since $u \in [0, \alpha]$ and $\sigma \in [0, \beta]$, as long as the solution exists,

$$0 \leq \frac{d\langle u \rangle}{dt} \leq h^* \langle u(\alpha - u) \rangle.$$

Therefore,

$$0 \leq \frac{d\langle u\rangle}{dt} + h^*\alpha\langle u\rangle \leq h^*\langle -u^2 + 2\alpha u\rangle \leq h^*\alpha^2.$$

It thus follows from Gronwall's lemma that

$$\langle u_0\rangle e^{-h^*\alpha t} \leq \langle u(t)\rangle \leq \langle u_0\rangle e^{-h^*\alpha t} + \alpha(1 - e^{-h^*\alpha t}).$$

It immediately follows from above that

$$\langle u(t)\rangle \in [\delta_1, \alpha - \delta_1],\ t \in [0, T^*),$$

where $\delta_1 \in (0, \alpha)$. Indeed, setting

$$\varphi(t) = \langle u_0\rangle e^{-h^*\alpha t} + \alpha(1 - e^{-h^*\alpha t}),$$

it's easy to see that φ takes values in such an interval, noting that φ is monotone increasing.

Similarly, we have

$$\frac{d\langle\sigma\rangle}{dt} + \gamma\langle\sigma\rangle + \langle\frac{u\sigma}{1+\sigma}\rangle = \gamma\beta,$$

and then

$$\gamma\beta - \frac{\alpha\beta}{1+\beta} \leq \frac{d\langle\sigma\rangle}{dt} + \gamma\langle\sigma\rangle \leq \gamma\beta.$$

It also follows from Gronwall's lemma that

$$\langle\sigma_0\rangle e^{-\gamma t} + \frac{\beta}{\gamma}(\gamma - \frac{\alpha}{1+\beta})(1 - e^{-\gamma t}) \leq \langle\sigma(t)\rangle \leq \langle\sigma_0\rangle e^{-\gamma t} + \beta(1 - e^{-\gamma t}) \tag{6.54}$$

as long as it exists.

Let us consider the function

$$\phi(t) = \langle\sigma_0\rangle e^{-\gamma t} + \beta(1 - e^{-\gamma t}).$$

Noting that $\phi(0) = \langle\sigma_0\rangle \in (0, \beta)$ and $\lim_{t\to+\infty} \phi(t) = \beta$, we easily see that

$$\langle\phi(t)\rangle \in (\delta_2, \beta - \delta_2),\ \delta_2 \in (0, \beta),\ t \in [0, T^*],$$

since ϕ is monotone. Proceeding similarly for the left-hand side of (6.54), we deduce that there exists $\delta_2 \in (0, \beta)$ depending only on T^*, such that the same conclusion can be obtained.

Having this, we can extend the solution (u, σ) by continuity, which finishes the proof. □

Remark 6.3.2. *Uniqueness and further regularity, in particular the existence of strong solutions, are open problems. Note that the difficulty here comes from the Cahn-Hilliard type equation and already appears without any coupling (see [96]).*

Deuxième partie

Modèles pour la segmentation d'images

Chapitre 7

On a Cahn-Hilliard model for image segmentation

Sur un modèle de Cahn-Hilliard pour la segmentation d'images

On a Cahn-Hilliard model for image segmentation

7.1 Introduction

Image segmentation plays an important role in image processing and computer vision. More precisely, its aim is the partition of a given image into regions in order to recognize different objects. It has a wide range of applications, including medical imaging, object detection and video surveillance.

During the last decades, several approaches have been proposed to handle this problem. These include clustering methods, graph partitioning methods, statistics based methods, variational methods and PDEs based methods. We refer the reader to, e.g., [19, 104, 117, 120, 121] and references therein for more details.

In particular, in [120], the authors proposed the following Cahn-Hilliard type model for image segmentation :

$$\frac{\partial u}{\partial t} + \varepsilon_1 \Delta^2 u - \frac{1}{\varepsilon_1}\Delta f(u) + \frac{\varepsilon_2 h(x)}{\varepsilon_2^2 + (u - \frac{1}{2})^2} = 0,$$

where f is a cubic nonlinear term and

$$h(x) = \frac{1}{\pi}(\lambda_1 (i(x) - c_1)^2 - \lambda_2 (i(x) - c_2)^2).$$

Here, ε_1, ε_2, λ_1 and λ_2 are positive constants and i is a given image taking values in $[0, 1]$. Such a model takes advantage of the favorable features of high-order PDEs and is also easier to handle than Euler's elastica based models. We can note that Euler's elastica models lead to the minimization of some functional. However, the associated Euler-Lagrange equations are highly nonlinear, which make numerical simulations delicate. By comparison, the highest order term in the Cahn-Hilliard model is linear, which significantly reduces the difficulty of developing effective numerical schemes and also makes the analysis of the equation possible. We refer the interested reader to [120, 121] and references therein for more details.

The authors in [120] proposed the following strategy in view of numerical simulations. Solve first the equation up to steady state, taking, say, $c_1 = 1$ and $c_2 = 0$. Then, modify c_1 and c_2, depending now on the above steady state, as follows :

$$c_1 = \frac{\int_\Omega (\frac{1}{2} + \frac{1}{\pi}\arctan(\frac{u-\frac{1}{2}}{\varepsilon_2}))i\,dx}{\int_\Omega (\frac{1}{2} + \frac{1}{\pi}\arctan(\frac{u-\frac{1}{2}}{\varepsilon_2}))\,dx},$$

$$c_2 = \frac{\int_\Omega (\frac{1}{2} - \frac{1}{\pi}\arctan(\frac{u-\frac{1}{2}}{\varepsilon_2}))i\,dx}{\int_\Omega (\frac{1}{2} - \frac{1}{\pi}\arctan(\frac{u-\frac{1}{2}}{\varepsilon_2}))\,dx}$$

and repeat the procedure until c_1 and c_2 converge.

The original Cahn-Hilliard equation,

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

was initially proposed to model phase separation processes in binary alloys (see [11, 12]). Since then, this equation, or some of its variants, were successfully applied to many other applications than just phase separation in alloys. We refer the interested reader to [96, 103] for reviews on the Cahn-Hilliard equation and some of its variants, as well as their mathematical analysis.

In particular, Cahn-Hilliard type models in the context of image processing can be found in, e.g., [9, 18, 24, 21, 22, 33]. The authors in [120] studied the existence of solutions for their model. However, their proof is strongly based on the fact that the solution u remains in the relevant interval $[0, 1]$. However, as we will see below, there exist solutions which are unbounded as time goes to infinity, which could be problematic in view of numerical simulations.

In this paper, we give a proof of existence and uniqueness of solutions which does not require such a strong assumption. We also propose a modification of the model proposed in [120], based on the Cahn-Hilliard-Oono equation proposed in [105] to account for long-ranged interactions in the phase separation processes and to simplify numerical simulations. In particular, this modification of the model ensures the global in time boundedness of the solutions. We finally give numerical simulations which illustrate our theoretical results.

7.2 Setting of the problem

We consider the following initial and boundary value problem :

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + \frac{h(x)}{1 + (u - \frac{1}{2})^2} = 0, \tag{7.1}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{7.2}$$

$$u|_{t=0} = u_0, \tag{7.3}$$

in a bounded and regular domain $\Omega \subset \mathbb{R}^n$, $n = 1$, 2 or 3, with boundary Γ. Here, we have set several constants equal to 1.

We assume that $h \in L^\infty(\Omega)$, which is consistent with what is considered in [120]. We further take, for simplicity,

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

though we can more generally consider any cubic polynomial with positive leading term, or even any regular function with such a cubic growth at infinity. Note in particular that

$$f' \geq -1, \ F \geq -c, \ c \geq 0, \tag{7.4}$$

where

$$F(s) = \int_0^s f(\xi)\, d\xi = \frac{1}{4}s^4 - \frac{1}{2}s^2.$$

We finally set

$$g(s) = \frac{1}{1 + (s - \frac{1}{2})^2}$$

and note that g is nonnegative and bounded by 1.

We set, for $v \in L^1(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \int_\Omega v(x)\, dx$$

and, for $v \in H^{-1}(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \langle v, 1 \rangle_{H^{-1}(\Omega), H^1(\Omega)}.$$

Furthermore, we set, whenever it makes sense,

$$\overline{v} = v - \langle v \rangle.$$

We denote by $((\cdot, \cdot))$ the usual L^2-scalar product, with associated norm $\|\cdot\|$. We also set $\|\cdot\|_{-1} = \|(-\Delta)^{-\frac{1}{2}} \cdot \|$, where $(-\Delta)^{-1}$ denotes the inverse of the minus Laplace operator associated with Neumann boundary conditions and acting on functions with null spatial average. More generally, we denote by $\|\cdot\|_X$ the norm on the Banach space X.

We note that

$$v \mapsto (\|\overline{v}\|_{-1}^2 + \langle v \rangle^2)^{\frac{1}{2}}, \ v \mapsto (\|\overline{v}\|^2 + \langle v \rangle^2)^{\frac{1}{2}},$$

$$v \mapsto (\|\nabla v\|^2 + \langle v \rangle^2)^{\frac{1}{2}} \text{ and } v \mapsto (\|\Delta v\|^2 + \langle v \rangle^2)^{\frac{1}{2}}$$

are norms on $H^{-1}(\Omega)$, $L^2(\Omega)$, $H^1(\Omega)$ and $H^2(\Omega)$, respectively, which are equivalent to the usual norms on these spaces. Furthermore, $\|\cdot\|_{-1}$ is a norm on $\{v \in H^{-1}(\Omega), \ \langle v \rangle = 0\}$ which is equivalent to the usual H^{-1}-norm.

We recall several inequalities (see, e.g., [96]) which we will frequently employ below.

• The Poincaré-Wirtinger inequality :

$$\|\overline{v}\| \leq c\|\nabla v\|, \ \forall v \in H^1(\Omega). \tag{7.5}$$

Note that a consequence of this inequality is that

$$\|(-\Delta)^{-1}v\| \leq c\|v\|_{-1},\ \forall v \in H^{-1}(\Omega),\ \langle v\rangle = 0. \tag{7.6}$$

• An interpolation inequality :

$$\|v\| \leq c\|v\|_{-1}^{\frac{1}{2}}\|\nabla v\|^{\frac{1}{2}},\ \forall v \in H^{1}(\Omega),\ \langle v\rangle = 0. \tag{7.7}$$

Throughout this paper, the same letters c and c' denote (generally positive) constants which may vary from line to line, or even in a same line.

7.3 Existence of unbounded solutions

One crucial question, in many applications of Cahn-Hilliard type models, and especially in view of applications to image segmentation, is whether or not the solutions remain in the relevant interval, say, $[0, 1]$. Note that, in the case of the original Cahn-Hilliard equation, one can construct simple counterexamples showing that the solutions can leave the relevant interval. However, one can prove, assuming that the initial data are regular enough, that the solutions are globally (in time) bounded. We refer the interested reader to, e.g., [96] for details.

Here, we cannot prove a similar result. Indeed, we have the following.

Proposition 7.3.1. *Assume that $h \equiv h_\star$ is a nonvanishing constant. Then (7.1)-(7.3) possesses unbounded solutions.*

Proof. Let us look for spatially homogeneous solutions, $u(x,t) \equiv y(t)$, so that the boundary conditions are automatically satisfied. We thus have to solve the separable ODE

$$y' + \frac{h_\star}{1 + (y - \frac{1}{2})^2} = 0,$$

which is equivalent to

$$y' + y'(y - \frac{1}{2})^2 = -h_\star.$$

This yields

$$\frac{1}{3}y^3 - \frac{1}{2}y^2 + \frac{5}{4}y = c(y_0) - h_\star t,$$

where y_0 is the initial datum. It immediately follows that
• $\lim_{t\to+\infty} y(t) = +\infty$ when $h_\star < 0$,
• $\lim_{t\to+\infty} y(t) = -\infty$ when $h_\star > 0$,
which finishes the proof.

□

Remark 7.3.1. *Also note that*

$$y' = -\frac{h_\star}{1 + (y - \frac{1}{2})^2}$$

has the opposite sign of $h_\star$, so that y is monotone increasing (resp., decreasing) when $h_\star < 0$ (resp., $h_\star > 0$).

Remark 7.3.2. *Of course, taking h constant is restrictive in view of applications to image segmentation. In particular, in the iterative algorithm considered in [120], this may only happen in the first iteration for a trivial image; indeed, in the subsequent ones, the only possible constant h would be 0, meaning that one has the original Cahn-Hilliard equation, for which one has bounded solutions under proper regularity assumptions on the initial data. Note however that the idea in this algorithm is to solve the equation up to steady state at each iteration. We also note that, in view of the numerical simulations performed below, one may have unbounded solutions also when h is nonconstant. One should thus be careful with the first iteration to avoid having an unbounded solution, even though the numerical simulations suggest that the convergence to infinity is slow.*

7.4 Existence and uniqueness of solutions

We have the following.

Theorem 7.4.1. *We assume that $u_0 \in H^1(\Omega)$. Then, (7.1)-(7.3) possesses a unique weak solution u such that*

$$u \in L^\infty(0, T; H^1(\Omega)) \cap L^2(0, T; H^2(\Omega))$$

and

$$\frac{\partial u}{\partial t} \in L^2(0, T; H^{-1}(\Omega)),$$

$\forall T > 0$.

Proof. Note that, integrating (7.1) over Ω, we have

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

We introduce the following weaker formulation of (7.1)-(7.3) :

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - \Delta \overline{u} + \overline{f(u)} + (-\Delta)^{-1}\overline{h(x)g(u)} = 0, \tag{7.8}$$

$$\frac{d\langle u\rangle}{dt} + \langle h(x)g(u)\rangle = 0, \tag{7.9}$$

$$\frac{\partial \overline{u}}{\partial \nu} = 0 \text{ on } \Gamma, \tag{7.10}$$

$$\overline{u}|_{t=0} = \overline{u}_0,\ \langle u\rangle|_{t=0} = \langle u_0\rangle, \tag{7.11}$$

where $u = \overline{u} + \langle u\rangle$. This formulation is associated with the following variational formulation : Find $u : [0,T] \to H^1(\Omega)$ such that

$$\frac{d}{dt}(((-\Delta)^{-1}\overline{u}, v)) + ((\nabla u, \nabla v)) + ((f(u), v)) + (((-\Delta)^{-1}\overline{h(x)g(u)}, v)) = 0 \text{ in } \mathcal{D}'(0,T),$$

$$\forall v \in H^1(\Omega),\ \langle v\rangle = 0,$$

$$\frac{d\langle u\rangle}{dt} + \langle h(x)g(u)\rangle = 0 \text{ in } \mathcal{D}'(0,T),$$

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

where $u = \overline{u} + \langle u\rangle$.

Existence : The proof of existence can be carried out via a standard Galerkin scheme based on the above variational formulation. Here below, we only give formal estimates which can be justified by the aforementioned scheme.

Note that, since g is bounded by 1 and $h \in L^\infty(\Omega)$,

$$|\langle h(x)g(u)\rangle| \le c, \tag{7.12}$$

so that, in view of (7.9),

$$|\langle \frac{\partial u}{\partial t}\rangle| \le c. \tag{7.13}$$

Furthermore, it follows from (7.9) and Young's inequality that

$$\frac{d\langle u\rangle^2}{dt} + \langle u\rangle^2 \le c\langle u\rangle^2 + 1. \tag{7.14}$$

Multiply (7.8) by $\frac{\partial \overline{u}}{\partial t}$ and integrate over Ω and by parts to obtain

$$\frac{1}{2}\frac{d}{dt}(\|\nabla u\|^2 + 2\int_\Omega F(u)\,dx) + \|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 - ((f(u), \langle \frac{\partial u}{\partial t}\rangle)) + ((h(x)g(u), (-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t})) = 0. \tag{7.15}$$

We note that, owing to (7.13) and Young's inequality,

$$|((f(u), \langle \frac{\partial u}{\partial t}\rangle))| \le c\int_\Omega |f(u)|\,dx \le \eta\int_\Omega u^4\,dx + c_\eta,\ \forall \eta > 0. \tag{7.16}$$

Furthermore, it follows from the properties of g and h, the Poincaré-Wirtinger inequality (7.6) and Young's inequality that

$$\begin{aligned} |((h(x)g(u), (-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t}))| &\leq c\|\frac{\partial \overline{u}}{\partial t}\|_{-1} \\ &\leq \frac{1}{2}\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + c. \end{aligned} \tag{7.17}$$

Combining (7.15)-(7.17), we arrive at

$$\frac{d}{dt}(\|\nabla u\|^2 + 2\int_\Omega F(u)\,dx) + \|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 \leq \eta \int_\Omega u^4\,dx + c_\eta,\ \forall \eta > 0. \tag{7.18}$$

Next, multiplying (7.8) by $\overline{u}$, we find

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 + ((f(u), \overline{u})) + ((h(x)g(u), (-\Delta)^{-1}\overline{u})) = 0. \tag{7.19}$$

We note that, recalling that $u = \overline{u} + \langle u \rangle$,

$$\begin{aligned} ((f(u), \overline{u})) &= ((f(u) - f(\langle u \rangle), \overline{u})) \\ &= \int_\Omega (\overline{u}^4 + 3\overline{u}^3\langle u \rangle + 3\overline{u}^2\langle u \rangle^2)\,dx - \|\overline{u}\|^2 \\ &\geq \int_\Omega (\overline{u}^4 + 3\overline{u}^2\langle u \rangle^2)dx - 3\int_\Omega |\overline{u}|^3|\langle u \rangle|dx - \|\overline{u}\|^2 \\ &\geq c_0 \int_\Omega (\overline{u}^4 + \overline{u}^2\langle u \rangle^2)\,dx - \|\overline{u}\|^2,\ c_0 > 0, \end{aligned} \tag{7.20}$$

owing to Young's inequality. Furthermore, recalling that g is bounded, employing the Poincaré-Wirtinger inequality (7.6) and noting that the embedding $L^2(\Omega) \subset H^{-1}(\Omega)$ is continuous, we have

$$|((h(x)g(u), (-\Delta)^{-1}\overline{u}))| \leq c\|\overline{u}\|^2 + c'. \tag{7.21}$$

It thus follows from (7.19)-(7.21) that

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

so that, owing to the interpolation inequality (7.7) and Young's inequality,

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 + c_0\int_\Omega (\overline{u}^4 + \overline{u}^2\langle u \rangle^2)dx \leq c. \tag{7.22}$$

We finally multiply (7.8) by $\overline{u}$ to obtain

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|^2 + \|\Delta u\|^2 + ((f'(u)\nabla u, \nabla u)) + ((h(x)g(u), \overline{u})) = 0,$$

which yields, recalling (7.4) and noting that, employing the Poincaré-Wirtinger inequality (7.5),

$$|((h(x)g(u), \overline{u}))| \leq c\|\overline{u}\| \leq c\|\nabla u\|,$$

the differential inequality

$$\frac{d}{dt}\|\overline{u}\|^2 + \|\Delta u\|^2 \leq c\|\nabla u\|^2 + c'. \tag{7.23}$$

Summing (7.14), (7.18), (7.22) and δ times (7.23), $\delta > 0$ small enough, we find the differential inequality

$$\frac{dE}{dt} + c(\|u\|^2_{H^2(\Omega)} + \int_\Omega (\overline{u}^4 + \overline{u}^2\langle u\rangle^2)\,dx + \|\frac{\partial \overline{u}}{\partial t}\|^2_{-1}) \leq c'(1 + \langle u\rangle^4),\ c > 0, \tag{7.24}$$

where

$$E = \langle u\rangle^2 + \|\overline{u}\|^2_{-1} + \delta\|\overline{u}\|^2 + \|\nabla u\|^2 + 2\int_\Omega F(u)dx$$

satisfies

$$E \geq c\|u\|^2_{H^1(\Omega)} - c',\ c > 0. \tag{7.25}$$

Also note that, owing to Hölder's and Young's inequalities,

$$\langle u\rangle^4 \leq c\int_\Omega u^4\,dx \leq c(\int_\Omega F(u)dx + 1),$$

so that it follows from (7.24) that

$$\frac{dE}{dt} \leq c(E + 1). \tag{7.26}$$

These estimates allow to deduce the existence results, passing to the limit in the Galerkin approximations by standard techniques.

Uniqueness : Let u_1 and u_2 be two solutions with initial data $u_{1,0}$ and $u_{2,0}$, respectively. We set $u = u_1 - u_2$ and $u_0 = u_{1,0} - u_{2,0}$. Then, u satisfies the following initial and boundary value problem :

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - \Delta\overline{u} + \overline{f(u_1) - f(u_2)} + (-\Delta)^{-1}\overline{h(x)(g(u_1) - g(u_2))} = 0, \tag{7.27}$$

$$\frac{d\langle u\rangle}{dt} + \langle h(x)(g(u_1) - g(u_2)\rangle = 0, \tag{7.28}$$

$$\frac{\partial \overline{u}}{\partial \nu} = 0 \text{ on } \Gamma, \tag{7.29}$$

$$\overline{u}|_{t=0} = \overline{u}_0,\ \langle u\rangle|_{t=0} = \langle u_0\rangle. \tag{7.30}$$

Multiply (7.27) by $\overline{u}$ to obtain, owing to (7.4),

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 - \mathrm{Vol}(\Omega)\langle f(u_1) - f(u_2)\rangle\langle u\rangle \\ +((h(x)(g(u_1) - g(u_2)), (-\Delta)^{-1}\overline{u})) \leq \|u\|^2. \tag{7.31}$$

Note that

$$g(u_1) - g(u_2) = -\frac{(u_1 + u_2 - 1)u}{(1 + (u_1 - \frac{1}{2})^2)(1 + (u_2 - \frac{1}{2})^2)},$$

which yields

$$|h(x)(g(u_1) - g(u_2))| \leq c|u|. \tag{7.32}$$

It thus follows from (7.32) that

$$|((h(x)(g(u_1) - g(u_2)), (-\Delta)^{-1}\overline{u}))| \leq c\|u\|\|\overline{u}\|_{-1} \\ \leq \frac{1}{4}\|\nabla u\|^2 + c(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2), \tag{7.33}$$

where we have also employed the Poincaré-Wirtinger inequality (7.6) and the interpolation inequality (7.7), together with Young's inequality. Furthermore,

$$\begin{aligned} |\int_\Omega (f(u_1) - f(u_2))dx| &\leq c\int_\Omega (u_1^2 + u_2^2 + 1)|u|dx \\ &\leq c(\|u_1\|_{L^4(\Omega)}^2 + \|u_2\|_{L^4(\Omega)}^2 + 1)\|u\| \\ &\leq c(\|u_1\|_{H^1(\Omega)}^2 + \|u_2\|_{H^1(\Omega)}^2 + 1)\|u\| \\ &\leq c_T\|u\|, \end{aligned} \tag{7.34}$$

where, here and below, c_T denotes a constant depending on the final time T, in view of the regularity of u_1 and u_2, which may change from line to line. Note that we have used the Cauchy-Schwartz inequality and the Sobolev embedding $H^1(\Omega) \subset L^4(\Omega)$. We deduce from (7.31)-(7.34), employing again the interpolation inequality (7.7) and Young's inequality to handle (7.34), that

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 \leq c_T(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2). \tag{7.35}$$

Next, proceeding as above, it follows from (7.28) that

$$\frac{d\langle u\rangle^2}{dt} \leq c\|u\|\|\langle u\rangle| \\ \leq \|\nabla u\|^2 + c(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2). \tag{7.36}$$

Summing finally (7.35) and (7.36), we have

$$\frac{d}{dt}(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2) \leq c_T(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2), \tag{7.37}$$

which yields, employing Gronwall's lemma, the continuous dependence with respect to the initial data in the H^{-1}-topology, as well as the uniqueness.

□

Remark 7.4.1. *It follows from the regularity stated in the above theorem and Lions-Magenes's theorem (see [74]; see also [96]) that* $u \in C([0,T]; H^{\frac{1}{2}}(\Omega))$. *It also follows from Strauss's lemma (see [110]) that* $u \in C([0,T]; H^1(\Omega)_{\mathrm{w}})$, *where the index w denotes the weak topology.*

We then have the following.

Theorem 7.4.2. *We further assume that* $u_0 \in H^2(\Omega)$, *with* $\frac{\partial u_0}{\partial \nu} = 0$ *on* Γ. *Then, the solution u given in Theorem 7.4.1 satisfies*

$$u \in C([0,T]; H^2(\Omega)) \cap L^2(0,T; H^4(\Omega))$$

and

$$\frac{\partial u}{\partial t} \in L^2(0,T; L^2(\Omega)),$$

$\forall T > 0$.

Proof. We again derive formal estimates.

Multiplying (7.1) by $\Delta^2 u$, we obtain

$$\frac{1}{2}\frac{d}{dt}\|\Delta u\|^2 + \|\Delta^2 u\|^2 - ((\Delta f(u), \Delta^2 u)) + ((h(x)g(u), \Delta^2 u)) = 0. \tag{7.38}$$

We note that

$$|((h(x)g(u), \Delta^2 u))| \leq c\|\Delta^2 u\| \leq \frac{1}{4}\|\Delta^2 u\|^2 + c. \tag{7.39}$$

Furthermore, we can prove that, say, for $n = 3$ (see [96], Chapter 3, inequality (3.35); this inequality is derived by properly employing the Agmon and several interpolation inequalities),

$$|((\Delta f(u), \Delta^2 u))| \leq \frac{1}{4}\|\Delta^2 u\|^2 + c(1 + \|u\|_{H^1(\Omega)}^{14}). \tag{7.40}$$

It thus follows from (7.38)-(7.40) that

$$\frac{d}{dt}\|\Delta u\|^2 + \|\Delta^2 u\|^2 \leq c(1 + \|u\|_{H^1(\Omega)}^{14}). \tag{7.41}$$

This allows us to conclude. In particular, the continuity again follows from Lions-Magenes's theorem.

□

Remark 7.4.2. *Note that it follows from Proposition 7.3.1 that we cannot expect to have uniform in time estimates on the solutions. Actually, in view of the proof of Theorem 7.4.1, we can be more precise. Indeed, we can have a global in time estimate on $\overline{u}$ in $L^2(\Omega)$, combining (7.22) and (7.23). However, as $\langle u\rangle$ can indeed go to infinity as t goes to infinity, (7.24) shows that we cannot expect a global in time estimate on u.*

Remark 7.4.3. *(i) One way to have a model which ensures global in time boundedness is to consider the following modified boundary value problem :*

$$\frac{\partial u}{\partial t} + \varepsilon_1 \Delta^2 u + \alpha u - \frac{1}{\varepsilon_1}\Delta f(u) + \frac{\varepsilon_2 h(x)}{\varepsilon_2^2 + (u - \frac{1}{2})^2} = 0,\ \alpha > 0, \tag{7.42}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma. \tag{7.43}$$

Here, when $h \equiv 0$, we obtain the Cahn–Hilliard–Oono equation (see [105]). Integrating (7.42) over Ω (we again set ε_1 and ε_2 equal to 1), we find

$$\frac{d\langle u\rangle}{dt} + \alpha\langle u\rangle + \langle h(x)g(u)\rangle = 0. \tag{7.44}$$

This yields that

$$\langle u\rangle = \langle u(0)\rangle e^{-\alpha t} + e^{-\alpha t}\int_0^t e^{\alpha s}\langle h(x)g(u)\rangle\, ds,$$

so that

$$|\langle u(t)\rangle| \le |\langle u(0)\rangle| e^{-\alpha t} + \frac{\|h\|_{L^\infty(\Omega)}}{\alpha}(1 - e^{-\alpha t}),\ t \ge 0. \tag{7.45}$$

In particular,

$$|\langle u(t)\rangle| \le |\langle u(0)\rangle| + \frac{\|h\|_{L^\infty(\Omega)}}{\alpha},\ t \ge 0. \tag{7.46}$$

Therefore, the spatial average of u is bounded, uniformly with respect to time. Proceeding then as in the proofs of Theorems 7.4.1 and 7.4.2, we can use this to deduce that $u \in L^\infty(\mathbb{R}^+; H^1(\Omega))$ and $u \in L^\infty(\mathbb{R}^+; H^2(\Omega))$, respectively, employing the uniform Gronwall lemma in the latter case.

It is proved in [96] that, when α is small, then the dynamics of the Cahn-Hilliard-Oono equation is close to that of the original Cahn-Hillard equation, in the sense that one can construct exponential attractors for the Cahn-Hilliard-Oono equation converging to exponential attractors for the Cahn-Hilliard equation as α goes to 0^+. This suggests that the Cahn-Hilliard-Oono segmentation model could also be relevant for applications to image segmentation, when α is small, even though we cannot construct such robust attractors here, since the limit model has unbounded solutions. In that case, however, the upper bound (7.46) is large. Nevertheless, we do not have unbounded solutions, avoiding the drawbacks mentioned in Remark 7.3.2. Then, for a large α, we lose the good properties of the model for image segmentation, as suggested by the numerical simulations below.

7.5 Numerical simulations

We emphasize that the theoretical results, obtained in the previous sections for $\varepsilon_1 = \varepsilon_2 = 1$, are still valid for arbitrary positive ε_1 and ε_2.

As far as the numerical simulations are concerned, we rewrite the equation in the equivalent form

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

$$w = -\varepsilon_1 \Delta u + \frac{1}{\varepsilon_1} f(u),$$

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

which has the advantage of splitting the fourth-order (in space) equation into a system of two second-order ones. Then, we consider a P_1 finite element approach for the space discretization. When $\varepsilon_1 = 1$, the computations are performed with a semi-implicit Euler time discretization (implicit for the linear terms and explicit for the nonlinear ones). However, when $\varepsilon_1 = 0.2$, the semi-implicit scheme becomes unstable and we use instead a linearized implicit scheme for the time discretization. The numerical simulations are performed with the software Freefem++ (see [50]).

In the simulations below, we set $\Omega = (0,1) \times (0,1)$, $f(s) = 4s^3 - 6s^2 + 2s$ (i.e., f is the derivative of the double-well potential $F(s) = s^2(s-1)^2$) and $g(s) = \frac{\varepsilon_2}{\varepsilon_2^2 + (s - \frac{1}{2})^2}$, with $\varepsilon_2 = 0.1$. The triangulation is obtained by dividing Ω into 100×100 squares and by dividing each square along the same diagonal. The time step is taken as $\delta t = 0.01$.

7.5.1 The function h has constant sign

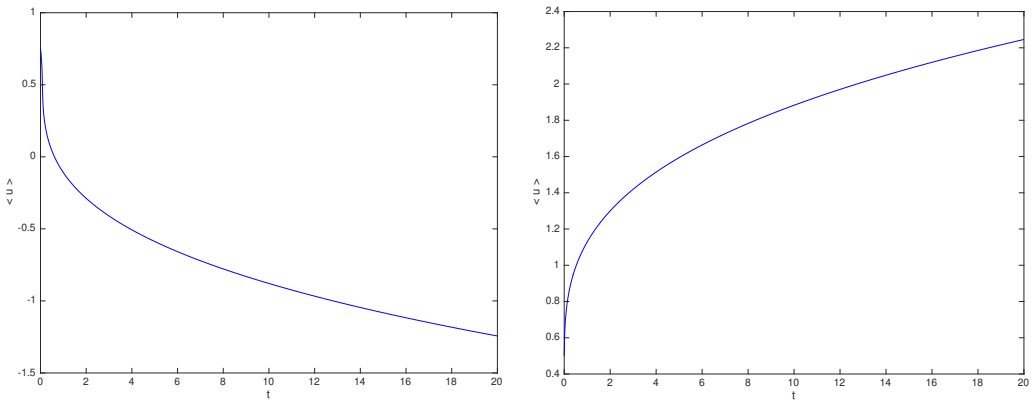

FIGURE 7.1 – $\varepsilon_1 = 1$, $h = h_1$ positive (left), $h = h_2$ negative (right)

We first test the problem for $h_1(x_1, x_2) = \frac{x_1}{x_2+0.2}$ (hence, h_1 is positive) and take u_0 randomly distributed between 0.5 and 1. The time evolution of the spatial average of the solution is displayed in the left part of Figure 7.1. We note that $\langle u \rangle$ is monotone decreasing and seems to tend to $-\infty$ as t tends to $+\infty$.

In the right part of Figure 7.1, we set $h_2(x_1, x_2) = -\frac{x_1}{x_2+0.2}$ (hence, h_2 is negative) and take u_0 randomly distributed between 0.25 and 0.75. In that case, the spatial average $\langle u \rangle$ is monotone increasing and seems to tend to $+\infty$.

These results are consistent with our theoretical results.

7.5.2 The function h does not have a constant sign

We set $\Omega^+ = \{x \in \Omega,\ h(x) \geq 0\}$ and $\Omega^- = \{x \in \Omega,\ h(x) \leq 0\}$.

In the left part of Figure 7.2, we choose u_0 randomly distributed between 0.25 and 0.75 and take $h_3(x_1, x_2) = (x_1 - 0.2)(x_2 - 0.2)$, meaning that h_3 does not have a constant sign. Also note that, in that case, $\mathrm{Vol}(\Omega^+) > \mathrm{Vol}(\Omega^-)$. The spatial average $\langle u \rangle$ is monotone decreasing and seems to tend to $-\infty$.

On the contrary, in the right part of Figure 7.2, we choose u_0 randomly distributed between 0.25 and 0.75 and take $h_4(x_1, x_2) = x_1(x_2 - 0.8)$. In that case, we have $\mathrm{Vol}(\Omega^+) < \mathrm{Vol}(\Omega^-)$. The spatial average $\langle u \rangle$ is monotone increasing and seems to tend to $+\infty$.

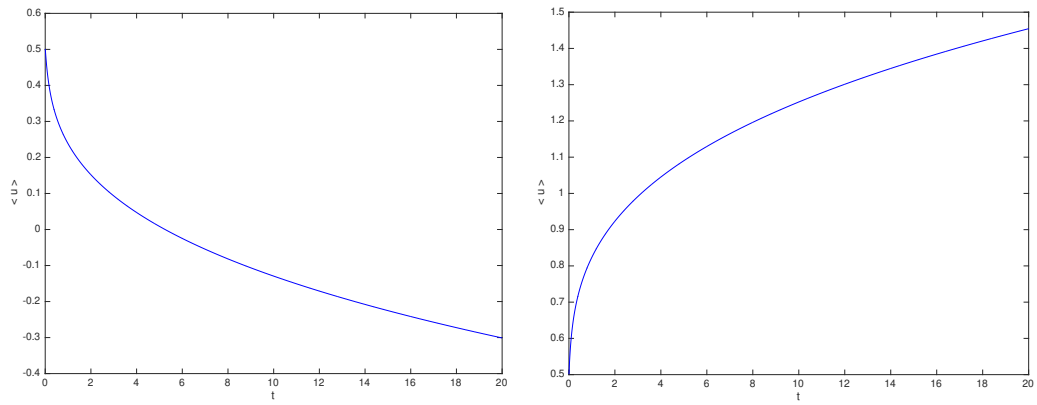

FIGURE 7.2 – $\varepsilon_1 = 1$, $h = h_3$, $\mathrm{Vol}(\Omega^+) > \mathrm{Vol}(\Omega^-)$ (left), $h = h_4$, $\mathrm{Vol}(\Omega^+) < \mathrm{Vol}(\Omega^-)$ (right)

We finally choose $u_0(x_1, x_2) = 0.6 \sin^2(2\pi x_1)|\sin(2\pi x_2)|$ and take $h_{5,\eta}(x_1, x_2) = 0.5$ on $(0, 1)\times(0, \eta)$, $h_{5,\eta}(x_1, x_2) = -0.5$ on $(0, 1)\times(\eta, 1)$. In Figure 7.3, we make η vary so as to compare the cases $\mathrm{Vol}(\Omega^+) > \mathrm{Vol}(\Omega^-)$, $\mathrm{Vol}(\Omega^+) = \mathrm{Vol}(\Omega^-)$ and $\mathrm{Vol}(\Omega^+) < \mathrm{Vol}(\Omega^-)$. We can see that the solution u reaches a steady state when $\mathrm{Vol}(\Omega^+) = \mathrm{Vol}(\Omega^-)$ or when $\mathrm{Vol}(\Omega^+)$ is slightly larger than $\mathrm{Vol}(\Omega^-)$, but not in general.

The time evolution of the maximal, averaged and minimal values of the solution are displayed in Figure 7.4, when $\eta = 0.5$ (hence, $\mathrm{Vol}(\Omega^+) = \mathrm{Vol}(\Omega^-)$). In the left part of

the figure, ε_1 is taken equal to 1 and, in the right part, ε_1 is taken equal to 0.2. In these two cases, the solution reaches a steady state.

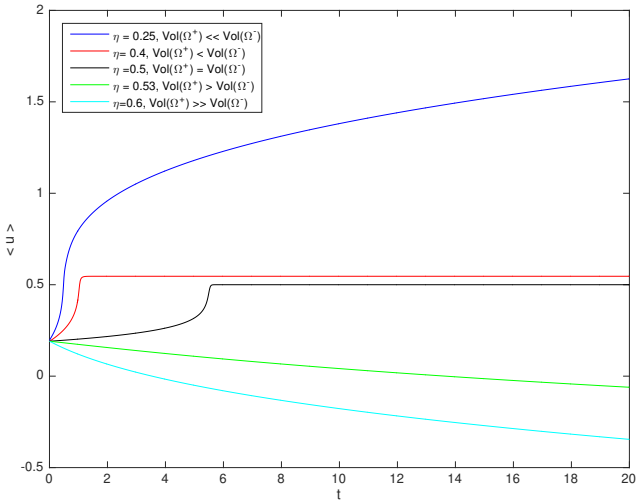

FIGURE 7.3 – Evolution of $\langle u \rangle$ when $\varepsilon_1 = 1$, $h = h_{5,\eta}$; η takes the values 0.25, 0.4, 0.5, 0.53 and 0.6

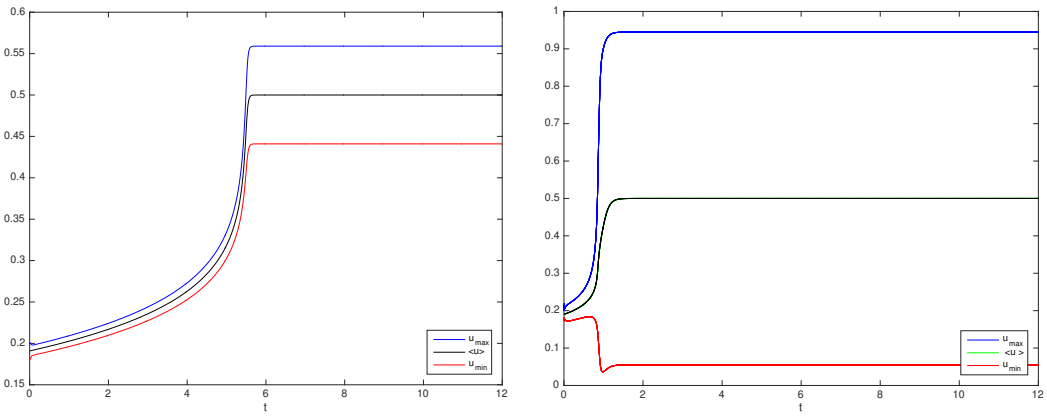

FIGURE 7.4 – $h = h_{5,\frac{1}{2}}$. Evolution of u_{max}, $\langle u \rangle$, u_{min} when $\varepsilon_1 = 1$ (left), $\varepsilon_1 = 0.2$ (right)

7.5.3 Comparison with the Cahn-Hilliard-Oono type model

Since the first model can be seen as a particular case of the second one, with $\alpha = 0$, we now compare the previous numerical results based on equation (7.1) with those based on equation (7.42), for $\alpha = 0.1$. The results are consistent with Remark 7.4.3, (ii). Although the solution to (7.1) seems to tend to $-\infty$ (left part of Figures 7.5 and 7.6) or

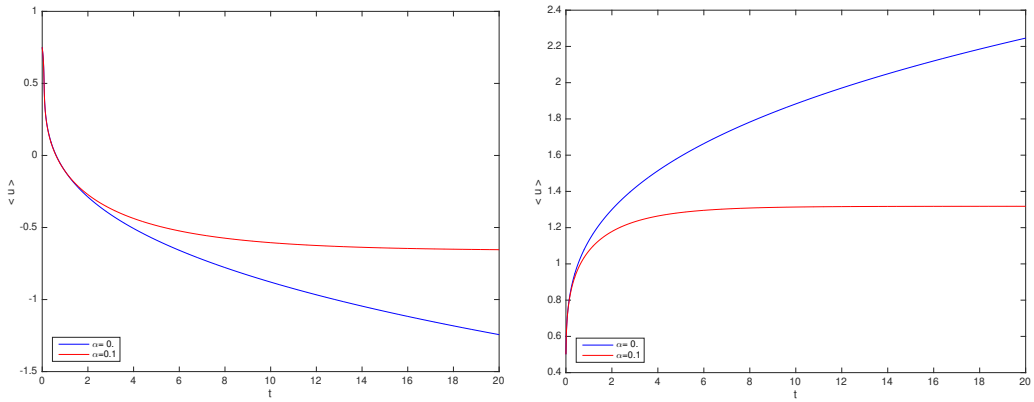

FIGURE 7.5 – $\varepsilon_1 = 1$, $h = h_1$ positive (left), $h = h_2$ negative (right)

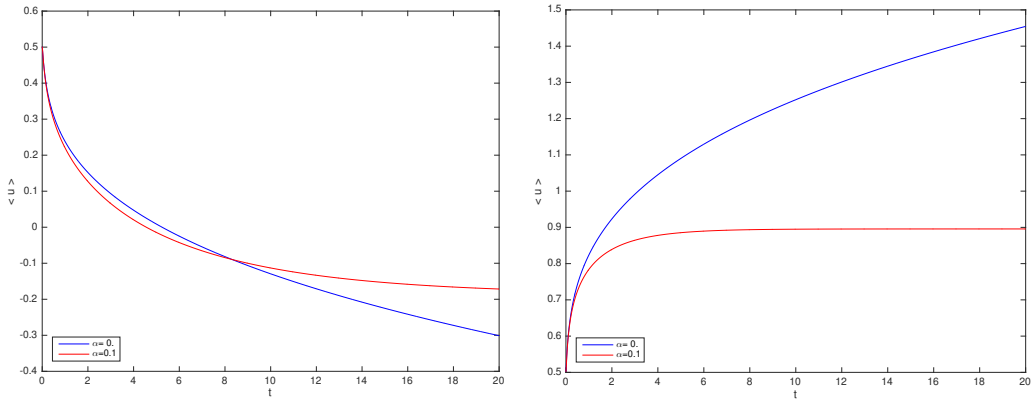

FIGURE 7.6 – $h = h_3$, $\varepsilon_1 = 1$, $\mathrm{Vol}(\Omega^+) > \mathrm{Vol}(\Omega^-)$ (left), $h = h_4$, $\varepsilon_1 = 1$, $\mathrm{Vol}(\Omega^+) < \mathrm{Vol}(\Omega^-)$ (right)

to $+\infty$ (right part of Figures 7.5 and 7.6), the solution to (7.42) with $\alpha = 0.1$ behaves as that to (7.1), but seems to remain bounded.

In Figure 7.7, we take $h = h_{5,\eta}$, with $\eta = \frac{1}{2}$. Moreover, we take $\varepsilon_1 = 1$ in the left part of the figure, $\varepsilon_1 = 0.2$ in the right part and make α vary. We observe that, in both cases, the steady state is reached for small values of α, but this is no longer true for larger values of α. Figure 7.8 displays the maximal and minimal values of the solution when $h = h_{5,\frac{1}{2}}$, $\varepsilon_1 = 0.2$ and for different values of α (the average $\langle u \rangle$ is displayed in the right part of Figure 7.7).

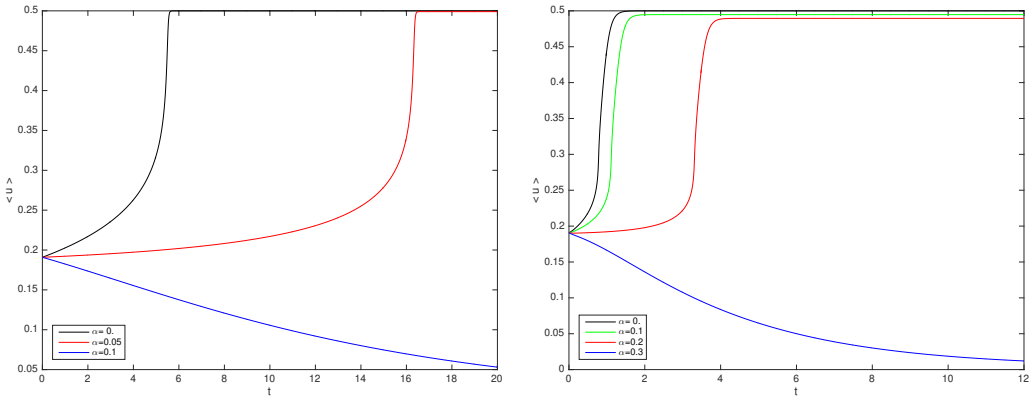

FIGURE 7.7 – Evolution of $\langle u \rangle$ when $\varepsilon_1 = 1$ (left) and $\varepsilon_1 = 0.2$ (right)

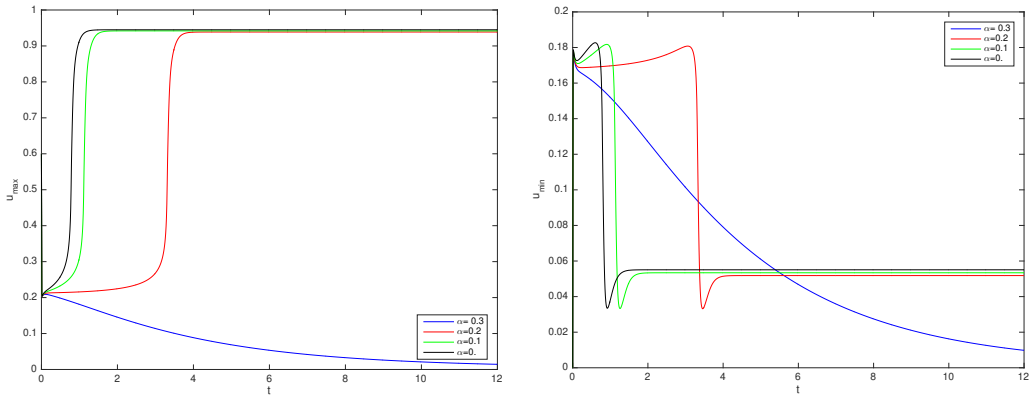

FIGURE 7.8 – Evolution of u_{max} (left) and $u_{\min}$ (right) when $\varepsilon_1 = 0.2$ and for different values of α

Chapitre 8

On a Cahn-Hilliard-Oono model for image segmentation

Sur un modèle de Cahn-Hilliard-Oono pour la segmentation d'images

On a Cahn-Hilliard-Oono model for image segmentation

8.1 Introduction

Image segmentation is the process of partitioning a image into multiple segments, which plays an significant role in image processing and computer vision. More precisely, it aims to partition a given image into regions in order to recognize and analyze different objects. The practical applications of image segmentation involve medical imaging, machine vision, object detection, video surveillance and so on. In the past few decades, a range of approaches have been proposed to deal with this problem, which include clustering methods, graph partitioning methods, statistics based methods, variational methods and PDEs based methods. We refer the reader to [19, 104, 117, 120, 121] and references therein for more details. And Cahn-Hilliard type models in the context of image processing can be found in [9, 18, 24, 21, 22, 33, 71].

In particular, a Cahn-Hilliard type model for image segmentation has been proposed and studied in [120], the authors prove the existence and uniqueness of solutions for the model, but their conclusion is based on the precondition that the solution u remains in the relevant interval $[0, 1]$. However, we have presented in [71] that there exist solutions which are unbounded when time goes to infinity, nevertheless, we can not obtain a global in time estimate on u. To overcome this, we consider a modified boundary value problem :

$$\frac{\partial u}{\partial t} + \alpha u + \varepsilon_1 \Delta^2 u - \frac{1}{\varepsilon_1}\Delta f(u) + \frac{\varepsilon_2 h(x)}{\varepsilon_2^2 + (u - \frac{1}{2})^2} = 0, \ \alpha > 0, \tag{8.1}$$

where f is a cubic nonlinear term and

$$h(x) = \frac{1}{\pi}(\lambda_1(i(x) - c_1)^2 - \lambda_2(i(x) - c_2)^2).$$

Here, $\varepsilon_1, \varepsilon_2, \lambda_1$ and λ_2 are positive constants and i is a given image taking values in $[0, 1]$. We will set $\varepsilon_i = 1, i = 1, 2$ in this paper for simplicity. Such a model takes advantage of the favorable features of high-order PDEs and is also easier to handle than Euler's elastica based models.

Furthermore, if we take $h(x) = 0$, the equation (8.1) will turn into the well-known Cahn-Hilliard equation when $\alpha = 0$, and the equation (8.1) will reduce to the Cahn-Hilliard-Oono equation when $\alpha > 0$. Note that the Cahn-Hilliard-Oono equation is proposed in [105] to account for long-ranged (i.e., nonlocal) interactions in the phase separation processes and also to simplify numerical simulations. We refer the interested reader to [11, 12, 97, 103] for reviews on the Cahn-Hilliard equation and some of its variants, as well as their mathematical analysis.

In this paper, we propose a modification of the model proposed in [120], based on the Cahn-Hilliard-Oono equation, which ensures the global in time boundedness of the solutions. We work on this model in two cases : $f(u)$ is a classic cubic term; $f(u)$ is a logarithmic term. We study the well-posedness and the asymptotic behavior of these models in different cases.

8.2 Setting of the problem

We consider the following initial and boundary value problem, in a bounded and regular domain $\Omega \subset \mathbb{R}^n$, $n = 1, 2$ or 3, with boundary Γ :

$$\frac{\partial u}{\partial t} + \alpha u + \Delta^2 u - \Delta f(u) + \frac{h(x)}{1 + (u - \frac{1}{2})^2} = 0, \tag{8.2}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{8.3}$$

$$u|_{t=0} = u_0. \tag{8.4}$$

We assume that $h \in L^\infty(\Omega)$, which is consistent with what is considered in [120]. We further take

$$f(s) = s^3 - s$$

for simplicity, though we can more generally consider any cubic polynomial with positive leading term, or even any regular function with such a cubic growth at infinity. Note in particular that the above nonlinear term satisfies the dissipativity properties

$$f' \geq -1 \tag{8.5}$$

and

$$F \geq -c, \ c \geq 0,$$

where

$$F(s) = \int_0^s f(\xi)\, d\xi = \frac{1}{4}s^4 - \frac{1}{2}s^2.$$

We then set

$$g(s) = \frac{1}{1 + (s - \frac{1}{2})^2}$$

and note that g is nonnegative and bounded by 1.

We finally set, for $v \in L^1(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \int_\Omega v(x)\, dx$$

and, for $v \in H^{-1}(\Omega)$,

$$\langle v \rangle = \frac{1}{\mathrm{Vol}(\Omega)} \langle v, 1 \rangle_{H^{-1}(\Omega), H^1(\Omega)}.$$

Furthermore, we set, whenever it makes sense,

$$\overline{v} = v - \langle v \rangle.$$

We denote by $((\cdot, \cdot))$ the usual L^2-scalar product, with associated norm $\|\cdot\|$. We also set $\|\cdot\|_{-1} = \|(-\Delta)^{-\frac{1}{2}} \cdot \|$, where $(-\Delta)^{-1}$ denotes the inverse of the negative Laplace operator associated with Neumann boundary conditions and acting on functions with null spatial average. More generally, we denote by $\|\cdot\|_X$ the norm on the Banach space X.

We note that

$$v \mapsto (\|\overline{v}\|_{-1}^2 + \langle v \rangle^2)^{\frac{1}{2}}, \ v \mapsto (\|\overline{v}\|^2 + \langle v \rangle^2)^{\frac{1}{2}},$$

$$v \mapsto (\|\nabla v\|^2 + \langle v \rangle^2)^{\frac{1}{2}} \text{ and } v \mapsto (\|\Delta v\|^2 + \langle v \rangle^2)^{\frac{1}{2}}$$

are norms on $H^{-1}(\Omega)$, $L^2(\Omega)$, $H^1(\Omega)$ and $H^2(\Omega)$, respectively, which are equivalent to the usual norms on these spaces. Furthermore, $\|\cdot\|_{-1}$ is a norm on $\{v \in H^{-1}(\Omega), \ \langle v \rangle = 0\}$ which is equivalent to the usual H^{-1}-norm.

At last, we recall several inequalities (see [71, 96]), which will be frequently applied below.

• The Poincaré-Wirtinger inequality :

$$\|\overline{v}\| \leq c\|\nabla v\|, \ \forall v \in H^1(\Omega). \tag{8.6}$$

Note that a consequence of this inequality is that

$$\|(-\Delta)^{-1} v\| \leq c\|v\|_{-1}, \ \forall v \in H^{-1}(\Omega), \ \langle v \rangle = 0. \tag{8.7}$$

• An interpolation inequality :

$$\|v\| \leq c\|v\|_{-1}^{\frac{1}{2}} \|\nabla v\|^{\frac{1}{2}}, \ \forall v \in H^1(\Omega), \ \langle v \rangle = 0. \tag{8.8}$$

Throughout this paper, the same coefficients c and c' denote (generally positive) constants which may change from line to line, or even in the same line.

8.3 The first model with cubic term

8.3.1 The well-posedness results

We first present the well-posedness result of the problem (8.2)-(8.4), which allows us to construct the dissipative semigroup so that we can prove the existence of the global attractor. The proof of existence is based on a standard Galerkin scheme.

Theorem 8.3.1. *For everty $u_0 \in H^1(\Omega)$ and every $T > 0$, (8.2)-(8.4) possesses a unique weak solution u such that*

$$u \in L^\infty(0,T;H^1(\Omega)) \cap L^2(0,T;H^2(\Omega)) \cap L^4(0,T;L^4(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0,T;H^{-1}(\Omega)).$$

Proof.

Integrating (8.2) over Ω to have

$$\frac{d\langle u\rangle}{dt} + \alpha\langle u\rangle + \langle h(x)g(u)\rangle = 0, \tag{8.9}$$

then it follows from (8.2) and (8.9) that

$$\frac{\partial \overline{u}}{\partial t} + \alpha\overline{u} + \Delta^2 u - \Delta f(u) + \overline{h(x)g(u)} = 0, \tag{8.10}$$

where $u = \overline{u} + \langle u\rangle$. We can rewrite in the equivalent weaker form of (8.2)-(8.4) :

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} + \alpha(-\Delta)^{-1}\overline{u} - \Delta u + \overline{f(u)} + (-\Delta)^{-1}\overline{h(x)g(u)} = 0, \tag{8.11}$$

$$\frac{\partial \overline{u}}{\partial \nu} = 0 \text{ on } \Gamma, \tag{8.12}$$

$$\overline{u}|_{t=0} = \overline{u}_0,\ \langle u\rangle|_{t=0} = \langle u_0\rangle. \tag{8.13}$$

Existence : The proof of existence is based on a standard Galerkin scheme and the a priori estimates. We consider the following approximated problem : for $m \in \mathbb{N}$ given, $\{\omega_i\}(i = 1, ..., m)$ forms an orthogonal in V basis, we set $V_m = span(\omega_1, ..., \omega_m)$ and find $u_m = \sum_{i=1}^m u_{i,m}\omega_i$, such that

$$\begin{aligned}&\frac{d}{dt}(((-\Delta)^{-1}\overline{u}_m, v)) + \alpha(((\Delta)^{-1}\overline{u}_m, v)) + ((u_m, v))_V + ((\overline{f(u_m)}, v))\\ &+ (((-\Delta)^{-1}\overline{h(x)g(u_m)}, v)) = 0 \text{ in } \mathcal{D}'(0,T), \forall v \in V_m,\end{aligned} \tag{8.14}$$

$$\frac{d\langle u_m\rangle}{dt} + \alpha\langle u_m\rangle + \langle h(x)g(u_m)\rangle = 0 \text{ in } \mathcal{D}'(0,T), \tag{8.15}$$

$$\overline{u}_m|_{t=0} = \overline{u}_0,\ \langle u_m\rangle|_{t=0} = \langle u_0\rangle, \tag{8.16}$$

where $u_m = \overline{u}_m + \langle u_m\rangle$ and $\mathcal{D}'$ denotes the space of distributions. In view of (8.15), employing the Gronwall's lemma to have

$$\langle u_m(t)\rangle = \langle u_0\rangle e^{-\alpha t} + e^{-\alpha t}\int_0^t e^{\alpha s}\langle h(x)g(u_m)\rangle\, ds,$$

so that

$$|\langle u_m(t)\rangle| \leq |\langle u_0\rangle| e^{-\alpha t} + \frac{\|h\|_{L^\infty(\Omega)}}{\alpha}(1 - e^{-\alpha t}),\ t \geq 0.$$

We further assume that $|\langle u_0\rangle| \leq M, M \geq 0$, in particular, we obtain that

$$|\langle u_m(t)\rangle| \leq |\langle u_0\rangle| + \frac{\|h\|_{L^\infty(\Omega)}}{\alpha} \leq M',\ \forall t \geq 0, \tag{8.17}$$

which means the spatial average of u_m is bounded, uniformly with respect to time.

Taking $v = \omega_i$ in (8.14), multiplying the resulting equality by $\overline{u}_{i,m}$ and summing over $i = 1, ..., m$ to have

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}_m\|_{-1}^2 + \alpha\|\overline{u}_m\|_{-1}^2 + \|\nabla u_m\|^2 + ((f(u_m), \overline{u}_m)) + ((h(x)g(u_m), (-\Delta)^{-1}\overline{u}_m)) = 0.$$

Noting that,employing the Young's inequality, we have

$$((f(u_m), u_m)) \geq \frac{3}{4}\|u_m\|_{L^4(\Omega)}^4 - c,$$

$$|\langle u_m\rangle \int_\Omega f(u_m)dx| \leq \frac{1}{4}\|u_m\|_{L^4(\Omega)}^4 + c_{M'},$$

and recalling that $h \in L^\infty(\Omega)$, g is bounded by 1, we have

$$|((h(x)g(u_m), (-\Delta)^{-1}\overline{u}_m))| \leq c\|u_m\| \leq \frac{1}{2}\|u_m\|^2 + c$$

by employing the Poincaré-Wirtinger inequality, Young's inequality and the embedding $L^2(\Omega) \hookrightarrow H^{-1}(\Omega)$ is continuous.

We deduce from the above that

$$\frac{d}{dt}\|\overline{u}_m\|_{-1}^2 + 2\alpha\|\overline{u}_m\|_{-1}^2 + \|\nabla u_m\|^2 + 2\|u_m\|_{L^4(\Omega)}^4 \leq c, \tag{8.18}$$

where c is may depend on M', we omit the subscript M' of constant c here and in the following.

In view of (8.15), we have

$$\frac{d\langle u_m\rangle^2}{dt} + \alpha\langle u_m\rangle^2 \leq c\langle u_m\rangle^2 + 1, \tag{8.19}$$

recalling (8.17) to deduce that

$$\frac{d}{dt}(\|\overline{u}_m\|_{-1}^2 + \langle u_m\rangle^2) + \alpha(\|\overline{u}_m\|_{-1}^2 + \langle u_m\rangle^2) + \|\nabla u_m\|^2 + 2\|u_m\|_{L^4(\Omega)}^4 \leq c. \tag{8.20}$$

Recalling that $V \mapsto (\|\overline{u}\|_{-1}^2 + \langle v \rangle^2)^{\frac{1}{2}}$ is a norm on $H^{-1}(\Omega)$, which is equivalent to the usual $H^{-1}(\Omega)$-norm. It thus follows from (8.20) and the Gronwall's lemma that u_m is bounded, independent of m, in $L^\infty(0,T;H^{-1}(\Omega)) \cap L^4(0,T;L^4(\Omega))$.

We then take $v = \omega_i$ in (8.14) and multiply the resulting equation by $\lambda_i u_{i,m}$ to find

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}_m\|^2 + \alpha\|\overline{u}_m\|^2 + \|\Delta u_m\|^2 + ((f'(u)\nabla u_m, \nabla u_m)) + ((h(x)g(u_m), u_m)) = 0,$$

employing the Poincaré–Wirtinger inequality again, we have

$$|((h(x)g(u_m), u_m))| \leq c\|u_m\| \leq c\|\nabla u_m\|,$$

it thus follows from (8.5),(8.19),(8.20) to obtain that

$$\frac{1}{2}\frac{d}{dt}\|u_m\|^2 + \alpha\|u_m\|^2 + \|\Delta u_m\|^2 \leq c\|\nabla u_m\|^2 + c', \tag{8.21}$$

it follows from (8.20),(8.21) and the uniform Gronwall's lemma that u_m is bounded, independent of m, in $L^\infty(0,T;L^2(\Omega)) \cap L^2(0,T;H^2(\Omega))$.

Finally, taking $v = \omega_i$ in (8.14) and multiply the resulting equation by $\frac{d\overline{u}_{i,m}}{dt}$ to have

$$\frac{d}{dt}(\alpha\|\overline{u}_m\|_{-1}^2 + \|\nabla u_m\|^2 + 2\int_\Omega F(u_m)dx) + 2\|\frac{\partial \overline{u}_m}{\partial t}\|_{-1}^2 - ((f(u_m), \langle \frac{\partial u_m}{\partial t} \rangle)) \\ + ((h(x)g(u_m), (-\Delta)^{-1}\frac{\partial \overline{u}_m}{\partial t})) = 0.$$

We note that, recalling (8.15),(8.17) and the properties of h and g, we have

$$-((f(u_m), \langle \frac{\partial u_m}{\partial t} \rangle)) = ((f(u_m), \alpha\langle u_m \rangle)) + ((f(u_m), \langle h(x)g(u_m) \rangle)) \\ \leq c\int_\Omega u_m^4 dx + c'$$

and

$$|((h(x)g(u_m), (-\Delta)^{-1}\frac{\partial \overline{u}_m}{\partial t}))| \leq c\|\frac{\partial \overline{u}_m}{\partial t}\|_{-1} \leq \frac{1}{2}\|\frac{\partial \overline{u}_m}{\partial t}\|_{-1}^2 + c.$$

Recalling (8.19), it thus follows from the above that

$$\frac{d}{dt}(\alpha\|u_m\|_{-1}^2 + \|\nabla u_m\|^2 + 2\int_\Omega F(u_m)dx) + \|\frac{\partial u_m}{\partial t}\|_{-1}^2 \leq c\int_\Omega u_m^4 dx + c', \tag{8.22}$$

which yields that u_m and $\frac{\partial u_m}{\partial t}$ are bounded, independent of m, in $L^\infty(0,T;H^1(\Omega))$ and $L^2(0,T;H^{-1}(\Omega))$, respectively.

It follows from the above and the Aubin-Lions compactness results that there exists $u \in L^\infty(0,T;H^1(\Omega)) \cap L^2(0,T;H^2(\Omega)) \cap L^4(0,T;L^4(\Omega))$, with $\frac{\partial u_m}{\partial t} \in L^2(0,T;H^{-1}(\Omega))$ such that

$$\begin{aligned}
u_m &\overset{*}{\rightharpoonup} u \text{ in } L^\infty(0,T;H^1(\Omega)),\\
u_m &\rightharpoonup u \text{ in } L^2(0,T;H^2(\Omega)),\\
u_m &\xrightarrow{a.e.} u \text{ in } L^4(0,T;L^4(\Omega)),\\
\frac{\partial u_m}{\partial t} &\rightharpoonup \frac{\partial u}{\partial t} \text{ in } L^2(0,T;H^{-1}(\Omega)),
\end{aligned}$$

passing to the limit in the linear terms is straightforward, the existence results can be deduced by the estimates above.

Uniqueness : Let u_1 and u_2 be two solutions with initial data $u_{1,0}$ and $u_{2,0}$, respectively, such that $\langle u_{1,0}\rangle = \langle u_{2,0}\rangle$. We set $u = u_1 - u_2$ and $u_0 = u_{1,0} - u_{2,0}$. We then have the following systerm :

$$\frac{\partial \overline{u}}{\partial t} + \alpha\overline{u} + \Delta^2 u - \Delta(f(u_1) - f(u_2)) + \overline{h(x)(g(u_1) - g(u_2))} = 0, \tag{8.23}$$

$$\frac{d\langle u\rangle}{dt} + \alpha\langle u\rangle + \langle h(x)(g(u_1) - g(u_2))\rangle = 0, \tag{8.24}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{8.25}$$

$$u|_{t=0} = u_0. \tag{8.26}$$

Proceeding as in the previous subsection, we can rewrite (8.23) in the equivalent weaker form

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} + \alpha(-\Delta)^{-1}\overline{u} - \Delta u + \overline{f(u_1) - f(u_2)} + (-\Delta)^{-1}\overline{h(x)(g(u_1) - g(u_2))} = 0. \tag{8.27}$$

Multiplying (8.27) by $\overline{u}$ to have

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

Noting that

$$((f(u_1) - f(u_2), \overline{u})) \geq -\|u\|^2 - \langle u\rangle \int_\Omega f(u_1) - f(u_2)dx$$

and

$$\begin{aligned}
|\langle u\rangle \int_\Omega f(u_1) - f(u_2)dx| &\leq c|\langle u\rangle| \int_\Omega |u|(u_1^2 + u_2^2 + 1)dx\\
&\leq c(\|u\|^2 + (\|u_1\|_{L^4(\Omega)}^4 + \|u_2\|_{L^4(\Omega)}^4 + 1)\langle u\rangle^2)\\
&\leq \frac{1}{4}\|\nabla u\|^2 + c(\|u_1\|_{L^4(\Omega)}^4 + \|u_2\|_{L^4(\Omega)}^4 + 1)(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2).
\end{aligned}$$

Furthermore, we note that

$$g(u_1) - g(u_2) = -\frac{(u_1 + u_2 - 1)u}{(1 + (u_1 - \frac{1}{2})^2)(1 + (u_2 - \frac{1}{2})^2)},$$

which yields

$$|h(x)(g(u_1) - g(u_2))| \leq c|u|$$

and

$$|((h(x)(g(u_1) - g(u_2)), (-\Delta)^{-1}\overline{u}))| \leq c\|u\|\|\overline{u}\|_{-1} \leq \frac{1}{4}\|\nabla u\|^2 + c(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2).$$

We then deduce from the above that

$$\frac{d}{dt}\|\overline{u}\|_{-1}^2 + 2\alpha\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 \leq c(\|u_1\|_{L^4(\Omega)}^4 + \|u_2\|_{L^4(\Omega)}^4 + 1)(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2).$$

In view of (8.9), we have

$$|\langle u(t)\rangle| \leq M', \ \forall t \geq 0, \tag{8.28}$$

and

$$\frac{d\langle u\rangle^2}{dt} + 2\alpha\langle u\rangle^2 \leq c\langle u\rangle^2, \tag{8.29}$$

to deduce that

$$\begin{aligned} &\frac{d}{dt}(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2) + 2\alpha(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2) + \|\nabla u\|^2 \\ &\leq c(\|u_1\|_{L^4(\Omega)}^4 + \|u_2\|_{L^4(\Omega)}^4 + 1)(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2). \end{aligned} \tag{8.30}$$

It follows from (8.20), (8.30) and the Gronwall's lemma that

$$\|u_1(t) - u_2(t)\|_{-1} \leq ce^{c't}\|u_{0,1} - u_{0,2}\|_{-1}, \ 0 \leq t \leq T, \tag{8.31}$$

which yields the uniqueness, as well as the continuous dependence with respect to the initial data in the H^{-1} topology. □

Remark 8.3.1. *It follows from the Lions-Magenes theorem (see[74, 96]) that if* $u \in L^2(0,T;H^2(\Omega))$ *and* $\frac{du}{dt} \in L^2(0,T;H^{-1}(\Omega))$*, then* $u \in C([0,T];H^{\frac{1}{2}}(\Omega))$*. It also follows from Strauss's lemma (see[110]) that if* $u \in C([0,T];H^{\frac{1}{2}}(\Omega)) \cap L^\infty(0,T;H^1(\Omega))$*, then* $u \in C([0,T];H^1_w(\Omega))$*, where the index w denotes the weak topology.*

8.3.2 Further a priori estimates

We need to derive higher regularities of the solutions and show that absorbing sets exist before we prove the existences of the attractors. We first write

$$\frac{d}{dt}\|u\|_{-1}^2 + 2\alpha\|u\|_{-1}^2 + \|\nabla u\|^2 + 2\|u\|_{L^4(\Omega)}^4 \le c, \tag{8.32}$$

it follows from (8.32) and the Gronwall's lemma that

$$\|u\|_{-1}^2 \le e^{-\alpha t}\|u_0\|_{-1}^2 + c,\ c > 0. \tag{8.33}$$

We deduce from (8.33) that exists a bounded subset B of $H^{-1}(\Omega)$ and t_0 such that $u_0 \in B$ and $t \ge t_0$ implies $u(t) \in \mathcal{B}_0$, where $\mathcal{B}_0 = \{\phi \in H^{-1}(\Omega), |\langle\phi\rangle| \le M', \|\phi\|_{H^{-1}(\Omega)}^2 \le c\}$ is the bounded absorbing set for the associated dynamical system on $H^{-1}(\Omega)$, then we can rewrite (8.33) as

$$\|u(t)\|_{-1} \le c, \tag{8.34}$$

and deduce from (8.32) that

$$\int_t^{t+r} \|\nabla u\|^2 ds \le c_r,\ t \ge t_0, r > 0, \tag{8.35}$$

$$\int_t^{t+r} \|u\|_{L^4(\Omega)}^4 ds \le c_r,\ t \ge t_0, r > 0. \tag{8.36}$$

We next write

$$\frac{1}{2}\frac{d}{dt}\|u\|^2 + \alpha\|u\|^2 + \|\Delta u\|^2 \le c\|\nabla u\|^2 + c'. \tag{8.37}$$

Noting that

$$\|u\|^2 \le 2(\|\overline{u}\|^2 + \langle u\rangle^2) \le c(\|\nabla u\|^2 + M'^2),$$

we deduce from (8.35),(8.37) and the uniform Gronwall's lemma that

$$\|u(t)\| \le c,\ t \ge t_1(\ge t_0), \tag{8.38}$$

$$\int_t^{t+r} \|\Delta u\|^2 ds \le c_r,\ t \ge t_1, \tag{8.39}$$

which yields the existence of a bounded absorbing set for the associated dynamical system on $L^2(\Omega)$.

Similarly, we write

$$\frac{d}{dt}(\alpha\|\overline{u}\|_{-1}^2 + \|\nabla u\|^2 + 2\int_\Omega F(u)dx) + \|\frac{\partial\overline{u}}{\partial t}\|_{-1}^2 \le c\int_\Omega u^4 dx + c', \tag{8.40}$$

and then deduce from (8.40) and the uniform Gronwall's lemma that

$$\|u(t)\|_{H^1(\Omega)} \leq c, \ t \geq t_2 (\geq t_1), \tag{8.41}$$

which yields the existence of a bounded absorbing set for the associated dynamical system in $H^1(\Omega)$.

We note that all estimates derived from these differential inequalities are justified within the above Galerkin scheme, passing to the (weak lower) limit.

We finally multiply (8.2) by $\Delta^2 u$ to obtain

$$\frac{1}{2}\frac{d}{dt}\|\Delta u\|^2 + \alpha\|\Delta u\|^2 + \|\Delta^2 u\|^2 - ((\Delta f(u), \Delta^2 u)) + ((h(x)g(u), \Delta^2 u)) = 0,$$

employing the interpolation inequality and Young's inequality, we have (see [96])

$$\begin{aligned} |((\Delta f(u), \Delta^2 u))| &\leq \|\Delta f(u)\|\|\Delta^2 u\| \\ &\leq c(1 + \|u\|^{\frac{7}{3}}_{H^1(\Omega)})\|\Delta^2 u\|^{\frac{5}{3}} \\ &\leq \frac{1}{4}\|\Delta^2 u\|^2 + c(1 + \|u\|^{14}_{H^1(\Omega)}). \end{aligned}$$

We further have

$$|((h(x)g(u), \Delta^2 u))| \leq c\|\Delta^2 u\| \leq \frac{1}{4}\|\Delta^2 u\|^2 + c,$$

hence, owing to (8.29), we have

$$\frac{d}{dt}(\|\Delta u\|^2 + \langle u\rangle^2) + \alpha(\|\Delta u\|^2 + \langle u\rangle^2) + \|\Delta^2 u\|^2 \leq c(1 + \|u\|^{14}_{H^1(\Omega)} + \langle u\rangle^2),$$

and, owing to (8.28) and (8.41), $\exists t_1$ such that, $\forall t \geq t_1$, we have

$$\frac{d}{dt}(\|\Delta u\|^2 + \langle u\rangle^2) + \alpha(\|\Delta u\|^2 + \langle u\rangle^2) + \|\Delta^2 u\|^2 \leq c, \tag{8.42}$$

We deduce from (8.42) and the uniform Gronwall's lemma that

$$\|u(t)\|_{H^2(\Omega)} \leq c, \ t \geq t_1, \tag{8.43}$$

$$\int_t^{t+r} \|\Delta^2 u\|^2 ds \leq c_r, \ t \geq t_1, \tag{8.44}$$

which yields the existence of a bounded absorbing set for the associated dynamical system in $H^2(\Omega)$.

We then obtain the following theorem :

Theorem 8.3.2. *We assume that $u_0 \in H^2(\Omega)$, with $\frac{\partial u_0}{\partial \nu} = 0$ on Γ. Then, the solution u given in Theorem 8.3.1 satisfies*

$$u \in C([0,T]; H^2(\Omega)) \cap L^2(0,T; H^4(\Omega))$$

and

$$\frac{\partial u}{\partial t} \in L^2(0,T; L^2(\Omega)),\ \forall T > 0.$$

Remark 8.3.2. (*i*) *Here we can more generally consider any cubic polynomial with positive leading coefficient or even any regular function with such a cubic growth at infinity, but with restrictions on the degree in two or three space dimensions. In two space dimensions, noting that the embedding $H^{\frac{2}{3}}(\Omega) \subset L^6(\Omega)$ is continuous and employing the interpolation inequality $\|v\|_{H^{\frac{2}{3}}(\Omega)} \leq c\|v\|^{\frac{2}{3}}\|v\|^{\frac{1}{3}}_{H^2(\Omega)}, \forall v \in H^{\frac{2}{3}}(\Omega)$, we can see that $\overline{f(u)} \in L^2(0,T;H)$, which yields the strong continuity in H; In three space dimensions, noting that the embedding $H^1(\Omega) \subset L^6(\Omega)$ and employing the interpolation inequality $\|v\|_{H^1(\Omega)} \leq c\|v\|^{\frac{1}{2}}\|v\|^{\frac{1}{2}}_{H^2(\Omega)}, \forall v \in H^1(\Omega)$, it follows that $\overline{f(u)} \in L^{\frac{4}{3}}(0,T;H)$ and $\frac{d\overline{u}}{dt} \in L^{\frac{4}{3}}(0,T; D(A^{-1}))$, which yields the weak continuity of $\overline{u}$ in H.*
(*ii*) *In particular, we can consider polynomials of degree $2p+1, p \in \mathbb{N}$, with positive leading coefficient in three space dimensions. We further note the following assumptions on the nonlinear term f :*

$$f \text{ is of class } C^2,\ f(0) = 0,$$

$$f'(s) \geq -c_0,\ c_0 \geq 0,\ s \in \mathbb{R},$$

$$|f(s)| \leq \varepsilon F(s) + c_\varepsilon,\ \forall \varepsilon > 0,\ s \in \mathbb{R},$$

$$f(s)(s-\kappa) \geq c_1 F(s) - c_2,\ F(s) \geq -c_3,\ \kappa = \langle s \rangle,\ c_1 > 0,\ c_2, c_3 \geq 0,\ s \in \mathbb{R},$$

where $F(s) = \int_0^s f(\xi)d\xi$. We can differentiate (8.13) with respect to time and obtain the H^2-estimate of u, which is globally in time, by steps. And prove the uniqueness, as well as the continuous dependence with respect to the initial data for $V-$norm, without any restriction on p in three space dimensions. The proof is essentially the same as that for the classical Cahn-Hilliard equation, more details can be found in [96].

8.3.3 Asymptotic behavior

We first give the preliminary materials and prove the existence of the global attractor.

Proposition 8.3.1. *We have the continuous (with respect to the H^{-1}-norm) semigroup $S(t)$ defined as*

$$S(t) : L^2(\Omega) \to L^2(\Omega), u_0 \mapsto u(t),\ t \geq 0.$$

The proposition directly follows from Section 8.3.1. Furthermore, it follows from Section 8.3.2 that $S(t)$ possesses a bounded absorbing set $\mathcal{B}_0'$ which is compact in $L^2(\Omega)$ and bounded in $H^2(\Omega)$, i.e.,

$$S(t) : L^2(\Omega) \to H^2(\Omega),\ t > 0.$$

Setting

$$\Phi_{M'} = \{v \in L^2(\Omega), |\langle v \rangle| \leq M'\},\ M' \geq 0,$$

it follows from the uniform estimates obtained in Section 8.3 that we have the dissipative semigroup (still denoted by $S(t)$) acting on the phase space $\Phi_{M'}$,

$$S(t) : \Phi_{M'} \to \Phi_{M'},\ t \geq 0.$$

Finally, it is deduced from standard results that we have the following theorem.

Theorem 8.3.3. *The semigoup $S(t)$ possesses a global attractor $\mathcal{A}$ such that $\mathcal{A}$ is compact in $L^2(\Omega)$ and bounded in $H^2(\Omega)$.*

Remark 8.3.3. *It is easy to see that we can assume, without loss of generality, that $\mathcal{B}_0'$ is positively invariant by $S(t)$, i.e. $S(t)\mathcal{B}_0' \subset \mathcal{B}_0',\ \forall t \geq 0$.*

We next give the definition of the fractal dimension, and prove that the dimension of the global attractor is finite in the next section.

Definition 8.3.1. Let $X \subset E$ be a (relatively) compact set. For $\varepsilon > 0$, let $N_\varepsilon(X)$ (if it is necessary to make the topology precise, we will also use the notation $N_\varepsilon(X, E)$) be the minimal number of balls of radius ε which are necessary to cover X. Then, the fractal dimension of X is the quantity (which belongs to $[0, +\infty]$)

$$\dim_F X = \limsup_{\varepsilon \to 0^+} \frac{\log_2 N_\varepsilon(X)}{\log_2 \frac{1}{\varepsilon}} \left(= \limsup_{\varepsilon \to 0^+} \frac{\ln N_\varepsilon(X)}{\ln \frac{1}{\varepsilon}} \right).$$

Furthermore, the quantity $\mathcal{H}_\varepsilon(X) (= \mathcal{H}_\varepsilon(X, E)) = \log_2 N_\varepsilon(X)$ is called the Kolmogorov $\varepsilon-$entropy of X.

Theorem 8.3.4. *Let X be a compact subset of E. We assume that there exist a Banach space E_1, with norm $\|\cdot\|_{E_1}$, such that E_1 is compactly embedded in E, and a mapping $L : X \to X$ such that $L(X) = X$ and L satisfies the following smoothing property on the difference of two solutions :*

$$\|Lx_1 - Lx_2\|_{E_1} \leq \eta \|x_1 - x_2\|_E,\ \forall x_1, x_2 \in X, c > 0.$$

Then, the fractal dimension of X is finite and satisfies

$$\dim_F X \leq \mathcal{H}_{\frac{1}{4\eta}}(B_{E_1}(0, 1), E),$$

where $B_{E_1}(0, 1)$ is the unit ball in E_1 (note that it is relatively compact in E, so that its $\frac{1}{4\eta}-$entropy is finite).

Proof. We recommend [96, 111] to interested readers for more details about the proof. □

We again consider the initial and boundary value problem (8.23)-(8.26), and it is sufficient here to take initial data belonging to the bounded absorbing set $\mathcal{B}_0'$ defined in the previous section. We first derive a smoothing property on the difference of the two solutions, which is vital to prove the existence of exponential attractors.

Multiplying (8.23) by $t\overline{u}$ to have

$$\frac{d}{dt}(t\|\overline{u}\|^2) + \alpha t\|\overline{u}\|^2 + t\|\Delta u\|^2 \leq \|\overline{u}\|^2 + ct\|\nabla u\|^2, \tag{8.45}$$

noting that

$$|(\overline{(h(x)(g(u_1) - g(u_2))}, t\overline{u}))| \leq ct\|\overline{u}\|^2 \leq ct\|\nabla u\|^2$$

and

$$((\nabla f(u_1) - \nabla f(u_2), \nabla u)) = ((f'(u_1)\nabla u, \nabla u)) + (((f'(u_1) - f'(u_2))\nabla u_2, \nabla u)),$$

where

$$((f'(u_1)\nabla u, \nabla u)) \geq -\|\nabla u\|^2$$

and

$$|(((f'(u_1) - f'(u_2))\nabla u_2, \nabla u))| = 3\int_\Omega (u_1^2 - u_2^2)\nabla u_2 \cdot \nabla u dx \leq c\|\nabla u\|^2$$

by employing (8.5), the generalized Hölder inequality, interpolation inequality and Theorem 8.3.1.

Integrating (8.30) between 0 and t, it follows from (8.31) that

$$\int_0^t \|\nabla u\|^2 ds \leq ce^{c't}\|u_{0,1} - u_{0,2}\|_{-1}^2.$$

Recalling again

$$\|u\|_{H^1(\Omega)}^2 \leq c(\|\nabla u\|^2 + \langle u\rangle^2)$$

so that

$$\int_0^t \|u\|_{H^1(\Omega)}^2 ds \leq ce^{c't}\|u_{0,1} - u_{0,2}\|_{-1}^2.$$

Owing to (8.29), we deduce from the above that

$$\frac{d}{dt}(t\|\overline{u}\|^2 + t\langle u\rangle^2) \leq \|\overline{u}\|^2 + \langle u\rangle^2 + ct(\|\nabla u\|^2 + \langle u\rangle^2), \tag{8.46}$$

Integrating (8.46) between 0 and t, we obtain

$$\|u(t)\|^2 \leq c\frac{1+t}{t}\int_0^t \|u\|_{H^1(\Omega)}^2 ds \leq c\frac{1+t}{t}e^{c't}\|u_{0,1} - u_{0,2}\|_{-1}^2, \tag{8.47}$$

where the constants c and c' are depend on M'.

We finally derive a Hölder (both with respect to space and time) estimate. Actually, the Hölder continuity with respect to x follows from (8.31). To prove the Hölder continuity with respect to t, we have

$$\|u(t_1) - u(t_2)\|_{-1} = \| \int_{t_1}^{t_2} \frac{\partial u}{\partial t} d\tau \|_{-1} \leq |t_1 - t_2|^{\frac{1}{2}} \Big| \int_{t_1}^{t_2} \| \frac{\partial u}{\partial t} \|_{-1}^2 d\tau \Big|^{\frac{1}{2}},$$

we note that, owing to (8.40),

$$\Big| \int_{t_1}^{t_2} \| \frac{\partial u}{\partial t} \|_{-1}^2 d\tau \Big| \leq c,$$

where the constant c depends on $\mathcal{B}_0'$ and T such that $t_1, t_2 \in [0, T]$ and

$$\|u(t_1) - u(t_2)\|_{-1} \leq c|t_1 - t_2|^{\frac{1}{2}}. \tag{8.48}$$

We finally deduce from (8.31), (8.47) and (8.48) the following results.

Theorem 8.3.5. *The semigroup $S(t)$ possesses an exponential attractor $\mathcal{M} \subset \mathcal{B}_0'$, i.e.*
(i) $\mathcal{M}$ is compact in $H^{-1}(\Omega)$;
(ii) $\mathcal{M}$ is positively invariant, $S(t)\mathcal{M} \subset \mathcal{M}, \forall t \geq 0$;
(iii) $\mathcal{M}$ has finite fractal dimension in $H^{-1}(\Omega)$;
(iv) $\mathcal{M}$ attracts exponentially fast the bounded subsets of $L^2(\Omega)$, $\forall B \subset L^2(\Omega)$ bounded,

$$\mathrm{dist}_{H^{-1}(\Omega)}(S(t)B, \mathcal{M}) \leq Q(\|B\|_{L^2(\Omega)}) e^{-ct}, \ c > 0, t \geq 0,$$

where the constant c is independent of B and $\mathrm{dist}_{H^{-1}(\Omega)}$ denotes the Hausdorff semidistance between sets defined by

$$\mathrm{dist}_{H^{-1}(\Omega)}(A, B) = \sup_{a \in A} \inf_{b \in B} \|a - b\|_{H^{-1}(\Omega)}.$$

Corollary 2. The semigroup $S(t)$ possesses the finite-dimensional global attractor $\mathcal{A} \subset \mathcal{B}_0'$.

Proof. According to Theorem 8.3.4 and (8.47), the conclusion follows immediately. □

Remark 8.3.4. *It follows from Theorem 8.3.4 and (8.47) that η is monotonically increasing with respect to M'. Owing to (8.17), one can easily deduce that $\eta \to +\infty$ as $\alpha \to 0$, which means $\frac{1}{4\eta} \to 0$ and it is then clear that the estimate on the dimension goes to $+\infty$.*

Remark 8.3.5. *A. Miranville has proved in [96, 86] that the dynamics of the Cahn-Hilliard-Oono equation is close to that of the original Cahn-Hilliard equation when α is small. In another word, we can construct exponential attractors for the Cahn-Hilliard-Oono equation converging to the exponential attractors for Cahn-Hilliard equation as $\alpha \to 0^+$. However, the conclusion is not valid in our case, we can not obtain the robustness here, since the solutions to the Cahn-Hilliard type model for image segmentation would be unbounded as time goes to infinity, and we can not obtain a global in time estimate on u.*

8.4 The second model with logarithmic term

In this section, we study the Cahn-Hilliard-Oono equation with logarithmic terms as following

$$\frac{\partial u}{\partial t} + \alpha u + \Delta^2 u - \Delta f(u) + h(x)g(u) = 0,\ \alpha > 0, \tag{8.49}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{8.50}$$

$$u|_{t=0} = u_0, \tag{8.51}$$

where

$$f(s) = -c_0(s - \frac{1}{2}) + \theta \ln \frac{s}{1-s},\ s \in (0,1), 0 < \theta < \frac{c_0}{4},$$

we can note that f is of class C^∞, which satisfies

$$f' \geq -c_0 \tag{8.52}$$

and

$$f(s)(s-m) \geq c_m(|f(s)| + F(s)) - c'_m,\ s \in \mathbb{R}, m \in (0,1),\ c_m > 0,\ c'_m \geq 0, \tag{8.53}$$

where $F(s) = \int_{\frac{1}{2}}^{s} f(\xi)\, d\xi$ and c_m and c'_m depend continuously on m. Furthermore, we can write

$$f(s) = f_1(s) - c_0 s, f_1' \geq 0.$$

The function f also enjoys the above properties.

8.4.1 The well-posedness results

We again employ a Galerkin scheme. The crucial step, to prove the existence of a solution to the above problem, consists of deriving an a priori estimate independent of N on the approximated logarithmic term $f_N(u_N)$ so that we can pass to the limit $N \to +\infty$ in the following approximated problems.

Theorem 8.4.1. *We assume that u_0 is given such that $u_0 \in H^1(\Omega)$, $0 < u_0(x) < 1$ and $0 < \langle u_0 \rangle < 1$, a.e. $x \in \Omega$. Then there exists $T_0 = T_0(u_0) > 0$, (8.49)-(8.51) possesses a weak solution u on $[0, T_0]$ such that*

$$u \in C([0,T_0]; H^1(\Omega)_W) \cap L^\infty(0,T_0; H^1(\Omega)) \cap L^2(0,T_0; H^2(\Omega)),$$

$$\frac{\partial u}{\partial t} \in L^2(0,T_0; H^{-1}(\Omega)).$$

Furthermore, $0 < u(x,t) < 1$, a.e $(x,t) \in \Omega \times (0,T_0)$.

Proof. We first define, for $N \in \mathbb{N}$, the approximated functions $f_N \in C^1(\mathbb{R})$ as

$$f_N(s) = \begin{cases} f(-1+\frac{1}{N}) + f'(-1+\frac{1}{N})(s+1-\frac{1}{N}), & s < -1+\frac{1}{N}, \\ f(s), & |s| \le 1-\frac{1}{N}, \\ f(1-\frac{1}{N}) + f'(1-\frac{1}{N})(s-1+\frac{1}{N}), & s > 1-\frac{1}{N}. \end{cases}$$

We easily see that f_N also satisfies

$$f_N' \ge -c_0, \tag{8.54}$$

and, for $s \in \mathbb{R}, m \in (0,1)$ and N large enough, f_N also enjoys the following inequality

$$f_N(s)(s-m) \ge c_m(|f_N(s)| + F_N(s)) - c_m', \ c_m > 0, \ c_m' \ge 0, \tag{8.55}$$

where $F_N(s) = \int_{\frac{1}{2}}^{s} f_N(\xi)\, d\xi$ and the constants are independent of N, we refer the reader to, e.g., [96] for the proof.

We then rewrite (8.49) in the following approximated form, for $N \in \mathbb{N}$:

$$\frac{\partial u_N}{\partial t} + \alpha u_N + \Delta^2 u_N - \Delta f_N(u_N) + h(x) g(u_N) = 0, \tag{8.56}$$

$$\frac{\partial u_N}{\partial \nu} = \frac{\partial \Delta u_N}{\partial \nu} = 0 \ on \ \Gamma, \tag{8.57}$$

$$u_N|_{t=0} = u_0, \tag{8.58}$$

We first integrate (8.56) over Ω and integrate by parts to have

$$\langle \frac{\partial u_N}{\partial t} \rangle + \alpha \langle u_N \rangle + \langle h(x) g(u_N) \rangle = 0, \tag{8.59}$$

which yields that

$$\langle u_N \rangle = \langle u_0 \rangle e^{-\alpha t} + e^{-\alpha t} \int_0^t e^{\alpha s} \langle h(x) g(u_N) \rangle ds, \tag{8.60}$$

so that

$$|\langle u_N(t) \rangle| \le \langle u_0 \rangle e^{-\alpha t} + \frac{\|h\|_{L^\infty(\Omega)}}{\alpha}(1 - e^{-\alpha t}), \tag{8.61}$$

it then follows from the above that there exists $T_0 = T_0(\delta, u_0) > 0$ such that, for $t \in [0, T_0]$,

$$|\langle u_N(t) \rangle| \le 1 - \delta, \ \delta \in (0, \frac{1}{2}). \tag{8.62}$$

Here, we assume that $2\delta < \langle u_0 \rangle \leq 1 - 2\delta$. Noting that T_0 can be chosen independent of the approximation parameter, which is essential to pass to the limit.

Then we rewrite (8.56) in the following equivalent form :

$$\frac{\partial \overline{u}_N}{\partial t} + \alpha \overline{u}_N + \Delta^2 \overline{u}_N - \Delta \overline{f_N(u_N)} + \overline{h(x)g(u_N)} = 0, \tag{8.63}$$

$$\frac{\partial \overline{u}_N}{\partial \nu} = \frac{\partial \Delta \overline{u}_N}{\partial \nu} = 0 \text{ on } \Gamma, \tag{8.64}$$

$$u_N|_{t=0} = \overline{u}_0. \tag{8.65}$$

Let us multiply (8.63) by $(-\Delta)^{-1}\overline{u}_N$ to obtain

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

It follows from (8.55), where we assume that $s = u_N$ and $m = \langle u_N \rangle$ to have

$$((\overline{f_N(u_N)}, \overline{u}_N)) = ((f_N(u_N), \overline{u}_N)) \geq c(\|f_N(u_N)\|_{L^1(\Omega)} + \int_\Omega F_N(u_N)dx) - c', \ c > 0,$$

and noting that

$$|((\overline{h(x)g(u_N)}, (-\Delta)^{-1}\overline{u}_N))| \leq c\|\overline{u}_N\|_{-1} \leq \frac{\alpha}{2}\|\nabla u_N\|_{-1}^2 + c.$$

We deduce from the above that

$$\frac{d}{dt}\|\overline{u}_N\|_{-1}^2 + \alpha\|\overline{u}_N\|_{-1}^2 + 2\|\nabla u_N\|^2 + c(\|f_N(u_N)\|_{L^1(\Omega)} + \int_\Omega F_N(u_N)dx) \leq c', \ c > 0.$$

In view of (8.59), we have

$$\frac{d\langle u_N \rangle^2}{dt} + \alpha\langle u_N \rangle^2 \leq c\langle u_N \rangle^2 \tag{8.66}$$

and

$$\frac{d}{dt}(\|\overline{u}_N\|_{-1}^2 + \langle u_N \rangle^2) + \alpha(\|\overline{u}_N\|_{-1}^2 + \langle u_N \rangle^2) + 2\|\nabla u_N\|^2$$
$$+c(\|f_N(u_N)\|_{L^1(\Omega)} + \int_\Omega F_N(u_N)dx) \leq +\langle u_N \rangle^2 + c', \ c > 0. \tag{8.67}$$

It follows from the above and the uniform Gronwall lemma that u_N is bounded, independent of N, in $L^\infty(0, T; H^{-1}(\Omega)) \cap L^2(0, T; H^1(\Omega))$.

Let us next multiply (8.63) by $(-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t}$ to have

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

Noting that

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

and

$$((\overline{h(x)g(u_N)}, (-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t})) \leq c\|\frac{\partial \overline{u}_N}{\partial t}\|_{-1} \leq \frac{1}{2}\|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 + c.$$

We obtain that

$$\frac{d}{dt}(\|\nabla u_N\|^2 + \alpha\|\overline{u}_N\|_{-1}^2 + 2\int_\Omega F_N(u_N)dx) + \|\frac{\partial \overline{u}_N}{\partial t}\|_{-1}^2 \leq c\|f_N(u_N)\|_{L^1(\Omega)} + c'. \tag{8.68}$$

It thus follows from (8.66)-(8.68) and the uniform Gronwall's lemma that u_N and $\frac{\partial u}{\partial t}$ are bounded, independent of N, in $L^\infty(0,T;H^1(\Omega))$ and $L^2(0,T;H^{-1}(\Omega))$, respectively.

We finally multiply (8.63) by $\overline{u}_N$ to have

$$\frac{1}{2}\frac{d}{dt}\|\overline{u}_N\|^2 + \alpha\|\overline{u}_N\|^2 + \|\Delta u_N\|^2 + ((f'(u)\nabla u_N, \nabla u_N)) + ((\overline{h(x)g(u_N)}, \overline{u}_N)) = 0,$$

it follows from (8.54) that

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

and noting that

$$\|((h(x)g(u_N), \overline{u}_N))\| \leq c\|\overline{u}_N\| \leq c'\|\nabla u_N\|,$$

and considering the inequality

$$\|\nabla u_N\|^2 \leq \frac{1}{2}\|\Delta u_N\|^2 + c\|\overline{u}_N\|^2 + c',$$

which follows from standard elliptic regularity results and a proper interpolation inequality. Combining the inequalities above to deduce

$$\frac{d}{dt}\|\overline{u}_N\|^2 + \|\Delta u_N\|^2 \leq c\|\overline{u}_N\|^2 + c'. \tag{8.69}$$

It follows from (8.66), (8.69) and the uniform Gronwall's lemma that u_N is bounded, independent of N, in $L^\infty(0,T;L^2(\Omega)) \cap L^2(0,T;H^2(\Omega))$.

Summing (8.67),(8.68),(8.69) multiplied by $\delta > 0$ small enough and (8.66), we finally obtain the energy inequality as following

$$\frac{dE_N}{dt} + c(E_N + \|\overline{u}_N\|^2_{H^2(\Omega)} + \|\frac{\partial \overline{u}_N}{\partial t}\|^2_{-1} + \|f_N(u_N)\|_{L^1(\Omega)}) \leq c', c' > 0,$$

where

$$E_N = \langle u_N \rangle^2 + \|\overline{u}_N\|^2_{-1} + \|\nabla u_N\|^2 + 2\int_\Omega F_N(u_N)dx + \delta\|\overline{u}_N\|^2$$

satisfies

$$E_N \geq c\|u_N\|^2_{H^1(\Omega)} - c', c > 0.$$

We also note that the dissipative estimate follows immediately by employing the Gronwall lemma

$$E_N(t) \leq e^{-ct}E_N(0) + c', c > 0, t \geq 0, \tag{8.70}$$

which yields

$$\|u_N(t)\|_{H^1(\Omega)} \leq ce^{-c't}(E_N(0) + 1), c' > 0, t \geq 0, \tag{8.71}$$

Note indeed that (8.63) yields

$$\overline{f_N(u_N)} = \Delta\overline{u}_N - (-\Delta)^{-1}\alpha\overline{u}_N - (-\Delta)^{-1}\frac{\partial \overline{u}_N}{\partial t} - (-\Delta)^{-1}\overline{h(x)g(u_N)},$$

so that

$$\|\overline{f_N(u_N)}\| \leq c(\|\Delta\overline{u}_N\| + \|\overline{u}_N\|_{-1} + \|\frac{\partial \overline{u}_N}{\partial t}\|_{-1} + 1)$$

and

$$\|\overline{f_N(u_N)}\|_{L^2(\Omega\times(0,T_0)} \leq cE_N(0). \tag{8.72}$$

Next, taking $s = u_N$ and $\langle u_N \rangle$ in (8.55), it follows from (8.62) that

$$\begin{aligned} |\langle f_N(u_N)\rangle| &\leq c((f_N(u_N), \overline{u}_N)) + c' \\ &= c((\overline{f_N(u_N)}, u_N)) + c' \\ &\leq c\|\overline{f_N(u_N)}\|\|u_N\| + c', \end{aligned} \tag{8.73}$$

where the above constants depend on δ and $\langle u_0 \rangle$. Therefore,

$$\begin{aligned}\|f_N(u_N)\|^2_{L^2(\Omega\times(0,T_0))} &\leq c(\|\overline{f_N(u_N)}\|^2_{L^2(\Omega\times(0,T_0)} + \int_0^{T_0} \langle f_N(u_N)\rangle^2 dt) \\ &\leq cE_N^2(0) + c'E_N(0)\|u_N\|^2 + c'' \\ &\leq cE_N^2(0) + c'\end{aligned}$$

so that

$$\|f_N(u_N)\|_{L^2(\Omega\times(0,T_0))} \leq c(E(0)+1). \tag{8.74}$$

As mentioned above, (8.74) is the crucial estimate to pass to the limit in the nonlinear term. Since the above estimates are independent of N, the solution of the approximated problems converges to a limit function u in the sense

$$\begin{aligned}&u_N \overset{*}{\rightharpoonup} u \text{ in } L^\infty(0,T_0;H^1(\Omega)),\\ &u_N \rightharpoonup u \text{ in } L^2(0,T_0;H^2(\Omega)),\\ &\frac{\partial u_N}{\partial t} \rightharpoonup \frac{\partial u}{\partial t} \text{ in } L^2(0,T_0;H^{-1}(\Omega)),\\ &f_N \rightharpoonup f \text{ in } L^2(\Omega\times(0,T_0))\end{aligned}$$

and

$$u_N \xrightarrow{a.e.} u \text{ in } C([0,T_0];H^1_W(\Omega))$$

by using the Aubin-Lions compactness results and W.A. Strauss lemma. We thus finish the proof of the existence.

The uniqueness follows instantly. Let u_1 and u_2 be two solutions with initial data $u_{1,0}$ and $u_{2,0}$, respectively, such that $\langle u_{1,0}\rangle = \langle u_{2,0}\rangle$. Setting $u = u_1 - u_2$, $u_0 = u_{1,0} - u_{2,0}$, we then have

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} + \alpha(-\Delta)^{-1}\overline{u} - \Delta u + \overline{f(u_1) - f(u_2)} + (-\Delta)^{-1}\overline{h(x)(g(u_1)-g(u_2))} = 0, \tag{8.75}$$

$$\frac{d\langle u\rangle}{dt} + \alpha\langle u\rangle + \langle h(x)(g(u_1)-g(u_2)\rangle = 0, \tag{8.76}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial \Delta u}{\partial \nu} = 0 \text{ on } \Gamma, \tag{8.77}$$

$$u|_{t=0} = u_0. \tag{8.78}$$

Multiplying (8.75) by $\overline{u}$, we obtain

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

in view of (8.52), employing the interpolation inequality, which yields

$$((f(u_1) - f(u_2), \overline{u})) \geq -c_0\|u\|^2 \geq -c_0\|u\|_{-1}\|\nabla u\|,$$

and noting that

$$|h(x)(g(u_1) - g(u_2))| \leq c|u|$$

so that

$$|((h(x)(g(u_1) - g(u_2)), (-\Delta)^{-1}\overline{u}))| \leq c\|u\|\|\overline{u}\|_{-1} \leq \frac{1}{4}\|\nabla u\|^2 + c(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2)$$

by using interpolation inequality and Poincaré-Wirtinger inequality. It follows from (8.76) that

$$\frac{d\langle u\rangle^2}{dt} + 2\alpha\langle u\rangle^2 \leq c\langle u\rangle^2, \tag{8.79}$$

we then deduce from the above that

$$\frac{d}{dt}(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2) + 2\alpha(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2) + \|\nabla u\|^2 \leq c(\|\overline{u}\|_{-1}^2 + \langle u\rangle^2), \tag{8.80}$$

employing the uniform Gronwall's lemma, we obtain

$$\|u_1(t) - u_2(t)\|_{-1} \leq ce^{c't}\|u_{1,0} - u_{2,0}\|_{-1},\ 0 \leq t \leq T, \tag{8.81}$$

which yields the uniqueness, as well as the continuous dependence with respect to the initial data in the H^{-1} topology. □

Remark 8.4.1. *(i) Note that if $\|h\|_{L^\infty(\Omega)} \leq \alpha$, then it follows from (8.61) that $\delta \leq \langle u_N(t)\rangle \leq 1 - \delta$ for all times, so that the solution is actually global in time.*
(ii) When $\|h\|_{L^\infty(\Omega)} = 0$, it follows from (8.61) that $\langle u\rangle \in (0, 1)$ holds for all times, and the global in time existence of the solution for the Cahn-Hilliard-Oono equation can be obtained easily.

8.4.2 Regularity and separation from the pure states

We have the following results.

Proposition 8.4.1. *The solution u to (8.49)-(8.51) given in Theorem8.4.1 satisfies*

$$\frac{\partial u}{\partial t} \in L^\infty(r, +\infty; H^{-1}(\Omega)) \cap L^2(r, T; H^1(\Omega))$$

$\forall r < T$, where $r > 0$ and $T > 0$ are given.

Proof. We recall that we have the equation

$$(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} + \alpha(-\Delta)^{-1}\overline{u} - \Delta u + \overline{f(u)} + (-\Delta)^{-1}\overline{h(x)g(u)} = 0. \tag{8.82}$$

Differentiating (8.82) with respect to time, we have

$$(-\Delta)^{-1}\frac{\partial}{\partial t}\frac{\partial \overline{u}}{\partial t} + \alpha(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} - \Delta\frac{\partial \overline{u}}{\partial t} + \overline{f'(u)\frac{\partial u}{\partial t}} + (-\Delta)^{-1}\overline{h(x)g'(u)\frac{\partial u}{\partial t}} = 0, \tag{8.83}$$

multiplying (8.83) by $\frac{\partial \overline{u}}{\partial t}$, we obtain

$$\frac{1}{2}\frac{d}{dt}\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + \alpha\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + \|\nabla\frac{\partial u}{\partial t}\|^2 + ((f'(u)\frac{\partial u}{\partial t}, \frac{\partial \overline{u}}{\partial t})) + ((h(x)g'(u)\frac{\partial u}{\partial t}, (-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t})) = 0,$$

recalling the properties of h, g and (8.52), we write instead

$$|((h(x)g'(u)\frac{\partial u}{\partial t}, (-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t}))| \leq c\|\frac{\partial u}{\partial t}\|\|\frac{\partial \overline{u}}{\partial t}\|_{-1}$$

and

$$\begin{aligned}((f'(u)\frac{\partial u}{\partial t}, \frac{\partial \overline{u}}{\partial t})) &= ((f'(u)\frac{\partial u}{\partial t}, \frac{\partial u}{\partial t})) - \frac{d\langle u\rangle}{dt}((f'(u)\frac{\partial u}{\partial t}, 1)) \\ &\geq -c_0\|\frac{\partial u}{\partial t}\|^2 - \frac{d\langle u\rangle}{dt}\frac{d}{dt}\int_\Omega F(u)dx \\ &= -c_0\|\frac{\partial u}{\partial t}\|^2 - \frac{d}{dt}(\frac{d\langle u\rangle}{dt}\int_\Omega F(u)dx) + \frac{d^2\langle u\rangle}{dt^2}\int_\Omega F(u)dx.\end{aligned}$$

Setting

$$\Lambda = \frac{1}{2}\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 - \frac{d\langle u\rangle}{dt}\int_\Omega F(u)dx,$$

we deduce from the above that

$$\frac{d\Lambda}{dt} + \alpha\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + \frac{1}{2}\|\nabla\frac{\partial u}{\partial t}\|^2 \leq c(\|\frac{\partial u}{\partial t}\|_{-1}^2 + |\frac{d\langle u\rangle}{dt}|^2) - \frac{d^2\langle u\rangle}{dt^2}\int_\Omega F(u)dx \tag{8.84}$$

by employing proper interpolation inequalities.

Recalling (8.60) and (8.70), we can see that Λ is bounded from below :

$$\Lambda \geq \frac{1}{2}\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 - c.$$

Similarly, it is easy to prove that the last two terms on the right-hand side of (8.84) are bounded from the above. We finally obtain the differential inequality of the form

$$\frac{d\Lambda}{dt} + \alpha\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + \frac{1}{2}\|\nabla\frac{\partial u}{\partial t}\|^2 \leq c(\|\frac{\partial u}{\partial t}\|_{-1}^2 + \langle u_0\rangle^2 + E(0)^2 + 1), \tag{8.85}$$

where E is the equivalent of E_N for u, the resulte follows from (8.66) and (8.85) by using the uniform Gronwall's lemma. □

Proposition 8.4.2. *We assume that* $2 \le p < +\infty$ *when* $n = 2$ *and* $2 \le p \le 6$ *when* $n = 3$. *Then, the solution* u *further satisfies*

$$\|f(u)\|_{L^\infty(r,t;L^p(\Omega))} \le c,\ \|u(t)\|_{W^{2,p}(\Omega)} \le c$$

$\forall t \ge r, r > 0$ *given, where the constant* c *depends on the* $H^1(\Omega)$*-norm of* u_0.

Proof. We rewrite (8.82) as an elliptic equation :

$$\begin{aligned} -\Delta u + f_1(u) &= -(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t} + \langle f(u)\rangle + c_0 u - \alpha(-\Delta)^{-1}\overline{u} - (-\Delta)^{-1}\overline{h(x)g(u)} \\ &\equiv h_u. \end{aligned} \tag{8.86}$$

Recall that $f(s) = f_1(s) - c_0 s$, $f_1' \ge 0$, (8.72) and (8.73) for u and f and note that, owing to Proposition8.4.1, $\overline{f(u)} \in L^\infty(r,t;L^2(\Omega))$, so that

$$\langle f(u)\rangle \in L^\infty(r,t).$$

Then, it follows from the above that

$$\begin{aligned} \|h_u\|_{H^1(\Omega)} &\le \|(-\Delta)^{-1}\frac{\partial \overline{u}}{\partial t}\|_{H^1(\Omega)} + |\langle f(u)\rangle| + c_0\|u\|_{H^1(\Omega)} + \alpha\|(-\Delta)^{-1}\overline{u}\|_{H^1(\Omega)} \\ &\quad + |(-\Delta)^{-1}\overline{h(x)g(u)}| \\ &\le c(\|\frac{\partial \overline{u}}{\partial t}\|_{-1} + |\langle f(u)\rangle| + \|u\|_{H^1(\Omega)} + \|\overline{u}\|_{-1}) \\ &\le c, t \ge r, \end{aligned}$$

so that

$$\|h_u\|_{L^\infty(r,t;H^1(\Omega))} \le c, t \ge r, \tag{8.87}$$

where the constant c depends on the $H^1(\Omega)$-norm of u_0.

We then multiply (8.86) by $|f_1(u)|^{p-2}f_1(u)$ to obtain

$$-\int_\Omega \Delta u|f_1(u)|^{p-2}f_1(u)dx + \int_\Omega |f_1(u)|^p dx = \int_\Omega h_u|f_1(u)|^{p-2}f_1(u)dx.$$

We note that

$$-\int_\Omega \Delta u|f_1(u)|^{p-2}f_1(u)dx = (p-1)\int_\Omega |f_1(u)|^{p-2}f_1'(u)|\nabla u|^2 dx \ge 0,$$

since $f_1' \ge 0$. Furthermore, we obtain, employing Young's inequality and proper Sobolev embedding theorems,

$$\begin{aligned} |\int_\Omega h_u|f_1(u)|^{p-2}f_1(u)dx| &\le \frac{1}{2}\|f_1(u)\|^p_{L^p(\Omega)} + \|h_u\|^p_{L^p(\Omega)} \\ &\le \frac{1}{2}\|f_1(u)\|^p_{L^p(\Omega)} + \|h_u\|^p_{H^1(\Omega)}. \end{aligned}$$

It thus follows that

$$\|f_1(u)\|^p_{L^p(\Omega)} \leq c\|h_u\|^p_{H^1(\Omega)},$$

so that

$$\|f(u)\|_{L^p(\Omega)} \leq c(\|h_u\|_{H^1(\Omega)} + \|u\|_{H^1(\Omega)}). \tag{8.88}$$

We finally deduce from (8.87)-(8.88) (and (8.70) again) that

$$\|f(u)\|_{L^\infty(r,t;L^p(\Omega))} \leq c, t \geq r. \tag{8.89}$$

Having this, it follows from standard elliptic regularity results applied to (8.86) and (8.87) that

$$\|u\|_{L^\infty(r,t;W^{2,p}(\Omega))} \leq c, t \geq r,$$

which finishes the proof, recalling that $u \in C([0,T];H^1(\Omega)), \forall T > 0$. □

As a consequence of (8.89) we have the following result.

Theorem 8.4.2. *We assume that $n = 1$. Then, there exists $\delta \in (0,1)$ depending on the $H^1(\Omega)$-norm of u_0 such that*

$$\|u(t)\|_{L^\infty(\Omega)} \leq 1 - \delta, t \geq r,$$

where $r > 0$ is given.

Proof. We can pass to the limit $p \to +\infty$ in (8.89) (see [1, 3]) and conclude the proof, owing to the continuity of u with respect to time. □

Remark 8.4.2. *The separation property from the pure states given in Theorem 8.4.1 means, roughly speaking, that we never completely reach the pure states during the phase separation process : there always remains at least some trace of the other component. The above strict separation property says that not only can we never completely reach the pure states, but also there remains some given quantity of the other component.*

Proving the strict separation property in two space dimensions is more involved and is based on the following result.

Proposition 8.4.3. *We assume that $n = 2$. Then, the following holds for every $t \geq r, r > 0$ given, and for every $p \in \mathbb{N}$:*

$$\|f'(u)\|_{L^p(\Omega\times(r,t))} \leq c,$$

where the constant c depends on p.

Proof. We also need to deal with the elliptic equation (8.86), the tricks we use here are similar to those in Proposition 8.4.2, we recommend to readers [96] for more details. □

Then we can prove additional regularity on the time derivative of u.

Proposition 8.4.4. *We assume that $n = 2$. Then, the weak solution u to (8.49)-(8.51) further satisfies*

$$\frac{\partial u}{\partial t} \in L^{\infty}(r, +\infty; L^2(\Omega)) \cap L^2(r, T; H^2(\Omega))$$

$\forall r < T$, where $r > 0$ and $T > 0$ are given.

Proof. We multiply (8.83) by $-\Delta\frac{\partial \overline{u}}{\partial t}$ to obtain

$$\frac{1}{2}\frac{d}{dt}\|\frac{\partial \overline{u}}{\partial t}\|^2 + \alpha\|\frac{\partial \overline{u}}{\partial t}\|^2 + \|\Delta\frac{\partial \overline{u}}{\partial t}\|^2 + ((f'(u)\frac{\partial u}{\partial t}, \Delta\frac{\partial \overline{u}}{\partial t})) + (((-\Delta)^{-1}\overline{h(x)g'(u)\frac{\partial u}{\partial t}}, -\Delta\frac{\partial \overline{u}}{\partial t})) = 0,$$

in view of the properties of h and g again, we have

$$(((-\Delta)^{-1}\overline{h(x)g'(u)\frac{\partial u}{\partial t}}, -\Delta\frac{\partial \overline{u}}{\partial t})) \leq c\|\frac{\partial \overline{u}}{\partial t}\|^2$$

and

$$\begin{aligned}
|((f'(u)\frac{\partial u}{\partial t}, \Delta\frac{\partial \overline{u}}{\partial t}))| &\leq \|f'(u)\|_{L^4(\Omega)}\|\frac{\partial u}{\partial t}\|_{L^4(\Omega)}\|\Delta\frac{\partial \overline{u}}{\partial t}\| \\
&\leq c\|f'(u)\|_{L^4(\Omega)}\|\frac{\partial u}{\partial t}\|^{\frac{1}{2}}\|\Delta\frac{\partial \overline{u}}{\partial t}\|^{\frac{3}{2}} \\
&\leq \frac{1}{2}\|\Delta\frac{\partial \overline{u}}{\partial t}\|^2 + c\|f'(u)\|^4_{L^4(\Omega)}\|\frac{\partial u}{\partial t}\|^2.
\end{aligned}$$

by employing the Hölder, Ladyzhenskaya, and Young inequalities. In view of (8.66), it is deduced from the above that

$$\frac{d}{dt}\|\frac{\partial u}{\partial t}\|^2 + \|\Delta\frac{\partial u}{\partial t}\|^2 \leq (c\|f'(u)\|^4_{L^4(\Omega)} + c')\|\frac{\partial u}{\partial t}\|^2,$$

we can conclude by applying the uniform Gronwall's lemma, with (8.84) and Proposition 8.4.3 (for $p = 4$). □

Remark 8.4.3. *This regularity also holds in one space dimension, owing to the strict separation property given in Theorem 8.4.2.*

We then obtain the following result.

Theorem 8.4.3. *We assume that $n = 2$. Then, there exists $\delta \in (0, 1)$ depending on the $H^1(\Omega)$-norm of u_0 such that*

$$\|u(t)\|_{L^{\infty}(\Omega)} \leq 1 - \delta, t \geq r,$$

where $r > 0$ is given.

Proof. We note that, owing to the regularity given in Proposition 8.4.4, the right-hand side h_u in (8.86) satisfies

$$\|h_u\|_{L^\infty(\Omega\times(r,t))} \leq c, t \geq r.$$

Having this, we can proceed as in the proof of Proposition 8.4.4 □

Remark 8.4.4. *(i) The strict separation property is still open in the three space dimension.*
(ii) Having the strict separation property also allows us to prove the finite fractal dimensionality of the global attractor.

8.4.3 Asymptotic behavior

Based on the dissipative estimations in Section 8.4.1, we set

$$\Phi = \{v \in H^1(\Omega) \cap L^\infty(\Omega), 0 < v(x) < 1 a.e., |\langle v \rangle| < 1\},$$

we can define the continuous (for the $H^{-1}(\Omega)$-norm) semigroup

$$S_\alpha(t) : \Phi \to \Phi, u_0, t \geq 0.$$

It follows from (8.71) that $S_\alpha(t)$ is dissipative in Φ, i.e., it possesses a bounded absorbing set $\mathcal{B}_1 \subset \Phi$. We then obtain the following result.

Theorem 8.4.4. *The semigoup $S_\alpha(t)$ possesses a global attractor $\mathcal{A}_\alpha$ such that $\mathcal{A}_\alpha$ is compact in Φ.*

Furthermore, we have the existence of a uniform (with respect to α) absorbing set $\mathcal{B}_1' \subset \Phi \cap H^2(\Omega)$, i.e., $\forall B \subset \Phi$ bounded, $\exists t_0 = t_0(B)$ independent of α such that

$$S_\alpha(t)B \subset \mathcal{B}_1', t \geq t_0,$$

it thus sufficient to construct the exponential attractors $\mathcal{M}_\alpha$.

Theorem 8.4.5. *The semigroup $S_\alpha(t)$ possesses an exponential attractor $\mathcal{M}_\alpha$ on $\mathcal{B}_1'$.*

Proof. We again consider the initial and boundary value problem (8.75)-(8.78), and derive a smoothing property on the difference of the two solutions, which is the crucial step to prove the existence of exponential attractors.

We next multiply (8.75) by $t\frac{\partial \overline{u}}{\partial t}$ to have

$$\frac{1}{2}\frac{d}{dt}(\alpha t\|\overline{u}\|_{-1}^2 + t\|\nabla u\|^2) + t\|\frac{\partial \overline{u}}{\partial t}\|_{-1}^2 + t((f(u_1) - f(u_2), \frac{\partial \overline{u}}{\partial t}))$$
$$+t(((-\Delta)^{-1}\overline{h(x)(g(u_1) - g(u_2))}, \frac{\partial \overline{u}}{\partial t})) = \frac{\alpha}{2}\|\overline{u}\|_{-1}^2 + \frac{1}{2}\|\nabla u\|^2.$$

We note that

$$\begin{aligned}((f(u_1)-f(u_2),\frac{\partial\overline{u}}{\partial t}))&\le c\|\nabla(f(u_1)-f(u_2))\|\|\frac{\partial\overline{u}}{\partial t}\|_{-1}\\&\le c\|\nabla(\int_0^1 f'(u_1+s(u_2-u_1))dsu)\|\|\frac{\partial\overline{u}}{\partial t}\|_{-1}\\&\le c\|\int_0^1 f'(u_1+s(u_2-u_1))ds\nabla u\|\|\frac{\partial\overline{u}}{\partial t}\|_{-1}\\&\quad+\|u\int_0^1 f''(u_1+s(u_2-u_1))(\nabla u_1+s\nabla(u_2-u_1))ds\|\|\frac{\partial\overline{u}}{\partial t}\|_{-1}\\&\le c(\|\nabla u\|+\|\|u\|\nabla u_1\|\|+\|\|u\|\nabla u_2\|\|)\|\frac{\partial\overline{u}}{\partial t}\|_{-1}\\&\le c\|u\|^2_{H^1(\Omega)}+\frac{1}{4}\|\frac{\partial\overline{u}}{\partial t}\|^2_{-1}\end{aligned}$$

and

$$|(((-\Delta)^{-1}\overline{h(x)(g(u_1)-g(u_2))},\frac{\partial\overline{u}}{\partial t}))|\le c\|u\|\|\frac{\partial\overline{u}}{\partial t}\|_{-1}\le c\|\nabla u\|^2+\frac{1}{4}\|\frac{\partial\overline{u}}{\partial t}\|^2_{-1}$$

by employing Hölder, Young, Poincaré inequality and continuous embedding, where the constant c only depends on $\mathcal{B}_1'$. We have

$$\frac{d}{dt}(\alpha t\|\overline{u}\|^2_{-1}+t\|\nabla u\|^2)+t\|\frac{\partial\overline{u}}{\partial t}\|^2_{-1}\le\alpha\|\overline{u}\|^2_{-1}+ct\|u\|^2_{H^1(\Omega)}+c't\|\nabla u\|^2.$$

Owing to (8.79), we further obtain

$$\begin{aligned}&\frac{d}{dt}(\alpha t\|\overline{u}\|^2_{-1}+t\|\nabla u\|^2+t\langle u\rangle^2)+t\|\frac{\partial\overline{u}}{\partial t}\|^2_{-1}+\alpha\langle u\rangle^2\\&\le\alpha(\|\overline{u}\|^2_{-1}+\langle u\rangle^2)+ct(\|u\|^2_{H^1(\Omega)}+\langle u\rangle^2)+c't(\|\nabla u\|^2+\langle u\rangle^2).\end{aligned}\tag{8.90}$$

Integrating (8.80) over $(0,t)$, we get

$$\int_0^t\|\nabla u\|^2ds\le ce^{c't}\|u_{0,1}-u_{0,2}\|^2_{-1},\tag{8.91}$$

where the constant c' only depends on $\mathcal{B}_1'$, hence

$$\int_0^t\|u\|^2_{H^1(\Omega)}ds\le ce^{c't}\|u_{0,1}-u_{0,2}\|^2_{-1}.\tag{8.92}$$

Owing to (8.81), (8.90)-(8.92) and the uniform Gronwall's lemma, we have

$$\|u_1-u_2\|^2_{H^1(\Omega)}\le ce^{c't}\|u_{0,1}-u_{0,2}\|^2_{-1},\ \forall t>0.\tag{8.93}$$

We finally derive a Hölder (both with respect to space and time) estimate. Actually, the Hölder continuity with respect to x follows from (8.81). To prove the Hölder continuity with respect to t, we have

$$\|u(t_1) - u(t_2)\|_{-1} = \| \int_{t_1}^{t_2} \frac{\partial u}{\partial t} d\tau \|_{-1} \leq |t_1 - t_2|^{\frac{1}{2}} \Big| \int_{t_1}^{t_2} \| \frac{\partial u}{\partial t} \|_{-1}^2 d\tau \Big|^{\frac{1}{2}},$$

we note, owing to Proposition 8.4.1, that

$$\Big| \int_{t_1}^{t_2} \| \frac{\partial u}{\partial t} \|_{-1}^2 d\tau \Big| \leq c,$$

where the constant c depends on $\mathcal{B}_1'$ and T such that $t_1, t_2 \in [0, T]$ and

$$\|u(t_1) - u(t_2)\|_{-1} \leq c|t_1 - t_2|^{\frac{1}{2}}. \tag{8.94}$$

The conclusion is finally deduced from (8.81), (8.93) and (8.94). □

Corollary 3. The semigroup $S_\alpha(t)$ possesses the finite-dimensional global attractor $\mathcal{A}_\alpha$.

Proof. It follows immediately in view of Theorem 8.3.4 and Theorem 8.4.5. □

Remark 8.4.5. *Because of the same reason we explained in Remark 8.3.5, we do not have the robustness of exponential attractor in this case.*

Chapitre 9

Conclusion générale et perspectives

We introduced the phase separation models associated with regular potential and logarithmic potential, and we focused on the mathematical analysis of the applications of Cahn-Hilliard type equations in biology and image processing. Results from these studies have led to a deeper understanding about tumor growth and image segmentation. We conclude our achievements as following :

In our study of Cahn-Hilliard models for glial cells, which was proposed to model some energy mechanisms in glial cells. We considered a thermodynamically relevant logarithmic nonlinear term to prove the existence of a biologically relevant solution, and obtained a strict separation from the pure states 0 and 1 in one and two space dimensions by proving additional regularity on the solutions. We further approached a second model based on the Chan-Hilliard-Oono equation with the same idea.

We next studied a coupled reaction-diffusion system, which accounts for the tumor and oxygen dynamics. By analogy, Cahn-Hilliard type equations in tumor growth were proposed to separate, e.g., different zones in the tumor such as quiescent and proliferative cells. Moreover, Cahn-Hilliard type equations also model clustering of brain tumor cells. Note that such effects can not be modeled by a reaction-diffusion equation. Therefore, we dealt with three variants of the coupled model for the proliferative-to-invasive transition of hypoxic glioma cells : In [72], we considered a Cahn-Hilliard type equation for the oxygen concentration, which accounts for the phase separation processes (e.g., different zones in the cells in which, typically, the concentration of oxygen may be high or very low) ; In [70], we considered a Cahn-Hilliard type equation for the tumor density, which accounts for phase separation processes (e.g., different zones in the tumor) and clustering effects in tumor growth. In[69], we considered Cahn-Hilliard type equations for both the tumor density and the oxygen concentration. We proved the existence of a biologically relevant solution by considering a modified model and taking a logarithmic nonlinear term in the Cahn-Hilliard equation. In particular, we studied permanence of the tumor, and gave some numerical simulations. Recall that a cubic nonlinear term can not prevent the solution becomes negative, which means the solution can not be

biologically relevant.

Note that the proof of existence is based on a standard Galerkin scheme, more precisely, deriving uniform (with respect to N) a priori estimates on the solution u^N to the approximated problems and passing to the limit $N \to \infty$. Compared with the regular potential, it is more difficult to pass to the limit of the approximated logarithmic potential, we need to take advantage of the properties of the logarithmic potential (see [32, 90, 96] for more informations), which indeed ensures the boundedness of solutions. As we explained in the above, logarithmic potential is thermodynamically relevant, it is nature to consider such a nonlinear term in certain models.

The last model was proposed for image segmentation. We firstly studied on a Cahn-Hilliard type model, the well-posedness have been derived, however, there exist solutions which are unbounded as time goes to infinity, this could be problematic in view of numerical simulations. To overcome this, we proposed a variant of the model, based on the Cahn-Hilliard-Oono equation proposed in [105] to account for long-ranged interactions in the phase separation processes and to simplify numerical simulations. In this case, the global in time boundedness of the solutions can be ensured, we then gave numerical simulations which illustrate the theoretical results. We further studied the well-posedness and the asymptotic behavior of a Cahn-Hilliard-Oono type model for image segmentation in two cases. In the case of a regular potential, the existences of the global attractor and the exponential attractor have been proved, and it shows that the fractal dimension of the global attractor will tend to infinity as $\alpha \to 0$. In the case of a logarithmic potential, we proved a strict separation from the pure states 0 and 1 in one and two space dimensions, and showed that the dimension of the global attractor is finite by proving the existence of the exponential attractor.

According to the conclusions we have obtained, we further present some perspectives on these models.

For the Cahn-Hilliard model with a symport term for glial cells, having the strict separation property and uniqueness, we can further study the asymptotic behavior of the associated dynamical system. In particular, we can prove the existence of finite dimensional attractors, meaning, roughly speaking, that the limit dynamics can be described by a finite number of degrees of freedom. We refer the interested reader to [96, 100, 111] for more discussions on this. Another interesting problem is the convergence of single trajectories to steady states. Not that, already for the original Cahn-Hilliard equation, such a question is not a trivial one, since one may have a continuum of steady states (see [109]). Here, due to the additional symport term, the problem is particularly challenging and we cannot proceed as in [109].

For the coupled Cahn-Hilliard model for the proliferative-to-invasive transition of hypoxic glioma cells, uniqueness and further regularity (in particular, the existence of strong solutions) are open problems, the difficulty comes from the Cahn-Hilliard type equation and already appears without any coupling (see [96]). Besides, taking into ac-

count the practical significance of the model, it is also necessary to study this model endowed with dynamic boundary conditions (see [14, 27, 42, 43, 93, 101]), as well as the numerical simulations.

For the image segmentation models, the robustness of exponential attractor of the model in [68], like A. Miranville presented in [86], can not be derived owing to the limitations of the Cahn-Hilliard type model for image segmentation, which we have studied in [71]. Moreover, since the long-ranged interactions have been taken into account, the next step is to apply the models to real images. In addition, we also note that it is observed in [24] that, when considering a logarithmic nonlinear term in the Cahn-Hilliard model for image inpainting, one has better results and convergence times. Hence, the performance of a Cahn-Hilliard-Oono model for image inpainting is desirable as well.

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Résumé : Cette thèse vise à approfondir les applications des modèles de type Cahn-Hilliard en biologie et en traitement d'images. Dans la première partie, nous étudions dans un premier temps un modèle de Cahn-Hilliard pour les cellules gliales, nous prouvons l'existence d'une solution biologiquement pertinente et une stricte séparation des états purs en 1D et 2D. Nous considérons ensuite un modèle de Cahn-Hilliard-Oono et en déduisons des conclusions similaires. De plus, nous étudions un modèle couplé pour la transition proliférative à invasive des cellules de gliome hypoxiques, nous considérons les équations de type Cahn-Hilliard dans trois cas, et prouvons principalement l'existence de solutions globales en temps, en particulier, nous étudions la permanence de la tumeur, et donnons quelques simulations numériques dans certains cas. Dans la deuxième partie, nous étudions un modèle de Cahn-Hilliard pour la segmentation d'images, le caractère bien-posé a été abordé, étant donné que la solution pourrait être non bornée quand le temps tend vers l'infini, nous considérons un modèle de Cahn-Hilliard-Oono pour pouvoir effectuer des simulations numériques qui illustrent les résultats théoriques. Nous étudions ensuite le comportement asymptotique des modèles de type Cahn-Hilliard-Oono à terme non linéaire cubique et terme non linéaire logarithmique, plus précisément, l'existence d'attracteurs de dimension finie.

Mots clés : modèle de Cahn-Hilliard, cellules gliales, solution biologiquement pertinente, séparation stricte, modèle de Cahn-Hilliard-Oono, cellules de gliome hypoxiques, simulations numériques, segmentation d'image, caractère bien-posé, comportement asymptotique

Abstract : This Thesis aim to delve the applications of Cahn-Hilliard type models in biology and image processing. In the first part, we initially study a Cahn-Hilliard model for glial cells, we prove the existence of a biologically relevant solution and a strict separation from the pure states in 1D and 2D. We further consider a Cahn-Hilliard-Oono model and deduce the similar conclusions. Moreover, we study a coupled model for the proliferative-to-invasive transition of hypoxic glioma cells, we consider the Cahn-Hilliard type equations in three cases, and mainly prove the existence of global in time solutions, in particular, we study permanence of the tumor, and give some numerical simulations in certain case. In the second part, we study a Cahn-Hilliard model for image segmentation, the well-posedness has been addressed, since the solution could be unbounded as time goes to infinity, we consider a Cahn-Hilliard-Oono model so that we can perform numerical simulations which illustrate the theoretical results. We further study the asymptotic behavior of the Cahn-Hilliard-Oono type models with cubic nonlinear term and logarithmic nonlinear term, more precisely, the existence of finite dimensional attractors.

Keywords : Cahn-Hilliard model, glial cells, biologically relevant solution, strict separation, Cahn-Hilliard-Oono model, hypoxic glioma cells, numerical simulations, image segmentation, well-posedness, asymptotic behavior