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Análisis teórico y numérico y control de varios modelos de crecimiento de tumores

Memoria presentada por
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para optar al grado de Doctor en Matemáticas

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Theoretical and numerical analysis and control of some models that describe tumor growth

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Introducción

En esta memoria se presentan resultados relativos a la existencia de solución de varios modelos matemáticos que describen el crecimiento tumoral. En general, los modelos que simulan el crecimiento de un tumor son problemas de frontera libre en los que interesa estudiar cómo cambia la forma del tumor con el tiempo; dichos modelos están basados en sistemas gobernados por ecuaciones en derivadas parciales no lineales.

También se abordarán cuestiones relacionadas con la aproximación de las soluciones y con su determinación en la práctica. El análisis teórico es completado en varios casos con el estudio de técnicas de control, orientadas hacia la determinación de terapias.

Por último, estudiaremos problemas de control óptimo correspondientes a algunos procesos de solidificación.

Modelado de tumores

El estudio de la naturaleza del cáncer se remonta a la antigüedad. De hecho, las primeras operaciones parecen haberse dado en Egipto, antes del año 3.500 a.C. Desde entonces, esta enfermedad se ha convertido en una de las grandes amenazas de la humanidad. Tanto es así, que se cree que el cáncer puede superar a las enfermedades cardíacas como causa más importante de muerte prematura en el mundo occidental.

Un informe reciente sobre la tasa de cáncer mundial, realizado por la Agencia Internacional para la Investigación sobre el Cáncer de la Organización Mundial de la Salud, asegura que la zona más afectada por esta enfermedad en adultos es Norte América, seguida muy de cerca por Europa Occidental, Australia y Nueva Zelanda. En 1994, en Inglaterra, por ejemplo, una de cada tres personas era propensa a contraer la enfermedad durante su vida, con un aumento probable a una de cada dos en 2010.

Reflexionando sobre la gravedad de la enfermedad, podemos deducir que el énfasis puesto en la investigación del cáncer ha beneficiado a varias áreas del conocimiento médico y no sólo a la correspondiente a esta enfermedad. De hecho, el esfuerzo para combatir el cáncer ha conducido a muchos descubrimientos en el campo de la Biología Celular.

En la batalla contra el cáncer, han emergido a lo largo de los últimos siglos muchas estrategias, técnicas experimentales y enfoques teóricos. No obstante, como en el caso de muchas otras áreas científicas, tenemos la posibilidad de recurrir al modelado matemático para interpretar y comprender los resultados experimentales. De ahí que el estudio matemático del crecimiento de tumores sea un tema de actualidad desde hace varios años. Las primeras aportaciones en este campo se efectuaron en las primeras décadas del siglo XX.

Siguiendo las reflexiones de Byrne [10], para desarrollar tratamientos eficaces es importante identificar los mecanismos que controlan el crecimiento del cáncer, cómo interactúan y cómo pueden ser manipulados para erradicar (o controlar) la enfermedad. Para llevar a cabo tales propósitos, es preciso efectuar un gran número de experimentos, unido a una dedicación considerable de tiempo, aunque no siempre: a través del desarrollo y solución de modelos matemáticos que describen diferentes aspectos del crecimiento del tumor, la Matemática Aplicada tiene el potencial de prevenir la experimentación excesiva y también “suministrar” mecanismos que, quizás, puedan controlar el desarrollo de los tumores sólidos.

Así, en el mundo de las Ciencias Experimentales y de la Medicina Clínica, se reconoce hoy día que el modelo matemático puede ser útil, a la vista de la gran dificultad que lleva consigo distinguir entre los distintos mecanismos a partir de las técnicas médicas y experimentales actuales. Una de las características esenciales del papel que las Matemáticas pueden jugar aquí es que los resultados a los que conducen pueden ser comparados con el trabajo experimental, sugiriendo eventualmente tratamientos terapéuticos.

Existe una cantidad considerable de publicaciones dedicadas a presentar resultados teóricos y experimentales que describen el crecimiento de tumores (para una lista completa de referencias, véase [1]). Podemos indicar varios hechos destacables y algunos aspectos presentes en casi todas ellas:

- El énfasis se ha puesto casi exclusivamente en el modelado determinista, aunque existen algunos artículos significativos que usan modelos estocásticos.

- El estudio de estos resultados parece haberse iniciado con Hill en 1928, que describió y analizó la difusión de células tumorales en tejidos sanos [32]. Él entendió que “la difusión de sustancias a través de células y tejidos es un factor determinante en muchos de los procesos vitales” y utilizó métodos matemáticos para estudiar una serie de importantes procesos fisiológicos, como la difusión de oxígeno en un sólido (donde es consumido por procesos metabólicos), la difusión de ácido láctico desde un sólido hacia el exterior, la difusión del oxígeno de un vaso sanguíneo en una región externa, etc. Entre 1928 y los años 70, los principales esfuerzos se dedicaron precisamente a describir este tipo de fenómenos.

  Si bien los procesos de difusión se convertirían más tarde en una parte importante del modelado, los primeros estudios matemáticos de tumores sólidos estaban centrados exclusivamente en la dinámica de crecimiento (véase, por ejemplo, [39]). Mientras continuaban los estudios experimentales sobre la Radioterapia, muchos investigadores se interesaron por el papel de la célula tumoral hipóxica en la radio-sensibilidad de los tumores, a partir de los estudios de irradiación de cortes del tumor *in vitro* realizados por Cramer (1934). En 1955, Thomlinson y Gray [45] propusieron un modelo matemático para la difusión y el consumo de oxígeno, para completar una investigación experimental sobre ciertos carcinomas bronquiales, que crecen en barras sólidas que “están fuera de los capilares, compuestas por las células alimentadas por la difusión de los metabolitos hacia el interior del estroma que rodean”.

  Fue Burton [9] en 1966, sin embargo, quien desarrolló un modelo de difusión que examinaba tanto la distribución de oxígeno en un tumor esférico “donde el suministro de sangre está completamente confinado sobre la superficie”, como el resultante “radio relativo de la zona central respecto del radio total”.

  En 1964, el trabajo sobre la angiogénesis tumoral realizado por Folkman [24] surgió del descubrimiento de los nódulos tumorales avasculares latentes *in vivo*. El interés surgido en los nódulos avasculares que preceden a la angiogénesis, así como el modelo esferoide multicelda, originó varios nuevos enfoques para el modelado matemático de los tumores sólidos. Greenspan [30] extendió en 1972 los modelos desarrollados por Burton y Thomlinson y Gray, introduciendo una tensión superficial entre las células tumorales vivas, con el fin de mantener una masa sólida compacta, suponiendo que “los residuos celulares necróticos se desintegran continuamente en compuestos químicos más simples que son permeables a través de las membranas celulares”. De esta forma, la pérdida de volumen del tejido debido a la necrosis se sustituye por el movimiento hacia el interior de las células de la región externa, como resultado de las fuerzas de adhesión y la tensión superficial, lo que explica la existencia de un estado estacionario en el tamaño del tumor.

- Aunque el estudio del crecimiento del tumor sólido había disfrutado de una considerable popularidad entre los matemáticos a partir de las primeras décadas del siglo XX, poco se había asimilado respecto a “los factores que determinan el mecanismo y el curso del tiempo de liberación de células tumorales”. De hecho, no fue hasta la década de los 70 cuando fueron propuestos modelos matemáticos para ilustrar la dinámica del proceso metastásico; así aparecieron los primeros análisis teóricos de tumores avasculares y esferoides multicelulares. Este desarrollo se debió en gran parte a Liotta y sus colaboradores.

  Liotta et al. [36] desarrollaron un primer modelo experimental “para cuantificar algunos de los principales procesos iniciados al trasplantar un tumor que culminan en metástasis pulmonares”, con la investigación de la tasa de entrada de las células tumorales en la circulación. El estudio demostró la presencia de células tumorales (por separado y en grupos) en la aspersión, poco después de la aparición de la red vascular del tumor, con la concentración de las células tumorales aumentando muy rápidamente inicialmente y disminuyendo posteriormente. En un estudio posterior, Liotta y colaboradores (1976) publicaron algunos trabajos teóricos sobre la terapia de micrometástasis y la cuantificación de la eliminación y la capacidad invasiva de las células tumorales.

- El estudio de tumores en fase avascular fue perfeccionado enormemente en la década de los 80, con aportaciones (entre otras) de Adam y Maggelakis entre 1986 y 1990. Al igual que Glass [28] en 1973, Adam [2] se dio cuenta en 1986 de los importantes resultados experimentales sobre el papel de los inhibidores de crecimiento en el desarrollo del tumor publicado varias décadas antes. Mientras que Glass había supuesto que la regulación de crecimiento se producía por un mecanismo de cambio discontinuo para el control de la actividad mitótica, con una producción del inhibidor espacialmente uniforme, Adam mantenía que una función de control mitótica espacialmente dependiente reflejaba mejor las observaciones experimentales y permitía un mayor estudio teórico. En contraste con el trabajo de Glass, este nuevo modelo predecía que, para un valor dado de la variable adimensional crítica, n^0, existe una gama limitada de tamaños de tejido estable, lo que aumenta monótonamente con el valor de la variable adimensionalizada. Cualitativamente, el modelo demostraba la sensibilidad del crecimiento de los tejidos a una fuente no uniforme de inhibidor.

  Pero el modelo matemático propuesto por Adam no incorporaba un mecanismo de pérdida de volumen tal como la necrosis, por lo que la estabilidad sólo podría producirse por inhibición del crecimiento total en todo el tejido (una noción parcialmente incongruente en el contexto del cáncer). El núcleo necrótico fue simplemente incorporado en este estudio como una fuente de inhibición del crecimiento (Adam y Maggelakis [3]), en lugar de representar un mecanismo de pérdida de volumen. Sin embargo, el modelo permitía hacer una comparación interesante con los trabajos anteriores de Greenspan en la investigación de dos fuentes distintas de la inhibición del crecimiento: la inhibición por la difusión de los desechos necróticos y la inhibición a través de un subproducto de los procesos que ocurren dentro de las células vivas.

  Desde esta época, se ha prestado mucha más atención a la descripción numérica o cuantitativa de los problemas considerados y al control óptimo orientado a terapias.

- Desde los 90, el número de publicaciones ha crecido enormemente. Se ha conseguido modelar fenómenos mucho más complejos e interesantes desde el punto de vista médico, como los procesos multifase, la invasión y metástasis y la angiogénesis. No sólo ha continuado el estudio de los tumores avasculares y vasculares (junto con sus homólogos *in vitro*, los esferoides multicelulares) con la aparición de algunos nuevos enfoques, sino que otras investigaciones experimentales en la biología del tumor, como la internalización de células marcadas en esferoides, se han convertido en objeto de estudio matemático. También se han publicado interesantes contribuciones al estudio de la invasión tumoral y la metástasis, además de las publicaciones en las áreas de tensiones residuales en el tumor y la mecánica del tumor multifase:

- La migración célular en esferoides multicelulares y cuerdas tumorales.
- Modelos multifase.
- Modelos mecánicos y modelos de formación de tensiones residuales.
- Los nuevos enfoques matemáticos para el estudio de la invasión tumoral y la metástasis.
- Modelos avanzados de crecimiento de tumores avasculares/vasculares y esferoides multicelulares.

En el primer Capítulo de esta memoria presentaremos varios problemas de frontera libre que modelan el crecimiento de un tumor e indicaremos resultados de existencia de solución relativos a cada uno de ellos. Estos modelos están basados en leyes de conservación, leyes constitutivas y procesos de transporte-reacción-difusión dentro del tumor. El tumor será tratado como un fluido incompresible, no teniéndose en cuenta la elasticidad del tejido. Las fuerzas de adhesión célula-célula se modelan mediante una tensión superficial en el tejido tumoral exterior. Por otra parte, el crecimiento de la masa del tumor viene gobernado por un equilibrio entre la mitosis celular y la apoptosis (entendida ésta última como la muerte programada de las células).

Nos centraremos en un modelo relativamente sencillo, descrito en los artículos [26], [5]. Consideraremos de inicio tres tipos de células en el tumor: proliferantes, quiescentes y necróticas. Supondremos que la razón de cambio que sufren las células es función de la concentración de nutrientes $C = C(x,t)$ y que ésta satisface una EDP de difusión en el dominio $\Omega(t)$ ocupado por el tumor en el instante t:

$$\begin{cases} C_t - \Delta C + \lambda C = 0, & x \in \Omega(t),\ t \in (0,T) \quad (\lambda > 0) \\ C = C_0, & x \in \partial\Omega(t),\ t \in (0,T) \end{cases} \tag{1}$$

Debido a la proliferación y eliminación de las células, hay un movimiento continuo en el tumor, que representaremos por el campo de velocidades $\overrightarrow{v}$. Supondremos que esta velocidad viene dada por la *ley de Darcy*, ley experimental bien conocida para el flujo de un fluido en un medio poroso:

$$\overrightarrow{v} = -\nabla \Pi. \tag{2}$$

Aquí, Π denota la presión a la que se ven sometidas las células tumorales (otra de las incógnitas del problema).

Una de las dificultades del estudio es que, en este tipo de problemas, el dominio ocupado por el tumor es desconocido, lo que convierte la superficie de éste en una incógnita. El movimiento de la frontera libre está determinado por la igualdad

$$\frac{\partial \Pi}{\partial n} = -\overrightarrow{v} \cdot \overrightarrow{n} = -V_n, \tag{3}$$

donde $\overrightarrow{n}$ es el vector normal exterior a la frontera y V_n es la velocidad de la frontera libre en la dirección del vector normal. Para un estudio detallado de éste y otros modelos, se pueden consultar, por ejemplo, las referencias [6], [11].

En este contexto los resultados numéricos no son numerosos y un análisis de los mismos parece de gran interés. La resolución numérica del problema que estamos considerando se apoyará en métodos de *dominios ficticios* y métodos de *conjuntos de nivel*.

En los Capítulos 2 y 3 nos centraremos en modelos que describen el crecimiento de un tumor influenciado por la acción mecánica de fármacos. De nuevo, nos enfrentaremos a la dificultad que supone el hecho de que el dominio ocupado por las células tumorales es desconocido.

Presentaremos las ideas básicas sobre el control de estos modelos en un caso sencillo: la ecuación que describe la evolución del *glioblastoma* (un tipo de tumor cerebral primario que se diferencia de la mayoría de los demás por una invasión agresiva de los tejidos circundantes normales, véase [44]):

$$\begin{cases} c_t - \nabla \cdot (D(x)\nabla c) = \rho c - G(\beta, c) \\ + \dots \end{cases} \tag{4}$$

Aquí, $c = c(x,t)$ es la concentración de células tumorales en la posición x y tiempo t, $D = D(x)$ es positiva y (por ejemplo) constante a trozos y representa el coeficiente de difusión de células en el tejido cerebral (en unidades de $\mathrm{cm}^2/\text{día}$), $\rho > 0$ es el índice neto de crecimiento de células tumorales, incluyendo proliferación, pérdida y muerte y $G = G(\beta, c)$ es un término de perturbación que se debe a la acción de una terapia concreta. La estructura de G cambia según los autores. Por ejemplo,

$$G(\beta, c) = \beta c \quad \text{y} \quad G(\beta, c) = \frac{m_1 \beta}{m_2 + \beta} c,$$

respectivamente en [42] y [33]; véase también [43].

En el caso más sencillo, $\beta = v 1_\omega$, donde $v = v(x,t)$ denota una función que podemos elegir libremente (el control). En casos más realistas, debemos imponer una o varias restricciones al control v: hay limitaciones en la talla, β es obtenido indirectamente (resolviendo otra ecuación, como cuando se recurre a la inmunoterapia), β tiene una estructura precisa, etc.

El estudio sobre la existencia de solución se realiza en el Capítulo 2. Dada una función de los estados c y β y la variable de control v, formularemos el correspondiente problema de control óptimo para (4): determinar controles v (por ejemplo en $L^2(\omega \times (0,T))$ y posiblemente sometidos a restricciones adecuadas) que, junto con las soluciones asociadas de (4), minimicen ésta.

La teoría de control óptimo permite resolver problemas de dinámica de naturaleza muy variada, donde la evolución de un sistema puede ser controlada en parte por las decisiones de un agente.

En nuestro contexto, un ejemplo típico de funcional de coste es

$$J(v) = \frac{a}{2} \iint |c - c_d|^2 \, dx \, dt + \frac{b}{2} \iint |v|^2 \, dx \, dt, \tag{5}$$

donde $a, b > 0$ y las integrales se realizan en dominios adecuados. En el Capítulo 3 estudiaremos varias posibles elecciones de J que parecen razonables y resolveremos el correspondiente problema de control óptimo (existencia de control óptimo, caracterización y aproximación numérica).

Consideraremos sólo el caso en que los datos y las soluciones poseen simetría radial. Esto permite llegar a resultados mucho más precisos. Esta hipótesis está avalada por el hecho de que un tumor avascular es muy aproximadamente esférico en la primera fase de desarrollo.

Por otra parte, los problemas de controlabilidad para (4) consisten en determinar controles v, de nuevo por ejemplo en $L^2(\omega \times (0,T))$, tales que, en el instante $t = T$, la solución asociada a (4) coincida o al menos "se parezca" a una función deseada $\hat{c}_T$. En particular, la controlabilidad exacta a trayectorias consiste en encontrar controles tales que, en el instante final, la solución coincide con $\hat{c}_T = \hat{c}(T)$, donde $\hat{c}$ es una solución no controlada (es decir, una solución correspondiente a $v = 0$). Los problemas de controlabilidad son más complicados que los problemas de control óptimo y no serán tratados en esta memoria.

En el Capítulo 4, nos centraremos en el estudio de fenómenos de otro tipo. Más precisamente, consideraremos un modelo matemático que describe el proceso de *solidificación* de metales, uno de los problemas más difíciles de resolver en la Ingeniería desde los puntos de vista teórico y tecnológico. La naturaleza compleja de los fenómenos involucrados es un obstáculo para obtener soluciones de una manera sencilla. Para realizar esta tarea, se han de usar modelos matemáticos sofisticados, una vez más basados en sistemas de ecuaciones en derivadas parciales no lineales.

Consideraremos una cavidad rectangular Ω (llamada molde) con frontera $\partial\Omega$, llena de una aleación binaria incompresible y diluida, inicialmente en estado líquido, con temperatura uniforme y composición bajo la influencia de la gravedad. El soluto es el componente en menor cantidad, recibiendo el otro el nombre de solvente; juntos, forman la solución. La concentración es la variable que indica la proporción de soluto en la solución.

La aleación es vertida en el molde de tal manera que, en el tiempo $t = 0$, la temperatura del lado izquierdo de Ω se reduce de forma instantánea y es mantenida bajo el punto de refrigeración, mientras que los otros lados de Ω se mantienen aislados térmicamente (ver Fig. 1). Esto da lugar a

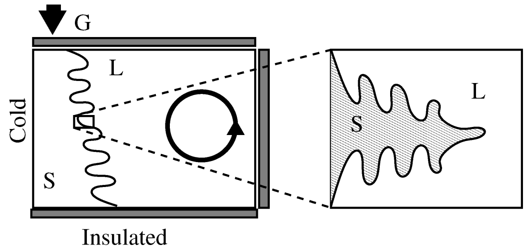

Figura 1: Visión esquemática del problema de la cavidad, con el detalle del frente de solidificación.

un gradiente de temperatura en la aleación. Si tenemos en cuenta la fuerza de gravedad, se obtiene además calor y transporte de soluto por convección. La acción conjunta de estos fenómenos puede introducir cambios en la densidad de la aleación. Por otra parte, en la región próxima al lado izquierdo del dominio experimenta un cambio de fase, pasando del estado líquido al estado sólido. La interfaz entre los estados líquido y sólido se llama frente de solidificación y, en general, puede tener una geometría muy irregular, presentando formas dendríticas, debido al rápido cambio de fase. De hecho, la formación de dendritas es una consecuencia de la inestabilidad del crecimiento del frente de solidificación.

Después de un tiempo, la aleación se encuentra en estado sólido. Si hacemos un análisis de la composición del material resultante, probablemente encontraremos variaciones del soluto. Estas variaciones se presentan en dos escalas. En la primera escala (macroscópica), el frente de solidificación actúa como un filtro en el soluto. El soluto es rechazado del estado sólido acumulado junto a la parte delantera y, entonces, se transporta al estado líquido. Este fenómeno se denomina *macro-segregación*. En la segunda escala (microscópica), una parte del soluto procedente del estado sólido es atrapado por las dendritas del frente de solidificación antes de que el transporte ocurra, generando alta concentración de granos de soluto. Éste es el fenómeno de *micro-segregación*.

En el Capítulo 4, presentamos varios resultados relacionados con el análisis teórico y el control del modelo de solidificación precedente.

Los resultados contenidos en los Capítulos 1 a 4 de esta memoria han dado lugar a varios trabajos, pendientes de publicación; véase [12, 15, 17, 18]; véase también [14]. Otros resultados adicionales están contenidos en los artículos [13, 16], actualmente en preparación.

A continuación, vamos a explicar con más detalle el desarrollo de cada uno de los Capítulos de esta memoria.

Análisis teórico y numérico de algunos modelos que describen el crecimiento de tumores

En la primera parte de esta memoria, se presentan los resultados conocidos de existencia de solución de un problema parecido a (1)–(3), donde aparece el nuevo término $\varepsilon_0 c_t$.

En el caso tridimensional, suponiendo que el dominio posee simetría radial, el problema se transforma en otro más sencillo:

$$
\left\{
\begin{array}{l}
\varepsilon_0 c_t = c_{rr} + \dfrac{2}{r} c_r - \lambda c, \quad 0 < r < R(t) \\[2ex]
c_r(0,t) = 0, \quad c(R(t),t) = \overline{c} \\[2ex]
c(r,0) = c_0(r), \quad 0 < r < R(0) \\[2ex]
\dot{R}(t) = \dfrac{1}{R(t)^2} \displaystyle\int_0^{R(t)} \mu\left(c(r,t) - \widetilde{c}\right) r^2 \, dr
\end{array}
\right. \tag{6}
$$

- Friedman y Reitich [27] demostraron, partiendo de datos pequeños, la existencia de soluciones radialmente simétricas globales en tiempo.
- En el caso de un tumor con núcleo necrótico, partiendo de datos pequeños, se puede probar la convergencia asintótica en tiempo hacia soluciones estacionarias radialmente simétricas (véase [22]).
- El esquema anterior también ha sido estudiado en presencia de inhibidores [21].

También describimos otro sistema asociado al crecimiento de un tumor [5], desarrollado con anterioridad por Greenspan [31], Byrne y Chaplain [11] y analizado con detalle por Bazaliy y Friedman [5], en ausencia de hipótesis de simetría.

En el tiempo t el tumor ocupa un dominio $\Omega(t)$ con frontera $\partial\Omega(t) = \Gamma(t)$. Denotemos la concentración de nutrientes por σ y la presión interna que causa el movimiento del material celular por p. El flujo neto de proliferación de las células tendrá por hipótesis la forma $\mu(\sigma - \tilde{\sigma})$, siendo $\mu, \tilde{\sigma} > 0$ constantes. Las incógnitas de nuestro problema, $p = p(x,t)$, $\sigma = \sigma(x,t)$, $\Omega = \Omega(t)$, han de verificar las ecuaciones

$$
\left\{
\begin{array}{ll}
\varepsilon_0 \sigma_t - \Delta\sigma + \sigma = 0, & x \in \Omega(t), \ t \in (0,T) \\
-\Delta p = \mu(\sigma - \tilde{\sigma}), & x \in \Omega(t), \ t \in (0,T)
\end{array}
\right. \tag{7}
$$

junto con las condiciones de contorno

$$
\left\{
\begin{array}{ll}
\sigma = \overline{\sigma}, & x \in \Gamma(t), \ t \in (0,T) \\
p = \gamma\kappa, & x \in \Gamma(t), \ t \in (0,T) \\
V_n = -\dfrac{\partial p}{\partial n}, & x \in \Gamma(t), \ t \in (0,T)
\end{array}
\right. \tag{8}
$$

y las condiciones iniciales

$$
\left\{
\begin{array}{ll}
\sigma_{|t=0} = \sigma_0, & x \in \Omega(0) \\
\Omega(0) \text{ dado} &
\end{array}
\right. \tag{9}
$$

donde γ, $\overline{\sigma} > 0$, κ es la curvatura de $\Gamma(t)$ (la curvatura media si $N = 3$), σ_0 es una función que toma valores positivos y $V_n = \overrightarrow{V} \cdot \overrightarrow{n}$ es la velocidad de la frontera libre en la dirección normal.

Se prueba en [5] que, si los datos $\Omega(0)$ y σ_0 son suficientemente regulares (*grosso modo*, de clase H^3), entonces existe $T_* > 0$ tal que, en $(0, T_*)$, el sistema (7)–(9) posee exactamente una solución regular.

La demostración de este resultado es técnicamente muy complicada. Se basa en introducir adecuados cambios de variable que permiten re-escribir el problema como una colección de problemas similares, formulados en abiertos fijos. Para cada uno de éstos, es preciso después proceder a una reformulación de tipo punto fijo; con ayuda de estimaciones adecuadas, se consigue finalmente probar la existencia de solucion regular.

Para la resolución numérica de (7)–(9), utilizaremos un esquema de discretización en tiempo que permite desacoplar las diferentes incógnitas. Partiendo del dominio inicial $\Omega(0)$, se calcula la concentración de nutrientes σ en cada instante posterior discretizando en tiempo y resolviendo la primera ecuación de (7) junto con la condición de contorno correspondiente en (8). Con este dato, se determina la presión p a partir de la segunda ecuación de (7) y la segunda condición frontera en (8).

Ambos problemas se deben resolver en un dominio diferente para cada etapa de tiempo (lo cual, al discretizar en espacio, significa en principio la necesidad de utilizar muchos mallados distintos). Conviene aplicar entonces un método que sirva para resolver cualquier problema de la forma

$$\left\{ \begin{array}{rcll} \alpha u - \beta \Delta u & = & f & \text{en} \quad \omega \\ u & = & g & \text{sobre} \quad \gamma = \partial\omega \end{array} \right. \tag{10}$$

donde ω es un abierto conexo y acotado variable, sin necesidad de cambiar el mallado.

Esto se consigue en esta memoria con el *método de dominios ficticios* [29]. La idea básica consiste en resolver en un abierto más grande (y geométricamente más simple) un problema similar, cuya solución sea de la forma $(\widetilde{u}, \lambda)$, con $\widetilde{u}$ tal que la restricción $u = \widetilde{u}|_\omega$ sea la solución de (10). Con ello se consiguen, al menos, dos ventajas desde el punto de vista computacional:

1. Se puede trabajar con mallados más regulares y se pueden aplicar métodos especiales de resolución rápida (por ejemplo, métodos para la resolución de problemas elípticos en dominios rectangulares).

2. El dominio extendido puede ser siempre el mismo. De esta forma, se puede utilizar un mallado fijo para todo el cálculo, eliminando la necesidad de remallar en cada etapa de tiempo.

Para calcular el nuevo dominio Ω en la siguiente etapa de tiempo, se utiliza un método de tipo *level set*, teniendo en cuenta que, a partir de la presión p y la tercera condición de (8), se puede conocer la componente normal de la velocidad de crecimiento de la frontera. Este método fue inicialmente desarrollado por Osher y Sethian (véase [41]) en un contexto más general y ha sido aplicado en una gran cantidad de situaciones desde entonces.

Las técnicas precedentes serán también usadas para resolver numéricamente el modelo correspondiente al crecimiento de un tumor con núcleo necrótico, descrito en [34]. En dicho modelo, consideraremos dos tipos de células (proliferantes y necróticas) y supondremos que el dominio que ocupa el tumor (de nuevo, una incógnita) viene dado por

$$\omega(t) = \omega_P(t) \cup \omega_N(t) \cup \Sigma_N(t),$$

donde $\omega_P(t)$ y $\omega_N(t)$ respectivamente denotan la región proliferante y el núcleo necrótico del tumor en el instante t. Por simplicidad, omitimos la derivada temporal de la concentración de nutrientes (esto es, suponemos que $\varepsilon_0 = 0$). El campo de velocidades $\overrightarrow{V}$ viene de nuevo dado por la ley de

Darcy y las ecuaciones que han de verificar σ, p, ω son las siguientes:

$$\begin{cases} \sigma - \Delta\sigma = 0, & x \in \omega(t),\ t \in (0,T) \\ \sigma = 1, & x \in \gamma(t),\ t \in (0,T) \\ -\Delta p = G(\sigma - A), & x \in \omega_P(t),\ t \in (0,T) \\ -\Delta p = -G\,G_N, & x \in \omega_N(t),\ t \in (0,T) \\ [p] = 0,\ \left[\dfrac{\partial p}{\partial n}\right] = 0, & x \in \Sigma_N(t),\ t \in (0,T) \\ p = \kappa, & x \in \gamma(t),\ t \in (0,T) \\ \dfrac{\partial p}{\partial n} = -V_n, & x \in \gamma(t),\ t \in (0,T) \end{cases} \tag{11}$$

De esta forma, tomando $N = 0$ obtenemos (7)–(9) con $\varepsilon_0 = 0$ como caso particular de (11). Para la resolución numérica de (11), utilizaremos de nuevo un esquema de discretización en tiempo que permite desacoplar las diferentes incógnitas, combinado con técnicas de dominios ficticios y conjuntos de nivel.

Las experiencias numéricas están realizadas tomando $\Omega = [-6,6] \times [-6,6]$ como dominio fijo. Los parámetros de discretización espacial son $h = 0.1$ (cuando la forma inicial del tumor se supone simétrica) y $h = 0.2$ (forma asimétrica); el paso de tiempo máximo vendrá dado por la correspondiente condición CFL.

En la literatura sobre el tema, se acepta que los distintos valores sobre los parámetros A y G determinan los diferentes niveles de vascularización en el crecimiento tumoral:

- Baja vascularización: $G \geq 0, A > 0$.
- Vascularización moderada: $G \geq 0, A \leq 0$.
- Alta vascularización: $G < 0$, $A < 0$ ó $A > 0$.

Así, hemos elegido valores particulares de G y A para reproducir los mismos experimentos descritos en Cristini, Lowengrub, Nie [20], Macklin [37].

Existencia de solución de algunos modelos que incluyen la acción de inhibidores

En el Capítulo 2, se describe un problema de crecimiento de un tumor en presencia de un inhibidor $\beta = \beta(x,t)$ y se estudia la existencia de solución.

Sea $\mathcal{O}$ un dominio acotado en $\mathbb{R}^N$ $(N = 2,3)$; se puede interpretar que $\mathcal{O}$ es el órgano donde se desarrolla el tumor. En nuestro modelo, denotaremos $\Omega(t) \subset \mathcal{O}$ la región ocupada por el tumor en el tiempo t y por $\partial\Omega(t)$ su frontera. El problema es el siguiente:

$$
\begin{cases}
\dfrac{\partial c}{\partial t} - \Delta c = \rho c - G(c,\beta), & x \in \Omega(t),\ t \in (0,T) \\[2mm]
\dfrac{\partial \beta}{\partial t} - \Delta \beta + m'\beta = -\widetilde{G}(c,\beta) + f, & x \in \mathcal{O},\ t \in (0,T) \\[2mm]
c(x,0) = c^0(x), & x \in \Omega(0) \\[2mm]
\beta(x,0) = \beta^0(x), & x \in \mathcal{O} \\[2mm]
c(x,t) = 0, & x \in \partial\Omega(t),\ t \in (0,T) \\[2mm]
\beta(x,t) = 0, & x \in \partial\mathcal{O},\ t \in (0,T) \\[2mm]
\dfrac{\partial c}{\partial n} \geq -kV_n & x \in \partial\Omega(t),\ t \in (0,T)
\end{cases}
\tag{12}
$$

Aquí, $\Omega(0)$ es dado; V_n es la velocidad de la frontera libre $\partial\Omega(t)$ en la dirección del vector normal exterior $\overrightarrow{n}$; esto es, $V_n = \overrightarrow{V} \cdot \overrightarrow{n}$. Por otra parte, $\rho, m' > 0$, $k \geq 0$ y f, G y $\widetilde{G}$ son funciones suficientemente regulares. En (12), $c = c(x,t)$ es la concentración de células tumorales, $\beta = \beta(x,t)$ es la densidad de población de un inhibidor y, en consecuencia, $-G(c,\beta)$ y $-\widetilde{G}(c,\beta)$ indican la forma en que β destruye las células tumorales y la pérdida de inhibidores debida a la acción de las células tumorales, respectivamente.

En una primera etapa, simplificaremos (12) suponiendo que no hay evolución en tiempo. Cambiemos ligeramente la notación utilizada hasta ahora. Sea $\mathcal{O}$ un dominio acotado fijo en $\mathbb{R}^N$ e introduzcamos el conjunto

$$
\widetilde{K} = \{(v,w) \ \in \ H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O}) \ : \quad v \geq 0\}
$$

Consideraremos el problema estacionario

$$
\begin{cases}
c \in \ H_0^1(\mathcal{O}) \cap \mathcal{C}^0(\overline{\mathcal{O}}),\ \beta \in H_0^1(\mathcal{O}) \\[2mm]
-\Delta c \geq \rho c - G(c,\beta) & \text{en } \ \mathcal{O} \\[2mm]
-\Delta c - \rho c + G(c,\beta) = 0 & \text{en } \ \Omega = \{x \in \mathcal{O} \ : \ c(x) > 0\} \\[2mm]
c \geq 0 & \text{en } \ \mathcal{O} \\[2mm]
-\Delta\beta + m'\beta = -Bc + f & \text{en } \ \mathcal{O}
\end{cases}
\tag{13}
$$

Teorema 1. *Supongamos que, en* (13)*,* $G \in \mathcal{C}^0(\mathbb{R} \times \mathbb{R})$ *y* $0 \leq G \leq C$*. Supongamos además que* ρ *no es un autovalor del operador Laplace-Dirichlet en* $\mathcal{O}$*,* $B > 0$ *y* $f \in L^2(\mathcal{O})$*. Entonces existe al menos una solución* (c,β) *de* (13)*, con* $c \in W^{2,p}(\mathcal{O})$ *para todo* $p \in [1,+\infty)$ *y* $\beta \in H^2(\mathcal{O})$*.*

La prueba de este resultado utiliza ideas previamente introducidas por Friedman para la resolución de problemas de problemas de frontera libre de tipo obstáculo; véase [25]. Se basa en el estudio de un problema penalizado:

$$
\begin{cases}
-\Delta c \ = \ \rho\, c + F - \gamma_{\varepsilon,M}(c) & \text{en} \quad \mathcal{O} \\[2mm]
\quad c \ = \ 0 & \text{sobre} \quad \partial\mathcal{O}
\end{cases}
\tag{14}
$$

Para demostrar la existencia de solución de (14), se descompone el problema ($c = u + w$) en dos problemas auxiliares, uno de ellos finito-dimensional, probamos la existencia de solución de cada uno de ellos y aplicamos un argumento de punto fijo que recurre al teorema de Schauder. Esto conduce a la existencia de solución $c_{\varepsilon,M}$ de (14) para cada $\varepsilon > 0$ y cada $M > 0$. Como consecuencia del principio del máximo, se prueba que

$$|\gamma_{\varepsilon,M}(c_{\varepsilon,M})| \leq C,$$

de donde se deduce que $c_{\varepsilon,M}$ está uniformemente acotada en $W^{2,p}(\mathcal{O})$. En consecuencia, es posible pasar al límite para acabar probando que existe al menos una solución (c, β) de (13).

Volvamos al problema de evolución (12). Supongamos dado $c^0 \in H_0^1(\mathcal{O}) \cap \mathcal{C}^0(\overline{\mathcal{O}})$ con $c^0 \geq 0$ y que $\Omega^0 := \{x \in \mathcal{O} \;:\; c^0(x) > 0\}$ es un abierto conexo completamente contenido en $\mathcal{O}$. Supongamos también que $\beta^0 \in H_0^1(\mathcal{O})$ y $\beta^0 \geq 0$. Fijemos $Q = \mathcal{O} \times (0,T)$, $\Sigma = \partial\mathcal{O} \times (0,T)$ y el conjunto

$$K = \left\{(v,w) \in H^1(Q)^2 \;:\; v \geq 0, \quad v|_{t=0} = c^0,\; w|_{t=0} = \beta^0, \quad v|_\Sigma = w|_\Sigma = 0\right\}.$$

Podemos formular el problema del siguiente modo:

$$\left\{\begin{array}{ll}
\multicolumn{2}{c}{c \in H_0^1(Q) \cap \mathcal{C}^0(\overline{Q}), \quad \beta \in H^1(Q)} \\[2ex]
\multicolumn{2}{c}{Q_+ := \{(x,t) \in Q \;:\; c(x,t) > 0\}, \quad \dfrac{\partial^2 c}{\partial x_i \partial x_j} \in L^2(Q_+) \quad \forall i,j} \\[2ex]
c_t - \Delta c = \rho c - G(c,\beta), & (x,t) \in Q_+ \\[2ex]
c \geq 0, & (x,t) \in Q \\[2ex]
\beta_t - \Delta\beta + m'\beta = -\widetilde{G}(c,\beta) + f, & (x,t) \in Q \\[2ex]
c = 0,\; \beta = 0, & (x,t) \in \Sigma \\[2ex]
\dfrac{\partial c}{\partial n} \geq -kV_n, & x \in \partial\Omega(t),\; t \in (0,T) \\[2ex]
c(x,0) = c^0(x),\; \beta(x,0) = \beta^0(x), & x \in \mathcal{O}
\end{array}\right. \tag{15}$$

Para cada solución (c,β) de (15), denotaremos $\Omega(t)$ el correspondiente conjunto abierto

$$\Omega(t) = \{x \in \mathcal{O} \;:\; c(x,t) > 0\}, \quad t \in [0,T].$$

Una formulación débil de (15) es entonces la siguiente:

$$\left\{\begin{array}{l}
-k \displaystyle\iint_Q H_0(c)\,(v-c)_t\; dx\,dt + k \int_{\mathcal{O}} H_0(c)\,(v-c)\; dx\Big|_{t=T} \\[2ex]
\quad + \displaystyle\iint_Q \big(c_t\,(v-c) + \nabla c \cdot \nabla(v-c)\big)\, dx\,dt \\[2ex]
\quad + \displaystyle\iint_Q \big(\beta_t(w-\beta) + \nabla\beta \cdot \nabla(w-\beta) + m'\beta(w-\beta)\big)\; dx\,dt \\[2ex]
\geq \displaystyle\iint_Q (\rho c - G(c,\beta))\,(v-c)\, dx\,dt + \iint_Q \Big(-\widetilde{G}(c,\beta) + f\Big)\,(w-\beta)\, dx\,dt \\[2ex]
\forall (v,w) \;\in\; K,\; (c,\beta) \;\in\; K
\end{array}\right. \tag{16}$$

donde H_0 denota la función de Heaviside. Aquí, $G, \widetilde{G} \in \mathcal{C}^0(\mathbb{R} \times \mathbb{R})$, con $G, \widetilde{G} \geq 0$, $G\big|_{c=0} \equiv 0$; $k, m' > 0$ y $f \in L^2(Q)$. De hecho, se puede establecer la equivalencia de (15) y (16) bajo ciertas hipótesis de regularidad de la solución.

Consideremos ahora el problema aproximado siguiente:

$$\begin{cases} \displaystyle\iint_Q \left((c + kH_\delta(c))_t (v - c) + \nabla c \cdot \nabla(v - c)\right) dx\, dt \\ \qquad \displaystyle + \iint_Q \big(\beta_t(w - \beta) + \nabla\beta \cdot \nabla(w - \beta) + m'\beta(w - \beta)\big)\, dx\, dt \\ \displaystyle \geq \iint_Q (\rho c - G(c, \beta))(v - c)\, dx\, dt + \iint_Q \left(-\widetilde{G}(c, \beta) + f\right)(w - \beta)\, dx\, dt \\ \forall (v, w) \in K, \quad (c, \beta) \in K \end{cases} \tag{17}$$

donde H_δ es una aproximación (por ejemplo Lipschitz-continua) de la función de Heaviside H_0. Con un razonamiento análogo al usado en la prueba del teorema 1, se puede demostrar el resultado siguiente:

Teorema 2. *Supongamos que G, $\widetilde{G}$ están dados (por ejemplo) por*

$$G(c, \beta) = \frac{M_1 c^+ \beta^+}{M_2 c^+ \beta^+}, \quad \widetilde{G}(c, \beta) = Bc \quad \forall (c, \beta) \in \mathbb{R}^2.$$

Entonces existe al menos una solución (c, β) de (17) para cada $\delta > 0$.

Hay una dificultad para pasar al límite cuando $\delta \to 0$. De poder superarla, quedaría demostrada la existencia de solución del problema original (12), pues la formulación del problema obtenido y (15) son equivalentes. Hasta donde podemos saber, no obstante, la existencia de solución de (12), entendida en el sentido de (15), es una cuestión abierta.

Control óptimo de algunos modelos que describen el crecimiento tumoral

Como se explicó en la Introducción, en el Capítulo 3 de esta memoria consideraremos problemas de control óptimo asociados al modelo que describe la evolución del *glioblastoma*.

Sea $\omega \subset \mathcal{O}$ un dominio de pequeño tamaño. Supongamos que los dominios $\mathcal{O}$, ω son esféricos y $\Omega(t) = \{x \in \mathcal{O} \ : \ |x| < R(t)\}$, con $R \in W^{1,\infty}(0, T)$. Dado un conjunto convexo cerrado $\mathcal{U}_{ad} \subset U = L^2(\omega \times (0, T))$, denotamos Y_{ad} el conjunto de soluciones admisibles de (12), esto es:

$$Y_{ad} = \Big\{(v, \Omega, c, \beta) \ : \ (\Omega, c, \beta) \ \text{ es solución de (12) (junto con } v); \\ c(\cdot, t) \in H^2(\Omega(t)) \cap H^1_0(\Omega(t)) \text{ c.p.d.; } v \in \mathcal{U}_{ad}\Big\},$$

Supongamos que las dos primeras ecuaciones en (12) se satisfacen, al menos, en el sentido de las distribuciones, con lo que tienen sentido el resto de las ecuaciones y desigualdades en el problema. Consideraremos problemas de control óptimo con la estructura siguiente:

$$\begin{cases} \text{Hallar } (v^*, \Omega^*, c^*, \beta^*) \in Y_{ad} \text{ tales que} \\ J(v^*, \Omega^*, c^*, \beta^*) \leq J(v, \Omega, c, \beta) \quad \forall (v, \Omega, c, \beta) \in Y_{ad}. \end{cases} \tag{18}$$

A lo largo del Capítulo 3 estudiamos la existencia de solución de (18), su caracterización y aproximación numérica en el caso de los dos funcionales siguientes:

- $$J_1(v,\Omega,c,\beta) = \frac{\varepsilon_1}{2}\int_0^T R(t)|\dot{R}(t)|^2 dt + \frac{\varepsilon_2}{2}\iint_{\omega\times(0,T)} |v(x,t)|^2 dx\, dt \qquad (19)$$

- $$J_2(v,\Omega,c,\beta) = \frac{1}{2}\int_{\Omega(T)} |c(x,T) - c_d(x)|^2 dx + \frac{\varepsilon_1}{2}\int_0^T |\dot{R}(t)|^2 R(t)\, dt + \frac{\varepsilon_2}{2}\iint_{\omega\times(0,T)} |v(x,t)|^2 dx\, dt \qquad (20)$$

Aquí, $\varepsilon_1, \varepsilon_2$ son dos números enteros no negativos y $c_d \in L^2(\mathcal{O})$.

Considerando la primera elección de J, podemos enunciar el siguiente resultado:

Teorema 3. *Existe al menos una solución* $(v^*, \Omega^*, c^*, \beta^*)$ *de* (18), (19).

Para demostrar la existencia del control óptimo, partiremos de una sucesión minimizante $\{(v^n, \Omega^n, c^n, \beta^n)\} \subset Y_{ad}$, teniendo en cuenta que, como $J_1(v,\Omega,c,\beta) \geq 0$ para cada $\{v,\Omega,c,\beta\} \in Y_{ad}$, se tiene $\alpha := \inf_{Y_{ad}} J_1(v,\Omega,c,\beta) \geq 0$; dicha sucesión verifica:

$$\lim_{n\to\infty} J_1(v^n, \Omega^n, c^n, \beta^n) = \alpha.$$

Dividiremos la prueba en dos etapas.

- Primero, analizaremos si en algún sentido se tiene:

  $$\lim_{n\to\infty} (v^n, \Omega^n, c^n, \beta^n) = (v^*, \Omega^*, c^*, \beta^*) \in Y_{ad}.$$

  Para ello, estudiaremos algunas propiedades de c^n, β^n y deduciremos estimaciones apropiadas que permitan afirmar la existencia de subsucesiones débilmente convergentes. Entonces, comprobaremos que cualquiera de estas subsucesiones converge fuertemente y el correspondiente límite es solución del problema (12).

- Por último, demostraremos que $J_1(v^*, \Omega^*, c^*, \beta^*) = \alpha$. Basta probar que el funcional es secuencialmente débilmente semicontinuo inferiormente.

Una vez demostrado que (18) admite al menos una solución óptima para esta primera elección del funcional, el siguiente objetivo será caracterizar la solución en términos de condiciones de optimalidad adecuadas, es decir, deducir un sistema de ecuaciones que deben satisfacer tanto la solución óptima como el estado adjunto asociado.
El resultado que probamos es el siguiente:

Teorema 4. *Sea* (v,Ω,c,β) *una solución del problema de control* (18), (19). *Existen funciones* (S,ξ,η) *que resuelven el llamado problema adjunto*

$$\begin{cases} -\xi_t - \Delta\xi = \rho\xi - m\xi\beta_+ - m'\eta\beta, & x \in \Omega(t),\ t \in (0,T) \\ -\eta_t - \Delta\eta = -a\eta - m'\eta c - m\xi c 1_{\{\beta>0\}}, & (x,t) \in \mathcal{O}\times(0,T) \end{cases} \qquad (21)$$

$$\begin{cases} \xi(x,T) = 0, & x \in \Omega(T) \\ \eta(x,T) = 0, & x \in \mathcal{O} \\ S(T) = \dfrac{\varepsilon_1}{2\pi k}\dot{R}(T) \end{cases} \qquad (22)$$

$$
\left\{
\begin{array}{ll}
\dfrac{\partial \eta}{\partial n} = 0, & (x,t) \in \partial\mathcal{O} \times (0,T) \\
\xi(x,t) = S(t), & x \in \partial\Omega(t),\ t \in (0,T) \\
k\left[\dot{S}(t) + \left(\dot{R}^2(t) + N\dfrac{\dot{R}(t)}{R(t)}\right)S(t)\right] = k\dot{R}(t)\dfrac{\partial\xi}{\partial n}\Big|_{\partial\Omega(t)} + \dfrac{\varepsilon_1}{4\pi}\left(\dfrac{\dot{R}^2(t)}{R(t)} + 2\ddot{R}(t)\right)
\end{array}
\right. \tag{23}
$$

y tales que

$$
\iint_{\omega\times(0,T)} (\eta + \varepsilon_2 v)\,(w - v)\,dx\,dt \geq 0 \qquad \forall w \in \mathcal{U}_{ad}, \quad v \in \mathcal{U}_{ad}. \tag{24}
$$

En el caso del segundo funcional, los resultados que se obtienen son análogos. Por simplicidad, los enunciamos en un único resultado:

Teorema 5. *Existe al menos una solución óptima* $(v^*, \Omega^*, c^*, \beta^*)$ *del problema de control* (18), (20). *Por otra parte, para cada solución* (v, Ω, c, β) *de este problema de control, existen funciones* (S, ξ, η) *que resuelven el problema adjunto*

$$
\left\{
\begin{array}{ll}
-\xi_t - \Delta\xi = \rho\xi - m\xi\beta_+ - m'\eta\beta, & x \in \Omega(t),\ t \in (0,T) \\
-\eta_t - \Delta\eta = -a\eta - m'\eta c - m\xi c 1_{\{\beta>0\}}, & (x,t) \in \mathcal{O} \times (0,T)
\end{array}
\right. \tag{25}
$$

$$
\left\{
\begin{array}{ll}
\xi(x,T) = c(x,T) - c_d(x), & x \in \Omega(T) \\
\eta(x,T) = 0, & x \in \mathcal{O} \\
S(T) = \dfrac{1}{4\pi k R(T)} \displaystyle\int_{\partial\Omega(T)} |c(x,T) - c_d(x)|^2 d\Gamma + \dfrac{\varepsilon_1}{2\pi k}\dot{R}(T) &
\end{array}
\right. \tag{26}
$$

$$
\left\{
\begin{array}{ll}
\dfrac{\partial \eta}{\partial n} = 0, & (x,t) \in \partial\mathcal{O} \times (0,T) \\
\xi(x,t) = S(t), & x \in \partial\Omega(t),\ t \in (0,T) \\
k\left[\dot{S}(t) + \left(\dot{R}^2(t) + N\dfrac{\dot{R}(t)}{R(t)}\right)S(t)\right] = k\dot{R}(t)\dfrac{\partial\xi}{\partial n}\Big|_{\partial\Omega(t)} + \dfrac{\varepsilon_1}{4\pi}\left(\dfrac{\dot{R}^2(t)}{R(t)} + 2\ddot{R}(t)\right)
\end{array}
\right. \tag{27}
$$

tales que

$$
\iint_{\omega\times(0,T)} (\eta + \varepsilon_2 v)\,(w - v)\,dx\,dt \geq 0 \qquad \forall w \in \mathcal{U}_{ad}, \quad v \in \mathcal{U}_{ad}. \tag{28}
$$

Para la resolución numérica de ambos problemas, podemos utilizar esquemas basados en un algoritmo iterativo de tipo punto fijo y, también, métodos de descenso de tipo gradiente. Mostramos, por ejemplo, cómo queda un método de gradiente para el problema (18), (19):

1. v^0 es dado; entonces, para $n = 0, 1, \ldots$ se hacen los pasos 2 a 5 hasta alcanzar el siguiente criterio de convergencia:

   $$\|v^{n+1} - v^n\|_{L^2(\omega\times(0,T))} < \varepsilon \|v^{n+1}\|_{L^2(\omega\times(0,T))}$$

   para ε suficientemente pequeño.

2. Resolver (12) para obtener (Ω^n, c^n, β^n);

3. Resolver (21)–(23) para obtener (ξ^n, η^n, S^n);

4. Definir $g^n = \eta^n|_{\omega\times(0,T)} + \varepsilon_2 v^n$.

5. Denotamos $j : \mathcal{U}_{ad} \subset L^2(\omega\times(0,T)) \mapsto \mathbb{R}$ el funcional dado por $j(v) = J_1(v, \Omega, c, \beta)$. Sugerimos tres formas diferentes para calcular v^{n+1}.

- Gradiente con proyección y paso fijo: $v^{n+1} = P_{\mathcal{U}_{ad}}(v^n - \rho g^n)$, con $\rho > 0$ dado.
- Gradiente con proyección y paso óptimo: Tomar ρ^n tal que

$$j(P_{\mathcal{U}_{ad}}(v^n - \rho^n g^n)) \leq j(P_{\mathcal{U}_{ad}}(v^n - \rho g^n)) \quad \forall \rho \geq 0$$

  y calcular $v^{n+1} = P_{\mathcal{U}_{ad}}(v^n - \rho^n g^n)$.
- Gradiente conjugado con proyección y paso fijo: Elegir $d^n = g^n + \langle \gamma^n, d^{n-1} \rangle$, con

$$\gamma^n = j'(v^n) + \frac{\|j'(v^n)\|^2}{\|j'(v^{n-1})\|^2} d^{n-1} \quad \text{(Fletcher-Reeves)}$$

  ó

$$\gamma^n = j'(v^n) + \frac{(j'(v^n) - j'(v^{n-1}), j'(v^n))}{\|j'(v^{n-1})\|^2} d^{n-1} \quad \text{(Polak-Riviere)}$$

  y tomar entonces $v^{n+1} = P_{\mathcal{U}_{ad}}(v^n - \rho d^n)$. Deste luego, también se puede optimizar en ρ aquí; esto conduciría al algoritmo de gradiente conjugado con proyección y paso óptimo.

Otros modelos de crecimiento tumoral

Hasta este momento nos hemos centrado en modelos que simulan el crecimiento de un tumor sólido que se alimenta únicamente de los nutrientes que le llegan desde la superficie y no de la sangre, pues no hemos tenido en cuenta el proceso que conduce a la formación de nuevos vasos sanguíneos a partir de la vasculatura pre-existente. A este fenómeno se le denomina *angiogénesis*.

Llegados a este punto, se hace también interesante considerar otros modelos que aparecen en el tratamiento matemático de tumores, ligados a la fase de crecimiento vacular.

- **Angiogénesis**

  Entre los modelos matemáticos en ecuaciones diferenciales usados en este proceso, cabe destacar a título de ejemplo los de [4] y [35]. El primero se reduce a un sistema de tres incógnitas, e (concentración de células endoteliales), u (factores angiogénicos segregados por el tumor) y f (fibronectina - matriz extracelular):

$$\begin{cases} e_t - D\nabla e = -\nabla \cdot \left(\dfrac{k}{1+\alpha u} e \nabla u \right) - \nabla \cdot (\rho e \nabla f) & \text{en} \quad \Omega \\ u_t = -\eta e u & \text{en} \quad \Omega \\ f_t = \beta e - \gamma u f & \text{en} \quad \Omega \\ \quad + \text{ condiciones de contorno} & \\ \quad + \text{ condiciones iniciales} & \end{cases}$$

  siendo D, k, α, ρ, β, γ constantes positivas.

  El segundo modelo incluye además otros factores como proteasas, macrófagos, etc. que complican enormemente su estudio (para un análisis detallado, véase [38]).

- **Procesos de invasión y metástasis**

  Los modelos conocidos pretenden considerar estos aspectos en sistemas de tipo parabólico o hiperbólico en los que aparecen términos de difusión y de quimiotaxis. Un ejemplo sencillo, para una situación geométrica 1-dimensional, es el siguiente:

$$\begin{cases} u_t = u\,(1-u) - (uc_x)_x\,, \\ c_t = -pc, \\ p_t = \dfrac{1}{\varepsilon}\,(uc-p)\,, \\ + \text{ condiciones iniciales y de contorno,} \end{cases}$$

donde u, c y p denotan las concentraciones de células tumorales, células del tejido conectivo y proteasas (proteínas segregadas que degradan la matriz extracelular), respectivamente.

En [19] se presenta un modelo más complicado que impone simetría radial y tiene en cuenta el efecto de falta de O_2 producido por el crecimiento de capilares.

Algunos problemas de control relacionados con el proceso de solidificación

En el Capítulo 4 de esta memoria, nos centraremos en el estudio de un sistema que modela el proceso de solidificación de metales.

Sea Ω un dominio abierto acotado regular y conexo de $\mathbb{R}^d$ $(d = 2,3)$, con frontera localmente regular tal que $\partial\Omega = \Gamma_D \cup \Gamma_N$, donde $\Gamma_D \cap \Gamma_N = \emptyset$ y $\Gamma_N \neq \emptyset$. Dado $T > 0$, fijamos el conjunto $Q^T := \Omega \times (0,T)$. El modelo matemático para el problema de solidificación (véase, por ejemplo, [7], [8] y [40]) es el siguiente:

$$c_t + \nabla\cdot(\boldsymbol{v}c_l(c,\theta) - D\nabla c) = 0 \tag{29}$$

$$\theta_t + \nabla\cdot(\boldsymbol{v}\theta - \chi\nabla\theta) = k1_\omega \tag{30}$$

$$\boldsymbol{v}_t + \nabla\cdot(\boldsymbol{v}\otimes\boldsymbol{v} - \nu\nabla\boldsymbol{v}) + F_i(c,\theta)\boldsymbol{v} + \nabla p = \boldsymbol{F}_e(c,\theta) \tag{31}$$

$$\nabla\cdot\boldsymbol{v} = 0 \tag{32}$$

En (29)–(32), c y c_l son respectivamente la concentración y la concentración líquida del soluto de la aleación, θ es la temperatura, de la humedad, $\boldsymbol{v}$ es la velocidad del líquido y p es la presión. D, χ y ν son constantes positivas que denotan el coeficiente de difusión de soluto, la conductividad térmica y la viscosidad, respectivamente; F_i y $\boldsymbol{F}_e$ son funciones que denotan las fuerzas internas y externas que actúan sobre el sistema (29)–(32) (en general, dependen de c y de θ). Sus expresiones vienen dadas por:

$$F_i = M_0\frac{f_s(c,\theta)^2}{(1-f_s(c,\theta))^3} \tag{33}$$

$$\boldsymbol{F}_e = \boldsymbol{g}(1+\beta_\theta\theta+\beta_c c_l(c,\theta)) \tag{34}$$

De esta forma, estamos considerando, respectivamente, la aproximación de *Carman-Kozeny* para modelar los efectos del molde como medio poroso, y la aproximación de *Boussinesq* para modelar las tensiones térmica y solutal.

El sistema es complementado con las siguientes condiciones de contorno para c y $\boldsymbol{v}$ sobre $\partial\Omega \times (0,T)$:

$$(D\nabla c)\cdot\boldsymbol{n} = 0 \tag{35}$$

$$\boldsymbol{v} = \boldsymbol{0} \tag{36}$$

y para θ sobre $\Gamma_N \times (0,T)$ y $\Gamma_D \times (0,T)$, respectivamente:

$$(\chi\nabla\theta)\cdot\boldsymbol{n} = 0 \tag{37}$$
$$\theta = 0 \tag{38}$$

Finalmente, imponemos las siguientes condiciones iniciales, válidas en Ω:

$$c(\boldsymbol{x},0) = c_0(\boldsymbol{x}); \quad \theta(\boldsymbol{x},0) = \theta_0(\boldsymbol{x}); \quad \boldsymbol{v}(\boldsymbol{x},0) = \boldsymbol{v}_0(\boldsymbol{x}). \tag{39}$$

Para evitar problemas motivados por el hecho de que el término de Carman-Kozeny posee una singularidad en las zonas donde la fracción sólida es igual a la unidad, trabajaremos con un término regularizado, introduciendo un parámetro $\epsilon \in (0,1]$ en la función $F_i(c,\theta)$:

$$F_i^\epsilon = M_0 \frac{f_s(c,\theta)^2}{(1 - f_s(c,\theta) + \epsilon)^3} . \tag{40}$$

Esto permitirá considerar y resolver todas las ecuaciones (29)–(39) en Q^T.

La existencia de solución débil del problema de solidificación regularizado se prueba mediante aplicación de argumentos de compacidad habituales a una familia de aproximaciones de Galerkin. También se demuestra la unicidad de solución en el caso bidimensional.

Consideremos los espacios

$$\boldsymbol{H} = \{\boldsymbol{v} \in \boldsymbol{L}^2(\Omega) \; : \; \operatorname{div}\boldsymbol{v} = 0 \text{ en } \Omega, \; \boldsymbol{v}\cdot\boldsymbol{n} = 0 \text{ sobre } \partial\Omega\}$$
$$\boldsymbol{V} = \{\boldsymbol{v} \in \boldsymbol{H}_0^1(\Omega) \; : \; \operatorname{div}\boldsymbol{v} = 0 \text{ en } \Omega\}$$

Se tiene entonces el resultado siguiente:

Teorema 6. *Sean $k \in L^2(\omega \times (0,T))$, $\boldsymbol{g} \in L^\infty(\Omega)$. Supongamos que $c_l \in W^{1,\infty}(\mathbb{R}^2)$, $c_0 \in L^\infty(\Omega)$, con $0 \le c_0 \le c_e$, $\theta_0 \in L^2(\Omega)$ y $\boldsymbol{v}_0 \in \boldsymbol{H}$. Entonces existe al menos una solución débil $(c,\theta,\boldsymbol{v})$ del problema regularizado:*

$$c_t + \nabla\cdot(\boldsymbol{v}c_l(c,\theta) - D\nabla c) = 0 \quad \text{en} \quad Q^T \tag{41}$$
$$\theta_t + \nabla\cdot(\boldsymbol{v}\theta - \chi\nabla\theta) = k1_\omega \quad \text{en} \quad Q^T \tag{42}$$
$$\boldsymbol{v}_t + \nabla\cdot(\boldsymbol{v}\otimes\boldsymbol{v} - \nu\nabla\boldsymbol{v}) + F_i^\epsilon(c,\theta)\boldsymbol{v} + \nabla p = \boldsymbol{F}_e(c,\theta) \quad \text{en} \quad Q^T \tag{43}$$
$$\nabla\cdot\boldsymbol{v} = 0 \quad \text{en} \quad Q^T \tag{44}$$
$$(D\nabla c)\cdot\boldsymbol{n} = 0 \quad \text{sobre} \quad \partial\Omega\times(0,T) \tag{45}$$
$$\boldsymbol{v} = \boldsymbol{0} \quad \text{sobre} \quad \partial\Omega\times(0,T) \tag{46}$$
$$(\chi\nabla\theta)\cdot\boldsymbol{n} = 0 \quad \text{sobre} \quad \Gamma_N\times(0,T) \tag{47}$$
$$\theta = 0 \quad \text{sobre} \quad \Gamma_D\times(0,T) \tag{48}$$
$$c(\boldsymbol{x},0) = c_0(\boldsymbol{x}); \quad \theta(\boldsymbol{x},0) = \theta_0(\boldsymbol{x}); \quad \boldsymbol{v}(\boldsymbol{x},0) = \boldsymbol{v}_0(\boldsymbol{x}) \tag{49}$$

Además, $0 \le c \le c_e$. Finalmente, si $d = 2$, la solución es única.

Consideremos ahora el problema de control asociado al sistema de solidificación regularizado: queremos controlar el crecimiento de un frente de solidificación (y, por tanto, su forma geométrica) imponiendo un mecanismo de calor que actúe sobre ω, un “pequeño” subconjunto no vacío de Ω.

Sean α, β, γ constantes no negativas, $c_d, \theta_d \in L^2(Q^T)$, $\boldsymbol{v}_d \in \boldsymbol{L}^2(Q^T)$ funciones “deseadas” dadas y supongamos que $N > 0$. Pondremos:

$$\begin{aligned} J(k,c,\theta,\boldsymbol{v}) = \; & \frac{\alpha}{2}\iint_{Q^T} |c - c_d|^2 \, dx\, dt + \frac{\beta}{2}\iint_{Q^T} |\theta - \theta_d|^2 \, dx\, dt \\ & + \frac{\gamma}{2}\iint_{Q^T} |\boldsymbol{v} - \boldsymbol{v}_d|^2 \, dx\, dt + \frac{N}{2}\iint_{\omega\times(0,T)} |k|^2 \, dx\, dt \end{aligned} \tag{50}$$

Fijado un convexo cerrado no vacío $\mathcal{U}_{ad} \subset L^2(\omega \times (0,T))$, introducimos el conjunto

$$\mathcal{E} \stackrel{def}{=} \{(k, c, \theta, \boldsymbol{v}) \ : \ k \in \mathcal{U}_{ad} \ , \ (c, \theta, \boldsymbol{v}) \text{ es, junto con alguna } p \text{, solución de (41)–(49)}\}.$$

Consideramos el problema

$$\begin{cases} \text{Hallar } (k^*, c^*, \theta^*, \boldsymbol{v}^*) \in \mathcal{E} \text{ tal que} \\ \\ J(k^*, c^*, \theta^*, \boldsymbol{v}^*) = \displaystyle\min_{(k,c,\theta,\boldsymbol{v}) \in \mathcal{E}} J(k, c, \theta, \boldsymbol{v}) \end{cases} \tag{51}$$

Se tiene el resultado siguiente:

Teorema 7. *En las condiciones precedentes, existe al menos una solución del problema de control óptimo* (51).

Podemos determinar el sistema de optimalidad asociado al problema de control anterior. El control óptimo k, el estado asociado $(c, \theta, \boldsymbol{v})$ y el estado adjunto $(\phi, \psi, \boldsymbol{w})$ deben satisfacer, junto con algunas p y q, las relaciones siguientes:

$$\begin{cases} c_t + \boldsymbol{v} \cdot \nabla c_l(c, \theta) - D\Delta c = 0 & \text{en} \quad Q^T \\ \\ \theta_t + \boldsymbol{v} \cdot \nabla \theta - \chi \Delta \theta = k 1_\omega & \text{en} \quad Q^T \\ \\ \boldsymbol{v}_t + (\boldsymbol{v} \cdot \nabla)\boldsymbol{v} - \nu \Delta \boldsymbol{v} + F_i^\epsilon(c, \theta)\boldsymbol{v} + \nabla p = \boldsymbol{F}_e(c, \theta) & \text{en} \quad Q^T \\ \\ \nabla \cdot \boldsymbol{v} = 0 & \text{en} \quad Q^T \\ \\ (D\nabla c) \cdot \boldsymbol{n} = (\chi \nabla \theta) \cdot \boldsymbol{n} = 0, \ \boldsymbol{v} = \boldsymbol{0} & \text{sobre} \quad \partial\Omega \times (0,T) \\ \\ c(\boldsymbol{x}, 0) = c^0(\boldsymbol{x}); \quad \theta(\boldsymbol{x}, 0) = \theta^0(\boldsymbol{x}); \quad \boldsymbol{v}(\boldsymbol{x}, 0) = \boldsymbol{v}^0(\boldsymbol{x}) & \text{en} \quad \Omega \end{cases} \tag{52}$$

$$\begin{cases} -\phi_t - \dfrac{\partial c_l}{\partial c}\boldsymbol{v} \cdot \nabla \phi - D\Delta\phi = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial c} - \dfrac{\partial F_i^\epsilon}{\partial c}\boldsymbol{v} \right) \cdot \boldsymbol{w} + \alpha(c - c_d) & \text{en} \quad Q^T \\ \\ -\psi_t - \boldsymbol{v} \cdot \nabla \psi - \dfrac{\partial c_l}{\partial \theta}\boldsymbol{v} \cdot \nabla \phi - \chi \Delta \psi = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial \theta} - \dfrac{\partial F_i^\epsilon}{\partial \theta}\boldsymbol{v} \right) \cdot \boldsymbol{w} + \beta(\theta - \theta_d) & \text{en} \quad Q^T \\ \\ -\boldsymbol{w}_t - \nu \Delta \boldsymbol{w} - (\boldsymbol{v} \cdot \nabla)\boldsymbol{w} + (\nabla \boldsymbol{v})^t \boldsymbol{w} + F_i^\epsilon(c, \theta)\boldsymbol{w} + \nabla q & \\ \qquad = -\phi \nabla c_l(c, \theta) - \psi \nabla \theta + \gamma(\boldsymbol{v} - \boldsymbol{v}_d) & \text{en} \quad Q^T \\ \\ \nabla \cdot \boldsymbol{w} = 0 & \text{en} \quad Q^T \\ \\ (D\nabla\phi) \cdot \boldsymbol{n} = (\chi \nabla \psi) \cdot \boldsymbol{n} = 0; \ \boldsymbol{w} = \boldsymbol{0} & \text{sobre } \partial\Omega \times (0,T) \\ \\ \phi(\boldsymbol{x}, T) = 0; \ \psi(\boldsymbol{x}, T) = 0; \ \boldsymbol{w}(\boldsymbol{x}, T) = \boldsymbol{0} & \text{en} \quad \Omega \end{cases} \tag{53}$$

$$\iint_{\omega \times (0,T)} (\psi + Nk)(k' - k) dx dt \geq 0 \quad \forall k' \in \mathcal{U}_{ad}, \ k \in \mathcal{U}_{ad}. \tag{54}$$

En el caso particular más sencillo, $\mathcal{U}_{ad} = L^2(\omega \times (0,T))$, y entonces (54) equivale a:

$$k = -\frac{1}{N}\psi \quad \text{en} \quad \omega \times (0,T). \tag{55}$$

En el Capítulo 4, hemos propuesto además varios algoritmos iterados para el cálculo del control óptimo. También, hemos realizado un estudio análogo en el caso de un segundo funcional:

$$\begin{aligned} J(k,c,\theta,\boldsymbol{v}) = \quad & \frac{\alpha}{2}\int_\Omega |c(\boldsymbol{x},T) - c_e(\boldsymbol{x})|^2\,dx + \frac{\beta}{2}\int_\Omega |\theta(\boldsymbol{x},T) - \theta_e(\boldsymbol{x})|^2\,dx \\ & + \frac{\gamma}{2}\int_\Omega |\boldsymbol{v}(\boldsymbol{x},T) - \boldsymbol{v}_e(\boldsymbol{x})|^2\,dx + \frac{N}{2}\iint_{\omega\times(0,T)} |k|^2\,dx\,dt \end{aligned} \tag{56}$$

Por último, se considera un problema de tiempo óptimo para el sistema de solidificación. Nos interesamos de nuevo por la existencia de solución y por las condiciones de optimalidad asociadas.

Fijado $T_0 > 0$, introducimos un conjunto convexo cerrado $\mathcal{U}_{ad} \subset L^2(\omega \times (0,T_0))$ y la familia

$$\mathcal{E}_0 = \Big\{(k,c,\theta,\boldsymbol{v}) \ : \ k \in \mathcal{U}_{ad}, \ (c,\theta,\boldsymbol{v}) \ \text{es solución de} \ (41)-(49) \quad \text{en} \quad \Omega \times (0,T_0)\Big\}.$$

Sea I el funcional definido por

$$I(k,c,\theta,\boldsymbol{v}) = \frac{1}{2}T^*(\theta;\theta_e,\delta)^2 + \frac{N}{2}\iint_{\omega\times(0,T_0)} |k|^2\,dx\,dt, \tag{57}$$

donde

$$T^*(\theta;\theta_e,\delta) = \inf\{T \in (0,T_0] \ : \ \|\theta(\cdot,T) - \theta_e\|_{L^2} \le \delta\}.$$

Consideraremos el siguiente problema de control de tiempo óptimo:

$$\begin{cases} \text{Hallar } (\hat{k},\hat{c},\hat{\theta},\hat{\boldsymbol{v}}) \in \mathcal{E}_0 \text{ tal que} \\ I(\hat{k},\hat{c},\hat{\theta},\hat{\boldsymbol{v}}) = \displaystyle\min_{(k,c,\theta,\boldsymbol{v})\in\mathcal{E}_0} I(k,c,\theta,\boldsymbol{v}) \end{cases} \tag{58}$$

Se tiene entonces:

Teorema 8. *Existe al menos una solución de* (57)–(58).

Introducimos ahora el funcional Φ, con

$$\Phi(T',k) = \frac{1}{2}T'^2 + \frac{N}{2}\iint_{\omega\times(0,T_0)} |k|^2\,dx\,dt \quad \forall (T',k) \in [0,T_0] \times L^2(\omega \times (0,T_0)) \tag{59}$$

Fijado un convexo cerrado $\mathcal{V}_{ad} = [0,T] \times \mathcal{U}_{ad}$, sea $\Xi = (K_0, H_0)$ la aplicación definida por:

$$\begin{aligned} K_0(T',k,c,\theta,\boldsymbol{v}) &= \frac{1}{2}\|\theta(T') - \theta_e\|_{L^2}^2 - \frac{\delta^2}{2} \\ H_0(T',k,c,\theta,\boldsymbol{v}) &= (H_1,H_2,H_3,H_4,H_5,H_6)\,(T',k,c,\theta,\boldsymbol{v}) \end{aligned}$$

Aquí, las funciones H_i vienen dadas como sigue:

$$
\begin{aligned}
&H_1(T',k,c,\theta,\boldsymbol{v}) = c_t + \boldsymbol{v}\cdot\nabla c_l(c,\theta) - D\Delta c\\
&H_2(T',k,c,\theta,\boldsymbol{v}) = \theta_t + \boldsymbol{v}\cdot\nabla\theta - \chi\Delta\theta - k1_\omega\\
&H_3(T',k,c,\theta,\boldsymbol{v}) = \boldsymbol{\xi},\ \text{ donde } \boldsymbol{\xi}\in L^\sigma(0,T_0;\boldsymbol{V}') \text{ es la única función que satisface}\\
&\begin{cases}\langle\boldsymbol{\xi},\boldsymbol{v}\rangle_{\boldsymbol{V}',\boldsymbol{V}} = \langle \boldsymbol{v}_t + (\boldsymbol{v}\cdot\nabla)\boldsymbol{v} - \nu\Delta\boldsymbol{v} + F_i^\epsilon(c,\theta)\boldsymbol{v} - \boldsymbol{F}_e(c,\theta),\boldsymbol{v}\rangle_{\boldsymbol{H}^{-1},\boldsymbol{H}_0^1}\\ \quad\forall \boldsymbol{v}\in\boldsymbol{V},\ \text{ c.p.d. en } [0,T_0]\end{cases}\\
&H_4(T',k,c,\theta,\boldsymbol{v}) = c(\cdot,0) - c^0\\
&H_5(T',k,c,\theta,\boldsymbol{v}) = \theta(\cdot,0) - \theta^0\\
&H_6(T',k,c,\theta,\boldsymbol{v}) = \boldsymbol{v}(\cdot,0) - \boldsymbol{v}^0
\end{aligned}
$$

Entonces (57)–(58) puede escribirse de la siguiente forma:

$$
\begin{cases}
\text{Minimizar} \quad \Phi(T',k) + I_{\mathcal{V}_{ad}}(T',k)\\
\text{sujeto a:} \quad (T',k,c,\theta,\boldsymbol{v})\in\boldsymbol{Y}\\
\qquad\qquad K_0(T',k,c,\theta,\boldsymbol{v}) = 0,\ H_0(T',k,c,\theta,\boldsymbol{v}) = 0
\end{cases}
\tag{60}
$$

donde $I_{\mathcal{V}_{ad}}$ denota la función indicatriz asociada al convexo.

El sistema de optimalidad se deduce a partir del teorema generalizado de Lagrange (véase, por ejemplo, [23]). Se deduce que, si $(T,k,c,\theta,\boldsymbol{v})$ es una solución no trivial de (60) (esto es, $0<T<T_0$), entonces existen $(\phi,\psi,\boldsymbol{w})$ y $\lambda\in\mathbb{R}$ tales que:

$$
\begin{cases}
c_t + \boldsymbol{v}\cdot\nabla c_l(c,\theta) - D\Delta c = 0 & \text{en} \quad Q^T\\
\theta_t + \boldsymbol{v}\cdot\nabla\theta - \chi\Delta\theta = k1_\omega & \text{en} \quad Q^T\\
\boldsymbol{v}_t + (\boldsymbol{v}\cdot\nabla)\boldsymbol{v} - \nu\Delta\boldsymbol{v} + F_i^\epsilon(c,\theta)\boldsymbol{v} + \nabla p = \boldsymbol{F}_e(c,\theta) & \text{en} \quad Q^T\\
\nabla\cdot\boldsymbol{v} = 0 & \text{en} \quad Q^T\\
(D\nabla c)\cdot\boldsymbol{n} = (\chi\nabla\theta)\cdot\boldsymbol{n} = 0,\ \boldsymbol{v} = \boldsymbol{0} & \text{sobre} \quad \partial\Omega\times(0,T)\\
c(\boldsymbol{x},0) = c^0(\boldsymbol{x});\quad \theta(\boldsymbol{x},0) = \theta^0(\boldsymbol{x});\quad \boldsymbol{v}(\boldsymbol{x},0) = \boldsymbol{v}^0(\boldsymbol{x}) & \text{en} \quad \Omega
\end{cases}
\tag{61}
$$

$$
\begin{cases}
-\phi_t - \dfrac{\partial c_l}{\partial c}\boldsymbol{v}\cdot\nabla\phi - D\Delta\phi = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial c} - \dfrac{\partial F_i^\epsilon}{\partial c}\boldsymbol{v}\right)\cdot\boldsymbol{w} & \text{en} \quad Q^T\\
-\psi_t - \boldsymbol{v}\cdot\nabla\psi - \dfrac{\partial c_l}{\partial\theta}\boldsymbol{v}\cdot\nabla\phi - \chi\Delta\psi = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial \theta} - \dfrac{\partial F_i^\epsilon}{\partial \theta}\boldsymbol{v}\right)\cdot\boldsymbol{w} & \text{en} \quad Q^T\\
-\boldsymbol{w}_t - \nu\Delta\boldsymbol{w} - (\boldsymbol{v}\cdot\nabla)\boldsymbol{w} + (\nabla\boldsymbol{v})^t\boldsymbol{w} + F_i^\epsilon(c,\theta)\boldsymbol{w} + \nabla q & \\
\qquad = -\phi\nabla c_l(c,\theta) - \psi\nabla\theta & \text{en} \quad Q^T\\
\nabla\cdot\boldsymbol{w} = 0 & \text{en} \quad Q^T\\
\phi = \psi = 0;\ \boldsymbol{w} = \boldsymbol{0} & \text{sobre} \quad \partial\Omega\times(0,T)\\
\phi(\boldsymbol{x},\hat{T}) = 0;\ \psi(\boldsymbol{x},\hat{T}) = -\lambda\left(\theta(\hat{T}) - \theta_e\right);\ \boldsymbol{w}(\boldsymbol{x},\hat{T}) = \boldsymbol{0} & \text{en} \quad \Omega
\end{cases}
\tag{62}
$$

$$
\begin{cases}
k = P_{\mathcal{U}_{ad}} \left(-\dfrac{1}{N}\psi\Big|_{\omega\times(0,\hat{T})} \right) \\[2ex]
\|\theta(\hat{T}) - \theta_e\|_{L^2}^2 = \delta^2 \\[2ex]
\hat{T} + \lambda \Big(\theta(\hat{T}) - \theta_e, \theta_t(\hat{T}) \Big)_{L^2} = 0
\end{cases}
\tag{63}
$$

Como tarea pendiente, que será acometida en el futuro, queda ver cómo aprovechar (61)–(63) para deducir algoritmos iterados que permitan calcular en la práctica una solución de (60).

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CHAPTER 1

Theoretical and numerical analysis of some models that describe tumor growth

1.1 Introduction

This Chapter is devoted to present a mathematical model of a solid tumor growth and study the existence and uniqueness of solution. We will also deal with the numerical analysis of the problem.

Thinking over the seriousness of the illness, in the battle against cancer many strategies, experimental techniques and theoretical approaches have emerged throughout the last centuries. Nevertheless, like in the case of many other scientific areas, we have the possibility to appeal to the mathematical modeling to interpret and understand the experimental results. Thus, the mathematical study of tumor growth is a topic of present time for several years. The first contributions in this field were made at the beginning of the twentieth Century. For the reader's convenience, we have summarized the main steps of the mathematical contributions in the Appendix to this Chapter.

Following Byrne's reflections [11], in order to develop effective treatments, it is important to identify the mechanisms controlling cancer growth, how the interact, and how they can most easily be manipulated to eradicate (or manage) the disease. To carry out such purposes, it becomes necessary to make a great number of experiments, together with a considerable dedication of time, although not always: through the development and solution of mathematical models that describe different aspects of tumor growth, applied mathematics has the potential of preventing the excessive experimentation and also "giving" to biologists the mechanisms that maybe can control the development of solid tumors.

In general, models that simulate the avascular phase are free-boundary problems for which it is interesting to study how the shape of the tumor changes with time. Our work will be focused on the growth of a solid tumor (carcinoma) in the avascular phase.

The tumor will be treated as an incompressible fluid where tissue elasticity is neglected. Cell-to-cell adhesive forces are modelled by a surface tension at the tumor-tissue interface. On the other hand, the growth of the mass of the tumor is governed by a balance between cell *mitosis* and *apoptosis* (programmed cell-death). The rate of mitosis depends on the nutrient density inside the tumor, where the concentration of capillaries is assumed to be uniform. It is also assumed that the tumor is nonnecrotic, with no inhibitor chemical species in the external tissues. These conditions apply to small-sized tumors, or when the nutrient concentrations in the blood and in the external tissues are high. Nevertheless, the model that we use can also serve to predict the behavior in other situations; see [13].

The outline of this Chapter is as follows. In Section 2, we will consider the theoretical analysis of the mathematical model proposed in [5], in particular questions related to the existence and regularity of solutions. The numerical analysis of the problem will be discussed in Section 3; we study fictitious domains and level set methods that serve to solve the problem numerically. Section 4 deals with numerical results for avascular tumors with necrotic regions. Finally, we summarize the main steps in the mathematical modelling in the Appendix.

1.2 Some theoretical results

In the last three decades, with the rising number of experimental results and clinical data, many models have been developed for tumor growth using partial differential equations. These models are based on conservation and constitutive laws and reaction-diffusion processes inside the tumor.

In the models considered in this Chapter, many important phenomena, such that angiogenesis, the effects of drug administration and others, will be neglected. This can be modelled introducing additional variables for chemical substances in the schemes below. For a more detailed study, see for instance Bellomo and Preziosi [6].

We will focus on a relatively simple problem, described in the two following articles:

- Avner Friedman, "*A hierarchy of cancer models and their mathematical challenges*" [22].
- Borys V. Bazaliy, Avner Friedman, "*A Free Boundary Problem for an Elliptic-Parabolic System: Application to a Model of Tumor Growth*" [5].

In this model, we consider at the beginning three types of cells: *proliferating* (with density P), *quiescent* (resp. Q) and *dead* (resp. D) cells. The rates of change from one phase to another are functions of the nutrient concentration C:

$$\begin{array}{lll} P \to Q & \text{at rate} & \overline{K}_Q(C) \\ Q \to P & \text{at rate} & \overline{K}_P(C) \\ P \to D & \text{at rate} & \overline{K}_A(C) \\ Q \to D & \text{at rate} & \overline{K}_D(C) \end{array}$$

Also, dead cells are removed at rate $\overline{K}_R$ (independent of C) and the rate of cell proliferation (new births) is $\overline{K}_B(C)$.

From now on, we will denote by $\Omega(t) \subset \mathbb{R}^d$ ($d = 2, 3$) the region occupied by the tumor at time t, and $\partial\Omega(t)$ will be its boundary. We assume that the nutrient concentration C satisfies a linear Poisson equation, together with some boundary conditions:

$$\left\{ \begin{array}{lll} -\Delta C + \alpha C = 0, & x \in \Omega(t),\ t \in (0,T) & (\alpha > 0) \\ C = C_0, & x \in \partial\Omega(t),\ t \in (0,T) & \end{array} \right. \tag{1.1}$$

In most papers, the rates indicated in the previous diagram are given by

$$\overline{K}_B(C) = K_B C, \quad \overline{K}_D(C) = K_D(C - C_0), \quad \overline{K}_P(C) = K_P C$$

$$\overline{K}_Q(C) = K_Q(C - C_0), \quad \overline{K}_A(C) = K_A(C_0 - C)$$

where these rates are natural, in view of the characteristics of the different types of cells. But other choices are also reasonable, such as replacing the linear rates by nonlinear rates which have the same monotonic behavior in C.

Due to proliferation and removal of cells, there is a continuous motion within the tumor. We shall represent this motion by a velocity field $\overrightarrow{v}$. We can then write the following mass conservation laws for the densities of P, Q and D in $\Omega(t)$:

$$\frac{\partial P}{\partial t} + \mathrm{div}(P\overrightarrow{v}) = (\overline{K}_B(C) - \overline{K}_Q(C) - \overline{K}_A(C))P + \overline{K}_P(C)Q \tag{1.2}$$

$$\frac{\partial Q}{\partial t} + \mathrm{div}(Q\overrightarrow{v}) = \overline{K}_Q(C)P - (\overline{K}_P(C) + \overline{K}_D(C))Q \tag{1.3}$$

$$\frac{\partial D}{\partial t} + \mathrm{div}(D\overrightarrow{v}) = \overline{K}_A(C)P + \overline{K}_D(C)Q - K_R D \tag{1.4}$$

We will also suppose that

- The velocity $\overrightarrow{v}$ is given by Darcy's law (a usual experimental law for flow in a porous medium): $\overrightarrow{v} = -\nabla\Pi$, where Π is the pressure to which the cells are surrendered.

- All cells are of the same size and density and the total density of cells within the tumor is constant:
$$P + Q + D \equiv N$$

From the previous equations and these two assumptions, we easily obtain an equation for the pressure Π:

$$-N\Delta\Pi = \overline{K}_B(C)P - K_R D$$

If we replace D by $N - P - Q$ and we set $c = \dfrac{C}{C_0}$, $p = \dfrac{P}{N}$, $q = \dfrac{Q}{N}$, then we arrive at the following system of partial differential equations:

$$\begin{cases} -\Delta c + \alpha c = 0, & x \in \Omega(t),\ t \in (0,T) \\ c = 1, & x \in \partial\Omega(t),\ t \in (0,T) \\ \dfrac{\partial p}{\partial t} - \mathrm{div}(p\nabla\Pi) = (K_B(c) - K_Q(c) - K_A(c))p + K_P(c)q, & x \in \Omega(t),\ t \in (0,T) \\ \dfrac{\partial q}{\partial t} - \mathrm{div}(q\nabla\Pi) = K_Q(c)p - (K_P(c) + K_D(c))q, & x \in \Omega(t),\ t \in (0,T) \\ -\Delta\Pi = -K_R + (K_B(c) + K_R)p + K_R q, & x \in \Omega(t),\ t \in (0,T) \end{cases} \tag{1.5}$$

where $K_X(c) = \overline{K}_X(C)$ for $X = B, Q, A, D$.

We will assume that the pressure Π on the surface of the tumor is equal to the surface tension, that is,

$$\Pi = \delta\kappa, \quad x \in \partial\Omega(t),\ t \in (0,T) \quad (\delta > 0),$$

where κ is the mean curvature. This is a very natural assumption, usually known as Laplace-Young law; it means that the points on the boundary where we find high curvature values are just those where the cells are subject to a high pressure.

The motion of the free boundary is governed by the equation

$$\overrightarrow{v} \cdot \overrightarrow{n} = V_n$$

or, equivalently,

$$\frac{\partial \Pi}{\partial n} = -V_n \text{ on } \partial\Omega(t),$$

where $\overrightarrow{n}$ is the outward normal vector and V_n is the velocity of the free boundary in the direction of $\overrightarrow{n}$.

The problem to analyze is the following: Given an initial domain $\Omega(0)$ and initial data p_0, q_0 in $\Omega(0)$ such that $p_0, q_0 \geq 0$ and $p_0 + q_0 \leq 1$, find a family of domains $\Omega(t)$ and functions p, q, Π, c depending on x and t and defined for $x \in \Omega(t)$ and $t \in (0, T)$ which satisfy the system (1.5) and the initial conditions

$$p(x, 0) = p_0(x), \; q(x, 0) = q_0(x),$$

such that

$$p, q \geq 0, \quad p + q \leq 1.$$

Thus, this free-boundary problem involves an elliptic-hyperbolic problem in

$$\Omega_\infty = \{(x, t) : \; x \in \Omega(t), \, t > 0\}.$$

We can simplify (1.5) by assuming that the removal rate K_R is very large, so that dead cells are effectively instantly removed. Then $p + q = 1$ and we can eliminate $q = 1 - p$ from the differential equations. We take also $K_A = 0$. Lastly, we shall further simplify the model (1.5) by assuming that all the cells are proliferating. Thus, we will set $K_Q \equiv 0$, $K_D \equiv 0$, $P \equiv$ constant.

In papers dealing with this simplified situation, the equation for c in (1.5) is often replaced by the following: $\varepsilon_0 \dfrac{\partial c}{\partial t} = \Delta c - \alpha c$. Therefore, the system takes the form

$$\begin{cases} \varepsilon_0 \dfrac{\partial c}{\partial t} = \Delta c - \alpha c, & x \in \Omega(t), \; t \in (0, T) \\ c = \overline{c}, & x \in \partial\Omega(t), \; t \in (0, T) \\ -\Delta \Pi = \mu(c - \tilde{c}), & x \in \Omega(t), \; t \in (0, T) \\ \Pi = \delta\kappa, & x \in \partial\Omega(t), \; t \in (0, T) \\ \dfrac{\partial \Pi}{\partial n} = -V_n, & x \in \partial\Omega(t), \; t \in (0, T) \\ c(x, 0) = c_0(x), & x \in \Omega(0) \end{cases} \tag{1.6}$$

where $\Omega(0)$ and c_0 are given.

Remark 1. In the spherically symmetric case, Friedman and Reitich [23] proved a local in time existence and uniqueness result and, with small data, a global in time existence and uniqueness result (with convergence toward a stationary solution).

Remark 2. Recently, Cui and Friedman [14] have proved a global existence result for (1.5) in the radially symmetric case and have derived uniform estimates on the radius of the free-boundary. This result suggests that stationary solutions of (1.5) must exist.

1.2.1 On the proof of local existence and uniqueness

From now on, we will change the notation slightly, focusing on the results of [5]. The system that we describe provides a mathematical model of a tumor growth, developed by Greenspan [28], Byrne and Chaplain [12].

At time t, the tumor occupies a domain $\Omega(t)$ with boundary $\Gamma = \partial\Omega(t)$. We denote the nutrient concentration by σ and the internal pressure that causes the motion of cellular material by p. The cell proliferation rate is assumed to have the form $\mu(\sigma - \tilde{\sigma})$, where $\mu, \tilde{\sigma} > 0$ are constants. The unknowns of the problem, $p = p(x,t)$, $\sigma = \sigma(x,t)$ and $\Omega = \Omega(t)$, satisfy the equations

$$\begin{cases} -\Delta p = \mu(\sigma - \tilde{\sigma}), & x \in \Omega(t),\ t \in (0,T) \\ \varepsilon_0 \sigma_t - \Delta\sigma + \sigma = 0, & x \in \Omega(t),\ t \in (0,T) \end{cases} \tag{1.7}$$

the boundary conditions

$$\begin{cases} p = \delta\kappa, & x \in \Gamma(t),\ t \in (0,T) \\ \sigma = \overline{\sigma}, & x \in \Gamma(t),\ t \in (0,T) \\ \overrightarrow{V} \cdot \overrightarrow{n} = -\dfrac{\partial p}{\partial n}, & x \in \Gamma(t),\ t \in (0,T) \end{cases} \tag{1.8}$$

and the initial conditions

$$\begin{cases} \sigma_{|t=0} = \sigma_0, & x \in \Omega(0) \\ \Omega(0) \text{ is given} \end{cases} \tag{1.9}$$

where ε_0, γ, $\overline{\sigma} > 0$, κ is (again) the mean curvature, σ_0 is a positive function and

$$V_n = \overrightarrow{V} \cdot \overrightarrow{n} = -\frac{\partial p}{\partial n}$$

is the velocity of the free-boundary $\Gamma(t)$ in the direction $\overrightarrow{n}$.

Our more immediate aim is to recall a local in time existence and uniqueness result for (1.7)–(1.9) for any initial data $\Omega(0)$, σ_0.

The method used in [5] to solve (1.7)–(1.9) relies on first transforming the problem into one in a fixed domain $\mathcal{O} \times (0,T)$, which provides some "a priori" estimates in Sobolev norms. This simplifies the analysis of the model problem (we note that the analysis become increasingly complicated as the spatial dimension increases; in particular, in three-dimensional case some unnatural restrictions have to be imposed on the geometry of $\Omega(0)$).

The main result in [5] is the following:

Theorem 1. *If T is sufficiently small, there exists a unique solution of* (1.7)–(1.9)*.*

The proof relies on the following:

1. An appropriate change of variables (valid for $t \in (0,T_*)$ with sufficiently small $T_* > 0$) that permits to rewrite locally the original problem as a family of problems associated to fixed domains which take the form

$$\begin{cases} -\Delta u = F & \text{in } \ \mathcal{O} \times (0,T) \\ \dfrac{\partial u}{\partial n} = -\rho_t + f & \text{on } \ \partial\mathcal{O} \times (0,T) \\ u = Q(D)\rho + g & \text{on } \ \partial\mathcal{O} \times (0,T) \\ \rho_{|t=0} = \rho^0 & \text{on } \ \partial\mathcal{O} \end{cases} \tag{1.10}$$

   where $Q(D)$ is a second-order elliptic operator on $\partial\mathcal{O}$, and F, f, g and ρ^0 are given.

2. The resolution of the problems (1.10). This relies on time discretization, the solution of the resulting problems by a fixed-point argument, appropriate estimates and passage to the limit as the time discretization parameter goes to zero.

1.3 The numerical solution of the problem

Let us consider again the free-boundary problem (1.7)–(1.9) but now let us take the coefficient ε_0 in the second equation of (1.7) equal to zero. This means that diffusion and dissipation of nutrients are much faster than local time changes.

For the numerical solution, we will use a time discretization scheme that allows to decouple the various unknowns:

$$[0,T] \cong \left\{0 = t^0 < t^1 < \ldots < t^M = T, \quad t^m = mk\right\}.$$

In the m-th time step, given the domain ω^m and its boundary γ^m, the concentration of nutrient σ^m is the solution of the problem

$$\begin{cases} \alpha\sigma^m - \Delta\sigma^m = 0 & \text{in } \omega^m \\ \sigma^m = \overline{\sigma} & \text{on } \gamma^m \end{cases} \tag{1.11}$$

Then, the pressure p^m is determined by solving

$$\begin{cases} -\Delta p^m = \mu(\sigma^m - \tilde{\sigma}) & \text{in } \omega^m \\ p^m = \delta\kappa & \text{on } \gamma^m \end{cases} \tag{1.12}$$

Both problems have to be solved at each step of time, in different domains. In principle, this requires a different mesh for each m when we discretize in space. This suggests to use a suitable method to solve any problem of the form

$$\begin{cases} \alpha u - \beta\Delta u = f & \text{in } \omega \\ u = g & \text{on } \gamma = \partial\omega \end{cases}$$

with $\omega \subset \Omega$ (Ω is a fixed regular open domain) with a mesh independent of ω. This is achieved by using a *fictitious domain technique* that is recalled below, in Section 1.3.1.

After computing σ^m and p^m, we will apply a *level set method* in order to compute the new domain ω^{m+1}, keeping in mind that one can know the normal component of the velocity of growth of the boundary from the third condition of (1.8):

$$V_n = -\frac{\partial p^m}{\partial n} \quad \text{on } \gamma^m \tag{1.13}$$

The details are given in Section 1.3.2.

1.3.1 The fictitious domain method

Let $\Omega \subset \mathbb{R}^d$ ($d \geq 2$) be a bounded (large) domain, with boundary $\Gamma = \partial\Omega$, for instance Lipschitz-continuous. Let $\omega \subset \Omega$ be a nonempty open set with boundary $\gamma = \partial\omega$, again Lipschitz-continuous. We want to solve numerically the following problem by using a mesh independent of ω:

"Find $u \in H^1(\omega)$ such that

$$\begin{cases} \alpha u - \beta\Delta u = f & \text{in } \omega \\ u = g & \text{on } \gamma = \partial\omega \end{cases} \tag{1.14}$$

where (for instance) $f \in L^2(\omega)$, $g \in H^{1/2}(\gamma)$, $\alpha \geq 0$ y $\beta > 0$".

Under the previous assumptions, this problem has a unique solution.

Let $\widetilde{g} \in H^1_0(\Omega)$ and $\widetilde{f} \in L^2(\Omega)$ be such that $\widetilde{g} = g$ on γ and $\widetilde{f} = f$ in ω and let us set

$$V_0 = \{v \in H^1_0(\Omega) \ : \ v = 0 \quad \text{in} \quad \Omega \setminus \overline{\omega}\}$$

and $V_g = \widetilde{g} + V_0$.

A fictitious domain method based on distributed Lagrange multipliers

Let u be the unique solution to (1.14) and let us introduce $\widetilde{u}$, with

$$\widetilde{u} = \begin{cases} u & \text{in } \omega \\ \widetilde{g} & \text{in } \Omega \setminus \overline{\omega} \end{cases} \tag{1.15}$$

It is then clear that

$$\begin{cases} \widetilde{u} \in V_g \\ \displaystyle\int_\Omega (\alpha \widetilde{u} v + \beta \nabla \widetilde{u} \cdot \nabla v)\, dx = \int_\Omega \widetilde{f} v\, dx \quad \forall\, v \in V_0 \end{cases} \tag{1.16}$$

Instead of (1.14), we will try to solve a problem where all $v \in H_0^1(\Omega)$ (and not only all $v \in V_0$) appear as test functions. The price we will have to pay is that we will have to consider a system where the unknown is not only $\widetilde{u}$ but a couple $(\widetilde{u}, \lambda)$, where λ is defined in $\Omega \setminus \overline{\omega}$.

Let us set $\Lambda = H^1(\Omega \setminus \overline{\omega})$ and let us consider the following scalar product in Λ:

$$s(\mu, \mu') = \int_{\Omega \setminus \overline{\omega}} (a \mu \mu' + b \nabla \mu \cdot \nabla \mu')\, dx \quad \forall\, \mu, \mu' \in \Lambda, \tag{1.17}$$

where a and b are positive constants.

Theorem 2. *Problem* (1.14) *is equivalent to*

$$\begin{cases} \widetilde{u} \in H_0^1(\Omega),\ \lambda \in \Lambda \\ \displaystyle\int_\Omega (\alpha \widetilde{u} v + \beta \nabla \widetilde{u} \cdot \nabla v)\, dx + s(\lambda, v) = \int_\Omega \widetilde{f} v\, dx \quad \forall\, v \in H_0^1(\Omega) \\ s(\mu, \widetilde{u} - \widetilde{g}) = 0 \quad \forall\, \mu \in \Lambda \end{cases} \tag{1.18}$$

in the following sense:

1. *If u solves* (1.14)*, there exists $\lambda \in \Lambda$ such that $(\widetilde{u}, \lambda)$, where $\widetilde{u}$ is given by* (1.15)*, solves* (1.18)*.*
2. *If $(\widetilde{u}, \lambda)$ solves* (1.18)*, then $u := \widetilde{u}|_\omega$ solves* (1.14)*.*

Proof: We first assume that $(\widetilde{u}, \lambda)$ is a solution of (1.18). Since $s(\mu, \widetilde{u} - \widetilde{g}) = 0$ for all $\mu \in \Lambda$, we necessarily have $\widetilde{u}_{|\Omega \setminus \overline{\omega}} = \widetilde{g}$. By definition, if $v \in V_0$, it follows that $v_{|\Omega \setminus \overline{\omega}} = 0$. Taking into account (1.18),

$$\int_\Omega (\alpha \widetilde{u} v + \beta \nabla \widetilde{u} \cdot \nabla v)\, dx = \int_\Omega \widetilde{f} v\, dx \quad \forall\, v \in V_0.$$

We thus get that a solution of (1.18) provides a solution of (1.16).

Conversely, let u be the unique solution of (1.14) and let $\widetilde{u}$ be constructed from u as in (1.15). Then, if we introduce $L := \widetilde{f} - \alpha \widetilde{u} + \beta \Delta \widetilde{u}$, one has $L \in H^{-1}(\Omega)$, $L = 0$ in ω and $\alpha \widetilde{u} - \beta \Delta \widetilde{u} + L = \widetilde{f}$. Let us set

$$\langle l, \mu \rangle = \int_\Omega \left(\widetilde{f} v - \alpha \widetilde{u} v - \beta \nabla \widetilde{u} \cdot \nabla v \right) dx \quad \forall \mu \in \Lambda \tag{1.19}$$

where $v \in H^1(\Omega)$ is any extension of μ to the whole set Ω. Then $\langle l, \mu \rangle$ is well-defined (since the right hand side of (1.19) is zero when $v = 0$ in ω) and $\mu \mapsto \langle l, \mu \rangle$ is a continuous linear form on Λ.

Let us consider the following variational problem in Λ:

$$\begin{cases} \lambda \in \Lambda \\ s(\lambda, \mu) = \langle l, \mu \rangle \quad \forall \mu \in \Lambda \end{cases} \tag{1.20}$$

Obviously, this possesses exactly one solution λ and it is clear that $(\widetilde{u},\lambda)$ solves (1.18).

From the proof, we see that, in particular,

$$\int_\Omega \left(\widetilde{f}v - \alpha\widetilde{u}v - \beta\nabla\widetilde{u}\cdot\nabla v\right)\,dx = \int_{\Omega\setminus\overline{\omega}} (a\lambda v + b\nabla\lambda\cdot\nabla v)\,dx \quad \forall v\in H_0^1(\Omega).$$

Therefore, the distribution L is given by

$$L = a\lambda - b\Delta\lambda.$$

■

Under the previous conditions, to solve (1.18) is just to find a saddle-point problem of the Lagrangian $\mathcal{L}: H_0^1(\Omega)\times\Lambda \mapsto \mathbb{R}$, given by

$$\mathcal{L}(v,\mu) = \frac{1}{2}\int_\Omega (\alpha|v|^2 + \beta|\nabla v|^2)\,dx - \int_\Omega \widetilde{f}v\,dx + s(\mu, v_{|\Omega\setminus\overline{\omega}} - \widetilde{g}).$$

Thus, in order to solve problem (1.14), we will look for a couple $(\widetilde{u},\lambda)\in H_0^1(\Omega)\times\Lambda$ such that

$$\mathcal{L}(\widetilde{u},\mu) \le \mathcal{L}(\widetilde{u},\lambda) \le \mathcal{L}(v,\lambda) \quad \forall\ (v,\mu)\in H_0^1(\Omega)\times\Lambda$$

and we will then use that the solution u of (1.14) is the restriction of $\widetilde{u}$ to ω.

If we introduce $G(\mu) = \inf_{v\in H_0^1(\Omega)} \mathcal{L}(v,\mu)$, what we have to do is to find $(\widetilde{u},\lambda)$ such that

$$\mathcal{L}(\widetilde{u},\lambda) = \inf_{v\in H_0^1(\Omega)} \left\{ \sup_{\mu\in\Lambda} \mathcal{L}(v,\mu) \right\} = \sup_{\mu\in\Lambda} G(\mu). \tag{1.21}$$

Since problem (1.18) is of the saddle-point kind, it can be solved by an Uzawa algorithm, which is just the gradient method for the maximization of G in Λ. In fact, we will see that an optimal step Uzawa algorithm seems to be very efficient in this setting.

Some numerical experiments for the fictitious domain method

We have compared the results obtained when applying distributed Lagrange multipliers and an optimal step Uzawa method for solving Poisson problems, with those presented in [26] (by using a fictitious domain method with boundary supported Lagrange multipliers and a conjugate gradient algorithm).

We consider the problem (1.14) with

$$\begin{aligned}
\omega &= \left\{(x,y)\ :\ \frac{(x-0.5)^2}{(1/4)^2} + \frac{(y-0.5)^2}{(1/8)^2} < 1\right\}\\
\alpha &= 100\\
\beta &= 0.1\\
f(x,y) &= \alpha(x^3-y^3) - 6\beta(x-y) \quad \forall (x,y)\in\omega\\
g(x,y) &= x^3 - y^3 \quad \forall (x,y)\in\gamma
\end{aligned}$$

With these data, the solution of (1.14) is given by

$$u(x,y) = x^3 - y^3. \tag{1.22}$$

We take $\Omega = [0,1]\times[0,1]$ in order to apply the fictitious domain method, and

$$\widetilde{f}(x,y) = \alpha(x^3-y^3) - 6\beta(x-y) \quad \forall (x,y)\in\Omega.$$

The comparison of numerical results by using P1-Lagrange finite elements in both cases is shown in Table 1.1.

	Results in [26]			Our results		
h	Number iter.	$\|u-u_h\|_{L^\infty(\omega)}$	$\|u-u_h\|_{L^2(\omega)}$	Number iter.	$\|u-u_h\|_{L^\infty(\omega)}$	$\|u-u_h\|_{L^2(\omega)}$
1/16	12	1.06×10^{-3}	1.11×10^{-4}	1	9.52×10^{-5}	4.53×10^{-6}
1/32	17	2.74×10^{-4}	1.76×10^{-5}	4	2.68×10^{-6}	8.87×10^{-8}
1/64	25	7.13×10^{-5}	3.51×10^{-6}	16	7.56×10^{-7}	1.11×10^{-8}

Table 1.1: Comparison of numerical results. P1-Lagrange finite elements.

On the other hand, table 1.2 shows a comparison of the results obtained with P1-Lagrange and P2-Lagrange finite elements.

	Our results (P1-Lagrange)			Our results (P2-Lagrange)			
h	N. iter.	$\|u-u_h\|_{L^\infty(\omega)}$	$\|u-u_h\|_{L^2(\omega)}$	N. iter.	$\|u-u_h\|_{L^\infty(\omega)}$	$\|u-u_h\|_{L^2(\omega)}$	$\|u-u_h\|_{H^1_0(\omega)}$
1/16	1	9.52×10^{-5}	4.53×10^{-6}	3	1.79×10^{-5}	3.91×10^{-7}	3.57×10^{-5}
1/32	4	2.68×10^{-6}	8.87×10^{-8}	8	1.68×10^{-7}	3.78×10^{-9}	4.41×10^{-7}

Table 1.2: Comparison of numerical results. P1-Lagrange and P2-Lagrange finite elements.

1.3.2 Level set methods

As we have already said, we will use a level set method in the context of (1.11)–(1.13), in order to compute the new domain at each step of time. These techniques were introduced by Osher and Sethian in [40] and, generally speaking, allow to follow the evolution of a moving boundary.

Let $\omega(t)$ be an arbitrary domain in $\mathbb{R}^d$ with boundary $\gamma(t)$. The basic idea of these methods is to introduce a scalar function $\varphi = \varphi(x,t)$ (we will call it a *level function*), defined in the whole computational domain Ω, so that its value at each point $x \in \Omega$ indicates whether x is inside or outside $\omega(t)$:

$$\varphi(x,t) \begin{cases} < 0 & \text{if} \quad x \in \omega(t) \\ = 0 & \text{if} \quad x \in \gamma(t) \\ > 0 & \text{if} \quad x \notin \omega(t) \end{cases}$$

Under these conditions, $\gamma(t)$ is given as the zero level set of φ, that is:

$$\gamma(t) = \{x \in \Omega \ : \ \varphi(x,t) = 0\}\,. \tag{1.23}$$

Let us suppose that $\gamma(t)$ moves with velocity V_n in the sense of the outward normal direction $\overrightarrow{n}$. The idea is to produce an evolution law for the function φ so that the zero level set evolves according to the identity $V \cdot \overrightarrow{n} = V_n$. To this end, let $x = x(t)$ be the trajectory of a point on the boundary, that is, $x|_{t=0}$ is a point in $\gamma(0)$ that moves according the differential equation $x_t = V(x,T)$. Since

$x(t)$ always belongs to the zero level set of φ, we can assume that $\varphi(x(t),t) \equiv 0$. Differentiating with respect to time and using the chain rule, we obtain

$$\varphi_t + \nabla\varphi(x(t),t) \cdot x_t(t) = 0. \tag{1.24}$$

As $\overrightarrow{n} = \dfrac{\nabla\varphi}{|\nabla\varphi|}$, we can replace x_t by $V_n \dfrac{\nabla\varphi}{|\nabla\varphi|}$ in (1.24), so that the level function satisfies

$$\varphi_t + V_n|\nabla\varphi| = 0 \quad \text{in} \;\; \Omega \times (0,T), \tag{1.25}$$

where V_n is the velocity of the free boundary $\Gamma(t)$. As initial data $\varphi(\cdot,0)$ we can take the signed distance to the boundary of $\gamma(0)$ (for instance, negative inside and positive outside).

This formulation possesses several advantages on front tracking explicit methods:

- The occupied domain ω at each time is simply identified by the sign of the level function.
- Starting from the function φ, the geometric properties of the boundary are easy to determine. For example, at any of its points, the normal vector $\overrightarrow{n}$ and the main curvature κ are respectively given by
$$\overrightarrow{n} = \frac{\nabla\varphi}{|\nabla\varphi|}, \quad \kappa = \nabla \cdot \frac{\nabla\varphi}{|\nabla\varphi|}.$$
- The same formulation is valid independently of the space dimension, and the topological changes in the evolution of the boundary can be treated in a natural way.

Remark 3. Equation (1.25) is of the Hamilton-Jacobi type:

$$\frac{\partial\varphi}{\partial t} + H(\nabla\varphi) = f, \quad \text{with} \;\; H(\nabla\varphi) = V_n|\nabla\varphi|\,, \; f \equiv 0.$$

Moreover, in this case, $H(\nabla\varphi)$ is homogeneous of degree 1.

□

In this Chapter, the level set equation (1.25) is solved by standard numerical algorithms for time-dependent Hamilton-Jacobi equations (see [19]). First, the spatial derivatives are computed by using an fifth-order *weighted essentially nonoscillatory* (WENO) discretization. The resulting semi-discrete equation is determined by a third-order *explicit total variation diminishing* (TVD) Runge-Kutta (RK) time integration. We have respected the CFL condition

$$\Delta t < \frac{h}{2.5 \, \max_\Omega |V_n|} \tag{1.26}$$

where h is the spatial discretization size.

The fictitious domain method allows the use of fixed Cartesian meshes. Thus, it is possible to combine finite elements for solving Poisson problems and finite differences for the level set equation. Figure 1.1 shows the nodes used for finite element and finite difference methods.

We use a bilinear interpolation to compute the level function at the P2-Lagrange nodes.

Remark 4. The computation of the normal velocity V_n is one of the drawbacks that level set methods usually present. In our case, as we have used a fictitious domain method for the solution of the Dirichlet problems, we can extend the velocity in a natural way to Ω, what avoids to have to carry out this amplification at each temporary step.

□

It is relevant to notice that, even if the initial condition $\varphi(\cdot\,,0)$ is a regular function, it can lose this regularity after several time steps, giving rise to numerical problems. We will return to this point in the following Subsection.

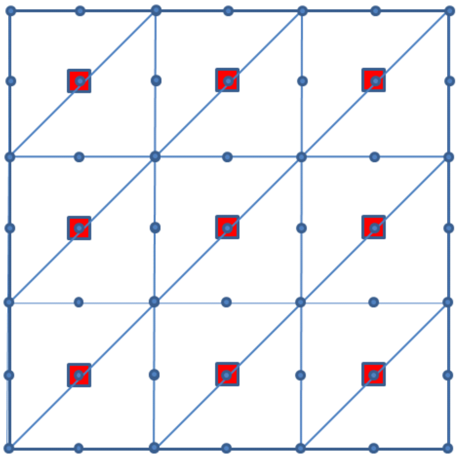


Figure 1.1: The circles are the FEM nodes (P2-Lagrange). The squares are the FDM nodes.

1.3.3 The numerical solution of the modified problem

Let us collect all the previous techniques and let us show how to apply them to the solution of (1.7)–(1.9).

We will proceed according to the following scheme:

1. The set ω^0 is given. Then:

   - Compute a level set function φ^0 and the associated normal vector $\overrightarrow{n}^0 = \dfrac{\nabla\varphi^0}{|\nabla\varphi^0|}$:

   $$\varphi^0(x) = \begin{cases} d\left(x,\gamma^0\right) & \text{if} \quad x \in \omega^0 \\ 0 & \text{if} \quad x \in \gamma^0 = \partial\omega^0 \\ -d\left(x,\gamma^0\right) & \text{if} \quad x \in \omega^0 \end{cases}$$

   (a signed distance function).

   - Solve for σ^0 by a fictitious domain method:

   $$\begin{cases} \sigma^0 - \Delta\sigma^0 = 0 & \text{in} \quad \omega^0 \\ \sigma^0 = 1 & \text{on} \quad \gamma^0 \end{cases} \tag{1.27}$$

   - Compute the curvature associated to φ^0:

   $$\kappa^0 = \nabla\cdot\overrightarrow{n}^0 = \frac{\varphi^0_{xx}\left(\varphi^0_y\right)^2 - 2\varphi^0_x\,\varphi^0_y\,\varphi^0_{xy} + \varphi^0_{yy}\left(\varphi^0_x\right)^2}{\left[\left(\varphi^0_x\right)^2 + \left(\varphi^0_y\right)^2\right]^{3/2}}$$

   - Solve for p^0 by a fictitious domain method:

   $$\begin{cases} -\Delta p^0 = \mu(\sigma^0 - \tilde{\sigma}) & \text{in} \quad \omega^0 \\ p^0 = \delta\kappa^0 & \text{on} \quad \gamma^0 \end{cases} \tag{1.28}$$

   - Compute the gradient of p^0 and the normal velocity $V^0_n = -\nabla p^0 \cdot \overrightarrow{n}^0$.

- Update φ according to the normal velocity

$$\begin{cases} \dfrac{\partial \varphi}{\partial t} + V_n^0 \, |\nabla \varphi| = 0 \\ \\ \varphi_{|t=0} = \varphi^0(x) \end{cases}$$

and obtain $\varphi^1 = \varphi(\cdot, t)$ where $t_1 = t_0 + \Delta t$, $\omega^1 = \{x \ : \ \varphi^1(x) < 0\}$ and $\overrightarrow{n}^1 = \dfrac{\nabla \varphi^1}{|\nabla \varphi^1|}$.

2. For any given $m \geq 1$, φ^m and ω^m:

- Solve for σ^m by a fictitious domain method:

$$\begin{cases} \sigma^m - \Delta \sigma^m = 0 & \text{in} \ \ \omega^m \\ \sigma^m = 1 & \text{on} \ \ \gamma^m \end{cases} \tag{1.29}$$

- Compute the curvature associated to φ^m:

$$\kappa^m = \nabla \cdot \overrightarrow{n}^m = \frac{\varphi^m_{xx} \left(\varphi^m_y\right)^2 - 2\varphi^m_x \, \varphi^m_y \, \varphi^m_{xy} + \varphi^m_{yy} \left(\varphi^m_x\right)^2}{\left[(\varphi^m_x)^2 + \left(\varphi^m_y\right)^2 \right]^{3/2}}.$$

- Solve for p^m by a fictitious domain method:

$$\begin{cases} -\Delta p^m = \mu(\sigma^m - \tilde{\sigma}) & \text{in} \ \ \omega^m \\ p^m = \delta \kappa^m & \text{on} \ \ \gamma^m \end{cases} \tag{1.30}$$

- Compute the gradient of p^m and the associated normal velocity $V_n^m = -\nabla p^m \cdot \overrightarrow{n}^m$.
- Update φ according to the normal velocity

$$\begin{cases} \dfrac{\partial \varphi}{\partial t} + V_n^m \, |\nabla \varphi| = 0 \\ \\ \varphi_{|t=t_m} = \varphi^m(x) \end{cases} \tag{1.31}$$

and obtain $\varphi^{m+1} = \varphi(\cdot, t_{m+1})$, with $t_{m+1} = t_m + \Delta t$, $\omega^{m+1} = \{x \ : \ \varphi^{m+1}(x) < 0\}$ and $\overrightarrow{n}^{m+1} = \dfrac{\nabla \varphi^{m+1}}{|\nabla \varphi^{m+1}|}$.

Even if the initial condition $\varphi^0 = \varphi(\cdot\,, 0)$ is a regular function, it can lose this regularity after several (few) steps of time, which leads very soon to numerical instability. Since we only need the contour that defines the boundary, it is possible and convenient to stabilize the function keeping the contour unchanged.

Several techniques of stabilization (or reinitialization) can be found in the literature; see [19, 41, 44]. In our case, as in [44], at each step we have built a signed distance starting from φ^m, computing the stationary solution of

$$\frac{\partial \widetilde{\varphi}^m}{\partial \tau} = \text{sign}\left(\varphi^m\right)\left(1 - |\nabla \widetilde{\varphi}^m|\right). \tag{1.32}$$

Then, we take $\varphi^m(x) \equiv \widetilde{\varphi}^m(x)$ and we solve (1.31).

In practice, in order to avoid computational singularities, the signed function in (1.32) is smeared out as follows ([19]):

$$\text{sign}\left(\varphi\right) = \frac{\varphi}{\sqrt{\varphi^2 + h^2}}.$$

Some numerical experiments concerning the tumor growth model (1.7)–(1.9)

We will present a series of two-dimensional numerical simulations of the growth of a tumor governed by the model (1.7)–(1.9). The results can be compared to those in [31] and [13].

Varying the parameters μ and $\widetilde{\sigma}$, it is possible to consider three different regimes: low vascularization regime ($\mu \geq 0$, $\widetilde{\sigma} > 0$), moderate vascularization regime ($\mu \geq 0$, $\widetilde{\sigma} \leq 0$) and high vascularization regime ($\mu < 0$, $\widetilde{\sigma} > 0$ or $\widetilde{\sigma} < 0$); see [31].

We will take in all cases the fictitious domain $\Omega = [-6, 6] \times [-6, 6]$. We have introduced a triangulation of meshsize $h = 0.2$. The time step is computed from the CFL condition (1.26).

A regime of low vascularization

First, let us take $\mu = 20$ and $\widetilde{\sigma} = 0.5$, which corresponds to a regime of low vascularization. The initial boundary of the tumor is a perturbed circumference, defined by the parametric equations

$$(x(\alpha), y(\alpha)) = (2.1 + 0.5\cos(2\alpha))\,(\cos(\alpha), \sin(\alpha))\,, \quad \alpha \in [0, 2\pi].$$

Figure 1.2 shows the mesh and the initial boundary of the tumor.

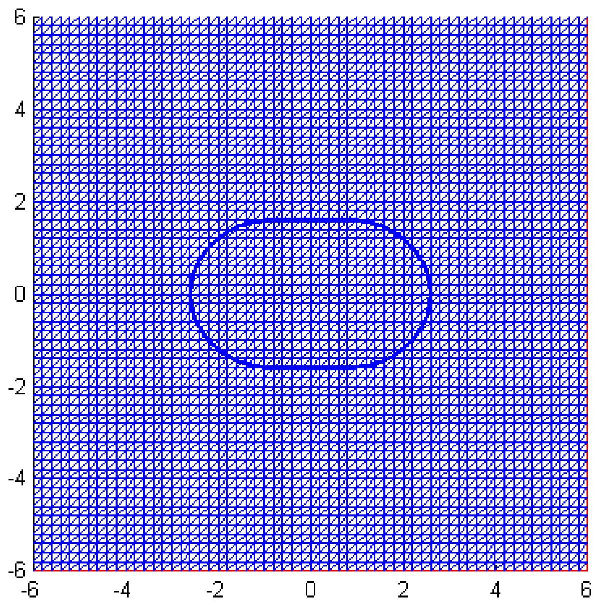


Figure 1.2: The initial boundary of the tumor. Mesh size $h = 0.2$.

The evolution of the tumor at $T = 3.6$ is shown in Figure 1.3. Its behaviour coincides with the one described in [13].

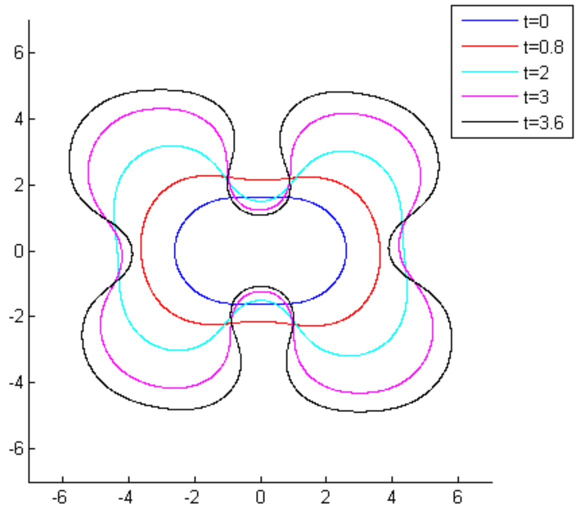


Figure 1.3: Nonlinear tumor evolution in time for unstable growth in the low vascularization regime.

Figures 1.4 and 1.5 show the nutrient concentration and the pressure inside the tumor at time $T = 3.6$.

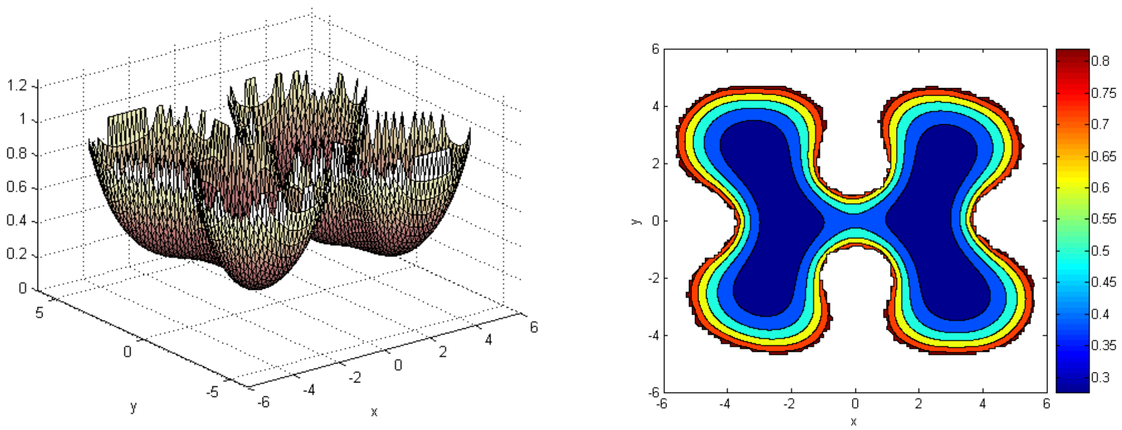


Figure 1.4: Nutrient concentration at $T = 3.6$.

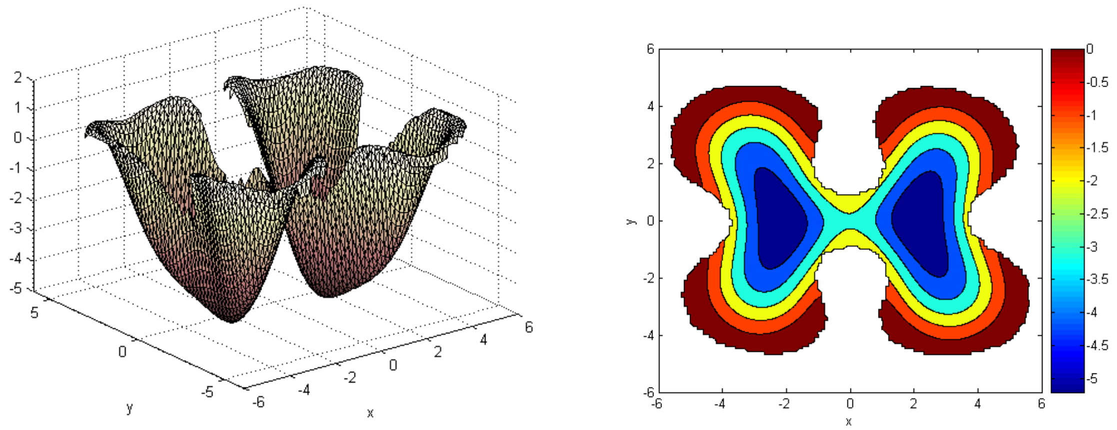


Figure 1.5: Distribution of pressure at $T = 3.6$.

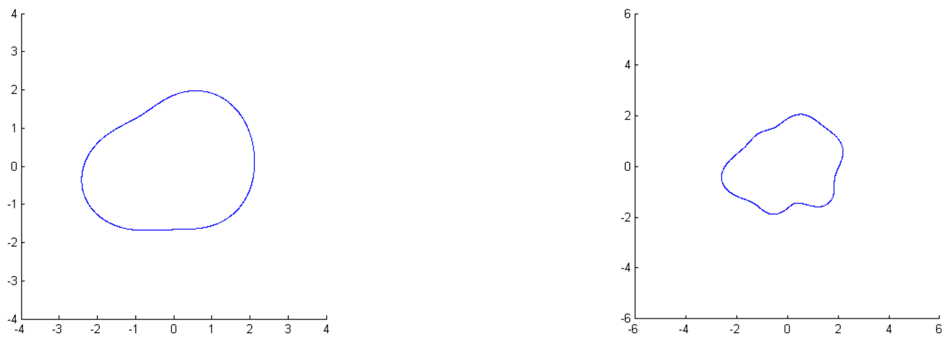
The high vascularization regime

We consider now the tumor evolution in time with the model parameters $\mu = -5$, $\widetilde{\sigma} = 0.8$. Accordingly, the mitosis rate is higher than the apoptosis rate, unbounded growth occurs, and the initially perturbed tumor evolves towards an expanding circle very soon.

The simulation starts from the initial tumor shape defined by

$$\begin{aligned}(x(\alpha), y(\alpha)) \;=\; & (2 + 0.24\cos(2\alpha) + 0.2\sin(2\alpha) + \\ & 0.12\cos(3\alpha) + 0.1\sin(3\alpha) + \\ & 0.08\cos(5\alpha) + 0.14\sin(6\alpha)) + \\ & (\cos(\alpha), \sin(\alpha)), \quad \alpha \in [0, 2\pi]\end{aligned} \tag{1.33}$$

(see Fig. 1.6(a)).



(a) Initial tumor boundary given by (1.33)

(b) Initial tumor boundary given by (1.34)

Figure 1.6: Initial tumor boundaries

Figure 1.7 shows the evolution of the tumor boundary at time $T = 2.4$. These results are again similar to those presented in [13].

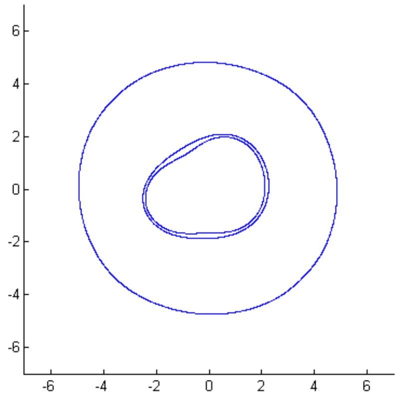


Figure 1.7: Evolution of tumor at time T=2.4 in the high vascularization regime ($\mu = -5$, $\widetilde{\sigma} = 0.8$). Initial tumor boundary given by (1.33), $h = 0.2$.

In Figure 1.8, the model parameters $\mu = -5$, $\widetilde{\sigma} = 0.2$ were used. In this case, the apoptosis rate is higher than the mitosis rate and the initial tumor boundary shrinks in time.

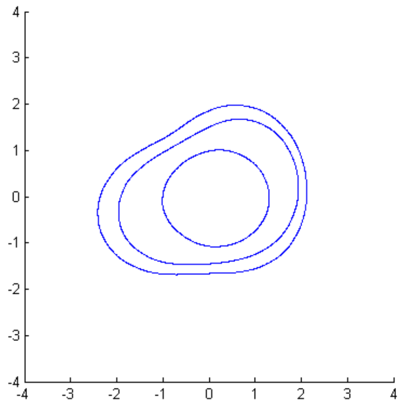


Figure 1.8: Evolution of tumor at time T=0.65 with $\mu = -5$, $\widetilde{\sigma} = 0.2$. Initial tumor boundary given by (1.33), $h = 0.4$.

Finally, we present in Figures 1.9 to 1.11 the time evolution of an asymmetric, multimodal initial tumor given by

$$\begin{aligned}(x(\alpha), y(\alpha)) &= (2 + 0.24\cos(2\alpha) + 0.2\sin(2\alpha) + 0.12\cos(3\alpha) + 0.1\sin(3\alpha)) \\ &\quad (\cos(\alpha), \sin(\alpha)), \quad \alpha \in [0, 2\pi]\end{aligned} \tag{1.34}$$

(see Fig. 1.6(b)).

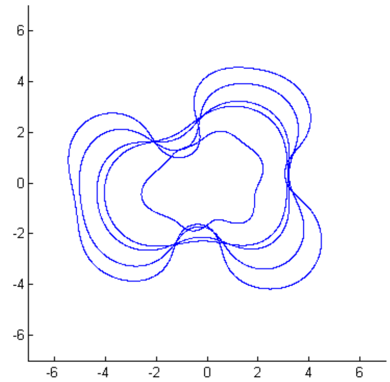


Figure 1.9: Evolution of tumor at time T=3 with $\mu = 20$, $\widetilde{\sigma} = 0.5$. Initial tumor boundary given by (1.34), $h = 0.2$.

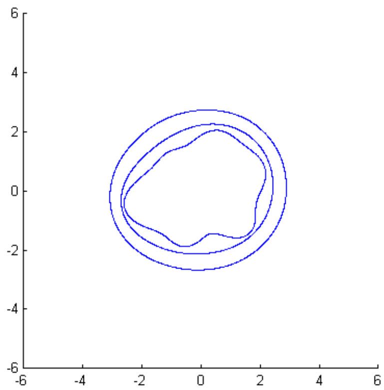


Figure 1.10: Evolution of tumor at time T=1.2 with $\mu = -5$, $\widetilde{\sigma} = 0.8$. Initial tumor boundary given by (1.34), $h = 0.2$.

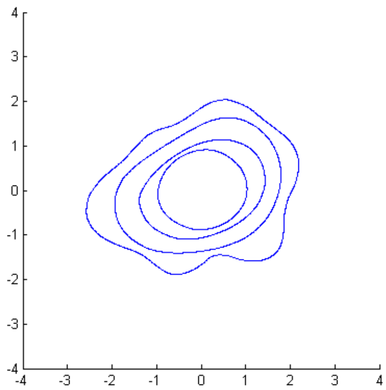


Figure 1.11: Evolution of tumor at time T=1 with $\mu = -5$, $\widetilde{\sigma} = 0.2$. Initial tumor boundary given by (1.34), $h = 0.4$.

1.4 A model for necrotic tumor growth

The techniques described in the previous Section have also been used to solve a more complex model that simulates the growth of a solid tumor with a necrotic core. We consider the case of cells of two kinds: proliferating and dead. Again, the tumor will be treated as an incompressible fluid.

At time t, the tumor occupies a domain $\Omega(t)$ with boundary $\partial\Omega(t) = \Gamma(t)$. We denote the nutrient concentration by $\sigma = \sigma(x,t)$.

Let $\omega_N(t) = \{x \ : \ \sigma(x,t) < N\}$ be the necrotic core, and let us set $\Sigma_N(t) = \partial\omega_N(t)$ for all t.

We will assume that the cells within the tumor are alive (and proliferating) while $\sigma(x,t) \geq N$. Let $\omega_P(t)$ be the proliferating region. Then we can write

$$\Omega(t) = \omega_P(t) \cup \omega_N(t) \cup \Sigma_N(t).$$

Due to the proliferation and removal of cells, there is an increase of mass and a continuous motion is produced by the internal pressure $p = p(x,t)$. The associated velocity field will be denoted again by $\overrightarrow{V} = \overrightarrow{V}(x,t)$. Then

$$\nabla \cdot \overrightarrow{V} = \begin{cases} \gamma_T\sigma - \delta_T & \text{in } \omega_P(t) \\ -\lambda_N & \text{in } \omega_N(t) \\ 0 & \text{otherwise} \end{cases} \tag{1.35}$$

where $\gamma_T, \delta_T, \lambda_N > 0$ are constants. In (1.35), in the proliferate rate $\gamma_T\sigma - \delta_T$ we interpret that $\gamma_T\sigma$ is the tumor cell birth rate and δ_T is the local death rate due to apoptosis. Finally, dead cells due to necrosis are removed at rate λ_N (we should clarify that, whereas apoptosis refers to natural cell death caused for example by aging, necrosis represents cell death caused by the micro-environment which occurs, for example, when the level of nutrient concentration is below a critical value necessary to sustain the cell).

For simplicity, we will assume that no nutrient is transported from $\omega_P(t)$ into $\omega_N(t)$, which means that the flux of cells across $\Sigma_N(t)$ is zero. The velocity $\overrightarrow{V}(t)$ in $\omega(t)$ is given by *Darcy's law*

$$\overrightarrow{V} = -w_T\nabla p, \tag{1.36}$$

where $w_T > 0$ is the (constant) cell mobility. Combining (1.35) and (1.36) we obtain $-\Delta p$ in the different areas.

The boundary condition for concentration at $\Gamma(t)$ is

$$\sigma = \sigma_{\Gamma(t)}, \tag{1.37}$$

where $\sigma_{\Gamma(t)}$ is the nutrient concentration outside the tumor volume, assumed to be uniform.

The pressure is again supposed to satisfy the Laplace-Young boundary condition on $\Gamma(t)$:

$$p = \delta\kappa \quad \text{on} \quad \Gamma(t), \tag{1.38}$$

where κ is the local total curvature. Finally, the normal velocity at the tumor boundary (with outward normal $\overrightarrow{n}$) is

$$V_n = \overrightarrow{V} \cdot \overrightarrow{n} = -w_T\nabla p \cdot \overrightarrow{n}. \tag{1.39}$$

After adimensionalization, the governing equations, the boundary conditions and the equation of the moving boundary become (see [31] for more details):

$$\sigma - \Delta\sigma = 0, \qquad x \in \Omega(t),\ t \in (0,T) \tag{1.40}$$

$$\sigma = 1, \qquad x \in \Gamma(t),\ t \in (0,T) \tag{1.41}$$

$$-\Delta p = G(\sigma - A), \quad x \in \omega_P(t),\ t \in (0,T) \tag{1.42}$$

$$-\Delta p = -G\,G_N, \qquad x \in \omega_N(t),\ t \in (0,T) \tag{1.43}$$

$$[p] = 0,\ \left[\frac{\partial p}{\partial n}\right] = 0, \qquad x \in \Sigma_N(t),\ t \in (0,T) \tag{1.44}$$

$$p = \kappa, \qquad x \in \Gamma(t),\ t \in (0,T) \tag{1.45}$$

$$\frac{\partial p}{\partial n} = -V_n, \qquad x \in \Gamma(t),\ t \in (0,T) \tag{1.46}$$

To simplify the notation, we have used the same symbols σ and p for the dimensionless variables and $\omega_P(t), \omega_N(t)$ and $\Omega(t)$ for the new domains. The dimensionless parameters that appear are:

$$A = \frac{\lambda_A}{\lambda_M}, \quad G = \frac{\lambda_M}{\lambda_R} \quad \text{and} \quad G_N = \frac{\lambda_N}{\lambda_M}, \tag{1.47}$$

where λ_A and λ_M are the characteristic apoptosis and mitosis rate respectively; λ_R^{-1} represents a relaxation time scale.

Based on (1.47), we can describe the tumor growth in terms of G and A: low vascularization ($G \geq 0, A > 0$), moderate vascularization ($G \geq 0, A \leq 0$) and high vascularization regimes ($G < 0$, $A < 0$ or $A > 0$). The first case is in agreement with the experimental observations of the *in vitro* growth of multicell avascular spheroids to a dormant steady state. Moderate and high vascularization correspond to the regimes observed in *in vivo* experiments. These three situations have been discussed in [13].

1.4.1 The numerical solution of (1.40)–(1.46)

As before, we have used a discretization in time scheme that allows to decouple the different unknowns. In the m-th time step, given the domain Ω^m and its boundary Γ^m, the concentration of nutrient σ^m is the solution of the problem

$$\begin{cases} \sigma^m - \Delta\sigma^m = 0 & \text{in } \Omega^m \\ \sigma^m = 1 & \text{on } \Gamma^m \end{cases} \tag{1.48}$$

Then, the pressure p^m is determined by solving

$$\begin{cases} -\Delta p^m = G(\sigma^m - A) & \text{in } \omega_P^m \\ -\Delta p^m = -G\,G_N & \text{in } \omega_N^m \\ [p^m] = 0,\ \left[\dfrac{\partial p^m}{\partial n}\right] = 0 & \text{on } \Sigma_N^m \\ p^m = \kappa^m & \text{on } \Gamma^m \end{cases} \tag{1.49}$$

Both problems have to be solved at each time step, in a different domain, what leads in principle to different meshes when discretizing in space. Thus, a *fictitious domain method* is again appropriate. We will also use, as above, a *level set method* in order to compute the new domain Ω^{m+1}, keeping in mind that one can know the normal component of the velocity of growth of the boundary:

$$V_n = -\frac{\partial p^m}{\partial n} \quad \text{on } \Gamma^m. \tag{1.50}$$

Thus, we will consider the following iterates:

1. The set Ω^0 is given. Then:
   - Compute a level set function φ^0 and the normal vector $\overrightarrow{n}^0 = \dfrac{\nabla\varphi^0}{|\nabla\varphi^0|}$:

$$\varphi^0(x) = \begin{cases} d\left(x, \Gamma^0\right) & \text{if} \quad x \in \Omega^0 \\ 0 & \text{if} \quad x \in \Gamma^0 = \partial\Omega^0 \\ -d\left(x, \Gamma^0\right) & \text{if} \quad x \in \Omega^0 \end{cases}$$

     (a signed distance function).
   - Solve for σ^0 by a fictitious domain method:

$$\begin{cases} \sigma^0 - \Delta\sigma^0 = 0 & \text{in} \quad \Omega^0 \\ \sigma^0 = 1 & \text{on} \quad \Gamma^0 \end{cases} \tag{1.51}$$

   - Compute the curvature associated to φ^0:

$$\kappa^0 = \nabla \cdot \overrightarrow{n}^0 = \frac{\varphi^0_{xx}\left(\varphi^0_y\right)^2 - 2\varphi^0_x\,\varphi^0_y\,\varphi^0_{xy} + \varphi^0_{yy}\left(\varphi^0_x\right)^2}{\left[(\varphi^0_x)^2 + \left(\varphi^0_y\right)^2\right]^{3/2}}.$$

   - Solve for p^0 by a fictitious domain method:

$$\begin{cases} -\Delta p^0 = G(\sigma^0 - A) & \text{in} \quad \omega^0_P \\ -\Delta p^0 = -G\,G_N & \text{in} \quad \omega^0_N \\ \left[p^0\right] = 0, \quad \left[\dfrac{\partial p^0}{\partial n}\right] = 0 & \text{on} \quad \Sigma^0_N \\ p^0 = \kappa^0 & \text{on} \quad \Gamma^0 \end{cases} \tag{1.52}$$

   - Compute the gradient of p^0 and the normal velocity $V^0_n = -\nabla p^0 \cdot \overrightarrow{n}^0$.
   - Update φ according to the normal velocity

$$\begin{cases} \dfrac{\partial\varphi}{\partial t} + V^0_n\,|\nabla\varphi| = 0 \\ \varphi_{|t=0} = \varphi^0(x) \end{cases}$$

     and obtain $\varphi^1 = \varphi(\cdot, t_1)$ with $t_1 = t_0 + \Delta t$, $\Omega^1 = \{x \ : \ \varphi^1(x) < 0\}$ and $\overrightarrow{n}^1 = \dfrac{\nabla\varphi^1}{|\nabla\varphi^1|}$.

2. For any given $m \geq 1$, φ^m and Ω^m:
   - Solve for σ^m by a fictitious domain method:

$$\begin{cases} \sigma^m - \Delta\sigma^m = 0 & \text{in} \quad \Omega^m \\ \sigma^m = 1 & \text{on} \quad \Gamma^m \end{cases} \tag{1.53}$$

   - Compute the curvature associated to φ^m:

$$\kappa^m = \nabla \cdot \overrightarrow{n}^m = \frac{\varphi^m_{xx}\left(\varphi^m_y\right)^2 - 2\varphi^m_x\,\varphi^m_y\,\varphi^m_{xy} + \varphi^m_{yy}\left(\varphi^m_x\right)^2}{\left[(\varphi^m_x)^2 + \left(\varphi^m_y\right)^2\right]^{3/2}}.$$

- Solve for p^m by a fictitious domain method:

$$\begin{cases} -\Delta p^m = G(\sigma^m - A) & \text{in } \omega_P^m \\ -\Delta p^m = -G\, G_N & \text{in } \omega_N^m \\ [p^m] = 0, \ \left[\dfrac{\partial p^m}{\partial n}\right] = 0 & \text{on } \Sigma_N^m \\ p^m = \kappa^m & \text{on } \Gamma^m \end{cases} \tag{1.54}$$

- Compute the gradient of p^m and the normal velocity $V_n^m = -\nabla p^m \cdot \overrightarrow{n}^m$.
- Update φ according to the normal velocity

$$\begin{cases} \dfrac{\partial \varphi}{\partial t} + V_n^m \, |\nabla \varphi| = 0 \\ \\ \varphi_{|t=t_m} = \varphi^m(x) \end{cases}$$

and obtain $\varphi^{m+1} = \varphi(\cdot, t_{m+1})$, with $t_{m+1} = t_m + \Delta t$, $\Omega^{m+1} = \{x \ : \ \varphi^{m+1}(x) < 0\}$ and $\overrightarrow{n}^{m+1} = \dfrac{\nabla \varphi^{m+1}}{|\nabla \varphi^{m+1}|}$.

As in the non-necrotic case considered in Section 1.3, in order to avoid numerical instability, we have followed the techniques in [44] and we have performed suitable reinitializations of the "initial" data φ^m.

1.4.2 Some numerical experiments concerning the tumor growth model (1.40)–(1.46)

The fictitious domain is again $\Omega = [-6, 6] \times [-6, 6]$. Let us consider two different initial data:

- As before, the initial interface of the tumor is a perturbed circle of radius 2:

$$(x(\alpha), y(\alpha)) = (2 + 0.2\cos(2\alpha))\,(\cos(\alpha), \sin(\alpha))\,, \quad \alpha \in [0, 2\pi]. \tag{1.55}$$

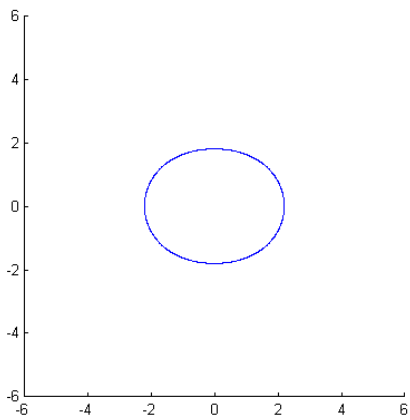


Figure 1.12: Symmetric tumor.

- The initial boundary of the tumor is defined by the parametric equations

$$\begin{aligned} (x(\alpha), y(\alpha)) \quad = \quad & (2 + 0.24\cos(2\alpha) + 0.2\sin(2\alpha) + 0.12\cos(3\alpha) + 0.1\sin(3\alpha)) \\ & (\cos(\alpha), \sin(\alpha))\,, \quad \alpha \in [0, 2\pi]. \end{aligned} \tag{1.56}$$

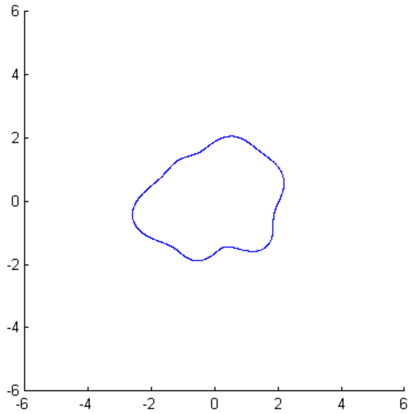


Figure 1.13: Asymmetric tumor.

We have introduced a triangulation of meshsize $h = 0.1$ in the first case and $h = 0.2$ when the tumor is asymmetric. The time step is computed from the CFL condition (1.26).

A regime of low vascularization

We fix the asymmetric initial tumor (1.56). Let us take $G = 20$, $A = 0.5$, that corresponds to a regime of low vascularization. We have also taken $G_N = 1$ and $N = 0.35$.

The evolution of the tumor at $T = 3$ is shown in Figure 1.14. The dark regions indicate ω_N.

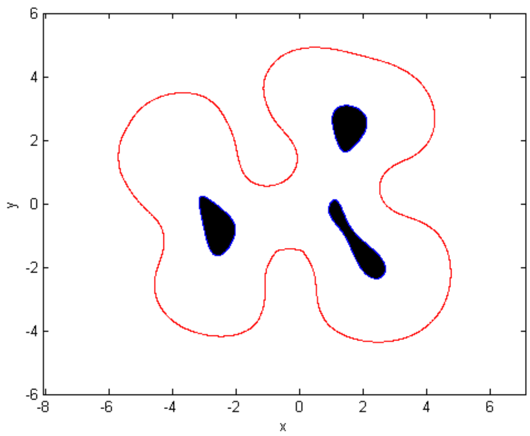


Figure 1.14: Asymmetric tumor evolution with necrotic core, $G_N = 1$, in low vascularization.

The high vascularization regime

We consider now the tumor evolution in time with parameters $G = -5$, $A = 0.8$. Accordingly, the mitosis rate is higher, unbounded growth occurs and the initially perturbed tumor evolves towards a circle very soon. We will take $G_N = 1$ and $N = 0.35$.

The simulation starts from the initial tumor shape again defined by (1.56). Figure 1.15 shows the evolution of the tumor boundary at time $T = 1.2$.

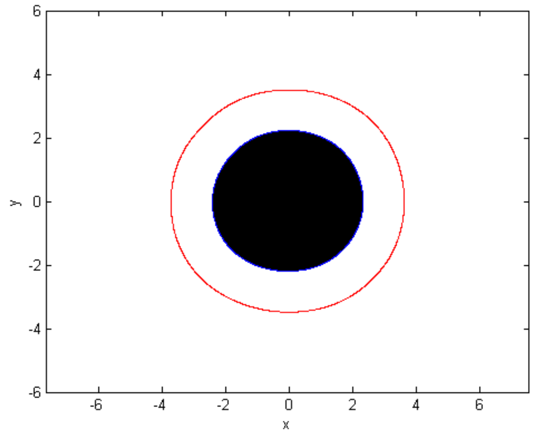


Figure 1.15: Asymmetric tumor evolution with necrotic core, $G_N = 1$. High vascularization ($A = 0.8$).

In Figure 1.16, we have chosen $A = 0.2$ and we have obtained a spherical decay with no presence of necrotic cells in the tumor. This means that the nutrient concentration is always above the threshold $N = 0.35$.

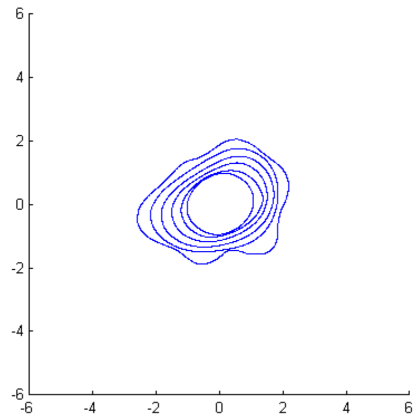


Figure 1.16: Asymmetric tumor with a decay until $T = 1$. High vascularization ($A = 0.2$).

The variation of G_N does not affect the results we have obtained above because it is related to the velocity of the dead cell dissipation and we have no dead cells in this case.

The moderate vascularization regime

- Symmetric initial tumor

  We test the scheme in the case of the tumor boundary (1.55). First of all, we simulate the evolution of a non-necrotic tumor ($N = 0$). The data are $G = 20$, $A = 0$, which correspond to a regime of moderate vascularization. Since there is no necrotic core initially, the value of G_N is irrelevant in the simulations.

  The evolution of the tumor at $T = 0.4$ is shown in Figure 1.17.

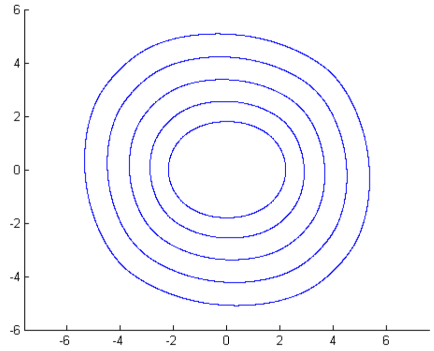


Figure 1.17: Evolution of a symmetric tumor with no necrotic core.

Let us study different situations dealing with necrotic tumor growth ($N = 0.35$) and corresponding to the regime of moderate vascularization ($G = 20$, $A = 0$).

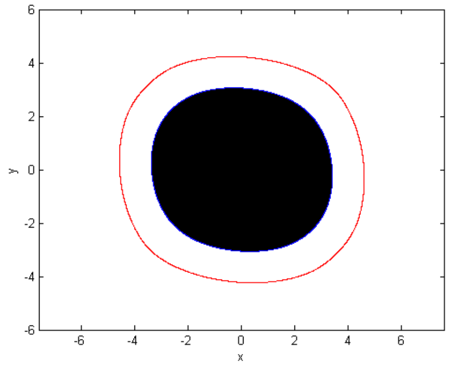


Figure 1.18: Evolution of a symmetric necrotic tumor at $T = 0.4$. $G_N = 0.1$.

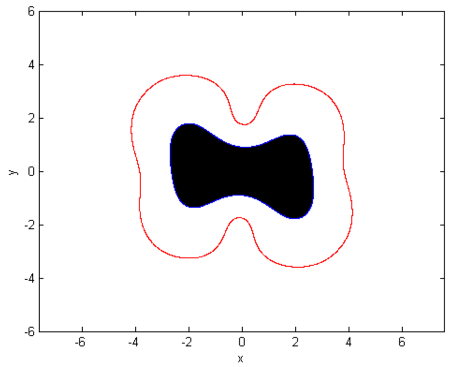


Figure 1.19: Evolution of a symmetric necrotic tumor at $T = 0.65$. $G_N = 1$.

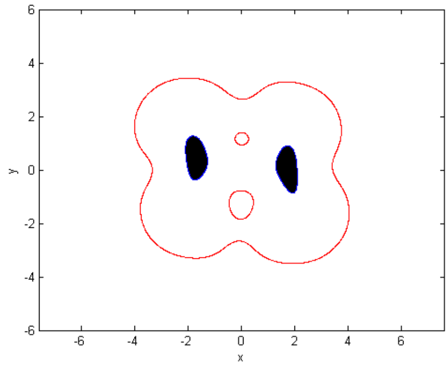


Figure 1.20: Evolution of a symmetric necrotic tumor at $T = 0.65$. $G_N = 10$.

These results are similar to those presented in [37]. As we can see, the tumor growth in the moderate vascularization regime is rapid and unbounded. When G_N is small, necrosis stabilizes the tumor growth: we observe that the tumor volume is larger in the non-necrotic case than if there is a necrotic core inside the tumor at the same time (by comparing Figures 1.17 and 1.18), although there are not considerable perturbations in the spherical growth. On the other hand, if G_N takes large values, necrosis make decrease the tumor growth, but then its morphology becomes unstable and perturbations grow rapidly at the same time (see Figures 1.19 and 1.20).

- Asymmetric initial tumor

  We have repeated the same tests now starting from the domain in Figure 1.13. Again, its behavior coincides with the description we made above.

  First, we simulate the evolution of a non-necrotic tumor ($N = 0$). The data are $G = 20$, $A = 0$, which correspond to a regime of moderate vascularization. Since there is no necrotic core initially, the value of G_N has no influence on the simulations.

  The evolution of the tumor at $T = 0.4$ is shown in Figure 1.21.

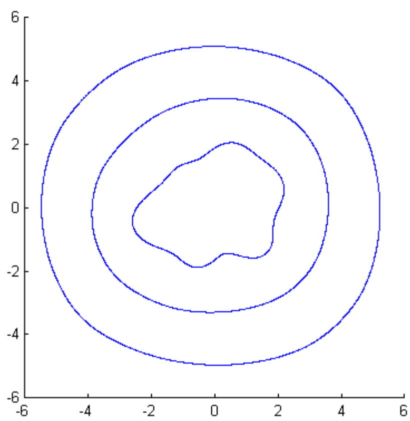


Figure 1.21: Evolution of an asymmetric tumor without necrotic core.

Finally, we consider in Figures 1.22 to 1.24 various situations concerning necrotic tumor growth ($N = 0.35$) in a moderate vascularization regime ($G = 20$, $A = 0$).

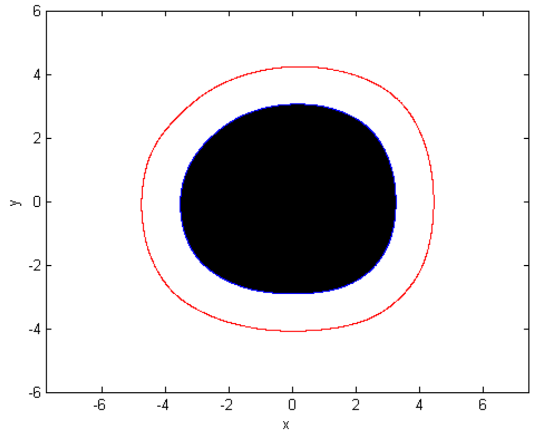


Figure 1.22: Evolution of an asymmetric necrotic tumor at $T = 0.4$. $G_N = 0.1$.

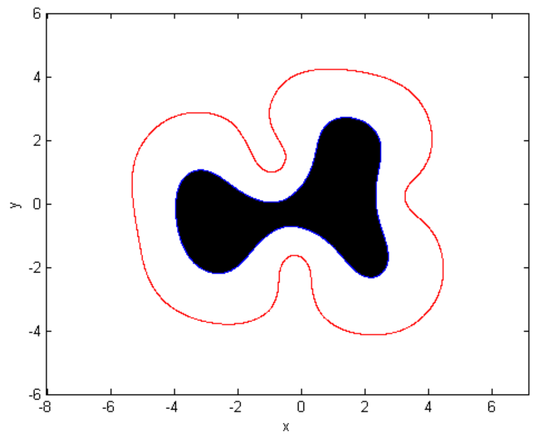


Figure 1.23: Evolution of an asymmetric necrotic tumor at $T = 0.8$. $G_N = 1$.

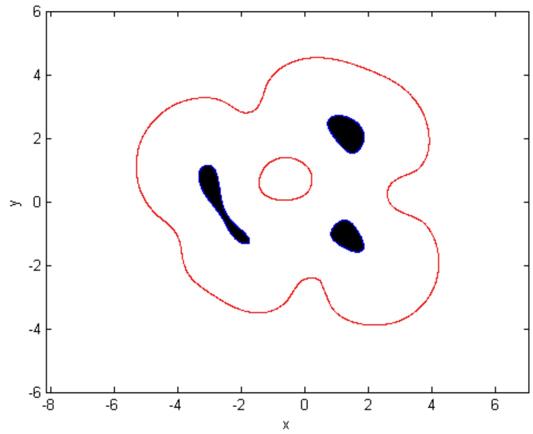


Figure 1.24: Evolution of an asymmetric necrotic tumor at $T = 0.8$. $G_N = 10$.

1.5 Appendix

To distinguish among the different mechanisms arising in the development of tumors is very difficult. Hence, starting from the current medical and experimental techniques, the mathematical modelling and analysis can be very useful. One of the key features is that the results of the mathematical modelling leads can be compared with the experimental work and can be of help for therapeutic treatments.

This appendix reviews some of the important mathematical contributions to the study of solid tumor growth.

- While the emphasis is primarily on deterministic models, some significant papers which employ stochastic approaches are also indicated. Maybe, the earliest mathematical contributions to the study of solid tumors began in 1928 with Hill's study of diffusion in tissues [29]. He understood that "the diffusion of dissolved substances through cells and tissues is a determining factor in many vital processes" and used mathematical approaches to study a number of important physiological processes, such as the diffusion of oxygen into a solid where it is consumed by metabolic processes, the outward diffusion of lactic acid from a solid which produces it by metabolic processes and the diffusion of oxygen away from a blood vessel into a region with an oxygen debt.

  While diffusion processes would later become an important part of tumor models, the first mathematical studies of solid tumors focused purely on growth dynamics (see, for example, [38]). As experimental studies on radiotherapy continued, many researchers became interested in the role of the hypoxic tumor cell in the radio-sensitivity of tumors, beginning with the irradiation studies of tumor slices in vitro by Cramer (1934). In 1955, Thomlinson and Gray [48] proposed a mathematical model of the diffusion and consumption of oxygen to supplement an experimental investigation of some types of bronchial carcinoma which grow in solid rods which "are out of capillaries and which comprise cells nourished by diffusion of metabolites inwards from the immediately surrounding stroma".

  It was Burton [10], however, who developed a diffusion model which examined both the distribution of oxygen in a spherical tumor "where the blood supply is completely confined to the surface" and the resulting "relative radius of the central zone to the total radius", which was then used to explain how the growth curve could fit a Gompertzian expression.

- The seminal work on tumor angiogenesis by Folkman [20] arose in 1964 from the discovery of dormant avascular tumor nodules *in vivo*. The emerging interest in both the avascular nodules which precede angiogenesis as well as the multicell spheroid model encouraged various new approaches to the mathematical modelling of solid tumors. Greenspan [27] extended the models by Burton and Thomlinson and Gray by introducing a surface tension among the living cancer cells in order to maintain a compact solid mass and by assuming that "necrotic cellular residue continually disintegrates into simpler chemical compounds that are freely permeable through cell membranes". In this way, the tissue volume loss due to necrosis would be replaced by the inward motion of cells from the outer region as a result of the forces of adhesion and surface tension, thereby explaining the existence of a steady-state tumor size.

- Although the study of solid tumor growth had enjoyed considerable popularity among mathematicians, beginning in the early decades of the twentieth century, few insights had been learned into "the factors that determine the mechanism and time course of tumor cell release". Indeed, it was not until the 1970s that quantitative experimental work and mathematical models were proposed to illustrate the dynamics of the metastatic process. An experimental model was first developed by Liotta et al. [36] "to quantify some of the major processes initiated by tumor transplantation and culminating in pulmonary metastases", by researching the entry rate of tumor cells into the circulation. The study demonstrated the presence of tumor cells (both alone and in crowds) in the perfusate shortly after the appearance of the tumor vascular network, with the concentration of tumor cells increasing quite rapidly initially, and later diminishing. In a later study, Liotta and others (1976) also published some theoretical work on micrometastasis therapy and quantitating tumor cell removal and tumor cell-invasive capacity.

- The development of mathematical avascular phase of tumors was improved in the 1980s with the prominent role of the studies by Adam and Maggelakis. Like Glass [25], Adam [2] noted in 1986 the important experimental results on the role of growth inhibitors in tumor development published several decades earlier. Glass had assumed that regulation of growth occurred by a discontinuous switch mechanism for the control of mitotic activity, with a spatially uniform production of inhibitor. Contrarily, Adam maintained that a spatially-dependent mitotic control function best reflected experimental observations and allowed further theoretical study. In contrast to the work of Glass, this new model predicted that for a given value of the critical dimensionless variable, n^0, a finite range of stable tissue sizes exists, which increases monotonically with the values of the dimensionless variable. Qualitatively, then, the model demonstrated the sensitivity of the growth of the tissue to a non-uniform source of inhibitor.

  But the mathematical model proposed by Adam did not incorporate a volume loss mechanism such as necrosis, so that stability could only occur by complete growth inhibition throughout the tissue. The necrotic core was simply incorporated as a source of growth inhibition in this study (see Adam and Maggelakis [3]), rather than representing a mechanism for volume loss. Nevertheless, the model enabled an interesting comparison to be made with the earlier work of Greenspan (1972) in the analysis of two different sources of growth inhibition: inhibition by diffusion of necrotic wastes, and inhibition via a by-product of processes occurring within living cells.

  From this time, much more attention has been paid to the numerical or quantitative description of the considered problems and the optimal control oriented to therapy strategies.

- In the 1990s, a huge body of mathematical papers on solid tumor growth appeared. It was possible to model a lot of phenomena that were complex and sufficiently interesting from the medical point of view (the multiphase models, invasion, metastasis and angiogenesis). Not only the study of both vascular and avascular tumors (along with their *in vitro* counterparts, the multicell spheroids) continue, with the emergence of some new approaches, but various other experimental investigations into tumor biology, such as the internalization of labelled cells in spheroids, became the subject of mathematical studies. Interesting mathematical contributions to the study of tumor invasion and metastasis were also published during this period, in addition to publications in the areas of tumor residual stresses and multiphase tumor mechanics:

  - Cell migration in multicell spheroids and tumor cords.
  - Multiphase models.
  - Mechanical models and models of residual stress formation.
  - New mathematical approaches to the study of tumor invasion and metastasis.
  - Further models of avascular/vascular tumors growth and multicell spheroids.

  For a complete list of references, see [1].

CHAPTER 2

The existence of solution of some models that include the action of chemicals

2.1 Introduction

In this Chapter we will focus on models that describe the growth of a tumor influenced by the mechanical action of chemicals (later, we will consider related control techniques oriented to therapy). One of the difficulties of the study will be that, in these problems, the domain occupied by the tumor cells is unknown.

We will show the basic ideas on the control of these models in Chapter 3 in a simple case, specifically for the equation that describes the evolution of the *glioblastoma*, a type of primary brain tumor that differs from others mainly by the aggressive diffuse invasion of the surrounding normal tissue, see [46]:

$$\begin{cases} c_t - \nabla \cdot (D(x)\nabla c) = \rho c - G(\beta, c) \\ + \ldots \end{cases} \tag{2.1}$$

Here, $c = c(x,t)$ is the tumor cell concentration at any position x and any time t, $D = D(x)$ is (for example) positive and piecewise constant and represents the diffusion coefficient of cells in brain tissue (in units of cm^2/day), $\rho > 0$ is the net rate of growth of tumor cells, including proliferation, loss and death - in units of per day and $G = G(\beta, c)$ is a perturbation term due to the action of a precise therapy. The structure of G changes according to the authors. For example,

$$G(\beta, c) = \beta c \quad \text{and} \quad G(\beta, c) = \frac{m_1 \beta}{m_2 + \beta} c,$$

in [43] and [30] respectively; see also [45].

In the simplest case, $\beta = v 1_\omega$, where $v = v(x,t)$ denotes a function that we can choose freely (the control). In more realistic cases, we should impose constraints to v in several possible ways:

limitations on the size, conditions on its time support, etc. In other even more complex and interesting situations, β is obtained indirectly from the data by solving another equation, as in immunotherapy and chemotherapy, or β has a definite structure, etc.

The outline of this Chapter is as follows. In Section 2 we will analyze a mathematical model for the *glioblastoma* and we will prove the existence of solution of some simplified systems in which there is no evolution in time. In Section 3, we will deal with a parabolic problem that models the evolution in time of the *glioblastoma*. Here, it will be seen that, in order to establish the existence of a solution, some nontrivial difficulties appear; as a consequence, only partial results can be obtained for the moment.

2.2 The model

In this Section we present a model related to tumor growth in the presence of an inhibitor $\beta = \beta(x,t)$. We study the existence of solution in three simplified situations.

Let $\mathcal{O}$ be a bounded domain in $\mathbb{R}^N$ $(N = 2,3)$. In our model, we will denote by $\Omega(t) \subset \mathcal{O}$ the region occupied by the tumor at time t and by $\partial\Omega(t)$ its boundary. Let us consider the following problem:

$$\begin{cases} \dfrac{\partial c}{\partial t} - \Delta c = \rho c - G(c,\beta), & x \in \Omega(t),\ t \in (0,T) \\ \dfrac{\partial \beta}{\partial t} - \Delta\beta + m'\beta = -\widetilde{G}(c,\beta) + f, & x \in \mathcal{O},\ t \in (0,T) \\ c(x,0) = c^0(x), & x \in \Omega(0) \\ \beta(x,0) = \beta^0(x), & x \in \mathcal{O} \\ c = 0, & x \in \partial\Omega(t),\ t \in (0,T) \\ \dfrac{\partial\beta}{\partial n} = 0, & x \in \partial\mathcal{O},\ t \in (0,T) \\ \dfrac{\partial c}{\partial n} \geq -kV_n, & x \in \partial\Omega(t),\ t \in (0,T) \end{cases} \tag{2.2}$$

Here, $\Omega(0)$ is given; V_n is the velocity of the free boundary $\partial\Omega(t)$ in the outward normal direction $\overrightarrow{n}$, that is, $V_n = \overrightarrow{V} \cdot \overrightarrow{n}$; $\rho, m' > 0$, $k \geq 0$ and f, G and $\widetilde{G}$ are smooth functions. In (2.2), $c = c(x,t)$ is the tumor cell concentration, $\beta = \beta(x,t)$ is the population density of an inhibitor and, consequently, $-G(c,\beta)$ and $-\widetilde{G}(c,\beta)$ indicate the way β destroys tumor cells and the price that β has to pay, respectively.

In (2.2) and the sequel, we will implicitly assume that the function c is extended by zero to the whole cylinder $\mathcal{O} \times (0,T)$. This gives a sense to the second partial differential equation.

In a first step, we will simplify (2.2) by assuming that there is no evolution in time. The existence and uniqueness of solution of this new problem will be our first goal.

2.2.1 A first simplified case: a stationary problem

We will change slightly the notation in this Subsection. Let $\mathcal{O}$ be a fixed bounded domain in $\mathbb{R}^N$ and let us introduce the set

$$\widetilde{K} = \{(v,w) \in H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O}) : \quad v \geq 0\}$$

and the following problems:

$$\left\{\begin{array}{l} \displaystyle\int_{\mathcal{O}} \nabla c\cdot\nabla(v-c)\,dx+\int_{\mathcal{O}}\nabla\beta\cdot\nabla(w-\beta)\,dx+\int_{\mathcal{O}} ac(v-c)\,dx+\int_{\mathcal{O}} b\beta(w-\beta)\,dx \\ \qquad\qquad \displaystyle\geq -\int_{\mathcal{O}} A\beta(v-c)\,dx-\int_{\mathcal{O}} Bc(w-\beta)\,dx+\int_{\mathcal{O}} f(w-\beta)\,dx \\ \forall\ (v,w)\ \in\ \widetilde{K},\ (c,\beta)\ \in\ \widetilde{K} \end{array}\right. \tag{2.3}$$

and

$$\left\{\begin{array}{ll} c,\beta\ \in\ H_0^1(\mathcal{O}),\quad c\ \in\ \mathcal{C}^0(\overline{\mathcal{O}}) & \\ -\Delta c+ac\geq -A\beta & \text{in }\ \mathcal{O} \\ (-\Delta c+ac+A\beta)\,c=0 & \text{in }\ \mathcal{O} \\ c\geq 0 & \text{in }\ \mathcal{O} \\ -\Delta\beta+b\beta=-Bc+f & \text{in }\ \mathcal{O} \end{array}\right. \tag{2.4}$$

Here, we will assume (at least) that $a, b, A, B \in L^\infty(\mathcal{O})$ with $a, b \geq 0$ and $f \in \mathcal{C}^0(\overline{\mathcal{O}})$ (for instance). We see that (2.3) is a non-scalar variational inequality, while (2.4) can be viewed as a free-boundary problem (the boundary of the open set $\{x \in \mathcal{O}\ :\ c(x) > 0\}$). We are considering a particular (stationary) case of (2.2), where $G(c,\beta) \equiv ac + A\beta$ and $\widetilde{G}(c,\beta) \equiv Bc$.

Our first step will be to establish the equivalence of solutions of (2.3) and (2.4) under some regularity assumptions on c.

Proposition 1.

1. *If (c,β) is a solution of (2.3) and $c \in \mathcal{C}^0(\overline{\mathcal{O}})$, then (c,β) is a solution of (2.4).*
2. *Let (c,β) be a solution of (2.4), with $c \in \mathcal{C}^1(\overline{\mathcal{O}})$ and assume that (for instance)*

$$\Omega := \{x \in \mathcal{O}\ :\ c(x) > 0\}$$

possesses a locally Lipschitz-continuous boundary. Then (c,β) is a solution of (2.3).

Proof: The main ideas in this proof are well known; see for instance [21]. However, for completeness, we will present the details.

1. Let us assume that (c,β) is a solution of (2.3). Then, we take:

$$v = c + \xi_1,\quad \xi_1 \geq 0,\ \xi_1 \in \mathcal{C}_0^\infty(\mathcal{O})$$

$$w = \beta + \xi_2,\quad \xi_2 \in \mathcal{C}_0^\infty(\mathcal{O})$$

According to (2.3), since $(v,w) \in \widetilde{K}$, we have:

$$\begin{array}{l} \displaystyle\int_{\mathcal{O}} \nabla c\cdot\nabla\xi_1\,dx+\int_{\mathcal{O}}\nabla\beta\cdot\nabla\xi_2\,dx+\int_{\mathcal{O}} ac\,\xi_1\,dx+\int_{\mathcal{O}} b\beta\xi_2\,dx \\ \qquad \displaystyle\geq -\int_{\mathcal{O}} A\beta\xi_1\,dx-\int_{\mathcal{O}} Bc\,\xi_2\,dx+\int_{\mathcal{O}} f\xi_2\,dx \end{array} \tag{2.5}$$

- Taking $\xi_2 = 0$ in (2.5), we see that

$$\int_{\mathcal{O}} \nabla c \cdot \nabla \xi_1 \, dx + \int_{\mathcal{O}} ac\, \xi_1 \, dx \geq - \int_{\mathcal{O}} A\beta \xi_1 \, dx.$$

  This means in practice that

$$\langle -\Delta c + ac, \xi_1 \rangle \geq \langle -A\beta, \xi_1 \rangle \quad \forall \xi_1 \geq 0,\, \xi_1 \in \mathcal{C}_0^\infty(\mathcal{O}).$$

  Or, equivalently: $-\Delta c + ac \geq -A\beta \quad \text{in} \quad \mathcal{D}'(\mathcal{O})$.
- If we choose $\xi_1 = 0$ in (2.5), then for any $\xi_2 \in \mathcal{C}_0^\infty(\mathcal{O})$ we find at once that

$$\int_{\mathcal{O}} \nabla \beta \cdot \nabla \xi_2 \, dx + \int_{\mathcal{O}} b\beta \xi_2 \, dx = - \int_{\mathcal{O}} Bc\, \xi_2 \, dx + \int_{\mathcal{O}} f \xi_2 \, dx.$$

  This way, we see that $-\Delta \beta + b\beta = -Bc + f \quad \text{in} \quad \mathcal{D}'(\mathcal{O})$.

Therefore, we have just proved that $(c, \beta) \in H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O})$, $c \geq 0$, $-\Delta c + ac \geq -A\beta$ in $\mathcal{O}$ and $-\Delta \beta + b\beta = -Bc + f$ in $\mathcal{O}$.

We have also supposed that $c \in \mathcal{C}^0(\overline{\mathcal{O}})$. In order to conclude that (c, β) solves (2.4), we have to show that

$$-\Delta c + ac = -A\beta \quad \text{in} \quad \Omega = \{x \in \mathcal{O} \;:\; c(x) > 0\}.$$

Since $c \in \mathcal{C}^0(\overline{\mathcal{O}})$, Ω is an open set (we will assume it is not an empty set – otherwise, $c \equiv 0$ and we would have nothing to prove).

Let us take $v = c + \varepsilon \xi$, with $\xi \in \mathcal{C}_0^\infty(\Omega)$ and $w = \beta$. There exists a constant $\delta_1 > 0$ such that $c(x) \geq \delta_1$ for all $x \in$ supp ξ, and, for any ε small enough:

$$c + \varepsilon\xi \geq \delta_1 - \varepsilon(\max |\xi|) > 0 \quad \text{in} \quad \text{supp}\, \xi$$
$$c + \varepsilon\xi \geq 0 \quad \text{outside} \quad \text{supp}\, \xi$$

Thus, for any small ε, (v, w) belongs to $\widetilde{K}$, and we can insert it in (2.3). Taking into account that ε is a positive constant and $\xi \in \mathcal{C}_0^\infty(\Omega)$, we easily deduce that

$$-\Delta c + ac = -A\beta \quad \text{in} \quad \mathcal{D}'(\Omega).$$

This completes the proof of the first part.

2. Now, we assume that (c, β) is a solution of (2.4) and $c \in \mathcal{C}^1(\overline{\mathcal{O}})$. Then:

$$\begin{cases} c, \beta \;\in\; H_0^1(\mathcal{O}), \quad c \;\in\; \mathcal{C}^1(\overline{\mathcal{O}}) \\ -\Delta c + ac \geq -A\beta & \text{in} \;\; \mathcal{O} \\ -\Delta c + ac = -A\beta & \text{in} \;\; \Omega := \{x \in \mathcal{O} \;:\; c(x) > 0\} \\ c \geq 0 & \text{in} \;\; \mathcal{O} \\ -\Delta \beta + b\beta = -Bc + f & \text{in} \;\; \mathcal{O} \end{cases}$$

In view of the regularity assumptions on c and Ω, we have

$$c \in H^2(\Omega) \cap H_0^1(\Omega) \quad \text{and} \quad \frac{\partial c}{\partial n} = 0 \;\text{ on } \partial\Omega.$$

Then, we choose $(v,w) \in H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O})$ with $v \geq 0$, and we make some computations:

$$\int_{\mathcal{O}} \nabla c \cdot \nabla (v-c)\, dx + \int_{\mathcal{O}} \nabla \beta \cdot \nabla (w-\beta)\, dx + \int_{\mathcal{O}} ac(v-c)\, dx + \int_{\mathcal{O}} b\beta (w-\beta)\, dx$$

$$= \int_{\mathcal{O}} \nabla c \cdot \nabla (v-c)\, dx + \int_{\mathcal{O}} ac(v-c)\, dx \tag{2.6}$$

$$- \int_{\mathcal{O}} Bc(w-\beta)\, dx + \int_{\mathcal{O}} f(w-\beta)\, dx$$

But

$$\int_{\mathcal{O}} \Big[\nabla c \cdot \nabla (v-c) + ac(v-c)\Big]\, dx = \int_{\Omega} \Big[\nabla c \cdot \nabla (v-c) + ac(v-c)\Big]\, dx$$

$$= \int_{\Omega} (-\Delta c)\,(v-c)\, dx + \int_{\partial\Omega} \frac{\partial c}{\partial n}(v-c)\, d\Gamma + \int_{\Omega} ac(v-c)\, dx$$

$$= \int_{\Omega} (-\Delta c + ac)(v-c)\, dx$$

$$= - \int_{\mathcal{O}} A\beta (v-c)\, dx + \int_{\mathcal{O}\setminus\overline{\Omega}} A\beta (v-c)\, dx$$

$$\geq - \int_{\mathcal{O}} A\beta (v-c)\, dx + \int_{\mathcal{O}\setminus\overline{\Omega}} (\Delta c - ac)(v-c)\, dx = - \int_{\mathcal{O}} A\beta (v-c)\, dx$$

Used in combination with (2.6), we deduce (2.3).

■

The equivalence of (2.3) and (2.4) has been proved under some regularity assumptions. We will now show the existence of a solution to (2.3) under some appropriate hypotheses:

Proposition 2.

a) Let $C_0 = C_0(\mathcal{O})$ be the Poincaré constant and suppose that

$$k := \|A + B\|_{L^\infty(\mathcal{O})} < \frac{2}{C_0^2}.$$

Then, there exists a unique solution of problem (2.3).

b) $(N = 3)$ *Let $\sqrt{C'}$ be the constant of the embedding of $H_0^1(\mathcal{O})$ in $L^6(\mathcal{O})$, and suppose that*

$$p = 3/2, \quad k' := \|A + B\|_{L^p(\mathcal{O})} < \frac{2}{C'}.$$

Then there exists a unique solution of (2.3).

c) ($N = 2$) Let $\sqrt{C''_r}$ be the constant of the embedding of $H^1_0(\mathcal{O})$ in $L^r(\mathcal{O})$, and let p and r be such that $\frac{1}{p} = 1 - \frac{2}{r}$. Assume that

$$p > 1, \quad k'' := \|A + B\|_{L^p(\mathcal{O})} < \frac{2}{C''_r}.$$

Then there exists a unique solution of (2.3).

Proof: The idea of the proof is to apply the Lions-Stampacchia theorem (see [35]) in the three cases.

Let us introduce the bilinear form

$$m((c,\beta),(v,w)) = \int_{\mathcal{O}} \nabla c \cdot \nabla v \, dx + \int_{\mathcal{O}} \nabla \beta \cdot \nabla w \, dx + \int_{\mathcal{O}} acv \, dx + \int_{\mathcal{O}} b\beta w \, dx$$

$$+ \int_{\mathcal{O}} A\beta v \, dx + \int_{\mathcal{O}} Bcw \, dx.$$

We are going to prove that, under any of the previous assumptions, m is coercive in $H^1_0(\mathcal{O}) \times H^1_0(\mathcal{O})$, that is to say, there exists $\alpha > 0$ such that

$$m((c,\beta),(c,\beta)) \geq \alpha \left(\int_{\mathcal{O}} |\nabla c|^2 \, dx + \int_{\mathcal{O}} |\nabla \beta|^2 \, dx \right) \quad \forall (c,\beta) \in H^1_0(\mathcal{O}) \times H^1_0(\mathcal{O}).$$

a) By hypothesis,

$$\left| \int_{\mathcal{O}} (A+B) c\beta \, dx \right| \leq k \int_{\mathcal{O}} |c\beta| \, dx \leq \frac{k}{2} \left(\|c\|^2_{L^2(\mathcal{O})} + \|\beta\|^2_{L^2(\mathcal{O})} \right)$$

$$\leq \frac{kC_0^2}{2} \left(\|\nabla c\|^2_{L^2(\mathcal{O})} + \|\nabla \beta\|^2_{L^2(\mathcal{O})} \right)$$

If $kC_0^2/2 < 1$, we thus have

$$m((c,\beta),(c,\beta)) \geq \|\nabla c\|^2_{L^2(\mathcal{O})} + \|\nabla \beta\|^2_{L^2(\mathcal{O})} - \frac{kC_0^2}{2} \left(\|\nabla c\|^2_{L^2(\mathcal{O})} + \|\nabla \beta\|^2_{L^2(\mathcal{O})} \right)$$

$$= \left[1 - \frac{kC_0^2}{2} \right] \left(\|\nabla c\|^2_{L^2(\mathcal{O})} + \|\nabla \beta\|^2_{L^2(\mathcal{O})} \right) = \alpha \left(\int_{\mathcal{O}} |\nabla c|^2 \, dx + \int_{\mathcal{O}} |\nabla \beta|^2 \, dx \right)$$

with $\alpha > 0$. Therefore, we have proved that $m(\cdot\,,\cdot)$ is coercive, and, from the Lions-Stampacchia theorem, we can deduce the existence and uniqueness of solution (c,β) of (2.3).

b) When $N = 3$, we have $H^1_0(\mathcal{O}) \hookrightarrow L^6(\mathcal{O})$. Holder's inequality with $p = 3/2$ then gives

$$\left| \int_{\mathcal{O}} (A+B) c\beta \, dx \right| \leq \|A + B\|_{L^p(\mathcal{O})} \|c\|_{L^6(\mathcal{O})} \|\beta\|_{L^6(\mathcal{O})}$$

$$\leq C' \|A + B\|_{L^p(\mathcal{O})} \|\nabla c\|_{L^2(\mathcal{O})} \|\nabla \beta\|_{L^2(\mathcal{O})}$$

$$\leq \frac{C'}{2} \|A + B\|_{L^p(\mathcal{O})} \left(\|\nabla c\|^2_{L^2(\mathcal{O})} + \|\nabla \beta\|^2_{L^2(\mathcal{O})} \right)$$

$$\leq \frac{k'C'}{2} \left(\|\nabla c\|^2_{L^2(\mathcal{O})} + \|\nabla \beta\|^2_{L^2(\mathcal{O})} \right)$$

Arguing as above, if we assume that $k'C'/2 < 1$, it follows that we have existence and uniqueness of solution of (2.3).

c) If $N = 2$, $H_0^1(\mathcal{O})$ is embedded continuously into $L^r(\mathcal{O})$ for any $r < +\infty$. Again, if we fix $p = r/(r-2)$ and we use Holder's inequality, it may be concluded that

$$\left| \int_{\mathcal{O}} (A+B)c\beta \, dx \right| \leq C_r'' \|A+B\|_{L^p(\mathcal{O})} \|\nabla c\|_{L^2(\mathcal{O})} \|\nabla \beta\|_{L^2(\mathcal{O})}.$$

Hence, we can apply once more the Lions-Stampacchia theorem.

■

Remark 5. In the sequel, we will denote by C a generic positive constant.

Theorem 3. *Let us assume that a, b, A and B are constant, $a, b > 0$, $f \in \mathcal{C}^0(\overline{\mathcal{O}})$, at least one of the conditions in proposition 1 is satisfied and, furthermore, $ab > AB$. Then* (2.3) *possesses exactly one solution (c, β) that belongs to $W^{2,p}(\mathcal{O}) \times W^{2,p}(\mathcal{O})$ for all finite p.*

For the proof, we will first consider a penalized problem. Let the functions $\gamma_\varepsilon = \gamma_\varepsilon(s)$ $(0 < \varepsilon < 1)$ be chosen as in [21], that is, $\mathcal{C}^\infty$ in $\mathbb{R}$, satisfying

$$\begin{aligned} &\gamma_\varepsilon'(s) \geq 0 \\ &\gamma_\varepsilon(s) \to -\infty \quad \text{if} \quad s < 0,\, \varepsilon \to 0 \\ &\gamma_\varepsilon(s) \to 0 \qquad \text{if} \quad s > 0,\, \varepsilon \to 0 \\ &\gamma_\varepsilon(s) \leq C, \qquad \gamma_\varepsilon(0) \geq -C \end{aligned} \tag{2.7}$$

where C is independent of ε. Consider the *penalized* problem

$$\begin{cases} -\Delta c + ac + \gamma_\varepsilon(c) = -A\beta & \text{in} \quad \mathcal{O} \\ -\Delta\beta + b\beta = -Bc + f & \text{in} \quad \mathcal{O} \\ c = 0 & \text{on} \quad \partial\mathcal{O} \\ \beta = 0 & \text{on} \quad \partial\mathcal{O} \end{cases} \tag{2.8}$$

The key point in the proof of theorem 3 is the following:

Lemma 1. *Under the assumptions of theorem 3, there exists a solution $(c, \beta) = (c_\varepsilon, \beta_\varepsilon)$ of* (2.8) *with $|\gamma_\varepsilon(c_\varepsilon)| \leq C$, where C is independent of ε.*

Proof: For any $M > 0$, we introduce a truncation $\gamma_{\varepsilon,M}$, with

$$\gamma_{\varepsilon,M}(s) = \begin{cases} M & \text{if} \quad \gamma_\varepsilon(s) > M \\ \gamma_\varepsilon(s) & \text{if} \quad \gamma_\varepsilon(s) \in [-M, M] \\ -M & \text{if} \quad \gamma_\varepsilon(s) < -M \end{cases} \tag{2.9}$$

and we consider the problem

$$\begin{cases} -\Delta c + ac + \gamma_{\varepsilon,M}(c) = -A\beta & \text{in} \quad \mathcal{O} \\ \\ -\Delta \beta + b\beta = -Bc + f & \text{in} \quad \mathcal{O} \\ \\ c, \beta \in H_0^1(\mathcal{O}) \end{cases} \tag{2.10}$$

As usual, we will solve (2.10) by applying a fixed-point argument and we will then try to get good uniform estimates for the solutions.

For each $z \in L^p(\mathcal{O})$ $(1 < p < \infty)$, there exists a unique solution (c, β) of

$$\begin{cases} -\Delta c + ac = -A\beta - \gamma_{\varepsilon,M}(z) & \text{in} \quad \mathcal{O} \\ \\ -\Delta \beta + b\beta = -Bc + f & \text{in} \quad \mathcal{O} \\ \\ c, \beta \in H_0^1(\mathcal{O}) \end{cases} \tag{2.11}$$

To deduce this, we consider the variational or weak formulation of (2.11):

$$\begin{cases} \displaystyle\int_{\mathcal{O}} \nabla c \cdot \nabla v \, dx + \int_{\mathcal{O}} \nabla \beta \cdot \nabla w \, dx + \int_{\mathcal{O}} (acv + b\beta w + A\beta v + Bcw) \, dx \\ \\ \displaystyle\qquad = -\int_{\mathcal{O}} \gamma_{\varepsilon,M}(z) v \, dx + \int_{\mathcal{O}} f w \, dx \qquad \forall v \in H_0^1(\mathcal{O}) \quad \forall w \in H_0^1(\mathcal{O}) \\ \\ c, \beta \in H_0^1(\mathcal{O}) \end{cases}$$

Let m and ℓ be given by

$$\begin{cases} \displaystyle m((c,\beta),(v,w)) = \int_{\mathcal{O}} \nabla c \cdot \nabla v \, dx + \int_{\mathcal{O}} \nabla \beta \cdot \nabla w \, dx + \int_{\mathcal{O}} (acv + b\beta w + A\beta v + Bcw) \, dx \\ \\ \forall (c,\beta),(v,w) \in H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O}) \end{cases}$$

$$\begin{cases} \displaystyle \ell(v,w) = -\int_{\mathcal{O}} \gamma_{\varepsilon,M}(z) v \, dx + \int_{\mathcal{O}} f w \, dx \\ \\ \forall (v,w) \in H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O}) \end{cases}$$

Then the weak formulation of (2.11) is the following:

$$\begin{cases} m((c,\beta),(v,w)) = \ell(v,w) \quad \forall (v,w) \in H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O}) \\ \\ (c,\beta) \in H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O}) \end{cases}$$

In order to prove existence and uniqueness, it suffices to check that the assumptions of the Lax-Milgram theorem are satisfied. Obviously, what we have to check is that m is a coercive continuous bilinear form on $H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O})$. But this is evident, in view of proposition 2.

We conclude that there exists a unique solution $(\widetilde{c}, \widetilde{\beta})$ of (2.11) and, moreover,

$$\|(\widetilde{c}, \widetilde{\beta})\|_{H_0^1(\mathcal{O}) \times H_0^1(\mathcal{O})} \leq C(\varepsilon, M).$$

Now, let p be given in $[1, +\infty)$. The equations in (2.11) imply that $\widetilde{c}$ is bounded in $W^{2,p}(\mathcal{O})$ by a suitable constant $C(\varepsilon, M)$ independent of $z \in L^p(\mathcal{O})$. Since $W^{2,p}(\mathcal{O}) \hookrightarrow L^p(\mathcal{O})$ with a continuous and compact embedding, it follows that

$$S: \ z \in L^p(\mathcal{O}) \mapsto \widetilde{c} \in L^p(\mathcal{O})$$

is a well-defined, continuous and compact mapping. The *Schauder fixed-point theorem* implies then that there exists $c_{\varepsilon,M}$ such that $S(c_{\varepsilon,M}) = c_{\varepsilon,M}$. We have thus proved the existence of at least one solution to the nonlinear problem

$$\left\{ \begin{array}{rcll} -\Delta c_{\varepsilon,M} + a c_{\varepsilon,M} & = & -A\beta_{\varepsilon,M} - \gamma_{\varepsilon,M}(c_{\varepsilon,M}) & \text{in} \quad \mathcal{O} \\ -\Delta \beta_{\varepsilon,M} + b\beta_{\varepsilon,M} & = & -Bc_{\varepsilon,M} + f & \text{in} \quad \mathcal{O} \\ c_{\varepsilon,M}, \beta_{\varepsilon,M} & = & 0 & \text{on} \quad \partial\mathcal{O} \end{array} \right. \tag{2.12}$$

with $c_{\varepsilon,M} \in W^{2,p}(\mathcal{O})$ for all finite p and $\beta_{\varepsilon,M} \in H^2(\mathcal{O})$.

Our next goal is to bound $\gamma_{\varepsilon,M}(c_{\varepsilon,M})$ by a constant independent of ε and M. First, from the definition of $\gamma_{\varepsilon,M}$, we have

$$\gamma_{\varepsilon,M}(s) \le \gamma_\varepsilon(s) \quad \text{whenever } \gamma_\varepsilon(s) \ge -M.$$

Therefore, $\gamma_{\varepsilon,M}(c_{\varepsilon,M}) \le C$, the constant C being independent of ε, M. Now, let μ be the minimum of $\gamma_{\varepsilon,M}(c_{\varepsilon,M})$ in $\overline{\mathcal{O}}$, with $\mu = \gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0))$. If $x_0 \in \partial\mathcal{O}$ and M is large enough, it is clear that $\gamma_\varepsilon(0) \in [-M, M]$ and

$$\mu = \gamma_{\varepsilon,M}(0) = \gamma_\varepsilon(0) \ge -C.$$

This way, we see that in this case $\gamma_{\varepsilon,M}(c_{\varepsilon,M}) \ge -C$. On the other hand, if $x_0 \in \mathcal{O}$, then $c_{\varepsilon,M}$ attains a minimum at x_0 (since $\gamma_{\varepsilon,M}$ is non decreasing). Suppose that $\mu \le 0$ (otherwise, the estimate from below of $\gamma_{\varepsilon,M}(c_{\varepsilon,M})$ is proved). It follows from the Sobolev embeddings that

$$\begin{array}{lll} H^2(\mathcal{O}) \hookrightarrow \mathcal{C}^{0,\alpha}(\overline{\mathcal{O}}) & \forall \alpha \in [0,1) & \text{for} \quad N = 2 \\ H^2(\mathcal{O}) \hookrightarrow \mathcal{C}^{0,1/2}(\overline{\mathcal{O}}) & & \text{if} \quad N = 3 \end{array}$$

Thus,

$$-A\beta_{\varepsilon,M}, \ -\gamma_{\varepsilon,M}(c_{\varepsilon,M}) \in \mathcal{C}^{0,\alpha}(\overline{\mathcal{O}}).$$

The first equation in (2.12) makes obvious that $c_{\varepsilon,M} \in \mathcal{C}^{2,\alpha}(\overline{\mathcal{O}})$ and it is possible to speak of $\nabla c_{\varepsilon,M}$, $\Delta c_{\varepsilon,M}$ at any point. Since $c_{\varepsilon,M}$ attains its minimum at $x_0 \in \mathcal{O}$,

$$\nabla c_{\varepsilon,M}(x_0) = 0, \ -\Delta c_{\varepsilon,M}(x_0) \le 0.$$

Let us assume that $\beta_{\varepsilon,M}$ attains the maximum at $x_1 \in \mathcal{O}$ (if $x_1 \in \partial\mathcal{O}$, then $\beta_{\varepsilon,M}(x_1) = 0$, and the first equation in (2.12) gives $\gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0)) + a c_{\varepsilon,M}(x_0) \ge 0$). We obtain that

$$\begin{aligned} \gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0)) + a c_{\varepsilon,M}(x_0) &= -A\beta_{\varepsilon,M}(x_0) + \Delta c_{\varepsilon,M}(x_0) \\ &\ge -A\beta_{\varepsilon,M}(x_0) \ge -A\beta_{\varepsilon,M}(x_1) \end{aligned}$$

Also, the second equation in (2.12) implies that

$$\begin{aligned} b\beta_{\varepsilon,M}(x_1) &= -Bc_{\varepsilon,M}(x_1) + f(x_1) + \Delta\beta_{\varepsilon,M}(x_1) \\ &\le -Bc_{\varepsilon,M}(x_0) + C \end{aligned}$$

Here, we have taken into account that β attains the maximum in x_1 and the fact that $f \in \mathcal{C}^0(\overline{\mathcal{O}})$. According to these inequalities, the following holds:

$$\gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0)) + a c_{\varepsilon,M}(x_0) \geq \frac{AB}{b} c_{\varepsilon,M}(x_0) - C$$

and thus

$$\gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0)) + \left(a - \frac{AB}{b}\right) c_{\varepsilon,M}(x_0) \geq -C. \tag{2.13}$$

By assumption, we have $\alpha := a - AB/b > 0$.
Observe that, if the $r_{\varepsilon,M}$ satisfy $\gamma_{\varepsilon,M}(r_{\varepsilon,M}) + \alpha r_{\varepsilon,M} \geq -C$, then necessarily there exists $C_0 > 0$ such that

$$\gamma_{\varepsilon,M}(r_{\varepsilon,M}) \geq -C_0 \quad \forall\varepsilon \quad \forall M.$$

Indeed, if this assertion were false, for each $k \geq 1$ there would exist ε_k, M_k with

$$\gamma_k := \gamma_{\varepsilon_k,M_k}(r_{\varepsilon_k,M_k}) < -k.$$

From the definition of $\gamma_{\varepsilon,M}$, we must have in that case $\gamma_{\varepsilon_k}(r_{\varepsilon_k,M_k}) < -k$. Therefore, $r_{\varepsilon_k,M_k} < 0$ by (2.7). But, in view of (2.13), this would imply

$$\gamma_k \geq -C - \alpha r_{\varepsilon_k,M_k} \geq -C,$$

which is the opposite to $\gamma_k < -k$, an absurd. From (2.13) and this argument, we have the desired conclusion: $\mu \geq -C$.

Note that we have actually shown that

$$|\gamma_{\varepsilon,M}(c_{\varepsilon,M})| \leq C, \quad C \text{ independent of } \varepsilon, M.$$

If M is large enough, then $\gamma_{\varepsilon,M}(s) \equiv \gamma_\varepsilon(s)$, $(c_{\varepsilon,M}, \beta_{\varepsilon,M}) \equiv (c_\varepsilon, \beta_\varepsilon)$ is a solution of the penalized problem (2.8) and

$$|\gamma_\varepsilon(c_\varepsilon)| \leq C. \tag{2.14}$$

This completes the proof of the lemma.

■

Let us now give the proof of theorem 3.

The last inequality (2.14) leads to an estimate of $\|(c_\varepsilon, \beta_\varepsilon)\|_{H^1_0(\mathcal{O})\times H^1_0(\mathcal{O})}$ independent of ε, M, which implies $\|c_\varepsilon\|_{W^{2,p}(\mathcal{O})}, \|\beta_\varepsilon\|_{W^{2,p}(\mathcal{O})} \leq C$. Then, since we have

$$W^{1,p}(\mathcal{O}) \hookrightarrow \mathcal{C}^{0,\alpha}(\overline{\mathcal{O}}) \hookrightarrow \mathcal{C}^0(\overline{\mathcal{O}})$$

for $p > N$ large enough and $\alpha \in [0, 1 - N/p)$ with compact embeddings, $(c_\varepsilon, \beta_\varepsilon)$ belongs to a fixed compact set of $\mathcal{C}^0(\overline{\mathcal{O}}) \times \mathcal{C}^0(\overline{\mathcal{O}})$. In particular, it follows that, at least for a subsequence,

$$c_\varepsilon \to c,\ \beta_\varepsilon \to \beta \quad \text{uniformly in } \overline{\mathcal{O}}.$$

Since $|\gamma_\varepsilon(c_\varepsilon)| \leq C$, we deduce that $c \geq 0$ in $\mathcal{O}$. Also, $\gamma_\varepsilon(c_\varepsilon) \to 0$ in the set $\Omega := \{x \in \mathcal{O} : c(x) > 0\}$. Consequently,

$$c(-\Delta c + ac + A\beta) = 0 \quad \text{and} \quad -\Delta\beta + b\beta = -Bc + f \tag{2.15}$$

almost everywhere in $\mathcal{O}$.

We now proceed to show that

$$-\Delta c + ac \geq -A\beta. \tag{2.16}$$

In order to get this inequality, it will be necessary to fix $\varphi \in \mathcal{D}(\mathcal{O})$, $\varphi \geq 0$. Multiplying by φ the equation satisfied by c_ε and integrating, we find:

$$\int_{\mathcal{O}} (\nabla c_\varepsilon \cdot \nabla \varphi + (a c_\varepsilon + A\beta_\varepsilon)\, \varphi)\; dx = - \int_{\mathcal{O}} \gamma_\varepsilon(c_\varepsilon)\varphi\, dx. \tag{2.17}$$

Taking limits as $\varepsilon \to 0$, we obtain that

$$\begin{aligned}
\int_{\mathcal{O}} (\nabla c \cdot \nabla \varphi + (a c + A\beta)\, \varphi)\; dx &= - \lim_{\varepsilon \to 0} \int_{\mathcal{O}} \gamma_\varepsilon(c_\varepsilon)\varphi\, dx \\
&= - \lim_{\varepsilon \to 0} \left[\int_{\Omega} \gamma_\varepsilon(c_\varepsilon)\varphi\, dx + \int_{\mathcal{O}\setminus\overline{\Omega}} \gamma_\varepsilon(c_\varepsilon)\varphi\, dx \right] \\
&= - \lim_{\varepsilon \to 0} \int_{\mathcal{O}\setminus\overline{\Omega}} \gamma_\varepsilon(c_\varepsilon)\varphi\, dx
\end{aligned}$$

Here, we have used that $|\gamma_\varepsilon(c_\varepsilon)|$ is uniformly bounded and $\gamma_\varepsilon(c_\varepsilon) \to 0$ in Ω. Finally,

$$\begin{aligned}
\lim_{\varepsilon \to 0} \int_{\mathcal{O}\setminus\overline{\Omega}} \gamma_\varepsilon(c_\varepsilon)\varphi\, dx &\leq \limsup_{\varepsilon \to 0} \int_{\mathcal{O}\setminus\overline{\Omega}} \gamma_\varepsilon(c_\varepsilon)^+ \varphi\, dx \\
&\leq \int_{\mathcal{O}\setminus\overline{\Omega}} \left(\limsup_{\varepsilon \to 0} \gamma_\varepsilon(c_\varepsilon)^+ \right) \varphi\, dx \\
&= 0
\end{aligned}$$

in view of Fatou's lemma. Here, we have used the notation $z^+ = \max(z, 0)$.

We deduce that

$$\int_{\mathcal{O}} (\nabla c \cdot \nabla \varphi + (a c + A\beta)\, \varphi)\; dx \geq 0 \quad \forall \varphi \in \mathcal{D}(\mathcal{O}),\; \varphi \geq 0$$

and, consequently, (2.16) holds.

In fact, we have proved that (c, β) verifies almost everywhere in $\mathcal{O}$ the following relations:

$$\begin{cases}
-\Delta c + a c \geq -A\beta \\
c \geq 0 \\
(-\Delta c + a c + A\beta)\, c = 0 \\
-\Delta \beta + b\beta = -Bc + f
\end{cases}$$

Also, as c_ε, β_ε are equal to zero on $\partial\mathcal{O}$, this clearly gives $c, \beta \in H_0^1(\mathcal{O})$. By the Sobolev embedding

$$W^{2,p}(\mathcal{O}) \hookrightarrow \mathcal{C}^{1,\alpha}(\overline{\mathcal{O}}) \quad \text{if} \quad 2 - N/p > 1 + \alpha,$$

we also have that $c, \beta \in \mathcal{C}^1(\overline{\mathcal{O}})$ and we can consider the functions $\partial c/\partial n$, $\partial \beta/\partial n$ on $\partial\mathcal{O}$. This way, for all $(v,w) \in \widetilde{K}$, we have

$$\int_{\mathcal{O}} \nabla c \cdot \nabla(v-c)\,dx + \int_{\mathcal{O}} ac(v-c)\,dx + \int_{\mathcal{O}} \nabla\beta \cdot \nabla(w-\beta)\,dx + \int_{\mathcal{O}} b\beta(w-\beta)\,dx$$

$$= \int_{\mathcal{O}} (-\Delta c)(v-c)\,dx + \int_{\partial\mathcal{O}} \frac{\partial c}{\partial n}(v-c)\,d\Gamma + \int_{\mathcal{O}} ac(v-c)\,dx$$

$$+ \int_{\mathcal{O}} (-\Delta\beta)(w-\beta)\,dx + \int_{\partial\mathcal{O}} \frac{\partial \beta}{\partial n}(w-\beta)\,d\Gamma + \int_{\mathcal{O}} b\beta(w-\beta)\,dx$$

$$\geq \int_{\mathcal{O}} (-A\beta)(v-c)\,dx + \int_{\mathcal{O}} (-Bc+f)\,(w-\beta)\,dx$$

Thus, we have proved that (c,β) is a solution of (2.4), $c \in \mathcal{C}^1(\overline{\mathcal{O}})$ and (c,β) is the unique solution of (2.3) in $H^1_0(\mathcal{O}) \times H^1_0(\mathcal{O})$. We have also obtained some estimates of the solution in $W^{2,p}(\mathcal{O}) \times W^{2,p}(\mathcal{O})$. This completes the proof of theorem 3.

Remark 6. In theorem 3, in order to prove the existence of solution, we have assumed that a, b, A and B are constant, $a, b > 0$, at least one of the conditions in proposition 1 is satisfied and, furthermore, $ab > AB$ (recall that this means in practice that A and B must be small in comparison to a and b).

In (2.4), the constant a is the rate of dissipation of the tumor cell concentration c. The presence in the tumor of an inhibitor acts as a sink of nutrient at rate A.
We have supposed that similar effects govern the evolution of the population density of the inhibitor. Thus, $-Bc$ determines the way β is consumed while the inhibitor is destroying tumor cells. The function f in the equation for β can be viewed as a control variable. It is absolutely meaningful to consider functions of this kind when analyzing the action of therapy strategies to diminish tumor cell proliferation.

□

2.2.2 A similar problem with nonhomogeneous boundary data

This Subsection is devoted to the study of a system similar to the previous one but with nonzero boundary data that play again the role of a therapy-control variable.

Let $\mathcal{O}$ be as above. We will denote by $\hat{K}$ the set

$$\hat{K} = \{(v,w) \in H^1(\mathcal{O}) \times H^1(\mathcal{O}) \;:\; v \geq 0,\; v = 0 \text{ on } \partial\mathcal{O},\; w = h \text{ on } \partial\mathcal{O}\},$$

where h is given. To fix ideas, we will assume that h is the trace on $\partial\mathcal{O}$ of some $\overline{\beta} \in W^{2,\infty}(\mathcal{O})$.

We consider the following problems:

$$\begin{cases} \displaystyle\int_{\mathcal{O}} \nabla c \cdot \nabla(v-c)\,dx + \int_{\mathcal{O}} \nabla\beta \cdot \nabla(w-\beta)\,dx + \int_{\mathcal{O}} ac(v-c)\,dx + \int_{\mathcal{O}} b\beta(w-\beta)\,dx \\ \qquad \displaystyle\geq -\int_{\mathcal{O}} A\beta(v-c)\,dx - \int_{\mathcal{O}} Bc(w-\beta)\,dx \\ \forall\,(v,w) \in \hat{K},\; (c,\beta) \in \hat{K} \end{cases} \tag{2.18}$$

and

$$\begin{cases} c \in H_0^1(\mathcal{O}) \cap \mathcal{C}^0(\overline{\mathcal{O}}), \quad \beta \in H^1(\mathcal{O}) \\ -\Delta c + ac \geq -A\beta & \text{in } \mathcal{O} \\ -\Delta c + ac = -A\beta & \text{in } \Omega := \{x \in \mathcal{O} \ : \ c(x) > 0\} \\ c \geq 0 & \text{in } \mathcal{O} \\ -\Delta\beta + b\beta = -Bc & \text{in } \mathcal{O} \\ \beta = h & \text{on } \partial\mathcal{O} \end{cases} \tag{2.19}$$

Here, $a, b, A, B \in L^\infty(\mathcal{O})$, with $a, b \geq 0$. As before, we establish the equivalence of (2.18) and (2.19) under some regularity assumptions on c.

Proposition 3.

1. *If (c, β) is a solution of* (2.18) *and $c \in \mathcal{C}^0(\overline{\mathcal{O}})$, then (c, β) is a solution of* (2.19).
2. *Let (c, β) be a solution of* (2.19)*, with $c \in \mathcal{C}^1(\overline{\mathcal{O}})$. Then (c, β) is a solution of* (2.18).

The proof is very similar to the proof of proposition 1 and is omitted.

We will now establish a result concerning the existence and uniqueness of solution of the variational inequality (2.18), similar to proposition 2.

Proposition 4.

a) *Let $C = C(\mathcal{O})$ be the Poincaré constant, and suppose that*

$$k := \|A + B\|_{L^\infty(\mathcal{O})} < \frac{2}{C^2}.$$

Then there exists a unique solution of (2.18).

b) $(N = 3)$ *Let $\sqrt{C'}$ be the constant of the embedding of $H_0^1(\mathcal{O})$ in $L^6(\mathcal{O})$ and suppose that*

$$p = 3/2, \quad k' := \|A + B\|_{L^p(\mathcal{O})} < \frac{2}{C'}.$$

Then there exists a unique solution of (2.18).

c) $(N = 2)$ *Let $\sqrt{C''_r}$ be the constant of the embedding of $H_0^1(\mathcal{O})$ in $L^r(\mathcal{O})$, and let p and r be such that $\frac{1}{p} = 1 - \frac{2}{r}$. Assume that*

$$p > 1, \quad k'' := \|A + B\|_{L^p(\mathcal{O})} < \frac{2}{C''_r}.$$

Then there exists a unique solution of (2.18).

The proof is similar to the proof of proposition 2. Indeed, let us introduce the bilinear form

$$\begin{cases} m((c, \beta), (v, w)) = \displaystyle\int_{\mathcal{O}} \nabla c \cdot \nabla v \, dx + \int_{\mathcal{O}} \nabla\beta \cdot \nabla w \, dx + \int_{\mathcal{O}} acv \, dx + \int_{\mathcal{O}} b\beta w \, dx \\ \qquad\qquad + \displaystyle\int_{\mathcal{O}} A\beta v \, dx + \int_{\mathcal{O}} Bcw \, dx \\ \forall \, (c, \beta), \, (v, w) \in H_0^1(\mathcal{O}) \times H^1(\mathcal{O}) \end{cases}$$

Then the task is to prove that, under the previous assumptions on $A+B$, one has existence and uniqueness for the variational problem

$$\begin{cases} m((c,\beta),(v,w)-(c,\beta)) \geq 0 \\ \forall\,(v,w) \in \hat{K},\ (c,\beta) \in \hat{K}. \end{cases}$$

From the Lions-Stampacchia theorem, we know that it suffices to check that, for some $\alpha > 0$,

$$\begin{cases} m((z,y)-(v,w),(z,y)-(v,w)) \geq \alpha \|(z,y)-(v,w)\|^2_{H^1_0 \times H^1} \\ \forall\,(z,y),(v,w) \in \hat{K} \end{cases}$$

But it is very easy to see that this is equivalent to the following:

$$\begin{cases} m((z_1,z_2),(z_1,z_2)) \geq \alpha \|(z_1,z_2)\|^2_{H^1_0 \times H^1_0} \\ \forall\,(z_1,z_2) \in H^1_0(\mathcal{O}) \times H^1_0(\mathcal{O}) \end{cases} \tag{2.20}$$

And it has already been proved in proposition 2 that the conditions imposed to $A+B$ imply (2.20). Therefore, there exists a unique solution (c,β) of (2.18), which is the desired conclusion.

Theorem 4. *Let us assume that a, b, A and B are constant, $a, b > 0$, at least one of the conditions in proposition 4 is satisfied and, furthermore, $ab > AB$. Suppose that there exists $\overline{\beta} \in W^{2,p}(\mathcal{O})$ with $\overline{\beta} = h$ on $\partial\mathcal{O}$. Then problem* (2.18) *possesses exactly one solution (c,β) in $W^{2,p}(\mathcal{O}) \times W^{2,p}(\mathcal{O})$.*

Again, the proof is similar to the proof of the corresponding result in Subsection 2.2.1 (theorem 3). We begin by considering the *penalized* problem

$$\begin{cases} -\Delta c + ac = -A\beta - \gamma_\varepsilon(c) & \text{in } \mathcal{O} \\ -\Delta\beta + b\beta = -Bc & \text{in } \mathcal{O} \\ c = 0 & \text{on } \partial\mathcal{O} \\ \beta = h & \text{on } \partial\mathcal{O} \end{cases} \tag{2.21}$$

Lemma 2. *Under the assumptions of theorem 4, there exists a solution $(c,\beta) = (c_\varepsilon, \beta_\varepsilon)$ of* (2.21)*, with $|\gamma_\varepsilon(c_\varepsilon)| \leq C$.*

Proof: As in the proof of lemma 1, for any $M > 0$, we introduce $\gamma_{\varepsilon,M}$ and we consider the problem

$$\begin{cases} -\Delta c + ac = -A\beta - \gamma_{\varepsilon,M}(c) & \text{in } \mathcal{O} \\ -\Delta\beta + b\beta = -Bc & \text{in } \mathcal{O} \\ c = 0 & \text{on } \partial\mathcal{O} \\ \beta = h & \text{on } \partial\mathcal{O} \end{cases} \tag{2.22}$$

It is not difficult to prove the existence of a solution $(c_{\varepsilon,M}, \beta_{\varepsilon,M})$ of (2.22), with $c_{\varepsilon,M}, \beta_{\varepsilon,M} \in W^{2,p}(\mathcal{O})$ for all finite $p \geq 1$. It suffices to apply a fixed-point argument.

The main point is to prove that

$$|\gamma_{\varepsilon,M}(c_{\varepsilon,M})| \leq C. \tag{2.23}$$

From the definition of γ_ε, we know that $\gamma_{\varepsilon,M}(c_{\varepsilon,M}) \leq C$. Now, assume that $\mu = \min_{\overline{\mathcal{O}}} \gamma_{\varepsilon,M}(c_{\varepsilon,M}(x)) = \gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0))$, for some $x_0 \in \mathcal{O}$ with $c_{\varepsilon,M}(x_0) < 0$ (if $x_0 \in \partial\mathcal{O}$ or $c_{\varepsilon,M} \geq 0$, we already have (2.23)). Then

$$0 \geq -\Delta c_{\varepsilon,M}(x_0) + a c_{\varepsilon,M}(x_0) \geq -A\beta_{\varepsilon,M}(x_1) - \mu$$

Here, it is assumed that $\beta_{\varepsilon,M}$ attains its maximum in $\overline{\mathcal{O}}$ at x_1.

- If $x_1 \in \partial\mathcal{O}$, then $\beta_{\varepsilon,M}(x_1) = h(x_1) \leq C$ and this gives directly

$$\mu = \gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0)) \geq -C. \tag{2.24}$$

- Assume now that $x_1 \in \mathcal{O}$. The second equation in (2.22) then gives

$$b\beta_{\varepsilon,M}(x_1) = -Bc_{\varepsilon,M}(x_1) + \Delta\beta_{\varepsilon,M}(x_1) \leq -Bc_{\varepsilon,M}(x_0)$$

  and we deduce that

$$\gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0)) + ac_{\varepsilon,M}(x_0) \geq \frac{AB}{b}c_{\varepsilon,M}(x_0)$$

  and

$$\gamma_{\varepsilon,M}(c_{\varepsilon,M}(x_0)) + \left(a - \frac{AB}{b}\right)c_{\varepsilon,M}(x_0) \geq 0.$$

As in the proof of lemma 1, since $a - \dfrac{AB}{b} > 0$, this also implies (2.24). Hence, we have (2.23).

Now, we can argue as in the final part of the proof of lemma 1 and deduce the existence of a solution $(c_\varepsilon, \beta_\varepsilon)$ to (2.21), with c_ε and β_ε uniformly bounded in $W^{2,p}(\mathcal{O})$ for all finite $p \geq 1$.

■

Using lemma 2, theorem 4 can now be proved easily, arguing as in the proof of theorem 3.

Remark 7. As in the stationary problem described in Subsection 2.2.1, h can be viewed as a control variable, oriented to therapy. This way, the inhibitor concentration β is prescribed by the control h on the boundary $\partial\mathcal{O}$. In practice, it is realistic to have $h = 0$ except on a (small) part of the boundary, that is,

$$h = k1_\gamma, \text{ for some } \gamma \subset \partial\mathcal{O}.$$

2.2.3 Another simplified (stationary) problem

After proving the existence and uniqueness of solution of (2.4), we are going to study a similar (but different) problem with a more complex term on the right hand side of the equation for c:

$$\begin{cases} c \in H_0^1(\mathcal{O}) \cap \mathcal{C}^0(\overline{\mathcal{O}}), \quad \beta \in H_0^1(\mathcal{O}) \\ -\Delta c \geq \rho c - G(c,\beta) & \text{in } \mathcal{O} \\ -\Delta c - \rho c + G(c,\beta) = 0 & \text{in } \Omega := \{x \in \mathcal{O} \ : \ c(x) > 0\} \\ c \geq 0 & \text{in } \mathcal{O} \\ -\Delta\beta + m'\beta = -Bc + f & \text{in } \mathcal{O} \end{cases} \tag{2.25}$$

Here, $G(c,\beta)$ will be nonlinear in c and β; the precise expression will be given below. For the moment, we only assume that $G \in \mathcal{C}^0(\mathbb{R} \times \mathbb{R})$ and $G(c,\beta) \geq 0$.

We will assume that $\rho, m' > 0$. Thus, the terms ρc and $m'\beta$ in the equations above show that the tumor cells proliferate and the inhibitor population β dissipates. We will also assume that $B > 0$. On the other hand, since ρ is positive, we lose the coerciveness that we had in (2.4). In order to overcome this difficulty and prove the existence of solution, we will assume that ρ is not an eigenvalue of $-\Delta$ in $\mathcal{O}$.

For any given $c^*, \beta^* \in L^\infty(\mathcal{O})$, we will try to solve the nonlinear problem

$$\left\{\begin{array}{ll} c \in H^1_0(\mathcal{O}) \cap \mathcal{C}^0(\overline{\mathcal{O}}) & \\ -\Delta c \geq \rho c - G(c^*, \beta^*) & \text{in } \mathcal{O} \\ -\Delta c - \rho c + G(c^*, \beta^*) = 0 & \text{in } \Omega := \{x \in \mathcal{O} \ : \ c(x) > 0\} \\ c \geq 0 & \text{in } \mathcal{O} \end{array}\right. \tag{2.26}$$

and the linear problem

$$\left\{\begin{array}{l} \beta \in H^1_0(\mathcal{O}) \\ -\Delta \beta + m'\beta = -Bc + f \quad \text{in } \mathcal{O} \end{array}\right. \tag{2.27}$$

Then, we will apply an appropriate fixed-point argument to deduce the existence of a solution to (2.25).

Notice that, if $c \in \mathcal{C}^1(\overline{\mathcal{O}})$ is a solution of (2.26) and $\partial\Omega$ is locally-Lipschitz, then c is also a solution of the variational problem

$$\left\{\begin{array}{l} \displaystyle\int_{\mathcal{O}} \nabla c \cdot \nabla(v - c)\, dx \geq \rho \int_{\mathcal{O}} c(v - c)\, dx + \int_{\mathcal{O}} F(v - c)\, dx \\ \forall\, v \in K_0, \ c \in K_0 \end{array}\right. \tag{2.28}$$

where we have set $F = -G(c^*, \beta^*) \in L^\infty(\mathcal{O})$ and $K_0 = \{v \in H^1_0(\mathcal{O}) \ : \ v \geq 0\}$.
Conversely, if $c \in \mathcal{C}^0(\overline{\mathcal{O}})$ is a solution of (2.28), then c also solves (2.26).
The proofs of these assertions can be obtained by arguing as in the proof of proposition 1.

Proposition 5. *Assume that $c^*, \beta^* \in L^\infty(\mathcal{O})$ and set $F = -G(c^*, \beta^*)$. Also, assume that $\rho > 0$ is not an eigenvalue of the Dirichlet Laplacian $-\Delta$. Then (2.28) possesses at least one solution c, with $c \in W^{2,p}(\mathcal{O})$ for all finite $p > 1$.*

Proof: Let us introduce again the functions γ_ε and $\gamma_{\varepsilon,M}$ (as in the proof of lemma 1). We now choose $R > \rho$ and we set

$$\gamma_{\varepsilon,M,R}(s) = Rs^- + \gamma_{\varepsilon,M}(s) \quad \forall s \in \mathbb{R} \tag{2.29}$$

(where $s^- = \max(-s, 0)$). It will be assumed that the functions γ_ε satisfy (2.7) and also the following:

$$\gamma_\varepsilon(s) - Rs \to -\infty \quad \text{as} \quad \varepsilon \to 0 \quad \forall s < 0. \tag{2.30}$$

We will consider again a penalized problem:

$$\left\{\begin{array}{rcll} -\Delta c & = & \rho\, c + F - \gamma_{\varepsilon,M}(c) & \text{in } \ \mathcal{O} \\ c & = & 0 & \text{on } \ \partial\mathcal{O} \end{array}\right. \tag{2.31}$$

We will use the following well known result, which is a consequence of the Hilbert-Schmidt theorem:

Lemma 3. *There exists a Hilbert basis $\{\varphi_1, \varphi_2, \ldots\}$ of $L^2(\mathcal{O})$ (and $H^1_0(\mathcal{O})$), with*

$$\left\{\begin{array}{l} (\nabla\varphi_i, \nabla v)_{L^2(\mathcal{O})} = \lambda_i(\varphi_i, v)_{L^2(\mathcal{O})} \quad \forall v \in H^1_0(\mathcal{O}),\ \varphi_i \in H^1_0(\mathcal{O}), \\ \|\varphi_i\|_{L^2(\mathcal{O})} = 1,\ 0 < \lambda_1 < \lambda_2 \leq \lambda_3 \leq \cdots \quad \text{with } \lambda_i \nearrow +\infty. \end{array}\right.$$

Let U be the space spanned by the first i eigenfunctions $\varphi_1, \dots, \varphi_i$, that is, $U = [\varphi_1, \dots, \varphi_i]$ and let us set $W = [\varphi_{i+1}, \dots, \varphi_n, \dots]$. Let i be such that $\rho \in (\lambda_i, \lambda_{i+1})$. We can write $c = u + w$, with $u \in U$ and $w \in W$:

$$c = u + w = \sum_{j \le i} \xi_j \varphi_j + \sum_{j \ge i+1} \xi_j \varphi_j$$

Then, an equivalent formulation of (2.31) is the following:

$$-\Delta u = \rho u + P_U F - P_U \gamma_{\varepsilon,M}(u+w), \quad u \in U \tag{2.32}$$

$$-\Delta w = \rho w + P_W F - P_W \gamma_{\varepsilon,M}(u+w), \quad w \in W \tag{2.33}$$

Here, $P_U : H_0^1(\mathcal{O}) \mapsto U$ and $P_W : H_0^1(\mathcal{O}) \mapsto W$ are the usual orthogonal projectors, given by

$$P_U g = \sum_{j \le i} (g, \varphi_j)\, \varphi_j, \quad P_W g = \sum_{j \ge i+1} (g, \varphi_j)\, \varphi_j \qquad \forall g \in H_0^1(\mathcal{O}).$$

Now, in order to prove the existence of solution of (2.32)–(2.33), we will try again to apply a fixed-point argument:

- Let $z = \widetilde{u} + \widetilde{w} \in L^2(\mathcal{O})$, with $\widetilde{u} \in U$ and $\widetilde{w} \in W$.
- We consider the solution $u = \sum_{j \le i} \xi_j \varphi_j$ of (2.32), with $u + w$ replaced by z. We have:

$$\begin{cases} -\Delta u = \rho u + P_U F - P_U \gamma_{\varepsilon,M}(z) & \text{in } \mathcal{O} \\ u = 0 & \text{on } \partial\mathcal{O} \end{cases} \tag{2.34}$$

  Multiplying the equation for u by φ_k and integrating in $\mathcal{O}$, we get

$$\lambda_k \xi_k = \rho\, \xi_k + (F, \varphi_k)_{L^2(\mathcal{O})} - (P_U \gamma_{\varepsilon,M}(z), \varphi_k)_{L^2(\mathcal{O})}, \quad 1 \le k \le i.$$

  Let $\Lambda_U : L^2(\mathcal{O}) \mapsto U$ be given by

$$\Lambda_U(z) = \sum_{j \le i} \xi_j \varphi_j$$

  where

$$(\lambda_k - \rho)\, \xi_k = (F - P_U \gamma_{\varepsilon,M}(z), \varphi_k)_{L^2(\mathcal{O})}, \quad 1 \le k \le i. \tag{2.35}$$

  Since ρ is not an eigenvalue of $-\Delta$ in $\mathcal{O}$ and $\gamma_{\varepsilon,M}(z) \in L^\infty(\mathcal{O})$, Λ_U is a well-defined continuous mapping that transforms $L^2(\mathcal{O})$ into a bounded set in U.

- Our next purpose is to solve (2.33) with $u + w$ replaced by z, that is

$$\begin{cases} -\Delta w - \rho w = P_W[F - \gamma_{\varepsilon,M}(z)] & \text{in } \mathcal{O} \\ w = 0 & \text{on } \partial\mathcal{O} \end{cases} \tag{2.36}$$

  To deduce the existence of a solution, we now consider the variational formulation of this problem. Let m_W and ℓ_W denote the following bilinear and linear forms:

$$\begin{aligned} m_W(w, v) &= \int_{\mathcal{O}} (\nabla w \cdot \nabla v - \rho w v)\, dx \quad \forall\, w, v \in W \\ \langle \ell_W, v \rangle &= \int_{\mathcal{O}} P_W[F - \gamma_{\varepsilon,M}(z)] v\, dx \quad \forall\, v \in W \end{aligned} \tag{2.37}$$

We want to solve the following variational inequality:

$$\begin{cases} m_W(w,v) = \langle \ell_W, v\rangle \\ \forall\, v \in W,\ \ w \in W \end{cases} \tag{2.38}$$

But this is easy. Indeed, m_W is a continuous bilinear form on W and obviously, for any $w \in W$, one has:

$$m_W(w,w) = \int_{\mathcal{O}} \left(|\nabla w|^2 - \rho |w|^2\right)\, dx$$

$$= \sum_{j \geq i+1} (\lambda_j - \rho)\, |\, (w, \varphi_j)\, |^2$$

Let $\alpha > 0$ be such that $\rho/\lambda_{i+1} \leq 1 - \alpha$. Then $\alpha\lambda_j \leq \lambda_j - \rho$ for all $j \geq i+1$, whence

$$m_W(w,w) \geq \alpha \sum_{j \geq i+1} \lambda_j |\, (w, \varphi_j)\, |^2 = \alpha \|w\|^2_{H^1_0(\mathcal{O})} \quad \forall w \in W. \tag{2.39}$$

This proves that m_W is coercive in W and, consequently, (2.38) possesses exactly one solution.

Notice that (2.36) and (2.38) are equivalent problems. Therefore, we have proved that, for any $z \in L^2(\mathcal{O})$, (2.36) is uniquely solvable. The solution w satisfies

$$\|w\|_{H^1_0} \leq C(\varepsilon, M). \tag{2.40}$$

We set $w = \Lambda_W(z)$. Then, $\Lambda_W : L^2(\mathcal{O}) \mapsto W$ is a well-defined continuous mapping that maps $L^2(\mathcal{O})$ into a bounded set in $H^1_0(\mathcal{O})$.

- Let us consider the mapping Λ that, to each $z \in L^2(\mathcal{O})$, assigns the function $c = u + w$, with $u = \Lambda_U(z)$ and $w = \Lambda_W(z)$. Since U is a finite-dimensional space, Λ_U maps the whole $L^2(\mathcal{O})$ into a bounded set in U and we have (2.40), we immediately deduce that $\Lambda : L^2(\mathcal{O}) \mapsto L^2(\mathcal{O})$ is continuous and compact and maps the space $L^2(\mathcal{O})$ into a ball. Consequently, we can apply Schauder's theorem and deduce that (2.32)–(2.33) possesses at least one solution.

In the sequel, we consider the family $\{c_{\varepsilon,M}\}$ where, for each (small) $\varepsilon > 0$ and (large) $M > 0$, $c_{\varepsilon,M}$ solves (2.32)–(2.33), that is, (2.31). From elliptic regularity, we have $c_{\varepsilon,M} \in W^{2,p}(\mathcal{O})$ for all finite $p \geq 1$.

Our next objective is to get an estimate of $\gamma_{\varepsilon,M}(c_{\varepsilon,M})$ independent of ε and M.

From (2.7), we first have $\gamma_{\varepsilon,R}(c_{\varepsilon,R}) \leq C$, where C is independent of ε and M.

On the other hand, let us set $\mu = \min\limits_{\overline{\mathcal{O}}} \gamma_{\varepsilon,M}(c_{\varepsilon,M}) = \gamma_{\varepsilon,M}\left(c_{\varepsilon,M}(x_0)\right)$. It can be assumed that $x_0 \in \mathcal{O}$ and $c_{\varepsilon,M}(x_0) < 0$. Since $c_{\varepsilon,M} \in W^{2,p}(\mathcal{O})$ for all finite p and $\gamma_{\varepsilon,M}$ is non-decreasing, we then have

$$0 \geq -\Delta c_{\varepsilon,M}(x_0) = \rho c_{\varepsilon,M}(x_0) + F(x_0) - \mu$$

$$= (R - \rho)\, c_{\varepsilon,M}(x_0)^- + F(x_0) - \gamma_{\varepsilon,M,R}(c_{\varepsilon,M}(x_0))$$

whence

$$\gamma_{\varepsilon,M,R}\left(c_{\varepsilon,M}(x_0)\right) \geq F(x_0) \geq -C \tag{2.41}$$

We now let $\varepsilon \to 0^+$ and $M \to +\infty$. Then, from (2.41), the properties of $\gamma_{\varepsilon,M}$ and $\gamma_{\varepsilon,M,R}$ and (2.30), we deduce that

$$\liminf_{\substack{\varepsilon \to 0^+ \\ M \to +\infty}} \ c_{\varepsilon,M}(x_0) \geq 0,$$

whence

$$\mu = \gamma_{\varepsilon,M}\left(c_{\varepsilon,M}(x_0)\right) = \gamma_{\varepsilon,M,R}\left(c_{\varepsilon,M}(x_0)\right) + Rc_{\varepsilon,M}(x_0) \geq -C.$$

This shows that

$$|\gamma_{\varepsilon,M}\left(c_{\varepsilon,M}\right)| \leq C. \tag{2.42}$$

We have thus found in particular that $\gamma_{\varepsilon,M}\left(c_{\varepsilon,M}\right)$ is uniformly bounded in $L^2(\mathcal{O})$, whence this is also the case for $P_U(\gamma_{\varepsilon,M}(c_{\varepsilon,M}))$ and $P_W(\gamma_{\varepsilon,M}(c_{\varepsilon,M}))$.

Coming back to (2.32), we see that $\Lambda_U(c_{\varepsilon,M})$ is uniformly bounded in any norm in U (recall that U is finite-dimensional). On the other hand, looking at (2.33), i.e. (2.37)–(2.38) with $z = c_{\varepsilon,M}$, we also see that $\Lambda_W(c_{\varepsilon,M})$ is uniformly bounded in the norm of $H_0^1(\mathcal{O})$ and, from a straightforward argument, $\Lambda_W(c_{\varepsilon,M})$ is also uniformly bounded in $H^2(\mathcal{O})$.
Therefore,

$$\|c_{\varepsilon,M}\|_{H^2} = \|\Lambda_U(c_{\varepsilon,M}) + \Lambda_W(c_{\varepsilon,M})\|_{H^2} \leq C \tag{2.43}$$

Finally from (2.31), (2.42) and (2.43), we deduce that $c_{\varepsilon,M}$ is uniformly bounded in $W^{2,p}(\mathcal{O})$ for all finite $p \geq 1$.

The rest of the proof is very similar to the proof of theorem 3 and will be omitted.

■

We can now state and prove the main result of this Section:

Theorem 5. *Assume that, in* (2.25)*, the function G satisfies*

$$G \in \mathcal{C}^0(\mathbb{R} \times \mathbb{R}), \quad 0 \leq G \leq C.$$

Also, assume that $m' \geq 0$, $B > 0$, ρ is not an eigenvalue of the Dirichlet Laplacian in $\mathcal{O}$ and $f \in L^2(\mathcal{O})$. Then there exists at least one solution (c, β) to (2.25)*, with*

$$c \in W^{2,p}(\mathcal{O}) \quad \forall p \in [1, +\infty), \quad \beta \in H^2(\mathcal{O}).$$

For the proof, we will use the following fixed-point theorem for set-valued mappings due to Kakutani:

Theorem 6. *Let X be a Banach space and let $\Lambda : X \mapsto X$ be a set-valued mapping satisfying the following:*

1. *$\Lambda(\xi)$ is a closed convex compact set in X and there exists a fixed compact set $K \subset X$ such that $\Lambda(\xi) \subset K$ for all $\xi \in X$.*

2. *Λ is upper-hemicontinuous, i.e.*

$$\xi_n \to \xi \text{ in } X \quad \Longrightarrow \quad \limsup_{n\to\infty}\left(\sup_{\eta\in\Lambda(\xi_n)} \langle \mu, \eta\rangle\right) \leq \sup_{\eta\in\Lambda(\xi)} \langle \mu, \eta\rangle$$

   for all $\mu \in X'$.

Then Λ possesses at least one fixed-point.

For a proof of this result, see for instance [4].

Proof of theorem 5: We will consider the set-valued mapping Λ that assigns to each $(c^*, \beta^*) \in L^2(\mathcal{O}) \times L^2(\mathcal{O})$ the following set:

$$\Lambda(c^*, \beta^*) = \{(c, \beta) \ : \ c \text{ solves } (2.26) \quad \text{and} \quad \beta \text{ solves } (2.27)\}$$

In view of proposition 5, $\Lambda(c^*, \beta^*)$ is a non-empty set of $L^2(\mathcal{O}) \times L^2(\mathcal{O})$ for all (c^*, β^*). Our goal is to prove that Λ possesses at least one fixed-point, that is, a couple (c, β) such that $\Lambda(c, \beta) \ni (c, \beta)$.

The assumptions of Kakutani's theorem are easy to check in our case. Indeed, it is clear that $\Lambda(c^*, \beta^*)$ is a closed convex set of $L^2(\mathcal{O}) \times L^2(\mathcal{O})$. Since all $(c, \beta) \in \Lambda(c^*, \beta^*)$ are uniformly bounded in $W^{2,p}(\mathcal{O}) \times H^2(\mathcal{O})$ (independently of (c^*, β^*)), assumption 1 holds. On the other hand, if $(c_n^*, \beta_n^*) \to (c^*, \beta^*)$ in $L^2(\mathcal{O}) \times L^2(\mathcal{O})$, it is easy to prove that

$$\limsup_{n\to\infty} \left(\sup_{(c,\beta)\in\Lambda(c_n^*,\beta_n^*)} ((z, y), (c, \beta))_{L^2\times L^2} \right) \leq \sup_{(c,\beta)\in\Lambda(c^*,\beta^*)} ((z, y), (c, \beta))_{L^2\times L^2}$$

for all $(z, y) \in L^2(\mathcal{O}) \times L^2(\mathcal{O})$. Therefore, assumption 2 is also satisfied.
The conclusion is that Λ possesses at least one fixed-point (c, β).

This ends the proof.

■

A particular function G is given by

$$G(c, \beta) = \frac{M_1 c^+ \beta^+}{M_2 + c^+ \beta^+} \qquad \forall (c, \beta) \in \mathbb{R}^2 \tag{2.44}$$

where $M_1, M_2 > 0$. For this G, the assumptions in theorem 5 are satisfied. Hence, we get the existence of a solution to (2.25).

In this case, the problem we have solved is the following:

$$\begin{cases} c \in H_0^1(\mathcal{O}) \cap \mathcal{C}^0(\overline{\mathcal{O}}), \quad \beta \in H_0^1(\mathcal{O}) \\ -\Delta c \geq \rho c - \dfrac{M_1 c^+ \beta^+}{M_2 + c^+ \beta^+} & \text{in } \mathcal{O} \\ -\Delta c = \rho c - \dfrac{M_1 c^+ \beta^+}{M_2 + c^+ \beta^+} & \text{in } \Omega := \{x \in \mathcal{O} \ : \ c(x) > 0\} \\ c \geq 0 & \text{in } \mathcal{O} \\ -\Delta \beta + m' \beta = -Bc + f & \text{in } \mathcal{O} \end{cases} \tag{2.45}$$

Remark 8. If G is defined by (2.44), we can interpret that it contributes to therapy (in the sense that, in (2.25), $G(c, \beta)$ indicates the way β destroys tumor cells). But the effect saturates for large β, that is to say, β becomes irrelevant if it is large enough, since

$$G(c, \beta) = \frac{M_1 c^+ \beta^+}{M_2 + c^+ \beta^+} \to M_1 \quad \text{as} \quad \beta^+ \to +\infty.$$

□

2.3 The evolution model

Now we return to the evolution problem (2.2) described at the beginning of Section 2.2. Let us assume that $c^0 \in H_0^1(\mathcal{O}) \cap L^\infty(\mathcal{O})$, $\beta^0 \in H_0^1(\mathcal{O})$, $c^0, \beta^0 \geq 0$ and $f \in \mathcal{C}^0(\overline{\mathcal{O}} \times [0,T])$. Let us set $Q = \mathcal{O} \times (0,T)$ and $\Sigma = \partial\mathcal{O} \times (0,T)$ and let us introduce the set

$$K = \left\{(v,w) \in H^1(Q)^2 \ : \ v \geq 0, \quad v|_{t=0} = c^0, \quad w|_{t=0} = \beta^0, \quad v|_\Sigma = w|_\Sigma = 0\right\}.$$

First, let us give a more convenient formulation of (2.2):

$$\begin{cases} c \in H_0^1(Q) \cap \mathcal{C}^0(\overline{Q}), \quad \beta \in H^1(Q) \\ Q_+ := \{(x,t) \in Q \ : \ c(x,t) > 0\}, \quad \dfrac{\partial^2 c}{\partial x_i \partial x_j} \in L^2(Q_+) \quad \forall i,j \\ c_t - \Delta c = \rho c - G(c,\beta), \qquad (x,t) \in Q_+ \\ c \geq 0, \qquad (x,t) \in Q \\ \beta_t - \Delta\beta + m'\beta = -\widetilde{G}(c,\beta) + f, \quad (x,t) \in Q \\ c = 0, \ \beta = 0, \qquad (x,t) \in \Sigma \\ \dfrac{\partial c}{\partial n} \geq -kV_n, \qquad x \in \partial\Omega(t), \ t \in (0,T) \\ c(x,0) = c^0(x), \ \beta(x,0) = \beta^0(x), \quad x \in \mathcal{O} \end{cases} \tag{2.46}$$

Given a solution (c,β) to (2.46), for each $t \in [0,T]$ we denote by $\Omega(t)$ the open set

$$\Omega(t) = \{x \in \mathcal{O} \ : \ c(x,t) > 0\}.$$

A weaker formulation of (2.46) is the following:

$$\begin{cases} c \in H_0^1(Q) \cap \mathcal{C}^0(\overline{Q}), \quad \beta \in H^1(Q) \\ Q_+ := \{(x,t) \in Q \ : \ c(x,t) > 0\}, \quad \dfrac{\partial^2 c}{\partial x_i \partial x_j} \in L^2(Q_+) \quad \forall i,j \\ c_t - \Delta c = \rho c - G(c,\beta), \qquad (x,t) \in Q_+ \\ c \geq 0, \qquad (x,t) \in Q \\ \beta_t - \Delta\beta + m'\beta = -\widetilde{G}(c,\beta) + f, \qquad (x,t) \in Q \\ c = 0, \ \beta = 0, \qquad (x,t) \in \Sigma \\ c(x,0) = c^0(x), \ \beta(x,0) = \beta^0(x), \qquad x \in \mathcal{O} \\ \displaystyle\int_{\Omega(t)} (\nabla c \cdot \nabla\psi + (\Delta c)\,\psi)\, dx \geq -k\frac{d}{dt}\int_{\Omega(t)} \psi\, dx \quad \forall\, \psi \in \mathcal{D}(\mathcal{O}), \ \psi \geq 0, \quad \forall t \in (0,T) \end{cases} \tag{2.47}$$

In fact, we can establish the equivalence of (2.46) and (2.47) under some regularity assumptions.

Let us now consider the following (apparently different) problems:

$$\begin{cases} c \in H^1(Q), \quad \beta \in H^1(Q) & \\ (c + kH_0(c))_t - \Delta c \geq \rho c - G(c,\beta), & (x,t) \in Q \\ \big((c + kH_0(c))_t - \Delta c - \rho c + G(c,\beta)\big)c = 0, & (x,t) \in Q \\ c \geq 0, & (x,t) \in Q \\ \beta_t - \Delta\beta + m'\beta = -\widetilde{G}(c,\beta) + f, & (x,t) \in Q \\ c = 0, \ \beta = 0, & (x,t) \in \Sigma \\ c(x,0) = c^0(x), \ \beta(x,0) = \beta^0(x), & x \in \mathcal{O} \end{cases} \tag{2.48}$$

$$\begin{cases} -k \iint_Q H_0(c)\,(v-c)_t \,dx\,dt + k \int_{\mathcal{O}} H_0(c)\,(v-c)\,dx\Big|_{t=T} \\ + \iint_Q \big(c_t\,(v-c) + \nabla c \cdot \nabla(v-c)\big)\,dx\,dt \\ + \iint_Q \big(\beta_t(w-\beta) + \nabla\beta\cdot\nabla(w-\beta) + m'\beta(w-\beta)\big)\,dx\,dt \\ \geq \iint_Q (\rho c - G(c,\beta))\,(v-c)\,dx\,dt + \iint_Q \Big(-\widetilde{G}(c,\beta) + f\Big)\,(w-\beta)\,dx\,dt \\ \forall (v,w) \in K, \ (c,\beta) \in K \end{cases} \tag{2.49}$$

where $H_0 = H_0(s)$ denotes the usual Heaviside function ($H_0(s) = 1$ if $s > 0$; $H_0(s) = 0$ otherwise). Here, $G, \widetilde{G} \in \mathcal{C}^0(\mathbb{R}\times\mathbb{R})$, with $G, \widetilde{G} \geq 0$, $G\big|_{c=0} \equiv 0$; $k, m' > 0$ and $f \in L^2(Q)$.

First, we will establish the equivalence of (2.46), (2.48) and (2.49) under some regularity assumptions on c.

Proposition 6. *The previous problems are* equivalent *in the following sense:*

1) *If (c,β) solves* (2.46)*, then it solves* (2.48)*. Conversely, if (c,β) solves* (2.48)*, $c \in \mathcal{C}^0(\overline{Q})$, $\dfrac{\partial^2 c}{\partial x_i \partial x_j} \in L^2(Q_+)$ $\forall i,j$ and the open sets $\Omega(t)$ are smooth enough, then (c,β) solves* (2.46)*.*

2) *The same assertion holds if we replace* (2.48) *by* (2.49)*.*

3) *Let (c,β) be a solution of* (2.49)*, with $c \in \mathcal{C}^0(\overline{Q})$. Then (c,β) solves* (2.48)*.*

Proof:

1) Let us first assume that (c,β) is a solution of (2.46). We have to prove that

$$(c + kH_0(c))_t - \Delta c \geq \rho c - G(c,\beta) \quad \text{in} \ \ Q.$$

Let us take $\varphi \in \mathcal{D}(Q)$, $\varphi \geq 0$. Then, if we denote by $\langle \cdot\,,\cdot\rangle$ the usual duality pairing for $\mathcal{D}'(Q)$ and $\mathcal{D}(Q)$, we see that

$$\langle (c + kH_0(c))_t - \Delta c - \rho c + G(c,\beta), \varphi\rangle$$

$$= \iint_{Q_+} (c_t\varphi + \nabla c\cdot\nabla\varphi - (\rho c - G(c,\beta))\,\varphi)\;dx\,dt - k\iint_{Q_+} \varphi_t\,dx\,dt$$

$$= \int_0^T\!\!\int_{\Omega(t)} (\nabla c\cdot\nabla\varphi + (\Delta c)\,\varphi)\;dx\,dt - k\int_0^T\!\!\int_{\Omega(t)} \varphi_t\,dx\,dt$$

$$\geq -k\int_0^T \left(\int_{\partial\Omega(t)} \varphi V_n\,d\Gamma + \int_{\Omega(t)} \varphi_t\,dx\right)\,dt$$

$$= -k\int_0^T \frac{d}{dt}\left(\int_{\Omega(t)} \varphi\,dx\right)\,dt = 0$$

This way, we see that $(c + kH_0(c))_t - \Delta c \geq \rho c - G(c,\beta)$ in $\mathcal{D}'(Q)$.

Now, we assume that (c,β) is a solution of (2.48) and $c \in \mathcal{C}^0(\overline{Q})$, $\dfrac{\partial^2 c}{\partial x_i\partial x_j} \in L^2(Q_+)$. Then, by choosing $\psi(x,t) = \psi_0(x)\psi_1(t)$, with $\psi_0 \in \mathcal{D}(\mathcal{O}), \psi_1 \in \mathcal{D}(0,T)$, $\psi_0, \psi_1 \geq 0$, after some computations, we find:

$$0 \leq \langle (c + kH_0(c))_t - \Delta c - \rho c + G(c,\beta), \psi\rangle$$

$$= \iint_{Q_+} (c_t\psi + \nabla c\cdot\nabla\psi - (\rho c - G(c,\beta))\,\psi)\;dx\,dt - k\int_0^T\!\!\int_{\Omega(t)} \psi_t\,dx\,dt$$

$$= \int_0^T\!\!\int_{\Omega(t)} (\nabla c\cdot\nabla\psi + (\Delta c)\,\psi)\;dx\,dt - k\int_0^T \left(\frac{d}{dt}\left(\int_{\Omega(t)} \psi\,dx\right) - \int_{\partial\Omega(t)} \psi V_n\,d\Gamma\right)\,dt$$

$$= \int_0^T \left(\int_{\partial\Omega(t)} \frac{\partial c}{\partial n}\psi\,d\Gamma + k\int_{\partial\Omega(t)} \left(\overrightarrow{V}\cdot\overrightarrow{n}\right)\psi\,d\Gamma\right)\,dt$$

$$= \int_0^T \left(\int_{\partial\Omega(t)} \left(\frac{\partial c}{\partial n} + k\overrightarrow{V}\cdot\overrightarrow{n}\right)\psi_0\,d\Gamma\right)\psi_1\,dt$$

Here, we have used that $\Omega(t)$ is regular enough for each t.

Since ψ_0 and ψ_1 are arbitrary, we get (2.46).

2) If (c,β) is a solution of (2.46), we have $(c,\beta) \in K$. Let us prove that, in that case, (c,β) satisfies (2.49).

Assume that $(v,w) \in K$. Then

$$-\iint_Q H_0(c)(v-c)_t\,dx\,dt + \int_{\mathcal{O}} H_0(c)(v-c)\,dx\Big|_{t=T}$$

$$= -\int_0^T \left(\int_{\Omega(t)} (v-c)_t\ dx\right) dt + \int_{\Omega(T)} (v-c)\,(x,T)\,dx$$

$$= \int_0^T\int_{\partial\Omega(t)} \left(\overrightarrow{V}\cdot\overrightarrow{n}\right) v\,d\Gamma\,dt$$

In the last equality, we have used that

$$\int_{\Omega(t)} (v-c)_t\ dx = \frac{d}{dt}\int_{\Omega(t)} (v-c)\ dx - \int_{\partial\Omega(t)} (v-c)\left(\overrightarrow{V}\cdot\overrightarrow{n}\right)\,d\Gamma$$

for all t.
Consequently, the left hand side of (2.49) is equal to

$$k\int_0^T\int_{\partial\Omega(t)} \left(\overrightarrow{V}\cdot\overrightarrow{n}\right) v\,d\Gamma\,dt + \int_0^T\int_{\partial\Omega(t)} \frac{\partial c}{\partial n} v\,d\Gamma\,dt$$

$$+ \iint_Q \left(\beta_t(w-\beta) + \nabla\beta\cdot\nabla(w-\beta) + m'\beta(w-\beta)\right)\,dx\,dt$$

$$= \int_0^T\int_{\partial\Omega(t)} \left(\frac{\partial c}{\partial n} + k\overrightarrow{V}\cdot\overrightarrow{n}\right) v\,d\Gamma\,dt + \iint_Q \left(\rho c - G(c,\beta)\right)(v-c)\ dx\,dt$$

$$+ \iint_Q \left(-\widetilde{G}(c,\beta) + f\right)(w-\beta)\,dx\,dt$$

and we have (2.49).

On the other hand, let us assume that (c,β) is a solution of (2.49) and $c \in \mathcal{C}^0(\overline{Q})$. From part 3) and the second part of part 1), we deduce that (c,β) is a solution of (2.46).

3) Let us suppose that (c,β) solves (2.49) and $c \in \mathcal{C}^0(\overline{Q})$. If $\varphi \in \mathcal{D}(Q)$, $\varphi \geq 0$, one has:

$$\langle\, (c + kH_0(c))_t - \Delta c - \rho c + G(c,\beta), \varphi\rangle$$

$$= -k\iint_Q H_0(c)\varphi_t\,dx\,dt + \iint_Q \left(c_t\varphi + \nabla c\cdot\nabla\varphi - \left(\rho c - G(c,\beta)\right)\varphi\right)\,dx\,dt \geq 0 \tag{2.50}$$

because of (2.49) with $v = c+\varphi$, $w=\beta$. Arguing as above, it follows that

$$\beta_t - \Delta\beta + m'\beta = -\widetilde{G}(c,\beta) + f \quad \text{in} \quad \mathcal{D}'(Q) \tag{2.51}$$

Also, if we choose $\varphi \in \mathcal{D}(Q_+)$ and $\varepsilon > 0$ small enough, then $v := c + \varepsilon\varphi$ and β are such that $(v,\beta) \in K$. Thus, since φ can be either positive or negative, we get

$$\langle (c + kH_0(c))_t - \Delta c - \rho c + G(c,\beta), \varphi\rangle = 0 \qquad \forall\varphi \in \mathcal{D}(Q_+), \tag{2.52}$$

that is, $c_t - \Delta c = \rho c - G(c,\beta)$ in Q_+.
This completes the proof of part 3).

■

To our knowledge, the existence of a solution to (2.46) is an open question; see remark 10 below. We will now present an existence result for a suitable regularized problem.
We introduce H_δ, with

$$H_\delta(s) = \begin{cases} 0, & s < 0 \\ s/\delta, & 0 \le s \le \delta \\ 1, & s > \delta \end{cases}$$

The regularized problem is then:

$$\begin{cases} -k \iint_Q H_\delta(c)\,(v-c)_t \; dx\,dt + k \int_{\mathcal{O}} H_\delta(c)\,(v-c)\; dx \Big|_{t=T} \\ \quad + \iint_Q \big(c_t\,(v-c) + \nabla c \cdot \nabla(v-c)\big)\, dx\,dt \\ \quad + \iint_Q \big(\beta_t(w-\beta) + \nabla\beta\cdot\nabla(w-\beta) + m'\beta(w-\beta)\big)\; dx\,dt \\ \ge \iint_Q (\rho c - G(c,\beta))\,(v-c)\,dx\,dt + \iint_Q \Big(-\widetilde{G}(c,\beta) + f\Big)\,(w-\beta)\,dx\,dt \\ \forall (v,w) \;\in\; K,\; (c,\beta) \;\in\; K \end{cases} \tag{2.53}$$

This is equivalent to

$$\begin{cases} \iint_Q \big(\,(c + kH_\delta(c))_t\,(v-c) + \nabla c\cdot\nabla(v-c)\big)\,dx\,dt \\ \quad + \iint_Q \big(\beta_t(w-\beta) + \nabla\beta\cdot\nabla(w-\beta) + m'\beta(w-\beta)\big)\; dx\,dt \\ \ge \iint_Q (\rho c - G(c,\beta))\,(v-c)\,dx\,dt + \iint_Q \Big(-\widetilde{G}(c,\beta) + f\Big)\,(w-\beta)\,dx\,dt \\ \forall (v,w) \;\in\; K,\; (c,\beta) \;\in\; K \end{cases} \tag{2.54}$$

Remark 9. Notice that, if (c,β) is a solution to (2.53) and $c \in \mathcal{C}^0(\overline{Q})$, then (c,β) solves the following problem, similar to (2.48):

$$\begin{cases} c \in H^1(Q), \quad \beta \in H^1(Q) \\ (c + kH_\delta(c))_t - \Delta c \geq \rho c - G(c,\beta), & (x,t) \in Q \\ \big((c + kH_\delta(c))_t - \Delta c - \rho c + G(c,\beta)\big)c = 0, & (x,t) \in Q \\ c \geq 0, & (x,t) \in Q \\ \beta_t - \Delta\beta + m'\beta = -\widetilde{G}(c,\beta) + f, & (x,t) \in Q \\ c = 0,\ \beta = 0, & (x,t) \in \Sigma \\ c(x,0) = c^0(x),\ \beta(x,0) = \beta^0(x), & x \in \mathcal{O} \end{cases} \tag{2.55}$$

The proof of this assertion can be obtained by arguing as in the proof of proposition 6.

□

We can now state and prove our main result:

Theorem 7. *Assume that $c^0 \in H^1_0(\mathcal{O}) \cap L^\infty(\mathcal{O})$, $\beta^0 \in H^1_0(\mathcal{O})$ with $c^0, \beta^0 \geq 0$, $f \in \mathcal{C}^0(\overline{Q})$ and G and $\widetilde{G}$ are given by*

$$G(c,\beta) = \frac{M_1 c^+ \beta^+}{M_2 + c^+\beta^+}, \quad \widetilde{G}(c,\beta) = Bc \qquad \forall (c,\beta) \in \mathbb{R}^2,$$

where $M_1, M_2, B > 0$. Then, for each $\delta > 0$, there exists at least one solution (c,β) to (2.53).

Proof: It consists of several steps:

STEP 1 - EXISTENCE OF A SOLUTION TO THE PROBLEM

$$\begin{cases} (c + kH_\delta(c))_t - \Delta c = \rho c - G(c,\beta) - \gamma_{\varepsilon,M}(c), & (x,t) \in Q \\ \beta_t - \Delta\beta + m'\beta = -Bc + f, & (x,t) \in Q \\ c = 0,\ \beta = 0, & (x,t) \in \Sigma \\ c(x,0) = c^0(x),\ \beta(x,0) = \beta^0(x), & x \in \mathcal{O} \end{cases} \tag{2.56}$$

To this respect, the following result holds:

Lemma 4. *For all $\varepsilon > 0$, $M > 0$, there exists a solution to (2.56), with*

$$\|c\|_{L^2(H^2)} + \|c_t\|_{L^2(L^2)} + \|\beta\|_{L^2(H^2)} + \|\beta_t\|_{L^2(L^2)} \leq C_\delta \tag{2.57}$$

Proof: For each $z \in L^2(Q)$, we consider the problem

$$\begin{cases} (c + kH_\delta(c))_t - \Delta c = \rho c - G(c,\beta) - \gamma_{\varepsilon,M}(z), & (x,t) \in Q \\ \beta_t - \Delta\beta + m'\beta = -Bc + f, & (x,t) \in Q \\ c = 0,\ \beta = 0, & (x,t) \in \Sigma \\ c(x,0) = c^0(x),\ \beta(x,0) = \beta^0(x), & x \in \mathcal{O} \end{cases} \tag{2.58}$$

Let us accept that, for all $z \in L^2(Q)$, (2.58) possesses a solution (c, β), with

$$\|c\|_{L^2(H^2)} + \|c_t\|_{L^2(L^2)} + \|\beta\|_{L^2(H^2)} + \|\beta_t\|_{L^2(L^2)} \le C_{\delta,\varepsilon,M}. \tag{2.59}$$

Then, a straightforward fixed-point argument shows that (2.56) also possesses a solution satisfying (2.59). From the maximum principle, arguing as for problem (2.25), it is again possible to prove that $|\gamma_{\varepsilon,M}(c)| \le C$. Consequently, the constant in (2.59) can be assumed to depend only on δ, i.e. (2.57) holds.

In order to prove the existence of solution to (2.58), we consider the auxiliary problem

$$\begin{cases} (c + kH_\delta(c))_t - \Delta c = \rho c + g, & (x,t) \in Q \\ \beta_t - \Delta\beta + m'\beta = -Bc + f, & (x,t) \in Q \\ c = 0,\ \beta = 0, & (x,t) \in \Sigma \\ c(x,0) = c^0(x),\ \beta(x,0) = \beta^0(x), & x \in \mathcal{O} \end{cases} \tag{2.60}$$

where $g \in L^\infty(Q)$. The existence of solution to (2.60) can be easily obtained by a Galerkin-compactness argument with special basis:

$$\begin{cases} ((c_m + kH_\delta(c_m))_t, v_j)_{L^2} + (\nabla c_m, \nabla v_j)_{L^2} = \rho\,(c_m, v_j)_{L^2} + (g, v_j)_{L^2} \\ (\beta_{m,t}, v_j)_{L^2} + (\nabla\beta_m, \nabla v_j)_{L^2} + m'\,(\beta_m, v_j)_{L^2} = -B\,(c_m, v_j)_{L^2} + (f, v_j)_{L^2} \\ \forall j = 1, \dots, m,\ c_m = \displaystyle\sum_{i=1}^m \xi_{im}(t) v_i,\ \beta_m = \sum_{i=1}^m \eta_{im}(t) v_i \\ c_m|_{t=0} = c_m^0 = P_m(c^0), \quad \beta_m|_{t=0} = \beta_m^0 = P_m(\beta^0) \end{cases} \tag{2.61}$$

(here, $P_m : L^2(\mathcal{O}) \mapsto V_m = [v_1, \dots, v_m]$ is the usual orthogonal projector). The existence of solution to (2.61) is standard. The estimates are easy to get:

1. Replacing v_j by c_m and β_m, we see that

$$\frac{1}{2}\frac{d}{dt}\|c_m\|_{L^2}^2 + k\int_{\mathcal{O}} H_\delta'(c_m) c_m c_{m,t}\,dx + \|\nabla c_m\|_{L^2}^2 = \rho\|c_m\|_{L^2}^2 + (g, c_m)_{L^2}$$

$$\frac{1}{2}\frac{d}{dt}\|\beta_m\|_{L^2}^2 + \|\nabla\beta_m\|_{L^2}^2 + m'\|\beta_m\|_{L^2}^2 = -B\,(c_m, \beta_m)_{L^2} + (f, \beta_m)_{L^2}$$

Therefore, we get:

$$\|c_m\|_{L^2}^2 + \int_0^t \|\nabla c_m\|_{L^2}^2\,ds \le C_1 + C\int_0^t \|c_m\|_{L^2}^2\,ds$$

$$\|\beta_m\|_{L^2}^2 + \int_0^t \|\nabla\beta_m\|_{L^2}^2\,ds \le C + C\int_0^t \left(\|c_m\|_{L^2}^2 + \|\beta_m\|_{L^2}^2\right)ds$$

(C_1 depends on $\|g\|_{L^\infty(Q)}$). Consequently,

$$\|c_m\|_{L^\infty(L^2)} + \|c_m\|_{L^2(H_0^1)} \le C_1$$

$$\|\beta_m\|_{L^\infty(L^2)} + \|\beta_m\|_{L^2(H_0^1)} \le C_1$$

2. Replacing v_j by $c_{m,t}$, we also obtain

$$\|c_{m,t}\|_{L^2}^2 + k\int_{\mathcal{O}} H'_\delta(c_m)|c_{m,t}|^2\,dx + \frac{1}{2}\frac{d}{dt}\|\nabla c_m\|_{L^2}^2 = \rho\,(c_m, c_{m,t}) + (g, c_{m,t})_{L^2}$$

This gives

$$\int_0^t \|c_{m,t}\|_{L^2}^2\,ds + \|\nabla c_m\|_{L^2}^2 \le C_1$$

and then

$$\|c_m\|_{L^\infty(H_0^1)} + \|c_{m,t}\|_{L^2(L^2)} \le C_1.$$

Analogously,

$$\|\beta_m\|_{L^\infty(H_0^1)} + \|\beta_{m,t}\|_{L^2(L^2)} \le C_1.$$

These estimates allow to take limits in (2.61) and obtain a solution to (2.60), with

$$\|c\|_{L^\infty(H_0^1)} + \|c_t\|_{L^2(L^2)} + \|\beta\|_{L^\infty(H_0^1)} + \|\beta_t\|_{L^2(L^2)} \le C_1. \tag{2.62}$$

Finally, taking into account that

$$\begin{aligned} &c_t - \Delta c = -kH'_\delta(c)c_t + \rho c + g \\ &\beta_t - \Delta\beta + m'\beta = -Bc + f \end{aligned}$$

we deduce that

$$\|c\|_{L^2(H^2)} + \|c_t\|_{L^2(L^2)} + \|\beta\|_{L^2(H^2)} + \|\beta_t\|_{L^2(L^2)} \le C_{\delta,2}, \tag{2.63}$$

where $C_{\delta,2}$ only depends on δ and $\|g\|_{L^\infty(Q)}$.

■

STEP 2 - ADDITIONAL ESTIMATES ON THE SOLUTIONS TO (2.56) AND CONSEQUENCES.
Recall that, in view of (2.62), the solutions to (2.56) satisfy some estimates independent of δ:

$$\|c\|_{L^\infty(H_0^1)} + \|c_t\|_{L^2(L^2)} + \|\beta\|_{L^\infty(H_0^1)} + \|\beta_t\|_{L^2(L^2)} \le C_{\varepsilon,M}. \tag{2.64}$$

Lemma 5. *One has*

$$|c| \le C. \tag{2.65}$$

Proof: Again, we will use that $|\gamma_{\varepsilon,M}(c)| \le C$ and the maximum principle. We thus have

$$(c + kH_\delta(c))_t - \Delta c = \rho c + g, \quad \text{with } |g| = |G(c,\beta) + \gamma_{\varepsilon,M}(c)| \le C.$$

Take $\widetilde{M}(t) = C_1 e^{C_2 t}$. Then:

$$\int_{\mathcal{O}} (c + kH_\delta(c))_t \left(c - \widetilde{M}\right)_+ dx + \int_{\mathcal{O}} \nabla c \cdot \nabla \left(c - \widetilde{M}\right)_+ dx$$

$$= \rho \int_{\mathcal{O}} c \left(c - \widetilde{M}\right)_+ dx + \int_{\mathcal{O}} g \left(c - \widetilde{M}\right)_+ dx.$$

But:

$$\int_{\mathcal{O}} c_t \left(c-\widetilde{M}\right)_+ dx = \frac{1}{2}\frac{d}{dt}\int_{\mathcal{O}} \left(c-\widetilde{M}\right)_+^2 dx + \int_{\mathcal{O}} \widetilde{M}'(t)\left(c-\widetilde{M}\right)_+ dx$$

$$\int_{\mathcal{O}} H_\delta(c)_t \left(c-\widetilde{M}\right)_+ dx = 0$$

$$\int_{\mathcal{O}} \nabla c\cdot\nabla\left(c-\widetilde{M}\right)_+ dx = \int_{\mathcal{O}} |\nabla\left(c-\widetilde{M}\right)_+|^2 dx$$

$$\int_{\mathcal{O}} c\left(c-\widetilde{M}\right)_+ dx = \int_{\mathcal{O}} \left(c-\widetilde{M}\right)_+^2 dx + \int_{\mathcal{O}} \widetilde{M}(t)\left(c-\widetilde{M}\right) dx$$

Consequently:

$$\frac{1}{2}\frac{d}{dt}\int_{\mathcal{O}} \left(c-\widetilde{M}\right)_+^2 dx + \int_{\mathcal{O}} |\nabla\left(c-\widetilde{M}\right)_+|^2 dx = \rho\int_{\mathcal{O}} \left(c-\widetilde{M}\right)_+^2 dx$$

$$+\int_{\mathcal{O}} \left(-\widetilde{M}'(t)+\rho\widetilde{M}(t)+g\right)\left(c-\widetilde{M}\right)_+ dx$$

If C_2 is large, depending on ρ and $\|g\|_{L^\infty(Q)}$, we have $-\widetilde{M}'(t)+\rho\widetilde{M}(t)+g\leq 0$. Hence

$$\frac{d}{dt}\int_{\mathcal{O}} \left(c-\widetilde{M}\right)_+^2 dx \leq 2\rho\int_{\mathcal{O}} \left(c-\widetilde{M}\right)_+^2 dx. \tag{2.66}$$

Also,

$$\int_{\mathcal{O}} \left(c-\widetilde{M}\right)_+^2 dx\Big|_{t=0} = 0 \tag{2.67}$$

if C_1 is large, depending in $\|c^0\|_{L^\infty(\mathcal{O})}$. From Gronwall's lemma, we deduce that $c\leq\widetilde{M}$. Similarly, using $\left(c+\widetilde{M}\right)_-$ instead of $\left(c-\widetilde{M}\right)_+$, we also deduce that $c\geq-\widetilde{M}$.

■

Now, recalling the way (2.62) and (2.63) were proved, we can improve (2.64) and (2.59):

$$\|c\|_{L^\infty(H_0^1)} + \|c_t\|_{L^2(L^2)} + \|\beta\|_{L^\infty(H_0^1)} + \|\beta_t\|_{L^2(L^2)} \leq C \tag{2.68}$$

$$\|c\|_{L^2(H^2)} + \|\beta\|_{L^2(H^2)} \leq C_\delta \tag{2.69}$$

(note that the estimate of $\|c\|_{L^2(H^2)}$ depends on δ).

From (2.65), we deduce that, for sufficiently large M, $\gamma_{\varepsilon,M}(c)$ can be replaced by $\gamma_\varepsilon(c)$ in (2.56).

We conclude from (2.65), (2.68) and (2.69) that the solutions to (2.56) converge in an appropriate sense (after extracting appropriate subsequences) as $\varepsilon\to 0^+$ and $M\to+\infty$:

$$\begin{cases} c_{\delta,\varepsilon,M} \rightharpoonup c_\delta & \text{in} \quad L^2(H^2) \\ c_{\delta,\varepsilon,M,t} \rightharpoonup c_{\delta,t} & \text{in} \quad L^2(L^2) \end{cases} \tag{2.70}$$

whence

$$\begin{cases} c_{\delta,\varepsilon,M} \rightharpoonup c_\delta & \text{in} \quad \mathcal{C}^0(H_0^1) \\ c_{\delta,\varepsilon,M} \to c_\delta & \text{in} \quad L^2(X_0) \quad \forall X_0 \ : \ H^2 \rightrightarrows X_0 \\ c_{\delta,\varepsilon,M} \to c_\delta & \text{in} \quad \mathcal{C}^0(X) \quad \forall X \ : \ H_0^1 \rightrightarrows X \end{cases}$$

Also, $c_{\delta,\varepsilon,M} \overset{*}{\rightharpoonup} c_\delta$ in $L^\infty(Q)$ and $c_\delta \geq 0$. If $\delta \to 0$, c_δ converges:

$$\begin{cases} c_\delta \overset{*}{\rightharpoonup} c & \text{in} \quad L^\infty(H_0^1) \\ \\ c_{\delta,t} \rightharpoonup c_t & \text{in} \quad L^2(L^2) \end{cases} \tag{2.71}$$

whence

$$c_\delta \to c \quad \text{in} \quad \mathcal{C}^0(X) \qquad \forall X \ : \ H_0^1 \rightrightarrows X.$$

Similar properties can be deduced for β_δ.

STEP 3 - PASSING TO THE LIMIT IN (2.56) AS $\varepsilon \to 0^+$, $M \to +\infty$.

This is now easy: take $(v, w) \in K$ and multiply the equations by $v - c$ and $w - \beta$ respectively and integrate in space and time. We suppress for simplicity the indices δ, ε, M.
We obtain

$$\iint_Q \Big[\big(c + kH_\delta(c)\big)_t (v - c) + \nabla c \cdot \nabla\,(v - c) - (\rho c + G(c, \beta))\,(v - c) \Big]\, dx\, dt$$

$$+ \iint_Q \Big[\beta_t (w - \beta) + \nabla\beta \cdot \nabla(w - \beta) + m'\beta(w - \beta) - (-Bc + f)\,(w - \beta) \Big]\, dx\, dt \tag{2.72}$$

$$= - \iint_Q \gamma_\varepsilon(c)\,(v - c)\ dx\, dt$$

All the terms in the left hand side converge as $\varepsilon \to 0^+$, $M \to +\infty$ (c and β converge strongly in $L^2(H_0^1)$ and c_t and β_t converge weakly in $L^2(L^2)$).
The term in the right hand side possesses a lower limit that is:

$$\lim \Big(- \iint_Q \gamma_\varepsilon(c) v\, dx\, dt + \iint_Q \gamma_\varepsilon(c) c\, dx\, dt \Big)$$
$$\geq - \limsup \iint_Q \gamma_\varepsilon(c) v\, dx\, dt + \liminf \iint_Q \gamma_\varepsilon(c) c\, dx\, dt$$

$$\geq - \limsup \iint_Q \gamma_\varepsilon(c^+) v\, dx\, dt + \liminf \iint_Q \gamma_\varepsilon(c) c\, dx\, dt$$

But

$$\limsup \iint_Q \gamma_\varepsilon(c^+) v\, dx\, dt = 0 \quad \text{by Lebesgue's theorem, in view of (2.65)}$$
$$\liminf \iint_Q \gamma_\varepsilon(c) c\, dx\, dt \geq 0 \quad \text{since } \gamma_\varepsilon(s) s \geq 0 \ \ \forall s$$

This way, we get (2.53) and the proof of theorem 7 is achieved.

■

Remark 10. Whether or not we can take limits in (2.53) as $\delta \to 0^+$ is unknown. Accordingly, as we have already said, the existence of a solution to (2.46) is open.

Coming back to the proof, from (2.72), after taking $\varepsilon \to 0^+$ and $M \to +\infty$, we get:

$$\begin{cases} \displaystyle\iint_Q \Big[\big(c + kH_\delta(c)\big)_t (v-c) + \nabla c \cdot \nabla (v-c) - (\rho c + G(c,\beta))(v-c)\Big]\, dx\, dt \\ \displaystyle + \iint_Q \Big[\beta_t (w-\beta) + \nabla\beta \cdot \nabla(w-\beta) + m'\beta(w-\beta) - (-Bc+f)(w-\beta)\Big]\, dx\, dt \geq 0 \\ \forall (v,w) \in K \end{cases}$$

This can be re-written as follows:

$$\iint_Q \Big(c_t(v-c) + \nabla c \cdot \nabla v - (\rho c(v-c) + G(c,\beta)(v-c))\Big)\, dx\, dt$$

$$+ \iint_Q \Big(\beta_t(w-\beta) + \nabla\beta \cdot \nabla w + m'\beta(w-\beta) - (-Bc+f)(w-\beta)\Big)\, dx\, dt$$

$$\geq \iint_Q \left(|\nabla c|^2 + |\nabla \beta|^2\right)\, dx\, dt + k\iint_Q H_\delta(c)\,(v-c)_t\, dx\, dt - k\int_{\mathcal{O}} H_\delta(c)\,(v-c)\, dx\Big|_{t=T}$$

The integrals in the left hand side converge as $\delta \to 0^+$, since c and β converge strongly in $L^2(L^2)$, c and β converge weakly in $L^2(H_0^1)$, and c_t and β_t converge weakly in $L^2(L^2)$.
The (upper) limit of the right hand side is greater or equal than

$$\begin{aligned} &\liminf_{\delta\to 0}\left(\iint_Q \left(|\nabla c_\delta|^2 + |\nabla\beta_\delta|^2\right)\, dx\, dt\right) \\ &\quad + \limsup_{\delta\to 0}\left(k\iint_Q H_\delta(c_\delta)\,(v-c_\delta)_t\, dx\, dt - k\int_{\mathcal{O}} H_\delta(c_\delta)\,(v-c_\delta)\, dx\Big|_{t=T}\right) \end{aligned} \tag{2.73}$$

In (2.73), taking into account that c and β converge weakly in $L^2(H_0^1)$, we have that

$$\liminf_{\delta\to 0}\left(\iint_Q \left(|\nabla c_\delta|^2 + |\nabla\beta_\delta|^2\right)\, dx\, dt\right) \geq \iint_Q \left(|\nabla c|^2 + |\nabla\beta|^2\right)\, dx\, dt$$

In order to conclude that (c,β) solves (2.49), we would have to prove that

$$\begin{aligned} &\limsup_{\delta\to 0}\left(\iint_Q H_\delta(c_\delta)\,(v-c_\delta)_t\, dx\, dt - \int_{\mathcal{O}} H_\delta(c_\delta)\,(v-c_\delta)\, dx\Big|_{t=T}\right) \\ &\qquad \geq \iint_Q H_0(c)\,(v-c)_t\, dx\, dt - \int_{\mathcal{O}} H_0(c)\,(v-c)\, dx\Big|_{t=T} \end{aligned} \tag{2.74}$$

We know that

$$\iint_Q H_\delta(c_\delta)\,(v-c_\delta)_t\, dx\, dt - \int_{\mathcal{O}} H_\delta(c_\delta)\,(v-c_\delta)\, dx\Big|_{t=T}$$

$$= \iint_Q H_\delta(c_\delta) v_t\, dx\, dt - \int_{\mathcal{O}} H_\delta(c_\delta) v\, dx\Big|_{t=T} + \int_{\mathcal{O}} c^0\, dx + \mathrm{O}(\delta)$$

and

$$\iint_Q H_0(c)\,(v-c)_t\;dx\,dt - \int_{\mathcal{O}} H_0(c)\,(v-c)\;dx\Big|_{t=T}$$

$$= \iint_Q H_0(c) v_t\,dx\,dt - \int_{\mathcal{O}} H_0(c) v\,dx\Big|_{t=T} + \int_{\mathcal{O}} c^0\,dx$$

So, what is needed is the following:

$$\limsup_{\delta\to 0}\left[\iint_Q H_\delta(c_\delta) v_t\,dx\,dt - \int_{\mathcal{O}} H_\delta(c_\delta) v\,dx\Big|_{t=T}\right] \geq \iint_Q H_0(c) v_t\,dx\,dt - \int_{\mathcal{O}} H_0(c) v\,dx\Big|_{t=T}.$$

However, it is not clear how this can be proved.

□

Remark 11. The choices we have made of G and $\widetilde{G}$ in theorem 7 are not obviously the unique that lead to an existence result for (2.53). In this particular case, we are simply assuming that the inhibitors tend to diminish the cell population (although saturation phenomena is not excluded) and the cell population enters the inhibitors balance law as a negative source.

Remark 12. The uniqueness of solution of (2.46) or (2.53) is open.

CHAPTER 3

Optimal control of some models that describe tumor growth

3.1 Introduction

This Chapter is devoted to present some mathematical techniques borrowed from optimal control theory that can help to the medical treatment of tumors in competition with the immune system. Our attention will be focused on the mechanical action of chemicals (control techniques oriented to therapies). One of the difficulties of the study will be that, in these models, the domain of definition is unknown.

We will show the basic ideas on the control of these models in a simple case, the equation that describes the evolution of the *glioblastoma*:

$$\begin{cases} c_t - \nabla \cdot (D(x)\nabla c) = \rho c - G(\beta, c) \\ + \dots \end{cases} \tag{3.1}$$

Here, c is the tumor cell concentration, $D = D(x)$ is (for example) positive and piecewise constant, $\rho > 0$ and $G = G(\beta, c)$ is a perturbation term due to the action of a precise therapy. In the literature, the function G can take different forms. For example,

$$G(\beta, c) = m\beta c \quad \text{and} \quad G(\beta, c) = \frac{m_1\beta}{m_2 + \beta}c,$$

in [43] and [30] respectively; see also [45].

In the simplest case, $\beta = v1_\omega$, with $v = v(x, t)$ being a function that we can choose freely. In more realistic cases, we should impose restrictions to v in several possible senses, such as the following: limitations of the size or the structure, β is obtained indirectly (solving another equation where v appears, as in immunotherapy treatments), β has a definite structure, etc.

Given a function of the states c, β and the control variable v, the general optimal control problem for (3.1) consists of determining controls v (for example in $L^2(\omega \times (0,T))$ and subject to appropriate constraints) such that the associated triplets (v, c, β) minimize a cost functional.

Optimal control theory allows to solve dynamic problems of very varied nature, where the evolution of a system that depends on the time can be controlled partly by the decisions of an agent. For the fundamental results of optimal control theory in the context of systems governed by partial differential equations, see for instance [33, 24]. For optimal control problems concerning biological systems, see [32].

In our context, a typical example of cost function is given by

$$(v, c, \beta) \mapsto \frac{a}{2} \iint |c - c_d|^2 \, dx \, dt + \frac{b}{2} \iint |v|^2 \, dx \, dt,$$

where $a, b > 0$ and the integrals are performed in appropriate domains. Accordingly, the associated optimal control problem is to find a control v (that is, a therapy strategy) such that an averaged quantity, obtained from the deviation of c to a desired function c_d and the norm of v, attains a minimum.

In this Chapter we will consider several possibilities for the choice of J that seem reasonable.

The plan is the following.

In Section 3.2, we present the governing system and the related optimal control problems. For simplicity, we have decided to consider problems with radial symmetry which, among other things, allow to identify the unknown moving domain with a function $R = R(t)$ (the radius of a ball).

In Section 3.3, we consider a first choice of the cost functional and we prove the existence of solution to the corresponding optimal control problem. We also deduce the related optimality system and propose an iterative algorithm, of the conjugate gradient kind, for the computation of the optimal control.

Section 3.4 deals with a second choice of the cost functional. Again, in this case, the existence of optimal solutions is proved and the optimality system is found.

Finally, for completeness, we give an existence result for the governing equations with small data in an Appendix.

3.2 Optimal control problems associated to (Ω, c, β)

Let $\mathcal{O}$ be a bounded and regular domain in $\mathbb{R}^N$ $(N = 2, 3)$. In our model, we will denote by $\Omega(t) \subset \mathcal{O}$ the region occupied by the tumor at time t, and by $\partial\Omega(t)$ its boundary.

Let $\omega \subset \mathcal{O}$ be a (small) domain. Let m, ρ, m', λ and k be positive constants, let $\Omega^0 \subset \mathcal{O}$ be a non-empty open set and let us fix $c^0 \in H^1(\Omega^0) \cap L^\infty(\Omega^0)$ and $\beta^0 \in H^1(\mathcal{O})$ with $c^0, \beta^0 \geq 0$. We will assume that $\omega \subset \Omega^0$. In the sequel, it will be assumed that $\mathcal{O}$ and ω are spherical and the initial data Ω^0, c^0 and β^0 are radially symmetric and sufficiently small. It is then possible to prove that, for each nonnegative radially symmetric control $v \in L^2(\omega \times (0,T))$ with $\|v\|_{L^2(\omega\times(0,T))}$ small enough, there exists at least one (strong) radially symmetric solution $\Omega = \Omega(t)$, c, β to the following problem:

$$\begin{cases} c_t - \Delta c = -m\beta c + \rho c, & x \in \Omega(t),\ t \in (0,T) \\ \beta_t - \Delta\beta = -m'\beta c - \lambda\beta + v1_\omega, & x \in \mathcal{O},\ t \in (0,T) \\ \Omega(0) = \Omega^0, & \\ c(x,0) = c^0(x), & x \in \Omega^0 \\ \beta(x,0) = \beta^0(x), & x \in \mathcal{O} \\ \dfrac{\partial\beta}{\partial n} = 0, & x \in \partial\mathcal{O},\ t \in (0,T) \\ c = 0, & x \in \partial\Omega(t),\ t \in (0,T) \\ \dfrac{\partial c}{\partial n} = -kV_n, & x \in \partial\Omega(t),\ t \in (0,T) \end{cases} \tag{3.2}$$

Here, V_n is the velocity of the free boundary $\partial\Omega(t)$ in the outward normal direction $\overrightarrow{n}$. Of course, c and β are ≥ 0.

This is proved in the Appendix to this Chapter (see theorem 12).

In the sequel, we will usually put $\mathcal{O} = \{x \in \mathbb{R}^N \ : \ |x| < \overline{R}\}$, $\Omega(t) = \{x \in \mathcal{O} \ : \ |x| < R(t)\}$ for all t and $R(0) = R^0$ (R^0 is prescribed). It will be assumed that

$$\|c^0\|_{H_0^1(\Omega^0)} + \|\beta^0\|_{H^1(\mathcal{O})} \leq \frac{\varepsilon}{2}, \tag{3.3}$$

where $\varepsilon = \varepsilon(\overline{R}, R^0, T, m, \rho, m', \lambda, k)$ is the small constant provided by theorem 12.

Accordingly, in (3.2) v is the control and the state is the triplet (R, c, β). Let us introduce

$$Y = \Big\{ (v, R, c, \beta) \ : \ v, c, \beta \text{ are radially symmetric; } v \in L^2(\omega \times (0,T));$$

$$R \in H^1(0,T),\ R(0) = R^0,\ R^0 \leq R \leq \overline{R};$$

$$c \in L^2(0,T; H_0^1(\mathcal{O})) \cap L^\infty(\mathcal{O} \times (0,T)),\ c(\cdot,t) \in H_0^1(\Omega(t)) \text{ a.e.};$$

$$\beta \in L^2(0,T; H^2(\mathcal{O})),\ \beta_t \in L^2(\mathcal{O} \times (0,T)) \Big\}$$

Let $\mathcal{U}_{ad}$ be a non-empty closed convex set of $L^2(\omega \times (0,T))$. It will be assumed that the functions $v \in \mathcal{U}_{ad}$ are ≥ 0 and, also, that $0 \in \mathcal{U}_{ad}$. In the interesting cases, for any small $\varepsilon > 0$ there must exist nontrivial controls $v \in \mathcal{U}_{ad}$ with $\|v\|_{L^2(\omega\times(0,T))} \leq \varepsilon$. In practice, this means that soft therapy strategies are admissible.

Let us set

$$Y_{ad} = \Big\{ (v, R, c, \beta) \in Y \ : \ (R, c, \beta) \text{ solves (3.2) (together with } v);$$

$$c(\cdot,t) \in H^2(\Omega(t)) \cap H_0^1(\Omega(t)) \text{ a.e.; } v \in \mathcal{U}_{ad} \Big\}$$

Here, we assume that the two first equations in (3.2) are satisfied (at least) in the distributional sense. As usual, this makes meaningful the remaining equalities and inequalities in this system. In view of the existence result in the Appendix, the set Y_{ad} is non-empty.

We will consider optimal control problems of the kind

$$\left\{ \begin{array}{l} \text{Find } (v^*, R^*, c^*, \beta^*) \in Y_{ad} \quad \text{such that} \\ \\ J(v^*, R^*, c^*, \beta^*) \leq J(v, R, c, \beta) \quad \forall (v, R, c, \beta) \in Y_{ad}. \end{array} \right. \tag{3.4}$$

We will make two different choices of the functional J. In both cases, we will prove an existence result, we will deduce an optimality system (a set of equations and inequalities that must be satisfied by the optimal controls and states) and we will present iterative algorithms for the computation of the solution.

We will need the following technical results:

Lemma 6. *Let $k < K$ and $v \in H_0^1(\mathbf{B}(0;K))$ and let us denote by $\gamma_k v$ the trace of v on $\partial\mathbf{B}(0;k)$. There exists a positive constant C, independent of v and k, such that*

$$\|\gamma_k v\|^2_{L^2(\partial\mathbf{B}(0;k))} \leq C(K-k)\|\nabla v\|^2_{\mathbf{B}(0;K)}. \tag{3.5}$$

Proof: By definition, when $N = 2$, we have

$$\|\gamma_k v\|^2_{L^2(\partial\mathbf{B}(0;k))} = \int_{\partial\mathbf{B}(0;k)} |v|^2 \, d\Gamma = k \int_0^{2\pi} |v(k\cos\theta, k\sin\theta)|^2 \, d\theta.$$

But

$$v(k\cos\theta, k\sin\theta) = v(K\cos\theta, K\sin\theta) - \int_k^K \left[\frac{d}{d\rho} v(\rho\cos\theta, \rho\sin\theta) \right] d\rho$$

$$= - \int_k^K (\partial_1 v(\rho\cos\theta, \rho\sin\theta)\cos\theta + \partial_2 v(\rho\cos\theta, \rho\sin\theta)\sin\theta) \, d\rho$$

Therefore,

$$\begin{aligned} k &\int_0^{2\pi} |\, v(k\cos\theta, k\sin\theta)\,|^2 \, d\theta \\ &\leq 2(K-k) \int_0^{2\pi}\int_k^K \left(|\partial_1 v(\rho\cos\theta, \rho\sin\theta)|^2 + |\partial_2 v(\rho\cos\theta, \rho\sin\theta)|^2 \right) \rho \, d\rho \, d\theta \\ &= 2(K-k)\|\nabla v\|^2_{\mathbf{B}(0;K)} \end{aligned}$$

For $N = 3$ the argument is very similar:

$$\|v_{|\partial\mathbf{B}(0;k)}\|^2_{L^2(\partial\mathbf{B}(0;k))} = k^2 \int_0^{2\pi}\int_{-\frac{\pi}{2}}^{\frac{\pi}{2}} |v(k\cos\theta\cos\varphi, k\cos\theta\sin\varphi, k\sin\theta)|^2 \cos\theta \, d\theta \, d\varphi,$$

with

$$\begin{aligned} v(k\cos\theta\cos\varphi, &\, k\cos\theta\sin\varphi, k\sin\theta) \\ &= - \int_k^K \Big(\partial_1 v(\rho\cos\theta\cos\varphi, \rho\cos\theta\sin\varphi, \rho\sin\theta)\cos\theta\cos\varphi \\ &\quad + \partial_2 v(\rho\cos\theta\cos\varphi, \rho\cos\theta\sin\varphi, \rho\sin\theta)\cos\theta\sin\varphi \\ &\quad + \partial_3 v(\rho\cos\theta\cos\varphi, \rho\cos\theta\sin\varphi, \rho\sin\theta)\sin\theta \Big) \, d\rho. \end{aligned}$$

We easily deduce that

$$\|\gamma_k v\|^2_{L^2(\partial\mathbf{B}(0;k))} \leq 3k^2(K-k)\int_0^{2\pi}\int_{-\frac{\pi}{2}}^{\frac{\pi}{2}}\int_k^K |\nabla v|^2 d\rho\, d\theta\, d\varphi$$

$$\leq C(K-k)\int_0^{2\pi}\int_{-\frac{\pi}{2}}^{\frac{\pi}{2}}\int_k^K |\nabla v|^2\rho^2\cos\theta\, d\rho\, d\theta\, d\varphi$$

$$= C(K-k)\|\nabla v\|^2_{\mathbf{B}(0;K)}$$

and this yields the proof.

■

Lemma 7. *If* $(v,\Omega,c,\beta)\in Y_{ad}$ *then* $c_t \in L^2(0,T;H^{-1}(\mathcal{O}))$ *and*

$$\begin{cases} \langle c_t, v\rangle + \displaystyle\int_{\Omega(t)} \nabla c\cdot\nabla v\, dx \geq \int_{\Omega(t)} (-m\beta + \rho)\, cv\, dx - k\int_{\partial\Omega(t)} V_n v\, d\Gamma \\ \text{a.e. in } (0,T), \quad \forall v\in H^1_0(\mathcal{O}) \text{ with } v\geq 0 \end{cases}$$

Proof: We have

$$\langle c_t - \Delta c, v\rangle = \int_{\Omega(t)} (-m\beta c + \rho c)\, v\, dx \quad \text{a.e. in } (0,T), \quad \forall v\in\mathcal{D}(\mathcal{O}).$$

It is not difficult to see that this is equivalent to say that

$$\langle c_t, v\rangle + \int_{\Omega(t)} \nabla c\cdot\nabla v\, dx - \int_{\partial\Omega(t)} \frac{\partial c}{\partial n} v\, d\Gamma = \int_{\Omega(t)} (-m\beta c + \rho c)\, v\, dx \tag{3.6}$$

a.e. in $(0,T)$ for any $v\in\mathcal{D}(\mathcal{O})$. By density, it is obvious that (3.6) must also hold for any $v\in H^1_0(\mathcal{O})$.

Consequently, if $v\in H^1_0(\mathcal{O})$ and $v\geq 0$,

$$\langle c_t, v\rangle \geq -\int_{\Omega(t)} \nabla c\cdot\nabla v\, dx + \int_{\Omega(t)} (-m\beta + \rho) cv\, dx - k\int_{\partial\Omega(t)} V_n v\, d\Gamma$$

$$= \langle L(t), v\rangle$$

a.e. in $(0,T)$. Lemma 6 shows that $L(t)\in H^{-1}(\mathcal{O})$ and $L\in L^2(0,T;H^{-1}(\mathcal{O}))$. This ends the proof.

■

3.3 First choice of the cost functional J

Let a, b be nonnegative numbers and let us set

$$J(v,R,c,\beta) = \frac{a}{2}\int_0^T R(t)|\dot{R}(t)|^2 dt + \frac{b}{2}\iint_{\omega\times(0,T)} |v|^2\, dx\, dt \tag{3.7}$$

for all $(v,R,c,\beta)\in Y$.

This functional associates to each (v, R, c, β) a cost involving a measure of the speed of propagation of the tumor during $[0, T]$

$$\int_0^T R(t)|\dot{R}(t)|^2\, dt = \int_0^T \int_{\partial\Omega(t)} |V_n|^2\, d\Gamma\, dt$$

and a measure of the total action corresponding to the chosen therapy

$$\iint_{\omega\times(0,T)} |v|^2\, dx\, dt.$$

Then we have the following:

Theorem 8. *There exists a solution* (v^*, R^*, c^*, β^*) *to* (3.4), (3.7).

Proof: Since $J(v, R, c, \beta) \geq 0$ for each $(v, R, c, \beta) \in Y_{ad}$, one has $\alpha := \inf_{Y_{ad}} J(v, R, c, \beta) \geq 0$. Let us consider a *minimizing sequence* $\{(v^n, R^n, c^n, \beta^n)\}$ in Y_{ad}.

The proof will be divided in two steps. In the first one, we will see that, in some sense,

$$\lim_{n\to\infty} (v^n, R^n, c^n, \beta^n) = (v^*, R^*, c^*, \beta^*) \in Y_{ad};$$

then, we will prove that $J(v^*, \Omega^*, c^*, \beta^*) = \alpha$.

STEP 1: If we take into account the definition of the cost function, we get:

$$\frac{a}{2}\int_0^T R^n(t)|\dot{R}^n(t)|^2 dt + \frac{b}{2}\iint_{\omega\times(0,T)} |v^n|^2\, dx\, dt = J(v^n, R^n, c^n, \beta^n) \leq C \tag{3.8}$$

for some constant $C > 0$. Consequently, there exist $v^* \in L^2(\omega \times (0, T))$ and $R^* \in H^1(0, T)$ such that

$$\begin{array}{l} v^n \rightharpoonup v \ \text{ in } \ L^2(\omega\times(0,T)) \\ R^n \rightharpoonup R^* \ \text{ in } \ H^1(0,T) \end{array} \tag{3.9}$$

From the compactness of the Sobolev embeddings

$$H^1(0, T) \hookrightarrow \mathcal{C}^{0,\alpha}([0, T]) \quad \forall\alpha \in [0, 1/2),$$

it follows that

$$R^n \to R^* \quad \text{strongly in } \ \mathcal{C}^{0,\alpha}([0, T]) \quad \text{for each } \ \alpha \in [0, 1/2). \tag{3.10}$$

Since $(v^n, R^n, c^n, \beta^n) \in Y_{ad}$, setting $\Omega^n(t) = \{x \in \mathcal{O} \,:\, |x| < R^n(t)\}$ for all t, we know that

$$\left\{\begin{array}{ll}
c^n_t - \Delta c^n = -m\beta^n\, c^n + \rho c^n, & x \in \Omega^n(t),\ t \in (0, T) \\
\beta^n_t - \Delta\beta^n = -m'\beta^n c^n - \lambda\beta^n + v^n 1_\omega, & x \in \mathcal{O},\ t \in (0, T) \\
\Omega^n(0) = \Omega^0, & \\
c^n(x, 0) = c^0(x), & x \in \Omega^0 \\
\beta^n(x, 0) = \beta^0(x), & x \in \mathcal{O} \\
\dfrac{\partial\beta^n}{\partial n} = 0, & x \in \partial\mathcal{O},\ t \in (0, T) \\
c^n = 0, & x \in \partial\Omega^n(t),\ t \in (0, T) \\
\dfrac{\partial c^n}{\partial n} = -kV_n, & x \in \partial\Omega^n(t),\ t \in (0, T)
\end{array}\right. \tag{3.11}$$

We are now going to study some properties of c^n and β^n and deduce appropriate estimates which lead to the existence of weakly convergent subsequences. Then, we will check that any of these subsequences converges strongly and the corresponding limit is a solution to problem (3.2).

First of all, we will prove that $0 \le c^n \le M$ for M large enough.

(a) That $c^n \ge 0$ is a consequence of the maximum principle. For completeness, let us however give the explicit argument. Let us multiply the first equation in (3.11) by $c_-^n = -\min(c^n, 0)$ and let us integrate over $\Omega^n(t)$. Taking into account that $c^n = c_+^n - c_-^n$, we see that

$$\int_{\Omega^n(t)} \left[(c_+^n)_t - (c_-^n)_t\right] c_-^n \, dx + \int_{\Omega^n(t)} \left(\nabla c_+^n - \nabla c_-^n\right) \cdot \nabla c_-^n \, dx$$

$$= - \int_{\Omega^n(t)} m\beta^n \left(c_+^n - c_-^n\right) c_-^n \, dx + \int_{\Omega^n(t)} \rho \left(c_+^n - c_-^n\right) c_-^n \, dx$$

whence

$$\frac{1}{2}\frac{d}{dt}\|c_-^n\|^2_{L^2(\mathcal{O})} + \int_{\mathcal{O}} |\nabla c_-^n|^2 \, dx = - \int_{\mathcal{O}} m\beta^n |c_-^n|^2 \, dx + \rho \|c_-^n\|^2_{L^2(\mathcal{O})}.$$

This, together with the fact that $\beta^n \ge 0$ and the initial condition satisfied by c^n, yields the following:

$$\begin{cases} \dfrac{1}{2}\dfrac{d}{dt}\|c_-^n\|^2_{L^2(\mathcal{O})} \le \rho \|c_-^n\|^2_{L^2(\mathcal{O})} \\ \|c_-^n\|^2_{L^2(\mathcal{O})}\big|_{t=0} = 0 \end{cases}$$

From Gronwall lemma, we find that $c_-^n \equiv 0$ and then $c^n \ge 0$.

(b) Let us now fix M_1 and M_2. We multiply the terms in the first equation in (3.11) by $\left(c^n - M_1 e^{M_2 t}\right)_+$ and we integrate over $\Omega^n(t)$. We easily get the following:

$$\frac{1}{2}\frac{d}{dt}\left\|(c^n - M_1 e^{M_2 t})_+\right\|^2_{L^2(\mathcal{O})} + M_1 M_2 e^{M_2 t} \int_{\mathcal{O}} \left(c^n - M_1 e^{M_2 t}\right)_+ dx$$

$$+ \int_{\mathcal{O}} \left|\nabla \left(c^n - M_1 e^{M_2 t}\right)_+\right|^2 dx$$

$$= - \int_{\mathcal{O}} m\beta^n \left(c^n - M_1 e^{M_2 t}\right)_+^2 dx - \int_{\mathcal{O}} m\beta^n M_1 e^{M_2 t} \left(c^n - M_1 e^{M_2 t}\right)_+ dx$$

$$+ \rho \left\|(c^n - M_1 e^{M_2 t})_+\right\|^2_{L^2(\mathcal{O})} + \rho M_1 e^{M_2 t} \int_{\mathcal{O}} \left(c^n - M_1 e^{M_2 t}\right)_+ dx$$

Therefore, if we take $M_1 = \sup_{\Omega^0} c^0$ and $M_2 = \rho$, we see that

$$\begin{cases} \dfrac{1}{2}\dfrac{d}{dt}\left\|(c^n - M_1 e^{\rho t})_+\right\|^2_{L^2(\mathcal{O})} \le \rho \left\|(c^n - M_1 e^{\rho t})_+\right\|^2_{L^2(\mathcal{O})} \\ \left\|(c^n - M_1 e^{\rho t})_+\right\|^2_{L^2(\mathcal{O})}\big|_{t=0} = 0 \end{cases}$$

Again, from Gronwall lemma, we deduce that $\left(c^n - M_1 e^{\rho T}\right)_+ \equiv 0$, whence $c^n \le M_1 e^{\rho T}$.

The previous computations show that

$$0 \le c^n \le \left(\sup_{\Omega^0} c^0 \right) e^{\rho T}. \tag{3.12}$$

On the other hand, since $(v^n, R^n, c^n, \beta^n) \in Y_{ad}$ and v^n is bounded in $L^2(\omega \times (0,T))$, the sequence $\{\beta^n\}$ is bounded as follows:

$$\|\beta^n\|_{L^2(0,T;H^2(\mathcal{O}))} + \|\beta^n_t\|_{L^2(\mathcal{O}\times(0,T))} \le C \tag{3.13}$$

This implies better estimates for c^n. Indeed, let us multiply the first equation in (3.11) by c^n and let us integrate over $\Omega^n(t)$. Then we obtain:

$$\int_{\Omega^n(t)} c^n_t c^n \, dx + \int_{\Omega^n(t)} |\nabla c^n|^2 \, dx = \int_{\Omega^n(t)} \left(-m\beta^n |c^n|^2 + \rho |c^n|^2 \right) dx,$$

that is,

$$\frac{1}{2}\frac{d}{dt}\|c^n\|^2_{L^2(\mathcal{O})} + \|\nabla c^n\|^2_{L^2(\mathcal{O})} = -m \int_{\mathcal{O}} \beta^n |c^n|^2 \, dx + \rho \|c^n\|^2_{L^2(\mathcal{O})} \le \rho \|c^n\|^2_{L^2(\mathcal{O})}.$$

In view of (3.12) and Gronwall lemma, we find:

$$\left\{ \begin{array}{l} \|c^n\|^2_{L^2(0,T;H^1_0(\mathcal{O}))} + \|c^n\|^2_{L^\infty(0,T;L^2(\mathcal{O}))} \le C \\ \\ \|c^n\|_{L^\infty(\mathcal{O}\times(0,T))} \le C \end{array} \right. \tag{3.14}$$

The estimates (3.13) and (3.14) do not suffice to pass to the limit in (3.11). We will also need some uniform estimates of c^n_t, β^n_t.

In order to obtain them, we argue as follows. First, we notice that

$$\langle c^n_t, w \rangle = \langle L^n_1(t), w \rangle + \langle L^n_2(t), w \rangle + \langle L^n_3(t), w \rangle \tag{3.15}$$

for all radial $w \in H^1_0(\mathcal{O})$ a.e. in $(0,T)$, where L^n_1, L^n_2 and L^n_3 are defined by the equalities

$$\langle L^n_1(t), w \rangle = -\int_{\mathcal{O}} \nabla c^n \cdot \nabla w \, dx$$

$$\langle L^n_2(t), w \rangle = -\int_{\mathcal{O}} m\beta^n c^n w \, dx + \int_{\mathcal{O}} \rho c^n w \, dx$$

$$\langle L^n_3(t), w \rangle = \langle \frac{\partial c^n}{\partial n}, w \rangle_{\partial\Omega^n(t)}$$

It is clear that $\|L^n_1\|_{L^2(0,T;H^{-1}(\mathcal{O}))} + \|L^n_2\|_{L^2(0,T;H^{-1}(\mathcal{O}))} \le C$ for some constant $C > 0$. On the other hand, since $\left|\dfrac{\partial c^n}{\partial n}\right| = k|\dot{R}^n(t)|$, we also have

$$|\langle L^n_3(t), w \rangle| = k|\dot{R}^n(t)| \left| \int_{\partial\Omega^n(t)} w \, d\Gamma \right| \le k|\dot{R}^n(t)| \, |\partial\Omega^n(t)|^{1/2} \left(\int_{\partial\Omega^n(t)} |w|^2 d\Gamma \right)^{1/2}$$

$$\le Ck|R^n(t)|^{1/2} \left(\widetilde{R} - R^n(t) \right)^{1/2} |\dot{R}^n(t)| \, \|w\|_{H^1_0(\mathcal{O})}$$

$$\le C \left(|\dot{R}^n(t)|^2 R^n(t) \right)^{1/2} \|w\|_{H^1_0(\mathcal{O})}$$

which is bounded in $L^2(0,T)$ by (3.8). Here, we have used lemma 6 in $\mathcal{O} = \mathbf{B}(0;\widetilde{R})$:

$$\int_{\partial\Omega^n(t)} |w|^2 d\Gamma \leq C_0 \left(\widetilde{R} - R^n(t)\right) \|w\|^2_{H_0^1(\mathcal{O})}.$$

As a consequence, we also have $\|L_3^n\|_{L^2(0,T;H^{-1}(\mathcal{O}))} \leq C$ and, taking into account (3.15), we find that

$$\|c_t^n\|_{L^2(0,T;H^{-1}(\mathcal{O}))} \leq C. \tag{3.16}$$

Next we will use (3.9), (3.10), (3.13), (3.14) and (3.16) to extract a subsequence of $\{(v^n, R^n, c^n, \beta^n)\}$ with appropriate convergence properties.

Notice that $L^2(0,T;H_0^1(\mathcal{O}))$ and $L^2(0,T;H^2(\mathcal{O}))$ are Hilbert spaces and c^n, β^n are uniformly bounded in $L^2(0,T;H_0^1(\mathcal{O}))$ and $L^2(0,T;H^2(\mathcal{O}))$ respectively. Hence, there exist two subsequences satisfying

$$\begin{array}{lll} c^n \to c^* & \text{weakly in} & L^2(0,T;H_0^1(\mathcal{O})) \\ \beta^n \to \beta^* & \text{weakly in} & L^2(0,T;H^2(\mathcal{O})) \end{array} \tag{3.17}$$

From (3.17), one also has $c^n \to c$ in $\mathcal{D}'(0,T;H^{-1}(\mathcal{O}))$, $\beta^n \to \beta$ in $\mathcal{D}'(0,T;(H^2(\mathcal{O}))')$, whence

$$\begin{array}{ll} c_t^n \to c_t^* & \text{in } \mathcal{D}'(0,T;H^{-1}(\mathcal{O})) \\ \beta_t^n \to \beta_t^* & \text{in } \mathcal{D}'(0,T;(H^2(\mathcal{O}))') \end{array} \tag{3.18}$$

Obviously, since c^n is uniformly bounded in $L^\infty(\mathcal{O}\times(0,T))$ (see (3.12)), we can also find a new subsequence satisfying (3.17) and

$$c^n \to c^* \quad \text{weakly-}* \text{ in } \; L^\infty(\mathcal{O}\times(0,T)). \tag{3.19}$$

Let us now consider the sequence $\{c_t^n\}$ in $L^2(0,T;H^{-1}(\mathcal{O}))$. Taking into account (3.16) and (3.18), we see that, at least for a new subsequence, we have (3.17), (3.19),

$$c_t^n \to c_t^* \quad \text{weakly in } \; L^2(0,T;H^{-1}(\mathcal{O})) \tag{3.20}$$

and

$$\beta_t^n \to \beta_t^* \quad \text{weakly in } \; L^2(\mathcal{O}\times(0,T)). \tag{3.21}$$

In order to deduce a strong convergence property for c^n, β^n, we will now use the following well known compactness result:

Proposition 7. *Let X^0, X and X^1 be three Banach spaces such that*

$$X^0 \hookrightarrow X \hookrightarrow X^1,$$

where the first embedding is compact and the second one is continuous. Assume that $1 < p_0, p_1 < +\infty$ and let us introduce the linear space

$$W^{p_0,p_1}(0,T;X^0;X^1) = \{z \in L^{p_0}(0,T;X^0) \;:\; z_t \in L^{p_1}(0,T;X^1)\},$$

which is endowed with the norm

$$\|z\|_{W^{p_0,p_1}(0,T;X^0;X^1)} = \|z\|_{L^{p_0}(0,T;X^0)} + \|z_t\|_{L^{p_1}(0,T;X^1)}.$$

Then $W^{p_0,p_1}(0,T;X^0;X^1)$ is a reflexive Banach space and the embedding

$$W^{p_0,p_1}(0,T;X^0;X^1) \hookrightarrow L^{p_0}(0,T;X)$$

is compact.

This result is essentially due to J.-L. Lions and J. Peetre; see [34]. See also [42] for a clarification of the role of the hypotheses and several extensions and variants.

Thus, in view of (3.17), (3.20) and (3.21), one has

$$\begin{array}{lll} c^n \to c^* & \text{strongly in} & L^2(0,T;F), \\ \beta^n \to \beta^* & \text{strongly in} & L^2(0,T;H), \end{array}$$

where F and H are arbitrary Banach spaces such that the embeddings $H_0^1(\mathcal{O}) \hookrightarrow F$ and $H^2(\mathcal{O}) \hookrightarrow H$ are compact. Obviously, this permits to assume that

$$c^n \to c^* \text{ and } \beta^n \to \beta^* \text{ strongly in } L^2(\mathcal{O} \times (0,T)) \text{ and a.e.} \tag{3.22}$$

We are now ready to pass to the limit in (3.11).

Let us consider two subsequences $\{c^n\}$, $\{\beta^n\}$ satisfying (3.17), (3.19)–(3.22). For any $\varphi \in \mathcal{D}(\mathcal{O} \times (0,T))$, one has

$$(\beta_t^n, \varphi) + (\nabla \beta^n, \nabla \varphi) = -m'(\beta^n c^n, \varphi) - \lambda(\beta^n, \varphi) + (v^n 1_\omega, \varphi). \tag{3.23}$$

Since $\beta_t^n \to \beta_t^*$ weakly in $L^2(\mathcal{O} \times (0,T))$, we have $(\beta_t^n, \varphi) \to (\beta_t^*, \varphi)$ in $L^2(\mathcal{O} \times (0,T))$. It is also clear in view of (3.17) that $(\nabla \beta^n, \nabla \varphi) \to (\nabla \beta^*, \nabla \varphi)$ strongly in $L^2(\mathcal{O} \times (0,T))$. Finally, from (3.19) and (3.22), we have $(\beta^n c^n, \varphi) \to (\beta^* c^*, \varphi)$ and $(\beta^n, \varphi) \to (\beta^*, \varphi)$ strongly in $L^2(\mathcal{O} \times (0,T))$. Taking into account that $v^n \to v^*$ weakly in $L^2(\mathcal{O} \times (0,T))$, we conclude that the functions c^* and β^* satisfy

$$\beta_t^* - \Delta \beta^* = -m' \beta^* c^* - \lambda \beta^* + v^* 1_\omega \quad \text{in } \mathcal{D}'(\mathcal{O} \times (0,T)). \tag{3.24}$$

Now, let us define

$$G^* = \{(x,t) \ : \ |x| < R^*(t), \, t \in (0,T)\}, \quad G^n = \{(x,t) \ : \ |x| < R^n(t), \, t \in (0,T)\}$$

and let us consider the equations

$$c_t^n - \Delta c^n = -m \beta^n c^n + \rho c^n, \quad (x,t) \in G^n. \tag{3.25}$$

We are going to prove that, for any $\Phi \in \mathcal{D}(G^*)$, there exists $n_0 \in \mathbb{N}$ such that $\operatorname{supp} \Phi \subset G^n$ for all $n \geq n_0$. First, by definition, we know that $\delta := \min_{(x,t) \in \operatorname{supp} \Phi} (R(t) - |x|) > 0$. We then have

$$|x| \leq R(t) - \delta \quad \forall (x,t) \in \operatorname{supp} \Phi.$$

On the other hand, taking into account (3.10), there exists n_0 such that $|R^n(t) - R^*(t)| \leq \delta/2$ for all $t \in [0,T]$ and for all $n \geq n_0$. Then $R^*(t) \leq R^n(t) + \delta/2$ and we deduce that $\operatorname{supp} \Phi \subset G^n$, since

$$(x,t) \in \operatorname{supp} \Phi \implies |x| \leq R^*(t) - \delta \leq R^n(t) - \frac{\delta}{2} < R^n(t).$$

Then, as we did in (3.23), we can pass to the limit in the equalities

$$\begin{aligned} \langle c_t^n - \Delta c^n, \Phi \rangle &= -m \iint_{G^n} \beta^n c^n \Phi \, dx \, dt + \iint_{G^n} \rho c^n \Phi \, dx \, dt \\ &= -m \iint_{G^*} \beta^n c^n \Phi \, dx \, dt + \iint_{G^*} \rho c^n \Phi \, dx \, dt \end{aligned}$$

and obtain

$$\langle c_t^* - \Delta c^*, \Phi \rangle = -m \iint_{G^*} \beta^* c^* \Phi \, dx \, dt + \iint_{G^*} \rho c^* \Phi \, dx \, dt$$

(we have used here the convergence properties (3.19) and (3.22)). The conclusion is that

$$c_t^* - \Delta c^* = -m\beta^* c^* + \rho c^* \quad \text{in} \;\; \mathcal{D}'(G^*). \tag{3.26}$$

In order to prove that $(v^*, R^*, c^*, \beta^*) \in \; Y_{ad}$, we still have to check that

$$\begin{cases} c^*(x,0) = c^0(x), & x \in \Omega^0 \\ \beta^*(x,0) = \beta^0(x), & x \in \mathcal{O} \\ \dfrac{\partial \beta^*}{\partial n} = 0, & x \in \partial\mathcal{O},\, t \in (0,T) \\ c^* = 0, & x \in \partial\Omega(t),\, t \in (0,T) \\ \dfrac{\partial c^*}{\partial n} = -kV_n, & x \in \partial\Omega(t),\, t \in (0,T) \end{cases}$$

The following result is well known; its proof can be found for instance in [15]:

Lemma 8. *Let V and H be Hilbert spaces satisfying $V \hookrightarrow H$ with a dense and continuous embedding. Assume that $1 < p < +\infty$, $f \in L^p(0,T;V)$ and $f_t \in L^{p'}(0,T;V')$. Then $f \in \mathcal{C}^0([0,T];H)$ and we have the estimate*

$$\|f\|_{\mathcal{C}^0([0,T];H)} \leq C \left(\|f\|_{L^p(0,T;V)} + \|f_t\|_{L^{p'}(0,T;V')} \right),$$

where C only depends on p.

Of course,

$$c^* \in L^2(0,T;H_0^1(\mathcal{O})), \beta^* \in L^2(0,T;H^2(\mathcal{O})), c_t^* \in L^2(0,T;H^{-1}(\mathcal{O})) \text{ and } \beta_t^* \in L^2(0,T;L^2(\mathcal{O}))$$

whence, in particular, $c^*, \beta^* \in \mathcal{C}^0([0,T];L^2(\mathcal{O}))$. Notice that

$$c^n(\cdot\,,0) \rightharpoonup c^*(\cdot\,,0) \text{ and } \beta^n(\cdot\,,0) \rightharpoonup \beta^*(\cdot\,,0) \text{ weakly in } L^2(\mathcal{O}) \tag{3.27}$$

Indeed, from (3.17), (3.20), (3.21) and lemma 8, we know that $c^n \to c^*$ and $\beta^n \to \beta^*$ weakly in the space $\mathcal{C}^0([0,T];L^2(\mathcal{O}))$. Since the linear mapping $w \mapsto w(\cdot\,,0)$ is continuous from $\mathcal{C}^0([0,T];L^2(\mathcal{O}))$ into $L^2(\mathcal{O})$, we have (3.27). From (3.27) and the facts that $c^n(\cdot\,,0) = c^0$ and $\beta^n(\cdot\,,0) = \beta^0$, the following holds:

$$c^*_{|t=0} = c^0, \quad \beta^*_{|t=0} = \beta^0. \tag{3.28}$$

This shows that the initial conditions are satisfied by c^*, β^*. Also, from the boundary conditions

$$\begin{aligned} &\frac{\partial \beta^n}{\partial n} = 0, && x \in \partial\mathcal{O},\, t \in (0,T) \\ &c^n = 0, && x \in \partial\Omega^n(t),\, t \in (0,T) \\ &\frac{\partial c^n}{\partial n} = -kV_n, && x \in \partial\Omega^n(t),\, t \in (0,T) \end{aligned}$$

we clearly get

$$\frac{\partial \beta^*}{\partial n} = 0, \qquad x \in \partial\mathcal{O},\ t \in (0,T)$$

$$c^* = 0, \qquad x \in \partial\Omega(t),\ t \in (0,T)$$

$$\frac{\partial c^*}{\partial n} = -kV_n, \quad x \in \partial\Omega(t),\ t \in (0,T)$$

Since $\mathcal{U}_{ad}$ is a closed convex set, it is sequentially weakly closed and it follows that $v^* \in \mathcal{U}_{ad}$. Consequently, we have proved that $(v^*, R^*, c^*, \beta^*) \in Y_{ad}$ and

$$\lim_{n\to\infty} (v^n, R^n, c^n, \beta^n) = (v^*, R^*, c^*, \beta^*)$$

in the sense of (3.9), (3.10), (3.17), (3.19), (3.20), (3.21) and (3.22).
STEP 2: Assume that J is sequentially lower semi-continuous for this convergence. Then, we will have

$$\alpha = \lim_{n\to\infty} J(v^n, R^n, c^n, \beta^n) = \liminf_{n\to\infty} J(v^n, R^n, c^n, \beta^n) \geq J(v^*, R^*, c^*, \beta^*)$$

and the proof will be achieved. Consequently, all what we need to prove is this property of J. But this is very easy. Indeed, it follows from (3.9), (3.10) and the fact that $R^0 \leq R^n \leq \overline{R}$ for all n that

$$\begin{cases} \liminf\limits_{n\to\infty} \displaystyle\iint_{\omega\times(0,T)} |v^n|^2 dx\,dt \geq \iint_{\omega\times(0,T)} |v^*|^2 dx\,dt \\ \liminf\limits_{n\to\infty} \displaystyle\int_0^T |\dot{R}^n(t)|^2 R^n(t)\,dt \geq \int_0^T |\dot{R}^*(t)|^2 R^*(t)\,dt \end{cases}$$

This ends the proof.

■

3.3.1 Optimality conditions

Once we have shown that (3.4) possesses at least one solution, our second goal in this Section will be to characterize the solutions in terms of appropriate optimality conditions, that is to say, to deduce a system of equations that the optimal control and the associated state and adjoint state must satisfy.

We will argue formally and with the main goal of finding the optimality system for (3.4). Thus, let us assume that, for each $v \in \mathcal{U}_{ad}$, there exists exactly one state, that is, exactly one triplet (R, c, β) such that $(v, R, c, \beta) \in Y_{ad}$. Assume that $(v, R, c, \beta) \in Y_{ad}$ is a solution of the control problem (3.4), with J defined by (3.7). Let us denote by $j : \mathcal{U}_{ad} \subset L^2(\omega \times (0,T)) \mapsto \mathbb{R}$ the function given by $j(v) = J(v, R, c, \beta)$, where (R, c, β) is the state associated to v.

For later use, we observe that the derivative of j at v in the direction w can be written in the form

$$\langle j'(v), w\rangle = \frac{a}{2}\int_0^T \left(\frac{d}{dv}(R\dot{R}^2)\cdot w\right)(t)\,dt + b\iint_{\omega\times(0,T)} v\cdot w\,dx\,dt,$$

where the first integrand is the derivative of $R\dot{R}^2$ with respect to v in the direction w. We will use the notation

$$\widetilde{R} = \frac{dR}{dv}\cdot w, \quad \widetilde{c} = \frac{dc}{dv}\cdot w, \quad \widetilde{\beta} = \frac{d\beta}{dv}\cdot w.$$

Thus, $\widetilde{R}$, $\widetilde{c}$ and $\widetilde{\beta}$ respectively denote the derivatives of R, c and β with respect to v in the direction w and we have:

$$\langle j'(v), w\rangle = \frac{a}{2}\int_0^T \left(\dot{R}^2\widetilde{R} + 2R\dot{R}\dot{\widetilde{R}}\right)(t)\,dt + b\iint_{\omega\times(0,T)} vw\,dx\,dt$$

$$= a\left(R\dot{R}\widetilde{R}\right)(T) - \frac{a}{2}\int_0^T \left(\dot{R}^2 + 2R\ddot{R}\right)(t)\widetilde{R}(t)\,dt \tag{3.29}$$

$$+ b\iint_{\omega\times(0,T)} vw\,dx\,dt.$$

Let (R', c', β') solve the problem (3.2) associated to $v + sw$. We introduce

$$\delta c = \frac{1}{s}(c' - c), \quad \delta\beta = \frac{1}{s}(\beta' - \beta), \quad \delta R = \frac{1}{s}(R' - R).$$

From (3.2) written for v and $v + sw$, we can deduce the equations satisfied by δc, $\delta\beta$ and δR. After taking limits as $s \to 0$, we obtain the following similar equations for $\widetilde{c}$ and $\widetilde{\beta}$:

$$\begin{aligned} \widetilde{c}_t - \Delta\widetilde{c} &= \rho\widetilde{c} - m\,\widetilde{c}\beta - m\,c\,\widetilde{\beta}1_{\{\beta>0\}}, && x \in \Omega(t),\ t \in (0,T) \\ \widetilde{\beta}_t - \Delta\widetilde{\beta} &= -m'\widetilde{\beta}c - m'\beta\,\widetilde{c} - \lambda\widetilde{\beta} + w1_\omega, && x \in \mathcal{O},\ t \in (0,T) \end{aligned} \tag{3.30}$$

The initial conditions for $\widetilde{c}$, $\widetilde{\beta}$ and $\widetilde{R}$ will be obviously

$$\begin{cases} \widetilde{c}(x,0) = 0, & x \in \Omega(0) \\ \widetilde{\beta}(x,0) = 0, & x \in \mathcal{O} \\ \widetilde{R}(0) = 0 \end{cases} \tag{3.31}$$

and we will also have

$$\frac{\partial\widetilde{\beta}}{\partial n} = 0, \quad x \in \partial\mathcal{O},\ t \in (0,T). \tag{3.32}$$

Let us see which boundary conditions must be satisfied by $\widetilde{c}$ for $x \in \partial\Omega(t)$, $t \in (0,T)$. Taking into account that

$$c'(R(t),t) = c'(R'(t),t) - \frac{\partial c'}{\partial n}(R(t),t)(R'(t) - R(t)) + O(s^2) \tag{3.33}$$

and $c(R(t),t) = c'(R'(t),t) = 0$, we get:

$$0 = \frac{c'(R'(t),t) - c(R(t),t)}{s} = \frac{c'(R'(t),t) - c'(R(t),t)}{s} + \frac{c'(R(t),t) - c(R(t),t)}{s}$$

$$= \frac{\partial c'}{\partial n}(R(t),t)(\delta R)(t) + (\delta c)(R(t),t) + O(s)$$

In the limit $s \to 0^+$, this yields:

$$0 = \frac{\partial c}{\partial n}(R(t),t)\widetilde{R}(t) + \widetilde{c}(R(t),t).$$

Equivalently, we have:

$$\widetilde{c}|_{\partial\Omega(t)} = k\dot{R}(t)\widetilde{R}(t), \quad t \in (0,T). \tag{3.34}$$

On the other hand, from the properties of the normal derivatives of c and c' on the appropriate boundaries, we see that

$$\frac{1}{s}\left[\frac{\partial c'}{\partial n}(R'(t),t) - \frac{\partial c'}{\partial n}(R(t),t)\right] + \frac{1}{s}\left[\frac{\partial c'}{\partial n}(R(t),t) - \frac{\partial c}{\partial n}(R(t),t)\right] = -k(\dot{\delta R}).$$

This leads easily to the equality

$$\left.\frac{\partial^2 c}{\partial n^2}\right|_{\partial\Omega(t)} \widetilde{R}(t) + \left.\frac{\partial \widetilde{c}}{\partial n}\right|_{\partial\Omega(t)} = -k\dot{\widetilde{R}}(t),$$

whence we obtain a condition on the normal derivative of $\widetilde{c}$:

$$\left.\frac{\partial \widetilde{c}}{\partial n}\right|_{\partial\Omega(t)} = -k\dot{\widetilde{R}}(t) - \left.\frac{\partial^2 c}{\partial n^2}\right|_{\partial\Omega(t)} \widetilde{R}(t), \quad t \in (0,T). \tag{3.35}$$

Here, we have taken into account the equation satisfied by c and the fact that $c = 0$ on the boundary $\partial\Omega(t)$.

In the next result, we present the optimality system for the optimal control problem (3.4), (3.7):

Theorem 9. *Let (v, R, c, β) be an optimal solution of the control problem (3.4), where J is given by (3.7). Assume that then, there exists (S, ξ, η) solving the so called adjoint problem*

$$\begin{cases}
-\xi_t - \Delta\xi = \rho\xi - m\beta\xi - m'\beta\eta, & x \in \Omega(t),\ t \in (0,T) \\
-\eta_t - \Delta\eta = -\lambda\eta - m'c\eta - mc\xi 1_{\{\beta>0\}}, & x \in \mathcal{O},\ t \in (0,T) \\
S(T) = \dfrac{1}{2\pi k}\dot{R}(T) & \\
\xi(x,T) = 0, & x \in \Omega(T) \\
\eta(x,T) = 0, & x \in \mathcal{O} \\
\dfrac{\partial\eta}{\partial n} = 0, & x \in \partial\mathcal{O},\ t \in (0,T) \\
\xi = S(t), & x \in \partial\Omega(t),\ t \in (0,T) \\
-k\dot{R}(t)\dfrac{\partial\xi}{\partial n} = L(t)S(t) + \dfrac{1}{4\pi R(t)}\dot{R}^2(t) + \dfrac{1}{2\pi}\ddot{R}(t), & x \in \partial\Omega(t),\ t \in (0,T)
\end{cases} \tag{3.36}$$

where we have set

$$L(t)S := -k\dot{S} + \left(\frac{\partial^2 c}{\partial n^2} - k\frac{\dot{R}(t)}{R(t)}\right)S, \tag{3.37}$$

such that

$$\iint_{\omega\times(0,T)} (a\eta + bv)\,(w - v)\,dx\,dt \geq 0 \qquad \forall w \in \mathcal{U}_{ad}, \quad v \in \mathcal{U}_{ad}. \tag{3.38}$$

Proof: First, notice that under the previous hypotheses the formal computations we have performed are in fact justified and one has (3.29), where w is arbitrary in $L^2(\omega\times(0,T))$ and $\widetilde{R}$ satisfies, together with $\widetilde{c}$ and $\widetilde{\beta}$, (3.30), (3.31), (3.32), (3.34) and (3.35).

Let (S,ξ,η) be the solution of the adjoint problem (3.36)–(3.37). Then, by multiplying the first equation of (3.30) by ξ, the second one by η, the equation (3.35) by S, and integrating each resulting identity respectively in $\{(x,t)\ :\ x\in\Omega(t),\, t\in(0,T)\}$, $\mathcal{O}\times(0,T)$ and $\{(x,t)\ :\ x\in\ \partial\Omega(t),\, t\in\ (0,T)\}$, we find after addition the following:

$$0=\int_0^T\int_{\Omega(t)}\left(\widetilde{c}_t-\Delta\widetilde{c}-\rho\widetilde{c}+m\,\widetilde{c}\beta+m\,c\,\widetilde{\beta}1_{\{\beta>0\}}\right)\xi\,dx\,dt$$

$$+\iint_{\mathcal{O}\times(0,T)}\left(\widetilde{\beta}_t-\Delta\widetilde{\beta}+m'\widetilde{\beta}c+m'\beta\,\widetilde{c}+\lambda\widetilde{\beta}-w1_\omega\right)\eta\,dx\,dt$$

$$=A_1+A_2.$$

Performing the usual integration by parts, we see that

$$A_1=\int_0^T\int_{\Omega(t)}\widetilde{c}\,(-\xi_t-\Delta\xi-\rho\xi+m\xi\beta)\ dx\,dt+\int_{\Omega(t)}\widetilde{c}(x,t)\xi(x,t)\,dx\Big|_{t=0}^{t=T}$$

$$+\int_0^T\int_{\partial\Omega(t)}\left(\widetilde{c}\frac{\partial\xi}{\partial n}-\frac{\partial\widetilde{c}}{\partial n}\xi\right)d\Gamma\,dt+\int_0^T\int_{\Omega(t)}mc\widetilde{\beta}1_{\{\beta>0\}}\xi\,dx\,dt$$

On the other hand,

$$A_2=\iint_{\mathcal{O}\times(0,T)}\widetilde{\beta}\,(-\eta_t-\Delta\eta+\lambda\eta+m'\eta c)\ dx\,dt+\int_{\mathcal{O}}\beta^*(x,t)\eta(x,t)\,dx\Big|_{t=0}^{t=T}$$

$$-\iint_{\omega\times(0,T)}w\eta\,dx\,dt+\iint_{\partial\mathcal{O}\times(0,T)}\left(\widetilde{\beta}\frac{\partial\eta}{\partial n}-\frac{\partial\widetilde{\beta}}{\partial n}\eta\right)d\Gamma\,dt+\iint_{\mathcal{O}\times(0,T)}m'\widetilde{\beta}c\eta\,dx\,dt$$

Consequently,

$$0=A_1+A_2=\int_0^T\int_{\partial\Omega(t)}\left(\widetilde{c}\frac{\partial\xi}{\partial n}-\frac{\partial\widetilde{c}}{\partial n}\xi\right)d\Gamma\,dt-\iint_{\omega\times(0,T)}w\eta\,dx\,dt.$$

In view of the boundary, initial and final conditions satisfied by $\widetilde{c}$, ξ, $\widetilde{R}$ and S, we see after some computations that

$$\int_0^T\int_{\partial\Omega(t)}\left(\widetilde{c}\frac{\partial\xi}{\partial n}-\frac{\partial\widetilde{c}}{\partial n}\xi\right)d\Gamma\,dt=2\pi\int_0^T R(t)\left(k\dot{R}(t)\widetilde{R}(t)\frac{\partial\xi}{\partial n}+k\dot{\widetilde{R}}(t)S(t)+\frac{\partial^2c}{\partial n^2}\widetilde{R}(t)S(t)\right)dt$$

$$=R(T)\dot{R}(T)\widetilde{R}(T)-\frac{1}{2}\int_0^T\left(\dot{R}(t)^2+2R(t)\ddot{R}(t)\right)dt$$

Consequently, in view of (3.29), we deduce that

$$\langle j'(v),w\rangle=\iint_{\omega\times(0,T)}(a\eta+bv)\,w\,dx\,dt \tag{3.39}$$

for all $w \in L^2(\omega \times (0,T))$. Since the optimality condition is given by

$$\langle j'(v), w - v\rangle \geq 0 \quad \forall w \in \mathcal{U}_{ad}, \quad v \in \mathcal{U}_{ad},$$

we have (3.38), which is in fact equivalent to

$$v = P_{\mathcal{U}_{ad}}\left(-\frac{a}{b}\eta\Big|_{\omega\times(0,T)}\right),$$

where $P_{\mathcal{U}_{ad}}$ is the usual orthogonal projector.

■

3.3.2 Computation of the optimal control

We will now present some iterative algorithms, of the gradient kind, that can be used to compute the optimal control.

1. v^0 is given; then, for $n = 0, 1, \ldots$ do steps 2 to 5 until the following convergence test is satisfied

$$\|v^{n+1} - v^n\|_{L^2(\omega\times(0,T))} < \varepsilon \|v^{n+1}\|_{L^2(\omega\times(0,T))}$$

   for ε small enough.

2. Solve (3.2) with $v = v^n$, to obtain (R^n, c^n, β^n);

3. Solve (3.36)–(3.37) with $(R, c, \beta) = (R^n, c^n, \beta^n)$, to obtain (S^n, ξ^n, η^n);

4. Define $g^n = a\eta^n|_{\omega\times(0,T)} + bv^n$.

5. We indicate three different ways to obtain v^{n+1}:

   - Gradient with projection and fixed step: $v^{n+1} = P_{U_{ad}}(v^n - \rho g^n)$, where $\rho > 0$ is given.
   - Gradient with projection and optimal step: Find ρ^n such that

$$j(P_{U_{ad}}(v^n - \rho^n g^n)) \leq j(P_{U_{ad}}(v^n - \rho g^n)) \quad \forall \rho \geq 0$$

     and compute $v^{n+1} = P_{U_{ad}}(v^n - \rho^n g^n)$.
   - Conjugate gradient with projection and fixed step: For $n = 0$, take $d^n = g^n$; for $n \geq 1$, take $d^n = g^n + \gamma^n d^{n-1}$, with

$$\gamma^n = \frac{\|g^n\|^2_{L^2(\omega\times(0,T))}}{\|g^{n-1}\|^2_{L^2(\omega\times(0,T))}} \quad \text{(Fletcher-Reeves)}$$

     or

$$\gamma^n = \frac{(g^n - g^{n-1}, g^n)_{L^2(\omega\times(0,T))}}{\|g^{n-1}\|^2_{L^2(\omega\times(0,T))}} \quad \text{(Polak-Riviere)}$$

     and, then, take $v^{n+1} = P_{U_{ad}}(v^n - \rho d^n)$. Of course, we can also optimize in ρ here; this would lead to the conjugate gradient algorithm with projection and optimal step.

3.4 Second choice of the cost function J

In this Section, we are going to consider the optimal control problem (3.4) with a different functional. More precisely, we will take

$$J(v,R,c,\beta)=\frac{1}{2}\int_{\Omega(T)}|c(x,T)-c_d(x)|^2\,dx$$
$$+\frac{a}{2}\int_0^T|\dot{R}(t)|^2R(t)\,dt+\frac{b}{2}\iint_{\omega\times(0,T)}|v|^2\,dx\,dt \tag{3.40}$$

where $c_d\in L^2(\mathcal{O})$ is given and radially symmetric and $a,b>0$.

Theorem 10. *There exists a solution (v^*,R^*,c^*,β^*) to the optimal control problem* (3.4), (3.40).

Proof: As in theorem 8, we start from a sequence $\{(v^n,R^n,c^n,\beta^n)\}$, with

$$\lim_{n\to\infty}J(v^n,R^n,c^n,\beta^n)=\alpha:=\inf_{Y_{ad}}J(v,R,c,\beta).$$

We now apply a similar argument to prove that J is a sequentially weakly lower semi-continuous functional. First of all, notice that

$$\int_{\Omega^n(T)}|c^n(x,T)-c_d(x)|^2\,dx=\int_{\mathcal{O}}|c^n(x,T)-c_d(x)|^2\,dx-\int_{\mathcal{O}\setminus\Omega^n(T)}|c_d(x)|^2\,dx. \tag{3.41}$$

According to (3.17), (3.20) and lemma 8, we can assume that $c^n\to c$ weakly in $\mathcal{C}^0([0,T];L^2(\mathcal{O}))$. Since the linear mapping $w\mapsto w(T)$ is continuous from $\mathcal{C}^0([0,T];L^2(\mathcal{O}))$ into $L^2(\mathcal{O})$, it follows that $c^n(T)\to c(T)$ weakly in $L^2(\mathcal{O})$. We thus get

$$\liminf_{n\to\infty}\int_{\mathcal{O}}|c^n(x,T)-c_d(x)|^2dx\geq\int_{\mathcal{O}}|c(x,T)-c_d(x)|^2dx. \tag{3.42}$$

We next pass to the limit in the second term in the right hand side of (3.41). Let us assume, for instance, that $N=2$; then

$$\begin{aligned}\int_{\mathcal{O}\setminus\Omega^n(T)}|c_d(x)|^2dx&=\int_0^{2\pi}\int_{R^n(t)}^{\widetilde{R}}|c_d(\rho\cos\theta,\rho\sin\theta)|^2\rho\,d\rho\,d\theta\\&=\int_0^{2\pi}\int_0^{\widetilde{R}}|c_d(\rho\cos\theta,\rho\sin\theta)|^2 1_{(R^n(T),\widetilde{R})}(\rho)\,\rho\,d\rho\,d\theta\end{aligned}$$

We can assume that, as in the proof of theorem 8, $R^n\to R$ strongly in $\mathcal{C}^{0,\alpha}([0,T])$ for each $\alpha\in[0,1/2)$. This implies

$$1_{(R^n(T),\widetilde{R})}(\rho)\to 1_{(R(T),\widetilde{R})}(\rho)$$

unless $\rho=R(T)$. The set

$$\{(\rho,\theta)\ :\ \rho=R(T),\ 0\leq\theta<2\pi\}$$

is of measure zero. Consequently, if we set

$$f_n(\rho,\theta)=1_{(R^n(T),\widetilde{R})}(\rho)|c_d(\rho\cos\theta,\rho\sin\theta)|^2\rho$$

$$f(\rho,\theta)=1_{(R(T),\widetilde{R})}(\rho)|c_d(\rho\cos\theta,\rho\sin\theta)|^2\rho$$

we get

- $f_n \to f$ a.e. in $A = \{(\rho,\theta) \ : \ 0 \le \rho < \widetilde{R}, \ 0 \le \theta < 2\pi\}$ and
- $|f_n| \le C|c_d|^2$ for each n.

Since $|c_d|^2 \in L^1(A)$, from *Lebesgue dominated convergence theorem*, we deduce that f is integrable and

$$\lim_{n\to\infty} \int_{\mathcal{O}\setminus\Omega^n(T)} |c_d(x)|^2 dx = \int_{\mathcal{O}\setminus\Omega(T)} |c_d(x)|^2 dx. \tag{3.43}$$

The same conclusion can be drawn for $N = 3$.

From (3.9) and (3.41)–(3.43), we deduce that

$$\liminf_{n\to\infty} J(v^n, R^n, c^n, \beta^n) \ge \frac{1}{2}\int_{\Omega(T)} |c(x,T) - c_d(x)|^2\, dx + \frac{a}{2}\int_0^T |\dot{R}(t)|^2 R(t)\, dt + \frac{b}{2}\iint_{\omega\times(0,T)} |v|^2 dx\, dt$$

$$= J(v, R, c, \beta)$$

and the theorem follows.

■

3.4.1 Optimality conditions

Let us now deduce the optimality system corresponding to the choice (3.40) of J in (3.4).

Assume that $(v, R, c, \beta) \in Y_{ad}$ is an optimal solution. First, we notice that

$$J(v, R, c, \beta) = \frac{1}{2}\int_{\Omega(T)} |c(x,T) - c_d(x)|^2\, dx + \frac{a}{2}\int_0^T |\dot{R}(t)|^2 R(t)\, dt + \frac{b}{2}\iint_{\omega\times(0,T)} |v|^2\, dx\, dt$$

$$= \frac{1}{2}\int_0^{R(T)} \left(\int_{\partial B(0;\rho)} |c(x,T) - c_d(x)|^2 d\Gamma(x) \right) d\rho + \frac{a}{2}\int_0^T |\dot{R}(t)|^2 R(t)\, dt + \frac{b}{2}\iint_{\omega\times(0,T)} |v|^2\, dx\, dt.$$

Theorem 11. *Let the assumptions of theorem 10 be satisfied. Let* (v, R, c, β) *be a optimal solution of the control problem* (3.4)*, where* J *is given by* (3.40)*. Then, there exists* (S, ξ, η) *solving the so called adjoint problem*

$$\begin{cases} -\xi_t - \Delta\xi = \rho\xi - m\beta\xi - m'\beta\eta, & x \in \Omega(t), \ t \in (0,T) \\ -\eta_t - \Delta\eta = -\lambda\eta - m'c\eta - mc\xi 1_{\{\beta>0\}}, & x \in \mathcal{O}, \ t \in (0,T) \\ S(T) = \dfrac{1}{2\pi k}\dot{R}(T) + \dfrac{1}{4\pi k R(T) a}\displaystyle\int_{\Omega(T)} |c(x,T) - c_d(x)|^2\, d\Gamma(x) & \\ \xi(x,T) = 0, & x \in \Omega(T) \\ \eta(x,T) = 0, & x \in \mathcal{O} \\ \dfrac{\partial\eta}{\partial n} = 0, & x \in \partial\mathcal{O}, \ t \in (0,T) \\ \xi = S(t), & x \in \partial\Omega(t), \ t \in (0,T) \\ -k\dot{R}(t)\dfrac{\partial\xi}{\partial n} = L(t)S(t) + \dfrac{1}{4\pi R(t)}\dot{R}^2(t) + \dfrac{1}{2\pi}\ddot{R}(t), & x \in \partial\Omega(t), \ t \in (0,T) \end{cases} \tag{3.44}$$

where $L(t)S$ is given by (3.37)*, such that*

$$\iint_{\omega\times(0,T)} (a\eta + bv)\,(w - v)\,dx\,dt \geq 0 \qquad \forall w \in \mathcal{U}_{ad}, \quad v \in \mathcal{U}_{ad}. \tag{3.45}$$

The proof is very similar to the proof of theorem 9. In fact, the unique actually different point is that, now, conserving the same notation, we have

$$\begin{aligned}\langle j'(v), w\rangle = &\int_{\Omega(T)} (c(x,T) - c_d(x))\,\tilde{c}(x,T)\,dx - \frac{a}{2}\int_0^T \left(\dot{R}^2(t) + 2R(t)\ddot{R}(t)\right)\widetilde{R}(t)\,dt \\ &+ \left(aR(T)\dot{R}(T) + \frac{1}{2}\int_{\partial\Omega(T)} |c(x,T) - c_d(x)|^2 d\Gamma(x)\right)\widetilde{R}(T) \\ &+ b\iint_{\omega\times(0,T)} vw\,dx\,dt\end{aligned} \tag{3.46}$$

for all $w \in L^2(\omega \times (0,T))$. This motivates the change we have made in the third equality of (3.44). With this (new) definition of (S, ξ, η), it is not difficult to show again (3.39), which leads to (3.45).

Remark 13. Obviously, for this second choice of the cost J, we can also indicate appropriate "gradient-like" algorithms for the computation of optimal solutions. The iterates are similar to those in Section 3.3.2.

3.5 Appendix: An existence result for (3.2)

Let us recall the hypotheses:

$$\mathcal{O} = \mathbf{B}(0;\overline{R}),\ \omega = \mathbf{B}(0;a),\ \Omega^0 = \mathbf{B}(0;R^0),\ \text{with } 0 < a < R^0 < \overline{R}$$

$$m, \rho, m', \lambda, k > 0, \quad v \in L^2(\omega \times (0,T)) \text{ is } \geq 0 \text{ and radially symmetric}$$

$$c^0 \in H^1_0(\Omega^0) \text{ and } \beta^0 \in H^1(\mathcal{O}) \text{ are} \geq 0 \text{ and radially symmetric}$$

Theorem 12. *There exists ε only depending on $\overline{R}, R^0, T, m, \rho, m', \lambda$ and k such that, whenever*

$$\|c^0\|_{H^1_0(\Omega^0)} + \|\beta^0\|_{H^1(\mathcal{O})} + \|v\|_{L^2(\omega\times(0,T))} \leq \varepsilon, \tag{3.47}$$

there exists at least one strong radial solution to (3.2)*, with $c, \beta \geq 0$.*

Proof: Let C_1, C_2 be two positive constants (to be determined below) and let us set

$$K = \Big\{(\widetilde{c}, \widetilde{R}) \ : \ \widetilde{c} \in L^\infty(\mathcal{O} \times (0,T)),\ 0 \leq \widetilde{c} \leq C_1, \\ \widetilde{R} \in H^1(0,T),\ R^0 \leq \widetilde{R} \leq \overline{R},\ \|\dot{\widetilde{R}}\|_{L^2(0,T)} \leq C_2\Big\} \tag{3.48}$$

The set K is non-empty, closed, bounded and convex.

For each $(\widetilde{c}, \widetilde{R}) \in K$, we define β, c and R as follows:

- First, β is the unique solution to the (radially symmetric) linear problem

$$\begin{cases} \beta_t - \Delta\beta = -m'\beta\hat{c} - \lambda\beta + v1_\omega, & x \in \mathcal{O},\ 0 < t < T \\ \beta(x,0) = \beta^0(x), & x \in \mathcal{O} \\ \dfrac{\partial\beta}{\partial n} = 0, & x \in \partial\mathcal{O},\ 0 < t < T \end{cases} \tag{3.49}$$

  Here, $\hat{c}$ is the function obtained from $\widetilde{c}$ and $\widetilde{R}$ as follows:

$$\hat{c}(x,t) = \begin{cases} \widetilde{c}\Big(\dfrac{\hat{R}}{\widetilde{R}(t)}x, t\Big) & \text{if } \ |x| < \widetilde{R}(t),\ 0 < t < T \\ 0 & \text{otherwise} \end{cases} \tag{3.50}$$

  We have $\beta \in L^2(0,T;H^2(\mathcal{O})) \cap \mathcal{C}^0([0,T];H^1(\mathcal{O}))$ and $\beta_t \in L^2(\mathcal{O}\times(0,T))$, with the norms of β and β_t in these spaces bounded by

$$C\left(\|\beta^0\|_{H^1(\mathcal{O})} + \|v\|_{L^2(\omega\times(0,T))}\right),$$

  where C depends on C_1, $\mathcal{O}$, T, m' and λ. Furthermore, $\beta \geq 0$.

- Then, c is the unique solution to the radially symmetric problem

$$\begin{cases} c_t - \Delta c = -m\beta c + \rho c, & |x| < \widetilde{R}(t),\ 0 < t < T \\ c(x,0) = c^0(x), & |x| < R^0 \\ c = 0, & |x| = \widetilde{R}(t),\ 0 < t < T \end{cases} \tag{3.51}$$

For convenience,we rewrite (3.51) as an equivalent problem in a cylindrical set. This can be made by introducing the new variables

$$\tau = t, \quad \xi = \frac{\overline{R}}{\widetilde{R}(t)}\, x \quad \left(\text{and} \quad \sigma = \frac{\overline{R}}{\widetilde{R}(t)}\, r \quad \text{with} \quad r = |x|\right)$$

Then (3.51) reads:

$$\begin{cases} c_\tau - \left(\dfrac{\overline{R}}{\widetilde{R}(t)}\right)^2 \Delta_\xi c - \dfrac{\dot{\widetilde{R}}(\tau)}{\widetilde{R}(\tau)}\, \xi \cdot \nabla_\xi c = -m\beta^* c + \rho c, & |\xi| < \overline{R},\ 0 < t < T \\ c(\xi, 0) = c^0 \left(\dfrac{R^0}{\overline{R}}\, \xi\right), & |\xi| < \overline{R} \\ c = 0, & |\xi| = \overline{R},\ 0 < t < T \end{cases} \tag{3.52}$$

where β^* is obtained from β and $\widetilde{R}$ as follows:

$$\beta^*(\xi, t) = \beta\left(\frac{\widetilde{R}(t)}{\overline{R}}\, \xi, t\right)$$

It is clear from (3.52) that (in the new variables) $c \in L^2(0, T; H^2(\mathcal{O})) \cap \mathcal{C}^0([0, T]; H^1(\mathcal{O}))$, $c_\tau \in L^2(\mathcal{O} \times (0, T))$ and the norms of c and c_τ in these spaces are bounded by

$$C\left(\|c^0\|_{H^1(\Omega^0)} + \|\beta^0\|_{L^\infty(\mathcal{O}\times(0,T))}\right),$$

where C depends on R^0, $\overline{R}$, C_2, $\mathcal{O}$, T, m and ρ. Consequently, they are also bounded by

$$C\left(\|c^0\|_{H_0^1(\Omega^0)} + \|\beta^0\|_{H^1(\mathcal{O})} + \|v\|_{L^2(\omega\times(0,T))}\right), \tag{3.53}$$

where C depends on C_1, C_2, R^0, $\overline{R}$, T and the constants m, ρ, m' and λ.

On the other hand, from the maximum principle, it is also clear that

$$0 \le c \le C_0, \tag{3.54}$$

where C_0 only depends on $\|c^0\|_{H_0^1(\Omega^0)}$, ρ and T and is nondecreasing with respect to these data.

- Finally, R is given by

$$R(t) = \min\left(R^0 + \int_0^t \left[-c_r(\widetilde{R}(s), s)\right] ds, \overline{R}\right) \quad \forall t \in [0, T], \tag{3.55}$$

  where c is the solution to (3.51).

  It is obvious that $R \in H^1(0, T)$, with $R^0 \le R \le \overline{R}$ and $\|\dot{R}\|_{L^2}$ bounded by a constant times the L^2 norm of c_{rr}. Consequently, it is also bounded by the expression in (3.53).

It is clear that any fixed point of the mapping $(\widetilde{c}, \widetilde{\beta}) \mapsto (c, \beta)$ is a solution to (3.2).

Let us first choose $\varepsilon_1 > 0$ and let us take $C_1 = C_0$, where C_0 is the constant in (3.54) associated to ε_1, ρ and T.

The mapping $(\widetilde{c},\widetilde{\beta}) \mapsto (c,\beta)$ is well-defined in K, with values in $L^\infty(\mathcal{O}\times(0,T))\times H^1(0,T)$. From the usual parabolic regularity theory, it is easy to check that it is continuous and compact. Furthermore, one has

$$0 \le C \le C_1\,, \quad R^0 \le R \le \overline{R}$$

and

$$\|\dot{R}\|_{L^2(0,T)} \le C_3 \left(\|c^0\|_{H_0^1(\Omega^0)} + \|\beta^0\|_{H^1(\mathcal{O})} + \|v\|_{L^2(\omega\times(0,T))} \right),$$

where C_3 only depends on C_1, C_2, R^0, $\overline{R}$, T and the constants m, ρ, m' and λ.

Consequently, if we choose $C_2 > 0$, $\varepsilon_2 = C_2/C_3$ and $\|c^0\|_{H_0^1(\Omega^0)} + \|\beta^0\|_{H^1(\mathcal{O})} + \|v\|_{L^2(\omega\times(0,T))} \le \varepsilon_2$, we see that $\|\dot{R}\|_{L^2(0,T)} \le C_2$. Finally, taking $\varepsilon = \min(\varepsilon_1,\varepsilon_2)$ and choosing c^0, β^0 and v as in (3.47), we deduce that K is mapped into itself.

In view of Schauder fixed-point theorem, there exists at least one solution to (3.2).

This ends the proof.

■

CHAPTER 4
Some optimal control problems for solidification processes

4.1 Introduction

The solidification of metals and castings is one of the most difficult problems to solve in engineering, from the technological and theoretical points of view. The complex nature of the involved phenomena is an obstacle to obtain solutions in a simple way. To accomplish this task, we have to use sophisticated mathematical models formed by systems of nonlinear partial differential equations. By using correctly the laws governing solidification processes, performing a profound mathematical analysis of the equations, applying appropriate numerical methods and implementing a good computational simulations, it is possible to gain insight in this phenomena, obtain products of better quality and, also, diminish the related costs.

In order to present the different elements associated to solidification processes, we consider a rectangular cavity Ω (called the mould) with boundary $\partial\Omega$, filled with an incompressible and diluted binary alloy, initially in liquid state, with uniform temperature and composition, under the gravity influence. The solute is the component in less quantity and the other one is called the solvent; together, they form the melting. The variable that indicates the proportion of solute in the melting is called the concentration.

The alloy is verted in the mould in such a way that, at time $t = 0$, the temperature of the left side of Ω is instantaneously dropped and maintained under the cooling point, while the other sides of Ω are maintained thermically isolated (see Figure 4.1). This makes appear a temperature gradient in the alloy and, if we consider the gravity force, we obtain heat and solute transport by convection. The coupled action of these phenomena may introduce changes in the alloy density. On the other hand, the region next to the left side of Ω experiments a phase change, passing from the liquid to the solid state. The interface between the liquid and solid state is called the solidification front. In general, it may have a highly irregular geometry and may exhibit dendritic forms for rapid solidification. The formation of dendrites is a consequence of the instability of growth of the solidification front.

After a time, the alloy is in solid state. If we make a material composition analysis of the resultant material, we will probably find variations of the solute. These variations are present in two scales. In the first (macroscopic) scale, the solidification front acts like a filter on the solute. The solute is rejected from the solid state accumulated next to the front and, then, it is transported to the liquid state. This phenomenon is called macro-segregation. In the second (microscopic) scale, a part of the solute rejected from the solid state is trapped by the dendrites of the solidification front before transport occurs, generating highly concentrate solute grains. This is the micro-segregation phenomenon.

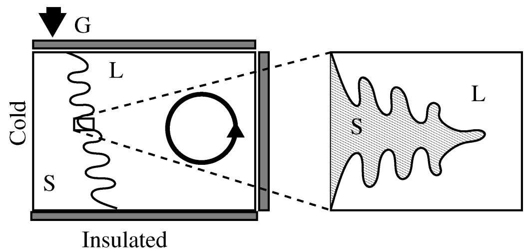


Figure 4.1: An schematic view of the cavity problem, with detail of the solidification front.

This Chapter deals with the theoretical analysis and optimal control of a model of solidification of a binary alloy. The outline is as follows. In Section 2, we consider the solidification problem and we present a regularized model. We study the existence of weak solutions for this regularized problem in Section 3. Section 4 deals with the optimal control of the solidification problem; here, the control variable is a localized in space heat source; we deduce the existence of optimal controls and we present the associated optimality system. In Section 5, we consider and solve a related time optimal control problem. Some numerical algorithms are also introduced and discussed in these Sections.

4.2 The solidification problem

Let Ω be a regular, connected and open bounded domain of $\mathbb{R}^d$ ($d = 2, 3$) with (locally) regular boundary $\partial\Omega$, such that $\partial\Omega = \Gamma_D \cup \Gamma_N$, where $\Gamma_D \cap \Gamma_N = \emptyset$ and $\Gamma_N \neq \emptyset$. Let $T > 0$ and let us set $Q^T := \Omega \times (0, T)$.

The mathematical model for the solidification problem (see for example, [7], [8] and [39]) is the following:

$$c_t + \nabla \cdot (\boldsymbol{v} c_l(c, \theta) - D\nabla c) = h_c \tag{4.1}$$

$$\theta_t + \nabla \cdot (\boldsymbol{v}\theta - \chi\nabla\theta) = h_\theta \tag{4.2}$$

$$\boldsymbol{v}_t + \nabla \cdot (\boldsymbol{v} \otimes \boldsymbol{v} - \nu\nabla\boldsymbol{v}) + F_i(c, \theta)\boldsymbol{v} + \nabla p = \boldsymbol{F}_e(c, \theta) + \boldsymbol{h}_{\boldsymbol{v}} \tag{4.3}$$

$$\nabla \cdot \boldsymbol{v} = 0 \tag{4.4}$$

where h_c, h_θ and $\boldsymbol{h}_{\boldsymbol{v}}$ are known functions.

In (4.1)–(4.4), c and c_l are the concentration and the liquid concentration of solute of the binary alloy (respectively), θ is the temperature of the moisture, $\boldsymbol{v}$ is the velocity of the liquid and p is the pressure. D, χ and ν are positive constants denoting the diffusive coefficient of solute, the thermal conductivity and the viscosity, respectively; F_i and $\boldsymbol{F}_e$ are functions denoting the internal and external forces acting on the system (4.1)–(4.4) (in general, these are bounded, positive functions depending on c and θ). Their most common expressions are given by

$$F_i = M_0 \frac{f_s(c,\theta)^2}{(1-f_s(c,\theta))^3} \tag{4.5}$$

$$\boldsymbol{F}_e = \boldsymbol{g}(1+\beta_\theta\theta+\beta_c c_l(c,\theta)) \tag{4.6}$$

Thus, we are considering, respectively, the *Carman-Kozeny approximation* to model the effects in the mould as a porous media, and the *Boussinesq approximation* to model the thermic and solutal stresses. Here, f_s denotes the solid fraction, M_0 is a positive constant depending on the material, $\boldsymbol{g}$ is the gravity force, β_θ and β_c are constants representing the thermal and solute expansion coefficients and $c = c_s f_s + (1-f_s)c_l$, where $c_s = rc_l$ and $0 < r < 1$ (c_s is the solid concentration of solute).

The equations (4.1) and (4.2) are valid in Q^T. The equations (4.3) and (4.4) must hold in the *non-solid space-time region*

$$Q^T_{ml} = \{(\boldsymbol{x},t) \;:\; \boldsymbol{x} \in \Omega_{ml}(t), t \in (0,T)\},$$

where $\Omega_{ml}(t)$ is the region of the mould Ω with no presence of solid at time t, i.e. the set of points of Ω that are not in solid phase at time t (ml means "moisture-liquid").

Analogously, we define the *solid region*

$$Q^T_s = \{(\boldsymbol{x},t) \;:\; \boldsymbol{x} \in \Omega_s(t), t \in (0,T)\},$$

where $\Omega_s(t) = \Omega \setminus \Omega_{ml}(t)$ for all time t, i.e. the set of points of Ω that are in solid phase at time t.

The sets Q^T_{ml} and Q^T_s can be computed via the phase diagram by using the values of c and θ (see Figure 4.2). In this diagram, θ_f and θ_e denote the *fusion* and *eutectic* temperature, respectively. By simplicity, we assume that the solid and liquid curves (denoted by $\gamma_s(\theta)$ and $\gamma_l(\theta)$ respectively) are straight lines. These lines give the points (c,θ) where the solid alloy begins to melt and the points where the liquid begins to solidify. Also, we can identify in the phase diagram the following sets:

$$L = \{(c,\theta) \;:\; \gamma_l(\theta) < c \text{ and } \theta_f < \theta\} \tag{4.7}$$

$$S = \{(c,\theta) \;:\; c < \gamma_s(\theta) \text{ and } \theta_e < \theta < \theta_f\} \cup \{(c,\theta) \;:\; \theta < \theta_e\} \tag{4.8}$$

$$M = \{(c,\theta) \;:\; \gamma_s(\theta) \le c \le \gamma_l(\theta) \text{ and } \theta_e \le \theta \le \theta_f\} \tag{4.9}$$

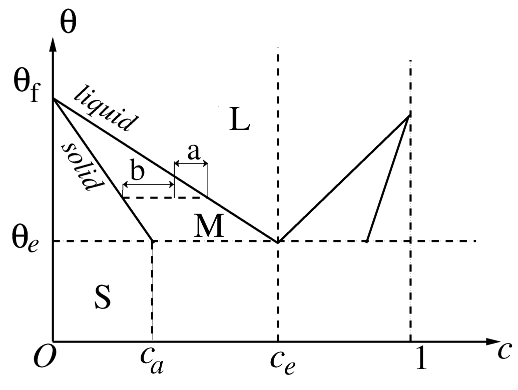


Figure 4.2: A typical phase diagram for a binary alloy

The temperature and the concentration are used in order to determine the solid fraction f_s

through the following equalities:

$$f_s(c,\theta) = \begin{cases} 0 & \text{if } (c,\theta) \in L \\ 1 & \text{if } (c,\theta) \in S \\ \dfrac{a}{a+b} & \text{if } (c,\theta) \in M \end{cases} \tag{4.10}$$

Taking into account this definition of f_s, we can deduce that the liquid concentration is given by:

$$c_l(c,\theta) = \begin{cases} c & \text{if } (c,\theta) \in L \\ \gamma_l(\theta) & \text{if } (c,\theta) \in M \\ 0 & \text{in } S \end{cases} \tag{4.11}$$

4.2.1 The regularized problem

Notice that the solid-moisture and liquid-moisture interfaces are not known a priori. This is an additional difficulty to the problem (4.1)–(4.3). Secondly, the Carman-Kozeny term is singular in Q_s^T because the solid fraction reaches 1 there. In order to avoid this problem, we introduce a parameter $\epsilon \in (0,1]$ and we replace the function $F_i(c,\theta)$ defined in (4.5) and appearing in (4.3) by the following:

$$F_i^\epsilon \;=\; M_0 \frac{f_s(c,\theta)^2}{(1-f_s(c,\theta)+\epsilon)^3}\,. \tag{4.12}$$

In this case, the equations (4.1) and (4.2) are the same, but now (4.3) and (4.4) must hold in the whole cylinder Q^T:

$$c_t + \nabla\cdot(\boldsymbol{v} c_l(c,\theta) - D\nabla c) \;=\; h_c \tag{4.13}$$

$$\theta_t + \nabla\cdot(\boldsymbol{v}\theta - \chi\nabla\theta) \;=\; h_\theta \tag{4.14}$$

$$\boldsymbol{v}_t + \nabla\cdot(\boldsymbol{v}\otimes\boldsymbol{v} - \nu\nabla\boldsymbol{v}) + F_i^\epsilon(c,\theta)\boldsymbol{v} + \nabla p \;=\; \boldsymbol{F}_e(c,\theta) + \boldsymbol{h}_{\boldsymbol{v}} \tag{4.15}$$

$$\nabla\cdot\boldsymbol{v} \;=\; 0 \tag{4.16}$$

The system (4.13)–(4.16) is complemented with boundary conditions for c and $\boldsymbol{v}$ on $\partial\Omega\times(0,T)$:

$$(D\nabla c)\cdot\boldsymbol{n} \;=\; 0 \tag{4.17}$$

$$\boldsymbol{v} \;=\; \boldsymbol{0} \tag{4.18}$$

and also for θ on $\Gamma_N\times(0,T)$ and $\Gamma_D\times(0,T)$:

$$(\chi\nabla\theta)\cdot\boldsymbol{n} \;=\; 0 \tag{4.19}$$

$$\theta \;=\; 0 \tag{4.20}$$

Finally, we add initial conditions for c, θ and $\boldsymbol{v}$:

$$c(\boldsymbol{x},0) = c_0(\boldsymbol{x}); \quad \theta(\boldsymbol{x},0) = \theta_0(\boldsymbol{x}); \quad \boldsymbol{v}(\boldsymbol{x},0) = \boldsymbol{v}_0(\boldsymbol{x}). \tag{4.21}$$

4.3 The existence of weak solutions for the regularized problem

In this Section we study the existence of weak solutions for the regularized solidification problem considered above. The problem is given by equations (4.13)–(4.16) and the boundary and initial conditions are given by (4.17)–(4.21). For simplicity, we assume that $h_c = 0$, $\boldsymbol{h}_{\boldsymbol{v}} = \boldsymbol{0}$ and $h_\theta = k 1_\omega$, with $\omega \subset\subset \Omega$.

Some previous works related with this topic are [9], [16] and [17].

4.3.1 Preliminaries and weak formulation

In the sequel, we consider the usual Sobolev spaces, given by

$$W^{m,q}(\Omega) = \{\ f\ \in L^p(\Omega)\ :\ \partial^\alpha f \in L^p(\Omega) < \infty,\ \forall |\alpha| \leq m\ \}$$

for all $m \geq 1$ and $1 \leq p \leq +\infty$. When $p = 2$, we write $H^m(\Omega) := W^{m,2}(\Omega)$; we denote by $H_0^m(\Omega)$ the closure of $C_0^\infty(\Omega)$ in $H^m(\Omega)$. Sometimes, if there is no confusion, we write L^p instead of $L^p(\Omega)$, and $W^{m,q}$ instead of $W^{m,q}(\Omega)$.

If X is a Banach space and $1 \leq q \leq +\infty$, we denote by $L^q(0,T;X)$ the Banach space of X-valued (classes of) functions defined on the interval $[0,T]$ that are L^q-integrable in the Bochner's sense. Spaces of $\mathbb{R}^d$-valued functions, as well as their elements, are represented by bold face letters. We denote by $\|\cdot\|_X$ the norm of the normed space X.

We will consider the space

$$\boldsymbol{C}_{0,\sigma}^\infty(\Omega) = \{\boldsymbol{v} \in \boldsymbol{C}_0^\infty(\Omega)\ :\ \operatorname{div} \boldsymbol{v} = 0 \text{ in } \Omega\}$$

If $\boldsymbol{H}$, $\boldsymbol{V}$ stand for the closures of $\boldsymbol{C}_{0,\sigma}^\infty(\Omega)$ in $\boldsymbol{L}^2(\Omega)$ and $\boldsymbol{H}^1(\Omega)$, respectively, denoting by $\boldsymbol{n}$ the outward normal vector to $\partial\Omega$, it is possible to show that (see [47])

$$\begin{aligned}\boldsymbol{H} &= \{\boldsymbol{v}\ \in \boldsymbol{L}^2(\Omega)\ :\ \operatorname{div} \boldsymbol{v} = 0 \text{ in } \Omega,\ \boldsymbol{v}\cdot\boldsymbol{n} = 0 \text{ on } \partial\Omega\}\\ \boldsymbol{V} &= \{\boldsymbol{v}\ \in \boldsymbol{H}_0^1(\Omega)\ :\ \operatorname{div} \boldsymbol{v} = 0 \text{ in } \Omega\}\end{aligned}$$

In the following, in order to simplify the notation, we denote by C a generic positive constant depending only on Ω and the other prescribed data of the problem. As usual, it may have different values in different expressions. When necessary, we will emphasize that the constants may have different values by putting $C_1, C_2, \ldots$

For the weak formulation of the regularized solidification problem described by (4.13)–(4.21), we will need the following space:

$$\mathcal{H}_\theta(\Omega) = \{\psi \in H^1(\Omega)\ :\ \psi = 0 \text{ on } \Gamma_D\}.$$

Also, we can extend by continuity the definition of the liquid concentration c_l to the whole $\mathbb{R}^2$, with

$$c_l \in W^{1,\infty}_{\text{loc}}(\mathbb{R}^2). \tag{4.22}$$

From now on, we suppose that:

$$k \in L^2(\omega \times (0,T)) \tag{4.23}$$
$$c_0 \in L^\infty(\Omega),\ 0 \leq c_0(\boldsymbol{x}) \leq c_e \quad \forall \boldsymbol{x} \in \Omega \tag{4.24}$$
$$\theta_0 \in L^2(\Omega) \tag{4.25}$$
$$\boldsymbol{v}_0 \in \boldsymbol{H} \tag{4.26}$$
$$\boldsymbol{g} \in L^\infty(\Omega) \tag{4.27}$$

Definition 1. *We say that* $(c,\theta,\boldsymbol{v})$ *is, together with* p, *a* weak solution *of* (4.13)–(4.21) *if*

$$c \in L^2(0,T;H^1(\Omega)) \cap L^\infty(0,T;L^2(\Omega)) \tag{4.28}$$
$$\theta \in L^2(0,T;\mathcal{H}_\theta(\Omega)) \cap L^\infty(0,T;L^2(\Omega)) \tag{4.29}$$
$$\boldsymbol{v} \in L^2(0,T;\boldsymbol{V}) \cap L^\infty(0,T;\boldsymbol{H}) \tag{4.30}$$

the following relations hold

$$\langle c_t, \varphi\rangle + \int_\Omega \boldsymbol{v}\cdot\nabla c_l(c,\theta)\varphi\,dx + \int_\Omega D\nabla c\cdot\nabla\varphi\,dx = 0 \tag{4.31}$$

$$\langle \theta_t, \psi\rangle + \int_\Omega \boldsymbol{v}\cdot\nabla\theta\psi\,dx + \int_\Omega \chi\nabla\theta\cdot\nabla\psi\,dx = \int_\omega k\psi\,dx \tag{4.32}$$

$$\langle \boldsymbol{v}_t, \boldsymbol{w}\rangle + \int_\Omega (\boldsymbol{v}\cdot\nabla)\boldsymbol{v}\cdot\boldsymbol{w}\,dx + \int_\Omega \nu\nabla\boldsymbol{v}\cdot\nabla\boldsymbol{w}\,dx + \int_\Omega F_i^\epsilon(c,\theta)\boldsymbol{v}\cdot\boldsymbol{w}\,dx = \int_\Omega \boldsymbol{F}_e\cdot\boldsymbol{w}\,dx \tag{4.33}$$

for all $\varphi \in H^1(\Omega)$, $\psi \in \mathcal{H}_\theta(\Omega)$, $\boldsymbol{w} \in \boldsymbol{V}$ *and*

$$c|_{t=0} = c_0, \quad \theta|_{t=0} = \theta_0, \quad \boldsymbol{v}|_{t=0} = \boldsymbol{v}_0. \tag{4.34}$$

Let c_g be given by $c_g := \int_\Omega c_0(\boldsymbol{x})\,dx$, i.e. the initial total amount of solute in the moisture. By using (4.24), we have

$$0 \le c_g \le \int_\Omega c_e\,dx = c_e|\Omega| < \infty.$$

If we take $\varphi = 1$ in (4.31), a short computation shows that, for all $t > 0$,

$$\frac{d}{dt}\int_\Omega c(\cdot,t)\,dx = -\int_\Omega \boldsymbol{v}\cdot\nabla c_l\,dx = \int_\Omega c_l\nabla\cdot\boldsymbol{v}\,dx - \int_\Omega \nabla\cdot(\boldsymbol{v}c_l)\,dx = -\int_{\partial\Omega}(\boldsymbol{v}\cdot\boldsymbol{n})c_l\,\mathrm{ds} = 0,$$

in view of (4.30). Thus, $\int_\Omega c(\cdot,t)\,dx$ is constant in time, and we obtain that

$$c_g = \int_\Omega c_0(\boldsymbol{x})\,dx = \int_\Omega c(\cdot,t)\,dx \quad \forall t > 0.$$

Therefore, the amount of solute in the moisture does not depend on time.

Let us assume that (4.23)–(4.27) hold. It is not difficult to check that any $(c,\theta,\boldsymbol{v})$ satisfying (4.28)–(4.30) and (4.31)–(4.33) also satisfies $c,\theta \in C^0([0,T];L^2(\Omega))$ and $\boldsymbol{v} \in C^0([0,T];\boldsymbol{H})$ if $d = 2$ and $c,\theta \in C^0_w([0,T];L^2(\Omega))$ and $\boldsymbol{v} \in C^0_w([0,T];\boldsymbol{H})$ when $d = 3$. In particular, the initial conditions (4.34) make sense.

4.3.2 On the existence and uniqueness of solution of the regularized problem

We will use the following result in the proof of existence of weak solutions to the regularized problem (4.13)–(4.21).

Proposition 8 (Maximum principle). *Assume that* $(c,\theta,\boldsymbol{v})$ *is a weak solution of the regularized problem* (4.13)–(4.21)*. Then*

$$0 \le c(\boldsymbol{x},t) \le c_e \quad a.e.\ in\ \ \Omega\times[0,T]. \tag{4.35}$$

Proof: We put some terminology before beginning. If for each $t \in [0,T]$ we have a function $\varphi^t : \Omega \to \mathbb{R}$, we denote by φ^t_+ and φ^t_- its positive and negative parts (respectively) and we associate to φ^t the following sets:

$$\Omega^t_+ = \{\boldsymbol{x}\in\Omega \ : \ \varphi^t(\boldsymbol{x}) \ge 0\}, \quad \Omega^t_- = \{\boldsymbol{x}\in\Omega \ : \ \varphi^t(\boldsymbol{x}) < 0\}.$$

For each $t \in [0,T]$, let us choose $\varphi(\cdot) = c_-(\cdot,t)$ in (4.31). Since $c = c_+ - c_-$, taking into account the definition of c_l (see Section 2), we easily get:

$$-\frac{1}{2}\frac{d}{dt}\|c_-\|^2_{L^2} - D\|\nabla c_-\|^2_{L^2} = 0.$$

Integrating in time, we have

$$-\frac{1}{2}\|c_-(\cdot,t)\|_{L^2}^2 - D\int_0^t \|\nabla c_-\|_{L^2}^2\,\mathrm{ds} = -\frac{1}{2}\|c_-(\cdot,0)\|_{L^2}^2.$$

But, by (4.24), $\|c_-(\cdot,0)\|_{L^2}^2 = 0$. Therefore, we deduce that $\|c_-(\cdot,t)\|_{L^2}^2 = 0$ for all $t \geq 0$, that is, $c \geq 0$.

Now, for each $t \in [0,T]$, we choose $\varphi(\cdot) = (c - c_e)_+(\cdot,t)$ in (4.31). By using an argument similar to the previous one, we obtain that

$$\frac{1}{2}\|(c(\cdot,t) - c_e)_+\|_{L^2}^2 + D\int_0^t \|\nabla(c - c_e)_+\|_{L^2}^2\,\mathrm{ds} = 0,$$

whence $c \leq c_e$. ■

Our main result concerning the existence of a solution to (4.13)–(4.21) is the following:

Theorem 13. *There exists at least a weak solution $(c,\theta,\boldsymbol{v})$ of the regularized problem* (4.13)–(4.21), *with* $0 \leq c \leq c_e$.

Proof: In order to apply a Galerkin method, we consider three "special" bases $\mathcal{B}_c = \{\varphi_k(\boldsymbol{x}) : k \in \mathbb{N}\}$, $\mathcal{B}_\theta = \{\psi_k(\boldsymbol{x}) : k \in \mathbb{N}\}$ and $\mathcal{B}_{\boldsymbol{v}} = \{\boldsymbol{w}_k(\boldsymbol{x}) : k \in \mathbb{N}\}$ respectively in $H^1(\Omega)$, $\mathcal{H}_\theta(\Omega)$ and $\boldsymbol{V}$. It will be assumed that they are orthogonal for the scalar product in H^1 and orthonormal for the scalar product in L^2.

Let us fix $N \in \mathbb{N}$. We consider the N-dimensional spaces $\mathcal{S}_c^N \subset H^1(\Omega)$, $\mathcal{S}_\theta^N \subset \mathcal{H}_\theta(\Omega)$ and $\boldsymbol{\mathcal{S}}_{\boldsymbol{v}}^N \subset \boldsymbol{V}$ spanned by the first N functions of $\mathcal{B}_c$, $\mathcal{B}_\theta$ and $\mathcal{B}_{\boldsymbol{v}}$, respectively.

For $t \in [0,T]$, we define the approximations c^N, θ^N and $\boldsymbol{v}^N$ of c, θ and $\boldsymbol{v}$, respectively, as

$$c^N(\boldsymbol{x},t) = \sum_{k=1}^N \lambda_{k,N}(t)\varphi_k(\boldsymbol{x}) \tag{4.36}$$

$$\theta^N(\boldsymbol{x},t) = \sum_{k=1}^N \xi_{k,N}(t)\psi_k(\boldsymbol{x}) \tag{4.37}$$

$$\boldsymbol{v}^N(\boldsymbol{x},t) = \sum_{k=1}^N \sigma_{k,N}(t)\boldsymbol{w}_k(\boldsymbol{x}) \tag{4.38}$$

The coefficients $\lambda_{k,N}(t), \xi_{k,N}(t)$ and $\sigma_{k,N}(t)$ are computed in such way that

$$\langle \partial_t c^N, \varphi_k \rangle + \int_\Omega \boldsymbol{v}^N \cdot \nabla \widetilde{c}_l(c^N,\theta^N)\varphi_k\,dx + \int_\Omega D\nabla c^N \cdot \nabla\varphi_k\,dx = 0 \tag{4.39}$$

$$\langle \partial_t \theta^N, \psi_k \rangle + \int_\Omega \boldsymbol{v}^N \cdot \nabla\theta^N \psi_k\,dx + \int_\Omega \chi\nabla\theta^N \cdot \nabla\psi_k\,dx = \int_\omega k\psi_k\,dx \tag{4.40}$$

$$\begin{aligned}\langle \partial_t \boldsymbol{v}^N, \boldsymbol{w}_k \rangle &+ \int_\Omega (\boldsymbol{v}^N \cdot \nabla)\boldsymbol{v}^N \cdot \boldsymbol{w}_k\,dx + \int_\Omega \nu\nabla\boldsymbol{v}^N \cdot \nabla\boldsymbol{w}_k\,dx \\ &= -\int_\Omega \widetilde{F}_i^\epsilon(c^N,\theta^N)\boldsymbol{v}^N \cdot \boldsymbol{w}_k\,dx + \int_\Omega \widetilde{\boldsymbol{F}}_e(c^N,\theta^N) \cdot \boldsymbol{w}_k\,dx\end{aligned} \tag{4.41}$$

for all $k = 1, \ldots, N$ and

$$c^N(\boldsymbol{x},0) = P_{c,N}(c_0(\boldsymbol{x})), \quad \theta^N(\boldsymbol{x},0) = P_{\theta,N}(\theta_0(\boldsymbol{x})), \quad \boldsymbol{v}^N(\boldsymbol{x},0) = \boldsymbol{P}_{\boldsymbol{v},N}(\boldsymbol{v}_0(\boldsymbol{x})) \quad \text{in} \quad \Omega \tag{4.42}$$

Here, $P_{c,N} : H^1(\Omega) \mapsto \mathcal{S}_c^N, P_{\theta,N} : \mathcal{H}_\theta(\Omega) \mapsto \mathcal{S}_\theta^N$ and $\boldsymbol{P}_{\boldsymbol{v},N} : \boldsymbol{V} \mapsto \boldsymbol{\mathcal{S}}_{\boldsymbol{v}}^N$ are the usual orthogonal projection operators. In (4.39) and (4.41), the following notation has been introduced:

$$\widetilde{c_l}(c,\theta) := c_l(c^*,\theta) \qquad \text{with} \quad c^* = \begin{cases} 0 & \text{if} \quad c < 0 \\ c & \text{if} \quad 0 \le c \le c_e \\ c_e & \text{if} \quad c > c_e \end{cases}$$

and similar equalities for $\widetilde{F}_i^\epsilon$ and $\widetilde{\boldsymbol{F}}_e$.

For each N, (4.39)–(4.41) is an ordinary differential system for the $\lambda_{k,N}(t), \xi_{k,N}(t)$ and $\sigma_{k,N}(t)$. It is complemented with initial conditions (4.42). This initial value problem has a global in time solution $(c^N, \theta^N, \boldsymbol{v}^N)$ defined in some interval $[0, t^N)$. In order to prove that $t^N = T$, we need to show some a priori estimates.

If we multiply equations (4.39), (4.40) and (4.41) by $\lambda_{k,N}(t)$, $\xi_{k,N}(t)$ and $\sigma_{k,N}(t)$, respectively, and we sum over k, we obtain (using that $\boldsymbol{v}^N \in \boldsymbol{V}$):

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt}\|c^N(t)\|_{L^2}^2 + D\|\nabla c^N(t)\|_{L^2}^2 &= -\int_\Omega \boldsymbol{v}^N(t)\cdot\nabla\widetilde{c_l}(c^N,\theta^N)c^N(t)\,dx \\
\frac{1}{2}\frac{d}{dt}\|\theta^N(t)\|_{L^2}^2 + \chi\|\nabla\theta^N(t)\|_{L^2}^2 &= \int_\omega k\theta^N(t)\,dx \\
\frac{1}{2}\frac{d}{dt}\|\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2}^2 + \nu\|\nabla\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2}^2 &= \int_\Omega \widetilde{\boldsymbol{F}}_e(c^N,\theta^N)\cdot\boldsymbol{v}^N(t)\,dx - \int_\Omega \widetilde{F}_i^\epsilon(c^N,\theta^N)|\boldsymbol{v}^N(t)|^2\,dx
\end{aligned}$$

Now, we have to estimate the terms in the right hand side of these inequalities. By using (4.22) and Hölder and Young inequalities, we can bound the first term as follows:

$$\begin{aligned}
\left|\int_\Omega \boldsymbol{v}^N(t)\cdot\nabla\widetilde{c_l}(c^N,\theta^N)c^N(t)\,dx\right| &= \left|-\int_\Omega \widetilde{c_l}(c^N,\theta^N)\boldsymbol{v}^N(t)\cdot\nabla c^N(t)\,dx\right| \\
&\le \frac{D}{2}\|\nabla c^N(t)\|_{L^2}^2 + C_1\|\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2}^2
\end{aligned} \tag{4.43}$$

By using Poincaré and Young inequalities, we find the following for the second term:

$$\int_\omega k\theta^N(t)\,dx \le C_2\|k\|_{L^2(\omega)}^2 + \frac{\chi}{2}\|\nabla\theta^N(t)\|_{L^2}^2. \tag{4.44}$$

Finally, for the third term we have

$$\begin{aligned}
\left|\int_\Omega \widetilde{\boldsymbol{F}}_e(c^N,\theta^N)\cdot\boldsymbol{v}^N(t)\,dx\right| &\le C_3\|\theta^N\|_{L^2}\|\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2} + C_4 + \frac{1}{2}\|\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2}^2 \\
&\le C_4 + C_3\|\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2}^2 + C_5\|\theta^N\|_{L^2}^2
\end{aligned} \tag{4.45}$$

Taking into account (4.43)–(4.45), we deduce that

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\left(\|c^N(t)\|_{L^2}^2 + \|\theta^N\|_{L^2}^2 + \|\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2}^2\right) \\
&\qquad \le C_6(1 + \|k\|_{L^2(\omega)}^2) + C_7\left(\|c_N(t)\|_{L^2}^2 + \|\theta^N\|_{L^2}^2 + C_3\|\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2}^2\right)
\end{aligned} \tag{4.46}$$

Let us define $f(t) = \|c^N(t)\|_{L^2}^2 + \|\theta^N(t)\|_{L^2}^2 + \|\boldsymbol{v}^N(t)\|_{\boldsymbol{L}^2}^2$. Then, integrating (4.46) with respect to t, we obtain:

$$\begin{aligned}
f(t) &\le f(0) + C\int_0^t (1 + \|k\|_{L^2(\omega)}^2)\,\mathrm{ds} + C\int_0^t f(s)\,\mathrm{ds} \\
&\le f(0) + C\int_0^T (1 + \|k\|_{L^2(\omega)}^2)\,\mathrm{ds} + C\int_0^t f(s)\,\mathrm{ds}
\end{aligned} \tag{4.47}$$

From Gronwall lemma, we have, for all $t \in [0, T]$,

$$f(t) \le \left(f(0) + C \int_0^T (1 + \|k\|^2_{L^2(\omega)})\,\mathrm{ds} \right) e^{Ct}. \tag{4.48}$$

We conclude that $t^N = T$ and, also, that the following estimates hold:

$$\begin{aligned} &\{c^N(t)\}_N \text{ and } \{\theta^N(t)\}_N \ \text{ are bounded in } \ L^2(0,T;H^1) \cap L^\infty(0,T;L^2) \\ &\{\boldsymbol{v}^N(t)\}_N \ \text{ is bounded in } \ L^2(0,T;\boldsymbol{V}) \cap L^\infty(0,T;\boldsymbol{H}) \end{aligned} \tag{4.49}$$

Unfortunately, (4.49) does not suffice to pass to the limit in (4.39)–(4.42). We also need uniform estimates of c_t^N, θ_t^N and $\boldsymbol{v}_t^N$ for instance in $L^\sigma(0,T;(H^1)')$, $L^\sigma(0,T;(H^1)')$ and $L^\sigma(0,T;\boldsymbol{V}')$, where

$$\sigma = \begin{cases} 2 & \text{if } d = 2 \\ 4/3 & \text{if } d = 3 \end{cases}$$

To this end, we argue as follows.
First, we notice that

$$\langle c_t^N, \varphi_k \rangle = -\int_\Omega \boldsymbol{v}^N \cdot \nabla \widetilde{c}_l(c^N, \theta^N) \varphi_k \, dx - \int_\Omega D \nabla c^N \cdot \nabla \varphi_k \, dx \quad \forall k = 1, \dots, N$$

Consequently, $c_t^N = P_{c,N}\left(-\boldsymbol{v}^N \cdot \nabla \widetilde{c}_l(c^N,\theta^N) - D\Delta c^N\right)$, where $P_{c,N} : \left(H^1(\Omega)\right)' \mapsto \mathcal{S}_c^N$ is the usual orthogonal projection operator. In view of the choice we have made of $\mathcal{B}_c$, we have:

$$\begin{aligned} \|c_t^N\|_{(H^1)'} &= \left\| P_{c,N}\left(-\boldsymbol{v}^N \cdot \nabla \widetilde{c}_l(c^N,\theta^N) - D\Delta c^N\right) \right\|_{(H^1)'} \\ &\le C \left\| \widetilde{c}_l(c^N,\theta^N)\boldsymbol{v}^N + D\nabla c^N \right\|_{L^2} \\ &\le C \left(\|\boldsymbol{v}^N\|_{L^2} + \|\nabla c^N\|_{L^2} \right) \end{aligned}$$

which is bounded in $L^2(0,T)$ by (4.49). Consequently,

$$\|c_t^N\|_{L^2(0,T;\,(H^1)')} \le C \quad \text{if} \quad d = 2, 3.$$

A similar argument shows that

$$\|\theta_t^N\|_{(H^1)'} \le C \left(\| - v^N \cdot \nabla \theta^N\|_{(H^1)'} + \|\nabla \theta^N\|_{L^2} + \|k\|_{L^2(\omega)} \right). \tag{4.50}$$

Notice that

$$\begin{aligned} \| - \boldsymbol{v}^N \cdot \nabla \theta^N\|_{(H^1)'} &\le C \|\theta^N \boldsymbol{v}^N\|_{\boldsymbol{L}^2} \le C \|\theta^N\|_{L^4} \|\boldsymbol{v}^N\|_{\boldsymbol{L}^4} \\ &\le C \|\theta^N\|_{L^2}^\alpha \|\nabla\theta^N\|_{L^2}^{1-\alpha} \|\boldsymbol{v}^N\|_{\boldsymbol{L}^2}^\alpha \|\nabla \boldsymbol{v}^N\|_{\boldsymbol{L}^2}^{1-\alpha} \end{aligned} \tag{4.51}$$

where $\alpha = 1/2$ for $d = 2$ and $\alpha = 1/4$ if $d = 3$. From (4.49), (4.50) and (4.51), it is immediate that

$$\|\theta_t^N\|_{L^\sigma(0,T;\,(H^1)')} \le C, \tag{4.52}$$

where σ is as before. In a very similar way, it can be shown that

$$\|\boldsymbol{v}_t^N\|_{L^\sigma(0,T;\,\boldsymbol{V}')} \le C. \tag{4.53}$$

Therefore, the classical compactness method can be applied in order to deduce a strong convergence property and we can now pass to the limit in (4.39)–(4.42):

We can extract several subsequences of $\{c^N(t)\}_N$, $\{\theta^N(t)\}_N$ and $\{\boldsymbol{v}^N(t)\}_N$, all them being indexed again with N, with appropriate convergence properties:

$$c^N \to c \text{ weakly in } L^2(0,T;H^1),\ \text{weakly-}* \text{ in } L^\infty(0,T;L^2) \text{ and strongly in } L^2(0,T;L^2) \quad (4.54)$$
$$\theta^N \to \theta \text{ weakly in } L^2(0,T;\mathcal{H}_\theta),\ \text{weakly-}* \text{ in } L^\infty(0,T;L^2) \text{ and strongly in } L^2(0,T;L^2) \quad (4.55)$$
$$\boldsymbol{v}^N \to \boldsymbol{v} \text{ weakly in } L^2(0,T;\boldsymbol{V}),\ \text{weakly-}* \text{ in } L^\infty(0,T;\boldsymbol{H}) \text{ and strongly in } L^2(0,T;\boldsymbol{H}) \quad (4.56)$$

These sequences can be chosen in such way that they converge a.e. in Q^T.

Let $\phi \in C^1([0,T])$ such that $\phi(T) = 0$. If we multiply (4.41) by $\phi(t)$ and we integrate in time, we obtain:

$$-\int_0^T \langle \boldsymbol{v}^N, \boldsymbol{w}_k\rangle \phi'(t)\,dt + \iint_{Q^T} (\boldsymbol{v}^N\cdot\nabla)\boldsymbol{v}^N \cdot \boldsymbol{w}_k\,dx\ \phi(t)\,dt + \iint_{Q^T} \nu\nabla\boldsymbol{v}^N\cdot\nabla\boldsymbol{w}_k\,dx\ \phi(t)\,dt$$

$$= -\iint_{Q^T} \widetilde{F}_i^\epsilon(c^N,\theta^N)\boldsymbol{v}^N\cdot\boldsymbol{w}_k\,dx\ \phi(t)\,dt + \iint_{Q^T} \widetilde{\boldsymbol{F}}_e(c^N,\theta^N)\cdot\boldsymbol{w}_k\,dx\ \phi(t)\,dt$$

$$+\ \phi(0)\int_\Omega \boldsymbol{P}_{\boldsymbol{v},N}(\boldsymbol{v}_0)\cdot\boldsymbol{w}_k\,dx$$

Using (4.54)–(4.56) and the a.e. convergence and letting $N \to +\infty$, we obtain the following for all $k \in \mathbb{N}$:

$$-\int_0^T \langle \boldsymbol{v}, \boldsymbol{w}_k\rangle \phi'(t)\,dt + \iint_{Q^T} (\boldsymbol{v}\cdot\nabla)\boldsymbol{v} \cdot \boldsymbol{w}_k\,dx\ \phi(t)\,dt + \iint_{Q^T} \nu\nabla\boldsymbol{v}\cdot\nabla\boldsymbol{w}_k\,dx\ \phi(t)\,dt$$

$$= -\iint_{Q^T} \widetilde{F}_i^\epsilon(c,\theta)\boldsymbol{v}\cdot\boldsymbol{w}_k\,dx\ \phi(t)\,dt + \iint_{Q^T} \widetilde{\boldsymbol{F}}_e(c,\theta)\cdot\boldsymbol{w}_k\,dx\ \phi(t)\,dt \quad (4.57)$$

$$+\ \phi(0)\int_\Omega \boldsymbol{v}_0\cdot\boldsymbol{w}_k\,dx$$

By density and continuity arguments, (4.57) still holds if we replace $\boldsymbol{w}_k$ by an arbitrary function $\boldsymbol{w} \in \boldsymbol{V}$. Therefore, $\boldsymbol{v}$ satisfies (4.33). Similarly, we can prove that c and θ satisfy (4.31) and (4.32), respectively. Also, by using standard arguments it is possible to see that $\boldsymbol{v}(0) = \boldsymbol{v}_0$, $\theta(0) = \theta_0$ and $c(0) = c_0$.

Finally, in view of proposition 8, we see that $(c, \theta, \boldsymbol{v})$ is a weak solution of the regularized problem (4.13)–(4.21).

■

We will now prove that, when $d = 2$, (4.13)–(4.21) possesses at most one solution:

Theorem 14. *Assume that* $d = 2$*. Then* (4.13)–(4.21) *possesses exactly one weak solution.*

Proof: Assume that $(c^1, \theta^1, \boldsymbol{v}^1)$ and $(c^2, \theta^2, \boldsymbol{v}^2)$ are weak solutions of the regularized problem and set $(c, \theta, \boldsymbol{v}) = (c^1, \theta^1, \boldsymbol{v}^1) - (c^2, \theta^2, \boldsymbol{v}^2)$. Then we have:

$$c_t + \nabla\cdot(\boldsymbol{v}^1 c_l(c^1,\theta^1) - \boldsymbol{v}^2 c_l(c^2,\theta^2) - D\nabla c) = 0 \quad (4.58)$$
$$\theta_t + \nabla\cdot(\boldsymbol{v}^1\theta^1 - \boldsymbol{v}^2\theta^2 - \chi\nabla\theta) = 0 \quad (4.59)$$
$$\boldsymbol{v}_t + \nabla\cdot(\boldsymbol{v}^1\otimes\boldsymbol{v}^1 - \boldsymbol{v}^2\otimes\boldsymbol{v}^2 - \nu\nabla\boldsymbol{v}) + F_i^1\boldsymbol{v}^1 - F_i^2\boldsymbol{v}^2 + \nabla p = \boldsymbol{F}_e(c^1,\theta^1) - \boldsymbol{F}_e(c^2,\theta^2) \quad (4.60)$$
$$\nabla\cdot\boldsymbol{v} = 0 \quad (4.61)$$

for some p, where we have put $F_i^k = F_i^\epsilon(c^k,\theta^k)$ for $k=1,2$. By summing and substracting $\nabla\cdot\big(\boldsymbol{v}^1 c_l(c^2,\theta^2)\big)$ in (4.58), $\boldsymbol{v}^1\theta^2$ in (4.59), and $\boldsymbol{v}^1\otimes\boldsymbol{v}^2, F_i^1\boldsymbol{v}^2$ in (4.60), we obtain:

$$\begin{aligned} c_t+\nabla\cdot\big(\boldsymbol{v}^1[c_l^1-c_l^2]+\boldsymbol{v}c_l^2-D\nabla c\big) &= 0 && (4.62)\\ \theta_t+\nabla\cdot(\boldsymbol{v}^1\theta+\boldsymbol{v}\theta^2-\chi\nabla\theta) &= 0 && (4.63)\\ \boldsymbol{v}_t+\nabla\cdot(\boldsymbol{v}^1\otimes\boldsymbol{v}-\boldsymbol{v}\otimes\boldsymbol{v}^2-\nu\nabla\boldsymbol{v})+F_i^1\boldsymbol{v}+(F_i^1-F_i^2)\boldsymbol{v}^2+\nabla p &= (\beta_\theta\theta+\beta_c(c_l^1-c_l^2))\boldsymbol{g} && (4.64)\\ \nabla\cdot\boldsymbol{v} &= 0 && (4.65)\end{aligned}$$

Here, we have put $c_l^k = c_l(c^k,\theta^k)$ for $k=1,2$. Now we multiply (4.62)–(4.64) by $c,\theta,\boldsymbol{v}$ respectively and we integrate:

$$\frac{1}{2}\frac{d}{dt}\|c\|_{L^2}^2+\frac{D}{2}\|\nabla c\|_{L^2}^2=\int_\Omega c_l^2\boldsymbol{v}\cdot\nabla c\,dx+\int_\Omega[c_l^1-c_l^2]\boldsymbol{v}^1\cdot\nabla c\,dx \tag{4.66}$$

$$\frac{1}{2}\frac{d}{dt}\|\theta\|_{L^2}^2+\frac{\chi}{2}\|\nabla\theta\|_{L^2}^2=\int_\Omega\theta^2\boldsymbol{v}\cdot\nabla\theta\,dx \tag{4.67}$$

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\boldsymbol{v}\|_{\boldsymbol{L}^2}^2+\frac{\nu}{2}\|\nabla\boldsymbol{v}\|_{\boldsymbol{L}^2}^2+\int_\Omega F_i^1|\boldsymbol{v}|^2\,dx &= -\int_\Omega\nabla\cdot(\boldsymbol{v}\otimes\boldsymbol{v}^2)\cdot\boldsymbol{v}\,dx\\ &\quad-\int_\Omega(F_i^1-F_i^2)\boldsymbol{v}^2\cdot\boldsymbol{v}\,dx+\int_\Omega(\beta_\theta\theta+\beta_c(c_l^1-c_l^2))\boldsymbol{g}\cdot\boldsymbol{v}\,dx\end{aligned} \tag{4.68}$$

But, in view of (4.22), we have:

$$\left|\int_\Omega c_l^2\boldsymbol{v}\cdot\nabla c\,dx\right|\le\varepsilon\|\nabla c\|_{L^2}^2+C_\varepsilon\|\boldsymbol{v}\|_{\boldsymbol{L}^2}^2 \tag{4.69}$$

On the other hand,

$$\begin{aligned}\left|\int_\Omega\big[c_l^1-c_l^2\big]\boldsymbol{v}^1\cdot\nabla c\,dx\right| &\le C\int_\Omega(|c|+|\theta|)\,|\boldsymbol{v}^1|\,|\nabla c|\,dx\\ &\le C\,(\|c\|_{L^4}+\|\theta\|_{L^4})\,\|\boldsymbol{v}^1\|_{\boldsymbol{L}^4}\|\nabla c\|_{L^2}\\ &\le C\left(\|c\|_{L^2}^{1/2}\|\nabla c\|_{L^2}^{1/2}+\|\theta\|_{L^2}^{1/2}\|\nabla\theta\|_{L^2}^{1/2}\right)\|\boldsymbol{v}^1\|_{\boldsymbol{L}^4}\|\nabla c\|_{L^2}\\ &\le\varepsilon\|\nabla c\|_{L^2}^2+C_\varepsilon\|\boldsymbol{v}^1\|_{\boldsymbol{L}^4}^4\|c\|_{L^2}^2+\varepsilon\|\nabla c\|_{L^2}^{4/3}\|\nabla\theta\|_{L^2}^{2/3}+C_\varepsilon\|\boldsymbol{v}^1\|_{\boldsymbol{L}^4}^4\|\theta\|_{L^2}^2\\ &\le C\varepsilon\|\nabla c\|_{L^2}^2+C\varepsilon\|\nabla\theta\|_{L^2}^2+C_\varepsilon\|\boldsymbol{v}^1\|_{\boldsymbol{L}^4}^4\|\theta\|_{L^2}^2\end{aligned} \tag{4.70}$$

Let us introduce the function $H_\epsilon(f)=M_0f^2(1-f+\epsilon)^{-3}$, where $0\le f\le 1$. From (4.10), there exists $\hat f\in(0,1)$ such that

$$\begin{aligned}F_i^1-F_i^2 &= F_i^1(c^1,\theta^1)-F_i^2(c^2,\theta^2)=H_\epsilon(f_s(c^1,\theta^1))-H_\epsilon(f_s(c^2,\theta^2))\\ &= H'_\epsilon(\hat f)(f_s(c^1,\theta^1)-f_s(c^2,\theta^2))=H'_\epsilon(\hat f)(a_s^{1,2}c+b_s^{1,2}\theta)\end{aligned}$$

with $a_s^{1,2},b_s^{1,2}\in L^\infty(\Omega)$. Then

$$\begin{aligned}\left|-\int_\Omega(F_i^1-F_i^2)\boldsymbol{v}^2\cdot\boldsymbol{v}\,dx\right| &= \left|-\int_\Omega H'_\epsilon(\hat f)(a_s^{1,2}c+b_s^{1,2})\boldsymbol{v}^2\cdot\boldsymbol{v}\,dx\right|\\ &\le C_1\int_\Omega|c||\boldsymbol{v}^2||\boldsymbol{v}|\,dx+C_2\int_\Omega|\theta||\boldsymbol{v}^2||\boldsymbol{v}|\,dx\end{aligned} \tag{4.71}$$

Arguing as before, we thus find:

$$\left| -\int_\Omega \left(F_i^1 - F_i^2\right) \boldsymbol{v}^2 \cdot \boldsymbol{v}\, dx \right| \le C\varepsilon \left(\|\nabla c\|_{L^2}^2 + \|\nabla\theta\|_{L^2}^2 + \|\nabla \boldsymbol{v}\|_{\boldsymbol{L}^2}^2\right)$$
$$+ C_\varepsilon \|\boldsymbol{v}^2\|_{\boldsymbol{L}^4}^4 \left(\|c\|_{L^2}^2 + \|\theta\|_{L^2}^2\right) \tag{4.72}$$

Finally, since $\boldsymbol{g} \in \boldsymbol{L}^\infty(\Omega)$ we also have

$$\left| \int_\Omega (\beta_\theta \theta + \beta_c(c_l^1 - c_l^2))\boldsymbol{g} \cdot \boldsymbol{v}\, dx \right| \le C_1 \int_\Omega |\theta||\boldsymbol{v}|\, dx + C_2 \int_\Omega |c_l^1 - c_l^2||\boldsymbol{v}|\, dx$$
$$\le C_3 \int_\Omega |c||\boldsymbol{v}|\, dx + C_4 \int_\Omega |\theta||\boldsymbol{v}|\, dx \tag{4.73}$$
$$\le C \left(\|c\|_{L^2}^2 + \|\theta\|_{L^2}^2 + \|\boldsymbol{v}\|_{\boldsymbol{L}^2}^2\right)$$

Therefore, taking into account (4.66)–(4.73), we obtain that

$$\frac{1}{2}\Big(\frac{d}{dt}\|c\|_{L^2}^2 + \|\theta\|_{L^2}^2 + \|\boldsymbol{v}\|_{\boldsymbol{L}^2}^2\Big) + C\left(\|\nabla c\|_{L^2}^2 + \|\nabla\theta\|_{L^2}^2 + \|\nabla \boldsymbol{v}\|_{\boldsymbol{L}^2}^2\right)$$
$$\le C\left(1 + \|\boldsymbol{v}^1\|_{\boldsymbol{L}^4}^4 + \|\boldsymbol{v}^2\|_{\boldsymbol{L}^4}^4\right)\left(\|c\|_{L^2}^2 + \|\theta\|_{L^2}^2 + \|\boldsymbol{v}\|_{\boldsymbol{L}^2}^2\right)$$

and, from Gronwall lemma and the fact that $\boldsymbol{v}^i \in L^4(0,T;\boldsymbol{L}^4)$, we find that $c = \theta = 0$, $\boldsymbol{v} = \boldsymbol{0}$ and $(c^1, \theta^1, \boldsymbol{v}^1)$ and $(c^2, \theta^2, \boldsymbol{v}^2)$ must coincide.

This ends the proof.

■

4.4 Optimal control and solidification processes

Let us consider some control problems for (4.1)–(4.4): we want to control the growth of a solidification front (and its geometrical form) by imposing a heating mechanism acting on ω, a non-empty subset of Ω such that $\omega \subset\subset \Omega$.

A mathematical formulation can be obtained under the form of an optimal control problem. More precisely, we will try to minimize an appropriate cost function subject to equations (4.1)–(4.4) and some additional constraints on the control k.

We propose several choices for the cost functional (see equations (4.75) and (4.76) below). In each case, our purpose in this Section is to achieve three main tasks:

- To prove the existence (and maybe uniqueness) of an optimal control.
- To characterize (or, at least, obtain necessary conditions) the optimality of a control.
- To compute the optimal controls.

Let $J = J(k, c, \theta, \boldsymbol{v})$ be a cost function. The considered optimal control problem will have the general form:

$$\begin{cases} \text{Find } (k^*, c^*, \theta^*, \boldsymbol{v}^*) \in \mathcal{E} \text{ such that} \\ J(k^*, c^*, \theta^*, \boldsymbol{v}^*) = \min\limits_{(k,c,\theta,\boldsymbol{v}) \in \mathcal{E}} J(k, c, \theta, \boldsymbol{v}) \end{cases} \tag{4.74}$$

where $\mathcal{E}$ is a non-empty set that will be specified later. In practice, any $(k, c, \theta, \boldsymbol{v}) \in \mathcal{E}$ will be assumed to satisfy (4.13)–(4.21). Furthermore, it will be realistic to consider appropriate constraints on k, i.e., to impose that k belongs to a set of *admissible controls* $\mathcal{U}_{ad} \subset L^2(\omega \times (0,T))$.

Let α, β, γ be nonnegative constants and let us assume that $N > 0$. We will consider the following two possible choices of J that seem reasonable:

First Choice Let $c_d, \theta_d \in L^2(Q^T)$ and $\boldsymbol{v}_d \in \boldsymbol{L}^2(Q^T)$ be given. Then we set

$$\begin{aligned} J_1(k, c, \theta, \boldsymbol{v}) &= \frac{\alpha}{2} \iint_{Q^T} |c - c_d|^2 \, dx \, dt + \frac{\beta}{2} \iint_{Q^T} |\theta - \theta_d|^2 \, dx \, dt \\ &+ \frac{\gamma}{2} \iint_{Q^T} |\boldsymbol{v} - \boldsymbol{v}_d|^2 \, dx \, dt + \frac{N}{2} \iint_{\omega \times (0,T)} |k|^2 \, dx \, dt \end{aligned} \tag{4.75}$$

Second Choice Let $c_e, \theta_e \in L^2(\Omega)$ and $\boldsymbol{v}_e \in \boldsymbol{L}^2(\Omega)$ be given. We now set

$$\begin{aligned} J_2(k, c, \theta, \boldsymbol{v}) &= \frac{\alpha}{2} \int_{\Omega} |c(\boldsymbol{x}, T) - c_e(\boldsymbol{x})|^2 \, dx + \frac{\beta}{2} \int_{\Omega} |\theta(\boldsymbol{x}, T) - \theta_e(\boldsymbol{x})|^2 \, dx \\ &+ \frac{\gamma}{2} \int_{\Omega} |\boldsymbol{v}(\boldsymbol{x}, T) - \boldsymbol{v}_e(\boldsymbol{x})|^2 \, dx + \frac{N}{2} \iint_{\omega \times (0,T)} |k|^2 \, dx \, dt \end{aligned} \tag{4.76}$$

4.4.1 The existence of optimal controls

Let us fix a closed convex subset $\mathcal{U}_{ad} \subset L^2(\omega \times (0,T))$. We introduce the set

$$\mathcal{E} \stackrel{def}{=} \{(k, c, \theta, \boldsymbol{v}) \ : \ k \in \mathcal{U}_{ad} \ , \ (c, \theta, \boldsymbol{v}) \text{ satisfies, together with } k \text{ and some } p, \text{ (4.13)–(4.21)}\}.$$

Notice that $\mathcal{E} \subset L^2(\omega \times (0,T)) \times E$, where E is the energy space for the weak solutions to (4.13)–(4.21), i.e. the space of triplets $(c, \theta, \boldsymbol{v})$ satisfying (4.28)–(4.30). Let us consider the control problem (4.74).

The following result holds:

Theorem 15. *Assume that $\mathcal{U}_{ad}$ is weakly closed in $L^2(\omega \times (0,T))$ and the followings hypotheses are satisfied:*

1. *Either J is a coercive functional, or $\mathcal{U}_{ad}$ is a bounded set.*
2. *J is sequentially weakly-$*$ lower semicontinuous: if $(k_n, c_n, \theta_n, \boldsymbol{v}_n) \stackrel{*}{\rightharpoonup} (k, c, \theta, \boldsymbol{v})$ in the norm of E, then*

$$\liminf_{n \to +\infty} J(k_n, c_n, \theta_n, \boldsymbol{v}_n) \geq J(k, c, \theta, \boldsymbol{v}).$$

Then, there exists a solution of (4.74)*, that is, an optimal control and associated state.*

Remark 14. The hypotheses in this result are satisfied when $\mathcal{U}_{ad}$ is, for instance, one of the sets

$$\begin{aligned} \mathcal{U}_{ad} &= L^2(\omega \times (0,T)) \\ \mathcal{U}_{ad} &= \left\{ k \in L^2(\omega \times (0,T)) \ : \ \|k\|_{L^2(\omega \times (0,T))} \leq R \right\} \\ \mathcal{U}_{ad} &= L^2(\omega \times (0,T)) \cap L^\infty(\omega \times (0,T)) \end{aligned}$$

and J has the form given in (4.75) or (4.76). Consequently, in those cases, there exists at least one solution of (4.74).

4.4.2 The optimality system

Next, we determine the optimality system associated to the previous control problems (see Section 4.5 for a more detailed computation in the context of a time optimal control problem). In the case of the functional defined by (4.75), any optimal control and the associated state $(c, \theta, \boldsymbol{v})$ and adjoint state $(\phi, \psi, \boldsymbol{w})$ must satisfy (together with some p and q) the following:

$$\begin{cases} c_t + \boldsymbol{v} \cdot \nabla c_l(c,\theta) - D\Delta c = 0 \\ \theta_t + \boldsymbol{v} \cdot \nabla\theta - \chi\Delta\theta = k1_\omega \\ \boldsymbol{v}_t + (\boldsymbol{v}\cdot\nabla)\boldsymbol{v} - \nu\Delta\boldsymbol{v} + F_i^\epsilon(c,\theta)\boldsymbol{v} + \nabla p = \boldsymbol{F}_e(c,\theta) \\ \nabla\cdot\boldsymbol{v} = 0 \\ (D\nabla c)\cdot\boldsymbol{n} = (\chi\nabla\theta)\cdot\boldsymbol{n} = 0, \ \boldsymbol{v} = \boldsymbol{0} \quad \text{on} \quad \partial\Omega\times(0,T) \\ c(\boldsymbol{x},0) = c^0(\boldsymbol{x}); \quad \theta(\boldsymbol{x},0) = \theta^0(\boldsymbol{x}); \quad \boldsymbol{v}(\boldsymbol{x},0) = \boldsymbol{v}^0(\boldsymbol{x}) \quad \text{in} \quad \Omega \end{cases} \tag{4.77}$$

$$\begin{cases} -\phi_t - \dfrac{\partial c_l}{\partial c}\boldsymbol{v}\cdot\nabla\phi - D\Delta\phi = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial c} - \dfrac{\partial F_i^\epsilon}{\partial c}\boldsymbol{v}\right)\cdot\boldsymbol{w} + \alpha(c - c_d) \\ -\psi_t - \boldsymbol{v}\cdot\nabla\psi - \dfrac{\partial c_l}{\partial\theta}\boldsymbol{v}\cdot\nabla\phi - \chi\Delta\psi = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial \theta} - \dfrac{\partial F_i^\epsilon}{\partial \theta}\boldsymbol{v}\right)\cdot\boldsymbol{w} + \beta(\theta-\theta_d) \\ -\boldsymbol{w}_t - \nu\Delta\boldsymbol{w} - (\boldsymbol{v}\cdot\nabla)\boldsymbol{w} + (\nabla\boldsymbol{v})^t\boldsymbol{w} + F_i^\epsilon(c,\theta)\boldsymbol{w} + \nabla q \\ \qquad = -\phi\nabla c_l(c,\theta) - \psi\nabla\theta + \gamma(\boldsymbol{v} - \boldsymbol{v}_d) \\ \nabla\cdot\boldsymbol{w} = 0 \\ (D\nabla\phi)\cdot\boldsymbol{n} = (\chi\nabla\psi)\cdot\boldsymbol{n} = 0; \ \boldsymbol{w} = \boldsymbol{0} \quad \text{on} \quad \partial\Omega\times(0,T) \\ \phi(\boldsymbol{x},T) = 0; \ \psi(\boldsymbol{x},T) = 0; \ \boldsymbol{w}(\boldsymbol{x},T) = \boldsymbol{0} \quad \text{in} \quad \Omega \end{cases} \tag{4.78}$$

$$\iint_{\omega\times(0,T)} (\psi + Nk)(k' - k)\,dxdt \geq 0 \quad \forall k' \in \mathcal{U}_{ad}, \ k \in \mathcal{U}_{ad}. \tag{4.79}$$

In (4.78), it is assumed that the partial derivatives of F_i^ϵ and $\boldsymbol{F}_e$ are computed at (c, θ).

For the second choice of the functional, defined by (4.76), the optimality system is given by (4.77),

$$
\begin{cases}
-\phi_t - \dfrac{\partial c_l}{\partial c}\boldsymbol{v}\cdot\nabla\phi - D\Delta\phi = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial c} - \dfrac{\partial F_i^\epsilon}{\partial c}\boldsymbol{v}\right)\cdot\boldsymbol{w} \\[2ex]
-\psi_t - \boldsymbol{v}\cdot\nabla\psi - \dfrac{\partial c_l}{\partial \theta}\boldsymbol{v}\cdot\nabla\phi - \chi\Delta\psi = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial \theta} - \dfrac{\partial F_i^\epsilon}{\partial \theta}\boldsymbol{v}\right)\cdot\boldsymbol{w} \\[2ex]
-\boldsymbol{w}_t - (\boldsymbol{v}\cdot\nabla)\boldsymbol{w} + (\nabla\boldsymbol{v})^t\boldsymbol{w} + \nabla q = -\phi\nabla c_l - \psi\nabla\theta \\[2ex]
\nabla\cdot\boldsymbol{w} = 0 \\[2ex]
(D\nabla\phi)\cdot\boldsymbol{n} = (\chi\nabla\psi)\cdot\boldsymbol{n} = 0;\ \boldsymbol{w} = \boldsymbol{0} \quad \text{on} \quad \partial\Omega\times(0,T) \\[2ex]
\phi(\boldsymbol{x},T) = \alpha(c(\boldsymbol{x},T) - c_e(\boldsymbol{x})) \quad \text{in} \quad \Omega \\[2ex]
\psi(\boldsymbol{x},T) = \beta(\theta(\boldsymbol{x},T) - \theta_e(\boldsymbol{x})) \quad \text{in} \quad \Omega \\[2ex]
\boldsymbol{w}(\boldsymbol{x},T) = \gamma(\boldsymbol{v}(\boldsymbol{x},T) - \boldsymbol{v}_e(\boldsymbol{x})) \quad \text{in} \quad \Omega
\end{cases}
\tag{4.80}
$$

and (4.79).

In the most simple case, $\mathcal{U}_{ad} = L^2(\omega\times(0,T))$, and (4.79) means that

$$k = -\frac{1}{N}\psi \quad \text{in} \quad \omega\times(0,T). \tag{4.81}$$

More generally, whenever $\mathcal{U}_{ad}$ is a closed convex set of $L^2(\omega\times(0,T))$, (4.79) is equivalent to

$$k = P_{\mathcal{U}_{ad}}\left(-\frac{1}{N}\psi|_{\omega\times(0,T)}\right), \tag{4.82}$$

where $P_{\mathcal{U}_{ad}} : L^2(\omega\times(0,T)) \mapsto \mathcal{U}_{ad}$ is the usual orthogonal projection operator.

4.4.3 Some algorithms

We will now propose some iterative algorithms to compute the solution of the previous optimality systems.

In Table 4.1 we present a first algorithm, corresponding to (4.77)–(4.79).

Algorithm 4.1
a. Choose $k^0 \in \mathcal{U}_{ad}$;
b. Then, for given $n \geq 0$ and $k^n \in \mathcal{U}_{ad}$, do the following until convergence (see Remark 15);
1. Solve (4.77) with $k = k^n$, to obtain the state $(c^n, \theta^n, \boldsymbol{v}^n)$;
2. Solve (4.78) with $(c, \theta, \boldsymbol{v}) = (c^n, \theta^n, \boldsymbol{v}^n)$, to obtain the adjoint state $(\phi^n, \psi^n, \boldsymbol{w}^n)$;
3. Use (4.79) with $\psi = \psi^n$, to compute the new control k^{n+1}.

Table 4.1: Algorithm for the solution of the optimality system (4.77)–(4.79).

Let us assume that (4.77) possesses exactly one weak solution $(c, \theta, \boldsymbol{v})$ for each $k \in \mathcal{U}_{ad}$ (this is the case if $d = 2$). Then algorithm 4.1 must be viewed as a classical fixed-point iterative method for the mapping $\Lambda : \mathcal{U}_{ad} \to \mathcal{U}_{ad}$, which is defined as follows:

$$\Lambda(k) = P_{\mathcal{U}_{ad}}\left(-\frac{1}{N}\psi|_{\omega\times(0,T)}\right).$$

Here, ψ is, together with $\phi, \boldsymbol{w}$ and q, the solution to (4.78), and $(c, \theta, \boldsymbol{v})$ is, together with some p, the solution to (4.77).

Remark 15. The convergence criteria can be of the form

$$\|k^{n+1} - k^n\|_{L^2(\omega\times(0,T))} < \rho\|k^{n+1}\|_{L^2(\omega\times(0,T))}$$

for ρ small enough.

Since (4.77) is nonlinear and we have to solve this system by using an iterative scheme, it is reasonable to introduce a variant where we perform mixed loops. This is described in Table 4.2.

Algorithm 4.2
a. Choose $k^0 \in \mathcal{U}_{ad}$;
b. Then, for given $n \geq 0$ and $k^n \in \mathcal{U}_{ad}$, do the following until convergence (see Remark 15);
1. Solve (4.77) with $k = k^n$ and c_l, F_i^ϵ and $\boldsymbol{F}_e$ computed at (c^{n-1}, θ^{n-1}), to obtain the state $(c^n, \theta^n, \boldsymbol{v}^n)$;
2. Solve (4.78) with $(c, \theta, \boldsymbol{v}) = (c^n, \theta^n, \boldsymbol{v}^n)$, to obtain the adjoint state $(\phi^n, \psi^n, \boldsymbol{w}^n)$;
3. Use (4.79) with $\psi = \psi^n$, to compute the new control k^{n+1}.

Table 4.2: Modification of the algorithm in Table 4.1 in order to solve the optimality system (4.77)–(4.79).

In Table 4.3 we present the algorithm described in Table 4.1 in the case of the second choice of J. The corresponding modified version is given in Table 4.4.

Algorithm 4.3
a. Choose $k^0 \in \mathcal{U}_{ad}$;
b. Then, for given $n \geq 0$ and $k^n \in \mathcal{U}_{ad}$, do the following until convergence (see Remark 15);
1. Solve (4.77) with $k = k^n$, to obtain the state $(c^n, \theta^n, \boldsymbol{v}^n)$;
2. Solve (4.80) with $(c, \theta, \boldsymbol{v}) = (c^n, \theta^n, \boldsymbol{v}^n)$, to obtain the adjoint state $(\phi^n, \psi^n, \boldsymbol{w}^n)$;
3. Use (4.79) with $\psi = \psi^n$, to compute the new control k^{n+1}.

Table 4.3: Algorithm for the solution of the optimality system (4.77), (4.80), (4.79).

Algorithm 4.4	
a.	Choose $k^0 \in \mathcal{U}_{ad}$;
b.	Then, for given $n \geq 0$ and $k^n \in \mathcal{U}_{ad}$, do the following until convergence (see Remark 15);
1.	Solve (4.77) with $k = k^n$ and c_l, F_i^ϵ and $\boldsymbol{F}_e$ computed at (c^{n-1},θ^{n-1}), to obtain the state $(c^n, \theta^n, \boldsymbol{v}^n)$;
2.	Solve (4.80) with $(c, \theta, \boldsymbol{v}) = (c^n, \theta^n, \boldsymbol{v}^n)$, to obtain the adjoint state $(\phi^n, \psi^n, \boldsymbol{w}^n)$;
3.	Use (4.79) with $\psi = \psi^n$, to compute the new control k^{n+1}.

Table 4.4: Modification of the algorithm in Table 4.3.

Another possibility is to consider gradient-type methods. This relies on the computation of the gradient of the function $k \mapsto j(k)$, where $j(k) = J(k, c, \theta, \boldsymbol{v})$. In the case of (4.75), assuming again that (4.77) possesses exactly one solution for each k, the gradient of j at k in the direction of h is

$$\langle j'(k), h \rangle = \iint_{\omega \times (0,T)} (Nk + \psi)\, h \, dx \, dt, \tag{4.83}$$

where ψ is, together with ϕ, $\boldsymbol{w}$ and q, the solution to (4.78). An algorithm is presented in Table 4.5 in the particular and simple case in which $\mathcal{U}_{ad} = L^2(\omega \times (0,T))$.

Algorithm 4.5	
1.	Given k^0, for $n = 0, 1, \ldots$ do the following steps until convergence;
2.	Solve (4.77) with $k = k^n$, to obtain $(c^n, \theta^n, \boldsymbol{v}^n)$;
3.	Solve (4.78) with $(c, \theta, \boldsymbol{v}) = (c^n, \theta^n, \boldsymbol{v}^n)$, to obtain $(\phi^n, \psi^n, \boldsymbol{w}^n)$;
4.	Compute the gradient $g^n = (Nk^n + \psi^n)\,|_{\omega \times (0,T)}$;
5.	Take $k^{n+1} = k^n - \rho g^n$, for $\rho > 0$ fixed.

Table 4.5: The fixed step gradient algorithm to solve the system (4.77)–(4.79) with $\mathcal{U}_{ad} = L^2(\omega \times (0,T))$.

4.5 A time optimal control for the solidification problem

In this Section we will study the existence of a time optimal control for (4.13)–(4.21). Then, we will try to characterize the solutions in terms of appropriate optimality conditions.

Let us fix $T_0 > 0$ and let us introduce a closed convex set $\mathcal{U}_{ad} \subset L^2(\omega \times (0,T_0))$ and the set

$$\mathcal{E}_0 = \Big\{ (k, c, \theta, \boldsymbol{v}) \;:\; k \in \mathcal{U}_{ad},\ (c, \theta, \boldsymbol{v}) \text{ solves } (4.13)-(4.21) \text{ in } \Omega \times (0, T_0) \Big\}.$$

Again $\mathcal{E}_0 \subset L^2(\omega \times (0,T_0)) \times E_0$, where E_0 is the energy space for the solutions to (4.13)–(4.21) in $\Omega \times (0,T_0)$. Then, we set

$$I(k, c, \theta, \boldsymbol{v}) = \frac{1}{2} T^*(\theta; \theta_e, \delta)^2 + \frac{N}{2} \iint_{\omega \times (0,T_0)} |k|^2 \, dx \, dt \tag{4.84}$$

where $\theta_e \in L^2(\Omega)$ and, by definition,

$$T^*(\theta; \theta_e, \delta) = \inf\{ T \in [0, T_0] \;:\; \|\theta(\cdot, T) - \theta_e\|_{L^2} \leq \delta \}.$$

We will consider the following control problem, where we are looking for an optimal time:

$$\begin{cases} \text{Find } (\hat{k}, \hat{c}, \hat{\theta}, \hat{\boldsymbol{v}}) \in \mathcal{E}_0 \text{ such that} \\ I(\hat{k}, \hat{c}, \hat{\theta}, \hat{\boldsymbol{v}}) = \min_{(k,c,\theta,\boldsymbol{v}) \in \mathcal{E}_0} I(k, c, \theta, \boldsymbol{v}) \end{cases} \tag{4.85}$$

Theorem 16. *There exists at least one solution to* (4.85)*.*

Proof: Since it is immediate that $\mathcal{U}_{ad}$ is weakly closed in $L^2(\omega \times (0, T_0))$ and I is coercive, we only have to check that this functional is sequentially weakly-$*$ lower semicontinuous for the norm of E_0.

Let $(k_n, c_n, \theta_n, \boldsymbol{v}_n)$ be a sequence in $\mathcal{E}_0$ such that $k_n \rightharpoonup \hat{k}$ in $L^2(\omega \times (0, T_0))$ and $(c_n, \theta_n, \boldsymbol{v}_n) \overset{*}{\rightharpoonup} (\hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$ in E_0. Then

$$\liminf_{n\to+\infty} \iint_{\omega\times(0,T_0)} |k_n|^2 \, dx \, dt \geq \iint_{\omega\times(0,T_0)} |\hat{k}|^2 \, dx \, dt.$$

On the other hand, if we set $T_n^* := T^*(\theta_n; \theta_e, \delta)$ and $T^* := T^*(\hat{\theta}; \theta_e, \delta)$, we also have

$$\liminf_{n\to+\infty} \; T_n^* \geq T^*. \tag{4.86}$$

Indeed, if this assertion were false, we could assume the existence of $\widetilde{T}$ such that

$$\widetilde{T} = \lim_{n\to+\infty} T_n^* < T^*. \tag{4.87}$$

We will use the following result, whose proof is postponed to the end of this paragraph:

Lemma 9. *Under the assumption* (4.87)*, we have:*

$$(\hat{\theta}(\widetilde{T}) - \theta_e, \psi)_{L^2} \leq \|\psi\|_{L^2} \quad \forall \psi \in H_0^1(\Omega). \tag{4.88}$$

But, in view of the definition of T^*, we must have $\|\hat{\theta}(\widetilde{T}) - \theta_e\|_{L^2} > \delta$, which is the opposite to (4.88), an absurd. We have then proved that

$$\liminf_{n\to+\infty} \; T_n^* \geq T^*,$$

which completes the proof of theorem 16. ■

Proof of lemma 1. We can write that

$$\begin{aligned} |(\hat{\theta}(\widetilde{T}) - \theta_e, \psi)_{L^2}| &\leq |(\hat{\theta}(\widetilde{T}) - \hat{\theta}(T_n^*), \psi)_{L^2}| \\ &\quad + |(\hat{\theta}(T_n^*) - \theta_n(T_n^*), \psi)_{L^2}| + |(\theta_n(T_n^*) - \theta_e, \psi)_{L^2}| \end{aligned} \tag{4.89}$$

Let us estimate the terms in the right hand side of (4.89). To this end, we use the following well known result from J. Simon (see [42]):

Lemma 10. *Let us consider three Banach spaces $X \subset B \subset Y$ with compact embedding $X \mapsto B$ and continuous embedding $B \mapsto Y$. Let F be bounded in $L^\infty(0, T; X)$ and let $\partial F/\partial t = \{\partial f/\partial t \;:\; f \in F\}$ be bounded in $L^r(0, T; Y)$, where $r > 1$. Then F is relatively compact in $\mathcal{C}^0([0, T]; B)$.*

First of all, we will prove that there exists $C > 0$ such that $\|\theta_{n,t}\|_{L^\sigma(H^{-1})} \leq C$, where $\sigma = 2$ if $d = 2$ and $\sigma = 4/3$ if $d = 3$. Taking into account that $\boldsymbol{v}_n \in \boldsymbol{V}$, we obtain from (4.14)

$$\theta_{n,t} = k_n 1_\omega + \chi\Delta\theta_n - \nabla\cdot(\theta_n \boldsymbol{v}_n)\,. \tag{4.90}$$

Now,

- $k_n 1_\omega$, $\chi\Delta\theta_n$ are bounded in $L^2(0, T_0; H^{-1}(\Omega))$
- If $d = 2$, $\nabla\cdot(\theta_n \boldsymbol{v}_n)$ is bounded in $L^2(0, T_0; H^{-1}(\Omega))$. Indeed, it is easy to see that $L^2(0, T_0; H^1(\Omega)) \cap L^\infty(0, T_0; L^2(\Omega))$ is continuously embedded in $L^4(0, T_0; L^4(\Omega))$, whence θ_n is bounded in this space; similarly, $\boldsymbol{v}_n$ is bounded in $L^4(0, T_0; \boldsymbol{L}^4(\Omega))$; therefore, $\theta_n \boldsymbol{v}_n$ is bounded in $L^2(0, T_0; \boldsymbol{L}^2(\Omega))$ and the assertion holds.
- If $d = 3$, $\nabla\cdot(\theta_n \boldsymbol{v}_n)$ is bounded in $L^{4/3}(0, T_0; H^{-1}(\Omega))$. Indeed, in this case $L^2(0, T_0; H^1(\Omega)) \cap L^\infty(0, T_0; L^2(\Omega)) \hookrightarrow L^{8/3}(0, T_0; L^4(\Omega))$ (with a continuous embedding; more generally, one has $L^2(0, T_0; H^1(\Omega)) \cap L^\infty(0, T_0; L^2(\Omega)) \hookrightarrow L^a(0, T_0; L^b(\Omega))$ for any $b \in [2, 6]$ and any $a \leq 4b/\left(3(b-2)\right)$; in particular, for $b = 12/5$ we get $a \leq 8/3$); consequently, θ_n is bounded in $L^{8/3}(0, T_0; L^4(\Omega))$; a similar argument shows that $\boldsymbol{v}_n$ is bounded in $L^{8/3}(0, T_0; \boldsymbol{L}^4(\Omega))$ and thus $\theta_n \boldsymbol{v}_n$ is bounded in $L^{4/3}(0, T_0; \boldsymbol{L}^2(\Omega))$.

In view of (4.90), these estimates give the desired conclusion: $\|\theta_{n,t}\|_{L^\sigma(H^{-1})} \leq C$.

Lemma 10 shows that θ_n belongs to a compact set in $\mathcal{C}^0([0, T_0]; B)$ for any Banach space B with $L^2(\Omega) \subset B \subset H^{-1}(\Omega)$, the first embedding being compact. Consequently, $\theta_n \to \hat{\theta}$ strongly in $\mathcal{C}^0([0, T_0]; B)$ and

$$|(\hat{\theta}(T_n^*) - \theta_n(T_n^*), \psi)_{L^2}| \leq C\|\hat{\theta}(T_n^*) - \theta_n(T_n^*)\|_B \|\psi\|_{H_0^1} \to 0. \tag{4.91}$$

Also, since $T_n^* \to \widetilde{T}$ and $\hat{\theta} \in \mathcal{C}^0([0, T_0]; L^2)$, we have $\hat{\theta}(T_n^*) \to \hat{\theta}(\widetilde{T})$ in $L^2(\Omega)$, whence

$$|(\hat{\theta}(\widetilde{T}) - \hat{\theta}(T_n^*), \psi)_{L^2}| \leq \|\hat{\theta}(\widetilde{T}) - \hat{\theta}(T_n^*)\|_{L^2} \|\psi\|_{L^2} \to 0. \tag{4.92}$$

Finally,

$$|(\theta_n(T_n^*) - \theta_e, \psi)_{L^2}| \leq \|\theta_n(T_n^*) - \theta_e\|_{L^2} \|\psi\|_{L^2} \leq \delta\|\psi\|_{L^2} \tag{4.93}$$

by the definition of T_n^*. From (4.89) and (4.91)–(4.93), we deduce the inequality (4.88).

■

4.5.1 The optimality conditions

Once we have shown that problem (4.84)–(4.85) admits at least one optimal solution, our second goal will be to characterize the solutions in terms of appropriate optimality conditions, that is to say, to deduce a system of equations that the optimal solution and an associated adjoint state must satisfy.

If we introduce the functional Φ, with

$$\Phi(T', k) = \frac{1}{2}\left(T'\right)^2 + \frac{N}{2}\iint_{\omega\times(0,T_0)} |k|^2\,dx\,dt \quad \forall (T', k) \in [0, T_0] \times L^2(\omega \times (0, T_0)) \tag{4.94}$$

then problem (4.84)–(4.85) can also be written in the form

$$\left\{\begin{array}{ll} \text{Minimize} & \Phi(T', k) \\ \text{Subject to:} & T' \in [0, T_0],\ k \in \mathcal{U}_{ad} \\ & (k, c, \theta, \boldsymbol{v}) \text{ satisfies (4.13)–(4.21) in } \Omega \times (0, T_0) \\ & \|\theta(\,\cdot\,, T') - \theta_e\|_{L^2} \leq \delta \end{array}\right. \tag{4.95}$$

Theorem 16 asserts the existence of a solution $(\hat{T}, \hat{k})$ to (4.95) with $\hat{k} \in \mathcal{U}_{ad}$, $(\hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$ solving (4.13)–(4.21) for this $\hat{k}$. Let us now give a new (modified) formulation of (4.84)–(4.85).

A reformulation of the control problem

First, we introduce the spaces

$$\begin{aligned} \boldsymbol{Y} &= \mathbb{R} \times L^2(\omega \times (0,T)) \times W(0,T_0) \times X_\sigma(0,T_0) \times Z_\sigma(0,T_0) \\ \boldsymbol{Z} &= \mathbb{R} \times L^2(0,T_0;H^{-1}(\Omega)) \times L^\sigma(0,T_0;H^{-1}(\Omega)) \times L^\sigma(0,T_0;\boldsymbol{V}') \times L^2(\Omega)^2 \times \boldsymbol{H} \end{aligned}$$

where $W(0,T_0)$ (resp. $X_\sigma(0,T_0)$, $Z_\sigma(0,T_0)$) is the Banach space of the functions $c \in L^2(0,T_0;H^1(\Omega))$ (resp. $\theta \in L^2(0,T_0;H^1(\Omega))$, $\boldsymbol{v} \in L^2(0,T_0;\boldsymbol{V})$) such that $c_t \in L^2(0,T_0;H^{-1}(\Omega))$ (resp. $\theta_t \in L^\sigma(0,T_0;H^{-1}(\Omega))$, $\boldsymbol{v}_t \in L^\sigma(0,T_0;\boldsymbol{V}')$). Let $\Xi = (K_0, H_0)$ be the mapping defined by

$$\begin{aligned} K_0(T',k,c,\theta,\boldsymbol{v}) &= \frac{1}{2}\|\theta(T') - \theta_e\|^2_{L^2} - \frac{\delta^2}{2}, \\ H_0(T',k,c,\theta,\boldsymbol{v}) &= (H_1,H_2,H_3,H_4,H_5,H_6)\,(T',k,c,\theta,\boldsymbol{v}). \end{aligned}$$

Here, the functions H_i are given by

$$\begin{aligned} &H_1(T',k,c,\theta,\boldsymbol{v}) = c_t + \boldsymbol{v}\cdot\nabla c_l(c,\theta) - D\Delta c, \\ &H_2(T',k,c,\theta,\boldsymbol{v}) = \theta_t + \boldsymbol{v}\cdot\nabla\theta - \chi\Delta\theta - k1_\omega, \\ &H_3(T',k,c,\theta,\boldsymbol{v}) = \boldsymbol{\xi}, \text{ where } \boldsymbol{\xi} \in L^\sigma(0,T_0;\boldsymbol{V}') \text{ is the unique function satisfying} \\ &\begin{cases} \langle \boldsymbol{\xi}, \boldsymbol{v}\rangle_{\boldsymbol{V}',\boldsymbol{V}} = \langle \boldsymbol{v}_t + (\boldsymbol{v}\cdot\nabla)\boldsymbol{v} - \nu\Delta\boldsymbol{v} + F_i^\epsilon(c,\theta)\boldsymbol{v} - \boldsymbol{F}_e(c,\theta), \boldsymbol{v}\rangle_{\boldsymbol{H}^{-1},\boldsymbol{H}^1_0} \\ \quad \forall \boldsymbol{v} \in \boldsymbol{V}, \text{ a.e in } [0,T_0], \end{cases} \\ &H_4(T',k,c,\theta,\boldsymbol{v}) = c(\cdot,0) - c^0, \\ &H_5(T',k,c,\theta,\boldsymbol{v}) = \theta(\cdot,0) - \theta^0, \\ &H_6(T',k,c,\theta,\boldsymbol{v}) = \boldsymbol{v}(\cdot,0) - \boldsymbol{v}^0, \end{aligned}$$

We will also need to speak of the *indicator* $I_\mathcal{A}$ of a closed convex set $\mathcal{A}$:

$$I_\mathcal{A}(x) = \begin{cases} 0 & \text{if} \quad x \in \mathcal{A} \\ +\infty & \text{if} \quad x \notin \mathcal{A} \end{cases}$$

If we fix the closed convex set $\mathcal{V}_{ad} = [0,T] \times \mathcal{U}_{ad}$, then (4.84)–(4.85) can be rewritten in the following way:

$$\begin{cases} \text{Minimize} \quad \Phi(T',k) + I_{\mathcal{V}_{ad}}(T',k) \\ \text{Subject to:} \quad (T',k,c,\theta,\boldsymbol{v}) \in \boldsymbol{Y}, \\ \qquad K_0(T',k,c,\theta,\boldsymbol{v}) = 0, \; H_0(T',k,c,\theta,\boldsymbol{v}) = 0 \end{cases} \tag{4.96}$$

The following result is well known. Its proof can be found for instance in [18].

Lemma 11. *Let F, G be Banach spaces. Assume that $\Psi : F \mapsto \overline{\mathbb{R}}$ is a functional of the form $\Psi(v) = \Psi_0(v) + I(v)$, where I denotes the indicator of a closed convex set $\mathfrak{C} \subset F$, and let $k : F \mapsto G$ be given. Let $\hat{v}$ be a solution of the problem*

$$\begin{cases} \textit{Minimize} \quad \Psi(v) \\ \textit{Subject to} \quad v \in F, \; k(v) = 0 \end{cases} \tag{4.97}$$

and suppose that Ψ_0 and k are $\mathcal{C}^1$ in a neighborhood of $\hat{v}$. Then there exists $\Lambda \in G'$ such that

$$\Psi_0'(\hat{v}) + \partial I(\hat{v}) \ni -\Lambda \circ k'(\hat{v}) \tag{4.98}$$

(here, $\partial I(\hat{v})$ denotes the subdifferential of I at the point $\hat{v}$).

Remark 16. Let $f : V \mapsto \overline{\mathbb{R}}$ be a proper, lower semicontinuous, convex function. The subdifferential of f at a point $v_0 \in V$ is the set

$$\partial f(v_0) = \{v' \in V' \ : \ f(v) - f(v_0) \geq \big(v', v - v_0\big) \quad \forall v \in V\}.$$

In the particular case of the indicator function, we have $\partial I(v_0) = \emptyset$ if $v_0 \notin \mathfrak{C}$ and

$$\partial I(v_0) = \big\{v' \in V' \ : \ \sup \big(v', v\big) = \big(v', v_0\big) \quad \forall v \in V\big\}$$

otherwise.

□

Consequently, if we introduce $\hat{p} = -\Psi_0'(\hat{v}) - \Lambda \circ k'(\hat{v})$, then assertion (4.98) indicates that $(\hat{p}, v) \leq (\hat{p}, \hat{v})$ for each $v \in \mathfrak{C}$ or, equivalently, that

$$(\hat{p}, v - \hat{v}) \leq 0 \quad \forall v \in \mathfrak{C}.$$

Thus, lemma 11 guarantees the existence of $\Lambda \in G'$ such that

$$\big(\Psi_0'(\hat{v}) + \Lambda \circ k'(\hat{v}), v - \hat{v}\big) \geq 0 \quad \forall v \in \mathfrak{C}. \tag{4.99}$$

Let us return to the minimization problem (4.96). Let us assume that $(\hat{T}, \hat{k})$ is a solution and let $(\hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$ be an associated state. From lemma 11, it follows that there exists $\Lambda \in \boldsymbol{Z}'$, with $\Lambda := (\lambda, \boldsymbol{\xi}, \boldsymbol{z}) = (\lambda, \xi_1, \xi_2, \boldsymbol{\xi}_3, z_1, z_2, \boldsymbol{z}_3)$, such that

$$\Phi'(\hat{T}, \hat{k}) \cdot (T' - \hat{T}, k - \hat{k}) + \lambda K_0'(\hat{\boldsymbol{y}}) \cdot (\boldsymbol{y} - \hat{\boldsymbol{y}}) + (\boldsymbol{\xi}, \boldsymbol{z}) \circ H_0'(\hat{\boldsymbol{y}}) \cdot (\boldsymbol{y} - \hat{\boldsymbol{y}}) \geq 0 \qquad \forall \boldsymbol{y} \in \boldsymbol{Y}. \tag{4.100}$$

Here, we have used the notation $\boldsymbol{y} = (T', k, c, \theta, \boldsymbol{v})$, $\hat{\boldsymbol{y}} = (\hat{T}, \hat{k}, \hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$.

Next, we compute each derivative in the optimality condition (4.100).

Taking into account the definitions of K_0 and Φ_0, we easily obtain that

$$K_0'(\hat{\boldsymbol{y}}) \cdot (\boldsymbol{y} - \hat{\boldsymbol{y}}) = (T' - \hat{T})\big(\hat{\theta}(\hat{T}) - \theta_e, \hat{\theta}_t(\hat{T})\big)_{L^2} + \big(\hat{\theta}(\hat{T}) - \theta_e, \theta(\hat{T}) - \hat{\theta}(\hat{T})\big)_{L^2}, \tag{4.101}$$

$$\Phi'(\hat{T}, \hat{k}) \cdot (T' - \hat{T}, k - \hat{k}) = \hat{T}(T' - \hat{T}) + N \iint_{\omega \times (0,T)} \hat{k}(k - \hat{k}) \, dx \, dt. \tag{4.102}$$

The functions H_4, H_5 and H_6 have similar derivatives:

$$H_4'(\hat{\boldsymbol{y}}) \cdot (\boldsymbol{y} - \hat{\boldsymbol{y}}) = c(\cdot, 0) - \hat{c}(\cdot, 0) \tag{4.103}$$

$$H_5'(\hat{\boldsymbol{y}}) \cdot (\boldsymbol{y} - \hat{\boldsymbol{y}}) = \theta(\cdot, 0) - \hat{\theta}(\cdot, 0) \tag{4.104}$$

$$H_6'(\hat{\boldsymbol{y}}) \cdot (\boldsymbol{y} - \hat{\boldsymbol{y}}) = \boldsymbol{v}(\cdot, 0) - \hat{\boldsymbol{v}}(\cdot, 0) \tag{4.105}$$

On the other hand,

$$\begin{aligned} H_2'(\hat{\boldsymbol{y}}) \cdot (\boldsymbol{y} - \hat{\boldsymbol{y}}) =& (\theta - \hat{\theta})_t - \chi \Delta(\theta - \hat{\theta}) + \hat{\boldsymbol{v}} \cdot \nabla(\theta - \hat{\theta}) \\ &+ (\boldsymbol{v} - \hat{\boldsymbol{v}}) \cdot \nabla \hat{\theta} - (k - \hat{k}) 1_\omega \end{aligned} \tag{4.106}$$

In order to compute the derivative of H_1, we must take into account that, in $L^2(0, T_0; H^{-1}(\Omega))$,

$$\begin{aligned} &\lim_{h \to 0} \frac{\boldsymbol{v} \cdot \nabla c_l(c + h\bar{c}, \theta + h\bar{\theta}) - \boldsymbol{v} \cdot \nabla c_l(c, \theta)}{h} \\ &= \lim_{h \to 0} \nabla \cdot \left(\frac{c_l(c + h\bar{c}, \theta + h\bar{\theta}) - c_l(c, \theta)}{h} \boldsymbol{v} \right) \\ &= \nabla \cdot \left(\left(\frac{\partial c_l}{\partial c}(c, \theta)\bar{c} + \frac{\partial c_l}{\partial \theta}(c, \theta)\bar{\theta} \right) \boldsymbol{v} \right) \end{aligned} \tag{4.107}$$

and

$$\lim_{h\to 0} \overline{\boldsymbol{v}}\cdot\nabla c_l(c+h\overline{c},\theta+h\overline{\theta}) = \lim_{h\to 0} \nabla\cdot\big(c_l(c+h\overline{c},\theta+h\overline{\theta})\overline{\boldsymbol{v}}\big) \\ =\nabla\cdot(c_l(c,\theta)\overline{\boldsymbol{v}}) = \nabla c_l\cdot\overline{\boldsymbol{v}} \tag{4.108}$$

From (4.107) and (4.108), it follows that

$$H_1'(\hat{\boldsymbol{y}})\cdot(\boldsymbol{y}-\hat{\boldsymbol{y}}) = (c-\hat{c})_t - D\Delta(c-\hat{c}) + \nabla c_l(\hat{c},\hat{\theta})\cdot(\boldsymbol{v}-\hat{\boldsymbol{v}}) \\ + \nabla\cdot\left[\left(\frac{\partial c_l}{\partial c}(\hat{c},\hat{\theta})(c-\hat{c}) + \frac{\partial c_l}{\partial \theta}(\hat{c},\hat{\theta})(\theta-\hat{\theta})\right)\hat{\boldsymbol{v}}\right] \tag{4.109}$$

By a similar argument, taking into account the definitions of $\boldsymbol{F}_e$, F_i^ϵ, we obtain the derivative of H_3:

$$H_3'(\hat{\boldsymbol{y}})\cdot(\boldsymbol{y}-\hat{\boldsymbol{y}}) =(\boldsymbol{v}-\hat{\boldsymbol{v}})_t - \nu\Delta(\boldsymbol{v}-\hat{\boldsymbol{v}}) + (\hat{\boldsymbol{v}}\cdot\nabla)(\boldsymbol{v}-\hat{\boldsymbol{v}}) \\ + ((\boldsymbol{v}-\hat{\boldsymbol{v}})\cdot\nabla)\hat{\boldsymbol{v}} + \nabla(p-\hat{p}) + F_i^\epsilon(\hat{c},\hat{\theta})(\boldsymbol{v}-\hat{\boldsymbol{v}}) \\ + \left(\frac{\partial F_i^\epsilon}{\partial \hat{c}}(\hat{c},\hat{\theta})(c-\hat{c}) + \frac{\partial F_i^\epsilon}{\partial \hat{\theta}}(\hat{c},\hat{\theta})(\theta-\hat{\theta})\right)\hat{\boldsymbol{v}} \\ - \left(\frac{\partial \boldsymbol{F}_e}{\partial \hat{c}}(\hat{c},\hat{\theta})(c-\hat{c}) + \frac{\partial \boldsymbol{F}_e}{\partial \hat{\theta}}(\hat{c},\hat{\theta})(\theta-\hat{\theta})\right) \tag{4.110}$$

According to (4.100)–(4.106), (4.109) and (4.110), we must have:

$$\hat{T}(T-\hat{T}) + N\iint_{\omega\times(0,\hat{T})}\hat{k}(k-\hat{k})\,dx\,dt \\ + \lambda\left[\big(\hat{\theta}(\hat{T})-\theta_e,\theta_t(\hat{T})\big)_{L^2}\cdot(T-\hat{T}) + \big(\hat{\theta}(\hat{T})-\theta_e,\theta(\hat{T})-\hat{\theta}(\hat{T})\big)_{L^2}\right] \\ + \left\langle (c-\hat{c})_t - D\Delta(c-\hat{c}) + \nabla c_l\cdot(\boldsymbol{v}-\hat{\boldsymbol{v}}) + \nabla\cdot\left(\left(\frac{\partial c_l}{\partial c}(c-\hat{c}) + \frac{\partial c_l}{\partial \theta}(\theta-\hat{\theta})\right)\hat{\boldsymbol{v}}\right), \xi_1\right\rangle \\ + \left\langle (\theta-\hat{\theta})_t - \chi\Delta(\theta-\hat{\theta}) + \hat{\boldsymbol{v}}\cdot\nabla(\theta-\hat{\theta}) + (\boldsymbol{v}-\hat{\boldsymbol{v}})\cdot\nabla\hat{\theta} - (k-\hat{k})1_\omega, \xi_2\right\rangle \\ + \Big\langle (\boldsymbol{v}-\hat{\boldsymbol{v}})_t - \nu\Delta(\boldsymbol{v}-\hat{\boldsymbol{v}}) + (\hat{\boldsymbol{v}}\cdot\nabla)(\boldsymbol{v}-\hat{\boldsymbol{v}}) + ((\boldsymbol{v}-\hat{\boldsymbol{v}})\cdot\nabla)\hat{\boldsymbol{v}} \\ + F_i^\epsilon(\boldsymbol{v}-\hat{\boldsymbol{v}}) + \left(\frac{\partial F_i^\epsilon}{\partial c}(c-\hat{c}) + \frac{\partial F_i^\epsilon}{\partial \theta}(\theta-\hat{\theta})\right)\hat{\boldsymbol{v}} - \frac{\partial \boldsymbol{F}_e}{\partial c}(c-\hat{c}) - \frac{\partial \boldsymbol{F}_e}{\partial \theta}(\theta-\hat{\theta}), \boldsymbol{\xi}_3\Big\rangle \\ + \big(z_1, c(\cdot,0)-c^0\big)_{L^2} + \big(z_2,\theta(\cdot,0)-\theta^0\big)_{L^2} + \big(\boldsymbol{z}_3,\boldsymbol{v}(\cdot,0)-\boldsymbol{v}^0\big)_{\boldsymbol{L}^2} \geq 0 \tag{4.111}$$

for all $(T,k,c,\theta,\boldsymbol{v})\in\boldsymbol{Y}$, where c_l, $\dfrac{\partial c_l}{\partial c}$, etc. are valued at $(\hat{c},\hat{\theta})$.
Now, the following consequences are deduced:

- First, taking $T = \hat{T}$ and $(c, \theta, \boldsymbol{v}) = (\hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$, we see that

$$N \iint_{\omega \times (0,\hat{T})} \hat{k}(k - \hat{k})\, dx\, dt - \langle \xi_2, (k - \hat{k}) 1_\omega \rangle \geq 0.$$

for all $k \in \mathcal{U}_{ad}$. This means that

$$\hat{k} = P_{\mathcal{U}_{ad}} \left(-\frac{1}{N} \xi_2 \Big|_{\omega \times (0,\hat{T})} \right). \tag{4.112}$$

- Then, taking $k = \hat{k}$, $(c, \theta, \boldsymbol{v}) = (\hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$, we find:

$$\left(\hat{T} + \lambda \left(\hat{\theta}(\hat{T}) - \theta_e, \theta_t(\hat{T}) \right)_{L^2} \right) \cdot \left(T - \hat{T} \right) \geq 0.$$

for all $T \in [0, T_0]$, that is,

$$\hat{T} = P_{[0,T_0]} \left(-\lambda \left(\hat{\theta}(\hat{T}) - \theta_e, \theta_t(\hat{T}) \right)_{L^2} \right). \tag{4.113}$$

- Thirdly, we can take $T = \hat{T}$, $k = \hat{k}$, $\theta = \hat{\theta}$, $v = \hat{\boldsymbol{v}}$ and $c = \hat{c} + \eta$, with $\eta \in \mathcal{D}(\overline{\Omega} \times [0, \hat{T}])$. This gives:

$$\left\langle \eta_t - D\Delta\eta + \nabla \cdot \left(\frac{\partial c_l}{\partial c} \eta \hat{\boldsymbol{v}} \right), \xi_1 \right\rangle$$

$$+ \left\langle \frac{\partial F_i^\epsilon}{\partial c} \eta \hat{\boldsymbol{v}} - \frac{\partial \boldsymbol{F}_e}{\partial c} \eta, \boldsymbol{\xi}_3 \right\rangle$$

$$+ \left(z_1, \eta(\cdot, 0) \right)_{L^2} \geq 0$$

Since η is arbitrary, taking $\eta \in \mathcal{D}(\overline{\Omega} \times (0, \hat{T}])$, we first find:

$$\begin{cases} -\xi_{1,t} - D\Delta\xi_1 - \dfrac{\partial c_l}{\partial c} \hat{\boldsymbol{v}} \cdot \nabla \xi_1 = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial c} - \dfrac{\partial F_i^\epsilon}{\partial c} \hat{\boldsymbol{v}} \right) \cdot \boldsymbol{\xi}_3 & \text{in} \quad \Omega \times (0, \hat{T}) \\ (D\nabla\xi_1) \cdot \boldsymbol{n} = 0 & \text{on} \quad \partial\Omega \times (0, \hat{T}) \\ \xi_1(x, \hat{T}) = 0 & \text{in} \quad \Omega \end{cases} \tag{4.114}$$

Then, taking $\eta \in \mathcal{D}(\Omega \times [0, \hat{T}))$ we see that

$$z_1 = \xi_1(\cdot\,, 0). \tag{4.115}$$

- A similar argument leads to the following conclusions concerning ξ_2 and z_2:

$$\begin{cases} -\xi_{2,t} - \chi\Delta\xi_2 - \dfrac{\partial c_l}{\partial \theta} \hat{\boldsymbol{v}} \cdot \nabla \xi_1 - \hat{\boldsymbol{v}} \cdot \nabla \xi_2 = \left(\dfrac{\partial \boldsymbol{F}_e}{\partial \theta} - \dfrac{\partial F_i^\epsilon}{\partial \theta} \hat{\boldsymbol{v}} \right) \cdot \boldsymbol{\xi}_3 & \text{in} \quad \Omega \times (0, \hat{T}) \\ (\chi\nabla\xi_2) \cdot \boldsymbol{n} = 0 & \text{on} \quad \partial\Omega \times (0, \hat{T}) \\ \xi_2(x, \hat{T}) = -\lambda \left(\hat{\theta}(\hat{T}) - \theta_e \right) & \text{in} \quad \Omega \end{cases} \tag{4.116}$$

and

$$z_2 = \xi_2(\cdot\,, 0). \tag{4.117}$$

- Let us now take $T = \hat{T}$, $k = \hat{k}$, $c = \hat{c}$, $\theta = \hat{\theta}$ and $\boldsymbol{v} = \hat{\boldsymbol{v}} + \boldsymbol{\xi}$, where $\boldsymbol{\xi} \in \mathcal{D}(\Omega \times [0, \hat{T}])^d$, $\nabla \cdot \boldsymbol{\xi} = 0$ in $\Omega \times [0, T]$. This time, we get:

$$\begin{aligned}&\left\langle \boldsymbol{\xi}_t - \nu\Delta\boldsymbol{\xi} + (\hat{\boldsymbol{v}} \cdot \nabla)\,\boldsymbol{\xi} + (\boldsymbol{\xi} \cdot \nabla)\,\hat{\boldsymbol{v}} + F_i^{\epsilon}\boldsymbol{\xi}, \boldsymbol{\xi}_3 \right\rangle \\ &+ \left\langle \nabla c_l \cdot \boldsymbol{\xi}, \xi_1 \right\rangle + \left\langle \boldsymbol{\xi} \cdot \nabla\hat{\theta}, \xi_2 \right\rangle \\ &+ \left(\boldsymbol{z}_3, \boldsymbol{\xi}(\cdot\,, 0)\right)_{\boldsymbol{L}^2} \geq 0\end{aligned}$$

  Therefore, from De Rham's lemma, taking $\boldsymbol{\xi}$ arbitrary in $\mathcal{D}(\Omega \times (0, \hat{T}])^d$ with $\nabla \cdot \boldsymbol{\xi} \equiv 0$, we find that

$$\begin{cases} -\boldsymbol{\xi}_{3,t} - \nu\Delta\boldsymbol{\xi}_3 - (\hat{\boldsymbol{v}} \cdot \nabla)\,\boldsymbol{\xi}_3 + (\nabla\hat{\boldsymbol{v}})^t\,\boldsymbol{\xi}_3 + F_i^{\epsilon}\boldsymbol{\xi}_3 + \nabla q = -\xi_1\nabla c_l - \xi_2\nabla\hat{\theta} & \text{in} \quad \Omega \times (0, \hat{T}) \\ \boldsymbol{\xi}_3 = 0 & \text{on} \quad \partial\Omega \times (0, \hat{T}) \\ \boldsymbol{\xi}_3(x, \hat{T}) = 0 & \text{in} \quad \Omega \end{cases} \tag{4.118}$$

  for some $q \in \mathcal{D}'(\Omega \times (0, \hat{T}))$. Finally, it is also found that

$$\boldsymbol{z}_3 = \boldsymbol{\xi}_3(\cdot\,, 0). \tag{4.119}$$

In order to homogenize the notation, let us set $(\widehat{\phi}, \widehat{\psi}, \widehat{\boldsymbol{w}}) = -(\xi_1, \xi_2, \boldsymbol{\xi}_3)$.

Then we have proved the following result:

Theorem 17. *Let $(\hat{T}, \hat{k}, \hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$ be a solution to (4.94)–(4.95). Then there exist $\lambda \in \mathbb{R}$ and $(\widehat{\phi}, \widehat{\psi}, \widehat{\boldsymbol{w}})$ such that the following holds (for some $\hat{p}$ and $\hat{q}$):*

$$\begin{cases} \hat{c}_t - D\Delta\hat{c} + \hat{\boldsymbol{v}} \cdot \nabla c_l(\hat{c}, \hat{\theta}) = 0 & \text{in} \quad \Omega \times (0, \hat{T}) \\ \hat{\theta}_t - \chi\Delta\hat{\theta} + \hat{\boldsymbol{v}} \cdot \nabla\hat{\theta} = \hat{k}1_{\omega} & \text{in} \quad \Omega \times (0, \hat{T}) \\ \hat{\boldsymbol{v}}_t + (\hat{\boldsymbol{v}} \cdot \nabla)\hat{\boldsymbol{v}} - \nu\Delta\hat{\boldsymbol{v}} + F_i^{\epsilon}(\hat{c}, \hat{\theta})\hat{\boldsymbol{v}} + \nabla\hat{p} = \boldsymbol{F}_e(\hat{c}, \hat{\theta}) & \text{in} \quad \Omega \times (0, \hat{T}) \\ \nabla \cdot \hat{\boldsymbol{v}} = 0 & \text{in} \quad \Omega \times (0, \hat{T}) \\ (D\nabla\hat{c}) \cdot \boldsymbol{n} = (\chi\nabla\hat{\theta}) \cdot \boldsymbol{n} = 0, \ \hat{\boldsymbol{v}} = \boldsymbol{0} & \text{on} \quad \partial\Omega \times (0, \hat{T}) \\ \hat{c}(\boldsymbol{x}, 0) = c^0(\boldsymbol{x}); \quad \hat{\theta}(\boldsymbol{x}, 0) = \theta^0(\boldsymbol{x}); \quad \hat{\boldsymbol{v}}(\boldsymbol{x}, 0) = \boldsymbol{v}^0(\boldsymbol{x}) & \text{in} \quad \Omega \end{cases} \tag{4.120}$$

$$
\left\{
\begin{aligned}
&-\widehat{\phi}_t - \frac{\partial c_l}{\partial c}\hat{\boldsymbol{v}}\cdot\nabla\widehat{\phi} - D\Delta\widehat{\phi} = \left(\frac{\partial \boldsymbol{F}_e}{\partial c} - \frac{\partial F_i^\epsilon}{\partial c}\hat{\boldsymbol{v}}\right)\cdot\widehat{\boldsymbol{w}} && \text{in} \quad \Omega\times(0,\hat{T})\\
&-\widehat{\psi}_t - \hat{\boldsymbol{v}}\cdot\nabla\widehat{\psi} - \frac{\partial c_l}{\partial \theta}\hat{\boldsymbol{v}}\cdot\nabla\widehat{\phi} - \chi\Delta\widehat{\psi} = \left(\frac{\partial \boldsymbol{F}_e}{\partial \theta} - \frac{\partial F_i^\epsilon}{\partial \theta}\hat{\boldsymbol{v}}\right)\cdot\widehat{\boldsymbol{w}} && \text{in} \quad \Omega\times(0,\hat{T})\\
&-\widehat{\boldsymbol{w}}_t - \nu\Delta\widehat{\boldsymbol{w}} - (\hat{\boldsymbol{v}}\cdot\nabla)\widehat{\boldsymbol{w}} + (\nabla\hat{\boldsymbol{v}})^t\widehat{\boldsymbol{w}} + F_i^\epsilon(\hat{c},\hat{\theta})\widehat{\boldsymbol{w}} + \nabla\hat{q} && \\
&\qquad = -\widehat{\phi}\nabla c_l(\hat{c},\hat{\theta}) - \widehat{\psi}\nabla\hat{\theta} && \text{in} \quad \Omega\times(0,\hat{T})\\
&\nabla\cdot\widehat{\boldsymbol{w}} = 0 && \text{in} \quad \Omega\times(0,\hat{T})\\
&\left(D\nabla\widehat{\phi}\right)\cdot\boldsymbol{n} = \left(\chi\nabla\widehat{\psi}\right)\cdot\boldsymbol{n} = 0;\ \widehat{\boldsymbol{w}} = \boldsymbol{0} && \text{on} \quad \partial\Omega\times(0,\hat{T})\\
&\widehat{\phi}(\boldsymbol{x},\hat{T}) = 0;\ \widehat{\psi}(\boldsymbol{x},\hat{T}) = \lambda\left(\hat{\theta}(\hat{T}) - \theta_e\right);\ \widehat{\boldsymbol{w}}(\boldsymbol{x},\hat{T}) = \boldsymbol{0} && \text{in} \quad \Omega
\end{aligned}
\right. \tag{4.121}
$$

$$
\hat{k} = P_{\mathcal{U}_{ad}}\left(-\frac{1}{N}\widehat{\psi}\Big|_{\omega\times(0,\hat{T})}\right) \tag{4.122}
$$

$$
\hat{T} = P_{[0,T_0]}\left(-\lambda\left(\hat{\theta}(\cdot\,,\hat{T}) - \theta_e, \hat{\theta}_t(\cdot\,,\hat{T})\right)_{L^2}\right) \tag{4.123}
$$

$$
\|\hat{\theta}(\cdot\,,\hat{T}) - \theta_e\|_{L^2}^2 = \delta^2 \tag{4.124}
$$

Remark 17. Notice that, if $(\hat{T}, \hat{k}, \hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$ is a nontrivial solution of (4.94)–(4.95), i.e. $0 < \hat{T} < T_0$, then we necessarily have

$$
\hat{T} = -\lambda\left(\hat{\theta}(\cdot\,,\hat{T}) - \theta_e, \hat{\theta}_t(\cdot\,,\hat{T})\right)_{L^2}
$$

$$
\left(\hat{\theta}(\cdot\,,\hat{T}) - \theta_e, \hat{\theta}_t(\cdot\,,\hat{T})\right)_{L^2} = \frac{1}{2}\frac{d}{dt}\left\|\hat{\theta}(\cdot\,,\hat{T}) - \theta_e\right\|_{L^2}^2\Big|_{t=\hat{T}} < 0
$$

and

$$
\lambda > 0.
$$

□

Remark 18. The optimality system (4.120)–(4.124) can be used to deduce iterative algorithms for the computation of an optimal $(\hat{T}, \hat{k}, \hat{c}, \hat{\theta}, \hat{\boldsymbol{v}})$.

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