



ONDES PROGRESSIVES ET MODELISATION DES ACCIDENTS VASCULAIRES CEREBRAUX ISCHEMIQUES

Guillemette Chapuisat

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UNIVERSITE PARIS-SUD XI

ECOLE DOCTORALE DE MATHEMATIQUES

Doctorat de mathématiques

Guillemette CHAPUISAT

ONDES PROGRESSIVES ET MODELISATION DES ACCIDENTS
VASCULAIRES CEREBRAUX ISCHEMIQUES.

Thèse dirigée par Emmanuel Grenier
Soutenue le 1er décembre 2006

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Résumé :

Les accidents vasculaires cérébraux (AVC) sont un enjeu de santé publique majeur. Une façon de les étudier est d'établir des modèles mathématiques. Cette thèse comporte deux parties, l'une sur la modélisation et l'autre sur l'étude théorique de certaines équations qui en découlent.

Dans la première partie, on présente un modèle phénoménologique global d'AVC ischémique qui prend en compte une diminution du flux sanguin, la gestion de l'énergie par la cellule, la propagation des dépressions corticales envahissantes (onde de dépolarisation) et deux types de mort cellulaire (la nécrose et l'apoptose). Après avoir présenté les différents sous-modèles en détails, on simule différentes expériences dans des géométries de cerveau simplifiées. Les expériences numériques sur la reperfusion permettent de formuler de nouvelles hypothèses biologiques.

Dans la deuxième partie de cette thèse, on étudie divers problèmes théoriques issus de la modélisation des ondes de dépolarisation. On étudie l'existence de fronts progressifs généralisés solutions d'une équation de réaction-diffusion de type bistable dans un domaine cylindrique dont le diamètre augmente brutalement. Si l'augmentation du diamètre est trop importante, il n'existe pas de tels fronts. On s'intéresse aussi à l'existence de fronts progressifs courbes à la fois solutions d'une équation de réaction-diffusion dans un cylindre et d'une équation de diffusion et absorption en dehors de ce cylindre. Si le rayon du cylindre est petit, il n'existe pas d'onde mais s'il est grand, on montre l'existence de telles solutions en étudiant l'énergie dans un référentiel en mouvement.

Mots-clef :

Réaction-diffusion, Front progressif, Modélisation, Médecine.

Abstract :

Stroke is the third cause of death and the first cause of acquired handicap in occidental countries. One way to study it is to design mathematical models. This thesis is made of two parts, one on the modeling of stroke and the other on the theoretical study of some equations coming from the model.

In the first part, we present a phenomenological model of stroke that takes into account the reduction of the blood flow, the cell energy dealing, the spreading depressions (a depolarization of the neurons that spreads through the cortex) and two ways of cellular death (apoptosis and necrosis). Various numerical simulations are then made. The numerical results on the reopening of the vessel lead to new biological hypotheses.

In the second part of the thesis, we study some theoretical problems coming from numerical experiments on the model of spreading depression. In particular, we study the existence of generalized travelling fronts solutions of a bistable reaction-diffusion

equation on a cylinder which diameter is suddenly increased. We prove the non existence of such a front if the diameter is strongly increased. We also have interest in the existence of curved travelling fronts solutions of a reaction-diffusion equation in a cylinder and a diffusion-absorption equation outside the cylinder. If the diameter of the cylinder is large enough, we prove the existence of a curved front by studying the energy of the solution in a travelling referential.

Keywords :

Reaction-diffusion, Progressif front, Model, Biology.

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Introduction

C'est dans le cadre des mathématiques appliquées à la médecine que s'inscrit ce travail. Durant ma thèse, mes recherches ont porté sur la modélisation des accidents vasculaires cérébraux, ainsi que sur divers problèmes d'existence de fronts progressifs inspirés par les résultats de cette modélisation. Ces problèmes théoriques ne peuvent pas toujours être résolus directement par les méthodes développées par Fife et McLeod, Berestycki et Nirenberg, Hamel ou Roquejoffre, j'ai donc été amenée à utiliser une méthode récente imaginée par Risler dans le cadre des fronts vectoriels. Ce travail a également un intérêt biologique qui réside dans l'importance des accidents vasculaires cérébraux : troisième cause de mortalité et première cause de handicap acquis à l'âge adulte, dans les pays occidentaux.

Contrairement à la physique ou à la chimie, la biologie est longtemps restée un domaine fermement séparé des mathématiques. La complexité des phénomènes, les difficultés d'expérimentations ainsi que la grande variabilité entre les individus sont les raisons principales qui ont rendu difficile la réalisation de modèles mathématiques. Aujourd'hui, la modélisation d'organes vivants est en plein essor. De nombreux modèles de contraction du cœur sont maintenant établis, ainsi que des modèles de circulation de l'air dans les poumons (voir les travaux de Maday ou Maury par exemple). La modélisation du cerveau, elle, n'en est qu'à ses débuts. La difficulté de cette modélisation est due à la très grande complexité de composition et de fonctionnement de cet organe ainsi qu'au peu d'expériences possibles. Dans ce domaine, l'élaboration d'un modèle mathématique peut donc avoir deux intérêts :

- Premièrement, elle permet d'organiser la très grande quantité d'informations dont disposent les biologistes, c'est à dire de faire le lien entre les différents phénomènes et d'estimer leur importance relative.
- Deuxièmement, un modèle validé permet de simuler facilement et rapidement certaines expériences, alors que l'expérimentation sur le cerveau humain est extrêmement limitée.

Les mathématiques peuvent également aider à la compréhension de différentes pathologies. En particulier, différentes écoles travaillent actuellement sur la modélisation du cancer (Bellomo, Perthame, Clairembault...). Le projet AVC-iSi (autour de Boissel, Dronne et Grenier) a, quant à lui, été monté pour établir des modèles d'accidents vasculaires cérébraux.

On peut modéliser un phénomène biologique de deux façons. Dans l'approche dite mécanistique, on applique les règles de la physico-chimie à une situation de départ connue pour prévoir une évolution ou une situation finale. Dans l'approche phénoménologique, ce sont les résultats expérimentaux qui permettent d'établir qualitativement des relations entre grandeurs. Intellectuellement, l'approche mécanistique est plus satisfaisante, mais elle demande de connaître parfaitement la situation de départ ; or beaucoup de structures biologiques sont encore très mal connues (par exemple les membranes cellulaires). De plus, ce type d'approche aboutit généralement à des modèles très lourds avec un grand nombre d'équations interdépendantes. Les modèles phénoménologiques sont généralement moins exigeants en temps de calculs. On peut plus facilement les inclure dans des modèles plus généraux et ils ont globalement un fonctionnement plus souple permettant de tester des hypothèses et d'imaginer des expériences.

Actuellement, on cherche à établir un modèle mécanistique d'accident vasculaire cérébral. Une partie des phénomènes a déjà été modélisée, mais il reste encore beaucoup à faire avant d'obtenir un modèle général. Mon travail a donc porté sur la construction d'un modèle global, mais phénoménologique d'accident vasculaire cérébral.

Dans ce rapport, les différents chapitres ne font que présenter rapidement le travail que j'ai effectué durant ma thèse qui est exposé en détails dans les différents articles mis en annexe.

Chapitre 1. Ce premier chapitre est intégralement consacré à la présentation et à l'étude par des simulations numériques d'un modèle phénoménologique d'accident vasculaire cérébral. Ce modèle a été établi dans le cadre de l'ACI AVC-iSi regroupant des mathématiciens, des pharmacologues et des neurologues cliniciens de Lyon et de Grenoble.

J'expose tout d'abord les principales connaissances biologiques nécessaires à la compréhension du modèle. En particulier, j'insiste sur l'importance des dépressions corticales envahissantes qui sont des ondes de dépolarisation des neurones qui peuvent se propager dans le cerveau. Ces dépressions corticales ont une grande influence sur les séquelles d'un accident vasculaire. C'est le point central du modèle que je présente par la suite.

J'expose alors les principaux sous-modèles qui composent mon modèle : le modèle d'échange ionique et le modèle de mort cellulaire. Le modèle d'échange ionique a donné lieu à un article [16] (cf annexe A). Je donne enfin les principales hypothèses du modèle global présenté en détails dans l'article [15] en annexe B. Pour chaque sous-modèle, j'explique les équations et la façon dont les paramètres ont été fixés. Ensuite, j'étudie les résultats de ce modèle dans diverses situations : occlusion partielle, reperfusion, différentes géométries de domaine. Cela éclaire d'un jour nouveau certaines problématiques cliniques classiques.

Enfin, en abordant en particulier un modèle mécanistique plus complet d'échanges

ioniques entre les cellules du cerveau, j'expliquerai les perspectives ouvertes par mon modèle.

Chapitre 2. Le deuxième chapitre est motivé par les simulations numériques effectuées dans le premier chapitre. On étudie l'existence de fronts progressifs généralisés, solutions d'une équation de réaction-diffusion de type bistable dans un cylindre de section carrée dont le diamètre varie brusquement. Ce chapitre a donné lieu à un article [17] donné en annexe C.

Si le diamètre du cylindre augmente peu ou diminue, il existe des fronts progressifs généralisés. Cela se montre rapidement en utilisant les travaux de Roquejoffre [77]. En revanche, je montre que si le diamètre augmente fortement et brutalement, il n'existe pas de front progressif généralisé en dimension 2 ou 3. La méthode utilisée pour démontrer ce résultat est assez originale, elle est basée sur la symétrisation du domaine afin de se ramener à une équation dont on connaît la fonction de Green suffisamment précisément.

Chapitre 3. Le troisième chapitre est également motivé par les observations numériques effectuées sur le modèle du premier chapitre. On étudie l'existence de front progressifs courbes qui sont à la fois solutions d'une équation de réaction-diffusion de type bistable sur un cylindre et solutions d'une équation de diffusion et absorption en dehors du cylindre. Ce chapitre a aussi donné lieu à un article [14] présenté en annexe D.

J'ai prouvé qu'il n'existe pas de front progressif courbe si le rayon du cylindre est petit, mais qu'il en existe un si le rayon du cylindre est suffisamment grand.

Pour démontrer ce résultat, j'ai étudié tout d'abord les profils asymptotiques possibles pour un tel front, cela me permet de conclure sur la non-existence si le rayon du cylindre est petit. Pour démontrer l'existence dans le cas d'un rayon plus grand, j'ai étendu la méthode développée par Emmanuel Risler qui construit un front progressif comme la limite de la solution de l'équation avec une donnée initiale bien choisie. Pour cela, on étudie l'énergie de la solution avec donnée initiale dans divers référentiels en mouvement. Les méthodes développées par Berestycki [10], Vega [87, 88] ou Hamel, Monneau et Roquejoffre [42] pour montrer l'existence de fronts progressifs dans différentes situations ne peuvent en effet pas s'appliquer ici.

Chapitre 1

Un modèle d'accident vasculaire cérébral

1.1 Données biologiques générales

1.1.1 Les cellules du cerveau

Les neurones

Le cerveau est constitué de cellules diverses. Les plus connues sont les neurones. Ce sont des cellules nerveuses (c'est à dire excitables) qui permettent la réception, l'intégration et la transmission de l'information. Chaque neurone est composé de trois parties : le corps cellulaire (où se trouve le noyau de la cellule), les dendrites (qui reçoivent les différents messages nerveux venant des autres neurones) et l'axone (qui transmet le message nerveux). Ces neurones forment un réseau très complexe, les dendrites étant en contact avec les axones au travers de synapses.

Pour pouvoir transmettre le message nerveux, la membrane des neurones est polarisée, c'est à dire que différentes espèces ioniques (K^+ , Ca^{2+} , Na^+ , Cl^- , l'ion glutamate *Glu* ...) ont des concentrations différentes à l'intérieur et à l'extérieur des neurones. Le principe de Nernst affirme en effet que cette différence de concentration crée un potentiel électrique de membrane.

Les transporteurs membranaires

Le passage des différents ions de l'espace intracellulaire à l'espace extracellulaire ou vice-versa se fait à l'aide de "transporteurs membranaires" situés dans la membrane de la cellule.

- Transport passif : Les canaux ioniques assurent un transport passif (i.e. sans besoin d'énergie) d'ions à travers la membrane. Quand ces canaux sont ouverts, ils peuvent être perméables à un ou plusieurs types d'ions. Ces mouvements sont dûs à l'action de forces soit électriques soit osmotiques (un ion se déplace

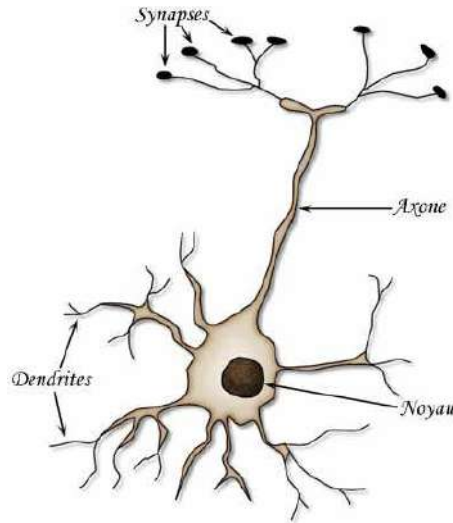


FIG. 1.1 – Schéma d'un neurone.

naturellement vers un milieu de potentiel chimique plus faible). Il existe des canaux ioniques voltage-dépendants dont l'ouverture dépend du potentiel de la membrane et des canaux chimio-dépendants qui s'ouvrent au contact d'un ligand (i.e. une autre molécule).

- Transport actif : Il existe deux grands types de transporteurs actifs. Le but des transporteurs actifs est de maintenir l'homéostasie de la cellule (i.e. maintenir les gradients de concentration ionique nécessaires à son bon fonctionnement). Les pompes ioniques se différencient des canaux ioniques par le fait que leur fonctionnement nécessite de l'énergie amenée par l'ATP. Le mouvement de l'ion est alors unidirectionnel et peut se produire contre son gradient de concentration.

Les symports assurent également le transport de certains ions contre leur gradient chimique, mais ils tirent l'énergie nécessaire du transport simultané d'une autre espèce ionique (qui voyage pour sa part dans le sens de son gradient ionique).

Enfin, les espèces ioniques peuvent passer d'une cellule à une autre par l'intermédiaire de gap-jonctions (ou jonctions lacunaires). Ces gap-jonctions ne sont pas à proprement parler des transporteurs membranaires mais des jonctions communicantes. Elles se comportent comme des pores qui laissent passer librement différentes espèces d'une cellule à l'autre en fonction de la taille de ces espèces.

Les cellules gliales

En dehors des neurones, le cerveau comprend d'autres types de cellules que l'on appelle les cellules gliales. Le rôle des cellules gliales est grossièrement de maintenir

un environnement favorable au bon fonctionnement des neurones. Dans ce travail, nous nous intéresserons particulièrement à un type de cellules gliales, les astrocytes ; ce sont les plus abondantes. Ces astrocytes sont impliqués dans de nombreuses fonctions [71] dont le maintien des équilibres ioniques entre espace extracellulaire et intracellulaire, le maintien du pH, l'apport énergétique des neurones, la régénération des axones... Ils forment un réseau entremêlé au réseau des neurones. Ils sont reliés entre eux par des gap-jonctions. Comme les neurones, la membrane des astrocytes

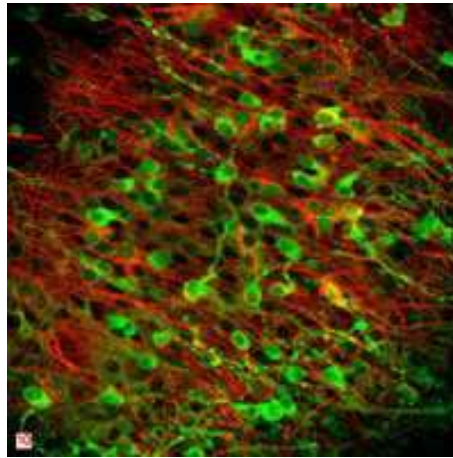


FIG. 1.2 – Image microscopique confocale d'une tranche cérébrale d'hippocampe marquée par GFAP (en rouge) afin d'identifier les astrocytes et par MAP-2 (en vert) afin d'identifier les neurones. Source : Institut des sciences biologiques du CNRC

est polarisée et contient des canaux et pompes ioniques [83].

Un autre type de cellules gliales est les oligodendrocytes. Ils se situent principalement dans ce qu'on appelle la substance blanche du cerveau. Ils assurent la formation de la gaine de myéline autour des axones neuronaux, ce qui permet une transmission rapide de l'influx nerveux.

Les autres cellules gliales forment la microglie.

1.1.2 Les accidents vasculaires cérébraux

Définitions

Un accident vasculaire cérébral (AVC) est défini comme une anomalie clinique secondaire à une lésion anatomique d'un ou de plusieurs vaisseaux cérébraux [54]. Autrement dit, l'AVC est la conséquence d'une diminution du flux sanguin dans une partie du cerveau. Cette diminution peut être due à la présence d'un caillot dans une des artères du cerveau, on parle d'un accident "ischémique", ou bien à un saignement sur l'artère, c'est alors un accident "hémorragique", c'est le cas d'une

rupture d'anévrisme par exemple. Dans les pays industrialisés, les AVC constituent un enjeu majeur de santé publique car ils représentent la troisième cause de mortalité et la première cause d'handicap acquis à l'âge adulte [68]. Aux Etats-Unis, les AVC touchent une personne sur cinq et 24% des AVC mènent au décès du patient. 80% des AVC sont d'origine ischémique et 20% d'origine hémorragique.

Les thérapeutiques

Les conséquences d'un AVC sont multiples selon la zone du cerveau touchée. Cela peut aller de la mort à un simple mal de tête en passant par une amnésie (perte de la mémoire), une aphasie (perte de la parole), une paralysie... Les phénomènes tels que l'amnésie, l'aphasie ou la paralysie peuvent être permanents ou transitoires.

Actuellement, la lutte contre les AVC passe principalement par la prévention. Une fois l'AVC déclenché, peu de thérapeutiques sont disponibles pour en limiter les effets. Il existe principalement deux approches thérapeutiques dans le cas de l'AVC ischémique. La première consiste à rétablir la circulation sanguine en dissolvant le caillot sanguin (ou reperfusion). Cependant dans certains cas, la reperfusion entraîne parfois une aggravation des symptômes qu'on ne peut pas expliquer par une hémorragie [39, 40]. L'autre approche thérapeutique consiste à administrer des agents neuroprotecteurs qui ont pour but d'empêcher l'extension des dommages neuronaux en inhibant certains mécanismes cellulaires mis en jeu dans le cadre de l'AVC ischémique. Les agents pharmaceutiques sont nombreux, mais aucun n'est complètement satisfaisant et les mécanismes d'action ne sont pas très bien compris.

Le développement de ces thérapeutiques se heurtent à de nombreuses difficultés.

- Les connaissances médicales sont gigantesques, mais essentiellement qualitatives et par là même difficiles à organiser.
- Les résultats des expériences effectuées chez le rongeur d'une part et chez l'homme d'autre part ont souvent été en opposition. Quelques explications ont été avancées [6], mais les raisons de ces différences profondes ne sont pas encore complètement connues.
- Les expériences *in vivo* (sur l'être vivant) comme *in vitro* (en dehors de l'être vivant) sont difficiles voire impossibles dans de nombreux cas et particulièrement sur l'homme.

Ces constatations ont amené les biologistes à faire appel à des modèles, d'une part pour permettre l'organisation des connaissances biologiques, d'autre part pour permettre des expériences numériques une fois le modèle validé (on parle d'expériences *in silico*). On ne peut pas obtenir ainsi des résultats certains, mais cela donne des pistes de recherche. Cependant, la modélisation mathématique de l'AVC n'en est qu'à ses débuts.

L'ACI AVC-iSi a pour but la construction d'un modèle mathématique global d'AVC ischémique. Cette ACI, basée à Lyon, est composée de mathématiciens, de pharmacologues et de neurologues cliniciens.

Les motivations du nouveau modèle d'AVC

Un premier modèle d'AVC ischémique a été établi par V. Duval dans [27]. C'est un modèle phénoménologique au niveau tissulaire qui prend en compte la réduction du flux sanguin, la diminution de l'énergie et les dommages aux cellules. Dans [22], M.-A. Dronne adapte ce modèle et y ajoute une partie mécanistique au niveau cellulaire qui constitue le coeur du modèle. Son modèle prend donc en compte de façon détaillée les échanges ioniques entre cellules voisines, la dépolarisation des membranes et le gonflement des cellules. Il a permis d'étudier l'évolution de la zone de pénombre (zone du cerveau touchée par le manque de sang mais qui n'est pas encore définitivement lésée) dans différentes conditions. En particulier, ce modèle permet de tester l'effet de différents neuroprotecteur. Cependant, ce modèle a ses limites. En particulier, il est impossible pour l'instant de distinguer les différents mécanismes de mort cellulaire, ni de prendre en compte les phénomènes qui se propagent sur l'ensemble du cerveau, comme les dépressions corticales envahissantes (DCE) qui ont pourtant une grande importance dans l'évolution de la zone de pénombre chez le rongeur [66, 62].

Le modèle d'AVC que je présente ici prend en compte la diminution du flux sanguin, la diminution de l'énergie, les DCE, les dommages aux cellules et les différents mécanismes de mort cellulaire. Les connaissances sur certains de ces points étant incomplètes et le but final étant de pouvoir faire de nombreuses expérimentations numériques dans un temps convenable, le modèle que je vais présenter est simplement phénoménologique, c'est à dire qu'il décrit qualitativement les relations entre les différentes entités sans entrer dans les détails physico-chimiques des mécanismes cellulaires.

Je vais tout d'abord présenter les deux principaux sous-modèles : le modèle de dépression corticale envahissante et le modèle de mort cellulaire.

1.2 Un modèle phénoménologique de dépression corticale envahissante

1.2.1 Les dépressions corticales envahissantes

Une dépression corticale envahissante (DCE), ou spreading depression (SD) en anglais, est une dépolarisation de grande ampleur et temporaire des neurones qui se propage lentement (3mm/min) dans la substance grise du cerveau. Ce phénomène a été observé en premier par Leão en 1957 [56] et est depuis le sujet de nombreuses études. Ces DCE semblent jouer un rôle important dans diverses pathologies, en particulier les AVC, les migraines avec aura, l'épilepsie et certains traumatismes crâniens [83].

La mesure des DCE est assez difficile. Un électroencéphalogramme ne suffit pas [48] et même l'IRM ne permet pas de conclure de manière définitive [41]. Les moyens

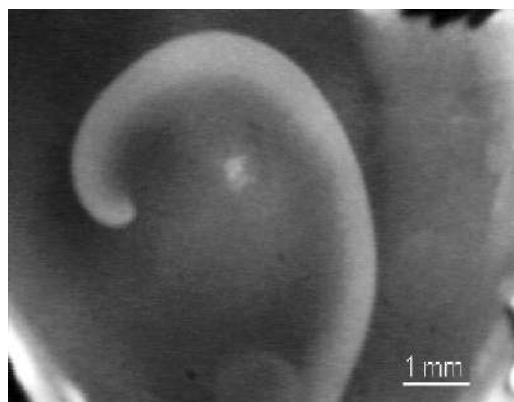


FIG. 1.3 – Une dépression corticale envahissante sur la rétine d'un poulet déclenchée par une injection de KCl. Les neurones qui composent la rétine ont la particularité d'être opaques quand ils sont dépolarisés.

de mesure efficaces sont donc invasifs.

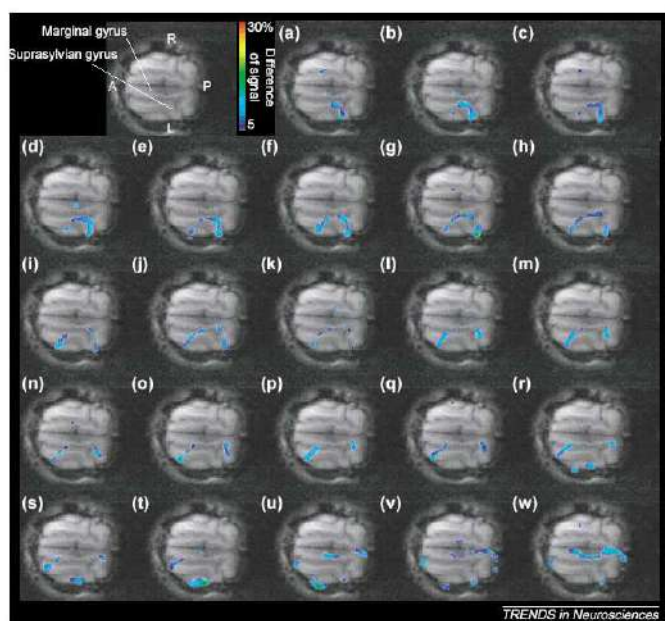


FIG. 1.4 – Une dépression corticale envahissante chez le chat suivie par IRM.

La dépolarisation des neurones est due à une répartition anormale des espèces ioniques entre les différentes cellules du cerveau. En particulier, au passage d'une DCE, le potassium sort des cellules. La concentration en potassium dans l'espace extracellulaire augmente donc très fortement (30 à 80 mM). L'injection de potassium

(sous la forme KCl) est d'ailleurs un des moyens expérimentaux pour déclencher une DCE [47]. A l'inverse, pendant une DCE le calcium rentre dans les neurones et les astrocytes. Les concentrations en calcium augmentent d'environ 0.1 mM dans les neurones et de 0.2 mM dans les astrocytes. Nedergaard a d'ailleurs observé une vague de calcium se propager dans le réseau des astrocytes pendant une DCE [13].

Dans le cadre d'un AVC chez le rongeur, le nombre de DCE a une claire influence sur la taille de la zone définitivement lésée [66, 62]. Certains essais thérapeutiques portent sur des bloqueurs de ces DCE et donnent de bons résultats chez le rongeur. Malheureusement la situation chez l'homme est moins claire, car les observations sont bien plus difficiles à obtenir. En réalité, la question de l'existence de ces DCE chez l'homme n'est toujours pas résolue. Diverses opinions s'affrontent [84, 61, 59, 2]. Pour l'instant aucune observation claire de ces DCE chez l'homme n'a été faite. Ce point est pourtant essentiel, car cela pourrait réorienter certains essais thérapeutiques.

La quantité importante de connaissances disponibles à propos des DCE et les difficultés d'expérimentation en particulier chez l'être humain ont mené les biologistes à créer des modèles mathématiques de DCE. Dans [83], G. Somjen expose un modèle de DCE qui s'intéresse particulièrement au déclenchement et à l'évolution de la DCE dans une cellule unique dans le cas de l'épilepsie et de l'AVC ischémique. Malheureusement, ce modèle ne peut pas prendre en compte la propagation des DCE dans le cerveau qui est pourtant probablement une des raisons de l'extension des dommages dans le cadre des AVC. D'autres modèles ont été développés dans [38, 65, 86, 72, 74]. Ces modèles plus simples sont en revanche centrés sur le problème de la propagation des DCE et ne sont que sommairement rattachés aux observations physico-biologiques au niveau membranaire. Par exemple, ils ne permettent pas d'expliquer les observations de Nedergaard sur la présence d'une vague de calcium dans les astrocytes. Enfin, Shapiro dans [81] présente un modèle très complet de DCE, mais ce modèle est très lourd et pourrait difficilement être inclus dans un modèle global d'AVC. Dans le cadre de notre projet, nous avons donc senti la nécessité d'établir un nouveau modèle phénoménologique de DCE pour construire un modèle d'AVC ischémique.

1.2.2 Les hypothèses biologiques du modèle

Les DCE étant le fait d'échanges ioniques anormaux entre les neurones, les astrocytes et l'espace extracellulaire, ce modèle de DCE considère trois compartiments différents : les neurones, les astrocytes et l'espace extracellulaire. Cependant, on se place à l'échelle du cerveau, les grandeurs varient donc continuellement dans ces trois compartiments.

Les concentrations en potassium et en calcium jouent des rôles essentiels dans le phénomène de DCE. Les principales fonctions de l'espace x et du temps t de ce modèle sont donc : $K_e(t, x)$ la concentration en potassium dans l'espace extracellulaire,

$Ca_n(t, x)$ la concentration en calcium dans les neurones et $Ca_g(t, x)$ la concentration en calcium dans les astrocytes (g pour gliale).

Le modèle de DCE a été basé principalement sur les observations de Nedergaard dans [13]. Les principaux faits sont les suivants :

- Les ions potassium peuvent diffuser dans l'espace extracellulaire.
- Un excès de potassium dans l'espace extracellulaire active des canaux ioniques sur la membrane des astrocytes qui font entrer du calcium dans la cellule.
- Le calcium diffuse à travers des gap-jonctions dans le réseau des astrocytes.
- Les ions calcium entrent dans les neurones “à travers des gap-jonctions entre neurones et astrocytes” (ce point est très discuté).
- L'excès de calcium dans les neurones active des canaux ioniques sur la membrane des neurones qui font sortir du potassium de la cellule.

Ces points sont résumés sur la figure 1.5.

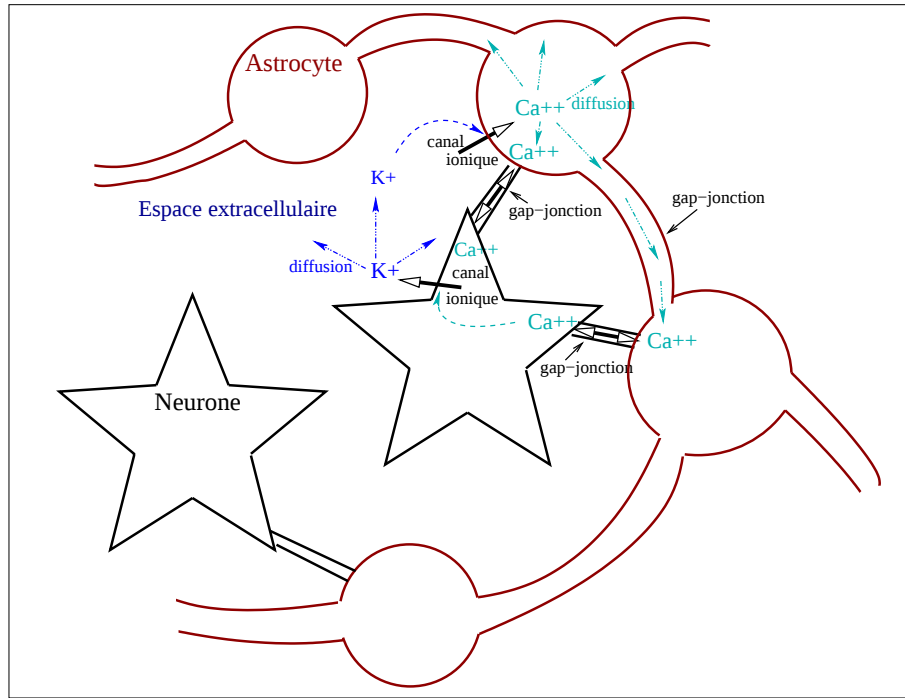


FIG. 1.5 – Le modèle de Nedergaard

Nous n'avons parlé pour l'instant que d'augmentations des concentrations ioniques, il est donc nécessaire d'ajouter des phénomènes de récupération. Les connaissances biologiques sur ces phénomènes sont limitées. On sait cependant qu'il existe différents mécanismes de retour à l'équilibre, pour les petites variations de concentrations (induites par le passage d'un signal nerveux par exemple) ou pour récupérer des larges variations de concentrations produites par une DCE.

La récupération des DCE nécessite deux nouvelles variables : $Cap(t, x)$ la capacité des cellules à récupérer des DCE et $R(t, x)$ l'intensité de cette récupération. Pour les détails de la construction du modèle, voir l'annexe A page 63.

On obtient finalement un système de trois équations aux dérivées partielles de réaction-diffusion pour les concentrations ioniques et de deux équations différentielles ordinaires pour gérer la récupération des DCE. Je renvoie à nouveau à l'annexe A pour le détail des équations.

Les paramètres

Une fois les équations établies, le problème de la valeur des paramètres du modèle se pose. On ne peut pas les trouver dans la littérature.

- En effet, certains paramètres n'ont pas de réalité biologique (car le modèle est phénoménologique).
- De nombreuses expériences sont techniquement ou éthiquement impossibles.
- Lorsque des expériences ont été faites, elles ont été menées dans différentes espèces et de ce fait, les résultats ne sont pas comparables.
- Par ailleurs, les résultats sont affectés de très larges marges d'erreur (jusqu'à 300% !).

Pour fixer la valeur des paramètres, on a donc choisi un algorithme aléatoire. Le principe est de tirer au hasard les paramètres dans des plages bien déterminées, puis de résoudre le modèle et de tester la solution sur un certain nombre de faits connus, si la réponse est positive, les paramètres sont conservés en mémoire, puis on recommence avec un nouveau jeu de paramètres. Dans le cas du modèle de DCE, il y avait 27 paramètres à déterminer. L'algorithme a effectué plus de 500 000 itérations pour obtenir cinq jeux de paramètres possibles. Tous les détails de cet algorithme sont donnés en annexe A page 65.

Etant donné l'algorithme utilisé, il est nécessaire de résoudre le système rapidement. De plus, les équations sont assez raides, c'est à dire que la solution peut varier fortement dans un court délai. Les méthodes numériques utilisées doivent être d'autant plus efficaces. Pour trouver les paramètres, on a donc décidé de résoudre le système en dimension 1 d'espace (le cerveau est représenté par un segment) avec des méthodes de différences finies semi-implicites. Les résultats obtenus sont présentés en détail dans l'annexe A page 88 et en figures 1.6 et 1.7. L'allure des courbes correspond bien à ce qu'on attendait d'après les résultats expérimentaux.

Une fois les valeurs des paramètres déterminées, le modèle peut être résolu en 2 dimensions d'espace sur un cerveau carré. Quelque soit le jeu de paramètres utilisé, les résultats sont qualitativement identiques. Ceci confirme les hypothèses choisies. Cependant, on n'a pas pu trouver de justification médicale aux valeurs des paramètres retenus. Les détails des résultats en 2D est donné en annexe A page 69.

La représentation du cerveau comme un carré homogène est sommaire, nous avons voulu aller plus loin.

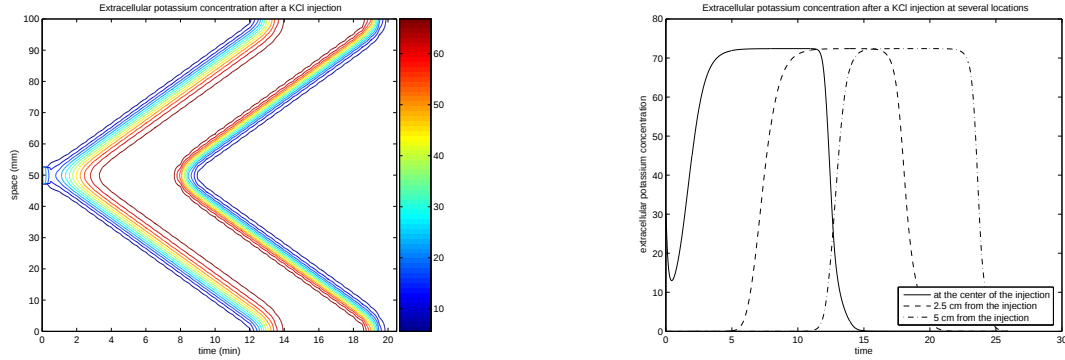


FIG. 1.6 – Concentration en potassium extracellulaire à la suite de la simulation d'une injection de KCl. A gauche, les lignes de niveau la concentration en fonction du temps (abscisse) et de l'espace (ordonnée). A droite, la concentration en fonction du temps pour différents points du cerveau.

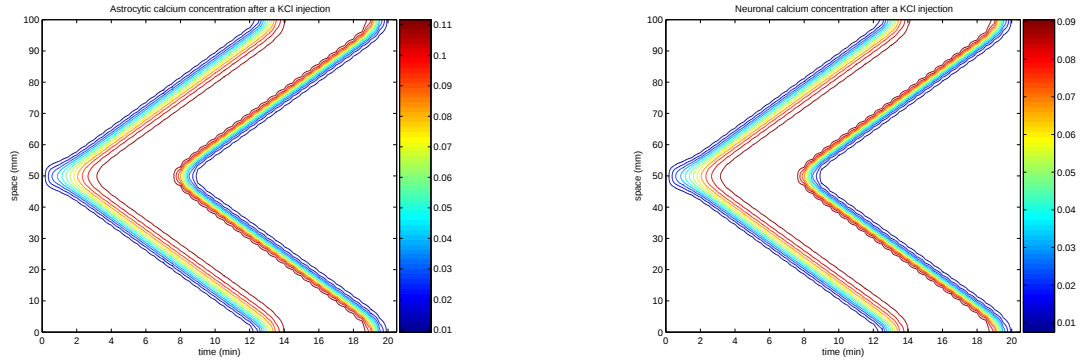


FIG. 1.7 – Lignes de niveau de la concentration en calcium. A gauche dans les astrocytes. A droite, dans les neurones.

1.2.3 Le rôle de la géométrie du cerveau

Composition et géométrie du cerveau

Le cerveau est composé de deux substances différentes.

- La substance grise, principalement composée des corps neuronaux et d'astrocytes, constitue donc le siège de l'activité cérébrale.
- La substance blanche, elle, contient principalement les axones neuronaux, des astrocytes et les oligodendrocytes. Elle assure donc surtout la conduction de l'influx nerveux.

Selon l'espèce, la composition et la géométrie du cerveau peut être très variable.

Le cerveau du rongeur par exemple est quasiment entièrement composé de substance grise. De plus, il présente très peu de replis.

Le cerveau du chat est un peu plus compliqué que celui du rongeur. Il comporte davantage de substance grise.

Le cerveau de l'homme en revanche est très différent. Il est divisé en deux hémisphères. Chaque hémisphère est divisé en quatre lobes, divisés eux-même en de nombreuses sous-parties appelées circonvolutions, séparées par des sillons ou scissures. De plus, il est principalement composé de substance blanche, la substance grise étant surtout présente au niveau du cortex cérébral qui compose une fine couche à la surface du cerveau. En raison des circonvolutions et des scissures, cette couche de substance grise peut être d'épaisseur très variable.

Effet d'une variation d'épaisseur de la substance grise

Les premiers calculs portaient sur un cerveau carré entièrement composé de substance grise. Dans cette partie, on teste l'influence de la géométrie de la substance grise sur la propagation des DCE. On sait en effet que dans certains phénomènes électromagnétiques, la propagation d'une onde peut être bloquée par une variation brutale du diamètre de la zone où elle se propage. Nous avons donc voulu voir si cet effet existe dans ce modèle de DCE. J'ai donc testé plusieurs géométries (cf annexe A page 71). J'ai constaté en particulier qu'une DCE est bloquée dans la zone d'augmentation brutale d'épaisseur de la substance grise (voir figure 1.11).

Ces résultats peuvent être interprétés biologiquement. On a vu que chez l'homme l'épaisseur de la substance grise varie beaucoup et qu'il est difficile d'observer des DCE, alors que chez le rat où on observe facilement les DCE, la substance grise est homogène. L'hypothèse est donc que la création des DCE se ferait de même chez l'homme et chez le rat, mais dans le cerveau humain, la propagation de ces ondes s'arrêterait à la première augmentation brutale de l'épaisseur de la substance grise, ce qui rendrait les ondes difficiles à observer.

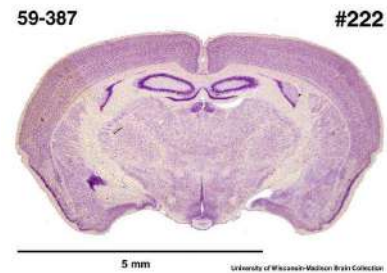
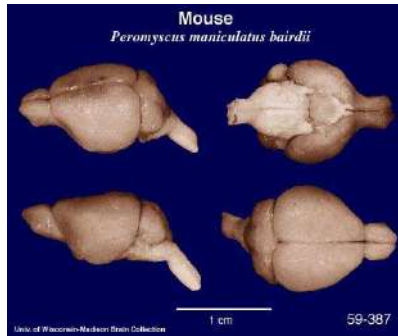


FIG. 1.8 – Le cerveau de la souris. A gauche, différentes vues. A droite, une coupe. (<http://www.brainmuseum.org/index.html>)

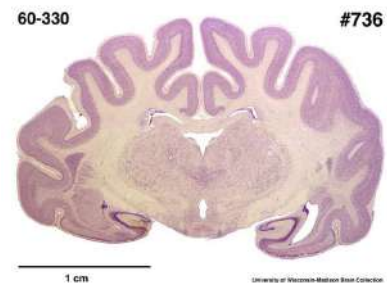
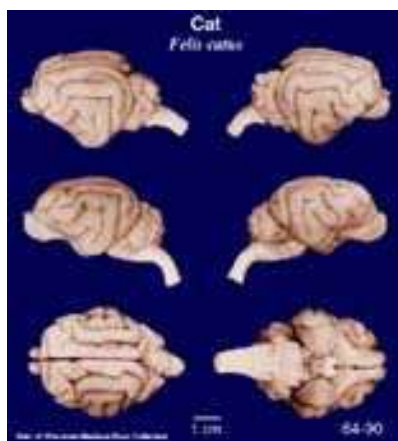


FIG. 1.9 – Le cerveau du chat. A gauche, différentes vues. A droite, une coupe. (<http://www.brainmuseum.org/index.html>)

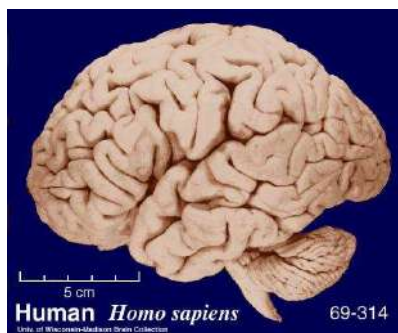


FIG. 1.10 – Le cerveau de l'homme. A gauche, une vue d'ensemble. A droite, une coupe. (<http://www.brainmuseum.org/index.html>)

Effet de la substance blanche

J'ai également étudié numériquement l'influence de la substance blanche sur la création de DCE. En effet, comme la substance blanche ne contient pas de neurone,

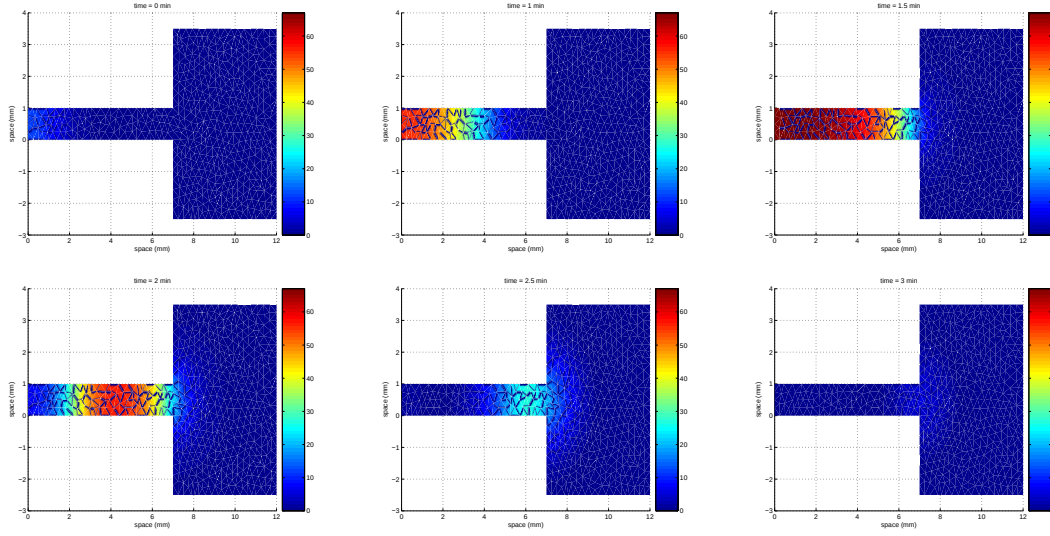


FIG. 1.11 – Concentration en potassium dans l'espace extracellulaire à différents temps. Ici, la substance grise est représentée par un cylindre de diamètre 1 puis 6. Les DCE sont arrêtées par l'augmentation brutale de l'épaisseur de la substance grise.

les ions responsables des DCE y diffusent simplement et sont progressivement absorbés. L'étape de réaction n'a lieu que dans la substance grise. L'effet absorbant de la substance blanche pourrait donc empêcher la création de DCE. Or le cerveau du rat contient très peu de substance blanche, alors que le cerveau humain est principalement composé de cette substance avec une fine couche de substance grise à la périphérie.

Avec ce modèle de DCE, j'ai effectivement constaté que si le cerveau est représenté par une fine bande de substance grise au milieu de la substance blanche, alors une simulation d'injection de potassium ne crée plus de DCE (cf annexe A page 69 et figures 1.12 et 1.13).

1.3 Un modèle de mort cellulaire

1.3.1 La mort des cellules

Divers ions, en particulier le calcium, peuvent endommager une cellule jusqu'à entraîner sa mort. Il y a deux grands mécanismes de mort cellulaires.

Si les dégâts sur la cellule sont importants et qu'elle dispose de peu de réserve énergétique, la cellule va mourir par nécrose en quelques minutes. Ensuite, la membrane de la cellule explose et tout le matériel génétique éventuellement dégradé va se

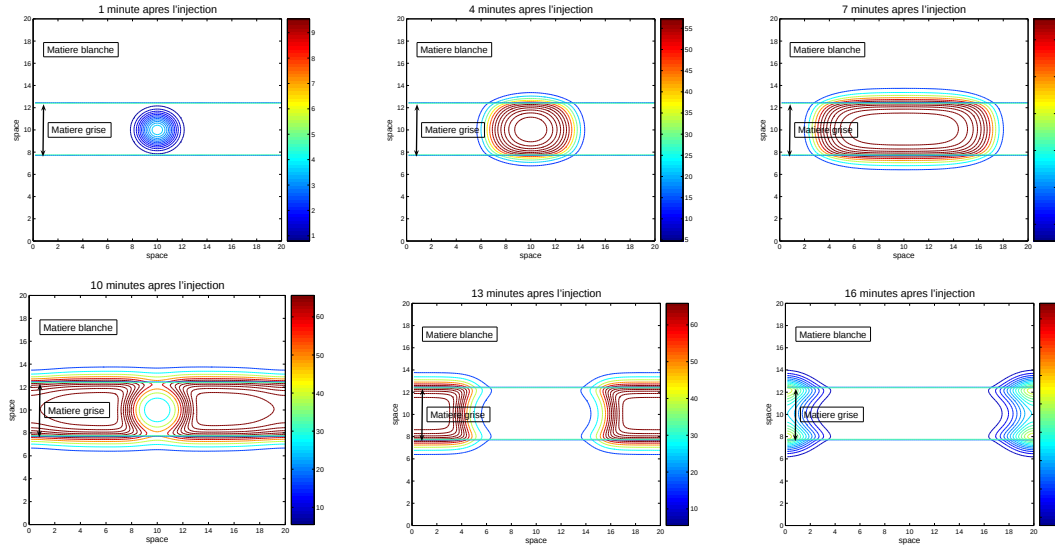


FIG. 1.12 – Concentration en potassium dans l'espace extracellulaire après une injection de KCl. La couche de substance grise est épaisse. Une DCE se crée.

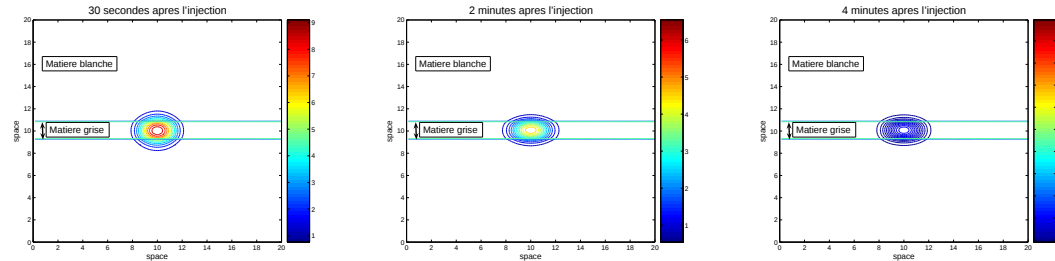


FIG. 1.13 – Concentration en potassium dans l'espace extracellulaire après une injection de KCl. La couche de substance grise est fine. Aucune DCE n'est créée.

répandre dans l'espace extracellulaire alentour. En conséquence, les cellules voisines peuvent être affaiblies par les différents produits de l'explosion.

Si la cellule subit des dégâts importants, mais qu'elle dispose encore de suffisamment d'énergie, elle va se "suicider" (cf [31]). On parle d'apoptose. La cellule rétrécit en évacuant toute l'eau qu'elle contient jusqu'à ce que le système immunitaire puisse l'absorber et l'éliminer. Cette opération peut nécessiter de 24 à 72h, mais la cellule entre dans la phase irréversible de l'apoptose en un peu moins d'une heure.

Distinguer ces deux types de mort peut être essentiel dans la compréhension de diverses pathologies (cancer, accidents vasculaires ...). Dans le cas de l'AVC, la nécrose des cellules sévèrement lésées se fait trop rapidement pour être une cible thérapeutique. Par contre, on peut espérer limiter l'apoptose car le délai d'irréversibilité est plus long. Les recherches pour découvrir un agent antiapoptotique sont d'ailleurs intenses aujourd'hui. Cela pourrait aboutir à un meilleur traitement de

l'accident vasculaire.

1.3.2 Les hypothèses du modèle

Ce modèle représente l'évolution de l'état d'une cellule en fonction de l'action d'un produit nocif et de sa capacité de récupération au cours du temps. On veut déterminer les conditions pour un retour à un état normal, une évolution vers une apoptose ou vers une nécrose. On introduit donc une fonction $\theta(t)$ qui décrit l'état de la cellule au temps t . $\theta = 1$ si la cellule est dans un état parfait et plus l'état de la cellule se dégrade, plus θ diminue. Les hypothèses retenues sont les suivantes :

- les dommages sur la cellule sont uniquement liés à la concentration en calcium intracellulaire [51] (l'excès de calcium fait donc diminuer θ),
- la cellule utilise une partie de son énergie pour se réparer (et donc faire augmenter θ).

Tant que θ reste au dessus d'un seuil θ_{apop} , la cellule est considérée comme en vie.

Pour pouvoir différencier nécrose et apoptose, il faut introduire une nouvelle variable A qui représente l'avancement du processus d'apoptose. $A = 0$ si l'apoptose n'a pas encore commencé ($\theta > \theta_{apop}$), puis A augmente quand le processus d'apoptose avance. On suppose que la vitesse de l'apoptose dépend de la quantité totale d'énergie disponible pour la cellule. On définit alors deux nouveaux seuils θ_{nec} et A_{apop} pour déterminer l'évolution finale de la cellule. Si l'état θ passe sous le seuil $\theta_{nec} < \theta_{apop}$ avant que l'avancement de l'apoptose A ne passe au dessus du seuil A_{apop} , alors la cellule est considérée comme étant morte par nécrose. Si en revanche, A passe au dessus de A_{apop} avant que θ ne passe en dessous de θ_{nec} , on considère que la cellule meurt par apoptose. Pour les détails des équations, voir l'annexe B page 75.

Ce modèle aboutit à un système simple d'équations différentielles. Il est très rapide à résoudre. Cependant pour que ce modèle donne des résultats satisfaisants une fois inclus dans le modèle d'AVC, le choix de la relation entre la concentration en calcium intracellulaire et les dommages sur la cellule est critique. En effet, le passage d'une DCE (qui induit une augmentation de la concentration en calcium intracellulaire) affaiblit les cellules saines sans les tuer, alors que l'augmentation de la concentration en calcium intracellulaire due à l'ischémie totale tue la cellule rapidement par nécrose. Or la différence des concentrations entre ces deux cas est faible. J'ai d'abord supposé une relation linéaire entre concentration en calcium et dommages sur la cellule, mais je ne pouvais alors pas retrouver les observations biologiques. Au lieu de prendre $Domage = k[Ca^{2+}]_{neurone}$, j'ai choisi

$$Domage = k_1 \frac{[Ca^{2+}]_{neurone}}{k_2 + [Ca^{2+}]_{neurone}}.$$

Ce choix n'est pas complètement arbitraire, en effet, on sait qu'il y a un mécanisme de stockage de l'excès de calcium dans les réticulums endoplasmiques (élément de la

cellule entouré d'une membrane présent dans le cytoplasme) qui régule la concentration de calcium dans certaines limites.

1.3.3 Résultats

La figure 1.14 représente l'évolution de l'état d'une cellule dont la concentration en calcium intracellulaire reste faible et qui dispose d'énergie pour se réparer. Le processus d'apoptose ne commence pas et la cellule reste en vie.

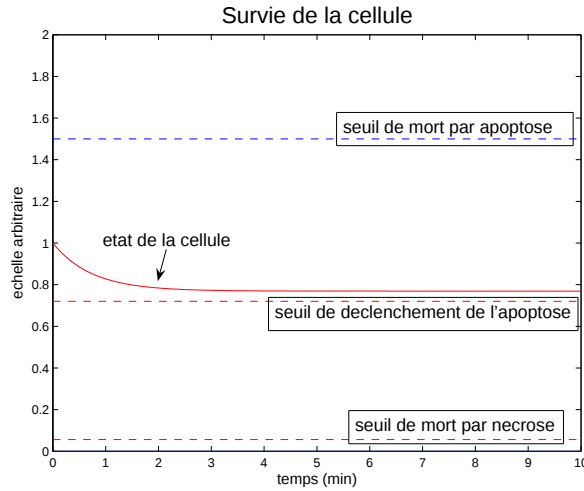


FIG. 1.14 – Evolution de l'état d'une cellule θ en rouge. La cellule est faiblement endommagée et dispose de suffisamment d'énergie pour se réparer.

La figure 1.15 présente maintenant le cas d'une cellule endommagée par la présence de calcium intracellulaire, mais qui dispose de suffisamment d'énergie pour effectuer son processus d'apoptose. Ici, l'apoptose commence pour $t = 0.8$ minutes quand θ passe sous le seuil $\theta_{apop} = 0.72$. Elle atteint son seuil d'irréversibilité $A_{apop} = 1.5$ en 15 minutes environ avant que θ n'atteigne le seuil de nécrose $\theta_{nec} = 0.0565$.

Enfin, la figure 1.16 montre l'exemple d'une cellule très gravement endommagée par le calcium et qui n'a pas suffisamment d'énergie pour effectuer une apoptose. Elle meurt par nécrose en 6 minutes.

1.4 Le modèle complet d'AVC

1.4.1 Les hypothèses du modèle

A l'aide des sous-modèles présentés ci-dessus et d'un modèle d'AVC précédent [25] développé par le groupe AVC-iSi, j'ai pu élaborer un modèle phénoménologique

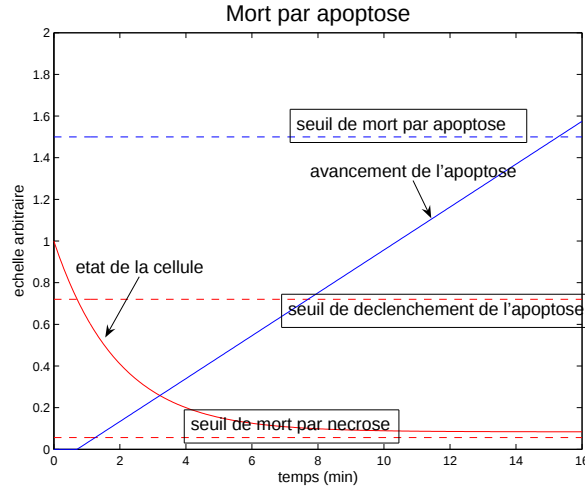


FIG. 1.15 – Evolution de l'état d'une cellule θ en rouge et du processus d'apoptose A en bleu en fonction du temps. La cellule est fortement endommagée par la présence de calcium intracellulaire et son énergie est supposé la moitié du niveau normal.

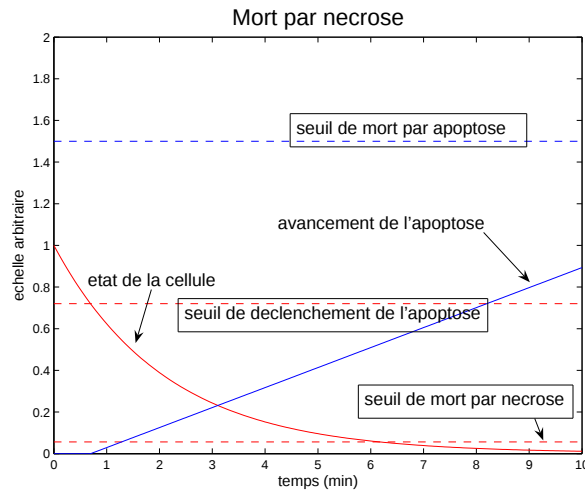


FIG. 1.16 – Evolution de l'état d'une cellule en rouge et du processus d'apoptose en bleu en fonction du temps. La cellule est fortement endommagée par la présence de calcium intracellulaire et elle dispose de 10% de son énergie normale.

global d'AVC. Les hypothèses biologiques sont les suivantes :

1. Le point de départ d'un AVC ischémique est une diminution soudaine du flux sanguin dans une partie du cerveau.

2. En réponse à cette diminution du flux sanguin, la cellule extrait d'avantage d'oxygène du sang qui continue à l'irriguer.
3. Si l'énergie disponible est insuffisante, les pompes ioniques ne fonctionnent plus, les différences de concentrations ioniques entre espace extracellulaire et intracellulaire tendent donc à s'équilibrer.
4. L'excès de potassium qui en découle entraine des dépressions corticales envahissantes (voir le modèle ci-dessus)
5. Pour récupérer des DCE, les cellules utilisent une partie de l'énergie dont elles disposent.
6. Les dommages sur la cellule sont liés à la concentration en calcium intracellulaire.
7. Selon les dommages et l'énergie dont elles disposent, les cellules meurent par nécrose ou par apoptose ou bien survivent (voir le modèle de mort ci-dessus).

Ces hypothèses biologiques amènent à un système de trois equations aux dérivées partielles de type réaction-diffusion, de 5 équations différentielles ordinaires et de 11 équations algébriques (voir annexe B pour les détails).

Les paramètres

Le système comporte encore un grand nombre de paramètres à fixer. Pour cela, j'ai utilisé le même algorithme aléatoire que présenté dans le cadre du sous-modèle de DCE. Après 50 000 itérations, j'ai obtenu 6 jeux complets de paramètres qui donne un comportement qualitatif raisonnable pour la simulation d'un AVC. Quelques résultats de la simulation d'un AVC sont présentés dans les figures 1.17 et 1.18.

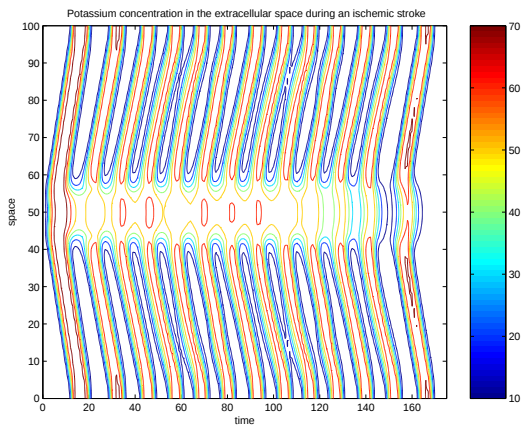


FIG. 1.17 – Lignes de niveau de la concentration en potassium extracellulaire sur un cerveau 1D.

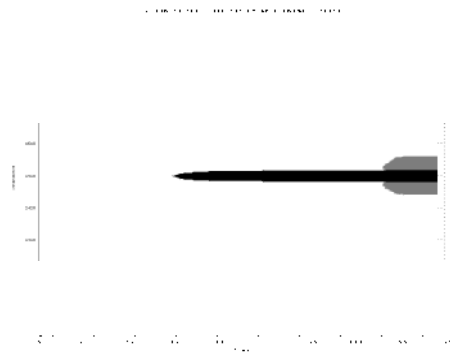


FIG. 1.18 – Mort des neurones au cours de l'AVC. En noir, la nécrose. En gris, l'apoptose.

Il est intéressant d'étudier la sensibilité du système aux paramètres.

- Le modèle de DCE est peu sensible à une variation de ses paramètres et l'algorithme aléatoire fonctionne bien pour cette partie.
- Pour les paramètres concernant la gestion de l'énergie par la cellule (cf annexe B page 135), les connaissances expérimentales sont trop faibles pour qu'on puisse vérifier précisément la validité des valeurs attribuées aux paramètres. J'ai donc fixé les valeurs des paramètres en partie arbitrairement. Ce choix retentit sur la taille de la zone atteinte par l'AVC qui n'est donc pas un résultat fiable du modèle.
- Le système est très sensible aux paramètres du modèle de mort. De petites variations de ces paramètres peuvent entraîner des comportements anormaux des solutions (en particulier, mort de cellules saines ou DCE qui ne s'arrête pas). Cela peut être dû à une mauvaise estimation des dommages en fonction de la concentration en calcium, ou bien à un mauvais lien entre quantité d'énergie utilisée et réparation de la cellule. Des modèles mécanistiques d'apoptose qui sont en cours d'élaboration pourront peut-être permettre d'affiner les valeurs des paramètres à choisir et ainsi améliorer notre modèle.

Sur un cerveau “carré” ...

J'ai utilisé les jeux de paramètres trouvés précédemment pour simuler un AVC en deux dimensions d'espace sur un cerveau “carré”. Je résoud le système d'équations à l'aide d'une transformée de Fourier rapide et d'un schéma semi-implicite en temps. On voit sur la figure 1.19 que plusieurs ondes de DCE se propagent dans le cerveau. Les résultats sont en accord avec les observations expérimentales [83] et les résultats obtenus en dimension 1.

1.4.2 Résultats du modèle

Effet des DCE sur la taille de la zone infarctique

Ce modèle a donné des résultats intéressants en deux dimensions d'espace. J'ai par exemple testé l'effet d'une occlusion partielle ou totale de l'artère (cf annexe B). En particulier, j'ai comparé la taille de la zone infarctique (définitivement morte par infarctus) avec des DCE ou en bloquant leur propagation (il suffit de couper la relation entre neurones et astrocytes). Dans mon modèle, chaque DCE fait augmenter d'un peu plus de 30% la zone infarctique (cf figure 1.20).

Ce type d'expérience a déjà été mené *in vivo* chez le rongeur [66, 53] et on a constaté expérimentalement que le passage de chaque DCE entraîne une augmentation d'environ 23% de la taille de la zone infarctique. L'accord théorie-expérience est donc ici tout à fait satisfaisant.

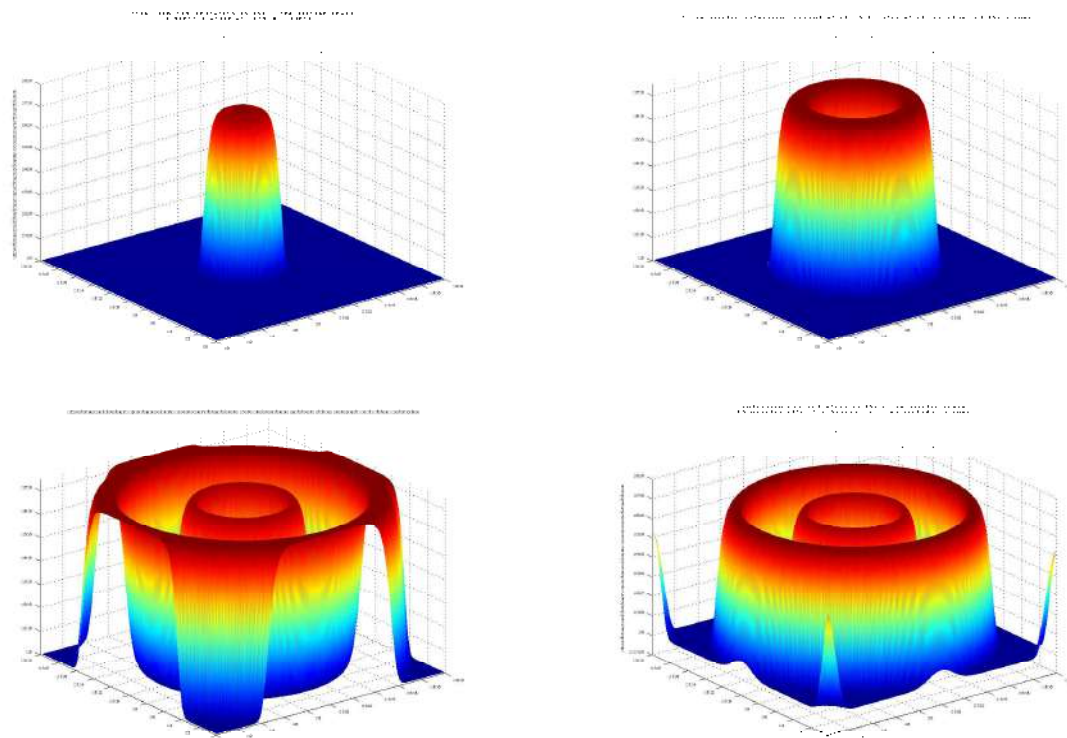


FIG. 1.19 – Concentration en potassium dans un cerveau carré à la suite d'un AVC (5, 15, 30 et 45 min après le début de l'AVC).

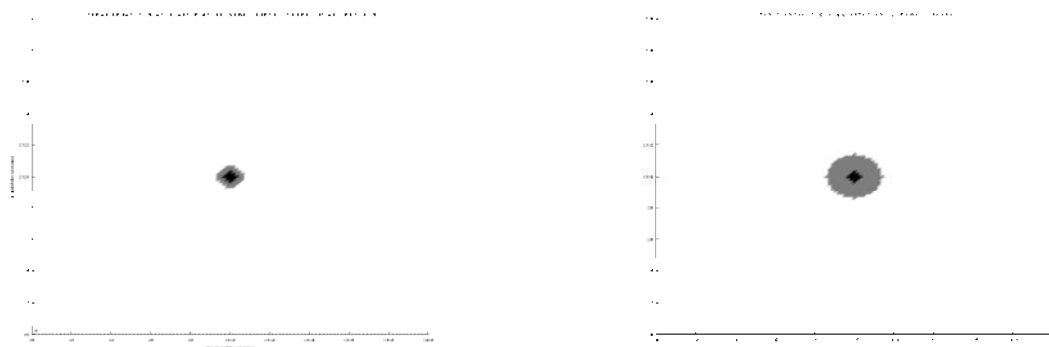


FIG. 1.20 – Comparaison des zones infarctées après un AVC sans DCE (à gauche) et avec (à droite).

La reperfusion

Le résultat le plus intéressant de ce modèle a été obtenu en étudiant l'influence de la reperfusion. L'idée de déboucher l'artère obturée est assez naturelle. En réta-

blissant le flux sanguin, on redonne de l'énergie aux cellules qui vont donc pouvoir revenir à leur état normal. Malheureusement, il a été prouvé expérimentalement que la reperfusion n'aboutissait pas systématiquement à une amélioration des symptômes. Au contraire, dans certains cas, la reperfusion aggrave les séquelles. Certaines explications ont été avancées, on soupçonne une influence des radicaux libres par exemple... Mais rien de définitif n'a été prouvé et dans ce modèle, aucune des hypothèses existantes n'a été incluses. Malgré cela, dans certains cas, les simulations de reperfusion aboutissent également à une aggravation des séquelles (cf figure 1.21). En particulier, cet effet délétère se produit si la reperfusion a lieu au début de la dernière ou avant-dernière DCE créée par l'AVC.

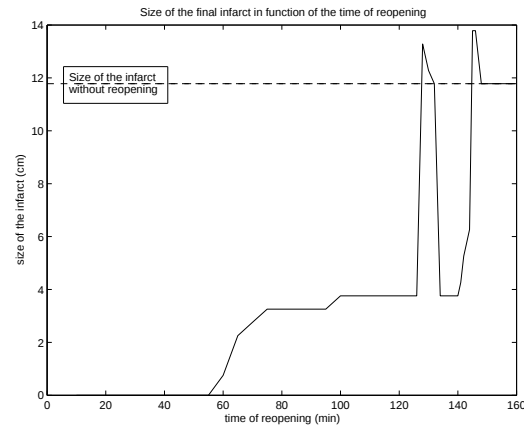


FIG. 1.21 – Graphique de la taille de la zone infarctée (en cm^2) en fonction du délai avant la reperfusion (en min).

Pour bien comprendre les raisons de l'effet délétère de la reperfusion dans ce modèle, il faut savoir tout d'abord que les DCE ont un comportement "tout ou rien", c'est à dire qu'il existe un seuil au niveau des concentrations ioniques en dessous duquel aucune DCE n'est créée, mais si les concentrations dépassent ce seuil, alors une DCE se produit et il est très compliqué de l'empêcher. Si la reperfusion se produit au moment où les concentrations ioniques ont déjà franchies ce seuil, le fait de redonner de l'énergie à la cellule n'empêche pas la création d'une onde de DCE qui se propage dans tout le cerveau.

Dans certains cas, il est même possible que deux DCE soient créées après la reperfusion. La première DCE est due comme précédemment au caractère "tout ou rien" et la suivante à une mauvaise synchronisation de la récupération entre la zone centrale qui a été touchée par le manque de sang et la zone périphérique. En effet, quand la zone centrale retrouve de l'énergie (grâce à la reperfusion), elle peut enfin récupérer, mais si cette récupération a lieu nettement avant que les cellules périphériques ne récupèrent elles-aussi, alors ces cellules périphériques recontaminent les

cellules centrales par diffusion des ions. Cela peut suffire pour dépasser à nouveau le seuil de création d'une DCE. La reperfusion ne stoppe donc pas immédiatement la propagation des DCE, ce qui signifie que les dommages sur les cellules liés à la présence de calcium intracellulaire peuvent persister quelques temps après la reperfusion.

En revanche, reperfusion redonne de l'énergie aux cellules, elles peuvent l'utiliser pour leur apoptose, or la vitesse de l'apoptose augmente avec la quantité d'énergie disponible. Les cellules qui avaient donc commencé leur phase réversible d'apoptose évoluent plus rapidement vers la mort. Or dans certains cas d'AVC, il existe des cellules à la périphérie de la zone infarctée qui approchent du seuil d'irréversibilité de l'apoptose au moment du passage de la dernière DCE, mais qui devraient finalement revenir à leur état normal. Dans le cas d'une reperfusion mal coordonnée avec la propagation des DCE, il peut y avoir le même nombre de DCE, mais ces cellules évoluent plus rapidement vers l'apoptose. Elles vont donc mourir par apoptose, alors qu'elles auraient normalement survécu.

Ces constatations permettent de fournir de nouvelles hypothèses aux biologistes et aux médecins pour expliquer l'effet délétère de la reperfusion. Cette hypothèse reste cependant à confirmer expérimentalement.

1.5 Quelques améliorations

1.5.1 Un modèle mécanistique de DCE

Il serait maintenant intéressant de modéliser les échanges ioniques entre les différentes cellules de façon plus précise. En effet le modèle phénoménologique précédent est une première étape, mais de nombreux phénomènes sont ignorés. Un modèle mécanistique de création puis propagation des DCE a été construit par Marie-Aimée Dronne [21]. Ce modèle est basé sur un recensement précis de toutes les pompes et canaux ioniques à la surface des cellules. Les équations modélisant le passage des ions d'un espace à l'autre sont donc basées sur les mécanismes cellulaires. Ce modèle donne des résultats quantitatifs prometteurs, mais il ne peut pour l'instant être inclus dans un modèle d'AVC car les cellules ne récupèrent pas de la dépolarisation. En effet, les connaissances sur cette récupération sont encore faibles, elle passe vraisemblablement par une augmentation du flux sanguin donc de l'énergie. Il serait donc intéressant d'ajouter des équations modélisant la récupération, comme je l'ai fait dans le modèle phénoménologique. Ce travail est en cours.

1.5.2 Perspectives

Le modèle global d'AVC peut encore être grandement amélioré. Deux axes principaux sont envisageables. On peut tout d'abord espérer de nouvelles connaissances expérimentales. Par exemple, il serait intéressant d'améliorer la modélisation de la

récupération des DCE. En particulier, on sait mal comment le flux sanguin intervient pour la récupération cellulaire. On pourrait également améliorer la modélisation de l'apoptose. Des modèles de la cascade apoptotique sont en train d'être établis et pourront certainement être insérés dans ce modèle global d'AVC. Dès aujourd'hui, il serait possible de prendre en compte davantage d'espèces ioniques, comme le sodium ou le glutamate par exemple. Le glutamate en particulier semble avoir un rôle important dans la propagation des DCE. Il est vraisemblable que l'augmentation de la concentration en calcium dans les astrocytes ne se communique pas directement aux neurones par des gap-jonctions, mais sans doute en activant des canaux ioniques qui font sortir du glutamate dans l'espace extracellulaire, ce qui entraîne une augmentation du calcium intraneuronal au travers d'autres canaux ioniques. Cependant, cela demanderait de rajouter une variable et il faut faire attention à ne pas trop surcharger le modèle pour que les simulations numériques soient possibles dans des temps raisonnables. Enfin, on connaît très mal la gestion de l'énergie dans la cellule et ce point paraît essentiel dans le fonctionnement du modèle.

Ensuite, on peut prendre en compte de nouveaux phénomènes. Par exemple, on pourrait ajouter le phénomène de suppléance (si le flux sanguin d'un vaisseau diminue, les vaisseaux voisins augmentent leur propre flux pour essayer de compenser le manque d'énergie). Ce point n'aurait d'intérêt que si l'on utilise une véritable carte de la vascularisation cérébrale, ce qui constitue également un axe d'amélioration. On pourrait également prendre en compte l'effet de l'inflammation ou de l'œdème (gonflement des cellules qui entraîne donc une augmentation des concentrations extracellulaires par exemple).

Enfin, pour pouvoir à terme comparer ce modèle avec des résultats expérimentaux, il serait intéressant de résoudre le système sur une vraie géométrie de cerveau. Le calcul en trois dimensions d'espace étant pour l'instant beaucoup trop lourd, on pourrait néanmoins faire les calculs sur une vraie coupe de cerveau.

Chapitre 2

Extinction de fronts progressifs

Je vais traiter dans ce chapitre de la non-existence de front progressif généralisé, solution d'une équation de réaction-diffusion de type bistable sur un cylindre de section carrée dont le diamètre augmente brutalement.

2.1 L'énoncé du théorème

2.1.1 Motivations

Cette étude est motivée par les simulations numériques du modèle phénoménologique de DCE construit dans le premier chapitre. Le problème est de comprendre pourquoi les DCE n'ont jamais été observées chez l'homme, alors qu'elles sont connues depuis longtemps chez le rat. Les mécanismes de base des DCE sont probablement les mêmes chez l'homme et chez le rat, mais la géométrie et la composition de leur cerveau sont très différentes comme expliqué dans la partie 1.2.3. En particulier, la substance grise du cerveau du rat peut être assimilée à une boule alors que chez l'homme, c'est une couche superficielle d'épaisseur très variable. Ces variations d'épaisseur dans le domaine où se propagent les DCE peuvent-elles être responsables de l'extinction de l'onde ?

J'ai étudié numériquement ce problème dans [16] (cf annexe A page 71). On constate qu'une augmentation importante et brutale du diamètre du domaine bloque la progression de l'onde. En revanche, une variation de faible ampleur ou progressive du diamètre du domaine ralentit l'onde mais ne l'empêche pas de continuer sa progression. Ceci constitue une explication possible de la non-observation des dépressions corticales envahissantes chez l'homme. Ces DCE seraient créées de la même façon que chez le rat, mais elles ne se propageraient que sur une faible distance car elles seraient bloquées à la première augmentation brutale de l'épaisseur de la substance grise. Elles seraient donc plus difficiles à observer.

L'étude théorique du système complet dans une géométrie réaliste étant trop compliquée, j'ai montré simplement qu'il n'existe pas de front progressif généralisé

solution d'une équation de réaction-diffusion de type bistable dans un cylindre de section carrée dont la longueur du côté augmente brutalement.

2.1.2 Cadre mathématique

Dans ce chapitre, on travaille dans $\mathbb{R}^3$, à l'exception d'une extension à d'autres dimensions dans la partie 2.2.2.

On étudie l'équation suivante

$$\begin{cases} \partial_t u - \nu \Delta u = f(u) & t \in \mathbb{R}, x \in \Omega, \\ \partial_n u = 0 & t \in \mathbb{R}, x \in \partial\Omega, \end{cases} \quad (2.1)$$

où $f(t) = f_0 t(t - \theta)(1 - t)$ est une nonlinéarité de type bistable avec $f_0 > 0$, $\theta \in]0, 1/2[$, $\nu > 0$ est une constante et Ω est un cylindre de section carrée de longueur de côté $2r$ pour $x_1 < 0$ et de longueur de côté $2R$ pour $x_1 > 0$ avec $r \leq R$. Plus précisément, on pose

$$\Omega_1 = \mathbb{R}_+^* \times]-R, R[\times]-R, R[, \quad \Omega_2 = \mathbb{R}_- \times]-r, r[\times]-r, r[,$$

$$\Omega = \Omega_1 \cup \Omega_2 \quad \text{et} \quad \Gamma = \partial\Omega.$$

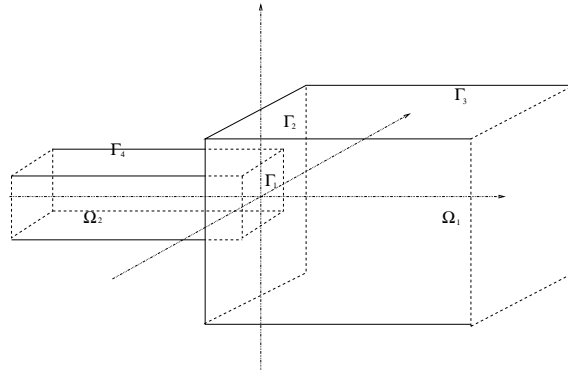


FIG. 2.1 – Le domaine Ω .

Pour la définition précise de la dérivée normale $\partial_n u = 0$ aux angles du domaine, se référer à l'annexe C page 105.

Dans l'article [17] en annexe C, j'ai montré le théorème suivant

Théorème 2.1 *Soit $u(t, x)$ une solution de*

$$\begin{cases} \partial_t u - \nu \Delta u = f(u) & t > 0, x \in \Omega. \\ \partial_n u = 0 & t > 0, x \in \partial\Omega. \\ u(0, x) = u_0(x) & x \in \Omega. \end{cases} \quad (2.2)$$

où il existe $\alpha_0 > 0$ tel que $u_0(x) < \frac{1}{2}\theta e^{-\alpha_0 x_1}$ pour tout $x \in \Omega_1$.

Il existe $R_{critique}(R, \nu) > 0$ tel que si $r < R_{critique}$, il existe $\rho > 0$ tel que

$$\forall x \in \Omega \quad x_1 > \rho \Rightarrow \forall t \geq 0 \quad u(t, x) \leq \frac{\theta}{2}.$$

En corollaire, on peut montrer facilement qu'il n'existe pas de front progressif généralisé solution de l'équation (2.1). Rappelons d'abord la définition d'un front progressif généralisé.

Tout d'abord un front progressif est une solution $u(t, \mathbf{x}) = U(\mathbf{k} \cdot \mathbf{x} - ct)$ où U est le profil du front à déterminer, $\mathbf{k}$ est un vecteur et c est une constante appelée vitesse du front. Ces deux constantes sont également à déterminer. On parle aussi de front progressif ou front progressif courbe si la solution dépend de $\mathbf{k} \cdot \mathbf{x} - ct$ et des variables transverses à la direction de $\mathbf{k}$.

Définition 2.1 $u(t, \mathbf{x})$ est un front progressif généralisé de (2.1) si c'est une solution de (2.1) telle qu'il existe U_1 et U_2 des fronts progressifs de (2.1) sur des cylindres de section carrée de diamètre respectif $2r$ et $2R$ de vitesse respective c_1 et c_2 et $L > 0$ tels que

$$\lim_{t \rightarrow +\infty} |u(t, \mathbf{x}) - U_1(x_1 - c_1 t, x_2, x_3)| = 0$$

uniformément sur tout ensemble $\Omega_1 \cap [L, +\infty[\times [-K, K] \times [-K, K]$ pour tout $K > 0$, et

$$\lim_{t \rightarrow -\infty} |u(t, \mathbf{x}) - U_2(x_1 - c_2 t, x_2, x_3)| = 0$$

uniformément sur tout ensemble $\Omega_2 \cap]-\infty, -L] \times [-K, K] \times [-K, K]$ pour tout $K > 0$.

Donc s'il existe un front progressif généralisé, pour $\mathbf{x} \in \Omega_1$ avec x_1 suffisamment grand $u(t, x) \xrightarrow{t \rightarrow +\infty} 1 > \theta/2$, ce qui contredit la conclusion du théorème ci-dessus.

Historiquement, l'étude de l'existence de front progressif bistable en une dimension d'espace a été faite par Aronson et Weinberger dans [3]. Quant à la convergence des solutions de l'équation avec donnée initiale vers ces fronts progressifs, elle a été montrée par Fife et McLeod dans [29] et [30]. Dans ces trois articles, les preuves sont principalement basées sur la construction de sur- et sous-solutions grâce au principe du maximum. En dimension d'espace supérieure, Berestycki et Nirenberg [10] ont

montré l'existence de fronts progressifs sur des cylindres en étudiant des solutions particulières du problème linéarisé à l'infini dans la direction de propagation. Roquejoffre [77] a montré la convergence vers un front progressif des solutions d'une équation de réaction-diffusion avec donnée initiale sur un cylindre en étudiant le problème linéarisé pour $t \rightarrow +\infty$.

Ces articles nous montrent que si la variation de diamètre du domaine est très petite, il existe un front progressif généralisé. Pour montrer le théorème 2.1 par contre, il a fallu développer une nouvelle méthode.

2.2 La preuve du théorème

2.2.1 Idées de la preuve du théorème 2.1

La preuve du théorème 2.1 comporte trois étapes. Pour les détails, je renvoie à l'article [17] donné en annexe C page 103.

1ère étape. On ramène l'étude du système (2.2) à un problème sur le demi-espace $\{x_1 > 0\}$.

Premièrement, d'après le principe du maximum, il suffit de considérer l'équation sur $\Omega_1 = \Omega \cap \{x_1 > 0\}$ avec une donnée de Dirichlet $u = 1$ sur $\Gamma_1 = \{0\} \times [-r, r] \times [-r, r]$. Pour pouvoir utiliser la décroissance de la fonction de Green par la suite, on pose $g(u) = f(u) - \eta f'(0)u$, $\eta \in]0, 1]$, et on a

$$\partial_t v - \nu \Delta v - \eta f'(0)v = g(v).$$

Maintenant, comme on a une condition de Neumann $\partial_n u = 0$ sur Γ , on peut étendre la solution de notre équation au demi-espace $\{x_1 > 0\}$ de façon à ce que la fonction soit paire à travers la frontière Γ_3 , c'est à dire que la fonction va être paire par rapport au plan $\{x_2 = R\}$, mais aussi par rapport aux plans $\{x_2 = -R\}$, $\{x_3 = R\}$ et $\{x_3 = -R\}$. La fonction étendue sera donc périodique. On se ramène ainsi au problème suivant

$$\begin{cases} \partial_t v - \nu \Delta v - \eta f'(0)v = g(v) & t > 0, x \in \mathbb{R}_+^* \times \mathbb{R}^2. \\ v(0, x) = \tilde{u}_0(x) & x \in \mathbb{R}_+ \times \mathbb{R}^2. \\ v(t, x) = \tilde{u}(t, x) & t > 0, x \in \tilde{\Gamma}_1. \\ \partial_n v = 0 & t > 0, x \in \tilde{\Gamma}_2 \end{cases} \quad (2.3)$$

où pour une fonction w , $\tilde{w}$ désigne l'extention paire de w à $\mathbb{R}^+ \times \mathbb{R}^2$ et pour un ensemble γ , $\tilde{\gamma}$ est l'union de tous les symétriques de γ par rapport aux frontières de Γ_3 (cf annexe C page 106 pour des définitions plus précises). Le problème du système (2.3) est que les conditions aux bords sont mixtes Neumann-Dirichlet.

2ème étape. Construction d'une sur-solution.

Pour construire une sur-solution, on utilise la formule de Duhamel.

$$v(t, x) = w(t, x) + \int_0^t \int_{\mathbb{R}^+ \times \mathbb{R}^2} F(t - \tau, x, \xi) g(v(\tau, \xi)) d\xi d\tau$$

où $w(t, x)$ vérifie

$$\begin{cases} \partial_t w - \nu \Delta w - \eta f'(0)w = 0 & t > 0, x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ w(0, x) = \tilde{u}_0(x) & x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ w = u, & t > 0, x \in \tilde{\Gamma}_1. \\ \partial_n w = 0 & t \geq 0, x \in \tilde{\Gamma}_2. \end{cases} \quad (2.4)$$

et $F(., ., \xi)$ est la solution élémentaire du problème suivant

$$\begin{cases} \partial_t F - \nu \Delta F - \eta f'(0)F = 0 & t > 0, x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ F(0, x) = \delta(x - \xi) & x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ F = 0, & t > 0, x \in \tilde{\Gamma}_1. \\ \partial_n F = 0 & t \geq 0, x \in \tilde{\Gamma}_2. \end{cases} \quad (2.5)$$

Pour construire une sur-solution de la partie linéaire w , on utilise la solution élémentaire du problème elliptique associé à (2.4)

$$E(x) = \frac{q}{4\pi} \frac{e^{-q|x|}}{|x|}$$

avec $q = \sqrt{-\eta f'(0)/\nu} < \alpha_0$, puis on pose

$$Q(x) = \sum_{(k,l) \in \mathbb{Z}^2} \int_{2kR-r}^{2kR+r} \int_{2lR-r}^{2lR+r} E(x - y^*) dy$$

où $y^* = (0, y_1, y_2) \in \mathbb{R}^3$ pour $y = (y_1, y_2) \in \mathbb{R}^2$. Alors, il existe $\alpha > 0$ dépendant de r , de R et de q tel que $\alpha Q \geq 1$ sur Γ_1 . Comme Q est périodique par rapport aux faces de Γ_3 , $\alpha Q \geq 1$ sur $\tilde{\Gamma}_1$. De plus, $\partial_n Q = 0$ sur $\tilde{\Gamma}_2$ et

$$\nu \Delta Q + \eta f'(0)Q = 0, \quad x \in \mathbb{R}^3.$$

αQ est donc bien une sur-solution de w (cf annexe C page 107 pour les détails). De plus, par des majorations simples, on montre

$$\alpha Q(x) \leq \frac{2\sqrt{2}r}{x_1} e^{3q\sqrt{2}r} \left(\sum_{(k,l) \in \mathbb{Z}^2} e^{-q2R\sqrt{k^2+l^2}} \right). \quad (2.6)$$

Pour tout $\varepsilon > 0$ (on fixera sa valeur ultérieurement), si on pose

$$\rho_1(r, R, q) = \frac{4\sqrt{2}r}{\varepsilon} e^{3q\sqrt{2}r} \left(\sum_{(k,l) \in \mathbb{Z}^2} e^{-q2R\sqrt{k^2+l^2}} \right), \quad (2.7)$$

on a $\forall x \in \Omega_1 \quad x_1 > \rho_1 \Rightarrow \alpha Q(x) \leq \frac{\varepsilon}{2}$.

Pour construire une sur-solution de la partie nonlinéaire dans la formule de Duhamel, on va tout d'abord remplacer g par $\tilde{g} = \max(g, 0)$ puis on utilise la fonction de Green de l'équation sur $\mathbb{R}^3$ entier

$$G(t, x) = \frac{1}{(4\nu\pi t)^{\frac{3}{2}}} e^{-\frac{|x|^2}{4\nu t}} e^{\eta f'(0)t}$$

qui est paire par rapport à $\{x_1 = 0\}$. A nouveau, d'après le principe du maximum, on obtient

$$v(t, x) \leq \underbrace{\alpha(r, R, q)Q(x)}_{=I(x)} + \underbrace{\int_0^t \int_{\mathbb{R}^+ \times \mathbb{R}^2} (G(t-\tau, x-\xi) + G(t-\tau, x-\xi')) \tilde{g}(v(\tau, \xi)) d\xi d\tau}_{=J(t,x)}.$$

où $\xi' = (-\xi_1, \xi_2, \xi_3)$.

3ème étape. Estimation de $J(t, x)$.

Pour majorer $J(t, x)$, on introduit quelques notations. Soit $\varepsilon \in]0, \theta/2[$ tel que $\tilde{g} = 0$ sur $[0, \varepsilon]$. Pour $x \in \mathbb{R}_+ \times \mathbb{R}^2$, on pose

$$t_x = \sup\{t \geq 0 \mid \forall \tau \in [0, t] \quad v(t, x) \leq \varepsilon\} \in \bar{\mathbb{R}}_+^*$$

puis pour $\rho > 0$, on définit

$$T(\rho) = \inf_{x \in]\rho, \infty[\times \mathbb{R}^2} t_x \in \bar{\mathbb{R}}_+.$$

Pour conclure la démonstration du théorème, il nous suffit de trouver les conditions sur r , R et ν telles que

$$\exists \rho > 0 \quad T(\rho) = +\infty.$$

Supposons par contradiction que

$$\forall \rho \geq \rho_1(r, R, q) \quad T(\rho) < +\infty.$$

Soit $\rho \geq \rho_1(r, R, q)$ fixé. Dans la suite, on écrira T pour $T(\rho)$.

D'après (2.7), il existe des suites $x_n \in]\rho, +\infty[\times \mathbb{R}^2$ et $t_n \in]T, T + \frac{1}{n}[$ telles que

$J(t_n, x_n) > \frac{\varepsilon}{2}$. Or

$$\begin{aligned} J(t_n, x_n) &= \int_T^{t_n} \int_{\mathbb{R}^+ \times \mathbb{R}^2} (G(t_n - \tau, x_n - \xi) + G(t_n - \tau, x_n - \xi')) \tilde{g}(v(\tau, \xi)) d\xi d\tau \\ &\quad + \underbrace{\int_0^T \int_{\mathbb{R}^+ \times \mathbb{R}^2} (G(t_n - \tau, x_n - \xi) + G(t_n - \tau, x_n - \xi')) \tilde{g}(v(\tau, \xi)) d\xi d\tau}_{=K(t_n, x_n)} \end{aligned}$$

Comme $\tilde{g}$ est bornée et G est intégrable, la première partie de cette équation tend vers 0 pour $n \rightarrow +\infty$. Il reste à estimer $K(t_n, x_n)$. Par des changements de variables dans l'intégrale et des majorations simples, on a

$$K(t_n, x_n) \leq \frac{M}{\pi^{\frac{3}{2}}} \int_0^{+\infty} \int_{\frac{-\rho}{2\sqrt{4\nu\tau}}}^{\frac{\rho}{2\sqrt{4\nu\tau}}} e^{-z_1^2} e^{\eta f'(0)\tau} dz_1 d\tau.$$

Donc à n fixé, par le théorème de convergence dominée, il existe $\rho_2(\nu) > 0$ tel que

$$\forall \rho < \rho_2(\nu) \quad K(t_n, x_n) \leq \frac{\varepsilon}{4}.$$

Si on a $\rho_2 > \rho_1$, on aboutit à une contradiction.

Conclusion. S'il existe r , R et ν tels que $\rho_2(\nu) > \rho_1(r, R, q)$, alors on peut trouver $\rho > 0$ tel que $T(\rho) = +\infty$, ce qui prouverait le théorème.

Comme $\rho_1(r, R, q) \xrightarrow{r \rightarrow 0} 0$ pour R et ν fixés, on obtient le résultat souhaité.

2.2.2 Cas de la dimension 2

En dimension 2, le résultat peut être démontré de la même manière, quitte à modifier les fonctions de Green.

G devient

$$G_2(t, x) = \frac{1}{4\nu\pi t} e^{-\frac{|x|^2}{4\nu t}} e^{\eta f'(0)t} \quad \text{pour } t > 0 \text{ et } x \in \mathbb{R}^2.$$

et E est remplacé par $E_2(x) = iH_0^{(1)}(iq|x|)$ où $H_0^{(1)}$ est la fonction de Hankel de type 1 et d'ordre 0.

Les sur-solutions des parties linéaires et non-linéaires ne sont donc plus exactement les mêmes, mais avec les estimations connues sur $H_0^{(1)}$, on peut de la même manière définir $\rho_1(r, R, q)$ et $\rho_2(\nu)$ et on a toujours $\rho_1(r, R, q) \xrightarrow{r \rightarrow 0} 0$. Le théorème reste donc vrai (cf annexe C page 112).

2.2.3 Perspectives

Cette méthode peut facilement être étendue au cas d'une équation de réaction-diffusion avec une nonlinéarité bistable f qui vérifie :

$$f(0) = f(1) = 0 \quad \text{et} \quad f'(0) < 0.$$

De même, on peut sans doute démontrer le même résultat en dimension quelconque.

En revanche, cette méthode est fortement dépendante du domaine et ne peut s'appliquer qu'à des cylindres de section carrée, à moins d'obtenir des estimations très précises des fonctions de Green sur un demi cylindre.

Chapitre 3

Fronts progressifs courbes

Dans cette partie, j'étudie les fronts progressifs solutions d'une équation de réaction-diffusion sur un cylindre de rayon R dans $\mathbb{R}^N$ et d'une équation de diffusion et absorption en dehors du cylindre.

3.1 L'énoncé du théorème

3.1.1 Motivations

Comme dans le chapitre précédent, cette étude est motivée par les simulations numériques du modèle phénoménologique de DCE construit dans le premier chapitre. Il s'agit d'étudier l'influence de la substance blanche sur la création des DCE. En effet, les espèces ioniques responsables des DCE diffusent dans la substance blanche et sont progressivement absorbées sans que la réaction qui se produit dans la substance grise ne se fasse. L'effet absorbant de la substance blanche pourrait donc empêcher la création des DCE. Or le cerveau humain est composé en majorité de substance blanche avec une fine couche de substance grise à la périphérie (cf paragraphe 1.2.3). Chez le rongeur, au contraire, le cerveau est principalement composé de substance grise. Comme il est pour l'instant impossible d'étudier le système complet dans une géométrie réaliste, j'étudie ici l'existence de fronts progressifs courbes à la fois solution d'une équation de réaction-diffusion sur un cylindre et d'une équation de diffusion et absorption en dehors du cylindre. L'existence d'un front solution va dépendre du rayon du cylindre.

3.1.2 Cadre mathématique

Je m'intéresse dans ce chapitre à l'équation suivante :

$$\frac{\partial u}{\partial t} - \Delta u = g(u)\mathbb{1}_\Omega - \alpha u\mathbb{1}_{\mathbb{R}^N \setminus \Omega}, \quad t \in \mathbb{R}, X \in \mathbb{R}^N, \quad (3.1)$$

où $g(u) = \lambda u(u - \theta)(1 - u)$ est la nonlinéarité bistable usuelle avec $\theta \in]0, 1/2[$, $\mathbb{1}$ désigne une fonction caractéristique d'un ensemble et Ω est un cylindre infini de rayon R représentant la substance grise (réaction-diffusion).

Dans la suite, on notera la variable d'espace $(x, z) \in \mathbb{R}^N$ avec $x \in \mathbb{R}$ et $z \in \mathbb{R}^{N-1}$, et $\Omega = \mathbb{R} \times B(0, R)$ le cylindre.

On cherche les solutions de (3.1) de type front progressif courbe, c'est à dire $u(t, x, z) = U(x - ct, z)$ pour un $c \in \mathbb{R}$ constant à déterminer, avec de plus les limites $\lim_{x \rightarrow -\infty} U(x, z)$ et $\lim_{x \rightarrow +\infty} U(x, z)$ qui existent et sont distinctes. Le profil de l'onde U vérifie donc l'équation

$$(TF) \begin{cases} \Delta U + c \partial_x U + g(U) \mathbb{1}_{\{|z| \leq R\}} - \alpha U \mathbb{1}_{\{|z| > R\}} = 0 & (x, z) \in \mathbb{R}^N, \\ U(x, z) \rightarrow 0 \text{ pour } |z| \rightarrow \infty, & x \in \mathbb{R} \end{cases}$$

et les profils asymptotiques $\phi_{\pm} = \lim_{x \rightarrow \pm\infty} U$ sont solutions de l'équation

$$(P_{\infty}) \begin{cases} \Delta_z \phi + g(U) \mathbb{1}_{\{|z| \leq R\}} - \alpha U \mathbb{1}_{\{|z| > R\}} = 0, & z \in \mathbb{R}^{N-1}, \\ \phi(z) \xrightarrow{|z| \rightarrow \infty} 0. \end{cases}$$

Dans [14], j'ai montré les théorèmes suivants.

Théorème 3.1 *Si $N = 2$, il existe $R_0 > 0$ tel que*

- *si $R < R_0$, $\phi \equiv 0$ est la seule solution C^1 de (P_{∞}) ,*
- *si $R > R_0$, (P_{∞}) admet au moins 3 solutions $C^1 : 0, \phi_1 > 0$ et $\phi_2 > 0$.*

Théorème 3.2 *Si $N \geq 3$, il existe $R_1 \geq R_0 > 0$ tel que*

- *si $R < R_0$, $\phi \equiv 0$ est la seule solution radiale C^1 de (P_{∞}) ,*
- *si $R > R_1$, (P_{∞}) admet au moins 2 solutions $C^1 : 0$ et $\phi > 0$.*

Corollaire 3.1 *Si $N = 2$ (resp. $N \geq 3$), il n'existe pas de front progressif (resp. de front progressif cylindrique) solution de (3.1) pour $R < R_0$.*

Si $R \geq R_0$, l'existence de front d'onde et la convergence des solutions vers ces fronts d'onde est plus délicate à montrer. Historiquement, l'étude des fronts d'onde en dimension 1 d'espace a commencé avec Aronson et Weinberger [3]. Ils ont montré l'existence de front en travaillant dans le plan de phase. Puis Fife et McLeod [29, 30] ont fait une démonstration de la convergence des solutions vers ces fronts en utilisant principalement le principe du maximum et en construisant des sur- et sous-solutions bien adaptées.

En dimension supérieure, il existe plusieurs types de résultats. Berestycki et Nirenberg [10] ont montré l'existence de fronts progressifs dans des cylindres avec un terme d'entraînement qui peut dépendre des coordonnées transverses. Vega [87, 88] a montré l'existence et l'unicité de front progresifs dans un cylindre avec des conditions aux bords de Dirichlet homogènes. Enfin, Roquejoffre a étudié la convergence

vers des fronts sur un cylindre [77]. Tous ces articles utilisent de façon plus ou moins précise l'énergie de la solution et le linéarisé à l'infini. Ils ont donc tous besoin que le cylindre soit de section bornée pour pouvoir utiliser des injections de Sobolev compactes, mais aussi des fonctions propres du linéarisé.

Sur l'espace entier, Hamel, Monneau et Roquejoffre ont étudié le problème de la combustion de la flamme du bec Bunsen [42]. Leur démonstration utilise de nombreuses fois la méthode de glissement introduite dans [11] par Berestycki et Nirenberg ainsi que l'existence d'un front en dimension 1 d'espace. En effet, leur front est un front conique, donc il ressemble à un front plan à l'infini (donc à un front en dimension 1 d'espace). En particulier, ils connaissent la vitesse du front a priori et peuvent ainsi construire des sur- et sous-solution adaptées.

L'autre approche de l'étude des fronts progressifs vient des problèmes de cinétique chimique. Dans ce cas, les fronts sont vectoriels et il n'existe plus de principe du maximum. Une possibilité est d'utiliser la méthode de Leray-Schauder comme Volpert [89] ou bien Gardner [32]. Une autre méthode a été développée par Emmanuel Risler [75]. Elle montre l'existence de fronts progressifs et un début de convergence en dimension 1 d'espace en étudiant l'énergie des solutions dans différents référentiels en mouvement. Cette méthode a été développée pour éviter l'utilisation du principe du maximum qui existe dans notre cas (cf annexe D page 153), mais elle présente également de nombreux autres intérêts. Tout d'abord, la méthode détermine directement la vitesse du front et ne demande pas d'en connaître un encadrement a priori. Ensuite, cette méthode utilise l'énergie des solutions, donc des intégrales. La taille de la section du cylindre n'a donc pas d'importance, il suffit que la solution soit intégrable en z à t et x fixés.

3.2 La preuve du théorème

3.2.1 Etude des profils asymptotiques

Avant de montrer l'éventuelle existence de front progressif, il est naturel de chercher à connaître les états que pourrait relier ce front, c'est à dire les différents profils asymptotiques possibles. Rappelons qu'un tel profil asymptotique est solution du problème

$$(P_\infty) \begin{cases} \Delta \phi + g(\phi) \mathbb{1}_{\{|z| \leq R\}} - \alpha \phi \mathbb{1}_{\{|z| > R\}} = 0 & z \in \mathbb{R}^{N-1}, \\ \phi(z) \xrightarrow{|z| \rightarrow \infty} 0. \end{cases}$$

En dimension $N = 2$, cette équation devient une équation différentielle ordinaire et on peut travailler dans le plan de phase.

Cas de la dimension $N = 2$

Cette partie donne les idées de la démonstration du théorème 3.1. Tout d'abord, introduisons quelques notations. On définit

$$(E_1) \quad \phi'' + g(\phi) = 0 \quad \text{et} \quad (E_2) \quad \phi'' - \alpha\phi = 0.$$

Le problème est de recoller une solution de (E_1) avec une solution de (E_2) de façon C^1 en $z = -R$ et en $z = R$. Les solutions de (E_2) qui tendent vers 0 en l'infini sont bien connues. On a donc $\phi(z) = Be^{\sqrt{\alpha}z}$ pour un $B \in \mathbb{R}$ si $z < -R$, et $\phi(z) = Ae^{-\sqrt{\alpha}z}$ pour un $A \in \mathbb{R}$ si $z > R$. Donc le problème est de trouver une solution de (E_1) telle que

$$(BC_1) \quad \phi'(-R) = \sqrt{\alpha}\phi(-R) \text{ et } \phi'(R) = -\sqrt{\alpha}\phi(R).$$

En travaillant dans le plan de phase (cf figure 3.1), on peut étudier le temps que met une trajectoire de (E_1) passant par $(\phi_c, -\sqrt{\alpha}\phi_c)$ pour joindre les deux droites $\phi' = \sqrt{\alpha}\phi$ et $\phi' = -\sqrt{\alpha}\phi$. Par continuité du flot, on voit assez facilement que ce

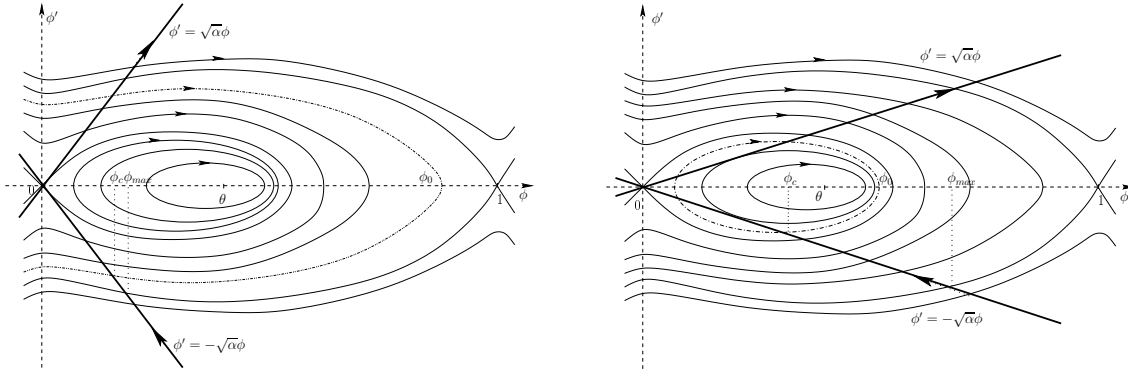


FIG. 3.1 – Superposition du plan de phase de (E_1) et des trajectoires de (E_2) qui nous intéressent ici. A gauche, dans le cas $\sqrt{\alpha} \geq \theta$ et à droite pour $\sqrt{\alpha} < \theta$.

temps est défini et continu en fonction de ϕ_c sur un intervalle $[0, \phi_{max}]$ et qu'en chaque extrémité de cet intervalle, ce temps tend vers $+\infty$ car la trajectoire devrait passer par un équilibre de (E_1) (0 ou 1). Ainsi, il existe un temps minimum $R_0 > 0$ pour qu'une trajectoire de (E_1) joigne les deux trajectoires voulues de (E_2) , on en déduit le théorème 3.1. Pour plus de détails, voir l'annexe D page 122.

Cas de la dimension $N > 2$

En dimension supérieure, si on suppose les solutions radiales, les profils asymptotiques vérifient l'équation

$$(ode) \quad \begin{cases} \psi'' + \frac{N-2}{r}\psi' + g(\psi)\mathbb{1}_{\{r \leq R\}} - \alpha\psi\mathbb{1}_{\{r > R\}} = 0 & r > 0, \\ \psi(r) \xrightarrow[r \rightarrow \infty]{} 0, \quad \psi'(0) = 0. \end{cases}$$

J'ai montré le théorème 3.2 en utilisant les solutions construites en dimension $N = 2$.

Supposons par l'absurde qu'il existe une solution ψ non identiquement nulle de (ode) pour $R < R_0$. Alors, si ψ est décroissante, ψ est clairement une sous-solution de (P_∞) en dimension 1. 1 étant une sursolution, on peut construire une solution de (P_∞) en dimension 1 comprise entre $\psi > 0$ et 1 (cf [28] ou [82] par exemple). Cela contredirait le théorème 3.1. Maintenant, ψ n'est pas nécessairement décroissante, mais par le principe du maximum, comme ψ tend vers 0 en l'infini, il existe $M > 0$ tel que ψ est décroissante sur $[M, +\infty[$ et $\psi'(M) = 0$. On peut alors construire une sous-solution non nulle de (P_∞) en dimension 1 en posant $\phi(z) = \psi(M + |z|)$. Ceci contredit donc le théorème 3.1, il n'existe donc pas de solution de (ode) pour $R < R_0$.

Pour trouver une solution de (ode) si R est suffisamment grand, on va construire une sous-solution strictement positive. Pour cela, on constate que pour ϕ la plus grande des solutions de (P_∞) construites en dimension 1, le terme $\frac{N-2}{r}\phi'$ peut être aussi petit que souhaité si R est suffisamment grand (voir annexe D page 126). On peut alors construire une nouvelle nonlinéarité g_0 et un coefficient α_0 qui vérifient les hypothèses du théorème 3.1 et tels que

$$\frac{N-2}{r}\phi' + (g(\phi) - g_0(\phi))\mathbb{1}_{\{r \leq R\}} - (\alpha - \alpha_0)\phi\mathbb{1}_{\{r > R\}} \geq 0.$$

La plus grande des solutions de l'équation avec g_0 et α_0 en dimension 1 est donc une sous-solution strictement positive de (ode) . On en déduit donc l'existence d'une solution. Tous les calculs sont détaillés dans l'annexe D page 125.

La non existence de profil asymptotique autre que 0 si $R < R_0$ entraîne la non existence de front progressif solution de (TF) si $R < R_0$. Il reste à montrer l'existence d'un front progressif lorsqu'il existe différents profils asymptotiques. On supposera donc désormais $R > R_1$.

3.2.2 Idées de la preuve de l'existence de fronts

Pour montrer l'existence d'un front progressif solution de (TF) si R est suffisamment grand, j'ai étendu la méthode développée par Emmanuel Risler dans [75] avec quelques simplifications dues au principe du maximum. L'idée est de construire le front progressif comme une limite extraite d'une solution de (3.1) pour certaines données initiales. On montre donc l'existence d'un front, et s'il y a unicité du front limite, on a même la convergence uniforme de certaines solutions vers ce front.

On appelle u la solution de (3.1) pour une donnée initiale u_0 . J'ai montré le théorème suivant.

Théorème 3.3 *Il existe $\delta > 0$ tel qu'on ait le résultat suivant. Si $u_0 \in H$ vérifie*

$$\limsup_{x \rightarrow +\infty} \int_{x-1}^{x+1} \int_{\mathbb{R}^{N-1}} (u_0(x, z)^2 + |\nabla u_0(x, z)|^2) dz dx \leq \delta \quad (3.2)$$

et

$$\int_L^0 \int_{\mathbb{R}^{N-1}} \frac{|\nabla u_0(x, z)|^2}{2} + F(u_0(x, z), z) dz dx \xrightarrow{L \rightarrow +\infty} -\infty, \quad (3.3)$$

alors il existe $\tilde{x}(t)$ tel que pour toute suite $(t_n)_{n \in \mathbb{N}}$ avec $t_n \geq 0$ et $t_n \rightarrow +\infty$, il existe U un front progressif de vitesse $c > 0$ avec $U \xrightarrow{x \rightarrow +\infty} 0$ et $U \xrightarrow{x \rightarrow -\infty} \phi > 0$, tel que, quitte à extraire,

$$\sup_{y \in [-L, +\infty[, z \in \mathbb{R}^{N-1}} |u(t_n, \tilde{x}(t_n) + y, z) - U(y, z)| \xrightarrow{n \rightarrow +\infty} 0$$

pour tout $L > 0$.

De plus, $\tilde{x}'(t) \xrightarrow{t \rightarrow +\infty} c$.

La démonstration de ce théorème se fait en plusieurs étapes.

Etape 1. Définition du point d'échappement.

L'idée de cette méthode est tout d'abord de supposer que la donnée initiale est proche de 0 pour x proche de $+\infty$ et proche d'un état non nul plus stable que 0 pour x proche de $-\infty$. C'est le sens des conditions (3.2) et (3.3) dans le théorème 3.3. On peut alors montrer que l'état non nul ne peut pas envahir l'état 0 trop rapidement (cf lemme D.3 page 131 en annexe). Pour cela, on étudie l'évolution en t et x d'une énergie "locale" en x . Ceci permet de définir le point d'échappement $\tilde{x}(t)$ qui est le premier point où la solution $u(t, x, z)$ de (3.1) quitte l'état 0 du point de vue énergétique. Autrement dit, pour $x \geq \tilde{x}(t)$, $u(t, x, z)$ est proche de 0 à $\varepsilon_{st} > 0$ près et pour $x < \tilde{x}(t)$, l'énergie locale de la solution $u(t, x, z)$ est supérieure ou égale à une valeur $\varepsilon > 0$ bien définie (cf 134 en annexe D).

Ces idées sont dues à Emmanuel Risler, bien que dans mon cas, la définition de l'énergie de la solution soit légèrement modifiée (car Risler travaillait en 1 dimension d'espace). De même, j'ai dû montrer que certains plongements de Sobolev étaient toujours valables ici (car la solution est exponentiellement décroissante pour $|z| \rightarrow \infty$ ainsi que son gradient).

L'idée est ensuite d'étudier l'énergie globale de la solution $u(t)$ dans un référentiel en mouvement linéaire uniforme qui "suit" le point d'échappement de façon à montrer la convergence de $u(t)$ vers une solution stationnaire non nulle dans ce référentiel. Cette solution stationnaire sera le front progressif recherché. Le premier problème est cependant de montrer que le point d'échappement a bien une vitesse asymptotique constante. On définit donc l'avancement maximal du point d'échappement

$$\tilde{X}(s) = \sup_{t \geq 0} (\tilde{x}(t + s) - \tilde{x}(t)),$$

ainsi que les vitesses asymptotiques

$$\tilde{c}_- = \liminf_{t \rightarrow +\infty} \frac{\tilde{x}(t)}{t}, \quad \tilde{c}_+ = \limsup_{t \rightarrow +\infty} \frac{\tilde{x}(t)}{t}, \quad \text{et} \quad c^* = \limsup_{s \rightarrow +\infty} \frac{\tilde{X}(s)}{s}.$$

On a clairement $\tilde{c}_- \leq \tilde{c}_+ \leq c^* \leq c_{max}$ où c_{max} est la vitesse maximale d'envahissement de l'état 0. Le problème est tout d'abord de montrer l'égalité de ces trois vitesses asymptotiques. Pour cela, on va étudier l'énergie de la solution dans divers référentiels en mouvement.

Etape 2. Energie dans un référentiel en mouvement.

Soit $c > 0$ la vitesse du référentiel. Soit $t_{init} \geq 0$ un temps initial et $x_{init} = \tilde{x}(t_{init})$ le point d'échappement à ce temps initial.

On se place dans le référentiel en translation uniforme de vitesse c dans la direction de l'axe du cylindre. Ainsi la coordonnée z reste inchangée, alors que les autres coordonnées deviennent

$$s = t - t_{init} \quad \text{et} \quad y = x - x_{init} - cs.$$

On pose alors $v(s, y, z) = u(t, x, z)$ la solution de (3.1) dans ce référentiel. Elle vérifie

$$\frac{\partial v}{\partial s} - c \frac{\partial v}{\partial y} - \Delta v + f(v, z) = 0. \quad (3.4)$$

Formellement, l'énergie de la solution v devrait être

$$\Phi(s) = \iint e^{cy} \left(\frac{|\nabla v|^2}{2} + F(v, z) \right) dy dz$$

et on aurait alors

$$\Phi'(s) = - \iint e^{cy} |\partial_s v|^2 dy dz.$$

Malheureusement, il n'y a pas de raison pour que ces termes soient bien définis, car un front d'onde est typiquement non intégrable. Il faut donc définir une nouvelle fonction de poids $\varphi(s, y)$ en tronquant l'exponentielle en un certain point $y_0 + \gamma_1 s$ où γ_1 est une constante fixée et y_0 est une constante à fixer selon le cas.

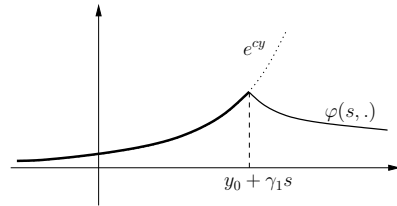
On définit donc $\varphi(s, y)$ par

$$\varphi(s, y) = \begin{cases} e^{cy} & \text{si } y \leq y_0 + \gamma_1 s, \\ e^{-\beta_1 y} e^{(c+\beta_1)(y_0 + \gamma_1 s)} & \text{si } y \geq y_0 + \gamma_1 s, \end{cases}$$

β_1 étant une constante fixée.

On peut alors définir l'énergie globale de la solution

$$\Phi(s) = \iint \varphi \left(\frac{|\nabla v|^2}{2} + F(v, z) \right) dy dz,$$



ainsi que son énergie de dissipation

$$\mathcal{D}(s) = \iint \varphi \partial_s v^2 dy dz.$$

Et on a la relation suivante

$$\Phi'(s) \leq -\frac{1}{2}\mathcal{D}(s) + K_2\Psi(s) \quad (3.5)$$

où $\Psi(s)$ est un terme de pollution lié à la troncature de l'exponentielle. Quelques calculs permettent de montrer que $\mathcal{D}'(s) \leq C\mathcal{D}(s)$ pour une certaine constante $C > 0$ (cf page 138 en annexe) et que le terme de pollution Ψ peut être contrôlé par y_0 sous certaines hypothèses sur la vitesse du référentiel $c > 0$ (cf page 138 en annexe). Précisément, si

$$(c + \beta_1)(c^* - c) \leq \frac{1}{4}\beta_1\gamma_1, \quad (3.6)$$

alors

$$\int_0^{+\infty} \Psi(s) ds \leq \frac{1}{\varepsilon_3}\Psi(0) + K_3 e^{-\beta_1 y_0} \quad (3.7)$$

avec ε_3 et K_3 des constantes fixées. Pour tous ces calculs et les définitions exactes des constantes, voir l'annexe D page 135.

Etape 3. Vitesse asymptotique du point d'échappement.

Les estimations d'énergie précédentes vont nous permettre tout d'abord de montrer l'existence de la vitesse asymptotique du point d'échappement. Supposons par l'absurde $\tilde{c}_- < c^*$. Alors, on peut construire un référentiel de vitesse $c > 0$ qui vérifie

$$\tilde{c}_- < c < c^* < c + \gamma_1 \quad \text{and} \quad (c + \beta_1)(c^* - c) \leq \frac{\beta_1\gamma_1}{4}. \quad (3.8)$$

Les estimations d'énergie du paragraphe précédent sont valides dans ce référentiel, mais le point d'échappement alterne de larges excursions vers la gauche avec de larges excursions vers la droite. Ceci va contredire l'équation (3.5). En effet, lorsque le point fait de large excursions vers la gauche, c'est que la solution est quasiment identiquement nulle. L'énergie globale $\Phi(s)$ est donc minorée par 0 (quitte à bien choisir le temps initial t_{init}). De l'autre côté, comme le point d'échappement fait de large excursion vers la droite (ce qui signifie grosso modo que la solution passe de 0 à ε) et que la troncature se fait toujours après le point d'échappement (car $c^* < c + \gamma_1$), l'énergie de dissipation va tendre vers l'infini. Or comme le terme de pollution Ψ est contrôlé par y_0 , on aboutit à une contradiction avec l'estimation (3.5). Pour le détail de ces calculs, voir annexe D page 140.

La vitesse asymptotique du point d'échappement sera désormais notée $\tilde{c}$.

Etape 4. Relaxation.

Maintenant que la vitesse asymptotique du point d'échappement est connue, il est possible de montrer le résultat suivant :

$$\forall L > 0 \quad \|\partial_t u(t, \tilde{x}(t) + \cdot, \cdot) + \tilde{c}\partial_x u(t, \tilde{x}(t) + \cdot, \cdot)\|_{L^2_{ul}(B(0,L))} \xrightarrow{t \rightarrow +\infty} 0.$$

Les détails de la démonstration sont donnés dans l'annexe D page 143. L'idée est de supposer par l'absurde que la propriété n'est pas vraie. Cela signifie que l'on peut trouver des temps initiaux t_n aussi grand que l'on veut tels que dans le référentiel de vitesse $\tilde{c}$ et de temps initial t_n , la dissipation ne tend jamais vers 0. Ainsi, l'énergie globale de la solution dans ces référentiels devrait tendre vers $-\infty$ d'après l'estimation d'énergie (3.5). Mais ces référentiels suivent de plus en plus précisément le point d'échappement, or sur $[\tilde{x}(t), +\infty[$, la solution est très proche de 0, ce qui ne peut entraîner de large variations de l'énergie. Et sur $] -\infty, \tilde{x}(t)]$, la solution varie de façon limitée et comme l'énergie fait intervenir un poids exponentiel, l'énergie ne peut pas non plus tendre vers $-\infty$. Enfin, le terme de pollution peut bien être contrôlé, d'où une contradiction.

Etape 5. Conclusion sur l'existence du front.

Pour toute suite de temps $(t_n)_{n \in \mathbb{N}}$ avec $t_n \rightarrow +\infty$, on peut définir

$$w_n(y, z) = u(t_n, \tilde{x}(t_n) + y, z) \quad \text{pour } (y, z) \in \mathbb{R}^N.$$

$$\bar{w}_n(y, z) = \partial_t u(t_n, \tilde{x}(t_n) + y, z) \quad \text{pour } (y, z) \in \mathbb{R}^N.$$

Comme $(w_n)_{n \in \mathbb{N}}$ est bornée dans l'espace de Kato $H^1_{ul}(\mathbb{R}^N)$ et $(\bar{w}_n)_{n \in \mathbb{N}}$ est bornée dans l'espace de Kato $L^2_{ul}(\mathbb{R}^N)$ (cf annexe D page 118 pour la définition de ces espaces), il existe $U \in H^1_{ul}(\mathbb{R}^N)$ et $\bar{U} \in L^2_{ul}(\mathbb{R}^N)$ tels que quitte à extraire une sous-suite,

$$w_n \rightarrow U \text{ dans } H^2([-L, L]^N) \quad \text{and} \quad \bar{w}_n \rightarrow \bar{U} \text{ dans } L^2([-L, L]^N).$$

Alors d'après ce qui précède, $\bar{U} + \tilde{c}U = 0$ et en passant à la limite dans (3.1), on a

$$\Delta U + \tilde{c}\partial_x U - f(U, z) = 0.$$

De plus, par définition du point d'échappement et de w_n , U est non nulle, c'est donc bien un front progressif solution de (3.1). On peut de plus montrer la convergence uniforme sur $[-L, +\infty[\times \mathbb{R}^{N-1}$ pour tout $L > 0$, en utilisant les propriétés de décroissance exponentielle des solutions en $+\infty$.

Enfin, pour conclure la démonstration du théorème, il reste à montrer qu'il existe bien des données initiales qui vérifient les hypothèses du théorème,

$$\int_L^0 \int_{\mathbb{R}^{N-1}} \frac{|\nabla u_0(x, z)|^2}{2} + F(u_0(x, z), z) \, dz dx \xrightarrow{L \rightarrow +\infty} -\infty$$

et

$$\limsup_{x \rightarrow +\infty} \int_{x-1}^{x+1} \int_{\mathbb{R}^{N-1}} (u_0(x, z)^2 + |\nabla u_0(x, z)|^2) dz dx \leq \delta.$$

Pour cela, il suffit de trouver un profil asymptotique de l'équation tel que

$$E(\phi) = \int_{\mathbb{R}^{N-1}} \left(\frac{|\nabla \phi|^2}{2} + F(\phi, z) \right) dz < 0.$$

C'est le sujet du lemme D.6 page 151 en annexe. En effet, dans ce cas,

$$u_0(x, z) = \begin{cases} \phi(z) & \text{if } x \leq 0, \\ \phi(z)e^{-x} & \text{if } x > 0, \end{cases}$$

conviendrait comme donnée initiale.

Le lemme se démontre en remarquant tout d'abord que

$$E(\phi) = \int_{\mathbb{R}^{N-1}} \left(F(\phi, z) - \frac{f(\phi, z)}{2} \phi \right) dz.$$

Si $|z| > R$, alors $F(\phi, z) - \frac{f(\phi, z)}{2} \phi = 0$, il reste donc à étudier

$$F(\phi, z) - \frac{f(\phi, z)}{2} \phi = -G(\phi) + \frac{g(\phi)}{2} \phi$$

pour $z \in B(0, R)$. En dimension 2, en utilisant le plan de phase, il n'est pas très compliqué de montrer que la zone où $-G(\phi) + \frac{g(\phi)}{2} \phi < -\varepsilon$ croît infiniment avec

R , alors que la zone où $-G(\phi) + \frac{g(\phi)}{2} \phi \geq -\varepsilon$ reste bornée (cf annexe D page 152). Cela montre que si R est suffisamment grand, la solution ϕ_2 en dimension 2 est bien d'énergie négative. Pour la dimension supérieure, la solution en dimension 2 étant une sous-solution, la conclusion est la même.

3.3 Les perspectives.

La méthode utilisée pour montrer l'existence d'un front courbe aboutit quasiment à la convergence des solutions vers ce front pour une large classe de données initiales, si on peut montrer l'unicité du front à vitesse et profils asymptotiques fixés. Classiquement, on utilise la méthode de glissement pour montrer l'unicité du front [11, 43]. Le problème est de pouvoir initialiser la méthode de glissement par exemple avec le principe du maximum si les solutions le permettent (il faut que la nonlinéarité soit décroissante autour des profils asymptotiques, ce qui n'est pas le cas ici) ou bien en connaissant précisément le comportement asymptotique du front. Dans [87], Vega ne peut utiliser le principe du maximum, il étudie donc le comportement

asymptotique d'un front avec donnée de Dirichlet nulle au bord d'un cylindre et il en déduit l'unicité. Malheureusement ici, dans le cas général, la méthode ne peut s'adapter car il n'existe pas forcément de valeur propre et de fonction propre du problème linéarisé (on est sur $\mathbb{R}^{N-1}$). Une autre méthode pour montrer l'unicité doit donc être trouvée.

On pourrait également envisager d'utiliser cette méthode pour étudier l'influence de la géométrie de certains domaines sur la propagation des DCE (par exemple cylindre dont le diamètre suit une sinusoïde).

Annexes

Annexe A

Discussion of a simple model of spreading depression

G. Chapuisat¹

Résumé

Les dépressions corticales envahissantes (DCE) sont des ondes de dépolarisation temporaire des neurones qui se propagent dans le cerveau à la suite d'une migraine avec aura, d'une crise d'épilepsie ou d'un accident vasculaire cérébral. Ces DCE sont connues depuis longtemps dans le cerveau du rongeur, mais n'ont pour l'instant jamais été observées chez l'homme. C'est pour essayer de comprendre la non-observation de ces ondes chez l'homme que nous avons développé un modèle mathématique de DCE.

Les DCE sont liées à des concentrations ioniques anormales dans les diverses cellules du cerveau et dans l'espace extracellulaire. En suivant les observations de Nedergaard [13], nous avons construit un modèle simple de DCE basé sur les échanges ioniques en calcium et en potassium entre les différents compartiments du cerveau. On obtient un système de réaction-diffusion.

Un problème est alors de déterminer les valeurs des paramètres du système. Les expériences étant souvent impossibles ou soumises à de fortes marges d'erreur, nous avons décidé d'utiliser un algorithme qui tire au hasard les paramètres du système, puis qui conserve les paramètres en mémoire si certaines propriétés qualitatives de la solution du modèle sont vérifiées.

Une fois le modèle établi et validé, nous avons pu tester l'effet des différences de géométrie et de composition des cerveaux sur les DCE. En effet, le cerveau du rongeur est lisse et intégralement composé de matière grise (zone où se trouvent les corps des neurones), alors que le cerveau de l'homme a de nombreuses circonvolutions et est

¹Article accepté par ESAIM proc.

principalement composé de matière blanche avec une fine couche de matière grise à la périphérie. Comme la matière blanche ne contient pas de neurone, le modèle montre que l'étape de réaction n'a pas lieu dans cette matière, les DCE y diffusent simplement et sont progressivement absorbées. On constate alors que si la couche de matière grise est fine, l'effet absorbant de la matière blanche empêche la création de DCE. D'autre part, une DCE stoppe sa progression à la première forte et brusque augmentation de l'épaisseur de la matière grise. Ainsi les différences de structure entre les cerveaux pourraient à elles-seules expliquer la non-observation des DCE.

A.1 Introduction

Spreading depressions (SD) consist of a transient suppression of all neuronal activities [83]. This suppression spreads slowly across a large region of the brain. They were first observed and described in 1944 by Leão in [56]. SD play most likely an important role in many diseases for example in migraine with aura, epilepsy and cerebral stroke. They have been observed in many species, but their existence is still discussed in the human cortex. For the moment, they have never been experimentally observed in human brain, perhaps because of the difficulties of in vivo measurements.

It is very important to understand the phenomena that are responsible for the creation or extinction of SD [36]. Indeed in cerebral strokes in rats, the number of SD has a clear influence on the size of the final infarcted area (i.e. area of the brain where all the cells are dead). Some chemicals that block the appearance of SD have already been studied and reduce importantly after-effects of strokes in the rat brain. Unfortunately, they seem to be ineffective on humans. Mathematical models of SD may help to explain this difference [86, 90, 22, 21, 83].

The aim of this paper is to present a model of SD based on the experimental observations of Nedergaard in [13]. SD are linked to ionic exchanges between the various cells that compose the brain and the extracellular space.

Indeed brain is composed of several types of cells. Neurons convey the electrical informations. They form a network which is surrounded by all the other cells called glial cells. Astrocytes are part of these glial cells. They also form a network. The role of astrocytes is mainly to maintain a favourable environment for neurons.

To convey electrical informations, the neurons need to be polarized. This polarization is due to a differential in ionic concentrations between intra- and extra-cellular spaces. For example, the potassium concentration is markedly higher in the neurons than in the extracellular space. It is the opposite for the calcium concentration. A cell has various possibilities to maintain this differential between intra- and extra-cellular concentration. A first possibility is to use ionic pumps. These pumps make a ionic species go through the cell's membrane in a specific sense. Their functioning depends on the other ionic concentrations. Moreover these pumps need energy to work. The second possibility for ions to go through the cell's membrane is gap junc-

tions. A gap junction can be considered as a hole between two cells that lets only a specific ionic species go through it.

It has been shown that SD are triggered by a large increase of the extracellular potassium concentration. Besides SD are characterized by a potassium wave that propagates through the extracellular space. Moreover during SD, a calcium wave through the astrocytes has been experimentally observed. Thus the model is centered around the ionic exchanges between neurons, astrocytes and extracellular space.

The detail of all the preceding points will be given in the next section. Then in section A.3, we will discuss the values of all the parameters involved in this model. Finally in section A.4, we will explain the results of this model, that means the new phenomena which appear when we combine all the preceding elementary points, but which are not programmed in the model.

A.2 Main features of the model of SD

In this model, we will consider three different spaces in the brain : the extracellular space, the neural network and the astrocytic network. Each space will be supposed continuous. We will take into account two cations : Ca^{2+} and K^+ .

SD look like propagative waves and as in many biological situations [63], Nedergaard's observations lead indeed to a reaction-diffusion system.

The basic phenomena that create spreading depressions are as follow :

- The potassium ions can diffuse in the extracellular space.
- An excess of potassium in the extracellular space activates ionic pumps on the astrocytes' membrane that make calcium enter the cell.
- The calcium diffuses through gap junctions in the astrocytic network.
- The calcium ions enter the neurons through gap junctions between neurons and astrocytes.
- The excess of calcium in the neuronal space activates ionic pumps on the neurons' membrane that make potassium go out of the cell.

All the preceding basic phenomena make ionic concentrations increase. We now have to add some recovery mechanisms in order to make the system go back to his rest state. First small variations in the ionic concentrations are quickly erased by various channels (ionic pumps, ...). If the variations are too large, then another mechanism takes place and tries to limit these variations. Few biological informations are available on this mechanism. At last there is a special phenomenon to recover from spreading depression which is expressed by a very important increase of calcium and potassium concentrations. This recovery from SD is either not perfectly understood, but at least we know that it needs several steps (in particular, a blood flow increase). This implies a delay before the cell is ready to recover.

Nedergaard's observations will permit us to construct a mathematical model of

SD that can be quickly numerically solved. This point is important since we want then to integrate this model in a global model of stroke. For example, the model of Shapiro in [81] is very complete, but really too heavy in order to be integrated. Another interest of this the model is that it is really based on some biophysical membrane mechanisms which was not the case in [86]. Finally, this model takes into account the propagation of SD unlike Somjen's model in [83] which is only valid for a single neuron. This model will be phenomenological which means that the links between the various variables are based on biophysical observations but qualitatively established.

Let us call Ca_g the variation of calcium concentration in the astrocytes (g stands for glia) in relation to the rest state. So Ca_g equals 0 when the calcium concentration in the astrocytes is normal. In the same way, we call Ca_n the variation of calcium concentration in the neurons and K_e the variation of potassium concentration in the extracellular space.

R represents the recovery mechanism from spreading depressions and Cap the capacity of the cell to recover from SD. When Cap reaches a fixed threshold, the phenomena that govern the recovery from SD can take place.

We obtain the following partial differential equations.

$$\begin{aligned} \partial_t Ca_g - \nu_{Ca_g} \Delta Ca_g &= -k_{Ca_g} \tanh \frac{Ca_g}{Ca_g^0} + h_{K,Ca} K_e - k_{gap} (Ca_g - Ca_n) \\ &\quad - \alpha_{Ca_g} Ca_g^2 - \alpha_{rec,g} R Ca_g \\ \partial_t Ca_n &= -k_{Ca_n} \tanh \frac{Ca_n}{Ca_n^0} + k_{gap} (Ca_g - Ca_n) - \alpha_{Ca_n} Ca_n^2 - \alpha_{rec,n} R Ca_n \\ \partial_t K_e - \nu_{K_e} \Delta K_e &= -k_{K_e} \tanh \frac{K_e}{K_e^0} + h_{Ca,K} Ca_n - \alpha_{K_e} K_e^2 - \alpha_{rec,e} R K_e \\ \partial_t Cap &= 1_{\{Ca_g > c_g\} \cup \{Ca_n > c_n\} \cup \{K_e > c_k\}} \frac{1 - Cap}{T_o} \\ &\quad - 1_{\{Ca_g < c_g\} \cap \{Ca_n < c_n\} \cap \{K_e < c_k\}} \frac{Cap}{T_f} \\ \partial_t R &= 1_{\{Cap > c_{cap}\}} \frac{1 - R}{\tau_o} - 1_{\{Cap < c_{cap}\}} \frac{R}{\tau_f} \end{aligned}$$

The first three equations govern the ionic movements. The last two equations govern the special mechanism to recover from SD. The biological meanings of the various parameters (and thus of the different terms of the equations) are gathered in table B.1.

This equations are valid in the gray matter of the brain (where there are neurons). The natural boundary condition is of homogeneous Neumann type.

ν_i	diffusion coefficient of ion i
k_i	strength of the recovery mechanism for small concentration variations of ion i
Ca_n^0, Ca_n^0, K_e^0	range of the variations that are concerned with the recovery for small variations
α_i	strength of the recovery mechanism for large variations of concentration of i
$\alpha_{rec,i}$	strength of the recovery from SD for ion i
$h_{K,Ca}$	activity of the ionic pumps on astrocyte's membrane sensitive to extracellular potassium that makes calcium enter the astrocyte.
k_{gap}	activity of the gap junctions between astrocytes and neurons
$h_{Ca,K}$	activity of the ionic pumps on neuron's membrane sensitive to intracellular calcium that makes potassium go out of the neuron.
c_i	concentration thresholds above which the cell begins to prepare for the SD recovery
T_o	typical time for the cell to be ready to recover from SD
T_f	typical time for the disappearance of the preparation to recover from SD
c_{cap}	threshold above which the cells are able to recover from SD, connected with the delay before the recovery from SD mechanism takes place
τ_o	typical time for the complete opening of the recovery mechanism
τ_f	typical time for the complete closure of the recovery mechanism

TAB. A.1 – Biological meanings of the parameters involved in the model

A.3 Discussion of parameters

A.3.1 A problem

In this model of SD, many parameters appear (see table B.1). They have to be fixed before we can solve the system of equations. Since each part of the model represents a biological phenomenon, the first natural idea is to search in the literature for data on this phenomenon in order to obtain the different values of the parameters. Several problems will be posed.

- First, for different reasons, data are lacking (impossible experiments, no precise biological meaning ...).
- If they exist, data come from different species or different types of neurons.

- The experimental error can be very large.

So even if we have a lot of data, to fit them together requires additional work. Moreover a large system of partial differential equations with a lot of parameters can have very different behaviours and may be very sensitive to variations of one parameter. Thus we had to find another method to fix the values of the parameters.

A.3.2 A basic random algorithm

To fix the values of the parameters, the first natural idea was to use a random algorithm, i.e. choose randomly the parameters and then test whether the solution obtained with these parameters well suits the biological observations. So, we first have to decide which qualitative properties the solution of the model must have. This set of properties will be called basis of rules in the following.

Here, the basis is composed of six rules that come from experimental observations :

- 0 is a stable state.
- An injection of KCl with a higher concentration than 10 mM creates one or more SD that are expressed by a calcium wave through the astrocytic network.
- This wave propagates with a speed about 3mm/min.
- The increase of potassium concentration in the extracellular space is between 30 and 80 mM and the increase of calcium concentration in the astrocytes is about 0.2 mM.
- The maximum of the potassium concentration in the extracellular space must look like a plateau.
- A continue injection of KCl creates successive SD.

Then the random algorithm to find the possible parameters of the model is as follows.

- Choose reasonable range for the values of all parameters.
- Choose at random the various parameters values of the set of partial differential equations.
- Test numerically whether the preceding basis of rules is satisfied.
- If the answers of this question is positive, then keep this set of parameters in memory.

Let us remark that of course, a limit of this algorithm is that it needs a basis of rules that can be numerically tested. Moreover the method to solve the system has to be fast and efficient so that a lot of sets of parameters can be tested. Here we have decided to model the brain as a segment and to use a semi-implicite finite differences method. The problem is that the ionic concentration have rather steep variations so the time and space steps have to be small. Another important point is the choice of the reasonable range for the parameters values. The larger the space where the parameters values are chosen is, the smaller the propability of finding suitable parameters is. And since there are many parameters to find, this probability can become really tiny if the space is too large.

A KCl injection is simulated using the initial conditions. In a part of the brain, the extracellular potassium concentration is assumed higher than the rest concentration. To simulate a continue KCl injection, we force the extracellular potassium concentration to stay higher than a certain concentration at every time step.

We have applied this procedure to the preceding model that govern ionic exchanges. It is composed of 5 equations and 27 parameters have to be fixed. At the end of a run, more than hundred thousands sets of parameters have been tested, leading to five suitable sets.

Examples of results that are kept by this algorithm are shown in figures B.5 and B.6. Ionic waves are created and spread through the entire brain. Every set of suitable parameters that was found with this algorithm gives similar qualitative results. For the moment, no correlation between these suitable sets has been established, but the very small number of sets prevents us from using any statistical method.

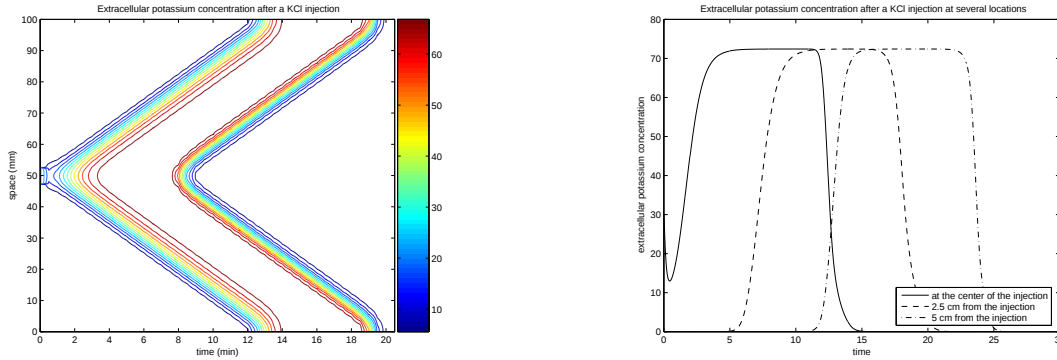


FIG. A.1 – Potassium concentration in the extracellular space after a KCl injection for suitable parameters. Left, the level lines of the potassium concentration in function of the time (x-coordinate) and of the place in the brain (y-coordinate). Right, potassium concentration at several locations in function of time. The solid line represents the extracellular potassium concentration in the middle of the area where the injection is made. The dashed line is the potassium concentration 2.5 cm further and the dashed-dotted is 5 cm further.

In this basis of rules, an important test is the creation of successive SD for a continue injection of KCl. As a matter of fact, when a stroke occurs, successive SD are created. The reaction of the system to a continue injection for suitable parameters is shown in figure B.7.

Another idea for fixing the values of all the parameters will be to use an algorithm where the random choice of the parameters is influenced by the preceding tested sets of parameters. In particular, we could try to use an evolutionary algorithm. An evolutionary algorithm is a stochastic search method that tries to reproduce the natural biological evolution. In particular, it uses the principle of survival of the fittest to produce better and better approximation of a solution of a problem.

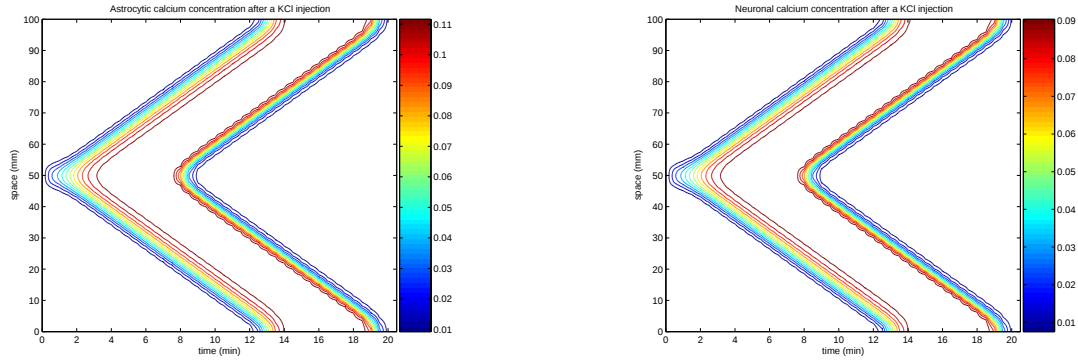


FIG. A.2 – Level lines of the calcium concentration after a KCl injection for suitable parameters. Left, the calcium concentration in the astrocytes and right, the calcium concentration in the neurons. As it has been observed by Nedergaard, a calcium wave propagates through the network of astrocytes.

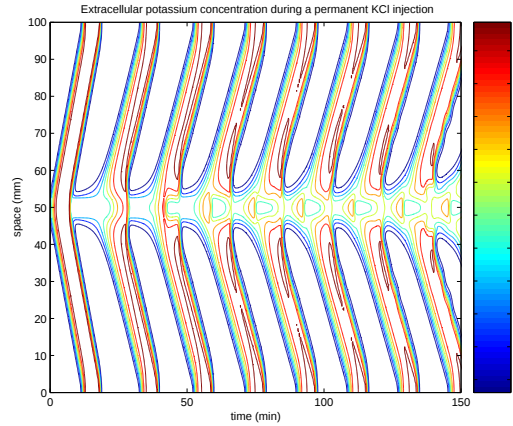


FIG. A.3 – Potassium concentration in the extracellular space during a continue KCl injection for suitable parameters. Here, the brain is supposed to be a segment. Successive ionic waves are created.

In our case, the problem was to define the “fitness” of a set of parameters. Indeed it is in function of the fitness that a set of parameters will be kept or not for the next iteration of the algorithm. Since SD can have various travelling speeds (between 2 and 6mm/min) or correspond to various potassium concentration increases (between 30 and 80 mM), the fitness can not be defined as the distance between the solution and a fixed function. The only reasonable possibility was to define the fitness of a set of parameters as the number of tests of our basis of rules that the solution has passed. Of course you can put weights on the various tests according

to their relative importance. But whatever the weights are, almost all the sets of parameters gives the same fitness and so no information can be used to select the next generation of sets of parameters. Hence it appears to us quite impossible to define a fitness function that really makes sense.

We now consider that the several sets of parameters found with the random algorithm explained above suit well. Let us see what happens in other geometries.

A.4 Two dimensional results

A.4.1 Propagation of SD in the gray matter

After having found suitable parameters for the model, we can use it to study the effect of SD in a more realistic geometry. First we decided to make the simulation in a 2 dimensions space. As a first step, the brain will be represented by a square of gray matter. Hence calculations can be done by Fast Fourier Transformation in space.

First, let us check the effect of a KCl injection in a normal tissue in 2 dimensions. The KCl injection is simulated by an initial condition with $K = 20$ mM on a central square and $K = 0$ mM outside. As we can see (figures B.12 to B.14), a potassium wave propagates through the extracellular space. Similarly, a calcium wave propagates through astrocytes and neurons. About 35 minutes later, the system is back to his rest state.

These results are consistent with the calculations made in a one dimension brain. Figure B.13 shows the potassium concentration in the extracellular space for a fixed y-coordinate. We find the same profile as in section 2.

A.4.2 Influence of the white matter

Now we will try to understand why SD have still not been observed in the human brain. Mechanisms that are responsible for the generation of SD are apparently identical in the rodent brain and in the human brain. Maybe some parameters of the model are modified in the human brain and since the system can be sensitive to some parameters, this could explain the non-observation of SD.

Another explanation may lie in the differences of geometry and composition of the rodent brain and of the human brain. Indeed a brain can eventually be composed of two different matters, the white and the gray matter. The rodent brain is smooth and entirely composed of gray matter while the human brain is mostly composed of white matter with a thin layer of gray matter at the surface. Moreover the human brain has a very complicate geometry with a lot of circumvolutions.

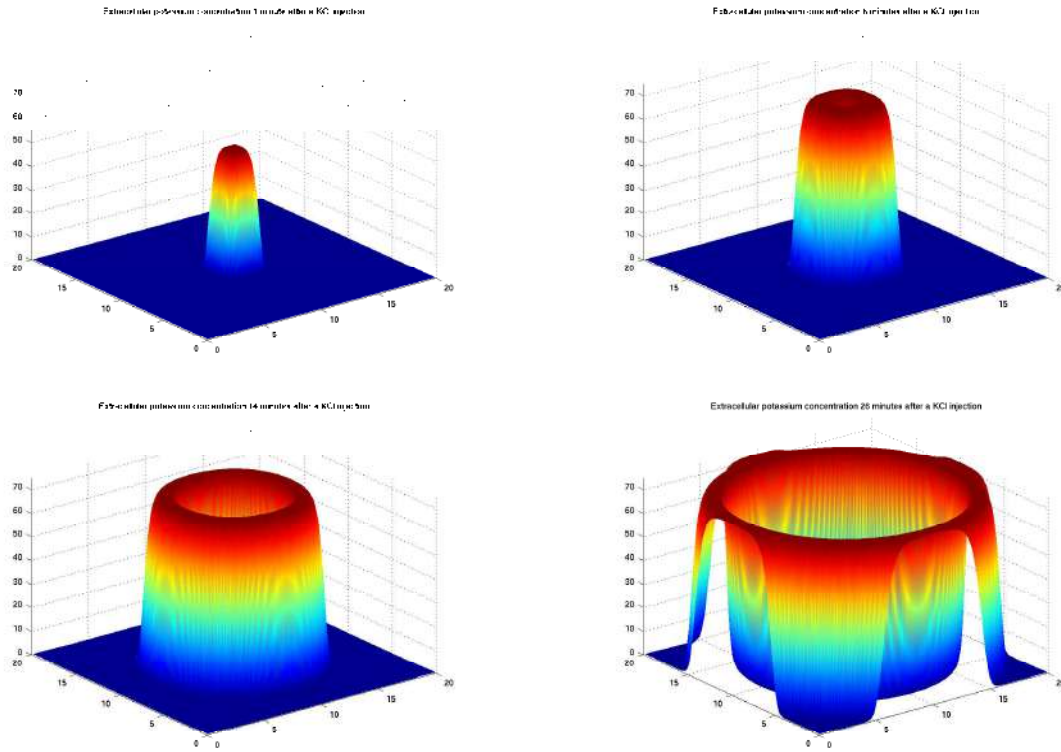


FIG. A.4 – Potassium concentration in the extracellular space after a KCl injection for several times (1, 6, 14 and 26 min after the injection). A SD propagates through the entire brain.

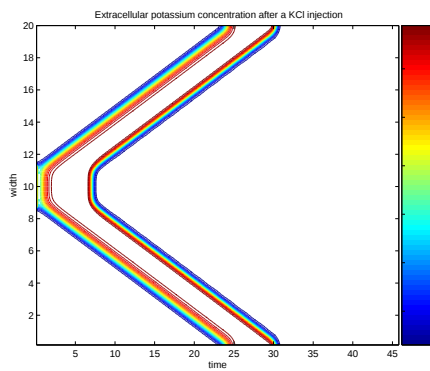


FIG. A.5 – Potassium concentration in the extracellular space after a KCl injection on a diameter of the brain. Here, the brain is supposed to be a square.

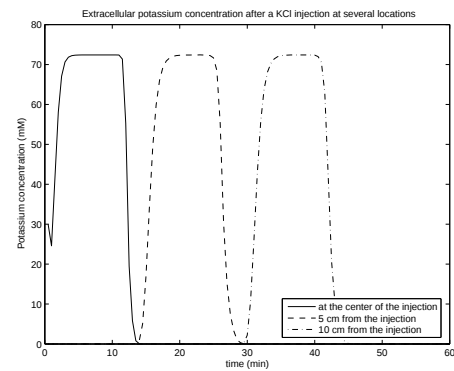


FIG. A.6 – Extracellular potassium concentration after a KCl injection for several locations in the brain (center of the injection, 5 cm further and 10 cm further).

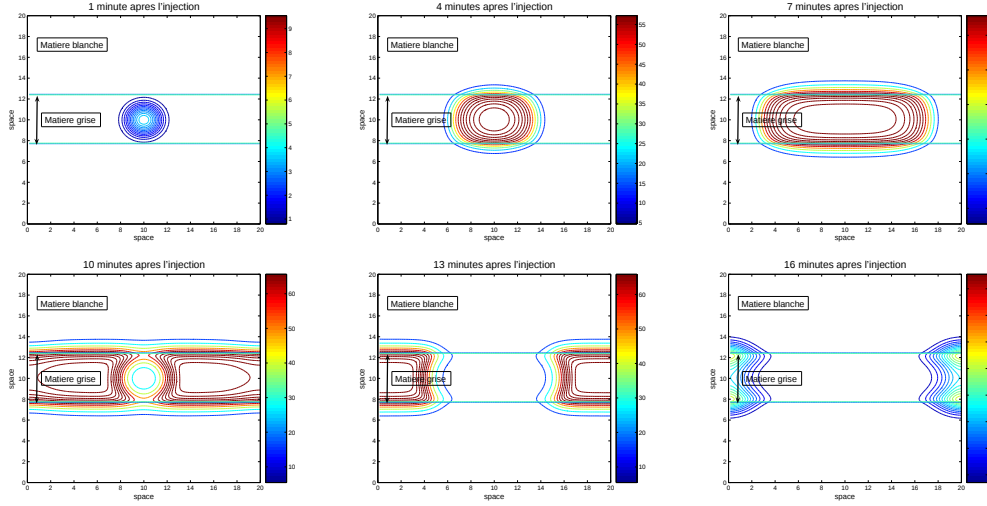


FIG. A.7 – Extracellular potassium concentration after a KCl injection in the gray matter. Here the layer of gray matter is thick and the SD spreads through this layer.

In this section we will study the influence of the white matter. Indeed, SD are modeled by a reaction-diffusion system in the gray matter described above. But in the white matter, there are no neuron, so the reaction loop described by Nedergaard is interrupted. Thus the ions responsible for SD just diffuse and are progressively absorbed in the white matter. This may prevent the creation of SD. In this model, the calcium concentration in neurons Ca_n is simply set to 0 in the white matter. Moreover we assume a Neumann condition for Ca_n at the boundary of the gray matter; the other functions are assumed C^1 on the interface between the white and the gray matter.

Let us first study the effect of white matter when the layer of gray matter is thick (figure A.7). SD normally spread through the entire gray matter.

Now, if the layer of gray matter is thin, we see that SD are not created despite the same initial condition as preceding (figure A.8).

The fact that the creation of SD depends on the thickness of the gray matter may be an explanation for the non-observation of SD in the human brain. This numerical observation has been mathematically studied in [14].

A.4.3 Influence of the geometry of the brain

In this part, we will numerically study the effect of the geometry of the gray matter on the propagation of SD. Gridding a real map of a human brain is for the moment still difficult so here, the domain will be a cylinder which diameter is suddenly increased. It is impossible to use the fast Fourier transformation to solve the numerical system, so we used a finite elements method.

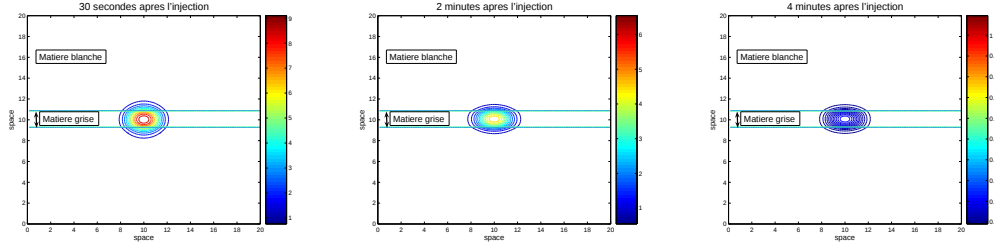


FIG. A.8 – Extracellular potassium concentration after a KCl injection in the gray matter. Here the layer of gray matter is thin and the SD are not created.

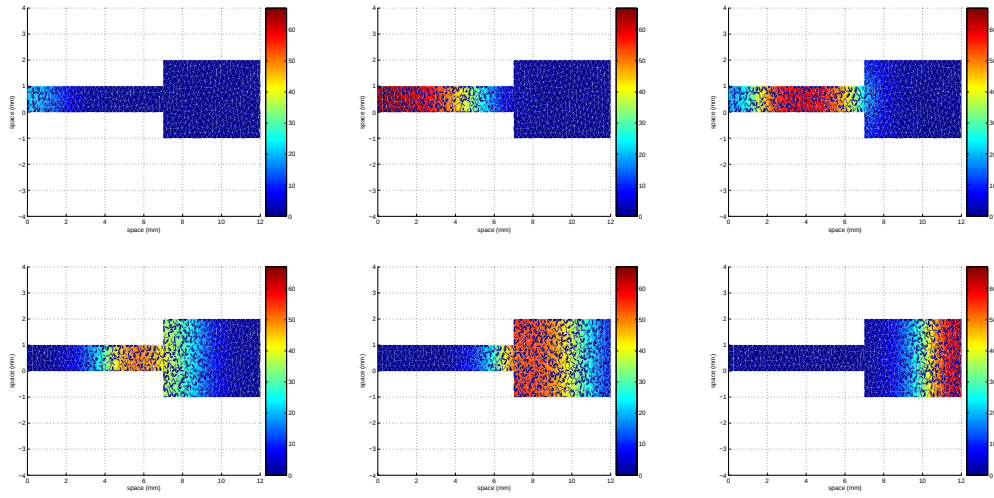


FIG. A.9 – Extracellular potassium concentration after a KCl injection. The sudden widening of the cylinder does not stop the SD.

First, if the diameter of the cylinder is slightly increased, the SD can still spread through the entire brain (figure A.9).

Now, if the diameter of the cylinder is largely increased, SD are stopped by this widening and can not spread through the entire brain (figure A.10).

However, an important point is that the widening of the cylinder is very sudden. Hence, if it is just a little more progressive, the SD can pass through this widening (figure A.11).

The stopping of SD by a sudden increase of the width of the gray matter may be an explanation for the non-observation of SD in the human brain. Indeed, even if the phenomena that create SD are the same as for the rodent, the SD will never spread across a large area of the brain, they will always be stopped by the first important increase of the width of the gray matter (and these increases are very frequent in

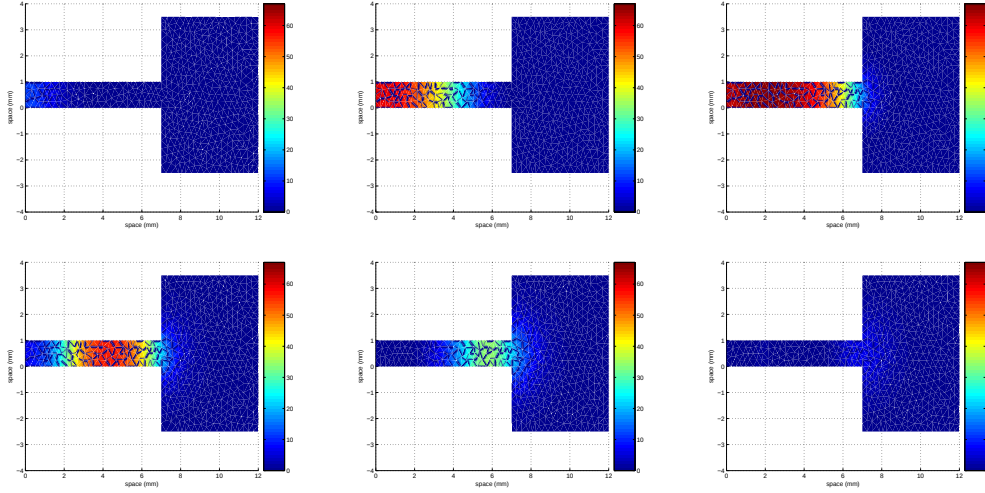


FIG. A.10 – Extracellular potassium concentration after a KCl injection. The sudden widening of the cylinder stop the propagation of SD.

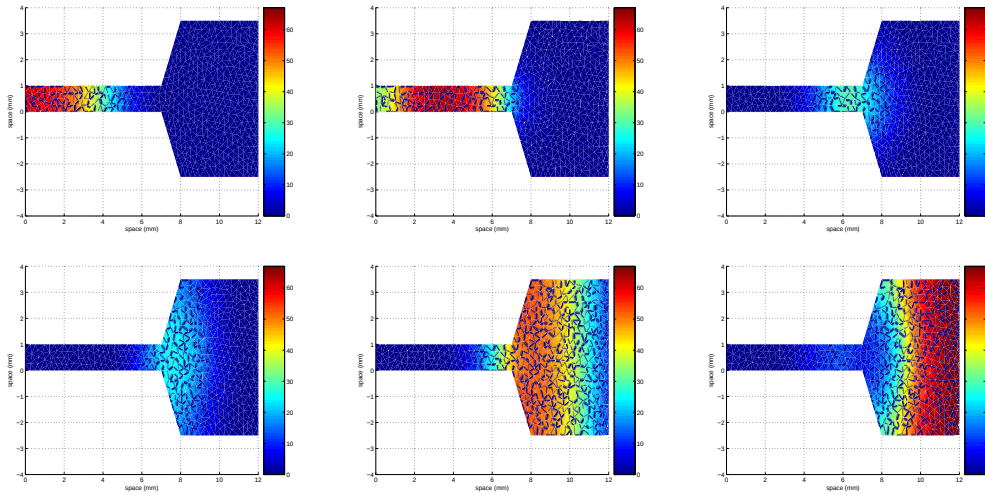


FIG. A.11 – Extracellular potassium concentration after a KCl injection. The progressive widening of the cylinder does not stop the SD.

the human brain). This numerical study has been confirmed in [17].

A.5 Conclusion

In this paper, we have detailed a model of spreading depressions. This model is centered around the ionic exchanges between neurons, astrocytes and extracellular space, particularly calcium and potassium. The model does not describe these phenomena down to the last detail, but in a phenomenological way.

A problem that we had to solve was to fix the values of all the parameters appearing in the mathematical system. The process that we have used takes a long time but gives results (It is almost impossible to find the parameters “by hand”) and those results seem to be reliable.

With the parameters found with the random algorithm, this model of SD seems to globally fit the reality and we have used it to study the influence of the geometry of the brain and the influence of the white matter on the nonobservation of SD in human brain.

The next step will be to include this model in a global model of stroke. Thus we will be able to study numerically the influence of SD on the size of the infarct and even to numerically test the effects of some pharmacological agents.

Then we could also apply this model to a more realistic geometry of the brain, for the moment we are trying to get reliable images of the brain (with white and gray matters) and to grid them.

Finally this model could largely be improved by adding the effect of others ions and describing their movement in more detail. In particular, we have planned to replace the simple ionic system by a model of ionic dynamic which is based on microscopic phenomena [21].

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Annexe B

A global model of ischemic stroke with stress on spreading depression

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M. Hommel, J.P. Boissel¹

B.1 Introduction

Cerebral stroke is the third cause of death and the first cause of acquired handicap in occidental countries. At the moment, no efficient medical treatment is available to fight it. One way to study it is to design mathematical models of this disease in order to understand better the various phenomena that compose it and their relative importance. It is with this aim in view that was created the AVC-iSi group. Precisely, AVC-iSi group studies ischemic stroke, i.e. stroke where a vessel is occluded unlike stroke where a vessel bleeds inside the brain.

Some models have already been designed. For example, Duval in [27] describes a first one which takes into account ischemia (i.e. stopping of the blood flow in a part of the brain), reduced oxygen, and damage to the cells. [22] continued this work and added ionic disturbance, cell swelling and cell death. In [25], Duval's first model is completed by adding spreading depressions, refined energy balance and oedema.

Spreading depressions (SD) consist of a transient suppression of all neuronal activities. This suppression spreads slowly across a large region of the brain. They were first observed and described in 1944 by Leão in [56]. SD play most likely an important role in many diseases [36, 37, 26] such as ischemic cerebral stroke, migraine with aura, epilepsy, etc... They have been observed in many species, but their existence is still discussed in the human cortex [84, 61, 59, 2]. For the moment, they have never been observed, perhaps because of the difficulties of in vivo measurements in human

¹Article soumis

with acute stroke.

It is very important to understand the phenomena that are responsible for the creation or extinction of SD. Indeed in cerebral strokes in rats, the number of SD has a clear influence on the size of the final infarcted area (i.e. area of the brain where all the cells are dead) [6, 62]. Some chemicals that block the appearance of SD have already been studied and reduce importantly after-effects of strokes in the rat brain [18, 64]. Unfortunately, they seem to be ineffective on humans. Mathematical models of stroke may help to explain this difference.

The aim of this paper is to present a new numerical model of stroke. A particular stress will be set on spreading depressions. Several models of spreading depression have been developed. In [83], Somjen exposes models of spreading depression in a single cell. In [38, 65, 86, 72, 74], the models of SD are more focused on the propagation of SD. In [81], Shapiro has built a rather complete model of stroke which leads to a very large number of equations. Here it is impossible to introduce directly one of these complex models of SD since the computations would be too long. In [25], SD are simply modeled by a function which follows a reaction-diffusion equation. Of course this function is not directly linked to the real phenomena that trigger spreading depressions. Since most of the details of the phenomena that govern spreading depression are still not precisely known, as a first step this model was necessary, but here we have tried to add to this preceding model a more detailed sub-model of SD following Lin and Nedergaard [13], based on the ionic exchanges between the various cells that compose the cortex and extracellular space. However this model is still phenomenological and does not enter the microscopic biological mechanisms that generate SD.

The brain is composed of several types of cells. Neurons convey the electrical information. They form a net which is surrounded by all the other cells called glial cells. Astrocytes are part of these glial cells. They also form a net. The role of glial cells is mainly to maintain a favourable environment for neurons.

To convey electrical information, the neurons need to be polarized. This polarization is due to a differential in ionic concentrations between intra- and extracellular spaces [83]. For example, the potassium concentration is markedly higher in the neurons than in the extracellular space. It is the opposite for the calcium concentration. Of course, the cells need energy to maintain this differential in ionic concentrations.

In this model, we also have added a sub-model of cell death which makes differences between apoptosis and necrosis. Indeed cells can evolve toward infarction via two different ways. If an irretrievably damaged cell has enough energy, it will “commit suicide”, it means that the cell will shrink until it can be absorbed by the scavenging system. This is called apoptosis. If the cell has not enough energy, it will swell until its membrane explodes. This is called necrosis. It is important to make a difference between these two ways of dying since after necrosis deleterious matters contained in the damaged cell are released in the surrounding and this is not the case with apoptosis. In addition, the time scale of the two processes are not the same,

with apoptosis occurring on average later [20]. Moreover, prevention of apoptosis is a new field of research for the treatment of acute stroke [57, 1].

The model was built from the following list of basic phenomena :

1. The starting point of an ischemic stroke is a sudden decrease of the blood flow in part of the brain.
2. As a response, the oxygen extraction factor increases in order to try to compensate for the lack of oxygen.
3. If the available energy is not sufficient then the ionic equilibrium between the extracellular and intracellular spaces can not be kept. Hence potassium concentration increases in the extracellular space.
4. Potassium diffuses in the extracellular space.
5. The increase of extracellular potassium concentration activates ionic pumps that make calcium enter neurons and astrocytes.
6. The excess of calcium propagates across astrocytes through gap junctions.
7. Finally the rise of calcium concentration in the neurons activates ionic pumps on the neuron's membrane that make potassium go out of the cells.
8. Recovering from SD requires energy. Both neurons and astrocytes will pick up in their energy stock to recover from the ionic disturbances induced by SD.
9. We consider that the only damage to the cells is the presence of calcium ions in it.
10. If a cell is badly damaged but has enough energy, it will die by apoptosis. If it has not enough energy, then this cell will die by necrosis.

Hence in this model, spreading depressions are not artificially put in. They do not appear explicitly in the model. Actually the only way of detecting them is to “measure” the membrane potential of the cells that is linked to the calcium and potassium concentrations as in the *in vivo* or *in vitro* experiments.

Of course, many points of this model could be refined. Any formal model of stroke can always be improved by taking into account new phenomena or by trying to describe them in more details or in a more microscopic way. Ischemic stroke is so complex and involves so many different space and time scales that it is never definite. However in any model that could be used to make *in silico* experiment, it is important to take into account the computation time to solve the equations of the model.

The detail of all the preceding points will be given in the next section. We will shortly describe the process we have used to determine the values of all the parameters involved in this model. Then we will look for the results of this model, that means the new phenomena which appear when we combine all the preceding elementary points, but which are not coded in the model. And finally we will discuss these results.

B.2 Mathematical model

The scale of our model is the entire brain. For reasons of complexity and time for calculations, in our model the cortex is assumed to be a square, so it has only two dimensions. Sometimes the brain will even be modeled as a line (see section B.2.3). Mathematically, it is clear that our model will behave qualitatively identically in three dimensions. In this paper, we will not have interest in the evolution of stroke in the white matter, we will always assume that the cortex is entirely composed of grey matter.

We consider three different compartments in the grey matter : the extracellular space, the neurons and the astrocytes. These three compartments are considered homogeneous and well-mixed and due to the scale of our model they are considered continuous. We do not take into account the volumes of the various compartments.

In animal and in in vitro preparation, SD are often created by an increase of the extracellular potassium concentration [83] and Nedergaard showed in [13] that they are preceded by a calcium wave in the astrocytes. Hence we will focus on two solutes : the potassium (K^+) and the calcium (Ca^{2+}). Precisely, only the extracellular potassium concentration ($[K^+]_e$), the astrocytic calcium concentration ($[Ca^{2+}]_a$) and the neuronal calcium concentration ($[Ca^{2+}]_n$) will appear in this model.

The important fact is that SD eventually propagate through the entire brain, hence it is important to study the above concentrations in function of time and of space. In fact, all the quantities in our model will depend on the time variable t and on the space variable x . For example, $[Ca^{2+}]_n(t, x)$ refers to the calcium concentration in the neurons near the point x at the time t and $[K^+]_e(t, x)$ designates the potassium concentration in the extracellular space near x at time t .

Since we want to build a global model of stroke, the blood flow irrigating the cells $BFlow(t, x)$ will be the entry function of our model and the model will end with the death or not of the neurons and more precisely the way of dying or not of the neurons.

B.2.1 The equations

Blood flow

Let us consider a particular blood vessel that will be occluded at the onset of the stroke. Let $\eta(t)$ be the fraction of blood flow in the occluded vessel during the stroke. Before the stroke, $\eta(t)$ equals 1. If the accident occludes completely the vessel, then $\eta(t)$ turns to 0. If the stroke only partially blocks the blood flow, then $\eta(t)$ only decreases to $\eta_0 < 1$. During the stroke, the total proportion of blood flow that irrigates the cells near x at the time t is described by $BFlow(t, x)$ with

$$BFlow(t, x) = \eta(t)BFlow_{vessel}(x) + BFlow_{others}(x). \quad (B.1)$$

where $BFlow_{vessel}(x)$ is the normal proportion of blood flow carried by the vessel that will suffer the stroke while the other vessels carry $BFlow_{others}$. We will assume $BFlow_{vessel}(x) + BFlow_{others}(x) = 1$.

In this model, the other vessels do not change their flow during the stroke. In fact, numerous studies have shown that a suppleance phenomenon takes place after an ischemic stroke, but it only changes the size of the area that suffers from the lack of blood. If we want to compare precisely the result of our model with real images of an ischemic stroke, then we will have to model this suppleance phenomenon, but for the moment we are only interested in the qualitative properties of the model. So it is not necessary to add equations describing suppleances.

Oxygen absorption

When blood flow is reduced, cells progressively increase their ability to extract oxygen from blood in order to maintain oxygen influx as constant as possible. This is of course possible only within some limits.

Let $OEF(t, x)$ describes the oxygen extraction factor. OEF varies progressively when $BFlow$ varies as in [25].

$$\frac{\partial OEF}{\partial t}(t, x) = \frac{OEF_{\infty}(BFlow(t, x)) - OEF(t, x)}{\tau_{OEF}} \quad (B.2)$$

where τ_{OEF} is the typical time of adaptation of OEF to changes of $BFlow$. Here we have taken τ_{OEF} equal to 1 minute.

OEF_{∞} describes the final value of the oxygen extraction factor. In order that the total quantity of extracted oxygen stays approximately equal to his normal quantity even if the blood flow decreases of a third, we have taken

$$OEF_{\infty}(BFlow) = OEF_{average} - OEF_{var} \tanh\left(\frac{BFlow - B_0}{\delta_{OEF}}\right) \quad (B.3)$$

where $OEF_{average} = 1.4$ is the normal OEF , $B_0 = 0.7$ a typical value where enhancement of oxygen begins, $OEF_{var} = 0.63$ the maximum possible variation of OEF and $\delta_{OEF} = 0.4$ measures the reaction of OEF to change of blood flow. Figure B.1 represents the total extracted oxygen in function of the proportion of blood flow irrigating the cells.

Energy

Energy needs

The cells need energy to maintain his metabolism, to maintain homeostasy, to recover from the spreading depressions and of course to have a normal electrical activity. These needs have various degrees of importance. Hence we split the total energy needs in four specific energies

$$E_{need} = E_{meta} + E_{homeo} + E_{SD} + E_{act} \quad (B.4)$$

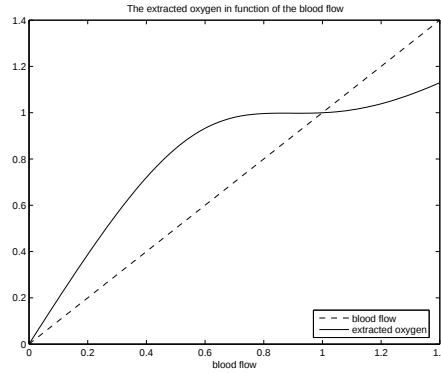


FIG. B.1 – The proportion of oxygen extracted by the cell depending of the blood flow irrigating this cell. Here, we assume that the normal quantity of extracted oxygen is 1. We notice that for blood flow close to 1, the proportion of oxygen extracted is almost 1.

where E_{meta} is the energy needed for maintaining life of the cell, E_{homeo} is the energy needed to maintain homeostasy, E_{SD} is the energy needed to recover from spreading depressions and E_{act} is the energy needed to have a normal electrical activity. In this model, we have chosen $E_{meta} = 0.2$, $E_{homeo} = 0.3$, $E_{SD} = 0.35$ and $E_{act} = 0.15$. These values were inspired by [4, 12, 53], but they could be at length discussed since the knowledge about energy dealing is very limited.

The way the cell deals with its energy depends on the available energy. In this model we assume that the available energy is proportionnal to the quantity of oxygen that irrigates the cell. Hence

$$E_{av} = BFlow(t, x) \times OEF(t, x). \quad (B.5)$$

Energy use

As well as the energy needs, the available energy is split in several terms.

$$E_{av} = E_{meta,used} + E_{homeo,used} + E_{SD,used} + E_{act,used} + E_{rem} \quad (B.6)$$

where $E_{meta,used} < E_{meta}$ is the energy used to maintain life and so on.

Let us now describe how the cells use the available energy. We assume that according to the available energy, the cell first try to maintain its metabolism upon all other tasks. If the cell has enough energy available to maintain its metabolism, it tries next to maintain the ionic concentrations. If possible it then uses the remainder of its energy to recover from spreading depressions and finally to have a normal electrical activity. Actually the strategy of the cells to deal with a shortage in energy can not be exactly such as described above and maybe that the energy

is simultaneously distributed to all tasks, but due to the weak knowledge on this strategy, this model appeared to us as the more realistic.

Hence we set

$$E_{meta,used} = E_{meta} \tanh\left(\frac{E_{av}}{E_{meta}}\right), \quad (B.7)$$

$$E_{homeo,used} = \frac{1}{2}E_{homeo} \left(1 + \tanh\left(\frac{E_{av} - E_{meta} - E_{homeo}/2}{E_{homeo}/2}\right)\right), \quad (B.8)$$

$$E_{SD,used} = \frac{1}{2}E_{SD} \left(1 + \tanh\left(\frac{E_{av} - E_{meta} - E_{homeo} - E_{SD}/2}{E_{SD}/2}\right)\right), \quad (B.9)$$

$$E_{act,used} = \frac{1}{2}E_{act} \left(1 + \tanh\left(\frac{E_{av} - E_{meta} - E_{homeo} - E_{SD} - E_{act}/2}{E_{act}/2}\right)\right) \quad (B.10)$$

and $E_{rem} = E_{av} - E_{meta,used} - E_{homeo,used} - E_{SD,used} - E_{act,used}$. These equations express that if the available energy is lower than E_{meta} then almost all the energy is used to maintain life and the other energy used are near zero. If the available energy is between E_{meta} and $E_{meta} + E_{homeo}$, then $E_{meta,used}$ is almost equal to E_{meta} , the remaining available energy is used to maintain ionic equilibrium and the other energy used are almost null. And so on... See figure B.2 for the repartition of the energy used in function of the available energy.

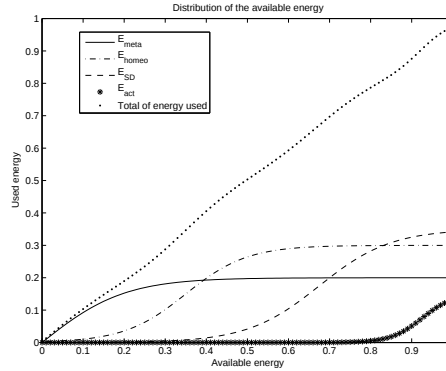


FIG. B.2 – The distribution of energy in the cell. Except for available energies near 1, all the available energy is used. If the available energy is near 0, all the energy is used to maintain life in the cell ($E_{meta,used}$). Then energy is progressively used for all the other cell's functions.

Ionic exchanges

In this part of the model, we have followed the model of SD proposed by Lin and Nedergaard in [13]. Nedergaard has observed that spreading depressions are linked

with calcium waves in the astrocytes network and are evoked by applying potassium to cortical tissue. Hence we remember that in this model, we will consider the potassium concentration in the extracellular space and the calcium concentrations in the neurons and in the astrocytes.

Following Nedergaard, the basic phenomena that create spreading depressions are as follow :

- The potassium ions can diffuse in the extracellular space.
- An excess of potassium in the extracellular space activates ionic pumps on the astrocytes' membrane that make calcium enter the cell.
- The calcium diffuse through gap junctions in the astrocytic network.
- The calcium ions enter the neurons "through gap junctions between neurons and astrocytes" (see below for the discussion of this point).
- The excess of calcium in the neuronal space activates ionic pumps on the neurons' membrane that make potassium go out of the cell.

It is important to precise what we mean by "gap junctions between neurons and astrocytes" since this point is still debated [70, 78, 79]. Mathematically, the increase of calcium in the astrocytes has to trigger an increase of calcium in the neurons. If we remove this connexion, the "reaction loop" is then interrupted and no propagative wave could be generated by the model. We have assumed here that the calcium passes through gap junctions, but it may be any other mechanism that make the calcium enter the neurons, particularly the increase of calcium can trigger an increase of extracellular glutamate that makes the calcium enters the neurone.

The last phenomenon that has to be taken into account in the ionic exchanges is the natural trend of ions to freely diffuse. So if the available energy is not sufficient, the ionic pumps that make the calcium go out of the astrocytes and the potassium stay in the neurons are no more active and the ionic concentrations tend to equilibrate between intra- and extracellular spaces.

All the preceding basic phenomena make ionic concentrations increase. We have to add some recovery mechanisms in order to allow the system to go back to his resting state. There is few knowledge about the recovery mechanism. Here we have consider that there exist two different ways for cells to recover. First small variations in the ionic concentrations are quickly erased by various channels (ionic pumps, ...). If the variations are too large, then another recovery mechanism takes place and try to limit these variations. At last there is a special phenomenon to recover from spreading depression which are expressed by a very important increase of calcium and potassium concentrations. Of course all these mechanisms need energy and moreover the recovery from SD needs several steps (particularly, a blood flow increase), this implies a delay before the cell is ready to recover.

Apart from these, very few data are available on these recovery mechanisms.

Let us call Ca_g the variation of calcium concentration in the astrocytes (g stands for glia) in relation to the resting state. So Ca_g equals 0 when the calcium concentration in the astrocytes is normal. In the same way, we call Ca_n the variation of calcium concentration in the neurons and K_e the variation of potassium concentration in the extracellular space.

R represents the strength of the recovery mechanism from spreading depressions and Cap the capacity of the cell to recover from SD. When Cap reaches a fixed threshold, the phenomena that govern the recovery from SD can take place.

We obtain the following partial differential equations.

$$\begin{aligned} \partial_t Ca_g - \nu_{Ca_g} \Delta Ca_g = & -k_{Ca_g} E_{homeo,us} \tanh \frac{Ca_g}{Ca_g^0} + h_{K,Ca} E_{homeo,us} K_e \\ & -k_{gap}(Ca_g - Ca_n) + c_{grad,Ca}(E_{homeo,us} - E_{homeo})(Ca_g - [Ca]_{ext}) \\ & -\alpha_{Ca_g} Ca_g^2 - \alpha_{rec,g} E_{SD,us} R Ca_g \end{aligned} \quad (B.11)$$

$$\begin{aligned} \partial_t Ca_n = & -k_{Ca_n} E_{homeo,us} \tanh \frac{Ca_n}{Ca_n^0} + k_{gap}(Ca_g - Ca_n) \\ & -\alpha_{Ca_n} Ca_n^2 - \alpha_{rec,n} E_{SD,us} R Ca_n \end{aligned} \quad (B.12)$$

$$\begin{aligned} \partial_t K_e - \nu_{K_e} \Delta K_e = & -k_{K_e} E_{homeo,us} \tanh \frac{K_e}{K_e^0} + h_{Ca,K} E_{homeo,us} Ca_n \\ & +c_{grad,K}(E_{homeo,us} - E_{homeo})(K_e - [K]_{int}) \\ & -\alpha_{K_e} K_e^2 - \alpha_{rec,e} E_{SD,us} R K_e \end{aligned} \quad (B.13)$$

$$\begin{aligned} \partial_t Cap = & 1_{\{Ca_g > c_g\} \cup \{Ca_n > c_n\} \cup \{K_e > c_k\}} \frac{1 - Cap}{T_o} \\ & -1_{\{Ca_g < c_g\} \cap \{Ca_n < c_n\} \cap \{K_e < c_k\}} \frac{Cap}{T_f} \end{aligned} \quad (B.14)$$

$$\partial_t R = 1_{\{Cap > c_{cap}\}} \frac{1 - R}{\tau_o} - 1_{\{Cap < c_{cap}\}} \frac{R}{\tau_f} \quad (B.15)$$

The first three equations (B.11), (B.12), (B.13) govern the ionic movements. The last two equations (B.14), (B.15) govern the special mechanism to recover from SD. The biological meanings of the various parameters are gathered in table B.1.

ν_i	diffusion coefficient of ion i
k_i	strength of the recovery mechanism for small concentration variations of ion i
Ca_n^0, Ca_n^0, K_e^0	range of the variations that are concerned with the recovery for small variations
α_i	strength of the recovery mechanism for large variations of concentration of i
$\alpha_{rec,i}$	strength of the recovery from SD for compartment i
$c_{grad,i}$	speed of the move towards the ionic equilibrium between extracellular and intracellular spaces when there is no more energy to maintain the membrane potential for ion i
$h_{K,Ca}$	activity of the ionic pumps on astrocyte's membrane sensitive to extracellular potassium that makes calcium enter the astrocyte.
k_{gap}	activity of the gap junctions between astrocytes and neurons
$h_{Ca,K}$	activity of the ionic pumps on neuron's membrane sensitive to intracellular calcium that makes potassium go out of the neuron.
c_i	concentration thresholds above which the cell begins to prepare for the SD recovery
T_o	typical time for the cell to be ready to recover from SD
T_f	typical time for the disappearance of the preparation to recover from SD
c_{cap}	threshold above which the cells are able to recover from SD, connected with the delay before the recovery from SD mechanism takes place
τ_o	typical time for the complete opening of the recovery mechanism
τ_f	typical time for the complete closure of the recovery mechanism

TAB. B.1 – Biological meanings of the parameters involved in the model

Cell death

In this model we assume that the only damage to the cell is the presence of calcium ions in it [51, 67]. If the cell is severely attacked and has not got enough energy available, then it will die by necrosis (the membrane of the cell falls into pieces.). If the cell has enough energy and is not so badly injured, then it dies by apoptosis (the cell shrinks and is eliminated by the immune system.) [31]. The problem is to quantify the “death”.

Let ϑ describe the condition of the cell. If ϑ almost equals one then the cell

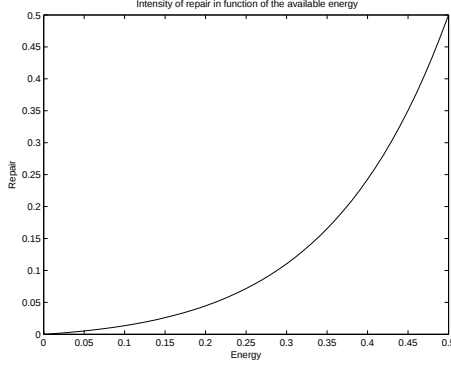


FIG. B.3 – Example of the ability to repair in function of the available energy for it.

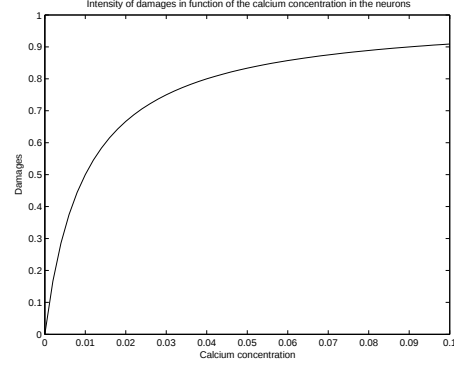


FIG. B.4 – Example of the “intensity” of the damages in function of the calcium concentration in the cell.

is perfectly well and the smaller ϑ is, the worse affected the cell is. If the cell has enough energy, it can repair the damages due to calcium. So ϑ is governed by the following equation.

$$\frac{\partial \vartheta}{\partial t} = \text{Repair} (1 - \vartheta) - \text{Damage} \vartheta \quad (\text{B.16})$$

where

$$\text{Repair} = R_0 (E_{\text{meta,used}} + E_{\text{homeo,used}}) \exp (E_0 (E_{\text{meta,used}} + E_{\text{homeo,used}})) \quad (\text{B.17})$$

and

$$\text{Damage} = D_0 \frac{Ca_n}{E_1 + Ca_n}. \quad (\text{B.18})$$

See figures B.3 and B.4 for representation of these functions. They have been determined so that small variations of the energy do not have too much influence on the capacity of the cell to repair and so that even slight excess of calcium in the cells badly damage them. These shapes of the *Repair* and *Damage* functions are necessary in order that a healthy cell rather quickly recovers from SD while an ischemic cell is more and more injured by the propagation of SD.

As long as the condition of the cells ϑ is bigger than a threshold ϑ_{apop} , the cell is considered as alive and the apoptosis phenomenon has not begun. If ϑ goes under ϑ_{apop} then the apoptosis phenomenon begins but it is for the moment reversible if the damages stop.

To describe apoptosis we need another equation. Let A be a mathematical variable that describe the progress of apoptosis. If A equal 0, the apoptosis has not begun yet. When apoptosis has begun, the cell uses all the available energy for this phenomenon. So

$$\frac{\partial A}{\partial t} = A_0 \frac{E_{av}}{E_2 + E_{av}}. \quad (\text{B.19})$$

To decide if the cell dies by apoptosis or necrosis, we need to define two other thresholds ϑ_{nec} and A_{apop} . We will always take $\vartheta_{nec} < \vartheta_{apop}$. If the condition of the cell ϑ stays between ϑ_{nec} and ϑ_{apop} and the progress of apoptosis A passes over A_{apop} then we consider that the cell will irremediately die by apoptosis. If ϑ passes under ϑ_{nec} before A passes over A_{apop} , then the cell dies by necrosis.

As a first step, when the cell is dead either by apoptosis or by necrosis, we set the available energy to zero. Ca_n and Ca_g turn to zero.

B.2.2 Discrete solution of the model

The model is a mix of algebraic equations (equations (B.1), (B.3), (B.17), (B.18) and all the equations dealing with the energy), ordinary differential equations (equations (B.2), (B.12), (B.14), (B.15), (B.16) and (B.19)) and partial differential equations (equations (B.11) and (B.13)). To solve these differential equations, the time is broken into discrete time steps of length Δt and we approximate the solutions of the equations at time $t_n = n\Delta t$. The same way, the space is decomposed in elementary little voxels of size Δx and we calculate approximatively the solutions at the corners of the elementary squares.

The methods to calculate these approximates solutions of partial differential equations are well studied (see [33] or [55] for an introduction to these methods). The method to compute the solution in time is called “semi-implicite finite differences method” and in space we have used a fast Fourier transformation method. Schematically, the fast Fourier transformation transforms the derivation in space into a “simple” multiplication by a complex function and the finite differences method computes the various variable at time $(n+1)\Delta t$ using the previously computed variables at time $n\Delta t$. We use a semi-implicite method so that the approximation of the solutions stays valid for long time computations.

B.2.3 The parameters

Method to fix the various parameters

A large system of partial differential equations with a lot of parameters can have very different behaviours and may be very sensitive to variations of one parameter. However, values of parameters are difficult to sort out from the literature. First, for various reasons, many parameters have not been explored. Second, when they exist, data come from different species or different types of neurons. Finally, the experimental error can be very large.

In order to fix the set of parameters, we have decided to split the model in many submodels and to use a random algorithm to find a set of relevant parameters for each submodel. This algorithm is described in more details in [16]. Since thousands sets of parameters have to be tested in this process, we did computations on a single dimension to save time. We have then validated the selected sets on two dimensions.

Beginning with the equations (B.11), (B.12), (B.13), (B.14), (B.15) that govern the ionic exchanges between the different cells, we first have to decide which qualitative properties the solution of the model must have. This set of properties is called basis of rules. It is derived from available evidence.

Here, the basis is composed of six rules that come from experimental observations :

- There exist a stable resting state.
- An injection of K^+ with a higher concentration than 12mM creates one or more SD that are expressed by a calcium wave through the glial network [47, 50].
- This wave propagates with a speed of about 3mm/min [83].
- The increase of potassium concentration in the extracellular space is between 30 and 80mM [60] and the increase of calcium concentration in the astrocytes is about 0,2mM [58].
- The maximum of the potassium concentration in the extracellular space must look like a plateau of approximately 7 minutes[60].
- A continue injection of KCl creates successive SD.

Let us notice that all these rules can be rapidly numerically tested. The random algorithm to find the possible parameters of the model is as follows.

- Choose reasonable range for the values of all parameters.
- Choose at random the various parameters values of the set of partial differential equations.
- Test numerically whether the resting state is stable.
- Test numerically whether SD are created by injection of K^+ , whether they have the right profile and whether they spread with the right speed or not.
- Test whether a continuous injection of potassium creates successive SD.
- If the answers of these last three questions are positive, then keep this set of parameters in memory.

We have applied this procedure to the submodel that govern ionic exchanges. It is composed of 5 equations with 27 parameters. At the end of a run, about hundred thousands sets of parameters have been tested, leading to five suitable sets.

Examples of results produced by this algorithm are shown in figures B.5 and B.6. Ionic waves are created and spread through the entire brain. All the set of suitable parameters that were found with this algorithm give similar qualitative results.

In this basis of rules, an important test is the creation of successive SD for a continuous injection of KCl. As a matter of fact, when an experimental stroke occurs, successive SD are created. The reaction of the system to a continuous injection with suitable parameters is shown in figure B.7.

Taking these parameters into account, we have then decided to find the possible values of the parameters that occur in the equations that govern the energy. Another condition has to be added to the basis of rules :

- a lack of energy generates SD.

More sets of parameters suit the basis of rules for the equations that govern the

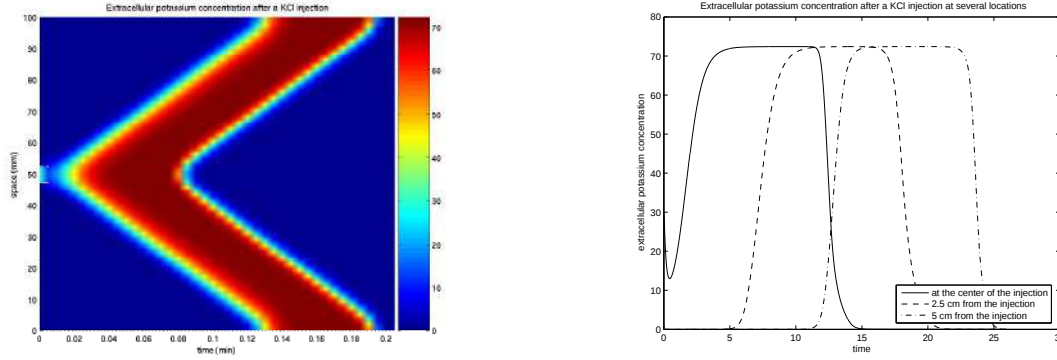


FIG. B.5 – Potassium concentration in the extracellular space after a KCl injection for an example of suitable parameters. Left, the level lines of the potassium concentration in function of the time (x-coordinate) and of the place in the brain (y-coordinate). Right, potassium concentration at several locations in function of time. The solid line represents the extracellular potassium concentration in the middle of the area where the injection is made. The dashed line is the potassium concentration 2.5 cm further and the dashed-dotted is 5 cm further.

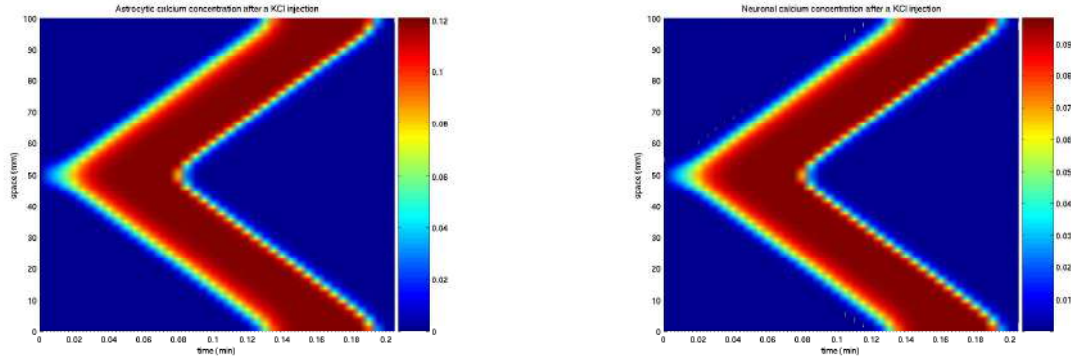


FIG. B.6 – Level lines of the calcium concentration after a KCl injection for an example of suitable parameters. Left, the calcium concentration in the astrocytes and right, the calcium concentration in the neurons. As it has been observed by Nedergaard, a calcium wave propagates through the net of astrocytes.

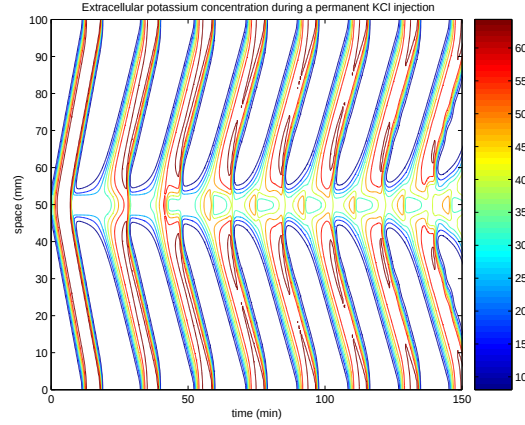


FIG. B.7 – Level lines of the potassium concentration in the extracellular space during a continue KCl injection for an example of suitable parameters. Here, the brain is supposed to be a line. Successive ionic waves are created and propagate through the entire “brain”.

energy since few knowledge is available on these phenomena.

At last, we look for the parameters that stand in the equations that govern the death of the cells with the same procedure. The condition added to the basis of rules is as follow :

- after an important ischemic stroke, the cells of the center of the ischemic area die by necrosis and the cells around die by apoptosis [20],
- necrosis occurs before apoptosis [20],
- a SD severely damages cells but does not kill healthy cells [66, 62],
- the cells that receive a normal blood flow stay alive at the end of the stroke,
- after a long time the healthy tissue must return to his rest state.

With the algorithm describes above, we found six suitable sets of parameters. An example of solution of the complete system with suitable parameters is shown in figures B.8 to B.11. In this example, 9 SD are created and spread through the cortex. Results for the others five suitable sets of parameters are similar. Between 4 and 12 SD are created. We can notice that in this model, it is the death of the acute ischemic area of the brain that stop the creation of SD.

Sensibility of the model to parameters

The solutions of the model for different suitable sets of parameters are qualitatively similar. Hence the rules are assumed to be met. Nevertheless, small differences in particular situations can be noticed (see the results section).

For the moment, no correlation between the various suitable sets of parameters

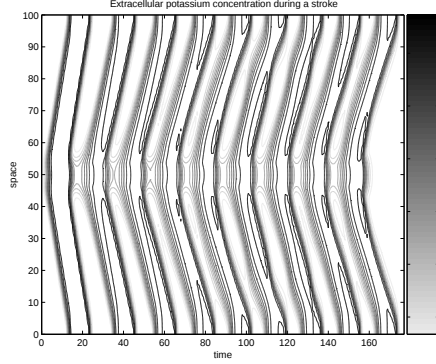


FIG. B.8 – Potassium concentration in the extracellular space after an ischemic stroke for suitable parameters. Here, we suppose the brain is a line. 9 SD are created before the system goes back to his rest state.

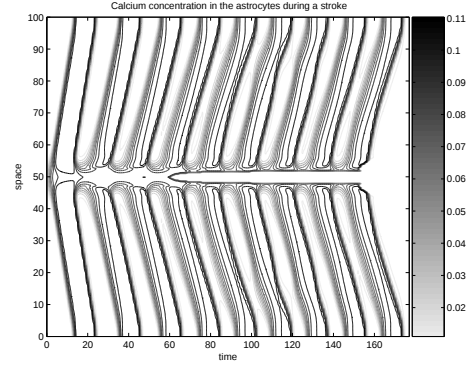


FIG. B.9 – Calcium concentration in the astrocytes after an ischemic stroke for suitable parameters. When the cell near x is dead, we assume that the calcium concentration is 0.

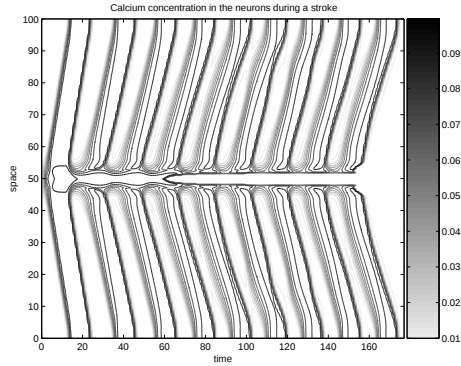


FIG. B.10 – Calcium concentration in the neurons after an ischemic stroke for suitable parameters. When the cell near x is dead, we assume that the calcium concentration is 0.

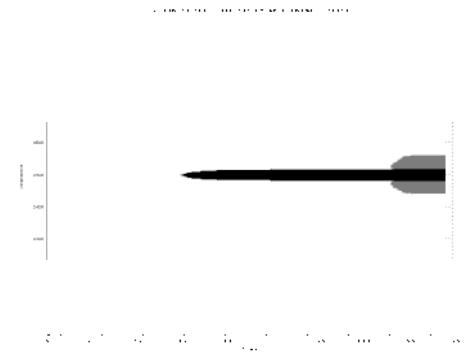


FIG. B.11 – Death of the cells during an ischemic stroke in function of time (x-coordinate). In black, the cells dead by necrosis. In grey, those dead by apoptosis.

have been noticed, but no general method can be used to detect a possible correlation. Indeed statistics are useless due to the great number of parameters and the small number of suitable sets.

Finally, we have noticed that the behaviour of the solution depends strongly on some parameters, particularly on the parameters relative to the recovery mechanism τ_o , τ_f and $\alpha_{rec,i}$, and on ϑ_{apop} , ϑ_{nec} and A_{apop} the thresholds concerning the death of the cells... It would be interesting to have more experimental knowledge on these mechanisms. Indeed, the high sensibility to the parameters may be due to a poor relevance of these parts of the model. Conversely, the model is rather unsensible to the value of the other parameters.

B.3 Results

In this part, the brain will be modeled by a square of grey matter.

B.3.1 Propagation of SD in a normal tissue

First, let us see the effect of a K^+ injection in a healthy tissue. According to [47] and [50], a KCl injection (the practical way of injecting K^+) of 12mM creates a SD that propagates through the brain at a speed of 3mm/min and that leads to an increase of calcium concentration of 0.1mM in the astrocytes [60]. A K^+ injection of 15 mM is thus simulated in the preceding model with usual oxygen supply. As we can see (figures B.12 to B.14), a potassium wave propagates through the extracellular space. Similarly, a calcium wave propagates through astrocytes and neurons. About 45 minutes later, the system is back to his resting state.

These results are consistent with [60] and with the calculations made in a one dimension brain. Figure B.13 shows the potassium concentration in the extracellular space for a fixed y-coordinate. We find the same profile as in section 2.

B.3.2 Creation of SD by an ischemic area

Experimental ischemia induces SD in the ischemic area in the rodent brain [83]. Between 8 and 14 SD propagate.

For the moment, we suppose that no blood can pass through the considered vessel during the stroke. Results are shown in figures B.15 and B.16. As preceding, we see the potassium waves that spread across the entire brain. In the same way, calcium waves propagate through the net of astrocytes and of neurons. Between 5 and 12 SD are created, depending on the set of suitable parameters chosen.

In the example shown here (figure B.15), 10 waves are created. Three and a half hours later, the system has come back to the resting state. At this moment, the central area of the brain suffering the stroke is dead by necrosis, while the area

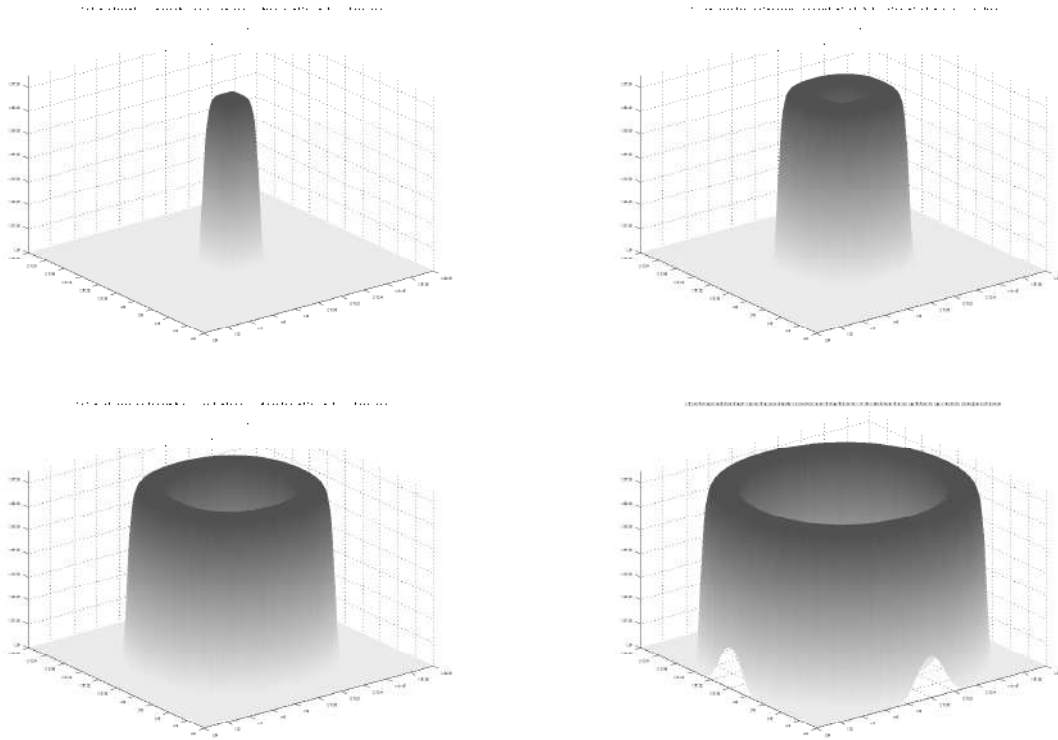


FIG. B.12 – Potassium concentration in the extracellular space after a KCl injection for several times (5, 15, 25 and 35 min after the injection). A SD propagates through the entire brain.

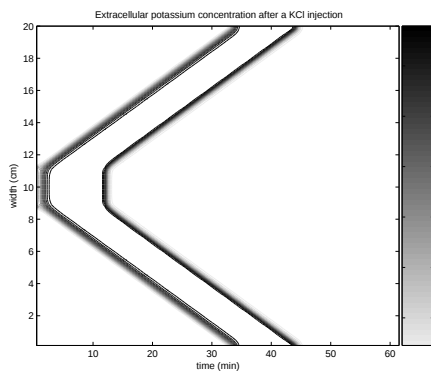


FIG. B.13 – Potassium concentration in the extracellular space after a KCl injection for a fixed y-coordinate. Here, the brain is supposed to be a square.

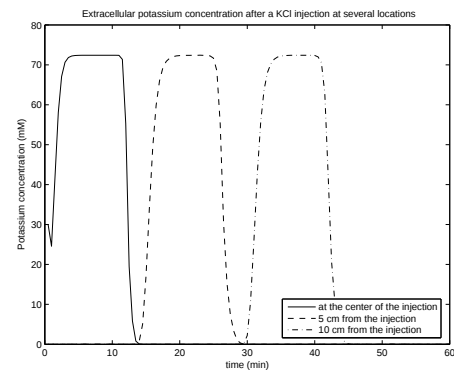


FIG. B.14 – Extracellular potassium concentration after a KCl injection for several locations in the brain (center of the injection, 5 cm further and 10 cm further).

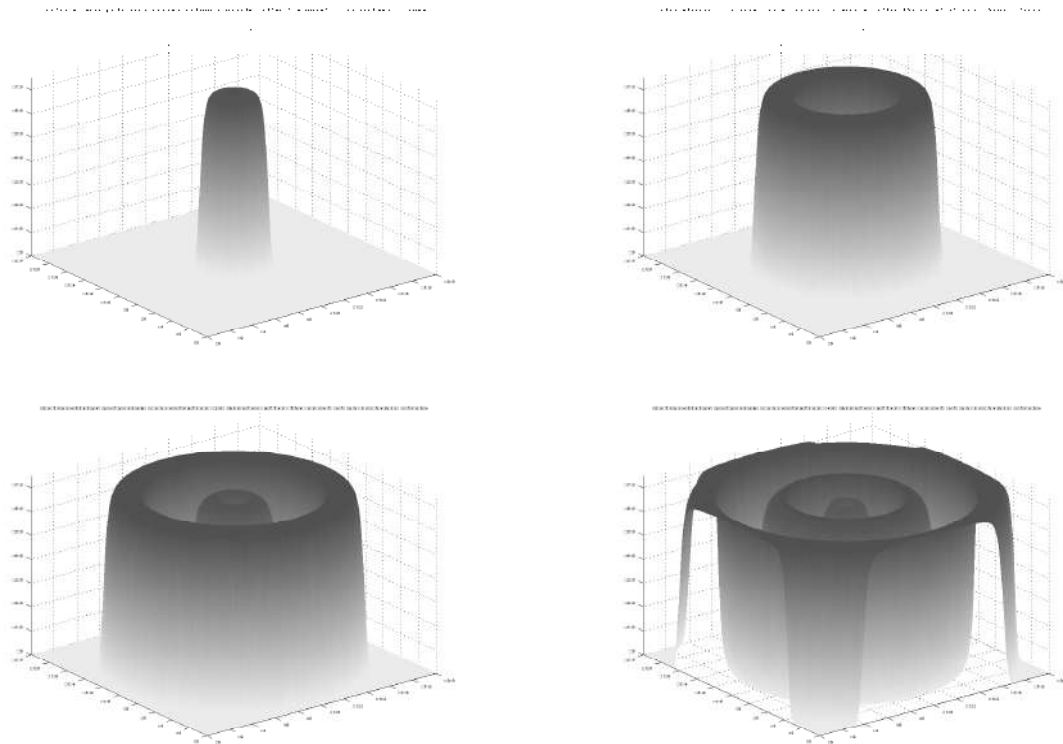


FIG. B.15 – Potassium concentration in the extracellular space during a stroke for several times (5, 15, 30 and 45 min after the onset of the stroke). Successive SD propagate through the brain.

around is dying by apoptosis (see figure B.16). So the set of parameters chosen here fits the reality in the rodent grey matter.

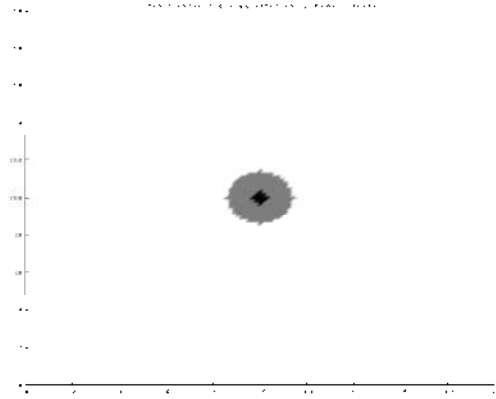


FIG. B.16 – The final dead zone after an ischemic stroke. In black, the cells dead by necrosis. In grey, the cells dead by apoptosis.

B.3.3 Partial occlusion of the vessel

In the preceding subsection, no blood could pass through the considered vessel from the beginning of the stroke. In the reality, the interruption of blood flow can be total or partial. [49] and [80] studied the partial occlusion of a vessel, but they were interested in the time before the cells die, not in the size of the final infarcted area.

Let see the influence of the proportion of blood that pass through the vessel during the stroke on the size of the final dead area in this model. We have taken the same set of suitable parameters as preceding.

Let η_0 be the proportion of blood that can pass through the vessel during the stroke.

If more than one third of the normal blood flow stays available during the stroke ($\eta_0 > 0.33$), the various ionic concentrations are slightly disturbed, but no SD occurs and no cell dies.

If $0.26 < \eta_0 < 0.33$, a SD is created and spreads across the entire brain, but no cell dies.

If $\eta_0 = 0.25$, 5 SD are created and a small part of the brain dies, but there is only apoptosis and no necrosis.

If $\eta_0 = 0.2$, 8 SD are created and a larger part of the brain than for $\eta_0 = 0.25$ dies, but there is once again only apoptosis.

If $\eta_0 = 0.1$, 9 SD are created as in the case where the stopping is total, but the size of

the necrosed area is smaller (see figures B.17 and B.18). So this model qualitatively fits the experimental data. However, it does not fit them quantitatively since it is only phenomenological. Also, the parameters and their values have been chosen rather arbitrary. If we want to have results that fits more quantitatively the reality, we would have to add other facts to the basis of rules and look for other parameters.

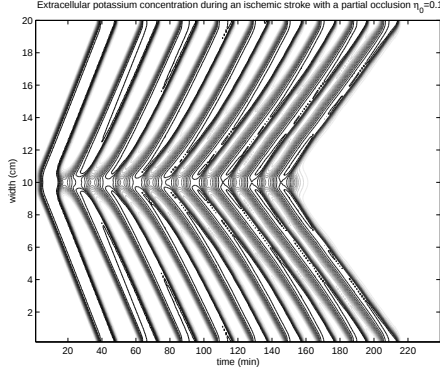


FIG. B.17 – Extracellular potassium concentration during a stroke on a diameter of the brain. The blood flow of the vessel changes from 1 to $\eta_0 = 0.1$.

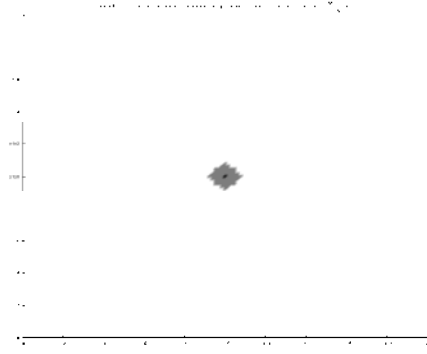


FIG. B.18 – Final states of the cells. In white, the cell that stay alive. In grey, those that die by apoptosis. In black, those dead by necrosis.

B.3.4 Effect of SD on the size of the final dead zone

In [66, 62], the authors insist on the importance of SD on the size of the final infarct area. SD could increase of 23% to 30% the size of the infarct.

If we solve this model without SD by blocking the ionic pumps (set h_{KG} and h_{NK} to 0), the final dead area is indeed much smaller than the one caused by stroke with SD (see figure B.19 and table B.2). In our example, the size of the final infarct with SD is increased by 330%. Since 10 SD have propagated, the result is consistent with the experimental results obtain in [62].

Hence, according to this model for species where SD exist, blocking the creation of SD seems to be a very good way to reduce the damages of an ischemic stroke.

B.3.5 Recovery of the blood flow

The last but not least experimental observations on stroke that we will use here is about the reopening of the vessel. Experiments on the rodent brain show various influence on the size of the infarct area [39, 40, 67]. The damages on the brain can

Proportion of occlusion	Extracellular potassium concentration for a fixed y-coordinate	Final infarcted areas. In black, the cells dead by necrosis. In grey those dead by apoptosis.
$\eta_0 = 0.3$	Extracellular potassium concentration during an ischemic stroke with a partial occlusion $\eta_0=0.3$	
$\eta_0 = 0.25$	Extracellular potassium concentration during an ischemic stroke with a partial occlusion $\eta_0=0.25$	
$\eta_0 = 0.23$	Extracellular potassium concentration during an ischemic stroke with a partial occlusion $\eta_0=0.23$	
$\eta_0 = 0.2$	Extracellular potassium concentration during an ischemic stroke with a partial occlusion $\eta_0=0.2$	

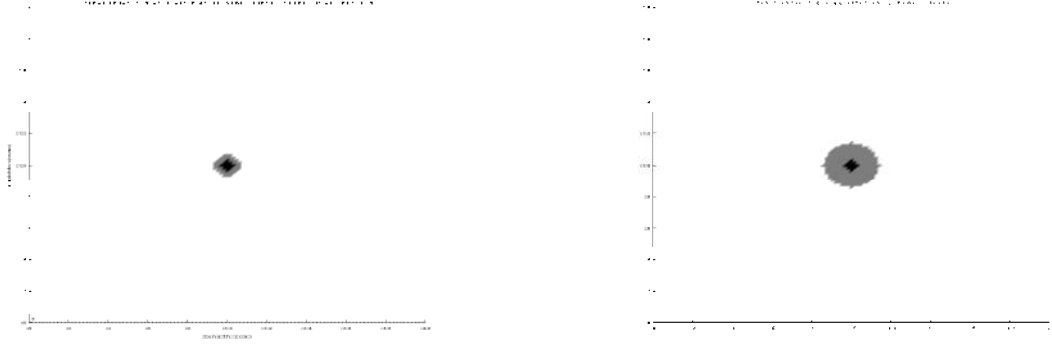


FIG. B.19 – The final dead zone after an ischemic stroke. Left, where the SD are blocked. Right, where ten SD propagate. In black, the cells dead by necrosis. In grey, those dead by apoptosis.

η_0	0	0.1	0.2	0.23	0.25	0.3
Size of the apoptotic area without SD	1.0742	0.5859	0.1221	0.0244	0	0
Size of the necrotic area without SD	0.3174	0.0244	0	0	0	0
Size of the final dead area without SD	1.3916	0.6104	0.1221	0.0244	0	0
Size of the apoptotic area with SD	5.6641	1.5625	0.9033	0.3174	0.1221	0
Size of the necrotic area with SD	0.3174	0.0244	0	0	0	0
Size of the final dead area with SD	5.9814	1.5869	0.9033	0.3174	0.1221	0
Number of SD	10	9	9	8	5	1

TAB. B.2 – Sizes in cm^2 of the various final dead areas depending on the proportion of the stopping of the blood flow

be stopped by the reopening, but the infarct area can also sometimes be bigger. This observation is still not very clearly explained.

In this model, it is easy to simulate the reopening of the vessel. Hence the cells get the energy they need back, the damages to the cells are more quickly stopped and the final infarct should then be smaller than the same simulated stroke without reopening.

In table B.3, we compare the sizes of the final dead zones for different times of reopening T_{reopen} for the same set of parameters than before. To reduce the computing duration, these calculations were done in one dimension in space.

T_{reopen}	Nbr of SD	Size of the apoptose	Size of the necrose	Size of the dead area
10	1	0	0	0
30	2	0	0	0
50	3	0	0	0
70	4	0	2.7569	2.7569
90	5	0	3.2581	3.2581
110	8	0	3.7594	3.7594
130	9	8.5213	3.7594	12.2807
140	8	0	3.7594	3.7594
142	8	1.5038	3.7594	5.2632
143	8	2.0050	3.7594	5.7644
144	8	2.5063	3.7594	6.2657
145	9	10.0251	3.7594	13.7845
146	9	10.0251	3.7594	13.7845
147	9	9.0226	3.7594	12.7820
148	9	8.0201	3.7594	11.7794
150	9	8.0201	3.7594	11.7794
160	9	8.0201	3.7594	11.7794
170	9	8.5213	3.7594	12.2807
∞	9	8.5213	3.7594	12.2807

TAB. B.3 – Number of SD and sizes (in cm^2) of the various final infarcted areas in function of the time (in minutes) of reopening of the vessel that suffers the stroke T_{reopen} .

We can notice that the effect of the reopening of the vessel suffering the occlusion is positive until 120 min after the onset of the stroke. The reopening of the vessel stops the SD and cells do not proceed to necrosis. The healthy cells recover quickly their rest state.

When apoptosis has begun and is about to enter its irreversible phase (between 130

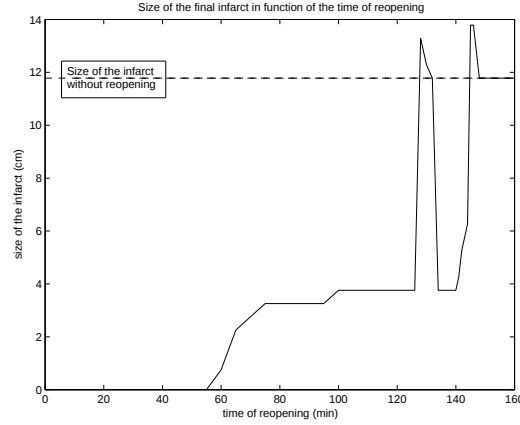


FIG. B.20 – Graphic of the size of the final infarct in function of the time of reopening.

and 150 min), the effect of reopening can be very variable. There is even a period where reopening the vessel kills more cells as doing nothing (between 145 and 147 min). Of course, if you reopen the vessel after the last SD has occurred (beyond 150 min), there is no more deleterious effects of calcium in the cells, so there is almost no effect.

Moreover if you block the propagation of SD, these deleterious effects of the reopening of the vessel do not exist anymore. Nevertheless, it is important to observe that this effect of the reopening on the size of the infarct depends strongly on the set of parameters chosen. For some of these sets, the reopening of the vessel has always a positive effect on the size of the infarct.

B.4 Discussion

In this paper, we have detailed a global model of ischemic stroke with a particular stress on spreading depressions. This model is centered around the ionic exchanges between neurons, astrocytes and extracellular space, particularly calcium and potassium. The model does not describe these phenomena down to the last details, but in a phenomenological way. As well as these ionic exchanges, the model takes into account the blood flow, the oxygen extraction factor, the management of the energy, the infarction of the cells via necrosis or apoptosis. This model is phenomenological and part of the equations are fixed rather arbitrarily due to the lack of knowledge (in particular, the energy dealing and the damage to the cells by calcium).

The first problem that we had to solve was to fix the values of all the parameters appearing in the mathematical system. The process that we have imagined takes a

long time but gives results (It is almost impossible to find the parameters “by hand”) and according to the experimental results, this process seems to be reliable if the basis of rules is well done. Particularly the model with the parameters found by this process gives results qualitatively similar to experimental data (see section Results) without that this was required by the basis of rules.

With the parameters hence found, this model of ischemic stroke seems to globally fit the reality. An injection of KCl creates a SD. A lack of blood in part of the brain creates several successive SD. The cells situated at the center of the area normally entirely irrigated by the occluded vessel die by necrosis while the cells in the surrounding die by apoptosis.

Besides, we have compared two situations with this model : with and without SD. If the SD are artificially blocked (by taking away the relation between neurons and extracellular space in this model), an ischemic stroke creates a smaller final dead zone. This fact had already been shown by experimental studies [66, 62] and may be a clue for the treatment of stroke for species where SD occur. It is important to explain that in this model it is very easy to stop the propagation of SD. It suffices to block any “ionic pumps or gap junction”. In the reality, it is more complicated. This difference is certainly due to the small number of ionic concentrations we have taken into account here.

This model also gives results similar to the experiments for the sometimes deleterious effects of the reopening of the occluded vessel. The interest is that in this model, it is rather simple to understand the facts that lead to this sometime deleterious effect. Indeed, deleterious effects of the reopening appear when the reopening takes place at the beginning of the last or the next to last SD that propagates through the brain. To understand the deleterious effects of reopening in this model, we have noticed two important facts. First, if you reopen the vessel just after that a SD has begun, this SD will go on. Second, around the ischemic area, there are cells that are exhausted by the SD and that are near their irreversible phase of apoptosis (so of their death), but the death of the cells around stop the creation of SD, so these cells can progressively come back to their resting state.

Hence if you reopen the vessel just after the beginning of the last SD, the system has got more energy and since the speed of the apoptosis depends on the total energy, the cells around the ischemic area advance quicker toward death (by apoptosis) and instead of surviving the last SD, they die. The assumptions of the model that are responsible for the deleterious effect of the reopening are thus the dependance of the speed of the apoptosis to the available energy and the all or nothing aspect of SD. However the question of the creation of SD after the recovery is difficult to explain. The all or nothing property of SD explains the creation of SD just after the reopening. Indeed, in this case, the ionic concentrations have already passed the threshold above which a SD is created when the reopening takes place. But sometimes more two SD propagate after the reopening of the vessel. This is due to a bad synchronisation of the recovery with the propagation of SD. In this case, the central area

that could not recover from SD because of the lack of energy will recover when the reopening occurs, but this recovery takes place too early compared to the recovery of the healthy area. Hence the central area should be to his resting state when the healthy area around starts to recover and due to the diffusion of the potassium in the extracellular space and of the calcium in the astrocyte, the ionic concentrations in the central pass once more over the threshold that creates SD. A new SD propagates.

To summarize, due to the propagation of SD and to their influence on the death by apoptosis of the cells, if the reopening of the vessel is not coordinated with SD, it can be more deleterious than no reopening. So blocking the SD or prevent the cells apoptosis before reopening could be an interesting experiment. Nevertheless, this phenomena depends on the set of parameters that has been chosen. They are sets where this deleterious effect of SD do not occur. It depends on the progress of the reversible phase of apoptosis of the cells around the infarct at the end of the last SD.

Of course, this model is just a first step in the global modelling of the ischemic stroke. Lot of things have to be improved such as the way the cells deal with energy or the way cells die or simply the path that leads to an increase of extracellular potassium when the calcium concentration increases in the astrocytes. This last point is almost clear and could rather quickly be modified in our model. But for the other points, the knowledge is for the moment insufficient and even when some knowledge is available, experimental data are lacking. Another interesting point to add to this model could be the oedema, but for the moment the size of the various compartments are not taken into account.

But before getting in more details into this model, we have planed to applied this model to a more realistic geometry of brain. Indeed the influence of the circumvolutions of the cortex may have a crucial influence on the propagation of SD and could explain the differences in the observation or non-observation of SD in rats or human brain. It would also be interesting to study the effect of the white matter on SD. In the white matter there is no neurons and the calcium diffuses freely, but no wave spreads. This points will be rather easy to include in the model.

Then this model could largely be improved by adding the effect of others ions and describing there movement in more detailed. We have planed to replace the simple ionic system by a model of ionic dynamic which is based on microscopic phenomena. We could also refine the distribution of the energy.

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Annexe C

Existence and nonexistence of travelling wave solutions for a bistable reaction-diffusion equation in an infinite cylinder whose diameter is suddenly increased

G. Chapuisat, E. Grenier¹

C.1 Theorem

Spreading depressions (SD) were first observed and described in 1944 by Leão in [56]. They consist of a transient suppression of all neuronal activities. This suppression spreads slowly across a large region of the brain. SD play an important role in many diseases [36, 37, 26] such as migraine with aura, epilepsy, ischemic cerebral stroke, etc... They have been observed in many species, but their existence is still discussed in the human cortex [79, 19, 70, 78]. For the moment, they have never been experimentally observed, perhaps because of the difficulties of in vivo measurements.

It is really important to understand the phenomena that are responsible for the creation or extinction of SD, for in cerebral strokes in rats, the number of SD has a clear influence on the size of the final dead zone of the brain. Some pharmacological agents that block the appearance of SD are already studied and work well on strokes in the rat brain, but for the moment, they seem to be ineffective on humans. Keeping in mind that cerebral strokes account for about 7 percent of all deaths in Canada and

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about 8.5 percent of all hospital bed occupancy [68], it is essential to understand the differences that could explain that no SD have yet been observed in human brains.

In a recent article [24], Grenier et al. try to explain the non observation of SD in the human cortex by the geometry of the brain. Indeed, the cortex is composed of two matters : grey and white matter, and SD spread only in grey matter. Most species, like rats, have a smooth brain entirely composed of grey matter which may therefore be considered as a convex. On the other hand, the human brain is very tortuous. Moreover the grey matter composes only a thin layer on the surface and the thickness of this layer can vary suddenly. Finally, SD are often modeled by a bistable reaction-diffusion equation, and this is why the hypothesis of Grenier et al. is that, in the human cortex, an SD can be generated, but it will stop at the first increase of the thickness of the grey matter. It will thus spread across a very small area and be very difficult to observe.

This paper is thus concerned with the non-existence of generalized progressive wave solutions for a bistable reaction diffusion equation in a cylinder whose diameter is suddenly increased.

Here, we will work in $\mathbb{R}^3$, since we want to answer a biological question about SD in the cortex which is, of course, set in $\mathbb{R}^3$. However since most of the numerical simulations are done in 2 dimensions, at the end of this paper, we explain what has to be changed to prove the same theorem in $\mathbb{R}^2$.

First, we define the domain Ω in $\mathbb{R}^3$ (figure C.1). Let

$$\begin{aligned} 0 < r \leq R, \\ \Omega_1 = \mathbb{R}_+^* \times]-R, R[\times]-R, R[, \quad \Omega_2 = \mathbb{R}_- \times]-r, r[\times]-r, r[, \\ \Omega = \Omega_1 \cup \Omega_2 \quad \text{and} \quad \Gamma = \partial\Omega. \end{aligned}$$

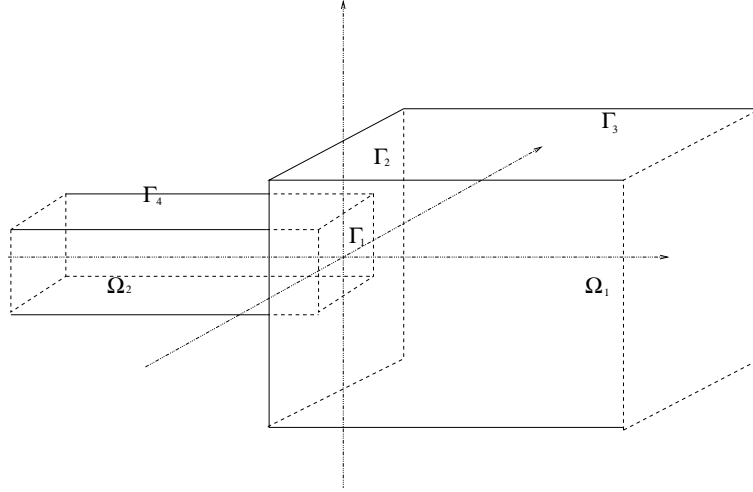
Set $f_0 > 0$ and $\theta \in]0, \frac{1}{2}[$. We consider $f(t) = f_0 t(t - \theta)(1 - t)$ for $t \in \mathbb{R}$. Choose $\nu > 0$. We study the following bistable reaction-diffusion system :

$$\begin{cases} \partial_t u - \nu \Delta u = f(u) & t \in \mathbb{R}, x \in \Omega. \\ \partial_n u = 0 & t \in \mathbb{R}, x \in \partial\Omega. \end{cases} \quad (\text{C.1})$$

Since $\partial\Omega$ is not smooth, we have to explain the precise meaning of $\partial_n u = 0$ for $t \in \mathbb{R}$ and $x \in \partial\Omega$. First, for x in the smooth part of $\partial\Omega$, $\partial_n u$ is defined as usual. Moreover, for $x_1 = 0$ and $(x_2, x_3) \in [-R, R]^2$, we define $\partial_n u = \partial_{x_1} u$ and for $x_1 > 0$ and $(x_2, x_3) \in \{-R, R\}^2$, $\partial_n u = 0$ means $\partial_{x_2} u = 0$ and $\partial_{x_3} u = 0$.

Our problem is to search if a local excitement may excite all the domain. That is what happens during SD. From [29] and [77], we know that if the initial value verify

$$\limsup_{|x| \rightarrow +\infty} u_0(x) < \theta \quad \text{and} \quad \forall |x| \leq L \quad u_0(x) \geq \theta + \eta$$

FIG. C.1 – Domain Ω .

for some $\eta > 0$ and $L > 0$ great enough, then the solution of (C.1) tends to the sum of travelling waves propagating into opposite directions. Biologically, in our problem, it means that a local strong enough stimulation should excite all the brain. But what happens if the initial value is small in Ω_1 ?

Théorème C.1 *Let $u(t, x)$ be a solution of*

$$\begin{cases} \partial_t u - \nu \Delta u = f(u) & t > 0, x \in \Omega. \\ \partial_n u = 0 & t > 0, x \in \partial\Omega. \\ u(0, x) = u_0(x) & x \in \Omega. \end{cases} \quad (\text{C.2})$$

where there exists $\alpha_0 > 0$ such that $u_0(x) < \frac{1}{2}\theta e^{-\alpha_0 x_1}$ for all $x \in \Omega_1$.

If r is small enough with respect to R and $\sqrt{\nu}$, then there exists $\rho > 0$ such that

$$\forall x \in \Omega \quad x_1 > \rho \Rightarrow \forall t \geq 0 \quad u(t, x) \leq \frac{\theta}{2}.$$

In this theorem, R may be equal to $+\infty$ without any problem. Moreover, in this theorem, we have kept the constants R and ν because of their biological meaning, but we recall that it is possible to change the scale in space in order to take R or ν as 1.

As a consequence of this theorem, if r is small enough with respect to R and $\sqrt{\nu}$, we know that there exists no generalized travelling wave solution of equation (C.1). It means that if u is solution of (C.1) such that there exists U_2 travelling wave solution of (C.1) on Ω_2 with

$$\lim_{t \rightarrow +\infty} |u(t, x) - U_2(t, x)| = 0$$

uniformly for $x \in \Omega_2$, then it is impossible to find U_1 travelling wave solution of (C.1) on Ω_1 with

$$\lim_{t \rightarrow +\infty} |u(t, x) - U_1(t, x)| = 0$$

uniformly for $x \in \Omega_1$.

This result is a corollary of the first theorem. Indeed, a travelling wave solution of a bistable reaction-diffusion equation in a cylinder is decreasing exponentially in space. As u tends to a travelling wave uniformly in Ω_2 , we just need to study the following problem

$$\begin{cases} \partial_t \tilde{u} - \nu \Delta \tilde{u} = f(\tilde{u}) & t > 0, x \in \Omega_1 \\ \tilde{u}(0, x) = u(t_0, x) & x \in \Omega_1 \\ \tilde{u}(t, x) = u(t + t_0, x) & t > 0, x \in \Gamma_1 = \partial\Omega_1 \cap \partial\Omega_2 \\ \partial_n \tilde{u} = 0 & t \geq 0, x \in \Gamma_2 = \partial\Omega_1 \setminus \Gamma_1. \end{cases} \quad (\text{C.3})$$

where t_0 has been chosen great enough such that $u(t_0, x) \leq \frac{\theta}{2} e^{-\alpha_0 x_1}$ for some $\alpha_0 > 0$. And thus the preceding theorem applies.

This result justifies our belief that SD are created in the human cortex, but that they can not spread across a large area. In fact, the large and frequent variations of the thickness of the grey matter in the human brain may rapidly stop the spread of an SD. On the contrary, in rat brains, if SD occur, they can spread across the entire cortex without any obstacle. Of course, in reality the grey matter of the cortex has a much more complex geometry than a cylinder whose diameter suddenly increases, but this theorem can be a first step of the proof in a more complicate geometry. In the future, it would be very interesting to show the same result in a cylinder whose diameter follows a sine curve. It would also be of great interest to study the behaviour of a solution of the same bistable reaction-diffusion equation in a cylinder coupled with a simple diffusion equation outside of the cylinder. Indeed, in the human brain, SD can not spread across the white matter, but they can diffuse in it and this diffusion may have an important impact on the spread of the depression in the grey matter.

Let us now prove the theorem.

C.2 Proof of the theorem

C.2.1 Rewritting the problem

First, by [29, 10], we know that u does indeed exist and since $\theta \in]0, \frac{1}{2}[$, the wave has the right propagation sense. In order to prove the theorem, we have to show that :

$$\exists \varepsilon \in]0, 1[\quad \exists \rho > 0 \quad \forall x \in \Omega_1 \quad x_1 > \rho \Rightarrow \forall t \geq 0 \quad |u(t, x)| \leq \varepsilon < 1.$$

1. Note that, by the parabolic maximum principle, $0 \leq u \leq 1$.

2. Let $\eta \in]0, 1[$ be such that

$$\sqrt{-\eta \frac{f'(0)}{\nu}} \leq \alpha_0$$

and let $g(t) = f(t) - \eta f'(0)t$. Note that $f'(0) < 0$. Let $0 < \varepsilon < \theta$ be such that g is non positive on $[0, \varepsilon]$ and positive on $]\varepsilon, 1]$.

3. We are only interested in $u(t, x)$ for $x \in \Omega_1$. Thus instead of studying u on Ω , we can reduce the problem to the study of $\tilde{u}$ on Ω_1 , where $\tilde{u}$ follows the same equations as u but with a Dirichlet boundary condition $\tilde{u} = u$ on $\Gamma_1 = \partial\Omega_1 \cap \partial\Omega_2$. As a matter of fact, by the uniqueness of solutions of this parabolic partial differential equation, we know that for all $x \in \Omega_1$ and for all $t \geq 0$, $\tilde{u}(t, x) = u(t, x)$.

We have reduced the problem to the following system :

$$\begin{cases} \partial_t \tilde{u} - \nu \Delta \tilde{u} - \eta f'(0) \tilde{u} = g(\tilde{u}) & t > 0, x \in \Omega_1. \\ \tilde{u}(0, x) = u_0(x) & x \in \Omega_1. \\ \tilde{u}(t, x) = u(t, x) & t > 0, x \in \Gamma_1. \\ \partial_n \tilde{u} = 0 & t \geq 0, x \in \partial\Omega_1 \setminus \Gamma_1. \end{cases} \quad (\text{C.4})$$

4. Finally, since $\partial_n \tilde{u} = 0$ on $\Gamma_3 = \{x_1 = 0\} \cap \partial\Omega_1$, we can extend $\tilde{u}$ to a function v defined in $\mathbb{R}^+ \times \mathbb{R}^2$ such that v is even across Γ_3 . We thus obtain :

$$\begin{cases} \partial_t v - \nu \Delta v - \eta f'(0) v = g(v) & t > 0, x \in \mathbb{R}_+^* \times \mathbb{R}^2. \\ v(0, x) = \bar{u}_0(x) & x \in \mathbb{R}_+ \times \mathbb{R}^2. \\ v(t, x) = \bar{u}(t, x) & t > 0, x \in \tilde{\Gamma}_1. \\ \partial_n v = 0 & t > 0, x \in \tilde{\Gamma}_2 \end{cases} \quad (\text{C.5})$$

where $\tilde{\Gamma}_1 = \bigcup_{(k,l) \in \mathbb{Z}^2} \{0\} \times [2kR - r, 2kR + r] \times [2lR - r, 2lR + r]$,

$\tilde{\Gamma}_2 = \{0\} \times \mathbb{R}^2 \setminus \tilde{\Gamma}_1$ and $\bar{u}$ denote u extended symmetrically across Γ_3 .

Our goal is to find $\rho > 0$ such that for all $x \in]\rho, +\infty[\times \mathbb{R}^2$ and for all $t \geq 0$, $|u(t, x)| \leq \varepsilon < 1$. The theorem will thus be proved.

C.2.2 Finding the supersolution

The system (C.5) is not easy to solve explicitly, but we just want to overvalue the solution, which is why we decide to search for a supersolution.

1. Using Duhamel's formula, we can rewrite the solution, v , of (C.5) as

$$v(t, x) = w(t, x) + \int_0^t \int_{\mathbb{R}^+ \times \mathbb{R}^2} F(t - \tau, x - \xi) g(v(\tau, \xi)) d\xi d\tau$$

where $w(t, x)$ verifies :

$$\begin{cases} \partial_t w - \nu \Delta w - \eta f'(0)w = 0 & t > 0, x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ w(0, x) = \bar{u}_0(x) & x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ w = u, & t > 0, x \in \tilde{\Gamma}_1. \\ \partial_n w = 0 & t \geq 0, x \in \tilde{\Gamma}_2. \end{cases} \quad (\text{C.6})$$

and $F(t, x)$ is the following Green's function

$$\begin{cases} \partial_t F - \nu \Delta F - \eta f'(0)F = 0 & t > 0, x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ F(0, x) = \delta(x) & x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ F = 0, & t > 0, x \in \tilde{\Gamma}_1. \\ \partial_n F = 0 & t \geq 0, x \in \tilde{\Gamma}_2. \end{cases} \quad (\text{C.7})$$

2. Supersolution of the linear part w :

The solution of (C.6) is overvalued by the solution S of the following stationary system :

$$\begin{cases} -\nu \Delta S - \eta f'(0)S = 0 & x \in \mathbb{R}^+ \times \mathbb{R}^2. \\ S = 1, & x \in \tilde{\Gamma}_1. \\ \partial_n S = 0 & x \in \tilde{\Gamma}_2. \end{cases} \quad (\text{C.8})$$

Now, to bound S , we will use the elementary solution in the whole space of

$$\nu \Delta \varphi + \eta f'(0)\varphi = 0 \quad x \in \mathbb{R}^3$$

that is

$$E(x) = \frac{q}{4\pi} \frac{e^{-q|x|}}{|x|}$$

where $q = \sqrt{-\eta \frac{f'(0)}{\nu}} < \alpha_0$.

Let now

$$Q(x) = \sum_{(k,l) \in \mathbb{Z}^2} \int_{2kR-r}^{2kR+r} \int_{2lR-r}^{2lR+r} E(x - y^*) dy$$

where $y^* = (0, y_1, y_2) \in \mathbb{R}^3$ for $y = (y_1, y_2) \in \mathbb{R}^2$.

We hope to find $\alpha \in \mathbb{R}$ such that αQ overvalues S . It is easy to see that Q is positive, $\partial_n Q = 0$ on $\tilde{\Gamma}_2$, and

$$\nu \Delta Q + \eta f'(0)Q = 0, \quad x \in \mathbb{R}^3.$$

Moreover Q is periodic in x_2 and x_1 of period $2R$.

Finally, it can be proved that Q is continuous and for $x_1 = 0$ and

$(x_2, x_3) \in [-r, r]^2$, $Q(x)$ reaches his minimum on the corners of the square $[-r, r]^2$.

So $\forall x \in \{0\} \times [-r, r] \times [-r, r]$

$$\begin{aligned} Q(x) &\geq \sum_{(k,l) \in \mathbb{Z}^2} \int_{2kR-r}^{2kR+r} \int_{2lR-r}^{2lR+r} \frac{q}{4\pi} \frac{e^{-q\sqrt{(y_1-r)^2 + (y_2-r)^2}}}{\sqrt{(y_1-r)^2 + (y_2-r)^2}} dy_1 dy_2 \\ &\geq \frac{rq}{2\pi\sqrt{2}} e^{-q2\sqrt{2}r}. \end{aligned}$$

So let $\alpha(r, R, q) = \frac{2\pi\sqrt{2}}{rq} e^{q2\sqrt{2}r}$.

Then, for $x \in \tilde{\Gamma}_1$, $\alpha(r, R, q)Q(x) \geq 1$.

Since $q \leq \alpha_0$, $\bar{u}_0 \leq \alpha Q$, and by the parabolic maximum principle, we have $w \leq \alpha Q$.

Moreover, for $x_1 \geq 0$ and $(x_2, x_3) \in [-R, R]^2$, $Q(x)$ reaches his maximum on $(x_2, x_3) = (0, 0)$. Thus

$$\begin{aligned} \alpha Q(x) &\leq \alpha \frac{q}{4\pi} \sum_{(k,l) \in \mathbb{Z}^2} \int_{2kR-r}^{2kR+r} \int_{2lR-r}^{2lR+r} \frac{e^{-q\sqrt{x_1^2 + y_1^2 + y_2^2}}}{\sqrt{x_1^2 + y_1^2 + y_2^2}} dy_1 dy_2 \\ &\leq \alpha \frac{q}{4\pi x_1} \sum_{(k,l) \in \mathbb{Z}^2} \int_{2kR-r}^{2kR+r} \int_{2lR-r}^{2lR+r} e^{-q|y|} dy_1 dy_2 \\ &\leq \frac{\alpha q}{\pi x_1} r^2 e^{q\sqrt{2}r} \left(\sum_{(k,l) \in \mathbb{Z}^2} e^{-q2R\sqrt{k^2 + l^2}} \right) \end{aligned}$$

by changing the variable in the integral and using the triangular inequality. Finally, we obtain

$$\alpha Q(x) \leq \frac{2\sqrt{2}r}{x_1} e^{3q\sqrt{2}r} \left(\sum_{(k,l) \in \mathbb{Z}^2} e^{-q2R\sqrt{k^2 + l^2}} \right).$$

And so, if

$$\rho_1(r, R, q) = \frac{4\sqrt{2}r}{\varepsilon} e^{3q\sqrt{2}r} \left(\sum_{(k,l) \in \mathbb{Z}^2} e^{-q2R\sqrt{k^2 + l^2}} \right)$$

then

$$\forall x \in \Omega_1 \quad x_1 > \rho_1 \Rightarrow \alpha Q(x) \leq \frac{\varepsilon}{2}.$$

3. Supersolution of the nonlinear part :

To begin with, we know that F is positive. Now, we want to overvalue the second part of $v(t, x)$ in Duhamel's formula, so we can replace g by $\tilde{g}$ where $\tilde{g} = g$ if $g \geq 0$ and $\tilde{g} = 0$ if $g < 0$, so $\tilde{g} = 0$ on $[0, \varepsilon]$.

Now let

$$G(t, x) = \frac{1}{(4\nu\pi t)^{\frac{3}{2}}} e^{-\frac{|x|^2}{4\nu t}} e^{\eta f'(0)t}$$

for $t > 0$ and $x \in \mathbb{R}^3$. We have

$$\begin{cases} \partial_t G - \nu \Delta G - \eta f'(0)G = 0 & t > 0, x \in \mathbb{R}^3 \\ G(0, \cdot) = \delta \end{cases}$$

Again, G is positive and radial, and by the parabolic maximum principle, $G \geq F$. Thus :

$$\int_0^t \int_{\mathbb{R}^+ \times \mathbb{R}^2} F(t - \tau, x - \xi) g(v(\tau, \xi)) d\xi d\tau \leq \int_0^t \int_{\mathbb{R}^+ \times \mathbb{R}^2} G(t - \tau, x - \xi) \tilde{g}(v(\tau, \xi)) d\xi d\tau.$$

4. Conclusion :

$$v(t, x) \leq \underbrace{\alpha(r, R, q)Q(x)}_{=I(x)} + \underbrace{\int_0^t \int_{\mathbb{R}^+ \times \mathbb{R}^2} G(t - \tau, x - \xi) \tilde{g}(v(\tau, \xi)) d\xi d\tau}_{=J(t, x)}$$

Remember that we want to find a $\rho > 0$ such that

$$\forall t \geq 0 \quad \forall x \in \Omega_1, \quad x_1 > \rho \Rightarrow v(t, x) \leq \varepsilon.$$

For $x \in \mathbb{R}_+ \times \mathbb{R}^2$, we set

$$t_x = \sup\{t \geq 0 \mid \forall \tau \in [0, t] \quad v(\tau, x) \leq \varepsilon\} \in \bar{\mathbb{R}}_+^*.$$

Our aim is to find $\rho > 0$ such that $\forall x \in \Omega_1 \quad x_1 > \rho \Rightarrow t_x = +\infty$.

Then for all $\rho > 0$, let

$$T(\rho) = \inf_{x \in]\rho, \infty[\times \mathbb{R}^2} t_x \in \bar{\mathbb{R}}_+.$$

We will try to find conditions on r , R and ν such that

$$\exists \rho > 0 \quad T(\rho) = +\infty.$$

The theorem will thus be proved.

We recall that we have already shown that

$$\exists \rho_1(r, R, q) > 0 \quad \forall x \in \Omega_1 \quad x_1 > \rho_1(r, R, q) \Rightarrow I(x) \leq \frac{\varepsilon}{2}.$$

C.2.3 Over-estimation of $J(t, x)$

1. First, let us show that for $\rho \geq \rho_1(r, R, q)$, $T(\rho) > 0$.

For all $\rho \geq \rho_1(r, R, q)$, if $T(\rho) = 0$, then there exists $x_n \in]\rho, +\infty[\times \mathbb{R}^2$ and $t_n \in]0, \frac{1}{n}[$ such that $v(t_n, x_n) > \varepsilon$, which means $J(t_n, x_n) > \frac{\varepsilon}{2}$. But

$$\begin{aligned} J(t_n, x_n) &= \int_0^{t_n} \int_{\mathbb{R}^+ \times \mathbb{R}^2} G(t_n - \tau, x_n - \xi) \tilde{g}(v(\tau, \xi)) d\xi d\tau \\ &\leq M t_n \xrightarrow{n \rightarrow +\infty} 0 \end{aligned}$$

where $M = \sup\{g(t), t \in [0, 1]\}$, which is absurd.

Thus for all $\rho \geq \rho_1(r, R, q)$, $T(\rho) > 0$.

2. We suppose *ad absurdum* that

$$\forall \rho \geq \rho_1(r, R, q) \quad T(\rho) < +\infty.$$

Let $\rho \geq \rho_1(r, R, q)$ be fixed. We will write T instead of $T(\rho)$.

• There exists $x_n \in]\rho, +\infty[\times \mathbb{R}^2$ and $t_n \in]T, T + \frac{1}{n}[$ such that $J(t_n, x_n) > \frac{\varepsilon}{2}$. But

$$\begin{aligned} J(t_n, x_n) &= \int_T^{t_n} \int_{\mathbb{R}^+ \times \mathbb{R}^2} G(t_n - \tau, x_n - \xi) \tilde{g}(v(\tau, \xi)) d\xi d\tau \\ &\quad + \underbrace{\int_0^T \int_{\mathbb{R}^+ \times \mathbb{R}^2} G(t_n - \tau, x_n - \xi) \tilde{g}(v(\tau, \xi)) d\xi d\tau}_{=K(t_n, x_n)} \end{aligned}$$

The first part of this equation tends to 0 as $n \rightarrow +\infty$ as in the case $T = 0$.

• Now

$$K(t_n, x_n) = \int_0^T \int_{[0, \rho] \times \mathbb{R}^2} G(t_n - \tau, x_n - \xi) \tilde{g}(v(\tau, \xi)) d\xi d\tau$$

because $\tilde{g} = 0$ on $[0, \varepsilon]$ and $v \leq \varepsilon$ on $] \rho, +\infty[\times \mathbb{R}^2$. So

$$\begin{aligned}
K(t_n, x_n) &\leq M \int_0^T \int_{[0, \rho] \times \mathbb{R}^2} G(t_n - \tau, x_n - \xi) d\xi d\tau \\
&= \frac{M}{\pi^{\frac{3}{2}}} \int_0^{+\infty} \int_{[\frac{x_n^1 - \rho}{\sqrt{4\nu\tau}}, \frac{x_n^1}{\sqrt{4\nu\tau}}] \times \mathbb{R}^2} e^{-|z|^2} e^{\eta f'(0)\tau} dz d\tau \\
&\leq \frac{M}{\pi^{\frac{3}{2}}} \int_0^{+\infty} \int_{\frac{-\rho}{2\sqrt{4\nu\tau}}^{\frac{\rho}{2\sqrt{4\nu\tau}}}} e^{-z_1^2} e^{\eta f'(0)\tau} dz_1 d\tau
\end{aligned}$$

where again $M = \sup\{g(t), t \in [0, 1]\}$.

And from Lebesgue's theorem, this integral tends to 0 when ρ tends to 0.

Hence there exists $\rho_2(\nu) > 0$ such that

$$\forall \rho < \rho_2(\nu) \quad K(t_n, x_n) \leq \frac{\varepsilon}{4}.$$

C.2.4 Conclusion

If there exists r, R and ν such that $\rho_2(\nu) > \rho_1(r, R, q)$, then we can find $\rho > 0$ such that $T(\rho) = +\infty$.

For R and $\sqrt{\nu}$ fixed, $\rho_1(r, R, q) \xrightarrow{r \rightarrow 0} 0$. As a conclusion, if r is small enough with respect to R and $\sqrt{\nu}$, we have $\rho_2(\nu) > \rho_1(r, R, q)$ and the theorem is proved. As a remark, we can add that the solution u of this theorem is in fact decreasing toward zero exponentially in time.

C.2.5 Proof in two dimensions

The same theorem holds in a 2 dimensions space. The proof is almost identical, even if the Green's functions are not exactly the same.

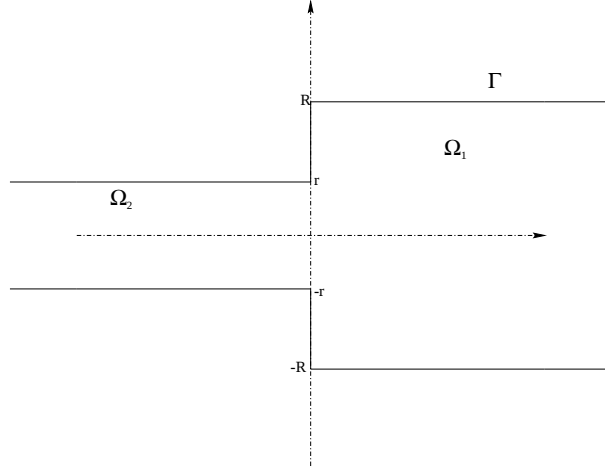
In order to be clear, we again have to define the domain Ω in $\mathbb{R}^2$ (figure C.2.5). Let

$$\begin{aligned}
0 &< r \leq R, \\
\Omega_1 &= \mathbb{R}_+^* \times]-R, R[, \quad \Omega_2 = \mathbb{R}_- \times]-r, r[, \\
\Omega &= \Omega_1 \cup \Omega_2 \quad \text{and} \quad \Gamma = \partial\Omega.
\end{aligned}$$

From now on, we use the same notations as in the 3 dimensions case, but with a 2 as index. Then the same simplifications holds and with the Duhamel's formula, we obtain

$$v_2(t, x) = w_2(t, x) + \int_0^t \int_{\mathbb{R}^+ \times \mathbb{R}} F_2(t - \tau, x - \xi) g(v_2(\tau, \xi)) d\xi d\tau$$

where $w_2(t, x)$ verifies :

FIG. C.2 – Domain Ω in $\mathbb{R}^2$.

$$\begin{cases} \partial_t w_2 - \nu \Delta w_2 - \eta f'(0) w_2 = 0 & t > 0, x \in \mathbb{R}^+ \times \mathbb{R}. \\ w_2(0, x) = \bar{u}_0(x) & x \in \mathbb{R}^+ \times \mathbb{R}. \\ w_2 = \bar{u}, & t > 0, x \in \tilde{\Gamma}_1. \\ \partial_n w_2 = 0 & t \geq 0, x \in \tilde{\Gamma}_2. \end{cases} \quad (\text{C.9})$$

and $F_2(t, x)$ is the following Green's function

$$\begin{cases} \partial_t F_2 - \nu \Delta F_2 - \eta f'(0) F_2 = 0 & t > 0, x \in \mathbb{R}^+ \times \mathbb{R}. \\ F_2(0, x) = \delta(x) & x \in \mathbb{R}^+ \times \mathbb{R}. \\ F_2 = 0, & t > 0, x \in \tilde{\Gamma}_1. \\ \partial_n F_2 = 0 & t \geq 0, x \in \tilde{\Gamma}_2. \end{cases} \quad (\text{C.10})$$

As in the preceding case, we try to find supersolution of w_2 and F_2 . We employ the same technics, but G becomes

$$G_2(t, x) = \frac{1}{4\nu\pi t} e^{-\frac{|x|^2}{4\nu t}} e^{\eta f'(0)t} \quad \text{for } t > 0 \text{ and } x \in \mathbb{R}^2.$$

and E is now $E_2(x) = iH_0^{(1)}(iq|x|)$ where $H_0^{(1)}$ is the Hankel's function of type 1 and order 0. Once again, E has a singularity in $\frac{1}{\sqrt{|x|}}$ and

$$E(x) \underset{|x| \rightarrow +\infty}{\sim} \sqrt{\frac{2}{\pi}} \frac{e^{-q|x|}}{\sqrt{q|x|}}.$$

So E is integrable on $0 \times \mathbb{R}^2$. With the same type of inequalities, we find that, if r

is small enough, we can take

$$\alpha(r, R, q) = \frac{1}{2rE((0, 2r))}.$$

At last, we find

$$\rho_1(r, R, q) = r \frac{2e^{2qr}}{\pi E((0, 2r))^2 \varepsilon^2} \left(\sum_{k \in \mathbb{Z}} e^{-q2|k|R} \right)^2$$

and the end of the proof is exactly the same as in 3 dimensions.

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Annexe D

Existence and non-existence of curved front solution of a biological equation

G. Chapuisat¹

D.1 Introduction

The existence of travelling fronts solutions of reaction-diffusion equations and the convergence of solutions toward these fronts is an important mathematical problem. Indeed reaction-diffusion equations take place in a lot of physical or biological models such as combustion, cinetic, genetic. See [3] or [63] for a list of examples. Here we will have interest in the following equation.

$$\frac{\partial u}{\partial t} - \Delta u = g(u)\mathbb{1}_\Omega - \alpha u\mathbb{1}_{\mathbb{R}^N \setminus \Omega}, \quad t \in \mathbb{R}, X \in \mathbb{R}^N, \quad (\text{D.1})$$

where $g(u) = \lambda u(u - \theta)(1 - u)$ is the usual bistable nonlinearity with $\theta \in]0, 1[$, $\mathbb{1}$ is a characteristic function and Ω is a cylinder of radius $R > 0$.

This equation comes from the modelling of spreading depressions (SD) [15]. SD are travelling waves that appear in the brain of a lot of species during stroke, migraine with aura or epilepsy [?]. SD follow a reaction-diffusion mechanism in the gray matter of the brain and are progressively absorbed in the white matter [?]. Experiments on rodent brain have shown the great importance of SD on the after-effects of stroke [66]. One question of biologists is the existence of these SD in the human brain where the thickness of the layer of gray matter is smaller than in other species [5, 85].

¹Article soumis

First let us introduce some notations that will be used in the following.

For any $n \geq 1$, $B(X, r)$ will designate the ball of center $X \in \mathbb{R}^n$ and radius $r \geq 0$ for the euclidian norm in $\mathbb{R}^n$.

In this paper, we work in $\mathbb{R}^N$ with $N \geq 2$ and we will take $\Omega = \mathbb{R} \times B(0, R)$ an infinite cylinder of radius $R > 0$.

The space variable $X \in \mathbb{R}^N$ will be written $X = (x, z)$ with $x \in \mathbb{R}$ the direction of the axis of the cylinder and $z \in \mathbb{R}^{N-1}$ the cross direction.

We will note $\partial_t u$ the derivation with respect to t and $\partial_x u$ the derivation with respect to x .

Precisely, we study the bounded solutions of the following problem that are C^1 with respect to $X \in \mathbb{R}^N$.

$$(P) \begin{cases} \partial_t u - \Delta u = g(u) \mathbb{1}_{\{|z| \leq R\}} - \alpha u \mathbb{1}_{\{|z| > R\}} & t > 0, (x, z) \in \mathbb{R}^N, \\ u(t = 0, x, z) = u_0(x, z) & (x, z) \in \mathbb{R}^N, \\ u(t, x, z) \rightarrow 0 \text{ for } |z| \rightarrow +\infty, & t > 0, x \in \mathbb{R}. \end{cases}$$

The main question is the existence or not of travelling fronts solutions in function of the radius of the cylinder R .

A travelling front solution of (D.1) is a function U of $\mathbb{R}^N$ such that $u(t, x, z) = U(x - ct, z)$ is a solution of (D.1) for a constant $c \in \mathbb{R}$ with moreover $\lim_{x \rightarrow -\infty} U(x, z)$ and $\lim_{x \rightarrow +\infty} U(x, z)$ exist and are distinct. All the limits are supposed uniform. A travelling front is thus a C^1 -solution of the following system for a constant $c \in \mathbb{R}$ to be determined

$$(TF) \begin{cases} \Delta U + c \partial_x U + g(U) \mathbb{1}_{\{|z| \leq R\}} - \alpha U \mathbb{1}_{\{|z| > R\}} = 0 & (x, z) \in \mathbb{R}^N, \\ U(x, z) \rightarrow 0 \text{ when } |z| \rightarrow \infty, & x \in \mathbb{R}. \end{cases}$$

A first natural question is the existence of the asymptotic profiles $\phi_{\pm} = \lim_{x \rightarrow \pm\infty} U$. These functions are solutions of the problem :

$$(P_{\infty}) \begin{cases} \Delta_z \phi + g(U) \mathbb{1}_{\{|z| \leq R\}} - \alpha U \mathbb{1}_{\{|z| > R\}} = 0, & z \in \mathbb{R}^{N-1}, \\ \phi(z) \xrightarrow{|z| \rightarrow \infty} 0. \end{cases}$$

0 is clearly a solution of this equation, but a travelling front must have two different profiles at $-\infty$ and $+\infty$.

In this paper, we will prove the following two theorems depending on the dimension N .

Théorème D.1 *If $N = 2$, there exist $R_0 > 0$ such that :*

- *if $R < R_0$, $\phi \equiv 0$ is the only C^1 -solution of (P_{∞}) ,*
- *if $R > R_0$, (P_{∞}) admits at least 3 C^1 -solutions 0, ϕ_- and ϕ_+ .*

Théorème D.2 *If $N \geq 3$, there exist $R_1 \geq R_0 > 0$ such that*

- if $R < R_0$, $\phi \equiv 0$ is the only radial C^1 -solution of (P_∞) ,*
- if $R > R_1$, (P) admits at least 2 C^1 -solutions 0 and $\phi > 0$.*

There is an easy corollary of these theorems.

Corollaire D.1 *If $N = 2$ (resp. $N \geq 3$), there exists no travelling wave (resp. no cylindrical travelling wave) solution of (D.1) for $R < R_0$.*

Now the problem of the existence of a travelling front when there exist possible different limits is more complicate. There are two possible approaches. One use essentially the maximum principle and/or some linearizations, the other use energy estimates in travelling referentials.

Historically, the study of travelling front and of convergence in one dimension in space begins with Aronson and Weinberger in [3] and Fife and McLeod in [29, 30]. They worked in the phase plane to obtain the existence of a travelling front and then used sub- and super-solutions to prove the convergence toward these fronts. Then Berestycki and Nirenberg [10], Vega [?] and Roquejoffre [77] studied travelling fronts in cylinders and the convergence of solutions toward these fronts for various boundary conditions. In these papers, they use maximum principles, but they also study the linearized equation so they have to work on bounded cylinders. Finally, Hamel, Monneau and Roquejoffre studied the conical fronts of reaction-diffusion equation [42]. They work on $\mathbb{R}^N$, but their proof use the existence of travelling front in one dimension in space. Indeed a conical front looks like a planar front at infinity and the progression of the conical front is mostly influenced by the behaviour of the front at infinity. So they a priori know the speed of the conical front and thus they can use sub- and super-solutions to construct it.

Another approach has been developped by Emmanuel Risler in [75]. In this work, he has interest in vectorial travelling front in one dimension in space. This type of travelling front arises in chemical kinetic. The problem is that these systems have no maximum principle. A possible solution to deal with the existence of multidimensional travelling fronts is to use the Leray-Schauder index as Volpert and Volpert do in [89], but for compacity reasons they have to work on cylinders with a bounded radius, moreover they do not have any result for the convergence toward these fronts. On the other hand, Risler proves the existence of travelling fronts and the “convergence” toward them with an energy method in a travelling referential for special initial conditions. In fact, the point is to find a travelling referential where a solution of (P) will tends to a constant non-zero solution. An interesting point of his method is that he does not need to a priori know the travelling speed, he determines it by studying the energy of the solution in various referentials.

In our case, there exists a maximum principle (see appendix in section D.12), but there are two difficulties. First we work on $\mathbb{R}^N$ and not on a cylinder with a bounded radius, so most compacity properties are lost. This is not completely true since

we work with exponentially decreasing functions so the compacity can very likely be proved. Second the speed of the travelling front is totally unknown. Indeed the behaviour of the front is mostly influenced by the “absorption” part of the equation and that could not be linked with any travelling front in one dimension (for which the speed is well known). So here we have decided to use the method developped by Risler in [75] with some simplifications due to the maximum principle. We will prove the following main existence theorem.

Théorème D.3 *There exists $R_1 \geq R_0 > 0$ such that for all $R > R_1$ equation (D.1) has a travelling front solution of speed $c > 0$.*

In the next section, we will make a list of the properties of the solutions of (P) that will be used throughout the paper. Then in section D.3, we will study the possible asymptotic profiles of the fronts in the propagation direction and prove the theorems D.1 and D.2. This will enable us to conclude with the nonexistence of travelling front of (D.1) if the radius of the cylinder R is small enough. Then in sections D.4 to D.9, we will construct a travelling front of (D.1) as a limit of the solution of (P) for some special initial condition. And finally we will prove that such initial conditions exist for R large enough in section D.10.

D.2 Preliminaries

D.2.1 Some definitions

In the following, we will study the solution of problem (P) in the uniformly local Sobolev space $H_{\text{ul}}^1(\mathbb{R}^N, \mathbb{R})$, introduced by Kato in [52], but this presentation can easily be adapted in $C^1(\mathbb{R}^N, \mathbb{R})$.

First we recall the definition of the uniform Sobolev spaces. For $k \in \mathbb{N}$, we set

$$H_{\text{ul}}^k(\mathbb{R}^N, \mathbb{R}) = \left\{ u \in H_{\text{loc}}^k(\mathbb{R}^N, \mathbb{R}) \mid \|u\|_{H_{\text{ul}}^k} < +\infty, \lim_{X \rightarrow 0} \|T_X u - u\|_{H_{\text{ul}}^k} = 0 \right\}$$

where $T_X u(Y) = u(Y - X)$ and $\|u\|_{H_{\text{ul}}^k} = \sup_{X \in \mathbb{R}^N} \|u|_{B(X,1)}\|_{H^k(B(X,1), \mathbb{R})}$.

$H_{\text{ul}}^k(\mathbb{R}^N, \mathbb{R})$ is a Banach space and C_b^∞ is dense in $H_{\text{ul}}^k(\mathbb{R}^N, \mathbb{R})$.

Now we introduce the space H of H_{ul}^1 functions exponentially decreasing with respect to $|z|$ by

$$H = \left\{ u \in H_{\text{ul}}^1(\mathbb{R}^N, \mathbb{R}) \mid \exists C > 0, 0 \leq u \leq \min(1, Ce^{-\beta|z|}) \text{ and } |\nabla u| \leq Ce^{-\beta|z|} \right\}$$

where $\beta = \frac{N-1}{2R} + \sqrt{\left(\frac{N-1}{2R}\right)^2 + \alpha}$.

D.2.2 Existence of solutions and regularity

First, if $u_0 \in H$, there exists a global solution of (P) . Indeed, 0 and 1 are respectively sub- and supersolutions of (P) and according to the comparison principle, we can easily construct a global solution of (P) (see [28] or [82]).

In the following, u will always refer to the solution of (P) when u_0 has been specified. We will note $u(t)$ the function $(x, z) \mapsto u(t, x, z)$.

For all $t \geq 0$, $u(t) \in H$. Indeed, by the comparison principle, we have $0 \leq u \leq 1$ and according to the choice of β , $(t, x, z) \mapsto Ce^{-\beta|z|}$ is also a supersolution of (P) for C large enough, so $u(t, x, z) \leq Ce^{-\beta|z|}$ for all $t \geq 0$ and all $(x, z) \in \mathbb{R}^N$. Then we can use local estimates to bound the gradient.

In addition, we have the mild equation

$$(M) \quad u(t, X) = \int_{\mathbb{R}^N} \mathcal{G}(t, X - \xi) u_0(\xi) d\xi + \int_0^t \int_{\mathbb{R}^N} \mathcal{G}(t - \tau, X - \xi) \tilde{g}(u(\tau, \xi), \xi) d\xi d\tau$$

where $\mathcal{G}(t, X) = \frac{1}{(4\pi t)^{\frac{N}{2}}} e^{-\frac{|X|^2}{4t}} e^{-\alpha t}$ and $\tilde{g}(u, z) = (g(u) + \alpha u) \mathbb{1}_{|z| \leq R}$.

Since $\tilde{g}$ is bounded, it is easy to prove that $u \in C^0([0, +\infty[, H)$ and that we have

$$\sup_{t \geq 0} \|u(t)\|_{H_{ul}^1} < +\infty. \quad (D.2)$$

Another important point that will be used several times is the bound on the gradient of u . Indeed there exists $M_0 > 0$ independant of $u_0 \in H$ such that

$$\forall t > 0 \quad \forall X \in \mathbb{R}^N \quad |\nabla u(t, X)| \leq M_0. \quad (D.3)$$

Moreover u has regularity properties.

First for all $t > 0$, $u(t) \in C_b^{1,\epsilon}(\mathbb{R}^N)$ and

$$\forall \epsilon > 0 \quad \sup_{t \geq \epsilon} \|u(t)\|_{C_b^{1,\epsilon}(\mathbb{R}^N)} < +\infty.$$

Second, u is clearly Hölder-continuous with respect to $t > 0$ and this continuity is uniform in $X \in \mathbb{R}^N$. Moreover, except in $|z| = R$, u is C^1 (and even C^∞) with respect to $t \in]0, +\infty[$ and $\partial_t u$ is uniformly bounded. Thus we can prove that

$$u \in C^1(]0, +\infty[, L_{ul}^2). \quad (D.4)$$

D.2.3 Compactness

In this presentation, we will use several times the following compactness argument. Let us fix $u_0 \in H$. For any sequences $(x_n)_{n \in \mathbb{N}}$ and $(t_n)_{n \in \mathbb{N}}$ with $x_n \in \mathbb{R}$ and $t_n \geq 0$, $t_n \xrightarrow{n \rightarrow +\infty} +\infty$, we define

$$w_n(x, z) = u(t_n, x + x_n, z) \quad \text{and} \quad \bar{w}_n(x, z) = \partial_t u(t_n, x + x_n, z)$$

for $(x, z) \in \mathbb{R}^N$ and any $n \in \mathbb{N}$.

According to the regularity properties above, and up to extraction, there exists $w_\infty \in H_{\text{ul}}^1(\mathbb{R}^N)$ and $\bar{w}_\infty \in L_{\text{ul}}^2(\mathbb{R}^N)$ such that for all $L > 0$,

$$w_n \rightarrow w_\infty \quad \text{in } H^1(B(0, L)) \quad \text{and} \quad \bar{w}_n \rightarrow \bar{w}_\infty \quad \text{in } L^2(B(0, L)).$$

And by passing to the limit in equation (1), we have

$$\bar{w}_\infty = \Delta w_\infty - \alpha w_\infty + \tilde{g}(w_\infty, z)$$

Hence the convergence of $(w_n)_{n \in \mathbb{N}}$ is even H_{ul}^2 .

D.2.4 Sketch of the proof

First let us rewrite the problem (P).

$$(P) \quad \begin{cases} \partial_t u - \Delta u + f(u, z) = 0 & t > 0, (x, z) \in \mathbb{R}^N, \\ u(t = 0, x, z) = u_0(x, z) & (x, z) \in \mathbb{R}^N, \\ u(t, x, z) \rightarrow 0 \text{ for } |z| \rightarrow \infty, & t > 0, x \in \mathbb{R}, \end{cases}$$

where

$$f(u, z) = \begin{cases} -g(u) & \text{if } |z| \leq R, \\ \alpha u & \text{if } |z| > R. \end{cases}$$

We will assume $\theta < 1/2$. We define the “potential functions” $F(u, z) = \int_0^u f(v, z) dv$ and $G(u) = \int_0^u g(v) dv$.

First, we will study the possible asymptotic profiles of the fronts in the propagation direction in dimension $N = 2$ in space. The problem is to glue a solution of the equation $u'' + g(u) = 0$ with a solution of $u'' - \alpha u = 0$ in $z = \pm R$. We will prove theorem D.1 by studying the solution of these equations in the phase plane. Then we will use this result to construct a subsolution in higher dimension. This will prove theorem D.2.

Let us remark that in theorem D.2, we have added the hypothesis that we consider only radial or cylindrical solutions of our equations, but this fact could very likely be suppressed by adapting the results of Gidas, Ni and Nirenberg [34] and Berestycki and Nirenberg [11] to the case of an unbounded domain with an exponential decrease.

The proof of theorem D.3 will have six steps and actually we will prove the following theorem.

Théorème D.4 *Let us fix a sequence $(t_n)_{n \in \mathbb{N}}$ with $t_n \geq 0$ such that $t_n \rightarrow +\infty$. There exists $\delta > 0$ such that if $u_0 \in H$ verifies*

$$\limsup_{x \rightarrow +\infty} \int_{x-1}^{x+1} \int_{\mathbb{R}^{N-1}} (u_0(x, z)^2 + |\nabla u_0(x, z)|^2) dz dx \leq \delta$$

and

$$\int_L^0 \int_{\mathbb{R}^{N-1}} \frac{|\nabla u_0(x, z)|^2}{2} + F(u_0(x, z), z) dz dx \xrightarrow{L \rightarrow +\infty} -\infty,$$

there exists $\tilde{x}(t)$ independant of the sequence $(t_n)_{n \in \mathbb{N}}$ and U a travelling front of speed $c > 0$ with $U \xrightarrow{x \rightarrow +\infty} 0$ and $U \xrightarrow{x \rightarrow -\infty} \phi > 0$, such that for all $L > 0$, up to extraction,

$$\sup_{y \in [-L, +\infty[, z \in \mathbb{R}^{N-1}} |u(t_n, \tilde{x}(t_n) + y, z) - U(y, z)| \xrightarrow{n \rightarrow +\infty} 0.$$

Moreover, $\tilde{x}'(t) \xrightarrow{t \rightarrow +\infty} c$.

First in the section D.4, we will prove that there exists a maximal speed $c_{max} > 0$ such that if the initial condition u_0 of problem (P) is near 0 far to the right, then any more stable state could not invade 0 faster than the speed c_{max} . The fact that the solution is “near 0” is defined using energy. Then in section D.5, we can define the point $\tilde{x}(t)$ where the solution escape from 0 in the energy sense. The first problem will be to prove that this escape point travels with an asymptotic constant speed. We will study the speed of the escape point using the energy of the solution in several different referentials. So the section D.6 is devoted to the definition of the energy in a travelling referential and to the proof of several energy estimates. Then in section D.7, we prove by contradiction that the escape point travels with a constant speed $c > 0$ for $t \rightarrow +\infty$. If it was not the case, then there would exist a travelling referential in which the escape point makes large excursions to the left followed by large excursions to the right. This would contradict the energy estimates established in the preceding sections. Indeed large excursions of the escape point to the left mean that the energy of the solution is bounded from below by 0 and large excursions to the right imply a strong dissipation. Once we know the asymptotic speed of the escape point, we will be able to prove the convergence of the solution toward a stationnary solution in a referential travelling at speed c with energy methods in sections D.8 and D.9. Finally, in section D.10, we will have to prove that there exist initial conditions that verifies the hypothesis of theorem D.4. So we will have to study the energy of the asymptotic profiles of the front in the propagation direction. We will prove that for $R > 0$ large enough there exists an asymptotic profile more stable than 0 and then construct an initial condition that suits.

D.3 Profile of a travelling front at infinity

Before studying the existence of travelling fronts, we will study their possible asymptotic profiles in the direction of propagation. This will be sufficient to prove theorem D.1. Indeed we will prove that 0 is the only possible profile at infinity if the radius R of the cylinder is small enough, and by definition a travelling front must have two different profiles at $+\infty$ and $-\infty$. This section is thus concerned with the existence of non-zero profile at infinity for travelling front solution of (D.1).

A travelling front solution of (D.1) is a solution of the following system

$$(TF) \begin{cases} \Delta U + c \frac{\partial U}{\partial x} + g(U) \mathbb{1}_{\{|z| \leq R\}} - \alpha U \mathbb{1}_{\{|z| > R\}} = 0 & (x, z) \in \mathbb{R}^N, \\ U(x, z) \rightarrow 0 \text{ when } |z| \rightarrow \infty, & x \in \mathbb{R}, \end{cases}$$

for a $c \in \mathbb{R}$ and where $\lim_{x \rightarrow -\infty} U(x, z)$ and $\lim_{x \rightarrow +\infty} U(x, z)$ exist and are distinct. In this section, we are thus interested in the following problem.

$$(P_\infty) \begin{cases} \Delta \phi + g(\phi) \mathbb{1}_{\{|z| \leq R\}} - \alpha \phi \mathbb{1}_{\{|z| > R\}} = 0 & z \in \mathbb{R}^{N-1}, \\ \phi(z) \xrightarrow{|z| \rightarrow \infty} 0. \end{cases}$$

Of course, $\phi = 0$ is a solution. The problem is to determine if there exist other solutions of (P_∞) .

D.3.1 Case of dimension $N = 2$: proof of theorem D.1

If $N = 2$, the system (P_∞) becomes an ordinary differential equation.

$$(ode1) \begin{cases} \phi'' + g(\phi) \mathbb{1}_{\{|z| \leq R\}} - \alpha \phi \mathbb{1}_{\{|z| > R\}} = 0 & y \in \mathbb{R}, \\ \phi(z) \xrightarrow{|z| \rightarrow \infty} 0. \end{cases}$$

We want to prove that there exist $R_0 > 0$ such that :

- if $R < R_0$, $\phi \equiv 0$ is the only C^1 -solution of $(ode1)$,
- if $R > R_0$, $(ode1)$ admits at least 3 C^1 -solutions 0, ϕ_- and ϕ_+ .

Let us define

$$(E_1) \quad \phi'' + g(\phi) = 0$$

and

$$(E_2) \quad \phi'' - \alpha \phi = 0.$$

In order to obtain a solution of $(ode1)$, we have to glue a solution of (E_1) with a solution of (E_2) in $z = R$ and $z = -R$ so that the solution we obtain is C^1 .

The solutions of (E_2) are well known :

$$\phi(z) = Ae^{-\sqrt{\alpha}z} + Be^{\sqrt{\alpha}z}$$

for some A and B in $\mathbb{R}$. Since $\phi(z) \xrightarrow{|z| \rightarrow \infty} 0$ and $0 \leq \phi \leq 1$ by the maximum principle (see appendix in section D.12), we must have $\phi(z) = Be^{\sqrt{\alpha}z}$ for some $B \in [0, e^{\sqrt{\alpha}R}]$ for $z < -R$, and $\phi(z) = Ae^{-\sqrt{\alpha}z}$ for some $A \in [0, e^{\sqrt{\alpha}R}]$ for $z > R$.

The problem is to find a solution of (E_1) such that

$$(BC_1) \quad \phi'(-R) = \sqrt{\alpha}\phi(-R) \text{ and } \phi'(R) = -\sqrt{\alpha}\phi(R).$$

We will work in the phase plane of (E_1) . By multiplying (E_1) by ϕ' and integrating, we have

$$\frac{1}{2}\phi'(z)^2 + G(\phi(z)) = \frac{1}{2}\phi'(0)^2 + G(\phi(0))$$

where $G(s) = \int_0^s g(t)dt$ is the potential function. Remember that $\theta < 1/2$. An example of phase plane for (E_2) is given figure D.1.

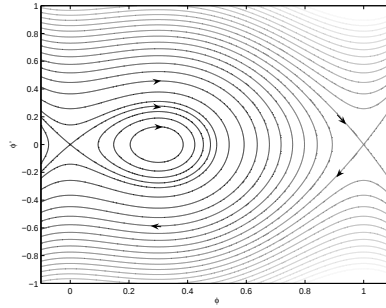


FIG. D.1 – An example of phase plane for (E_1)

It is easy to prove that (BC_1) is equivalent to

$$(BC_2) \quad \phi'(0) = 0 \text{ and } \phi'(R) = -\sqrt{\alpha}\phi(R).$$

Before we turn to the proof of the existence of a solution of (E_1) that verifies (BC_2) , we need some definitions.

First we will say that a trajectory of (E_1) is an acceptable trajectory if it cuts the x-axis of the phase plane between $[0, 1]$.

Now for any $\phi_c \in [0, +\infty[$, we will note Φ the trajectory of the phase plane of (E_1) that goes through the point $(\phi_c, -\sqrt{\alpha}\phi_c)$. ϕ_c is thus the abscissa of an intersection of the trajectory ϕ of (E_1) and the line $\phi' = -\sqrt{\alpha}\phi$ in the phase plane.

We define ϕ_{max} in $]0, 1[$ such that for all $\phi_c \in [0, \phi_{max}]$ the trajectory Φ is an acceptable trajectory and for any $\varepsilon > 0$ the trajectory ϕ for $\phi_c = \phi_{max} + \varepsilon$ is not a potential trajectory (see figure D.2).

For $\phi_c \in]0, \phi_{max}[$, we note ϕ_0 the abscissa of the intersection of Φ and the x-axis in $[\theta, 1]$. Remark that since $\phi_0 \in [\theta, 1]$, it is unique.

Finally for $\phi_c \in]0, \phi_{max}[$, we define $T_c(\phi_c) \in [0, +\infty]$ the minimal time for the trajectory Φ to join $(\phi_0, 0)$ to $(\phi_c, -\sqrt{\alpha}\phi_c)$.

The problem is now to know if there exists $\phi_c \in]0, \phi_{max}[$ such that $T_c(\phi_c) = R$. Precisely, our goal will be to show that the graph of T_c in function of ϕ_c lies above a line $T_c = R_0$ and moreover that it tends to infinity on both extremities of $[0, \phi_{max}]$. This will indeed proves theorem D.1.

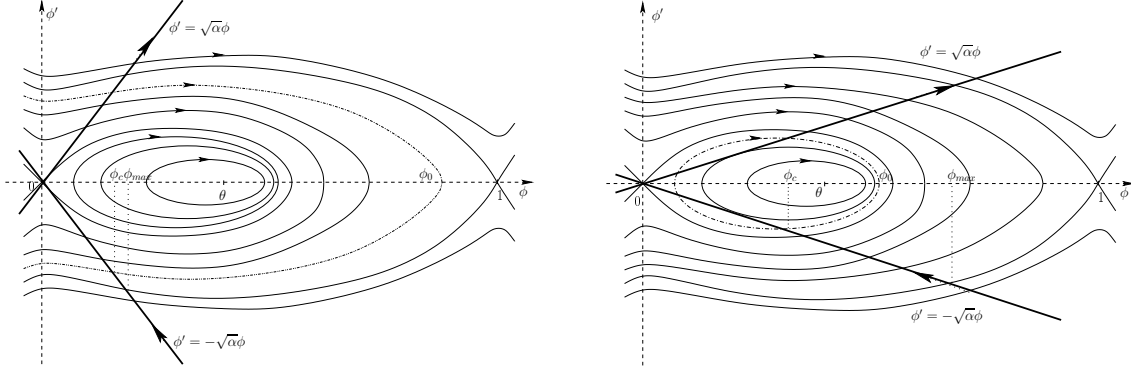


FIG. D.2 – Superposition of the phase plane for (E_1) and of the trajectories of (E_2) . Left for $\sqrt{\alpha} \geq \theta$ and right for $\sqrt{\alpha} < \theta$.

Let us first study the nonzero trajectory that cuts $\phi' = -\sqrt{\alpha}\phi$ in $\phi_c = 0$. This trajectory takes an infinite time to reach the stable equilibrium 0, so $T_c(0) = +\infty$ and by continuity of the flow of (E_1) with respect to the initial conditions, $T_c(\phi_c) \xrightarrow{\phi_c \rightarrow 0^+} +\infty$.

On the other hand, for the trajectory that cuts $\phi' = -\sqrt{\alpha}\phi$ in $\phi_c = \phi_{max}$, we also have $T_c(\phi_{max}) = +\infty$. Indeed this nonconstant trajectory comes from the equilibrium 1. So according to the continuity of the flow of (E_1) with respect to the initial conditions, $T_c(\phi_c) \xrightarrow{\phi_c \rightarrow \phi_{max}^-} +\infty$ and $\phi_c \mapsto T_c(\phi_c)$ is continuous on $]0, \phi_{max}[$. Thus we can define R_0 the minimum of $\phi_c \mapsto T_c(\phi_c)$ on $]0, \phi_{max}[$. This means that for $r < R_0$, it is impossible to construct a nonzero solution of $(ode1)$, whereas for $R > R_0$, we can construct two different nonzero solutions.

Actually we have not considered all the possible solutions of $(ode1)$ in the preceding paragraph. Indeed we have only considered the solutions of (E_1) that directly join a solution of (E_2) without cutting the x-axis $\phi' = 0$ another time. However, the time before these nonconsidered solutions cut the line $\phi' = -\sqrt{\alpha}\phi$ is necessarily bigger than R_0 .

D.3.2 Case of dimension $N \geq 3$: proof of theorem D.2

Using the theorem D.1 and the comparison principle enounced in the appendix (section D.12), we will now prove the theorem D.2.

First, we will show the nonexistence of radial nonzero profile when $R < R_0$. Then if R is large enough, we will construct a nonzero subsolution of (P_∞) using the solution of $(ode1)$ for a slightly different nonlinearity f .

If $R < R_0$

Let us choose R_0 as defined by theorem D.1 and let us suppose by contradiction that there exists $\phi(z) = \psi(|z|)$ a radial nonzero solution of (P_∞) .

$0 \leq \psi \leq 1$ by the maximum principle, and ψ is a solution of the following equation.

$$(ode2) \begin{cases} \psi'' + \frac{N-2}{r}\psi' + g(\psi)\mathbb{1}_{\{r \leq R\}} - \alpha\psi\mathbb{1}_{\{r > R\}} = 0 & r > 0, \\ \psi(r) \xrightarrow{r \rightarrow \infty} 0, \quad \psi'(0) = 0. \end{cases}$$

If we had $\psi' \leq 0$, ψ would be a subsolution of $(ode1)$. Unfortunately, it does not hold generally, but up to reduction of R , we are going to construct a subsolution of $(ode1)$.

We consider $E = \{r \geq 0, \psi'(r) > 0\}$. We set $r^* = \sup E \geq 0$. This supremum exists by the strong elliptic maximum principle since $\psi(r) \xrightarrow{r \rightarrow \infty} 0$.

We will prove that $\phi(z) = \psi(|z| + r^*)$ is a nonzero subsolution of $(ode1)$ where R is replaced by $R - r^* \in]0, R_0[$. This will contradict theorem D.1.

First let us show that $R - r^* > 0$. We have $\psi'(r^*) = 0$ and $\psi''(r^*) \leq 0$, so

$$g(\psi(r^*))\mathbb{1}_{\{r^* \leq R\}} - \alpha\psi(r^*)\mathbb{1}_{\{r^* > R\}} \geq 0.$$

Hence $r^* \leq R$ and $\psi(r^*) \geq \theta$ and moreover by the strong elliptic maximum principle on $[R, +\infty[$, $r^* < R$.

Let us set $\underline{\psi}(r) = \psi(r + r^*)$. We have $\underline{\psi} \leq 1$ and

$$\begin{cases} \underline{\psi}'' + g(\underline{\psi})\mathbb{1}_{\{r \leq R - r^*\}} - \alpha\underline{\psi}\mathbb{1}_{\{r > R - r^*\}} = -\frac{N-2}{r}\underline{\psi}' \geq 0, & r > 0, \\ \underline{\psi}(r) \xrightarrow{r \rightarrow \infty} 0, \quad \underline{\psi}'(0) = 0. \end{cases}$$

Thus $\phi(z) = \underline{\psi}(|z|)$ is a subsolution of $(ode1)$ with $(BC1)$ where R is replaced by $R - r^* \in]0, R_0[$. Moreover 1 is a supersolution of $(ode1)$ and $\underline{\psi} \leq 1$, so there is a solution ϕ of $(ode1)$ with $\underline{\psi} \leq \phi \leq 1$ and this contradicts theorem D.1.

If R is large enough

The aim of this proof is to construct a non-zero subsolution ψ of problem (P_∞) . To do it, we will have to study in more details the solutions of $(ode1)$. Particularly, we will need the following lemmas.

Lemma D.1 *For any $\varepsilon > 0$ there exists $R_1 > 0$ such that for all $R > R_1$ a solution ϕ of $(ode1)$ verifies $\phi(0) > 1 - \varepsilon$.*

Proof of lemma D.1 :

We have $\phi_0 \rightarrow 1$ for $R \rightarrow +\infty$. Since 1 is an stationary point of (E_1) , we have this lemma by continuity of the flow of $(ode1)$ with respect to the initial condition.

Lemma D.2 *Let us fix $\eta > 0$ as small as wanted and $\rho > 0$ as large as wanted. There exists $R_1 > 0$ such that for all $R > R_1$ a solution of $(ode1)$ verifies*

$$\forall r \in]0, \rho] \quad \frac{|\phi'(r)|}{r} \leq \eta. \quad (D.5)$$

It is this solution of $(ode1)$ that will be used to construct a subsolution of (P_∞) .

Proof of lemma D.2 :

Due to lemma D.1, it is sufficient to show (D.5) for $\phi(0) > 1 - \varepsilon$ for some $\varepsilon > 0$.

Let us fix $\varepsilon > 0$ such that $g(\phi_0) \leq \eta/2$ for all $\phi_0 \in [1 - \varepsilon, 1]$.

We have $\frac{\phi'(r)}{r} = \phi''(0) + \frac{r_m}{2}\phi'''(r_m)$ for some $r_m \in]0, r[$. Moreover $\phi''(0) = -g(\phi(0))$ and by the maximum principle there exists $M''' > 0$ independant of $\varepsilon > 0$ such that $|\phi'''| \leq M'''$. We set $\delta = \eta/M'''$. Then for any $\phi_0 \geq 1 - \varepsilon$, we have

$$\forall r \leq \delta \quad \frac{|\phi'(r)|}{r} \leq \eta.$$

Let us now bound $\frac{|\phi'(r)|}{r}$ for $r \in [\delta, \rho]$. As in the proof of theorem D.1, we study the time before the trajectory of (E_1) issued of $(\phi_0, 0)$ cuts the line $\phi' = -\sqrt{\alpha}\phi$ with $\alpha = (\delta\eta)^2$.

Up to reducing $\varepsilon > 0$, we have for all $\phi_0 > 1 - \varepsilon$, $T_c > \rho$. Hence

$$\forall r \leq \rho \quad |\phi'(r)| \leq \sqrt{\alpha}\phi(r) = \delta\eta\phi(r) \leq \delta\eta.$$

This implies $\forall r \in [\delta, \rho] \quad \frac{|\phi'(r)|}{r} \leq \eta$ and the lemma is thus proved.

Let us now turn to the proof of theorem D.2. Using the preceding lemma, we will construct a subsolution of $(ode2)$. We begin with some notations.

First, let us set $\mu > 0$ such that $g'(1) + \mu < 0$ and $g(\frac{1}{2}) - \frac{\mu}{4} > 0$.

We define the function g_0 by $g_0(u) = g(u) - \mu u(1 - u)$ for $u \in \mathbb{R}$.

By definition of μ , we have $g_0(u) = \lambda_0 u(u - \theta_0)(1 - u)$ for some $\lambda_0 > 0$ and $\theta_0 \in]0, 1/2[$. Moreover $g_0(u) < g(u)$ on $]0, 1[$.

Now let us set $0 < \theta_1 < \theta < \theta_2 < 1$ such that $g'(u) < 0$ for $u \in]0, \theta_1[\cup]\theta_2, 1[$ and $g'(u) > 0$ for $u \in]\theta_1, \theta_2[$ (see figure D.3). Moreover there exists $x_1 \in]\theta_1, 1/2[$ such that $g_0(x_1) = g(\theta_1)$. And we define $x_2 \in]0, 1[$ such that $g_0(x_2) = \max_{[0,1]} g_0$. We have

$x_2 < \theta_2$.

For $u \in [\theta_1, x_2]$, we can define

$$\varepsilon(u) = \max\{\varepsilon > 0, \forall \zeta \in [0, \varepsilon[\quad g(u - \zeta) - g_0(u) > 0\} \in]0, +\infty[.$$

By implicit function theorem, $u \mapsto \varepsilon(u)$ is continuous on $]x_1, x_2[$ and by continuity of g and g_0 , $\varepsilon(u) \xrightarrow{u \rightarrow x_1^+} \varepsilon(x_1) > 0$ and $\varepsilon(u) \xrightarrow{u \rightarrow x_2^-} \varepsilon(x_2) > 0$. Thus there exists $\varepsilon_{\min} = \min\{\varepsilon(u), x_1 \leq u \leq x_2\} > 0$. On $[\theta_1, x_1[$, $\varepsilon(u) = +\infty$.

Let us set $\varepsilon > 0$ such that $\varepsilon < \varepsilon_{\min}/2$.

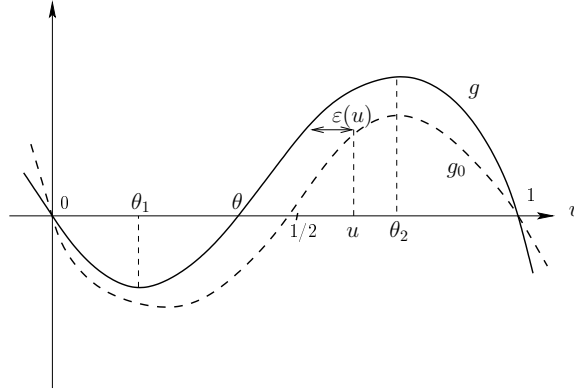


FIG. D.3 – g and g_0

By definition of $\varepsilon_{\min}$, $g(u - \varepsilon) - g_0(u) > 0$ on $[\theta_1, x_2]$, thus there exists $\eta > 0$ such that $g(u - \varepsilon) - g_0(u) > \eta$ for $u \in [x_1, x_2]$. Now up to reducing $\eta > 0$, we can prove that $g(u - \varepsilon) - g_0(u) \geq \eta > 0$ for $u \in [\varepsilon, 1]$. Indeed for $u \in]x_2, \theta_2 + \varepsilon]$, g_0 is decreasing and $g(\cdot - \varepsilon)$ is still increasing, for $u \in]0, \theta_1/2] \cup](\theta_2 + 1)/2, 1]$, we have $g(u - \varepsilon) - g(u) \geq M'\varepsilon$ where

$$M' = \max\{-g'(u), u \in]0, \theta_1/2] \cup](\theta_2 + 1)/2, 1]\} > 0$$

and $g \geq g_0$, and for $u \in]\theta_1/2, \theta_1] \cup]\theta_2 + \varepsilon, (\theta_2 + 1)/2]$, g is decreasing and $\mu u(1 - u) \geq \eta$. Now we recall that for ϕ the solution of (ode1) described in the proof of theorem D.1, we have for any $r \in [0, R]$ $\phi'(r) = -\sqrt{2(G_0(\phi(0)) - G_0(\phi(r)))}$. Let us set $\rho > 0$ such that $\frac{N-2}{\rho} \sqrt{2(G_0(1) - G_0(\theta))} < \eta$ where $G_0(u) = \int_0^u g_0$. Let us fix $\gamma > \alpha$.

Due to lemma D.2, there exists $R > 0$ such that the function $\phi(r)$ build in the proof of theorem D.1 verifies

$$\begin{cases} \phi'' + g_0(\phi) \mathbb{1}_{r \leq R} - \gamma \phi \mathbb{1}_{r > R} = 0, \\ \frac{N-2}{r} |\phi'(r)| < \eta, \quad r \in [0, \rho], \\ \phi(r) > \theta_2 + \epsilon, \quad r \in [0, \rho]. \end{cases}$$

And moreover by definition of ρ , we have $\frac{N-2}{r}|\phi'(r)| < \eta$ for all $r \leq R$. Now up to increase R , we may assume

$$\beta = \frac{N-2}{2R} + \sqrt{\left(\frac{N-2}{2R}\right)^2} + \alpha \leq \sqrt{\gamma}.$$

And we define the subsolution

$$\psi(r) = \begin{cases} \phi(r) - \varepsilon & r \in [0, R], \\ (\phi(R) - \varepsilon)e^{-\beta(r-R)} & r \in]R, +\infty[. \end{cases}$$

We have $\psi(0) > 0$ and $\psi' \leq 0$. Then for $r \in [0, R[$,

$$\begin{aligned} \psi''(r) + \frac{N-2}{r}\psi'(r) + g(\psi) &= \frac{N-2}{r}\phi'(r) + g(\phi - \varepsilon) - g_0(\phi) \\ &\geq -\eta + g(\phi - \varepsilon) - g_0(\phi) \geq 0. \end{aligned}$$

And for $r \in]R, +\infty[$,

$$\psi''(r) + \frac{N-2}{r}\psi'(r) - \alpha\psi \geq \psi''(r) + \frac{N-2}{R}\psi'(r) - \alpha\psi = 0$$

Finally in $r = R$, ψ is continuous. Moreover

$$\lim_{x \rightarrow R^-} \psi'(r) = \lim_{x \rightarrow R^-} \phi'(r) = -\sqrt{\alpha}\phi(R) \leq -\sqrt{\beta}\phi(R) \leq -\sqrt{\beta}(\phi(R) - \varepsilon) = \lim_{x \rightarrow R^+} \psi'(r).$$

ψ is thus a H^1 -subsolution of (P_∞) and 1 is a supersolution with $\psi \leq 1$, we can thus construct ϕ a solution of (P_∞) such that $\psi \leq \phi \leq 1$. $\phi \not\equiv 0$ and by the strong maximum principle, $\phi > 0$.

D.4 Maximal speed for invasion

Now that we have studied the possible profiles for travelling fronts solution of (D.1), we will assume $R > R_1$ and we will prove theorem D.3.

In this section, we will study the solutions of (P) that are near 0 far to the right. We will show that whatever the solution is to the left, an eventually more stable state could not invade the state 0 faster than a maximum speed $c_{max} > 0$. By the way we will study the conditions on u_0 so that the solution u of problem (P) stays near 0 when x tends to $+\infty$.

D.4.1 Definition of an energy function

For any regular and integrable function $\eta : \mathbb{R} \rightarrow \mathbb{R}$, we have

$$\begin{aligned} \frac{d}{dt} \iint \eta(x) \left(\frac{|\nabla u(t, x, z)|^2}{2} + F(u(t, x, z), z) \right) dx dz = \\ - \iint \eta(x) \partial_t u(t, x, z)^2 dx dz - \iint \eta'(x) \partial_t u \partial_x u dx dz \end{aligned}$$

and

$$\begin{aligned} \frac{d}{dt} \iint \eta(x) \frac{u(t, x, z)^2}{2} dx dz &= - \iint \eta(x) f(u(t, x, z), z) u(t, x, z) dx dz \\ &\quad - \iint \eta |\nabla u|^2 dx dz + \iint \eta'' \frac{u^2}{2} dx dz \end{aligned}$$

In order to precisely estimate the solution of (P) when it is near 0, we need to define the following constants.

Let us set $\lambda_{min} = \min(\alpha, \lambda\theta)$ and $\lambda_{max} = \max(\alpha, \lambda\theta)$.

By definition of f and F , there exists $v_{st} \in]0, \theta[$ such that for all $v \in [0, v_{st}]$ and for all $z \in \mathbb{R}^{N-1}$ we have

$$\frac{\lambda_{min}}{2} v \leq f(v, z) \leq 2\lambda_{max} v \quad (D.6)$$

$$\text{and } \frac{\lambda_{min}}{4} v^2 \leq F(v, z) \leq \lambda_{max} v^2. \quad (D.7)$$

If we were considering the simple ordinary differential equation that corresponds to (D.1) (i.e. without the diffusion term), $[0, v_{st}]$ would be an “asymptotic stability area” for the equilibrium 0, i.e. that a trajectory that enters this area will finally tends to 0.

Let us now fix $\alpha_0 \in]0, \frac{1}{2\lambda(1+\theta)}]$ so that

$$\forall v \in [0, 1] \quad \forall z \in \mathbb{R}^{N-1} \quad \alpha_0 F(v, z) \geq -\frac{v^2}{4}. \quad (D.8)$$

Last we set $\beta_0 = \min(1, \sqrt{\lambda_{min}/2})$, $\psi_0(x) = \exp(-\beta_0|x|)$ for $x \in \mathbb{R}$ and $T_x \psi_0 : y \rightarrow \psi_0(y - x)$.

Finally we can define the local energy function $\Psi_0(t, x)$ by

$$\Psi_0(t, x) = \iint T_x \psi_0(y) \left(\alpha_0 \left(\frac{|\nabla u(t, y, z)|^2}{2} + F(u(t, y, z), z) \right) + \frac{u(t, y, z)^2}{2} \right) dy dz.$$

$\Psi_0(t, x)$ corresponds to an energy of the solution of (P) around x at time t where the equilibrium state 0 is favoured. Indeed by definition of α_0 , we have the following “coercivity” inequality

$$\Psi_0(t, x) \geq \min \left(\frac{\alpha_0}{2}, \frac{1}{4} \right) \iint T_x \psi_0(y) (|\nabla u(t, y, z)|^2 + u(t, y, z)^2) dy dz. \quad (D.9)$$

This inequality links the energy Ψ_0 with the value of u . Indeed, for all $v \in H$ and for all $z \in \mathbb{R}^{N-1}$ we have

$$\begin{aligned} v(0, z)^2 &= \psi_0(0) v(0, z)^2 \leq \frac{1}{2} \int_{\mathbb{R}} |\partial_y (\psi_0(y) v(y, z)^2)| \\ &\leq \int \psi_0(y) |v(y, z)^2 + \partial_y v(y, z)^2| dy \\ &\leq \int \psi_0(y) (v(y, z)^2 + |\nabla v(y, z)|^2) dy \end{aligned}$$

Hence

$$\Psi_0(t, x) \geq \min\left(\frac{\alpha_0}{2}, \frac{1}{4}\right) \int_{\mathbb{R}^{N-1}} u(t, x, z)^2 dz.$$

And as stated in (D.3), $|\nabla u|$ is bounded by M_0 and this bound is independent of $u_0 \in H$. So let us set $v_1 > 0$ with $v_1 < \text{vol}(\frac{v_{st}}{2M_0}) \frac{v_{st}^2}{4}$ where $\text{vol}(\rho)$ is the volume of the ball of radius ρ in $\mathbb{R}^N$.

If $\int_{\mathbb{R}^{N-1}} u(t, x, z)^2 dz \leq v_1$, then for all $z \in \mathbb{R}^{N-1}$, $u(t, x, z) \leq v_{st}$.

Thus let us set $\varepsilon_{st} = \min\left(\frac{\alpha_0}{2}, \frac{1}{4}\right) v_1$. Finally, we get

$$\Psi_0(t, x) \leq \varepsilon_{st} \quad \Rightarrow \quad \forall z \in \mathbb{R}^{N-1} \quad u(t, x, z) \leq v_{st}. \quad (\text{D.10})$$

Now we want to study the evolution of $\Psi_0(t, x)$ in function of time t . Since $|\psi'_0(x)| = \beta_0 \psi_0(x)$ and $\psi''_0 = \beta_0^2 \psi_0 - 2\beta_0 \delta$ where δ is a Dirac mass in 0, we have

$$\begin{aligned} \partial_t \Psi_0(t, x) &\leq \iint T_x \psi_0 \left(\frac{\alpha_0 \beta_0^2}{4} \partial_x u^2 - |\nabla u|^2 + \frac{\beta_0^2}{2} u^2 - u f(u, z) \right) dy dz \\ &\leq \iint T_x \Psi_0 \left(\left(\frac{\alpha_0 \beta_0^2}{4} - 1 \right) |\nabla u|^2 + \frac{\beta_0^2}{2} u^2 - u f(u, z) \right) dy dz. \end{aligned}$$

and by definition $\frac{\alpha_0 \beta_0^2}{4} - 1 \leq -\frac{3}{4}$.

In order to clearly link $\partial_t \Psi_0$ and Ψ_0 , we introduce

$$\frac{\lambda_{min}}{4(\alpha_0 \lambda_{max} + 1/2)} \left(\alpha_0 F(u, z) + \frac{u^2}{2} \right)$$

and we obtain

$$\begin{aligned} \partial_t \Psi_0(t, x) &\leq - \iint T_x \psi_0 \left(\frac{3}{4} |\nabla u|^2 + \frac{\lambda_{min}}{4(\alpha_0 \lambda_{max} + 1/2)} \left(\alpha_0 F(u, z) + \frac{u^2}{2} \right) \right) dy dz \\ &\quad + \iint T_x \psi_0 \left(\frac{\lambda_{min}}{4(\alpha_0 \lambda_{max} + 1/2)} \left(\alpha_0 F(u, z) + \frac{u^2}{2} \right) + \frac{\beta_0^2}{2} u^2 - u f(u, z) \right) dy dz \\ &\leq -\varepsilon_1 \Psi_0(t, x) \\ &\quad + \iint T_x \psi_0 \left(\frac{\lambda_{min}}{4(\alpha_0 \lambda_{max} + 1/2)} \left(\alpha_0 F(u, z) + \frac{u^2}{2} \right) + \frac{\beta_0^2}{2} u^2 - u f(u, z) \right) dy dz \end{aligned}$$

where $\varepsilon_1 = \min\left(\frac{3}{2\alpha_0}, \frac{\lambda_{min}}{4(\alpha_0 \lambda_{max} + 1/2)}\right)$. Now we set

$$S_{far}(t) = \{x \in \mathbb{R} \mid \exists z \in \mathbb{R}^{N-1} \quad u(t, x, z) > v_{st}\}.$$

According to the choice of $\frac{\lambda_{min}}{4(\alpha_0\lambda_{max} + 1/2)}$, for $y \notin S_{far}(t)$ or $|z| > R$,

$$\frac{\lambda_{min}}{4(\alpha_0\lambda_{max} + 1/2)} \left(\alpha_0 F(u(t, y, z), z) + \frac{u(t, y, z)^2}{2} \right) + \frac{\beta_0^2}{2} u(t, y, z)^2 - u(t, y, z) f(u(t, y, z), z) \leq 0.$$

Hence

$$\partial_t \Psi_0(t, x) \leq -\varepsilon_1 \Psi_0(t, x) + \int_{S_{far}(t)} K_1 T_x \psi_0 dy \quad (D.11)$$

where $K_1 = \text{vol}(R) \frac{\lambda_{min}}{4(\alpha_0\lambda_{max} + 1/2)} (\alpha_0 M + 1/2) + \frac{\beta_0^2}{2} + m$ with $\text{vol}(R)$ the volume of a ball of radius R in $\mathbb{R}^{N-1}$, $M = \max_{[0,1]}(-G)$ and $m = \max_{[0,1]}(-g)$.

D.4.2 Localization of the energy

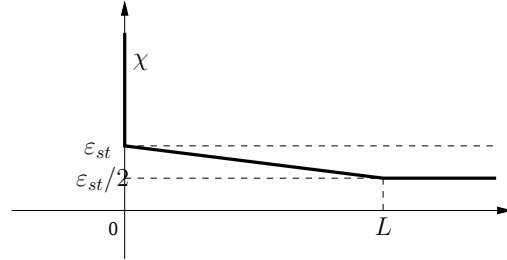
In this section, we want to prove that if the solution is near 0 far to the right in the sense defined by the energy Ψ_0 , then a more stable state could not invade 0 faster than a maximum speed $c_{max} > 0$.

For technical reason, it is not sufficient to directly study whether $\Psi_0(t, x) \leq \varepsilon_{st}$, that is why we have to define the function χ below.

Let us set $L = \frac{2}{\beta_0} \log \left(\frac{2K_1}{\varepsilon_1 \varepsilon_{st} \beta_0} \right)$. This constant is defined in order to have $K_1 \int_{-\infty}^{-\frac{L}{2}} \psi_0 = \frac{\varepsilon_1 \varepsilon_{st}}{2}$.

And we define $\chi : \mathbb{R} \rightarrow \bar{\mathbb{R}}$ by

$$\chi(x) = \begin{cases} +\infty & \text{if } x < 0, \\ \varepsilon_{st} \left(1 - \frac{1}{2L}x\right) & \text{if } 0 \leq x \leq L, \\ \frac{\varepsilon_{st}}{2} & \text{if } x > L. \end{cases}$$



In the following, we will consider the next important assertion that express that u is near 0 far to the right :

$$\mathcal{P}(t, x_0) : \quad \forall x \in \mathbb{R} \quad \Psi_0(t, x) \leq \chi(x - x_0)$$

Particularly, if $\mathcal{P}(t_0, x_0)$ holds, then $u(t_0) \leq v_{st}$ right from x_0 .

Lemma D.3 *There exists $c_{max} > 0$ depending only on f such that for all $x_0 \in \mathbb{R}$ and for all $t_0 \geq 0$*

$$\mathcal{P}(t_0, x_0) \text{ holds} \Rightarrow \forall t \geq t_0 \quad \mathcal{P}(t, x_0 + c_{max}(t - t_0)) \text{ holds.}$$

This lemma means that there exists a maximum speed above which the “energy” of the solution can not travel.

Proof of the lemma :

We set $c_{max} = \frac{4LK_1}{\varepsilon_{st}\beta_0} > 0$.

Let us fix $x_0 \in \mathbb{R}$ and $t_0 \geq 0$ such that $\mathcal{P}(t_0, x_0)$ holds and let us suppose by contradiction that

$$\mathcal{E} = \{t > t_0 \mid \mathcal{P}(t, x_0 + c_{max}(t - t_0)) \text{ does not hold}\}$$

is not empty.

First, remark that if $\mathcal{P}(t, x)$ holds then $\mathcal{P}(t, \bar{x})$ holds for all $\bar{x} \geq x$.

Let us set $t_1 = \inf \mathcal{E}$ and $x_1 = x_0 + c_{max}(t_1 - t_0)$. By continuity of $\Psi_0(t, x)$ with respect to t , $\mathcal{P}(t_1, x_1)$ holds.

We are going to prove that c_{max} has been chosen large enough so that for all $s \geq 0$ small enough, $\mathcal{P}(t_1 + s, x_1 + c_{max}s)$ holds. This will be a contradiction with the definition of t_1 .

In order to simplify the writing, we set $\tilde{\chi}(s, x) = \chi(x - x_1 - c_{max}s)$ for $x \in \mathbb{R}$ and $s \geq 0$.

Remember that

$$\mathcal{P}(t_1 + s, x_1 + c_{max}s) \text{ holds} \quad \Leftrightarrow \quad \forall x \geq x_1 + c_{max}s \quad \Psi_0(t_1 + s, x) \leq \tilde{\chi}(s, x).$$

Now let us show the right part inequality for small s and $x > x_1 + L$. Since $\mathcal{P}(t_1, x_1)$ holds,

$$\forall x > x_1 + \frac{L}{2} \quad \Psi_0(t_1, x) \leq \frac{3\varepsilon_{st}}{4}$$

Thus with the same reasoning as in inequality (D.10), we obtain

$$\forall x > x_1 + \frac{L}{2} \quad \forall z \in \mathbb{R}^{N-1} \quad u(t_1, x, z) \leq \frac{\sqrt{3}\varepsilon_{st}}{2}$$

and by continuity of u with respect to t uniformly in $(x, z) \in \mathbb{R}^N$, there exists $\varepsilon > 0$ such that

$$\forall s < \varepsilon \quad \forall x > x_1 + \frac{L}{2} \quad \forall z \in \mathbb{R}^{N-1} \quad u(t_1 + s, x, z) \leq \varepsilon_{st}.$$

Hence for $s < \varepsilon$, $S_{far}(t_1 + s) \subset]-\infty, x_1 + \frac{L}{2}[$ and by (D.11), we have

$$\forall s < \varepsilon \quad \forall x > x_1 + L \quad \frac{\partial \Psi_0}{\partial t}(t_1 + s, x) \leq -\varepsilon_1 \left(\Psi_0(t_1 + s, x) - \frac{\varepsilon_{st}}{2} \right) \leq 0.$$

Thus for $s < \varepsilon$ and $x > x_1 + L$, $\Psi_0(t_1 + s, x) \leq \frac{\varepsilon_{st}}{2} \leq \tilde{\chi}(s, x)$.

Let us now study the case where $x \in [x_1 + cs, x_1 + L]$. The result is due to the choice of c large enough.

Indeed for all $s \geq 0$ and $x \in \mathbb{R}$ we have $\partial_t \Psi_0(t_1 + s, x) \leq \frac{2K_1}{\beta_0}$ and for $x \in [x_1 + c_{max}s, x_1 + c_{max}s + L]$, $\frac{\partial \tilde{\chi}}{\partial s}(s, x) = \frac{c_{max}\varepsilon_{st}}{2L}$. According to the choice of c_{max} , we thus have

$$\forall s \geq 0 \quad \forall x \in [x_1 + c_{max}s, x_1 + c_{max}s + L] \quad \Psi_0(t_1 + s, x) \leq \tilde{\chi}(s, x)$$

and the lemma is proved.

Let us now study the condition on the initial data such that the solution u of (P) is near 0 far to the right. Let us define a particular set of initial conditions.

$$\mathcal{A} = \left\{ u_0 \in H \left| \limsup_{x \rightarrow +\infty} u(t, x, z) \xrightarrow{t \rightarrow +\infty} 0 \right. \right\}$$

where the limit is uniform with respect to $z \in \mathbb{R}^N$.

Corollaire D.2 *The following assertions are equivalent :*

1. $u_0 \in \mathcal{A}$
2. *There exists $t_0 > 0$ and $x_0 \in \mathbb{R}$ such that $\mathcal{P}(t_0, x_0)$ holds.*

Proof of the corollary :

If $\limsup_{x \rightarrow +\infty} u(t, x, z) \xrightarrow{t \rightarrow +\infty} 0$, then $\limsup_{x \rightarrow +\infty} |\nabla u(t, x, z)| \xrightarrow{t \rightarrow +\infty} 0$ by local estimates.

Hence if t_0 and x_0 are large enough, $\mathcal{P}(t_0, x_0)$ holds.

Conversely, due to lemma 1,

$$\forall t \geq t_0 \quad S_{far}(t) \subset]-\infty, x_0 + c_{max}(t - t_0)].$$

Thus $\forall t \geq t_0 \quad \forall x > x_0 + (c_{max} + 1)(t - t_0)$

$$\begin{aligned} \frac{\partial \Psi_0}{\partial t}(t, x) &\leq -\varepsilon_1 \Psi_0(t, x) + K_1 \int_{-\infty}^{x_0 + c_{max}(t - t_0)} e^{-\beta_0|y-x|} dy \\ &\leq -\varepsilon_1 \Psi_0(t, x) + \frac{K_1}{\beta_0} e^{-\beta_0(t - t_0)}. \end{aligned}$$

Hence

$$\Psi_0(t, x) \leq \varepsilon_{st} e^{-\varepsilon_1(t - t_0)} + \frac{K_1}{\beta_0(\varepsilon_1 - \beta_0)} (e^{-\beta_0(t - t_0)} - e^{-\varepsilon_1(t - t_0)})$$

and

$$\sup_{x \geq x_0 + (c_{max} + 1)(t - t_0)} \Psi_0(t, x) \xrightarrow{t \rightarrow +\infty} 0$$

which proves that $u_0 \in \mathcal{A}$.

The condition $\mathcal{P}(t, x)$ is not very practical to handle, so the following corollary exhibits more explicit conditions on u_0 so that $u_0 \in \mathcal{A}$.

Corollaire D.3 *There exist $\delta > 0$ such that for all $u_0 \in H$*

$$\limsup_{x \rightarrow +\infty} \int_{x-1}^{x+1} \int_{\mathbb{R}^{N-1}} (u_0(x, z)^2 + |\nabla u_0(x, z)|^2) dz dx \leq \delta \quad \Rightarrow \quad u_0 \in \mathcal{A}.$$

Proof of the corollary :

Due to the definition of $\Psi_0(t, x)$, it is clear that $\mathcal{P}(0, x)$ will hold for x large enough. So with the preceding corollary $u_0 \in \mathcal{A}$.

D.5 The escape point

In the preceding section, we have found a sufficient condition so that the solution u of problem (P) with initial condition u_0 converges to 0 for x near $+\infty$ when t tends to $+\infty$. Now we will look for extra conditions so that a nonzero state invades the domain. We already know that this invasion will occur with a maximal speed $c_{max} > 0$.

Let us first define the set of initial data that creates “invading” solution of (P) :

$$\mathcal{A}_{inv} = \left\{ u_0 \in \mathcal{A} \mid \exists \varepsilon > 0 \quad \limsup_{t \rightarrow +\infty} \sup_{x \geq \varepsilon t, z \in \mathbb{R}^{N-1}} u(t, x, z) > 0 \right\}.$$

In the following, this set will be assumed not empty. The conditions that ensure this property will be established in section D.10.

So let us fix $u_0 \in \mathcal{A}_{inv}$.

Since $u_0 \in \mathcal{A}$, up to changing the origin of time, we assume that there exists $x_0 \in \mathbb{R}$ so that $\mathcal{P}(0, x_0)$ holds (see section D.4.2 for the definition of $\mathcal{P}$).

We recall that $\forall t \geq 0$ $\mathcal{P}(t, x_0 + c_{max}t)$ holds and that if $\mathcal{P}(t, x)$ holds, then for all $y \geq x$, $\mathcal{P}(t, y)$ holds.

Moreover since $u_0 \in \mathcal{A}_{inv}$, $\{x \in \mathbb{R} \mid \mathcal{P}(t, x) \text{ holds}\}$ can not be $\mathbb{R}$ or for all superior time, this set would also be $\mathbb{R}$ which contradicts the definition of $\mathcal{A}_{inv}$.

Thus we may define $\tilde{x}(t)$ for $t \geq 0$ by

$$\tilde{x}(t) = \inf \{x \in \mathbb{R} \mid \mathcal{P}(t, x) \text{ holds}\}$$

and by continuity of Ψ_0 , we have

$$\{x \in \mathbb{R} \mid \mathcal{P}(t, x) \text{ holds}\} = [\tilde{x}(t), +\infty[.$$

As Risler does in [75], we will refer to this point $\tilde{x}(t)$ as the escape point. In fact, this point is the first point, starting from $+\infty$ in x , where the solution “escapes” from 0 in the energy sense defined by Ψ_0 .

By definition of $\mathcal{P}(t, x)$ and ε_{st} , we have

$$\forall x \geq \tilde{x}(t) \quad u(t, x) \leq \varepsilon_{st}. \quad (\text{D.12})$$

We want to study the evolution of $\tilde{x}(t)$ in function of the time t and to do so we will work in travelling referentials “following” the escape point, thus for all $s \geq 0$ we define the maximal advance of the escape point

$$\tilde{X}(s) = \sup_{t \geq 0} (\tilde{x}(t + s) - \tilde{x}(t)).$$

According to lemma D.3, we have $\tilde{X}(s) \leq c_{\max} s$ for $s \geq 0$.

Let us now define the “speeds” of the escape point

$$\tilde{c}_- = \liminf_{t \rightarrow +\infty} \frac{\tilde{x}(t)}{t}, \quad \tilde{c}_+ = \limsup_{t \rightarrow +\infty} \frac{\tilde{x}(t)}{t}, \quad \text{and} \quad c^* = \limsup_{s \rightarrow +\infty} \frac{\tilde{X}(s)}{s}.$$

We have $\tilde{c}_- \leq \tilde{c}_+ \leq c^* \leq c_{\max}$. Moreover since $u_0 \in \mathcal{A}_{\text{inv}}$, $\tilde{c}_+ > 0$. Indeed, if $\tilde{c}_+ \leq 0$, according to lemma 1, for all $\varepsilon > 0$

$$\sup_{x \geq \varepsilon t} \Psi_0(t, x) \xrightarrow{t \rightarrow +\infty} 0$$

and this would contradicts $u_0 \in \mathcal{A}_{\text{inv}}$.

The aim of the section D.7 will be to demonstrate that these three speeds are equal using energy in a travelling referential. So first we have to define the energy in a travelling referential.

D.6 Energy in a travelling referential

In the following, we will have to study the energy of the solution u of (P) in several different travelling referentials. Indeed, in order to prove the convergence of u toward a travelling front, we will try to show the convergence toward a stationary solution in a referential travelling at the same speed as the escape point. Hence in this part, we show general results for the energy of a solution of (P) in a referential travelling at a constant speed. We keep the same notations as preceding.

D.6.1 Estimation of the “energy” in a travelling referential

Let us fix $c > 0$ with $c \leq c_{\max}$ the speed of the referential. We give ourselves $t_{\text{init}} \geq 0$ and set $x_{\text{init}} = \tilde{x}(t_{\text{init}})$, the escape point at the initial time.

We work in a referential travelling at speed c in the direction of the x -axis, hence the coordinate z is unchanged and the other coordinates are given by

$$y = x - x_{init} - cs \quad \text{and} \quad s = t - t_{init}.$$

We set $v(s, y, z) = u(t, x, z)$ the solution of (P) in this new referential, then v is solution of the following equation

$$\frac{\partial v}{\partial s} - c \frac{\partial v}{\partial y} - \Delta v + f(v, z) = 0. \quad (\text{D.13})$$

The definition of the “global energy” of the solution will thus be slightly different from the energy in the initial referential.

For $\eta(s, y)$ a sufficiently regular and integrable function, we have

$$\begin{aligned} \frac{d}{ds} \iint \eta \left(\frac{|\nabla v|^2}{2} + F(v, z) \right) dydz &= - \iint \eta \partial_s v^2 dydz \\ &+ \iint \partial_s \eta \left(\frac{|\nabla v|^2}{2} + F(v, z) \right) dydz + \iint (c\eta - \partial_y \eta) \partial_v v \partial_y v dx dz \end{aligned}$$

and

$$\begin{aligned} \frac{d}{ds} \iint \eta \frac{v^2}{2} dydz &= - \iint \eta (|\nabla v|^2 + f(v, z)v) dydz \\ &+ \iint (\partial_s \eta + \partial_y^2 \eta - c \partial_y \eta) \frac{v^2}{2} dydz. \end{aligned}$$

Formally, we would like to define the energy by

$$\Phi(s) = \iint e^{cy} \left(\frac{|\nabla v|^2}{2} + F(v, z) \right) dydz.$$

Hence, we would have

$$\Phi'(s) = - \iint e^{cy} |\partial_s v|^2 dydz.$$

and the convergence toward a constant solution in time (i.e. a travelling front) would be easy to prove. The problem is that the solution of (P) are not necessarily integrable. So we have to cut off the exponential.

In order to define the “cut off” function, we fix the following parameters :

$$\beta_1 = \min \left(1, \frac{\lambda_{min}}{8(c_{max} + 1)} \right), \quad \gamma_1 = \min \left(\frac{\lambda_{min}}{8\lambda_{max}}, \frac{\lambda_{min}}{8(c_{max} + 1)} \right) \quad \text{and} \quad y_0 \in \mathbb{R}.$$

Now we define the new “exponential” function $\varphi(s, y)$ (see figure D.4) by

$$\varphi(s, y) = \begin{cases} e^{cy} & \text{if } y \leq y_0 + \gamma_1 s, \\ e^{-\beta_1 y} e^{(c+\beta_1)(y_0+\gamma_1 s)} & \text{if } y \geq y_0 + \gamma_1 s, \end{cases}$$

and we set for $s \geq 0$

$$\Phi(s) = \iint \varphi \left(\frac{|\nabla v|^2}{2} + F(v, z) \right) dydz.$$

We will refer to Φ as the global energy of the solution of (P) in a travelling referential. The parameters have been chosen so that $\partial_s \varphi = c\varphi - \partial_y \varphi = 0$ if $y \leq y_0 + \gamma_1 s$ and if $y \geq y_0 + \gamma_1 s$, we have $\partial_s \varphi = \gamma_1(c + \beta_1)\varphi$ and $c\varphi - \partial_y \varphi = (c + \beta_1)\varphi$. Hence

$$\begin{aligned} \Phi'(s) &\leq - \iint \varphi \partial_s v^2 dydz \\ &+ \int_{\mathbb{R}^{N-1}} \int_{y_0 + \gamma_1 s}^{+\infty} \varphi \left(\gamma_1(c + \beta_1) \left(\frac{|\nabla v|^2}{2} + F(v, z) \right) + \frac{\partial_s v^2}{2} + (c + \beta_1)^2 \frac{\partial_y v^2}{2} \right) dydz. \end{aligned}$$

Thus if we set $C_1 = \sup_{0 < w \leq 1} \frac{-G(w)}{w^2} < +\infty$ and

$$C_2 = \max \left(\frac{\gamma_1(c_{max} + \beta_1)}{2} + \frac{(c_{max} + \beta_1)^2}{2}, \gamma_1(c_{max} + \beta_1) \max(C_1, \alpha) \right),$$

we have

$$\Phi'(s) \leq -\frac{1}{2} \mathcal{D}(s) + C_2 \int_{\mathbb{R}^{N-1}} \int_{y_0 + \gamma_1 s}^{+\infty} \varphi (|\nabla v|^2 + v^2) dydz \quad (\text{D.14})$$

where $\mathcal{D}(s) = \iint \varphi \partial_s v^2 dydz$ is the dissipation energy.

We can observe that since we have cut off the exponential weight function in the definition of these energies, it is impossible to directly link the global energy and the dissipation energy. There is another flux of energy and we have to control this pollution term to bound the variations of Φ . So in order to estimate the second part of the right-hand side of (D.14), we define a “fire-wall” functional $\Psi(s)$. We first set

$$\psi(s, y) = \begin{cases} e^{(c+\beta_1)y} e^{-\beta_1(y_0 + \gamma_1 s)} & \text{if } y \leq y_0 + \gamma_1 s, \\ e^{-\beta_1 y} e^{(c+\beta_1)(y_0 - \gamma_1 s)} & \text{if } y \geq y_0 + \gamma_1 s \end{cases}$$

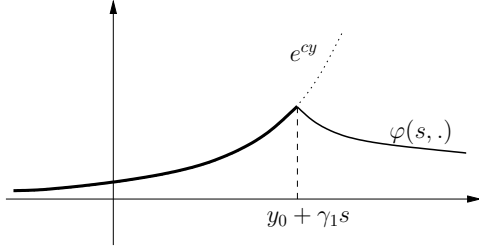
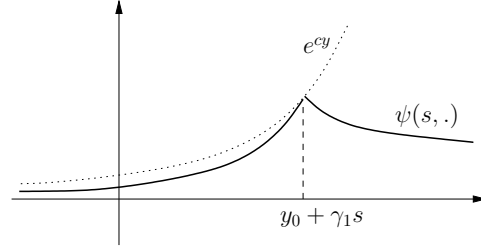
and $\alpha_1 = \min \left(1, \alpha_0, \frac{1}{(c_{max} + 1)^2} \right)$. Then we set for all $s \geq 0$

$$\Psi(s) = \iint \psi \left(\alpha_1 \left(\frac{|\nabla v|^2}{2} + F(v, z) \right) + \frac{v^2}{2} \right) dydz$$

Like in section D.4, this term is an energy that “favors” the equilibrium 0. This is logical since this term is build in order to control the flux of energy due to the cut off and it would naturally be less important if the solution was near 0.

Since $\alpha_1 \leq \alpha_0$, we have

$$\Psi(s) \geq \min \left(\frac{\alpha_1}{2}, \frac{1}{4} \right) \iint \psi (|\nabla v|^2 + v^2)$$

FIG. D.4 – Graph of $\varphi(s, \cdot)$.FIG. D.5 – Graph of $\psi(s, \cdot)$.

and therefore

$$\Phi'(s) \leq -\frac{1}{2}\mathcal{D}(s) + K_2\Psi(s) \quad (\text{D.15})$$

where $K_2 = \frac{C_2}{\min(\frac{\alpha_1}{2}, \frac{1}{4})}$.

Now we want to control the behaviour of Φ . So first we estimate the variations of the dissipation energy $\mathcal{D}(s)$.

$$\begin{aligned} \frac{d}{ds} \iint \varphi \frac{\partial_s v^2}{2} dydz &= \iint \partial_s \varphi \frac{\partial_s v^2}{2} dydz - \iint \varphi ((\partial_s |\nabla v|)^2 + \partial_s v^2 \partial_v f(v, z)) dydz \\ &\quad + \iint (c\varphi - \partial_y \varphi) \partial_s v \partial_{sy} v dydz. \end{aligned}$$

So we have $\mathcal{D}'(s) \leq C\mathcal{D}(s)$ where

$$C = \gamma_1(c_{max} + \beta_1) + 2 \sup_{0 \leq w \leq 1, z \in \mathbb{R}^{N-1}} (-\partial_v f(v, z)) + (c_{max} + \beta_1)^2$$

which means that the dissipation can not increase too fast. The problem is now to control $\Psi(s)$.

D.6.2 Control of the “fire-wall” functional

Since $|\partial_s \psi| \leq \gamma_1(c + \beta_1)\psi$, $|c\psi - \partial_y \psi| \leq (c + \beta_1)\psi$ and $\partial_y^2 \psi - c\partial_y \psi \leq \beta_1(c + \beta_1)\psi$, we have

$$\begin{aligned} \Psi'(s) &\leq \iint \psi \left(\left(\frac{\alpha_1 \gamma_1 (c + \beta_1)}{2} + \frac{\alpha_1 (c + \beta_1)^2}{4} - 1 \right) |\nabla v|^2 \right. \\ &\quad \left. + \alpha_1 \gamma_1 (c + \beta_1) |F(v, z)| - v f(v, z) + \frac{(\gamma_1 + \beta_1)(c + \beta_1)}{2} v^2 \right) dydz. \end{aligned}$$

But α_1 , β_1 and γ_1 have been chosen so that this inequality becomes

$$\Psi'(s) \leq \iint \psi \left(-\frac{|\nabla v|^2}{2} + \frac{\lambda_{min}}{8\lambda_{max}} |F(v, z)| - v f(v, z) + \frac{\lambda_{min}}{8} v^2 \right) dydz.$$

And by adding and deducting

$$\iint \psi \frac{\lambda_{min}}{4(\alpha_1 \lambda_{max} + 1/2)} \left(\alpha_1 F(v, z) + \frac{v^2}{2} \right) dydz,$$

we obtain

$$\begin{aligned} \Psi'(s) \leq & \iint \psi \left(-\frac{|\nabla v|^2}{2} - \frac{\lambda_{min}}{4(\alpha_1 \lambda_{max} + 1/2)} \left(\alpha_1 F(v, z) + \frac{v^2}{2} \right) \right) dydz + \\ & \iint \psi \left(\frac{\lambda_{min}}{4(\alpha_1 \lambda_{max} + 1/2)} \left(\alpha_1 F(v, z) + \frac{v^2}{2} \right) + \frac{\lambda_{min}}{8\lambda_{max}} |F(v, z)| \right. \\ & \quad \left. - v f(v, z) + \frac{\lambda_{min}}{8} v^2 \right) dydz. \end{aligned}$$

Let us once again define

$$S_{far}(s) = \{y \in \mathbb{R} \mid \exists z \in \mathbb{R}^{N-1} \quad v(s, y, z) > v_{st}\}.$$

The constants have been chosen in order that the second part of the right-hand side inequality is negative for $y \notin S_{far}(s)$ and for any z with $|z| \geq R$. Hence for all $s \geq 0$

$$\Psi'(s) \leq -\varepsilon_3 \Psi(s) + C_3 \Theta(s) \tag{D.16}$$

with $\Theta(s) = \int_{S_{far}(s)} \psi(s, y) dy$, $\varepsilon_3 = \min \left(\frac{1}{\alpha_1}, \frac{\lambda_{min}}{4(\alpha_1 \lambda_{max} + 1/2)} \right)$ and

$$C_3 = vol(R) \max_{0 \leq w \leq 1} \left\{ \frac{\lambda_{min}}{4(\alpha_1 \lambda_{max} + 1/2)} \left(-\alpha_1 G(w) + \frac{w^2}{2} \right) + \frac{\lambda_{min}}{8\lambda_{max}} |G(w)| + wg(w) + \frac{\lambda_{min}}{8} w^2 \right\}$$

where $vol(R)$ is the volume of the ball of radius R in $\mathbb{R}^{N-1}$.

It remains to estimate $\Theta(s)$. Let us call $\tilde{y}(s) = \tilde{x}(t) - x_{init} - cs$. We know that $S_{far}(s) \subset]-\infty, \tilde{y}(s)[$ and since $\psi(s, y) \leq e^{c+\beta_1 y} e^{-\beta_1(y_0+\gamma_1 s)}$, we obtain

$$\Theta(s) \leq \frac{1}{\beta_1} e^{-\beta_1 y_0} e^{(c+\beta_1)\tilde{y}(s)-\beta_1 \gamma_1 s}.$$

Now we had chosen $x_{init} = \tilde{x}(t_{init})$, so we have $\tilde{y}(s) \leq \tilde{X}(s) - cs$, thus

$$\Theta(s) \leq \frac{1}{\beta_1} e^{-\beta_1 y_0} e^{-\frac{1}{2}\beta_1 \gamma_1 s} e^{(c+\beta_1)(\tilde{X}(s)-c^*s)} e^{((c+\beta_1)(c^*-c)-\frac{1}{2}\beta_1 \gamma_1)s}$$

and $\tilde{X}(s) - c^*s \leq 0$ for s large. So if we have the important condition

$$(c + \beta_1)(c^* - c) \leq \frac{1}{4}\beta_1 \gamma_1, \tag{D.17}$$

i.e. the speed of the referential c is close enough to c^* , we obtain

$$\Theta(s) \leq C_4 e^{-\beta_1 y_0} e^{-\frac{1}{2}\beta_1 \gamma_1 s}$$

where $C_4 = \frac{1}{\beta_1} \exp \left(\sup_{s \geq 0} \left\{ (c_{max} + \beta_1)(\tilde{X}(s) - c^*)s - \frac{1}{4}\beta_1 \gamma_1 s \right\} \right)$.

Then with (D.16) we can estimate $\Psi(\bar{s})$ for $\bar{s} \geq 0$ like its integral. We have

$$\Psi(\bar{s}) \leq \Psi(0) - \varepsilon_3 \int_0^{\bar{s}} \Psi(s) ds + \frac{2C_3 C_4}{\beta_1 \gamma_1} e^{-\beta_1 y_0}$$

and since $\Psi(\bar{s}) \geq 0$, we have

$$\int_0^{+\infty} \Psi(s) ds \leq \frac{1}{\varepsilon_3} \Psi(0) + K_3 e^{-\beta_1 y_0} \quad (\text{D.18})$$

where $K_3 = \frac{2C_3 C_4}{\varepsilon_3 \beta_1 \gamma_1}$.

D.7 Speed of the escape point

The aim of this section is to control the escape point, that means that we will study his asymptotic speed for $t \rightarrow +\infty$. To do so, we will use the preceding estimations for the energy of a solution in a travelling referential. We recall that $\tilde{c}_- \leq \tilde{c}_+ \leq c^* \leq c_{max}$ and $\tilde{c}_+ > 0$ (See section D.5 for the definitions of these speeds).

Proposition D.1 *We have $\tilde{c}_- = \tilde{c}_+ = c^*$.*

Let us suppose by contradiction that $\tilde{c}_- < c^*$.

- For any $c > 0$ such that

$$\tilde{c}_- < c < c^* < c + \gamma_1 \quad \text{and} \quad (c + \beta_1)(c^* - c) \leq \frac{\beta_1 \gamma_1}{4}, \quad (\text{D.19})$$

the computations of section D.6 in a referential travelling at speed c hold. So let us fix $c > 0$ that verifies (D.19). In any referential travelling at speed c , the escape point will make large excursions to the left followed by large excursion to the right and moreover, the cut off point in the definition of Φ will always be to the right of the escape point (where the solution is near 0).

- Take any sequence $(s_n)_{n \in \mathbb{N}}$ that tends to $+\infty$ such that $\frac{\tilde{X}(s_n)}{s_n}$ tends to c^* .

For all $n \in \mathbb{N}$ we set $t_n \geq 0$ such that $\tilde{x}(t_n + s_n) - \tilde{x}(t_n) \geq \frac{s_n}{\tilde{X}(s_n)} - 1$.

Let us fix $n \in \mathbb{N}$. We will apply the computations of the preceding section with

$$t_{init} = t_n, \quad x_{init} = \tilde{x}(t_n), \quad y_0 = 0$$

and $c > 0$ chosen above.

We will use the same notations as in the preceding section with an exponent (n) , hence Ψ becomes $\Psi^{(n)}$.

• First let us show that the global energy $\Phi^{(n)}(s)$ can not tends to $-\infty$ for $s \rightarrow +\infty$ due to the large excursions to the left of the escape point.

We have $\tilde{y}^{(n)}(s) = \tilde{x}(t_n + s) - \tilde{x}(t_n) - cs$, thus

$$\liminf_{s \rightarrow +\infty} \frac{\tilde{y}^{(n)}(s)}{s} = \tilde{c}_- - c < 0.$$

So $\liminf_{s \rightarrow +\infty} \tilde{y}^{(n)}(s) = -\infty$. Moreover by definition of $\tilde{y}^{(n)}$, for all $y \geq \tilde{y}^{(n)}(s)$ and all $z \in \mathbb{R}^{N-1}$, we have $v^{(n)}(s, y, z) \leq v_{st}$ and then $F(v^{(n)}(s, y, z), z) \geq 0$. By definition of F , for all $|z| \geq R$ and for all $y \in \mathbb{R}$, we have

$$F(v^{(n)}(s, y, z), z) = \frac{\alpha}{2} v^{(n)}(s, y, z) \geq 0.$$

We thus have for all $s \geq 0$,

$$\Phi^{(n)}(s) \geq \text{vol}(R) \min_{0 \leq w \leq 1} (-G(w)) \int_{-\infty}^{\tilde{y}^{(n)}} e^{cy} dy$$

and $\limsup_{s \rightarrow +\infty} \Phi^{(n)}(s) \geq 0$.

bullet According to the bound on $t \mapsto \|u(t)\|_{H_{ul}^1}$,

$$\Phi^{(n)}(0) = \iint \varphi(0, y) \left(\frac{|\nabla u(t_n, \tilde{x}(t_n) + y, z)|^2}{2} + F(u(t_n, \tilde{x}(t_n) + y, z), z) \right) dy dz$$

is bounded from above with respect to $n \in \mathbb{N}$.

• Likewise, since $t \mapsto \|u(t)\|_{H_{ul}^1}$ is bounded, $\Psi^{(n)}(0)$ is also bounded from above with respect to $n \in \mathbb{N}$ and according to the preceding section and equation (D.18),

$$\int_0^{+\infty} \Psi^{(n)}(s) ds \leq \frac{1}{\varepsilon_3} \Psi^{(n)}(0) \text{ is bounded with respect to } n \in \mathbb{N}.$$

• Hence the dissipation must also be bounded with respect to $n \in \mathbb{N}$. Indeed by

(D.15), we have $\int_0^{+\infty} \mathcal{D}^{(n)}(s) ds < +\infty$ and uniformly bounded with respect to $n \in \mathbb{N}$.

Moreover we have shown in the preceding section that $\mathcal{D}'(s) \leq C\mathcal{D}(s)$ with C independant of $n \in \mathbb{N}$ and since $\partial_t u$ is bounded for $t \geq 1$, $\mathcal{D}^{(n)}(1)$ is bounded with respect to $n \in \mathbb{N}$. Hence $\mathcal{D}^{(n)}(s)$ is bounded uniformly with respect $n \in \mathbb{N}$ and $s \in [1, +\infty[$ and we will prove that it is contradictory with the fact that the escape point makes large excursions to the right.

• In fact, the bound on $\mathcal{D}^{(n)}(s)$ implies that $\partial_s v^{(n)}$ tends to 0 in quadratic norm. Indeed, we have by definition of $\mathcal{D}^{(n)}(s)$,

$$\mathcal{D}^{(n)}(s) \geq \int_{\mathbb{R}^{N-1}} \int_{-\infty}^{\gamma_1 s_n} e^{cy} \partial_s v^{(n)}(s_n, y, z)^2 dy dz.$$

And if we set $y = \tilde{y}^{(n)}(s_n) + \bar{y}$, we have

$$\mathcal{D}^{(n)}(s) \geq e^{c\tilde{y}^{(n)}(s_n)} \int_{\mathbb{R}^{N-1}} \int_{-\infty}^{\gamma_1 s_n - \tilde{y}^{(n)}(s_n)} e^{c\bar{y}} \partial_s v^{(n)}(s_n, \tilde{y}^{(n)}(s_n) + \bar{y}, z)^2 d\bar{y} dz$$

But due to the choice of t_n , $\tilde{y}^{(n)}(s_n) \rightarrow +\infty$ and $\gamma_1 s_n - \tilde{y}^{(n)}(s_n) \rightarrow +\infty$. Indeed we have

$$\tilde{X}(s_n) - 1 - cs_n \leq \tilde{y}^{(n)}(s_n) = \tilde{x}(t_n + s_n) - \tilde{x}(t_n) - cs_n \leq \tilde{X}(s_n) - cs_n$$

which means that $\tilde{y}^{(n)}(s_n) \sim (c^* - c)s_n$ and $\gamma_1 s_n - \tilde{y}^{(n)}(s_n) \sim (\gamma_1 + c - c^*)s_n \rightarrow +\infty$. Since $\mathcal{D}^{(n)}(s)$ is bounded and $e^{c\tilde{y}^{(n)}(s_n)} \rightarrow +\infty$, necessarily for all $L > 0$

$$\|\partial_s v^{(n)}(s_n, \tilde{y}^{(n)}(s_n) + \cdot, \cdot)\|_{L^2(B(0,L))} \xrightarrow{n \rightarrow +\infty} 0.$$

• But we have

$$\begin{aligned} \partial_s v^{(n)}(s_n, \tilde{y}^{(n)}(s_n) + y, z) = \\ \partial_t u(t_n + s_n, \tilde{x}(t_n + s_n) + y, z) + c \partial_x u(t_n + s_n, \tilde{x}(t_n + s_n) + y, z). \end{aligned}$$

So we set for all $(y, z) \in \mathbb{R}^N$

$$w_n(y, z) = u(t_n + s_n, \tilde{x}(t_n + s_n) + y, z)$$

and

$$\bar{w}_n(y, z) = \partial_t u(t_n + s_n, \tilde{x}(t_n + s_n) + y, z).$$

By compacity, up to extraction, there exists $w_\infty \in H_{ul}^2(\mathbb{R}^N)$ and $\bar{w}_\infty \in L_{ul}^2(\mathbb{R}^N)$ such that for all $L > 0$, $w_n \rightarrow w_\infty$ in $H_{ul}^2(B(0, L))$ and $\bar{w}_n \rightarrow \bar{w}_\infty$ in $L_{ul}^2(B(0, L))$. By passing to the limit, we have

$$\bar{w}_\infty + c \partial_x w_\infty = 0.$$

• Now to conclude, let us show that $w_\infty = 0$. First notice that the preceding computations could have been done with any c that respects conditions (D.19), but w_n and $\bar{w}_n$ (and thus their limits neither) do not depend on c .

Thus $\bar{w}_\infty = 0$ and $\partial_x w_\infty = 0$, so w_∞ only depends on $z \in \mathbb{R}^{N-1}$. By passing to the limit in (P), we obtain

$$\Delta_z w_\infty - f(w_\infty, z) = 0.$$

This equation has been studied in the section D.3 and it is easy to see that we have $w_\infty \equiv 0$ or there exists $z_0 \in \mathbb{R}^{N-1}$ such that $w_\infty(\cdot, z_0) \geq \theta$. But by definition of w_n , for all $z \in \mathbb{R}^{N-1}$ we have $w_\infty(0, z) \leq v_{st} < \theta$, hence $w_\infty \equiv 0$.

• But this contradicts the definition of $\tilde{x}(t_n + s_n)$. in particular, for any $y < 0$, there exists $y_n \in [y, y + L]$ such that $\Psi_0(t - n, \tilde{x}(t_n + s_n) + y_n) \geq \varepsilon_{st}/2$. Thus by compacity and continuity of Ψ_0 , there exists y_∞ such that

$$\iint T_{y_\infty} \psi_0(y) \left(\alpha_0 \left(\frac{|\nabla w_\infty(y, z)|^2}{2} + F(w_\infty(y, z), z) \right) + \frac{w_\infty(y, z)^2}{2} \right) dy dz \geq \frac{\varepsilon_{st}}{2},$$

this contradicts $w_\infty = 0$.

In the following, we will note $\tilde{c} = \tilde{c}^- = \tilde{c}^+ = c^*$ and we have $\tilde{c} > 0$.

D.8 Relaxation

We keep the same notations as in the preceding sections. The aim of this section is to prove the convergence of the solution u of (P) toward a travelling front in L^2_{ul} -norm. Precisely, we will prove the following proposition.

Proposition D.2

$$\forall L > 0 \quad \|\partial_t u(t, \tilde{x}(t) + \cdot, \cdot) + \tilde{c} \partial_x u(t, \tilde{x}(t) + \cdot, \cdot)\|_{L^2_{ul}(B(0, L))} \xrightarrow{t \rightarrow +\infty} 0$$

Proof of proposition D.2 :

Let us first remark that

$$\partial_t u(t, \tilde{x}(t) + \cdot, \cdot) + \tilde{c} \partial_x u(t, \tilde{x}(t) + \cdot, \cdot) = \partial_s v(s + t_{init}, \cdot, \cdot)$$

where v is the solution of (P) in a referential travelling at speed $\tilde{c}$ centered on the escape point. Let us now suppose by contradiction that there exists $L_0 > 0$, $\varepsilon_0 > 0$ and a sequence $(t_n)_{n \in \mathbb{N}}$ with $t_n \xrightarrow{n \rightarrow +\infty} +\infty$ such that

$$\forall n \in \mathbb{N} \quad \|\partial_t u(t_n, \tilde{x}(t_n) + \cdot, \cdot) + \tilde{c} \partial_x u(t_n, \tilde{x}(t_n) + \cdot, \cdot)\|_{L^2_{ul}(B(0, L))} \geq \varepsilon_0 \quad (\text{D.20})$$

For all $n \in \mathbb{N}$, we define $w_n(y, z) = u(t_n, \tilde{x}(t_n) + y, z)$ for $(y, z) \in \mathbb{R}^N$.

By compactity, there exists $w_\infty \in H^2_{ul}(\mathbb{R}^N)$ such that for all $L > 0$, $w_n \rightarrow w_\infty$ in $H^2_{ul}(B(0, L))$.

Let us fix $n \in \mathbb{N}$. By definition of $\tilde{c}$, we have $\frac{\tilde{x}(t_p) - \tilde{x}(t_n)}{t_p - t_n} \xrightarrow{p \rightarrow +\infty} \tilde{c}$. So we define

$$p(n) = \min \left\{ p \in \mathbb{N}, t_p - t_n \geq n \text{ and } \left| \frac{\tilde{x}(t_p) - \tilde{x}(t_n)}{t_p - t_n} - \tilde{c} \right| \leq \frac{1}{n} \right\}.$$

We set $s_n = t_{p(n)} - t_n$ and $c_n = \frac{\tilde{x}(t_{p(n)}) - \tilde{x}(t_n)}{t_{p(n)} - t_n}$. We clearly have $s_n \rightarrow +\infty$ and $c_n \rightarrow \tilde{c}$. Moreover, due to lemma 1, we have $c_n \leq c_{max}$.

In the following, we will assume that n is large enough so that $\tilde{c}/2 < c_n \leq c_{max}$ and $(c_n + \beta_1)(\tilde{c} - c_n) \leq \beta_1 \gamma_1/4$. Hence we can once again apply the computations of section 6 with $t_{init} = t_n$, $x_{init} = \tilde{x}(t_{init})$, $c = c_n$ and $y_0 > 0$ to be chosen below. The quantities defined in section 6 are once more denoted with the same notations plus a (n) as exponent.

Let us remark that this referential has been constructed in order to “follow the escape point”, i.e. we have $\tilde{y}^{(n)}(0) = \tilde{y}^{(n)}(s_n) = 0$.

Moreover $v^{(n)}(0, y, z) = w_n(y, z)$ and $v^{(n)}(s_n, y, z) = w_{p(n)}(y, z)$.

We are going to prove a contradiction thanks to the 5 following claims.

First we prove that the dissipation can not tend to 0.

Claim 1 *There exist $N_0 \in \mathbb{N}$ and $\varepsilon_{dissip} > 0$ such that for all $n \in \mathbb{N}$ and for all $y_0 \geq 0$*

$$\frac{1}{2} \int_0^{s_n} \mathcal{D}^{(n)}(s) ds \geq \varepsilon_{dissip}$$

Proof of claim 1 :

By definition, $\mathcal{D}^{(n)}(s)$ is increasing with $y_0 \in \mathbb{R}$, thus it is sufficient to prove the inequality with $y_0 = 0$. Let us suppose by contradiction that there exist a sequence $(n_k)_{k \in \mathbb{N}}$ with $n_k \rightarrow +\infty$ such that

$$\int_0^{s_{n_k}} \mathcal{D}^{(n_k)}(s) ds \xrightarrow{k \rightarrow +\infty} 0.$$

Since we have $\mathcal{D}' \leq C\mathcal{D}$ with C independant of $n \in \mathbb{N}$, we have $\mathcal{D}^{(n_k)}(s) \geq \mathcal{D}^{(n_k)}(s_{n_k})e^{c(s-s_{n_k})}$ for $s \leq s_{n_k}$. So necessary we obtain $\mathcal{D}^{(n_k)}(s_{n_k}) \xrightarrow{k \rightarrow +\infty} 0$. On the other hand, we have

$$\mathcal{D}^{(n_k)}(s_{n_k}) \geq \int_{\mathbb{R}^{N-1}} \int_{-\infty}^{\gamma_1 s_{n_k}} e^{c_{n_k} y} \partial_s v^{(n_k)}(s_{n_k}, y, z)^2 dy dz.$$

Thus we have

$$\|\partial_s v^{(n_k)}(s_{n_k}, \cdot, \cdot)\|_{L^2([-L, L] \times \mathbb{R}^{N-1})} \xrightarrow{k \rightarrow +\infty} 0.$$

for all $L > 0$. Now

$$\partial_s v^{(n_k)}(s_{n_k}, y, z) = \partial_t u(t_{p(n_k)}, \tilde{x}(t_{p(n_k)}) + y, z) + c_{n_k} \partial_x u(t_{p(n_k)}, \tilde{x}(t_{p(n_k)}) + y, z)$$

and this would contradict the beginning hypothesis (D.20).

Now we define $\Phi^{(\infty)} \in \mathbb{R}$.

Claim 2 $\Phi^{(\infty)} = \iint_{\mathbb{R}^N} e^{\tilde{c}y} \left(\frac{|\nabla w_\infty|^2}{2} + F(w_\infty, z) \right) dy dz$ is a converging integral.

Proof of claim 2 :

Let us fix $y_0 > 0$ just for this proof.

Since $\tilde{c}/2 < c_n \leq c_{max}$ and $t \mapsto \|u(t)\|_{H_{ul}^1}$ is bounded, $\Phi^{(n)}(0)$ and $\Psi^{(n)}(0)$ are bounded from above with respect to $n \in \mathbb{N}$. Thus according to (D.18), $\int_0^{s_n} \Psi^{(n)}(s) ds$ is also bounded from above and according to (D.15), there exists $C > 0$ such that for all $n \in \mathbb{N}$, $\Phi^{(n)}(s_n) \leq C$.

Now we have chosen s_n in order that $\tilde{y}^{(n)}(s_n) = 0$, so for all $y \geq 0$, $F(v^{(n)}(s_n, y, z), z) \geq 0$ and thus

$$\Phi^{(n)}(s_n) \geq \int_{\mathbb{R}^{N-1}} \int_{-\infty}^{\gamma_1 s_n} e^{c_n y} \left(\frac{|\nabla w_{p(n)}|^2}{2} + F(w_{p(n)}, z) \right) dy dz.$$

Then for all $L > 0$ and for all $n \in \mathbb{N}$ large enough,

$$\int_{\mathbb{R}^{N-1}} \int_{-\infty}^L e^{c_n y} \left(\frac{|\nabla w_{p(n)}|^2}{2} + F(w_{p(n)}, z) \right) dy dz \leq C$$

and passing to the limit in n , we obtain

$$\int_{\mathbb{R}^{N-1}} \int_{-\infty}^L e^{\tilde{c}y} \left(\frac{|\nabla w_\infty|^2}{2} + F(w_\infty, z) \right) dy dz \leq C$$

with C independent of L . The result is thus proved.

In the next claim, we study the behaviour of $\Phi^{(n)}(0)$.

Claim 3 *There exists $N(y_0) \in \mathbb{N}$ such that for all $n \geq N(y_0)$*

$$\Phi^{(n)}(0) \leq \Phi^{(\infty)} + \frac{\varepsilon_{dissip}}{4}.$$

Proof of claim 3 :

This claim is easy to prove, but we introduce some notations that will be used thereafter. First, for $(y, z) \in \mathbb{R}^N$ we set

$$h^{(n)}(y, z) = \varphi^{(n)}(y, 0) \left(\frac{|\nabla w_n(y, z)|^2}{2} + F(w_n(y, z), z) \right).$$

We have

$$\Phi^{(n)}(0) = \iint_{\mathbb{R}^N} h^{(n)}(y, z) dy dz$$

Now we set

$$\varphi^{(\infty)} = \begin{cases} e^{\tilde{c}y} & \text{if } y \leq y_0, \\ e^{-\beta_1 y} e^{(\tilde{c} + \beta_1)y_0} & \text{if } y \geq y_0 \end{cases}$$

and

$$h^{(\infty)}(y, z) = \varphi^{(\infty)}(y) \left(\frac{|\nabla w_\infty(y, z)|^2}{2} + F(w_\infty(y, z), z) \right).$$

For any $y \in \mathbb{R}$, we have $\varphi^{(n)}(0, y) \xrightarrow{n \rightarrow +\infty} \varphi^{(\infty)}(y)$. Moreover since $\tilde{c}/2 < c_n \leq c_{max}$, for a fixed $y_0 \geq 0$, we can overestimate $\varphi^{(n)}(y, 0)$ by an integrable function of y independent of $n \in \mathbb{N}$ and by the dominated convergence theorem, we have $h^{(n)}$ tends to $h^{(\infty)}$ in $L^1(\mathbb{R}^N)$ for $n \rightarrow +\infty$.

Finally we set

$$k^{(\infty)}(y, z) = e^{\tilde{c}y} \left(\frac{|\nabla w_\infty(y, z)|^2}{2} + F(w_\infty(y, z), z) \right).$$

We have

$$\Phi^{(\infty)} = \iint_{\mathbb{R}^N} k^{(\infty)}(y, z) dy dz \geq \iint_{\mathbb{R}^N} h^{(\infty)}(y, z) dy dz.$$

Indeed, for $y \geq 0$ and for all $z \in \mathbb{R}^{N-1}$, we have $w_n(y, z) \leq v_{st}$ and passing to the limit, $w_\infty(y, z) \leq v_{st}$ so $F(w_\infty, z) \geq 0$. And claim 3 follows.

Now we will study the behaviours of $\Phi^{(n)}(s_n)$.

Claim 4 *There exists $N_0 \in \mathbb{N}$ such that for all $n \geq N_0$ and for all $y_0 \geq 0$*

$$\Phi^{(n)}(s_n) \geq \Phi^{(\infty)} - \frac{\varepsilon_{dissip}}{4}.$$

Proof of claim 4 :

We now set

$$k^{(n)}(y, z) = \varphi^{(n)}(y, s_n) \left(\frac{|\nabla w_{p(n)}(y, z)|^2}{2} + F(w_{p(n)}(y, z), z) \right)$$

and we have $\Phi^{(n)}(s_n) = \iint_{\mathbb{R}^N} k^{(n)}(y, z) dy dz$. Set $L > 0$ such that

$$\int_{\mathbb{R}^{N-1}} \int_{-\infty}^L k^{(\infty)}(y, z) dy dz \geq \Phi^{(\infty)} - \frac{\varepsilon_{dissip}}{8}.$$

For all $y \leq y_0 + \gamma_1 s_n$ (then for all $y \leq \gamma_1 s_n$), $\varphi^{(n)}(y, s_n) = e^{c_n y} \xrightarrow{n \rightarrow +\infty} e^{\tilde{c} y}$ and $\tilde{c}/2 < c_n \leq c_{max}$, so by the dominated convergence theorem, we have $k^{(n)}$ tends to $k^{(\infty)}$ in $L^1([-\infty, L] \times \mathbb{R}^{N-1})$ uniformly in y_0 .

Finally

$$\Phi^{(n)}(s_n) \geq \int_{\mathbb{R}^{N-1}} \int_{-\infty}^L k^{(n)}(y, z) dy dz$$

since $w_{p(n)}(y, z) \leq v_{st}$ for all $y \geq 0$ and $L > 0$. The claim 4 is thus proved.

Finally, we bound the pollution term.

Claim 5 *For y_0 large enough and $n \geq N(y_0)$,*

$$K_2 \int_0^{s_n} \Psi^{(n)}(s) ds \leq \frac{\varepsilon_{dissip}}{4}.$$

Proof of claim 5 :

First according to (D.18), we have

$$K_2 \int_0^{s_n} \Psi^{(n)}(s) ds \leq \frac{K_2}{\varepsilon_3} \Psi^{(n)}(0) + K_2 K_3 e^{-\beta_1 y_0}.$$

For y_0 large enough, we have $K_2 K_3 e^{-\beta_1 y_0} \leq \frac{\varepsilon_{dissip}}{8}$. Let us show that for y_0 and n large enough, we have $\Psi^{(n)}(0) \leq \varepsilon_4$ where

$$\varepsilon_4 = \frac{\varepsilon_3 \varepsilon_{dissip}}{8 K_2}.$$

We will use the following notations. We set, for $(y, z) \in \mathbb{R}^N$

$$l^{(n)}(y, z) = \psi^{(n)}(y, 0) \left(\alpha_1 \left(\frac{|\nabla w_n(y, z)|^2}{2} + F(w_n(y, z), z) \right) + \frac{w_n(y, z)^2}{2} \right)$$

and we have $\Psi^{(n)}(0) = \iint_{\mathbb{R}^N} l^{(n)}(y, z) dy dz$.

Now we set

$$\psi^{(\infty)} = \begin{cases} e^{(\tilde{c}+\beta_1)y} e^{-\beta_1 y_0} & \text{if } y \leq y_0, \\ e^{-\beta_1 y} e^{(\tilde{c}+\beta_1)y_0} & \text{if } y \geq y_0, \end{cases}$$

$$l^{(\infty)}(y, z) = \psi^{(\infty)}(y) \left(\alpha_1 \left(\frac{|\nabla w_\infty(y, z)|^2}{2} + F(w_\infty(y, z), z) \right) + \frac{w_\infty(y, z)^2}{2} \right).$$

and $\Psi^{(\infty)} = \iint_{\mathbb{R}^N} l^{(\infty)}(y, z) dy dz$. For any $y \in \mathbb{R}$, we have $\psi^{(n)}(0, y) \xrightarrow{n \rightarrow +\infty} \psi^{(\infty)}(y)$

and since $\frac{\tilde{c}}{2} < c_n \leq c_{max}$, for any fixed $y_0 \geq 0$, we can apply the dominated convergence theorem and thus $l^{(n)}$ tends to $l^{(\infty)}$ in $L^1(\mathbb{R}^N)$ for $n \rightarrow +\infty$. Thus for any y_0 fixed, there exists $N_0(y_0) \in \mathbb{N}$ such that for all $n \geq N_0$

$$\Psi^{(n)}(0) \leq \Psi^{(\infty)} + \frac{\varepsilon_4}{2}.$$

It remains to prove that $\Psi^{(\infty)} \leq \frac{\varepsilon_4}{2}$ for y_0 large enough.

We set

$$\bar{l}^{(\infty)}(y, z) = e^{\tilde{c}y} \left(\alpha_1 \left(\frac{|\nabla w_\infty(y, z)|^2}{2} + F(w_\infty(y, z), z) \right) + \frac{w_\infty(y, z)^2}{2} \right).$$

We recall that due to the choice of α_1 , $l^{(\infty)}$ and $\bar{l}^{(\infty)}$ are non-negative functions. We set $\bar{\Psi}^{(\infty)} = \iint_{\mathbb{R}^N} \bar{l}^{(\infty)}(y, z) dy dz$. This integral is indeed converging since for $y \geq 0$, $w_\infty \leq v_{st}$ so $w_\infty^2 \sim CF(w_\infty, z)$ and we can then use the claim 2.

Since $l^{(\infty)}(y, z) \leq \bar{l}^{(\infty)}(y, z)$ and moreover for $y \leq \frac{y_0}{2}$, we have $l^{(\infty)}(y, z) \leq e^{-\beta_1 y_0/2} \bar{l}^{(\infty)}(y, z)$, we have

$$\Psi^{(\infty)} \leq e^{-\beta_1 y_0/2} \bar{\Psi}^{(\infty)} + \int_{y_0/2}^{+\infty} \bar{l}^{(\infty)}(y, z) dy dz.$$

Thus for y_0 large enough, we have $\Psi^{(\infty)} \leq \frac{\varepsilon_4}{2}$. The claim 5 is then proved.

Conclusion :

All these claims together lead to a contradiction with the equation (D.15). The proposition is thus proved.

D.9 Existence of travelling fronts and convergence

Now we are able to conclude with the proof of theorem D.3. Let us fix any sequence $(t_n)_{n \in \mathbb{N}}$ with $t_n \rightarrow +\infty$.

We set

$$w_n(y, z) = u(t_n, \tilde{x}(t_n) + y, z) \quad \text{for } (y, z) \in \mathbb{R}^N.$$

and we have the following lemma.

Lemma D.4 *There exists $w_\infty \in H_{ul}^2(\mathbb{R}^N)$ a travelling front of (P) such that, up to extraction, for all $L > 0$*

$$\sup_{(y,z) \in B(0,L)} |w_n(y, z) - w_\infty(y, z)| \xrightarrow{n \rightarrow +\infty} 0.$$

This lemma proves the theorem D.3 if $\mathcal{A}_{inv}$ is not empty.

Proof of lemma D.4 :

Let us write for $(y, z) \in \mathbb{R}^N$

$$\bar{w}_n(y, z) = \partial_t u(t_n, \tilde{x}(t_n) + y, z).$$

By compactity, there exist $w_\infty \in H_{ul}^2(\mathbb{R}^N)$ and $\bar{w}_\infty \in L_{ul}^2(\mathbb{R}^N)$ such that, up to extraction, for all $L > 0$

$$w_n \rightarrow w_\infty \text{ in } H^2([-L, L]^N) \quad \text{and} \quad \bar{w}_n \rightarrow \bar{w}_\infty \text{ in } L^2([-L, L]^N).$$

According to proposition D.2 we have $\bar{w}_\infty + \tilde{c}w_\infty = 0$ and passing to the limit in (P) , we see that w_∞ is a solution of the equation

$$\Delta w + \tilde{c} \partial_x w - f(w, z) = 0.$$

w_∞ is a travelling front since for all $y \geq 0$ and for all $z \in \mathbb{R}^{N-1}$, $0 \leq w_\infty \leq v_{st}$, hence by the parabolic maximum principle $w_\infty \xrightarrow{x \rightarrow +\infty} 0$ uniformly in $z \in \mathbb{R}^{N-1}$ and by definition of $\tilde{x}$, $w_\infty \not\equiv 0$.

Now $\psi_- = \lim_{x \rightarrow -\infty} w$ exists uniformly for $z \in \mathbb{R}^{N-1}$ and is positive since the energy

$$x \mapsto \int_{\mathbb{R}^{N-1}} \frac{|\nabla_z w_\infty(x, z)|^2}{2} + F(w_\infty(x, z), z) dz$$

increases with respect to x ($c > 0$).

Now the uniform convergence on $B(0, L)$ for any $L > 0$ is easy to prove.

Indeed (as shown in the section D.2) ∇w_n and ∇w_∞ are bounded uniformly in n and (y, z) , so if there exists $\varepsilon > 0$ such that for all n

$$\sup_{(y,z) \in B(0,L)} |w_n(y, z) - w_\infty(y, z)| \geq \varepsilon,$$

the L^2 -convergence is contradicted.

In fact, we have a slightly better result exposed in theorem D.4. Indeed the solution is exponentially decreasing in $|z|$, thus for z large enough $\sup |w_n(y, z) - w_\infty(y, z)|$ tends to 0 and the same manner, for y large enough $\sup |w_n(y, z) - w_\infty(y, z)|$ tends to 0 when $n \rightarrow +\infty$. Indeed w_∞ is uniformly exponentially decreasing toward 0 when $y \rightarrow +\infty$ and w_n too due to the parabolic maximum principle and equation (D.6).

So we obtain uniform convergence on $[-L, +\infty[\times \mathbb{R}^{N-1}$ for all $L > 0$.

The problem would now be to prove that this limit travelling front do not depend on the sequence (t_n) . We know that $\tilde{c}$ depends only on f and not on $(t_n)_{n \in \mathbb{N}}$, but for the moment we have not found any result on unicity of travelling front up to shifting for this nonlinearity.

D.10 Study of $\mathcal{A}_{inv}$

D.10.1 A sufficient condition for invasion to occur

This subsection is devoted to the proof of the following proposition.

Proposition D.3 *Let us choose $u_0 \in \mathcal{A}$. If*

$$\int_L^0 \int_{\mathbb{R}^{N-1}} \frac{|\nabla u_0(x, z)|^2}{2} + F(u_0(x, z), z) dz dx \xrightarrow{L \rightarrow +\infty} -\infty,$$

$$\text{then } u_0 \in \mathcal{A}_{inv} = \left\{ u_0 \in \mathcal{A} \mid \exists \varepsilon > 0 \limsup_{t \rightarrow +\infty} \sup_{x \geq \varepsilon t, z \in \mathbb{R}^{N-1}} u(t, x, z) > 0 \right\}.$$

The proof of this proposition will need the following lemma.

Lemma D.5 *For any $h \in L^\infty(\mathbb{R})$,*

$$\text{if } \int_{-L}^0 h(x) dx \xrightarrow{L \rightarrow +\infty} -\infty, \text{ then } \int_{-\infty}^0 e^{cx} h(x) dx \xrightarrow{c \rightarrow 0^+} -\infty.$$

Proof of lemma D.5 :

Let us set

$$H(x) = \int_x^0 h(y) dy \quad \text{and} \quad I(c) = \int_{-\infty}^0 e^{cx} h(x) dx.$$

Since $H'(x) = -h(x)$, by integrating by part, we obtain

$$I(c) = \int_{-\infty}^0 c e^{cx} H(x) dx.$$

Let us fix $M > 0$ as large as wanted. There exists $L > 0$ such that $H(x) \leq -M$ for $x \leq -L$, thus we obtain

$$I(c) \leq -M e^{-cL} + (1 - e^{-cL}) \max_{x \in \mathbb{R}} H(x).$$

The right-hand side converges toward $-M$ when $c \rightarrow 0^+$, the lemma is thus proved.

Let us now turn to the proof of the proposition.

- First let us prove that the hypothesis of the proposition implies that

$$\forall t \geq 0 \quad \int_{-L}^0 \int_{\mathbb{R}^{N-1}} \frac{|\nabla u(t, x, z)|^2}{2} + F(u(t, x, z), z) \, dz dx \xrightarrow{L \rightarrow +\infty} -\infty.$$

Indeed, for $L > 0$ we can set

$$\varphi_L(x) = \begin{cases} e^{x+L} & \text{if } x \leq -L, \\ 1 & \text{if } -L \leq x \leq 0, \\ e^{-x} & \text{if } x \geq 0, \end{cases}$$

and

$$\Phi_L(t) = \iint \varphi_L \left(\frac{|\nabla u|^2}{2} + F(u, z) \right) dx dz.$$

According to the calculations of the beginning of section D.4, we have

$$\begin{aligned} \Phi'_L(t) &= - \iint \phi_L \partial_t u^2 dz dx - \iint \phi'_L \partial_t u \partial_x u dz dx \\ &\leq \iint_{x \notin [-L, 0]} \phi_L |\nabla u|^2 dz dx \\ &\leq C \|u(t)\|_{H_{ul}^1}. \end{aligned}$$

Φ'_L is thus bounded with respect to t and L and since $\Phi_L(0) \xrightarrow{L \rightarrow +\infty} -\infty$, the above result is proved.

- For $t \geq 0$, we set

$$\bar{x}(t) = \sup \{x \in \mathbb{R} \mid \exists z \in \mathbb{R}^{N-1} \quad u(t, x, z) > v_{st}\} \in [-\infty, +\infty].$$

$\bar{x}(t) = -\infty$ if the set is empty. Up to changing the origin of time, we may assume that $\forall t \geq 0 \quad \bar{x}(t) < +\infty$ since $u_0 \in \mathcal{A}$. According to the lemma (with $h(x) = \int_{\mathbb{R}^{N-1}} \frac{|\nabla u|^2}{2} + F(u, z) dz$) and to the preceding point, we have

$$\int_{-\infty}^0 \int_{\mathbb{R}^{N-1}} e^{cx} \left(\frac{|\nabla u(0, x, z)|^2}{2} + F(u(0, x, z), z) \right) dz dx \xrightarrow{c \rightarrow 0^+} -\infty. \quad (\text{D.21})$$

- Now we will prove that $\limsup_{t \rightarrow +\infty} \frac{\bar{x}(t)}{t} > 0$. This will indeed implies that $u_0 \in \mathcal{A}$. Let us suppose by contradiction that $\limsup_{t \rightarrow +\infty} \frac{\bar{x}(t)}{t} \leq 0$.

We will study the energy of the solution in a travelling referential of speed $c > 0$ with $t_{init} = 0$ and $x_{init} = 0$. c will be chosen small enough to have a contradiction. As in

section D.6, we define $\Phi(s)$, $\mathcal{D}(s)$, $\Psi(s)$ and $\Theta(s) = \int_{S_{far}(s)} \psi(s, y) dy$. Proceeding as in the section D.6.2 and since $S_{far}(s) \subset]-\infty, \bar{y}(s)]$ and $\bar{y}(s) = \bar{x}(s) - cs \xrightarrow{s \rightarrow +\infty} -\infty$, we have

$$\Theta(s) \leq C_5 e^{-\beta_1 \gamma_1 s}$$

where $C_5 = \frac{1}{\beta_1} \max_{s \in [0, +\infty[} e^{\beta_1 \bar{x}(s)}$. Thus

$$\int_0^{+\infty} \Psi(s) ds \leq \frac{1}{\varepsilon_3} \Psi(0) + \frac{C_3 C_5}{\beta_1 \gamma_1}$$

and since $\Psi(0)$ is bounded with respect to $c > 0$, $\int_0^{+\infty} \Psi(s) ds$ is also bounded with respect to $c > 0$.

- Moreover since $\bar{y}(s) \xrightarrow{s \rightarrow +\infty} -\infty$, we have $\liminf_{s \rightarrow +\infty} \Phi(s) \geq 0$ as in section D.7.
- To conclude, we recall that

$$\Phi(s) \leq \Phi(0) + K_2 \int_0^s \Psi(s) ds$$

and according to equation (D.21), $\Phi(0) \xrightarrow{c \rightarrow 0^+} -\infty$ which implies a contradiction with $\liminf_{s \rightarrow +\infty} \Phi(s) \geq 0$.

D.10.2 Construction of $u_0 \in \mathcal{A}_{inv}$

In order to construct $u_0 \in \mathcal{A}_{inv}$, we have to study in more details the possible profiles of the travelling front and specially their energy.

Lemma D.6 *There exists $R_2 > 0$ such that for all $R > R_2$ a solution $\phi > 0$ of (P_∞) verifies*

$$E(\phi) = \int_{\mathbb{R}^{N-1}} \frac{|\nabla \phi|^2}{2} + F(\phi, z) dz < 0.$$

Using this lemme, it is easy to construct a function $u_0 \in \mathcal{A}_{inv}$. For example, we can set

$$u_0(x, z) = \begin{cases} \phi(z) & \text{if } x \leq 0, \\ \phi(z) e^{-x} & \text{if } x > 0. \end{cases}$$

This function clearly satisfy all the hypothesis.

Let us now turn to the proof of the lemma.

Proof of lemma D.6 :

Let us recall the equation. For a profile ϕ of a travelling front, we have

$$(P_\infty) \quad -\Delta\phi + f(\phi, z) = 0, \quad z \in \mathbb{R}^{N-1},$$

$\phi \in C^1(\mathbb{R}^{N-1})$ and exponentially decreasing in $|z| \rightarrow +\infty$.

Multiplying (P_∞) by ϕ and using Green-Riemann formula, we obtain

$$\int_{\mathbb{R}^{N-1}} \frac{|\nabla\phi|^2}{2} + f(\phi, z)\phi dz = 0,$$

thus

$$E(\phi) = \int_{\mathbb{R}^{N-1}} F(\phi, z) - f(\phi, z)\phi dz$$

for a solution of (P_∞) . For $|z| > R$, we have $F(\phi, z) - f(\phi, z)\phi < 0$ since $\phi > 0$. The problem is thus to study $F(\phi, z) - f(\phi, z)\phi = -G(\phi) + g(\phi)\phi$ for $z \in B(0, R)$.

Clearly, $\phi \mapsto -G(\phi) + g(\phi)\phi$ is continuous on $[0, 1]$ so it is bounded by a constant $C_6 > 0$ and moreover $-G(1) + g(1) = -G(1) < 0$ since $\theta < \frac{1}{2}$. Let us fix $\varepsilon \in]0, G(1)[$. We can define $\phi_l < 1$ such that for all $\phi \geq \phi_l$, we have $-G(\phi) + g(\phi)\phi < -\varepsilon$.

We now have to compare the sizes of the sets $\{z \in B(0, R) | \phi(z) \geq \phi_l\}$ where $-G(\phi) + g(\phi)\phi < -\varepsilon$ and $\{z \in B(0, R) | \phi(z) < \phi_l\}$ where $-G(\phi) + g(\phi)\phi \in [-\varepsilon, C_6]$ for a profile ϕ .

First we will study the case of dimension $N = 2$. So here ϕ refer to the solution ϕ_+ constructed in theorem D.1 for R large enough. We have already shown that if R is large enough, then $\phi(0) = \phi_0 > \phi_l$. Now, we recall that we have

$$\frac{1}{2}\phi'(z)^2 + G(\phi(z)) = G(\phi(0)).$$

So if we set $z_l = \max\{z \geq 0 | \phi(z) \geq \phi_l\} > 0$, we have

$$z_l = \frac{1}{\sqrt{2}} \int_{\phi_l}^{\phi_0} \frac{du}{\sqrt{G(\phi_0) - G(u)}} \quad (\text{D.22})$$

while

$$R - z_l = \frac{1}{\sqrt{2}} \int_{\phi(R)}^{\phi_l} \frac{du}{\sqrt{G(\phi_0) - G(u)}} \quad (\text{D.23})$$

where $\phi(R) \in [0, 1]$.

The right-hand part of equation (D.23) can be bounded by C_7 with respect to R , while z_l can be as large as wanted if ϕ_0 is close enough to 1 which comes down to R large enough. To sum up, $E(\phi) < 0$ for R large enough.

Finally, if $N \geq 3$ the solution constructed in theorem D.2 for R large enough is greater than the solution ϕ_+ constructed in theorem D.1 if $N = 2$ for a similar equation. Thus we obtain

$$E(\phi) \leq -\text{vol}(B(0, 1))z_l^{N-1}\varepsilon + C_7C_8$$

and $z_l \rightarrow +\infty$ for $R \rightarrow +\infty$.

D.11 Conclusion

In this paper, we have proved the existence of a travelling front solution of a biological problem, precisely a reaction-diffusion equation of bistable type in a cylinder coupled with an equation of diffusion and absorption outside the cylinder, if the radius of the cylinder is large enough. We have used the method developed by Emmanuel Risler in [75] with some modifications. This method gives us the existence of a front and a beginning of proof for the convergence toward this front, but it is impossible to conclude about convergence without the unicity of travelling front up to shifting. To prove the unicity up to shifting of the travelling fronts, we could try to adapt the method of Berestycki and Nirenberg in [10] and Vega in [?] which has been developed on bounded cylinders.

D.12 Appendix : Maximum principle

D.12.1 Theorem

We set

$$Pu(t, x, z) = \partial_t u(t, x, z) - \Delta u(t, x, z) - g(u(t, x, z))1_{\{|y| \leq R\}} - \alpha u(t, x, z)1_{\{|y| > R\}}$$

Let $\Omega_1 = \{(x, z) \in \mathbb{R}^N, |z| < R\}$ and $\Omega_2 = \{(x, z) \in \mathbb{R}^N, |z| > R\}$.

In the following, all the functions are supposed to have the same regularity as exposed in section D.2.

Théorème D.5 *Let u^+ and u^- be two bounded uniformly continuous functions defined on $\mathbb{R} \times \mathbb{R}^N$.*

We suppose

$$\begin{aligned} Pu^- &\leq Pu^+ & t \in \mathbb{R}, (x, z) \in \mathbb{R}^N, \\ \limsup_{|z| \rightarrow \infty} u^- - u^+ &\leq 0 & t \in \mathbb{R}, x \in \mathbb{R}. \end{aligned}$$

where the limits are uniform with respect to t and x . If moreover g is nonincreasing on $] -\infty, \sup u^-]$, then $u^- \leq u^+$ on $\mathbb{R} \times \mathbb{R}^N$.

Remark : If the functions are independant of the time t , we obtain an elliptic comparison principle.

This theorem has been prooved by F. Hamel in [43] in the case where the functions are twice derivable in space on the whole domain. This proof is largely inspired by Hamel's proof.

D.12.2 Proof

Since u^+ and u^- are bounded, for $\varepsilon > 0$ large enough we have $u^- - \varepsilon \leq u^+$ on $\mathbb{R} \times \mathbb{R}^N$. We set

$$\varepsilon_* = \inf\{\varepsilon > 0 \mid u^- - \varepsilon \leq u^+ \text{ on } \mathbb{R}_+ \times \mathbb{R}^N\}.$$

By continuity, we have $u^- - \varepsilon_* = u^+$. Our goal is to show that $\varepsilon_* = 0$.

Suppose that $\varepsilon_* > 0$.

Let ε_k be a positive sequence such that $\varepsilon_k < \varepsilon_*$ and $\varepsilon_k \rightarrow \varepsilon_*$ for $k \rightarrow \infty$.

Let $(t_k, x_k, z_k) \in \mathbb{R}_+ \times \mathbb{R}^N$ such that

$$u^-(t_k, x_k, z_k) - \varepsilon_k > u^+(t_k, x_k, z_k).$$

Since

$$\limsup_{|z| \rightarrow +\infty} u^- - u^+ \leq 0$$

and $\varepsilon_* > 0$, $\{z_k\}$ is bounded. Up to extraction of some subsequence, we can suppose $z_k \rightarrow Z$ for a $Z \in \mathbb{R}^{N-1}$.

We can also suppose $t_k \rightarrow T \in [-\infty, +\infty]$.

We set

$$u_k^-(t, x, z) = u^-(t + t_k, x + x_k, z + z_k)$$

and

$$u_k^+(t, x, z) = u^+(t + t_k, x + x_k, z + z_k)$$

for $t \in \mathbb{R}$ and $(x, z) \in \mathbb{R}^N$. Finally, we set

$$w_k = u_k^+ - u_k^- + \varepsilon_*.$$

Since u^+ and u^- are uniformly continuous, C^1 and piecewise C^2 in space, up to extraction of some subsequence, there exists w such that $w_k \rightarrow w$ locally uniformly and in $C_{loc}^{0,1}([-\infty, +\infty[\times \mathbb{R}^N)$ and in $C_{loc}^{1,2}([-\infty, +\infty[\times \Omega_1^Z \cup \Omega_2^Z)$ in space, where

$$\Omega_1^Z = \{(x, z) \in \mathbb{R}^N, |z + Z| < R\} \text{ and } \Omega_2^Z = \{(x, z) \in \mathbb{R}^N, |z + Z| > R\}.$$

We have

$$w \geq 0 \quad \text{on }]-\infty, +\infty[\times \mathbb{R}^N$$

by definition of ε_* and

$$w(0, 0, 0) = 0$$

by definition of t_k, x_k and z_k .

Moreover,

$$\begin{aligned} P(u_k^+) &= \partial_t u_k^+ - \Delta u_k^+ - g(u_k^+) 1_{\{|z+z_k| \leq R\}} - \alpha u_k^+ 1_{\{|z+z_k| > R\}} \\ &\geq \partial_t u_k^- - \Delta u_k^- - g(u_k^-) 1_{\{|z+z_k| \leq R\}} - \alpha u_k^- 1_{\{|z+z_k| > R\}} \\ &\geq \partial_t (u_k^- - \varepsilon_*) - \Delta (u_k^- - \varepsilon_*) - g(u_k^- - \varepsilon_*) 1_{\{|z+z_k| \leq R\}} \\ &\quad - \alpha (u_k^- - \varepsilon_*) 1_{\{|z+z_k| > R\}} \end{aligned}$$

since $Pu^- \leq Pu^+$ and g is nonincreasing on $] -\infty, \sup u^-]$.

Finally, since u^+ and u^- are bounded and g is locally Lipschitz, there exists $C \geq 0$ such that

$$\partial_t w_k - \Delta w_k + Cw_k \geq 0.$$

By passing to the limit as $k \rightarrow +\infty$ locally uniformly in $\mathbb{R} \times \mathbb{R}^N$, we obtain

$$\partial_t w - \Delta w + Cw \geq 0.$$

There are two cases.

If $|Z| = R$ and $w(t, x, z) > 0$ for $|z + Z| \neq R$ (if not we can applied the case $|Z| \neq R$ with another point that $(0, 0, 0)$), by the strong maximum principle on Ω_1^Z (see for example [69] page 174), we have

$$\frac{\partial w}{\partial \nu_1}(0, 0, 0) < 0$$

where ν_1 is the outward normal vector of Ω_1^Z . And by the strong maximum principle on Ω_2^Z , we have

$$\frac{\partial w}{\partial \nu_2}(0, 0, 0) < 0$$

where $\nu_2 = -\nu_1$ is the outward normal vector of Ω_2^Z . Thus we get a contradiction since w is C^1 in space.

If $|Z| \neq R$, there are once again two cases.

- If $(0, 0, 0) \in \Omega_2^Z$, we choose a domain $D \in \mathbb{R}^N$ large enough so that $w > \varepsilon_*/2$ somewhere near the border and $D \cap \Omega_1^Z = \emptyset$. It is possible since

$$\limsup_{|z| \rightarrow +\infty} u^- - u^+ \leq 0.$$

Then by the strong maximum principle, we obtain $w = 0$ on $\mathbb{R} \times D$. And we get a contradiction with $w > \varepsilon_*/2$ near the border.

- If $(0, 0, 0) \in \Omega_1^Z$, then by the parabolic maximum principle, $w = 0$ on $\mathbb{R}_- \times \Omega_1^Z$. Hence by continuity of w , $w = 0$ for $t \leq 0$ and $(x, z) \in \partial\Omega_1^Z$ and by continuity of the first derivative,

$$\frac{\partial w}{\partial \nu_1} = 0 \text{ for } t \leq 0 \text{ and } (x, z) \in \partial\Omega_1^Z.$$

Then since $\partial\Omega_2^Z = \partial\Omega_1^Z$,

$$\frac{\partial w}{\partial \nu_2} = 0 \text{ for } t \leq 0 \text{ and } (x, z) \in \partial\Omega_2^Z.$$

Hence the minimum is also reached in Ω_2^Z and we can apply the preceding case.

D.12.3 Corollaries and extension

With almost the same proof, it is easy to show the following theorem.

Théorème D.6 *Let u^+ and u^- be two bounded uniformly continuous functions defined on $\mathbb{R}_+ \times \mathbb{R}^N$.*

We suppose

$$\begin{aligned} Pu^- &\leq Pu^+ & t \in \mathbb{R}_+^* \quad (x, z) \in \mathbb{R}^N, \\ u^- &\leq u^+ & t = 0, (x, z) \in \mathbb{R}^N, \\ \limsup_{|z| \rightarrow \infty} u^- - u^+ &\leq 0 & t > 0, x \in \mathbb{R}. \end{aligned}$$

where the limit are uniform in t and x .

Then $u^- \leq u^+$ on $\mathbb{R}_+ \times \mathbb{R}^N$.

The proof of this theorem is almost the same as the one of the preceding theorem, but we can use the classical parabolic maximum principle that apply whatever the monotony of g is.

The following classical corollaries are important too.

Corollaire D.4 *A bounded solution of $Pu = 0$ with $u \rightarrow 0$ for $|z| \rightarrow +\infty$ and with limit for $x \rightarrow \pm\infty$ verifies*

$$0 \leq u \leq 1.$$

Corollaire D.5 *A bounded solution of $Pu = 0$ with initial condition $u = u_0$ for $t = 0$, with $u \rightarrow 0$ for $|z| \rightarrow +\infty$ and with limit for $x \rightarrow \pm\infty$ verifies*

$$0 \leq u \leq 1$$

if $0 \leq u_0 \leq 1$

Indeed for $u^+ = 1$, we have $Pu \geq 0$.

We have a slightly better estimation. Let us set

$$\beta = \frac{N-2}{2R} + \sqrt{\left(\frac{N-2}{2R}\right)^2 + \alpha}.$$

Proposition D.4 *Let u be a bounded solution of $Pu = 0$ with initial condition $u = u_0$ for $t = 0$, $u \rightarrow 0$ for $|z| \rightarrow +\infty$.*

We suppose that u has limits for $x \rightarrow \pm\infty$. Moreover we suppose that there exists $C > e^{\sqrt{\beta}R}$ such that $0 \leq u_0 \leq \min\{1, C \exp(-\sqrt{\beta}|z|)\}$.

Then $0 \leq u \leq \min\{1, C \exp(-\sqrt{\beta}|z|)\}$.

Let us set $u^+(t, x, z) = C \exp(-\sqrt{\beta}|z|)$ and $u^- = u$.

We have $Pu(t, x, z) \geq 0$ for $|z| > R$, but not necessarily for $|z| \leq R$. Moreover u^+ is not C^1 in $z = 0$, but with the same notations as in the theorem, it is easy to show that $Z > R$. Indeed $C > e^{\sqrt{\beta}R}$ implies $u^+(t, x, z) > 1$ for $|z| \leq R$ and by the preceding corollary, $u^- = u \leq 1$. Since $Z > R$, the end of the proof is exactly the same as in the theorem.

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Liste des abbréviations

ACI Action Concertée Incitative

AVC Accident Vasculaire Cérébral

DCE Dépression Corticale Envahissante

EDP Equation aux Dérivées Partielles

EDO Equation Différentielle Ordinaire

SD Spreading Depression (DCE en anglais)

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Bibliographie

- [1] Adams, J.M. ; Cory, S. The Bcl-2 protein family : arbiters of cell survival. *Science* **1998**, 281 (5381), 1322-1326.
- [2] Aitken, P.G. ; Jing, J. ; Young, J. ; Friedman, A. ; Somjen, G.G. Spreading depression in human hippocampal tissue in vitro. Third IBRO Congr. Montreal Abstr., **1991**, 329.
- [3] Aronson, D.G. ; Weinberger, H.F. Nonlinear diffusion in population genetics, combustion, and nerve pulse propagation. *Partial differ. Equat. relat. Top.* **1975**, Lect. Notes Math. 446, 5-49.
- [4] Attwell, D ; Laughlin, S.B. An Energy Budget for Signaling in the Grey Matter of the Brain. *Journal of Cerebral Blood Flow and Metabolism*, **2001**, 21 (10), 1133-1145.
- [5] Back, T. ; Hirsch, J.G. ; Szabo, K. ; Gass, A. Failure to demonstrate peri-infarct depolarizations by repetitive MR diffusion imaging in acute human stroke. *Stroke* **2000**, 31 (12), 2901-2906.
- [6] Barber, P.A. ; Auer, R.N. ; Buchan, A.M. ; Sutherland, G.R. Understanding and managing ischemic stroke. *Canadian Journal of Physiological Pharmacology* **2001**, 79, 283-296.
- [7] Bellomo, N. From the mathematical kinetic theory to modelling complex systems in applied sciences. *Int. J. Mod. Phys.* **2004**, B 18, No.4-5, 487-500.
- [8] Berestycki, H. ; Hamel, F. Front propagation in periodic excitable media, *Commun Pure Appl Math* **2002**, 55 (8), 949-1032.
- [9] Berestycki, H. ; Hamel, F. Non-existence de fronts progressifs pour une équation de réaction-diffusion de type bistable. *C R Acad Sci, Paris* **1995**, *Sér. I* 321 (3), 287-292.
- [10] Berestycki, H. ; Nirenberg, L. Travelling fronts in cylinders. *Ann Inst Henri Poincaré* **1992**, *Anal. Non linéaire* 9 (5), 497-572.
- [11] Berestycki, H. ; Nirenberg, L. Monotonicity, symmetry and antisymmetry of solutions of semilinear elliptic equations. [J] *J. Geom. Phys.* **1988** 5, No.2, 237-275.

- [12] Brown, A.M. ; Wender, R. ; Ransom, B.R. Ionic mechanisms of aglycemic axon injury in mammalian central white matter. *J Cereb Blood Flow Metab* **2001**, 21 (4), 385-395.
- [13] Chan, P.H. *Cerebrovascular Disease 22nd Princeton Conference*. Cambridge University Press, 2002.
- [14] Chapuisat, G. Existence and non-existence of curved front solution of a biological equation. Preprint.
- [15] Chapuisat, G. ; Grenier, E. ; Dronne, M.A. ; Hommel, M. ; Boissel, J.P. A global model of ischemic stroke with stress on spreading depression. Preprint.
- [16] Chapuisat, G. Discussion of a simple model of spreading depression. To appear in ESAIM Proc.
- [17] Chapuisat, G. ; Grenier, E. Existence and nonexistence of traveling wave solutions for a bistable reaction-diffusion equation in an infinite cylinder whose diameter is suddenly increased. *Commun. Partial Differ. Equations* (**2005**) 30, No.10-12, 1805-1816
- [18] De Keyser, J. ; Sulter, G. ; Luiten, P.G. Clinical trials with neuroprotective drugs in acute ischaemic stroke : are we doing the right thing ? *Trends Neurosci* **1999**, 22 (12), 535-540.
- [19] Dienel, G.A. ; Cruz, N.F. Neighborly interactions of metabolically-activated astrocytes in vivo. *Neurochem Int* **2003**, 43 (4-5), 339-354.
- [20] Dirnagl, U. ; Iadecola, C. ; Moskowitz, M.A. Pathobiology of ischaemic stroke : an integrated view. *Trends Neurosci* **1999**, 22 (9), 391-397.
- [21] Dronne, M.A. ; Boissel, J.P. ; Grenier, E. A mathematical model of ion movements in grey matter during a stroke. *J Theor Biol.* **2005** Dec 17.
- [22] Dronne, M.A. ; Boissel, J.P. ; Grenier, E. ; Gilquin, H. ; Cucherat, M. ; Hommel, M. ; Barbier, E. ; Bricca, G. Mathematical modelling of an ischemic stroke : an integrative approach. *Acta Biotheoritica* **2004**, 52, 255-272.
- [23] Dronne, M.A. ; Grenier, E. ; Gilquin, H. Modelization of spreading depressions following Nedergaard, preprint (2004).
- [24] Dronne, M.A. ; Grenier, E. ; Gilquin, H. Influence of brain geometry on spreading depressions : a computationnal study, preprint (2004).
- [25] Dronne, M.A. ; Grenier, E. ; Gilquin, H. A global model of stroke, preprint (2003).
- [26] Ducros, A. ; Tournier-Lasserre, E. ; Boussier, M.G. The genetics of migraine, *Lancet Neurol* **2002**, 1 (5), 285-293.
- [27] Duval, V. ; Chabaud, S. ; Girard, P. ; Cucherat, M. ; Hommel, M. ; Boissel, J.P. Physiologically based model of acute ischemic stroke. *Journal of Cerebral Blood Flow and Metabolism* **2002**, 22, 1010-1018.

- [28] Evans, L.C. Partial differential equations. Graduate Studies in Mathematics. 19. Providence, RI : American Mathematical Society (AMS). xvii, 662 p. **1998**.
- [29] Fife, P.C. ; MacLeod, J.B. The approach of solutions of nonlinear diffusion equations to travelling front solutions. Arch Ration Mech Anal **1977**, 65, 335-361.
- [30] Fife, P.C. ; MacLeod, J.B. A phase plane discussion of convergence to travelling fronts for nonlinear diffusion. Arch Ration Mech Anal **1981**, 75, 281-314.
- [31] Friedlander, R.M. Apoptosis and caspases in neurodegenerative diseases. N Engl J Med **2003**, 348 (14), 1365-1375.
- [32] Gardner, R.A. Topological methods for the study of travelling wave solutions of reaction diffusion systems. Reaction-diffusion equations **1990**, Proc. Symp. Year, Edinburgh/UK 1987-1988, 173-198.
- [33] Gasquet, C. ; Witomski, P. Analyse de Fourier et applications. Filtrage, calcul numérique, ondelettes. Enseignement des Mathématiques. Paris : Masson. xi, **1995**, 355 p.
- [34] Gidas, B. ; Ni, W.M. ; Nirenberg, L. Symmetry and related properties via the maximum principle. Commun. Math. Phys. **1979** 68, 209-243.
- [35] Gilbarg, D. ; Trudinger, N.S. *Elliptic partial differential equations of second order* ; Classics in Mathematics ; Springer :Berlin, 2001.
- [36] Gorji, A. ; Scheller, D. ; Straub, H. ; Tegtmeyer, F. ; Kohling, R. ; Hohling, J.M. ; Tuxhorn, I. ; Ebner, A. ; Wolf, P. ; Werner Panneck, H. ; Oppel, F. ; Speckmann, E.J. Spreading depression in human neocortical slices. Brain Res **2001**, 906 (1-2), 74-83.
- [37] Gorji, A. Spreading depression : a review of the clinical relevance. Brain Res Rev **2001**, 38 (1-2), 33-60.
- [38] Grafstein, B. Neuronal release of potassium during spreading depression. In M.A.B. Brazier (eds), *Brain function : Cortical Excitability and Steady Potentials*. University of California Press : Berkeley, 1963.
- [39] Hacke, W. ; Kaste, M. ; Fieschi, C. ; Toni, D. ; Lesaffre, E. ; von Kummer, R. ; Boysen, G. ; Bluhmki, E. ; Hoxter, G. ; Mahagne, M.H. ; et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS), Jama **1995**, 274 (13), 1017-1025.
- [40] Hacke, W. ; Kaste, M. ; Fieschi, C. ; von Kummer, R. ; Davalos, A. ; Meier, D. ; Larrue, V. ; Bluhmki, E. ; Davis, S. ; Donnan, G. ; Schneider, D. ; Diez-Tejedor, E. ; Trouillas, P. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators, Lancet **1998**, 352 (9136), 1245-1251.

- [41] Hadjikhani, N. ; Sanchez del Rio, M. ; Wu, O. ; Schwartz, D. ; Bakker, D. ; Fischl, B. ; Kwong, K.K. ; Cutrer, F.M. ; Rosen, B.R. ; Tootell, R.B. ; Sorensen, A.G., Moskowitz, M.A. Mechanism of migraine aura revealed by functional MRI in human visual cortex. *Proc. Natl. Acad. Sci. USA* **2001**, 98, 4687-4692.
- [42] Hamel, F. ; Monneau, R. ; Roquejoffre, J.M. Existence and qualitative properties of multidimensional conical bistable fronts. *Discrete Contin. Dyn. Syst.* **2005** 13, No.4, 1069-1096.
- [43] Hamel, F. *Conical fronts and more general curved fronts for homogeneous equations in $\mathbb{R}^N$* , Ecole d'été Dynamique des équations aux dérivées partielles, Grenoble 2005.
- [44] Hamel, F. Reaction-diffusion problems in cylinders with no invariance by translation. I : Small perturbations. *Ann Inst Henri Poincaré* **1997**, *Anal. Non Linéaire* 14 (4), 457-498.
- [45] Hamel, F. Reaction-diffusion problems in cylinders with no invariance by translation. II : Monotone perturbations. *Ann Inst Henri Poincaré* **1997**, *Anal. Non Linéaire* 14 (5), 555-596.
- [46] Hamel, F. Problèmes de réaction-diffusion sans invariance par translation dans des cylindres infinis. *C R Acad Sci, Paris* **1995**, *Sér. I* 321 (7), 855-860.
- [47] Heinemann, U. ; Lux, H.D. Ceiling of stimulus induced rises in extracellular potassium concentration in the cerebral cortex of cat. *Brain Res.* **1977**, 120(2), 231-249.
- [48] James, M.F. ; Smith, J.M. ; Boniface, S.J. ; Huang, C.L. ; Leslie, R.A. Cortical spreading depression and migraine : new insights from imaging ?. *Trends Neurosci* **2001**, 24 (5) 266-271.
- [49] Jones, T.H. ; Morawetz, R.B. ; Crowell, R.M. ; Marcoux, F.W. ; FitzGibbon, S.J. ; DeGirolami, U. ; Ojemann, R.G. Thresholds of focal cerebral ischemia in awake monkeys. *J Neurosurg* **1981**, 54 (6), 773-782.
- [50] Kager, H. ; Wadman, W.J. ; Somjen, G.G. Conditions for the triggering of spreading depression studied with computer simulations. *J Neurophysiol.* **2002**, 88(5), 2700-2712.
- [51] Kato, H. ; Kogure, K. Biochemical and molecular characteristics of the brain with developing cerebral infarction. *Cell Mol Neurobiol* **1999**, 19 (1), 93-108.
- [52] Kato, T. The Cauchy problem for quasi-linear symmetric hyperbolic systems. *Arch. Ration. Mech. Anal.* **1975** 58, 181-205.
- [53] Kempfski, O. ; Otsuka, H. ; Seiwert, T. ; Heimann, A. Spreading depression induces permanent cell swelling under penumbra conditions. *Acta Neurochir Suppl* **2000**, 76, 251-255.
- [54] Kernbaum, S. ; Costa, J.M. ; Delatour, F. ; Faurisson, F. ; Girod, C. ; Kamoun, P. ; Rouveix, B. *Dictionnaire de médecine* **1998**, Flammarion Médecine-Sciences, Paris, 1030p.

- [55] Larsson, S. ; Thomée, V. Partial differential equations with numerical methods. Texts in Applied Mathematics. 45. Berlin : Springer. 2003 ; 259 p.
- [56] Leão, A.A.P. Spreading depression of activity in the cerebral cortex. J Neurophysiol, **1944**, 10 (7), 359-390.
- [57] Li, H. ; Colbourne, F. ; Sun, P. ; Zhao, Z. ; Buchan, A.M. ; Iadecola, C. Caspase inhibitors reduce neuronal injury after focal but not global cerebral ischemia in rats. Stroke **2000**, 31 (1), 176-182.
- [58] Lin, J.H. ; Weigel, H. ; Cotrina, M.L. ; Liu, S. ; Bueno, E. ; Hansen, A.J. ; Hansen, T.W. ; Goldman, S. ; Nedergaard, M. Gap-junction-mediated propagation and amplification of cell injury. Nat Neurosci **1998**, 1 (6), 494-500.
- [59] Mayevsky, A. ; Doron, A. ; Manor, T. ; Meilin, S. ; Zarchin, N. ; Ouaknine, G.E. Cortical spreading depression recorded from the human brain using a multiparametric monitoring system. Brain Res. **1996**, 740, 268-274.
- [60] Martins-Ferreira, H. ; Nedergaard, M. ; Nicholson, C. Perspectives on spreading depression. Brain Res Rev **2000**, 32 (1) 215-234.
- [61] McLachlan, R.S. ; Girvin, J.P. Spreading depression of Leao in rodent and human cortex. Brain Res. **1994**, 666(1), 133-136.
- [62] Mies, G. ; Iijima, T. ; Hossmann, K.A. Correlation between peri-infarct DC shifts and ischaemic neuronal damage in rat. Neuroreport, **1993**, 4, 709-711.
- [63] Murray, J.D. *Mathematical biology*, Biomathematics ; Springer-Verlag :Berlin, 1993.
- [64] Nedergaard M. ; Cooper, A.J. ; Goldman, S.A. Gap junctions are required for the propagation of spreading depression. J Neurobiol **1995**, 28 (4), 433-444.
- [65] Nicholson, C. Volume transmission and the propagation of spreading depression. In A. Lehmenkühler, K.-H. Grottemeyer and F. Tegtmeier (eds), *Migraine : basic mechanisms and treatment*. Urban & Schwarzenberg : München, 293-308, 1993.
- [66] Obeidat, A.S. ; Jarvis, C.R. ; Andrew, R.D. Glutamate does not mediate acute neuronal damage after spreading depression induced by O₂/glucose deprivation in the hippocampal slice. J Cereb Blood Flow Metab **2000**, 20 (2), 412-422.
- [67] Phan, T.G. ; Wright, P.M. ; Markus, R. ; Howells, D.W. ; Davis, S.M. ; Donnan, G.A. Salvaging the ischaemic penumbra : more than just reperfusion ? Clin Exp Pharmacol Physiol **2002**, 29 (1-2), 1-10.
- [68] Petrovits, A. ; Nair, C. *Epidemiology of stroke in Canada*, 1994, Statistics Canada Health Reports 6, 39-42.
- [69] Protter, M.H. ; Weinberger, H.F. *Maximum principles in differential equations*. Prentice hall : Englewood Cliffs, 1967.
- [70] Rash, J.E. ; Yasumura, T. ; Dudek, F.E. ; Nagy, J.I. Cell-specific expression of connexins and evidence of restricted gap junctional coupling between glial cells and between neurons. J Neurosci **2001**, 21 (6), 1983-2000.

- [71] Ramson et al 2003 Voir MAD car pas dans biblio (cellules gliales)
- [72] Reggia, J. ; Montgomery, D. A computational model of visual hallucinations in migraine. *Comput Biol Med* **1996**, 26 (2), 133-141.
- [73] Renardy, M. ; Rogers, R.C. *An introduction to partial differential equations*. Texts in Applied Mathematics. 13. New York : Springer-Verlag. xiii, 428 p, 1993.
- [74] Revett, K. ; Ruppin, E. ; Goodall, S. ; Reggia, J.A. Spreading depression in focal ischemia : a computational study. *J Cereb Blood Flow Metab* **1998**, 18 (9), 998-1007.
- [75] Risler, E. Global convergence toward travelling fronts for spatially extended gradient-like systems. Preprint.
- [76] Rogers, S.J. ; Sherman, D.G. Pathophysiology and treatment of acute ischemic stroke, *Clin Pharm* **1993**, 12 (5), 359-376.
- [77] Roquejoffre, J.-M. Eventual monotonicity and convergence to travelling fronts for the solutions of parabolic equations in cylinders. *Ann Inst Henri Poincaré* **1997**, *Anal. Non linéaire* 14 (4), 499-552.
- [78] Rouach, N. ; Avignone, E. ; Mème, W. ; Koulakoff, A. ; Venance, L. ; Blomstrand, F. ; Giaume, C. Gap junctions and connexin expression in the normal and pathological central nervous system. *Biol Cell* **2002**, 94 (7-8) 457-475.
- [79] Rozental, R. ; Andrade-Rozental, A.F. ; Zheng, X. ; Urban, M. ; Spray, D.C. ; Chiu, F.C. Gap junction-mediated bidirectional signaling between human fetal hippocampal neurons and astrocytes. *Dev Neurosci* **2001**, 23 (6), 420-431.
- [80] Sakoh, M. ; Ostergaard, L. ; Gjedde, A. ; Rohl, L. ; Vestergaard-Poulsen, P. ; Smith, D.F. ; Le Bihan, D. ; Sakaki, S. ; Gyldensted, C. Prediction of tissue survival after middle cerebral artery occlusion based on changes in the apparent diffusion of water. *J Neurosurg* **2001**, 95 (3), 450-458.
- [81] Shapiro, B. Osmotic forces and gap junctions in spreading depression : a computational model. *J Comput Neurosci* **2001**, 10 (1), 99-120.
- [82] Smoller, J. *Shock waves and reaction-diffusion equations*, 2nd Ed. ; Grundlehren der Mathematischen Wissenschaften ; Springer-Verlag :New-York, 1994 ; 258p.
- [83] Somjen, G. *Ions in the Brain : Normal Function, Seizures, and Stroke*. Oxford University Press : New York, 2004.
- [84] Šramka, M. ; Brozek, G. ; Buresš, J. ; Nádvorník, P. Functional ablation by spreading depression : possible use in human stereotactic surgery. *Appl. Neurophysiol.* **1977**, 40, 48-61.
- [85] Strong, A.J. ; Fabricius, M. ; Boutelle, M.G. ; Hibbins, S.J. ; Hopwood, S.E. ; Jones, R. ; Parkin, M.C. ; Lauritzen, M. Spreading and synchronous depressions of cortical activity in acutely injured human brain. *Stroke* **2002**, 33 (12), 2738-2743.

- [86] Tuckwell, H.C. ; Predictions and properties of a model of potassium and calcium ion movements during spreading cortical depression. *Int J Neurosci* **1980**, 10 (2-3), 145-164.
- [87] Vega, J.M. The asymptotic behavior of the solutions of some semilinear elliptic equations in cylindrical domains. *J. Differ. Equations* **1993** 102, No.1, 119-152.
- [88] Vega l'autre article...
- [89] Volpert, V.A. ; Volpert, A.I. Multidimensional travelling waves in the bistable case. Amann, H. (ed.) et al., *Progress in partial differential equations. Papers from the 3rd European conference on elliptic and parabolic problems, Pont-à-Mousson, France, June 1997. Vol. 2.* Harlow : Longman. Pitman Res. Notes Math. Ser. 384, 156-173, 1998.
- [90] Yi, C.S. ; Fogelson, A.L. ; Keener, J.P. ; Peskin, C.S. A mathematical study of volume shifts and ionic concentration changes during ischemia and hypoxia. *J Theor Biol* **2003**, 220 (1), 83-106.