# ASYMPTOTIC STABILITY OF CONSTANT STEADY STATES FOR A $2 \times 2$ REACTION–DIFFUSION SYSTEM ARISING IN CANCER MODELLING

MARCO DI FRANCESCO, MONIKA TWAROGOWSKA

Abstract. Dependence of tumor on essential nutrients is known to be crucial for its evolution and became one of the targets for medical therapies. Based on this fact a reaction–diffusion system with chemotaxis term and nutrient–based growth of tumors is presented. The formulation of the model considers also an influence of tumor and pharmacological factors on nutrient concentration. In the paper convergence of solutions to constant, stationary states in the one-dimensional case for small perturbation of the equilibria is investigated. The nonlinear stability results are obtained by means of the classical symmetrization method and energy Sobolev estimates.

## 1. Introduction

We consider a model, based on the one presented in [25], of nonlinear partial differential equations of reaction diffusion type, with cross diffusion terms, describing the evolution of a density of tumor cells, which depends on the concentration of a nutrient. The interaction is mutual: the cells use the nutrient in their metabolism and also stimulate the organism to increase its concentration. We also consider a pharmacological factor regulating nutrient concentration. Denoting by $\phi$ the tumor cells density and by $c$ the nutrient concentration, a general form of the system reads

$$\begin{cases} \dfrac{\partial \phi}{\partial t} = \nabla \cdot (\phi \nabla F(\phi)) - \nabla \cdot (\omega \phi \nabla c) + \alpha(\phi, c) \\ \dfrac{\partial c}{\partial t} = D \triangle c + \beta(\phi, c), \end{cases} \tag{1}$$

posed on a bounded domain $\Omega \subset \mathbf{R}^3$ with smooth boundary.

The motion of the tumor cells is described via the density $\phi$, which evolves according to the first equation in (1). It is a continuity equation in which the flux of cells is biased by diffusion and chemotactical transport up the gradient of a nutrient. Denoting the velocity of cells as $\overrightarrow{u}$, the flux equals $\phi \overrightarrow{u} = -\phi \nabla (F(\phi)) + \omega \phi \nabla c$. Here $F$ denotes a nonlinear diffusion function due to the presence of a density dependent random mobility for the tumor cells. We define $f'(\phi) = \phi F'(\phi)$ so that $f(\phi) = \int_0^\phi \xi F'(\xi) d\xi$. From now on we assume $F'(\phi) > 0$, which implies $f'(\phi) > 0$. Typical examples for the function $F(\phi)$ are $F(\phi) = \log \phi$ (classical linear diffusion), $F(\phi) = \phi^\gamma$ with $\gamma > 0$ (porous medium type diffusion) which models a divergent value for the random mobility as $\phi \to +\infty$ due to volume filling effects (cf. e. g. [4, 18]), or $F(\phi)$ being an increasing function such that the corresponding $f(\phi)$ has a finite limit as $\phi \to +\infty$, which models saturation for large densities. All the

above cases can be included in the present paper (as we shall work under in a small perturbation framework). The last term in the definition of the flux describes a directional movement of tumor cells towards higher concentration of nutrient. The parameter $\omega > 0$ is the *chemotactic sensitivity* of the tumor cells. The motion of the nutrient has a linear diffusion term with constant diffusivity $D > 0$. The above mentioned rules define the flux in the continuity equation for the cells and the nutrient. Both equations are as well endowed with terms describing production and degradation (reaction) processes. They are represented by the reaction terms $\alpha(\phi, c), \beta(\phi, c)$ having the form

$$\alpha(\phi, c) = \gamma_1 \widehat{p}\left(\frac{c}{c_0} - 1\right)\phi \widehat{H}(\phi^* - \phi) - \gamma_2 \widehat{p}\left(1 - \frac{c}{c_0}\right)\phi - \delta\phi \qquad (2)$$

$$\beta(\phi, c) = -dc\phi + G\phi - Rc. \qquad (3)$$

The first and the second term on the right hand side of the equation (2) contain functions $\widehat{H}(x)$, $\widehat{p}(x)$, which are regularized approximations of the Heaviside function and the 'positive part' function $(x)_+$ respectively [2]. The use of these mollifiers is motivated by the finite response time of cells to the changes in the surrounding environment. The analysis of the asymptotic behavior of the system requires $\alpha$ and $\beta$ to be at least $C^1$ functions. More precisely we define

$$\widehat{H}(x) = \widehat{H}_\sigma(x) = \begin{cases} 0 & x < 0 \\ h_\sigma(x) & 0 \le x \le \sigma \\ 1 & \sigma < x \end{cases}, \qquad (4)$$

with $h_\sigma(0) = 0$, $h_\sigma(\sigma) = 1$ and $h_\sigma \in C^\infty([0, \sigma])$. The second function is

$$\widehat{p}(z) = \widehat{p}_\epsilon(z) = \begin{cases} 0 & z < 0 \\ \frac{c_0}{2\epsilon} z^2 & 0 \le z \le \epsilon \\ c_0\left(z - \frac{\epsilon}{2}\right) - \frac{\epsilon}{2c_0} & \epsilon < z \end{cases}. \qquad (5)$$

The positive parameters $\sigma$, $\epsilon$, as described in [2], define the thickness of the transition between the two phases.

The first term in (2) describes the increase of the density of tumor cells as a result of multiplication in the mitosis cycle and the growth of cells. These processes depend on the number of cells undergoing duplication and the amount of essential nutrient. In the model we assume the presence of two threshold processes. The function $\widehat{H}_\sigma(\phi^* - \phi)$ describes the reduction of free space available to the cells and possibly, after crossing the threshold value $\phi^*$, the stopping of their growth. The rapidity of the switch from the proliferating stage to the quiescent one is controlled by the parameter $\sigma$. As a second switch off factor we consider the minimal nutrient concentration $c_0$ necessary for the cells to sustain their biological cycles. Following [26], [25] we assume that the concentration of nutrient below the threshold value results not only in limiting the growth but also in the cell's death, which is modeled by the second terms in (2). The parameters $\gamma_1$ and $\gamma_2$ are constant growth and death rates respectively. Based on [14] let us assume $\gamma_1 > \gamma_2$, which reflects independence of tumor on growth factors, its insensitivity to growth inhibitors and dependence on alternative, less demanding in nutrients, metabolisms such as in the Warburg effect [32].

The last term in (2) models the natural death of cells (apoptosis) which occurs after a definite number of multiplications. Telomeres are responsible for this intrinsic counting mechanism, capping both ends of chromosomes [12]. They are being shortened at every mitosis cycle. After reaching the threshold length, suspension of replication occurs obeying so called 'end-replication problem' stated by James D.Watson in 1970. The enzyme telomerase is responsible for elongation of telomeres. Researches in this field showed that although telomerase is absent in somatic cells its activity is reported in 90% of cancers. In chromosomes of tumor cells the threshold length of telomeres is passed leading to their further shortening, however, this process is accompanied by telomerase activation. Eventually telomeres are stabilised at a constant length, which gives tumor cells immortality and an ability to proliferate indefinitely. As highlighted in [31] immortality is not sufficient for the healthy cell to become cancerous one, however, it gives a significant advantage. This feature is a motivation to consider also a modified model, in which the death term $-\delta\phi$ is neglected (cf. Section 5).

Nutrients such as oxygen, glucose or iron are the essential ingredients used in cell cycles. Molecules are supplied by capillary network and consumed by cells. The minimal concentration of nutrient must be available for the cells to survive. While the tumor grows, uncontrolled processes and unnaturally high demand for nutrients cause occurrence of regions of death cells. One of the characteristic features of tumor cells is their capacity of increasing the availability of nutrient by stimulating formation of capillary network. Based on [26], [25] consumption and degradation of nutrient is modeled by the first and second term in (3). The rates $d$ and $G$ are assumed to be constant.

The last term in (3), with $R > 0$, models a pharmacological therapy the aim of which is to limit the feeding ability motivated by [10], where killing tumor by starvation is suggested. The first target would be destroying blood vessels supplying tissue in nutrients. In [13] a new group of drugs, acting on specific parts of signalling pathways, is described. One of the type of these molecular directed drugs works against angiogenesis by neutralizing VEGF (vascular endothelial growth factor), which stimulates multiplication of endothelial cells forming internal layer of capillaries. Approved in 2004 bewacyzumab is an antibody acting in that way. However, further research showed that antiangiogenic drugs don't help unless augmented with conventional chemotherapy. It was discovered that in the first phase of drug action the blood network around tumour, which is chaotic and of poor quality, is being normalized [15]. Remaining capillaries deliver drugs and nutrients more effectively, causing in some cases even increase in the rate of proliferation in some parts of tumour. In our model, as a simplification, we consider only a constant decrease of nutrient as a result of pharmacological therapy.

The mathematical structure of the system (1) is that of a nonlinear reaction–diffusion system with cross–diffusion terms. The literature related with the existence theory and the stability vs. instability properties of such systems is pretty large. The books [1, 27] are a good reference for the existence of global solutions of systems of reaction–diffusion type, see also [5, 29, 20], whereas the more recent [9, 6, 7] used Lyapunov functions and

entropy methods to achieve asymptotic stability of stationary solutions. The dichotomy between stability and instability is a classical problem which goes back to [30] and it has still many open issues.

Several applied contexts in which reaction–diffusion systems appear feature cross–diffusion terms, meaning that one species can be transported via a velocity field directed up the gradient of another species, such as in chemotaxis models. Starting from the earliy 80's, Mimura and other authors [23, 21, 22] addressed the problem of the asymptotic behavior of Lotka–Volterra type systems with cross diffusion, in terms of formation of inhomogeneous steady states (segregation) vs. stability of constant states (self–diffusion). See also the more recent papers my Ni and other authors [19, 24]. The recent [16] is a very exhaustive review for reaction–cross–diffusion systems.

Our results use as a main tool the classical *symmetrization method*, see for instance [17, 11, 28] in which this technique has been used for hyperbolic systems of conservation laws, and the more recent [8] which applies symmetrization and entropy methods to reaction–diffusion systems arising in the context of semiconductor modeling. Our nonlinear stability result is proven via energy Sobolev estimates and it holds for small perturbation of constant states. The symmetrization method works in any dimension for the linearized systems. However, due to the complexity of the Sobolev type energy estimate, we shall prove the nonlinear result only in one space dimension. The main technical difficulty in our computation lies in the fact that the diffusion matrix and the reaction matrix after linearization can never be symmetrized simultaneously in such a way to produce two negative definite quadratic forms. Therefore, the (symmetrized) diffusion term will compensate the lack of negativity in the quadratic form induced by the linearized reaction matrix.

The paper is organized as follows. In section 2 we provide a precise statement of the problem and we state our main results (cf. subsection 2.2). This subsection contains the precise statement of the structural conditions on the parameters needed to achieve stability of steady states together with a suitable interpretation of the result in Remark 1. In section 3 we show how to apply the classical symmetrization method needed to prove the main stability result to the linearized model. In section 4 we prove the main nonlinear stability result. Finally, in section 5 we prove a similar result to a model without death term in the evolution of the tumor cells density.

## 2. Preliminaries and results

2.1. **Constant stationary states.** Let us rewrite system (1) in a form

$$\begin{cases} \dfrac{\partial \phi}{\partial t} = \Delta f(\phi) - \nabla \cdot (\omega \phi \nabla c) \\ \qquad\qquad +\gamma_1 \widehat{p}\left(\dfrac{c}{c_0} - 1\right) \phi \widehat{H}(\phi^* - \phi) - \gamma_2 \widehat{p}\left(1 - \dfrac{c}{c_0}\right) \phi - \delta \phi \\ \dfrac{\partial c}{\partial t} = D \triangle c - dc\phi + G\phi - Rc \end{cases} \tag{6}$$

and seek for constant, positive, stationary states $(\phi_\infty, c_\infty)$. The reaction terms consist of regularised approximations of Heaviside and 'positive part'

functions. The transient regions, characterized by the structural constants $\sigma, \epsilon$, are quadratic polynomials. To simplify the analysis we assume the solutions to be outside the transient regions. It means that

$$c \in [0, c_0 - \epsilon] \cup \{c_0\} \cup [c_0 + \epsilon, \infty] \qquad \text{and} \qquad \phi \in [0, \phi^* - \sigma] \cup [\phi^*, \infty]. \quad (7)$$

Under this assumption we state the following simple lemma.

**Lemma 1.** *If*

$$\begin{cases} \dfrac{c_0 R\left(1 + \frac{\delta}{\gamma_1} + \frac{\epsilon}{2c_0}\right)}{G - dc_0\left(1 + \frac{\delta}{\gamma_1} + \frac{\epsilon}{2c_0}\right)} \leq \phi^* - \sigma \\ \dfrac{1}{2}\epsilon < c_0 \dfrac{\delta}{\gamma_1} \\ G > c_0 d\left(1 + \dfrac{\delta}{\gamma_1} + \dfrac{\epsilon}{2c_0}\right) \end{cases} \quad (8)$$

*then the system (6) has a constant, non trivial steady state*

$$(\phi_\infty, c_\infty) = \left( \frac{c_0 R\left(1 + \frac{\delta}{\gamma_1} + \frac{\epsilon}{2c_0}\right)}{G - dc_0\left(1 + \frac{\delta}{\gamma_1} + \frac{\epsilon}{2c_0}\right)}, c_0\left(1 + \frac{\delta}{\gamma_1} + \frac{\epsilon}{2c_0}\right) \right). \quad (9)$$

*Moreover, if one of conditions (8) is not satisfied, then the only steady states of system (6) in the range (7) is the trivial solution* $(0, 0)$.

*Proof.* To see this let us assume that $c_\infty > c_0 + \epsilon$. From the condition $\beta(\phi_\infty, c_\infty) = 0$ we obtain $c_\infty = \frac{G\phi_\infty}{R + d\phi_\infty}$ and the previous assumption turns to

$$\phi_\infty > \frac{(c_0 + \epsilon)R}{G - d(c_0 + \epsilon)}. \quad (10)$$

The condition $\alpha(\phi_\infty, c_\infty) = 0$ takes the form

$$\gamma_1 \left( \frac{G\phi_\infty}{c_0(R + d\phi_\infty)} - 1 - \frac{\epsilon}{2c_0} \right) \phi_\infty \widehat{H}(\phi^* - \phi_\infty) - \delta\phi_\infty = 0.$$

Now let us assume

$$\phi_\infty \leq \phi^* - \sigma. \quad (11)$$

Then the above condition becomes

$$\gamma_1 \left( \frac{G\phi_\infty}{c_0(R + d\phi_\infty)} - 1 - \frac{\epsilon}{2c_0} \right) \phi_\infty - \delta\phi_\infty = 0$$

and yields the non trivial solution

$$\phi_\infty = \frac{c_0 R\left(1 + \frac{\delta}{\gamma_1} + \frac{\epsilon}{2c_0}\right)}{G - dc_0\left(1 + \frac{\delta}{\gamma_1} + \frac{\epsilon}{2c_0}\right)}. \quad (12)$$

To simplify the notation, from now on let us denote $\Gamma = 1 + \frac{\delta}{\gamma_1} + \frac{\epsilon}{2c_0}$. Then $\phi_\infty = \frac{c_0 R\Gamma}{G - dc_0\Gamma}$. It satisfies (10) if $\frac{1}{2}\epsilon < c_0\frac{\delta}{\gamma_1}$ and (11) if

$$\frac{c_0 R\Gamma}{G - dc_0\Gamma} \leq \phi^* - \sigma.$$

On the other hand, if $\phi_\infty > \phi^*$ then the only solution is $\phi_\infty = 0$, which is a contradiction.

When $c_\infty < c_0 - \epsilon$, the only constant stationary solution is a trivial one $(\phi_\infty, c_\infty) = 0$, because $\alpha(\phi_\infty, c_\infty) = 0$ reduces to

$$-\gamma_2 \left(1 - \frac{c_\infty}{c_0} - \frac{\epsilon}{2c_0}\right) \phi_\infty - \delta\phi_\infty = 0.$$

□

2.2. **Results.** In the previous section we described a system of reaction-diffusion type with cross diffusion terms and found its constant, positive, stationary states. In this subsection we state our results concerning with the asymptotic behavior of the solutions near these equilibria. Due to complexity of a three dimensional analysis we restrict our results to one spatial dimension. Let us introduce vector notation

$$U = (\phi \quad c)^T \in (\mathbb{R} \times [0, \infty))^2 .$$

Then the system (1), reduced to one spatial dimension, can be written as

$$\frac{\partial}{\partial t} U = (\mathbf{D} U_x)_x + \vec{f}(U), \tag{13}$$

where

$$\mathbf{D} = \begin{pmatrix} f'(\phi) & -\omega\phi \\ 0 & D \end{pmatrix}, \qquad \vec{f}(U) = \begin{pmatrix} \alpha(\phi, c) \\ \beta(\phi, c) \end{pmatrix}.$$

To simplify the analysis we consider periodic boundary conditions on the torus.

**Structural conditions**

As we already stated above, our results uses symmetrization as a fundamental tool and there's a compensation between the symmetrized diffusion and the symmetrized reaction part. This leads to structural assumptions on the constants involved in the model which are quite involved. For the sake of completeness we state these structural conditions here and make some comments afterwards.

We shall prove our results under the following structural assumptions.

$$\frac{D - \widehat{f}}{c_0 \omega R \Gamma} \left[ \left(D - \widehat{f}\right) \frac{\gamma_1}{c_0 \omega} - \frac{RG}{G - c_0 d\Gamma} \right] > 1, \tag{14}$$

$$\frac{1}{\omega c_0} \left(D - \widehat{f}\right) \left[ \frac{(G - c_0 d\Gamma)^2 + \gamma_1 R\Gamma}{R\Gamma} \right] > \frac{Rc_0}{G - c_0 d\Gamma}, \tag{15}$$

$$\frac{(D - \widehat{f})}{\omega c_0} \left( \frac{(G - dc_0\Gamma)^2}{R\Gamma} \widehat{f} + D\gamma_1 \right) > R\omega c_0 \Gamma + \frac{GDR}{G - c_0 d\Gamma}, \tag{16}$$

$$
\begin{aligned}
&-E\frac{(RG+Dg)}{g^2}+\frac{R\Gamma(\omega c_0+\gamma_1)}{2gC_\Omega}+\frac{g}{2C_\Omega}\left(1-\widehat{f}\frac{D-\widehat{f}}{\omega c_0 R\Gamma}\right)\\
&-\frac{1}{2C_\Omega}\left[\left(\frac{D-\widehat{f}}{\omega c_0 R\Gamma}g\widehat{f}+\frac{DE}{g}-\frac{\omega c_0 R\Gamma}{g}\right)^2-4D\widehat{f}\left(\frac{D-\widehat{f}}{\omega R\Gamma c_0}E-1\right)\right]^{\frac{1}{2}} \qquad (17)\\
&+\left[\left(\frac{\gamma_1 R\Gamma}{g}-\frac{RG}{g^2}E+g\right)^2+4\gamma_1 R\Gamma\left(\frac{D-\widehat{f}}{\omega c_0 R\Gamma}E-1\right)\right]^{\frac{1}{2}}<0,
\end{aligned}
$$

where $E:=\left(\gamma_1\frac{D-\widehat{f}}{\omega c_0}-\frac{RG}{G-dc_0\Gamma}\right)$, $g:=G-dc_0\Gamma$, and $\widehat{f}=f'\left(\frac{c_0R\Gamma}{G-dc_0\Gamma}\right)$ to simplify the notation, $C_\Omega$ is the Poincaré constant of the domain and $\Gamma:=1+\frac{\delta}{\gamma_1}+\frac{\epsilon}{2c_0}$.

**Theorem 1.** *Suppose (8),(14),(15), (16), (17) are satisfied. Additionally let*

$$\| U_0-U_\infty \|_{H^2(\Omega)}\leq \widetilde{\delta}$$

*for $\widetilde{\delta}$ small enough. Then the non trivial equilibrium of the system (13)*

$$U_\infty=\left(\frac{c_0R\Gamma}{G-dc_0\Gamma}\quad c_0\Gamma\right)^T$$

*is asymptotically stable and*

$$||U-U_\infty||_{H^2(\Omega)}\leq C_1e^{-C_2t}||U_0-U_\infty||_{H^2(\Omega)},$$

*where $C_1$ and $C_2$ are positive constants depending on the structure parameters.*

**Remark 1.** A precise interpretation of the above structural conditions from a physiological point of view is pretty hard. However, it is easily check that, assuming $D>\widehat{f}$, conditions (14), (15) and (16) are satisfied if $\omega$ is small enough, which is reasonable as chemotaxis typically being a phenomenon which causes instabilities. The assumption $D>\widehat{f}$ can be justified by the macroscopic differences between the two groups: cells and molecules [25],[3]. As the latter move freely in the extracellular liquid, cells are attached to themselves and to extracellular matrix [2], [26]. One can also easily observe that conditions (14), (15) and (16) are satisfied for large enough value of $G$ and small enough value of $R$. Such combination of values of the parameters has a strong effect on the production of nutrient and consequently on the production of tumor cells. In principle, that could be seen as a destabilizing factor for the system. However, the higher the density of cells and the concentration of nutrient, the stronger the degradation of the latter. This results in the decrease in the tumor growth and as a consequence can imply stability. Choosing $G$ and $R$ on the contrary as above: $G$ small enough, $R$ large enough, the conditions (14), (15) and (16) are not satisfied. In this case the degradation dominates and concentration of nutrient goes to zero causing that the non-trivial equilibrium may be unstable. Condition (17) is definitely more a technical one: as it will be clear form the proof of theorem 1, it has to be intended as a *diffusion–dominated* assumption.

## 3. Stability of a linearised model

As usually, when studying behavior of nonlinear system, we first consider a linearized one. The null solution and the non trivial equilibrium (9) are taken into account. The results on the linearized problem are valid in any space dimension.

Let, in the vector notation introduced previously, $U_\infty$ be an equilibrium and $\widetilde{U}$ a small perturbation from it. Supposing the solution can be written as

$$U = U_\infty + \widetilde{U},$$

the linearised system (13) is

$$\widetilde{U}_t = \mathbf{D}\triangle\widetilde{U} + \mathbf{R}\widetilde{U}. \tag{18}$$

The matrices $\mathbf{D}, \mathbf{R} \in M_{2x2}(\mathbb{R})$, (diffusion and reaction matrix respectively), are

$$\mathbf{D} = \begin{pmatrix} f'(\phi_\infty) & -\omega\phi_\infty \\ 0 & D \end{pmatrix}, \tag{19}$$

$$\mathbf{R} = \begin{pmatrix} L_1 & L_2 \\ G - dc_\infty & -(R + d\phi_\infty) \end{pmatrix}, \tag{20}$$

where $L_1 = \frac{\partial\alpha(\phi,c)}{\partial\phi}|_{(\phi_\infty,c_\infty)}$ and $L_2 = \frac{\partial\alpha(\phi,c)}{\partial c}|_{(\phi_\infty,c_\infty)}$.

The following theorem, describing the stability of the stationary states of the system (18), holds under the structural conditions (14), (15), (16), (17).

**Theorem 2.** *The trivial solution of the linearized system (18) is asymptotically stable for any choice of the parameters. Moreover, if the condition (8) is satisfied, the non trivial equilibrium point (9) is asymptotically stable and we have the estimate*

$$||U - U_\infty||_{L^2(\Omega)} \leq C_1 e^{-C_2 t}||U_0 - U_\infty||_{L^2(\Omega)},$$

*where $C_1$ and $C_2$ are positive constants depending on the structure of the system.*

*Proof.* The proof of the stability result for the trivial stationary state is obtained by simple estimate of $L_2$ norm of $\widetilde{U}$ using the energy method. We are going to present a proof only in the case of non trivial equilibrium, since the computation follows the same strategy as for the trivial state.

The linearized diffusion and reaction matrices are in this case

$$\mathbf{D} = \begin{pmatrix} f'(\phi_\infty) & -\omega\phi_\infty \\ 0 & D \end{pmatrix} \quad \text{and} \quad \mathbf{R} = \begin{pmatrix} L_1 & L_2 \\ G - dc_\infty & -(R + d\phi_\infty). \end{pmatrix}.$$

The elements $L_1$ and $L_2$ of the reaction matrix are

$$\begin{aligned} L_1 &= \gamma_1\widehat{p}\left(\frac{c_\infty}{c_0}-1\right)\left(\phi\widehat{H}(\phi^*-\phi)\right)'_{(\phi_\infty,c_\infty)} - \gamma_2\widehat{p}\left(1-\frac{c_\infty}{c_0}\right)-\delta = \\ &= \delta\left(\widehat{H}(\phi^*-\phi_\infty)-\phi_\infty\widehat{H}'(\phi^*-\phi)|_{\phi_\infty}\right)-\delta = \delta\cdot 1-0-\delta = 0, \\ L_2 &= \gamma_1\phi_\infty\widehat{H}(\phi^*-\phi_\infty)\left[\widehat{p}\left(\frac{c}{c_0}-1\right)\right]'_{(\phi_\infty,c_\infty)} - \gamma_2\phi_\infty\left[\widehat{p}\left(1-\frac{c}{c_0}\right)\right]'_{(\phi_\infty,c_\infty)} = \\ &= \frac{\gamma_1}{c_0}\phi_\infty - 0 = \frac{\gamma_1}{c_0}\phi_\infty > 0. \end{aligned}$$

Now we want to show that under the structural conditions on parameters there exists a symmetric, positive definite matrix $S$ such that the matrices $SD, SR$ are symmetric. Let us assume that

$$S = \begin{pmatrix} M & K \\ K & N \end{pmatrix},$$

with $K, M, N \in \mathbb{R}$. Then

$$S\mathbf{D} = \begin{pmatrix} Mf'(\phi_\infty) & -M\omega\phi_\infty + KD \\ Kf'(\phi_\infty) & -K\omega\phi_\infty + ND \end{pmatrix}$$

and

$$S\mathbf{R} = \begin{pmatrix} K(G-dc_\infty) & ML_2 - K(R+d\phi_\infty) \\ N(G-dc_\infty) & KL_2 - N(R+d\phi_\infty) \end{pmatrix}.$$

We want these matrices to be symmetric so

$$\begin{aligned} Kf'(\phi_\infty) = -M\omega\phi_\infty + KD \quad &\Rightarrow \quad M = \frac{D-f'(\phi_\infty)}{\omega\phi_\infty}K, \\ N(G-dc_\infty) = ML_2 - K(R+d\phi_\infty) \quad &\Rightarrow \\ \Rightarrow N = \frac{1}{G-dc_\infty}\left(\frac{D-f'(\phi_\infty)}{\omega\phi_\infty} \quad L_2 \quad -(R+d\phi_\infty)\right)K. \end{aligned}$$

Of course, the matrix $S$ is determined up to a multiplying constant $K$ which we can assume to be $K = 1$.

$$S = \begin{pmatrix} \frac{D-f'(\phi_\infty)}{\omega\phi_\infty} & 1 \\ 1 & \frac{1}{G-dc_\infty}\left(\frac{D-f'(\phi_\infty)}{\omega}\frac{\gamma_1}{c_0} - (R+d\phi_\infty)\right) \end{pmatrix} = \begin{pmatrix} S_1 & 1 \\ 1 & S_2 \end{pmatrix}.$$

It is positive definite if the parameters of the system satisfy the conditions

$$\begin{cases} S_1S_2 - 1 > 0 \\ S_1 + S_2 > 0, \end{cases}$$

which are equivalent to structural conditions (14), (15). Moreover we require that the matrix $S\mathbf{D}$ is positive definite, which means

$$det(S\mathbf{D}) > 0 \quad \text{and} \quad tr(S\mathbf{D}) > 0.$$

Because

$$det(S\mathbf{D}) = (S_1S_2 - 1)Df'(\phi_\infty)$$

and $S_1S_2 - 1 > 0$, the determinant of the symmetrised diffusion matrix is always positive. It's trace is positive if

$$tr(S\mathbf{D}) = (S_1f'(\phi_\infty) - \omega\phi_\infty + S_2D) > 0,$$

which corresponds to the condition (16). For the symmetrised reaction matrix we obtain

$$det(S\mathbf{R}) = (S_1S_2 - 1)(-L_2(G - dc_\infty)),$$

which is always negative. It means that the matrix $S\mathbf{R}$ has eigenvalues with the opposite sign.

Now we prove the asymptotic convergence of the solution to the stationary state in the $L_2$ norm under the conditions specified in the theorem. In the proof we use the energy method. We define the energy as a positive, quadratic form

$$E(t) = \frac{1}{2}\int_\Omega \widetilde{U} \cdot S\widetilde{U}dx,$$

where $\widetilde{U} = U - U_\infty$.

Because the matrix $S$ is symmetric there exists an orthogonal matrix $F$ such that $F^TSF = \Lambda_s$ and $\Lambda_s$ is diagonal with the two eigenvalues of $S$ as entries. Using this property we obtain

$$\int_\Omega \widetilde{U}^TS\widetilde{U}dx = \int_\Omega \widetilde{U}^TFF^TSFF^T\widetilde{U}dx = \int_\Omega \widetilde{W}^T\Lambda_s\widetilde{W}dx,$$

where $\widetilde{W} = F^T\widetilde{U}$. Denoting by $min(S)$ the smallest eigenvalue of the matrix $S$ we get the estimate

$$\int_\Omega \widetilde{U}^TS\widetilde{U}dx \geq min(S)\int_\Omega |\widetilde{W}|^2dx = min(S)\int_\Omega |\widetilde{U}|^2dx.$$

In the last step we used the fact that the orthogonal transformation doesn't change the $L_2$ norm. From the above inequality we have

$$||\widetilde{U}||^2_{L_2(\Omega)} \leq \frac{1}{min(S)}\int_\Omega \widetilde{U} \cdot S\widetilde{U}dx. \tag{21}$$

To show the convergence of the solution $U$ to the stationary state $U_\infty$ it is sufficient to show that the quadratic form $E(t)$ goes to zero asymptotically. We therefore estimate time derivative of the energy. Let us remark that in the case of the trivial equilibrium, the matrix $S\mathbf{R}$ is negative definite, which helps the solution to get to equilibrium. Here the situation is different as $SR$ has eigenvalues with different sign. Let us denote by $pos(SR)$ the positive eigenvalue of $SR$.

$$\begin{aligned}
\frac{d}{dt}E(t) &= \frac{1}{2}\frac{d}{dt}\int_\Omega \widetilde{U} \cdot S\widetilde{U}dx = \int_\Omega \widetilde{U}^TS\widetilde{U}_tdx \leq \\
&\leq \left(-\frac{min(SD)}{C(\Omega)} + pos(SR)\right)\int_\Omega |\widetilde{U}|^2dx \leq \\
&\leq \frac{1}{min(S)}\left(-\frac{min(SD)}{C(\Omega)} + pos(SR)\right)\int_\Omega \widetilde{U} \cdot S\widetilde{U}dx,
\end{aligned}$$

where we used the fact that matrix $S\mathbf{D}$ is positive definite, the Poincaré inequality, and (21).

To prove the convergence using the symmetrization method we suppose

$$M = -\frac{min(SD)}{C(\Omega)} + pos(SR) < 0.$$

which corresponds to the condition (17). Under this assumption, applying Gronwall's lemma we obtain

$$E(t) \leq E(0) exp\left[-\frac{2}{min(S)}|M|t\right]. \tag{22}$$

Using a similar argument as in (21) we have

$$E(0) = \frac{1}{2}\int_\Omega \widetilde{U}_0 \cdot S\widetilde{U}_0 dx \leq \frac{1}{2} max(S) \int_\Omega |\widetilde{U}_0|^2 dx. \tag{23}$$

Further estimate of (21) by (22) and (23) with $\widetilde{U} = U - U_\infty$ gives

$$||U - U_\infty||_{L_2(\Omega)} \leq \sqrt{\frac{max(S)}{min(S)}} e^{-\frac{1}{min(S)}|M|t} ||U_0 - U_\infty||_{L_2(\Omega)},$$

where $C_1 = \sqrt{\frac{max(S)}{min(S)}}$ and $C_2 = \frac{1}{min(S)}|M|$. □

## 4. Proof of the main theorem

In the previous section we proved that linearizing our model around the unique non trivial equilibrium far from the transient region produces exponential asymptotic stability in any dimension and for any choice of the initial data in case our structural conditions are satisfied (the trivial equilibrium is stable regardless the system parameters).

In the non linear case we study the asymptotic behavior of a one dimensional model (13), for which we stated a theorem of convergence of solutions to the constant, stationary states in $H^2$ norm. In this section we present its proof.

4.1. **Proof.** As for the linear case, we shall rely on the standard symmetrization method. We consider a solution as a perturbation $\widetilde{U}$ from the equilibrium $U_\infty$, that is $U = U_\infty + \widetilde{U}$, and rewrite the system (13)

$$\widetilde{U}_t = \left(\mathbf{D}(U_\infty + \widetilde{U})\widetilde{U}_x\right)_x + \vec{f}(U_\infty + \widetilde{U}),$$

where

$$\vec{f}(U) = \begin{pmatrix} \gamma_1 \widehat{p}\left(\frac{c}{c_0} - 1\right)\phi\widehat{H}(\phi^* - \phi) - \gamma_2 \widehat{p}\left(1 - \frac{c}{c_0}\right)\phi - \delta\phi \\ -dc\phi + G\phi - Rc \end{pmatrix}$$

and

$$\mathbf{D}(U) = \begin{pmatrix} f'(\phi) & -\omega\phi \\ 0 & D \end{pmatrix}.$$

Expanding the vector $\vec{f}(U_\infty + \widetilde{U})$ in the Taylor series

$$\vec{f}(U_\infty + \widetilde{U}) = \vec{f}(U_\infty) + J\vec{f}(U_\infty)\widetilde{U} + h.o.t.$$

with $\vec{f}(U_\infty) = 0$ and the Jacobian $J\vec{f}(U_\infty) = \mathbf{R}$ corresponding to the reaction matrix of the linear case, we get

$$\widetilde{U}_t = \mathbf{D}(U_\infty)\widetilde{U}_{xx} + \left(\left[\mathbf{D}(U_\infty + \widetilde{U}) - \mathbf{D}(U_\infty)\right]\widetilde{U}_x\right)_x + \mathbf{R}\widetilde{U} + \vec{H}(\widetilde{U}). \tag{24}$$

The function $\vec{H}(\widetilde{U}) = \vec{f}(U_\infty + \widetilde{U}) - \mathbf{R}\widetilde{U}$ is continuous and $\vec{H}(\widetilde{U} = 0) = 0$.

To prove the convergence of the solution to the stationary state in the $H_2$ norm we estimate $L_2$ norms of $\widetilde{U}, \widetilde{U}_x, \widetilde{U}_{xx}$ using the energy method. As usual, when dealing with linearised stability, we assume a priori that

$$\| \widetilde{U} \|_{H^2} < \widetilde{\delta} \qquad \text{for} \qquad \widetilde{\delta} \ll 1.$$

A simple continuation argument implies that on stability result which hold under a smallness assumption on the initial data. For the sake of clarity, we state the continuation principle.

**Theorem 3.** *Suppose* $\| \widetilde{U}(t) \|_{H^2} \to 0$ *as* $t \to +\infty$ *under the a priori assumption* $\| \widetilde{U}(t) \|_{H^2} \leqslant \widetilde{\delta} \ll 1$. *Then* $\| \widetilde{U}(t) \|_{H^2} < \widetilde{\delta}$ *under the assumption* $\| \widetilde{U}_0 \|_{H^2} \leqslant \widetilde{\delta}$.

We define our first energy functional

$$E_1(t) = \frac{1}{2} \int_\Omega \widetilde{U} \cdot S\widetilde{U} dx$$

and estimate its time derivative

$$\begin{aligned} \frac{d}{dt} E_1 &= \int_\Omega \widetilde{U} \cdot S\widetilde{U}_t dx = \int_\Omega \widetilde{U} \cdot \left( S\mathbf{D}(U_\infty)\widetilde{U}_x \right)_x dx + \\ &+ \int_\Omega \widetilde{U} \cdot \left( \left[ S\mathbf{D}(U_\infty + \widetilde{U}) - \mathbf{D}(U_\infty) \right] \widetilde{U}_x \right)_x + \\ &+ \int_\Omega \widetilde{U} \cdot S\mathbf{R}\widetilde{U}_t dx + \int_\Omega \widetilde{U} \cdot S\vec{H}(\widetilde{U}) dx = \sum_{i=1}^{4} I_i. \end{aligned}$$

The $I_1$ and $I_3$ integrals are the same as in the linear case so we have

$$\begin{aligned} I_1 &\leq -min(S\mathbf{D}(U_\infty)) \int_\Omega |\widetilde{U}_x|^2 dx, \\ I_3 &\leq pos(S\mathbf{R}) \int_\Omega |\widetilde{U}|^2 dx. \end{aligned}$$

The $I_2$ and $I_4$ integrals we rewrite componentwise

$$\begin{aligned} I_2 &= \int_\Omega \widetilde{U} \cdot \left( S \left[ \mathbf{D}(U_\infty + \widetilde{U}) - \mathbf{D}(U_\infty) \right] \widetilde{U}_x \right)_x = \\ &= -\int_\Omega \widetilde{U}_x \cdot S \left[ \mathbf{D}(U_\infty + \widetilde{U}) - \mathbf{D}(U_\infty) \right] \widetilde{U}_x dx = \\ &= -K \left( S_1 \int_\Omega F(\widetilde{\phi}) \widetilde{\phi}_x^2 dx - S_1 \omega \int_\Omega \widetilde{\phi}\widetilde{\phi}_x \widetilde{c}_x + \int_\Omega F(\widetilde{\phi}) \widetilde{\phi}_x \widetilde{c}_x dx - \omega \int_\Omega \widetilde{\phi} \widetilde{c}_x^2 dx \right) \leq \\ &\leq |S_1| \int_\Omega |F(\widetilde{\phi})| \widetilde{\phi}_x^2 dx + \omega |S_1| \int_\Omega |\widetilde{\phi}| \cdot |\widetilde{\phi}_x \widetilde{c}_x| + \\ &+ \int_\Omega |F(\widetilde{\phi})| \cdot |\widetilde{\phi}_x \widetilde{c}_x| dx + \omega \int_\Omega |\widetilde{\phi}| \widetilde{c}_x^2 dx, \end{aligned}$$

where $F(\phi) = f'(\phi_\infty + \widetilde{\phi}) - f'(\phi_\infty)$. Using the fact that the function $\widehat{H}(\phi^* - \phi)$ coincides with the Heaviside function at the equilibrium we have

$$\vec{H}(\widetilde{U}) = \begin{pmatrix} \gamma_1 \frac{1}{c_0} \widetilde{\phi}\widetilde{c} \\ -d\widetilde{\phi}\widetilde{c} \end{pmatrix}$$

and the integral $I_4$ can be estimated by

$$\begin{aligned} I_4 &\leq \frac{\gamma_1}{c_0}|S_1|\int_\Omega \widetilde{\phi}^2\widetilde{c}dx + d\int_\Omega \widetilde{\phi}^2\widetilde{c}dx + \\ &+ \frac{\gamma_1}{c_0}\int_\Omega \widetilde{\phi}\widetilde{c}^2dx + d|S_2|\int_\Omega \widetilde{\phi}\widetilde{c}^2dx. \end{aligned}$$

From now on we denote all positive constants depending on the parameters of the system as $\widetilde{\mathcal{C}}$ and small parameter as $\widetilde{\delta}$.

Using the Sobolev inequality for a function $u \in H_0^1([0,1])$ and continuation principle we obtain

$$||\widetilde{U}||_{L^\infty} \leq \widetilde{\mathcal{C}}||\widetilde{U}||_{H^1} \leq \widetilde{\mathcal{C}}\widetilde{\delta}. \tag{25}$$

Moreover as a consequence of the continuity of the function $F$ and the condition $F(0) = 0$ we have

$$\exists \quad \widetilde{a}(F,\delta): \quad ||F(\widetilde{\phi})||_{L^\infty} \leq \widetilde{a} \qquad \forall \quad t \geq 0. \tag{26}$$

Using the above inequalities we estimate $I_2$ and $I_4$

$$\begin{aligned} I_2 &\leq \widetilde{\mathcal{C}}||F(\widetilde{\phi})||_{L^\infty}\int_\Omega \widetilde{\phi}_x^2dx + \widetilde{\mathcal{C}}||\widetilde{\phi}||_{L^\infty}\int_\Omega \left(\widetilde{\phi}_x^2 + \widetilde{c}_x^2\right)dx + \\ &+ ||F(\widetilde{\phi})||_{L^\infty}\int_\Omega \left(\widetilde{\phi}_x^2 + \widetilde{c}_x^2\right)dx + \widetilde{\mathcal{C}}||\widetilde{\phi}||_{L^\infty}\int_\Omega \widetilde{c}_x^2dx \leq \\ &\leq \widetilde{\mathcal{C}}\widetilde{\delta}\int_\Omega \left(\widetilde{\phi}_x^2 + \widetilde{c}_x^2\right)dx, \\ I_4 &\leq \widetilde{\mathcal{C}}||\widetilde{c}||_{L_\infty}\int_\Omega \widetilde{\phi}^2dx + \widetilde{\mathcal{C}}||\widetilde{\phi}||_{L_\infty}\int_\Omega \widetilde{c}^2dx \leq \\ &\leq \widetilde{\mathcal{C}}\widetilde{\delta}\int_\Omega \left(\widetilde{\phi}^2 + \widetilde{c}^2\right)dx. \end{aligned}$$

Summing four integrals we obtain

$$\frac{d}{dt}E(t)_1 \leq \left(\widetilde{\mathcal{C}}\widetilde{\delta} - min\left(S\mathbf{D}(U_\infty)\right)\right)\int_\Omega |\widetilde{U}_x|^2dx + \left(\widetilde{\mathcal{C}}\widetilde{\delta} + pos\left(S\mathbf{R}\right)\right)\int_\Omega |\widetilde{U}|^2dx.$$

Next we define energies $E_2$ and $E_3$ as

$$\begin{aligned} E_2(t) &= \frac{1}{2}\int_\Omega \widetilde{U}_x \cdot S\widetilde{U}_x dx, \\ E_3(t) &= \frac{1}{2}\int_\Omega \widetilde{U}_{xx} \cdot S\widetilde{U}_{xx} dx \end{aligned}$$

and estimate their time derivatives using the same method as for $E_1$.

$$\begin{aligned}
\frac{d}{dt}E_2(t) &= -\int_\Omega \widetilde{U}_{xx}\cdot S\mathbf{D}(U_\infty)\widetilde{U}_{xx}dx + \\
&- \int_\Omega \widetilde{U}_{xx}\cdot S\left[\mathbf{D}(U_\infty+\widetilde{U})-\mathbf{D}(U_\infty)\right]_x\widetilde{U}_x dx + \\
&- \int_\Omega \widetilde{U}_{xx}\cdot S\left[\mathbf{D}(U_\infty+\widetilde{U})-\mathbf{D}(U_\infty)\right]\widetilde{U}_{xx}dx + \int_\Omega \widetilde{U}_x\cdot S\mathbf{R}\widetilde{U}_x dx + \\
&+ \int_\Omega \widetilde{U}_x\cdot S\left[\vec{H}(\widetilde{U})\right]_x dx, \\
\frac{d}{dt}E_3(t) &= -\int_\Omega \widetilde{U}_{xxx}\cdot S\mathbf{D}(U_\infty)\widetilde{U}_{xxx}dx + \\
&- \int_\Omega \widetilde{U}_{xxx}\cdot S\left[\mathbf{D}(U_\infty+\widetilde{U})-\mathbf{D}(U_\infty)\right]_{xx}\widetilde{U}_x dx + \\
&- 2\int_\Omega \widetilde{U}_{xxx}\cdot S\left[\mathbf{D}(U_\infty+\widetilde{U})-\mathbf{D}(U_\infty)\right]_x\widetilde{U}_{xx} dx + \\
&- \int_\Omega \widetilde{U}_{xxx}\cdot S\left[\mathbf{D}(U_\infty+\widetilde{U})-\mathbf{D}(U_\infty)\right]\widetilde{U}_{xxx}dx + \\
&+ \int_\Omega \widetilde{U}_{xx}\cdot S\mathbf{R}\widetilde{U}_{xx}dx + \int_\Omega \widetilde{U}_{xx}\cdot S\left[\vec{H}(\widetilde{U})\right]_{xx} dx.
\end{aligned}$$

Rewriting all terms componentwise and using the smallness of the $L_\infty$ norm of $F(\phi)$, $\widetilde{U}$ and $\widetilde{U}_x$ we find that

$$\begin{aligned}
\frac{d}{dt}E_2 &\le \left(\widetilde{\mathcal{C}\delta}+pos(S\mathbf{R})\right)\int_\Omega \left|\widetilde{U}_x\right|^2 dx + \\
&+ \left(\widetilde{\mathcal{C}\delta}-|min(S\mathbf{D}(U_\infty))|\right)\int_\Omega \left|\widetilde{U}_{xx}\right|^2 dx, \\
\frac{d}{dt}E_3 &\le \widetilde{\mathcal{C}\delta}\int_\Omega \left|\widetilde{U}_x\right|^2 dx + \left(\widetilde{\mathcal{C}\delta}+pos(S\mathbf{R})\right)\int_\Omega \left|\widetilde{U}_{xx}\right|^2 dx + \\
&+ \left(\widetilde{\mathcal{C}\delta}-|min(S\mathbf{D}(U_\infty))|\right)\int_\Omega \left|\widetilde{U}_{xxx}\right|^2 dx,
\end{aligned}$$

where the last term, assumed to be negative, is estimated by zero. The sum of all three energies $E(t)$ is

$$\begin{aligned}
\frac{d}{dt}E(t) &\le \left(\widetilde{\mathcal{C}\delta}+pos(S\mathbf{R})\right)||\widetilde{U}||_{L^2}^2 + \left(\widetilde{\mathcal{C}\delta}+pos(S\mathbf{R})-|min(S\mathbf{D}(U_\infty))|\right)||\widetilde{U}_x||_{L^2}^2 + \\
&+ \left(\widetilde{\mathcal{C}\delta}+pos(S\mathbf{R})-|min(S\mathbf{D}(U_\infty))|\right)||\widetilde{U}_{xx}||_{L^2}^2.
\end{aligned}$$

Using Poincaré inequality with a constant $C(\Omega)$ we compensate the first, positive term and obtain

$$\begin{aligned}\frac{d}{dt}E(t) &\leq \left(\widetilde{\mathcal{C}}\widetilde{\delta} + pos(S\mathbf{R}) - \frac{min(S\mathbf{D}(U_\infty))}{2C(\Omega)}\right)||\widetilde{U}||^2_{L^2} + \\ &+ \left(\widetilde{\mathcal{C}}\widetilde{\delta} + pos(S\mathbf{R}) - \frac{min(S\mathbf{D}(U_\infty))}{2}\right)||\widetilde{U}_x||^2_{L^2} + \\ &+ \left(\widetilde{\mathcal{C}}\widetilde{\delta} + pos(S\mathbf{R}) - min(S\mathbf{D}(U_\infty))\right)||\widetilde{U}_{xx}||^2_{L^2} \leq \\ &\leq \left(\widetilde{\mathcal{C}}\widetilde{\delta} + pos(S\mathbf{R}) - \frac{min(S\mathbf{D}(U_\infty))}{2C(\Omega)}\right)\left(\parallel \widetilde{U} \parallel^2_{L^2} + \parallel \widetilde{U}_x \parallel^2_{L^2} + \parallel \widetilde{U}_{xx} \parallel^2_{L^2}\right).\end{aligned}$$

Supposing that $\widetilde{\delta}$ can be arbitrary small, we assume

$$M = \widetilde{\mathcal{C}}\widetilde{\delta} + pos(S\mathbf{R}) - \frac{min(S\mathbf{D}(U_\infty))}{2C(\Omega)} < 0$$

and using the relation (21) we obtain

$$\frac{d}{dt}E(t) \leq -\frac{2}{min(S)}|M|E(t).$$

From the Gronwall's lemma and the explicit form of $\widetilde{U}$ we get

$$||U - U_\infty||_{H^2(\Omega)} \leq \sqrt{\frac{max(S)}{min(S)}}||U_0 - U_\infty||_{H^2(\Omega)}e^{-\frac{M}{min(S)}t},$$

Denoting $C_1 = \sqrt{\frac{max(S)}{min(S)}}$ and $C_2 = \frac{\mathcal{M}}{min(S)}$ we obtain the result stated in the theorem, which proves the convergence of the solution $U$ to the constant, stationary state $U_\infty$ as $t \to \infty$.

## 5. Modified model: without the death term

In this section we consider a modified model, in which natural death of tumour cells is neglected. As explained in the introduction, this choice is motivated by the characteristic feature of cancer that is avoidance of apoptosis. As before we analyse the existence of stationary states and asymptotic behaviour of the solution. We consider a system

$$\begin{cases}\dfrac{\partial\phi}{\partial t} = \Delta f(\phi) - \nabla\cdot(\omega\phi\nabla c) \\ \qquad\qquad +\gamma_1\widehat{p}\left(\dfrac{c}{c_0} - 1\right)\phi\widehat{H}(\phi^* - \phi) - \gamma_2\widehat{p}\left(1 - \dfrac{c}{c_0}\right)\phi \\ \dfrac{\partial c}{\partial t} = D\triangle c - dc\phi + G\phi - Rc,\end{cases} \tag{27}$$

The system (27) has a trivial, stationary solution $(\phi_\infty, c_\infty) = (0, 0)$ regardless the parameters. Moreover, there exist a non trivial, positive, constant equilibrium

$$(\phi_\infty, c_\infty) = \left(\frac{c_0 R}{G - dc_0}, c_0\right) \qquad \text{if} \qquad G > dc_0. \tag{28}$$

**Remark 2.** Apart from stationary solutions stated above, the system (27) has a family of equilibrium states characterised by a parameter $p$ in the form

$$(\phi_\infty, c_\infty) = \left(p, \frac{Gp}{R+dp}\right)$$

if the following conditions are satisfied

$$\begin{cases} p > \phi^* \\ p > \frac{Rc_0}{G-dc_0} \\ G > dc_0. \end{cases}$$

This is motivated by the fact that assuming $c_\infty > c_0$ the condition

$$\gamma_1 \widehat{p}\left(\frac{c_\infty}{c_0} - 1 - \frac{\epsilon}{2c_0}\right)\phi_\infty \widehat{H}(\phi^* - \phi_\infty) - \gamma_2 \widehat{p}\left(1 - \frac{c_\infty}{c_0} - \frac{\epsilon}{2c_0}\right)\phi_\infty = 0$$

is satisfied for all $\phi_\infty > \phi^*$.

Let's denote $\widetilde{\alpha}(\phi, c) = \gamma_1 \widehat{p}\left(\frac{c}{c_0} - 1\right)\phi \widehat{H}(\phi^* - \phi) - \gamma_2 \widehat{p}\left(1 - \frac{c}{c_0}\right)_+ \phi$ and leave $\beta(\phi, c)$ the same as in the original model.

Again we shall study the asymptotic behaviour close to the non trivial, constant, stationary state of the one dimensional model

$$\begin{cases} \dfrac{\partial \phi}{\partial t} = (f(\phi))_{xx} - (\omega \phi c_x)_x + \widehat{\alpha}(\phi, c) \\ \dfrac{\partial c}{\partial t} = D c_{xx} + \beta(\phi, c). \end{cases} \tag{29}$$

In matrix form, with $U = (\phi \quad c)^T$, we have

$$U_t = (\mathbf{D}(U)U_x)_x + \vec{f}(U), \tag{30}$$

with $\vec{f}(U) = (\widetilde{\alpha}, \beta)^T$ and $\mathbf{D}(U) = \begin{pmatrix} f'(\phi) & -\omega\phi \\ 0 & D \end{pmatrix}$ being a diffusion matrix.

As previously, considering the solution as a small perturbation $\widetilde{U}$ from the equilibrium, $U = U_\infty + \widetilde{U}$, we get a system

$$\widetilde{U}_t = \mathbf{D}(U_\infty)\widetilde{U}_{xx} + \left(\left[\mathbf{D}(U_\infty + \widetilde{U}) - \mathbf{D}(U_\infty)\right]\widetilde{U}_x\right)_x + \mathbf{R}\widetilde{U} + \vec{H}(\widetilde{U}) \tag{31}$$

with a reaction matrix $\mathbf{R} = \begin{pmatrix} L_1 & L_2 \\ G - dc_\infty & -(R + d\phi_\infty) \end{pmatrix}$.

The diffusion and reaction matrices depend on the stationary state: $\mathbf{D} = \mathbf{D}(U_\infty)$, $\mathbf{R} = \mathbf{R}(U_\infty)$, so for both models they are different. However, for simplicity, we use the same notation as in the original model.

From the fact that $c_\infty = c_0$ the element $L_1$ equals

$$L_1 = \gamma_1 \widehat{p}\left(\frac{c_\infty}{c_0} - 1\right)\left(\phi \widehat{H}(\phi^* - \phi)\right)'_{(\phi_\infty, c_\infty)} - \gamma_2 \widehat{p}\left(1 - \frac{c_\infty}{c_0}\right) = 0,$$

and $L_2$ reduces to

$$L_2 = \frac{\gamma_1}{c_0}\phi_\infty.$$

The following theorem gives the description of the asymptotic behaviour of the solution for the initial state being a small perturbation form the equilibrium. We shall prove it under the assumption that structural conditions (14), (15), (16), (17) with $\Gamma = 1$ are satisfied.

**Theorem 4.** *Suppose $G > dc_0$ and*

$$\| U_0 - U_\infty \|_{H^2(\Omega)} \leq \delta$$

*for $\delta$ small enough. Then the equilibrium of the system (30)*

$$(\phi_\infty, c_\infty) = \left( \frac{Rc_0}{G - dc_0}, c_0 \right)$$

*is asymptotically stable and*

$$||U - U_\infty||_{H^2(\Omega)} \leq C_1 e^{-C_2 t} ||U_0 - U_\infty||_{H^2(\Omega)},$$

*where $C_1$ and $C_2$ are positive constants depending on the structure of the system.*

*Proof.* The proof is very similar to the one of the Theorem 1 so we only sketch it.

We consider a solution $\widetilde{U}$ of the system (31). Because $\widetilde{U} = U - U_\infty$ showing that, for small initial data, its $H^2$ norm converges to zero asymptotically means showing that $U$ converges to equilibrium in $H^2$ norm. As before, using classical symmetrization method, we define quadratic forms, energies, as

$$\int_\Omega \widetilde{U} \cdot S\widetilde{U} dx, \quad \int_\Omega \widetilde{U}_x \cdot S\widetilde{U}_x dx, \quad \int_\Omega \widetilde{U}_{xx} \cdot S\widetilde{U}_{xx} dx,$$

and estimate time derivatives. Symmetric and positive definite matrix $S$ is such that matrices $S\mathbf{D}$, $S\mathbf{R}$ are symmetric. It has the form

$$S = \begin{pmatrix} \frac{D - f'(\phi_\infty)}{\omega \phi_\infty} & 1 \\ 1 & \frac{1}{G - dc_\infty} \left( \frac{D - f'(\phi_\infty)}{\omega} \frac{\gamma_1}{c_0} - (R + d\phi_\infty) \right) \end{pmatrix}.$$

Moreover, if the structural conditions are satisfied then $\mathbf{SD}$ is positive definite. Denoting by $E(t)$ the sum of three energies, assuming the initial data is small enough, using the continuation principle and Poincaré inequality we obtain

$$\frac{d}{dt} E(t) \leq \frac{2}{min(S)} \left( \widetilde{C}\widetilde{\delta} + pos(S\mathbf{R}) - \frac{min(S\mathbf{D}(U_\infty))}{2C(\Omega)} \right) E(t),$$

where $min(S)$ is the smaller eigenvalue of the matrix $S$ and $pos(S\mathbf{R})$ is a positive eigenvalue. In the next step we suppose that

$$M = \widetilde{C}\widetilde{\delta} + pos(S\mathbf{R}) - \frac{min(S\mathbf{D}(U_\infty))}{2C(\Omega)} < 0$$

and use Gronwall's lemma to get

$$\| U - U_\infty \|_{H^2} \leq \sqrt{\frac{max(S)}{min(S)}} \| U_0 - U_\infty \|_{H^2} \, e^{-\frac{|M|}{min(S)} t},$$

where $C_1 = \sqrt{\frac{max(S)}{min(S)}}$ and $C_2 = \frac{|M|}{min(S)}$. □

## Acknowledgments

MDF acknowledges support from the KAUST award of Prof. Peter A. Markowich (University of Cambridge). The authors are grateful to Prof. Luigi Preziosi for helpful suggestions and comments. Part of this work has been performed when the authors were attending an advanced course in Biomathematics at CRM (Autonomous University of Barcelona): they are grateful to the organizers for their support.

## References

[1] H. Amann. Global existence for semilinear parabolic systems. *J. Reine Angew. Math.*, 360:47–83, 1985.

[2] S. Astanin and L. Preziosi. Multiphase modells of tumour growth. *Selected Topics on Cancer Modelling: Genesis - Evolution - Immune Competition - Therapy, Nicola Bellomo, Mark Chaplain, and Elena De Angelis*, 2007.

[3] N. Bellomo and L. Preziosi. Modelling and mathematical problems related to tumor evolution and its interaction with the immune system. *Math. Comput. Modelling*, 32(3-4):413–452, 2000.

[4] V. Calvez and J. A. Carrillo. Volume effects in the Keller-Segel model: energy estimates preventing blow-up. *J. Math. Pures Appl. (9)*, 86(2):155–175, 2006.

[5] E. Conway, D. Hoff, and J. Smoller. Large time behavior of solutions of systems of nonlinear reaction-diffusion equations. *SIAM J. Appl. Math.*, 35(1):1–16, 1978.

[6] L. Desvillettes and K. Fellner. Entropy methods for reaction-diffusion systems. *Discrete Contin. Dyn. Syst.*, (Dynamical Systems and Differential Equations. Proceedings of the 6th AIMS International Conference, suppl.):304–312, 2007.

[7] L. Desvillettes and K. Fellner. Entropy methods for reaction-diffusion equations: slowly growing a-priori bounds. *Rev. Mat. Iberoam.*, 24(2):407–431, 2008.

[8] M. Di Francesco, K. Fellner, and P. A. Markowich. The entropy dissipation method for spatially inhomogeneous reaction—diffusion-type systems. *Proc. R. Soc. Lond. Ser. A Math. Phys. Eng. Sci.*, 464(2100):3273–3300, 2008.

[9] W. B. Fitzgibbon, S. L. Hollis, and J. J. Morgan. Stability and Lyapunov functions for reaction-diffusion systems. *SIAM J. Math. Anal.*, 28(3):595–610, 1997.

[10] J. Folkman. Tumor angiogenesis. *Cancer Medicine, J.F.Holland, R.C.Bast, D.L.Morton, E.Frei, D.W.Kufe, R.R.Weichselbaum*, pages 181–204, 1997.

[11] K. O. Friedrichs. Differential equations of symmetric type. In *Fluid Dynamics and Applied Mathematics (Proc. Sympos., Univ. of Maryland, 1961)*, pages 51–65. Gordon and Breach, New York, 1962.

[12] C.W. Greider and E.H. Blackburn. Telomeres, telomerase and cancer. *Scientific American*, 2:92–97, 1996.

[13] C. Gridelli. Targeted therapy developments in the treatment of non-small cell lung cancer: a promising but long and winding road. *Current Opinion in Oncology*, 20(2):145–147, 2008.

[14] D. Hanahan and R. A. Weinberg. The hallmarks of cancer. *Cell*, 100(1):57–70, January 2000.

[15] R. K. Jain. Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy. *Science*, 307:58–62, January 2005.

[16] A. Juengel. Diffusive and nondiffusive population models. Technical report, Submitted for publication.

[17] S. Klainerman and A. Majda. Singular limits of quasilinear hyperbolic systems with large parameters and the incompressible limit of compressible fluids. *Comm. Pure Appl. Math.*, 34(4):481–524, 1981.

[18] R. Kowalczyk. Preventing blow-up in a chemotaxis model. *J. Math. Anal. Appl.*, 305(2):566–588, 2005.

[19] Y. Lou and W.-M. Ni. Diffusion, self-diffusion and cross-diffusion. *J. Differential Equations*, 131(1):79–131, 1996.

[20] R. H. Martin, Jr. and M. Pierre. Nonlinear reaction-diffusion systems. In *Nonlinear equations in the applied sciences*, volume 185 of *Math. Sci. Engrg.*, pages 363–398. Academic Press, Boston, MA, 1992.

[21] H. Matano and M. Mimura. Pattern formation in competition-diffusion systems in nonconvex domains. *Publ. Res. Inst. Math. Sci.*, 19(3):1049–1079, 1983.

[22] M. Mimura. Stationary pattern of some density-dependent diffusion system with competitive dynamics. *Hiroshima Math. J.*, 11(3):621–635, 1981.

[23] M. Mimura and K. Kawasaki. Spatial segregation in competitive interaction-diffusion equations. *J. Math. Biol.*, 9(1):49–64, 1980.

[24] W.-M. Ni. Diffusion, cross-diffusion, and their spike-layer steady states. *Notices Amer. Math. Soc.*, 45(1):9–18, 1998.

[25] L. Preziosi. Modelling tumour growth and progression. *Progress in industrial mathematics at ECMI 2002*, 5:53–66.

[26] L. Preziosi and A. Tosin. Multiphase modelling of tumour growth and extracellular matrix interaction: mathematical tools and applications. *J. Math. Biol.*, 58(4-5):625–656, 2009.

[27] F. Rothe. *Global Solutions of Reaction-Diffusion Systems*. Lecture Notes in Mathematics. Springer-Verlag, Berlin, 1984.

[28] Y. Shizuta and S. Kawashima. Systems of equations of hyperbolic-parabolic type with applications to the discrete boltzmann equation. *Hokkaido Math. J.*, 14:249–275, 1985.

[29] J. Smoller. *Shock waves and reaction-diffusion equations*, volume 258 of *Grundlehren der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Science]*. Springer-Verlag, New York, 1983.

[30] A. M. Turing. The chemical basis of morphogenesis. *Philo. Trans. Roy. Soc. Lond. Ser. B*, 237:5–72, 1952.

[31] L. K. Wai. Telomeres, telomerase, and tumorigenesis – a review. *MedGenMed*, 6(3):19, 2004.

[32] O. Warburg. On the Origin of Cancer Cells. *Science*, 123(3191):309–314, 1956.