Adhesion-driven patterns in a calcium-dependent model of cancer cell movement

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Received: date / Accepted: date

Abstract Cancer cells exhibit increased motility and proliferation, which are instrumental in the formation of tumours and metastases. These pathological changes can be traced back to malfunctions of cellular signalling pathways, and calcium signalling plays a prominent role in these. We formulate a new model for cancer cell movement which for the first time explicitly accounts for the dependence of cell proliferation and cell-cell adhesion on calcium. At the heart of our work is a non-linear, integro-differential (non-local) equation for cancer cell movement, accounting for cell diffusion, advection and proliferation. We also employ an established model of cellular calcium signalling with a rich dynamical repertoire that includes experimentally observed periodic wave trains and solitary pulses. The cancer cell density exhibits travelling fronts and complex spatial patterns arising from an adhesion-driven instability (ADI). We show how the different calcium signals and variations in the strengths of cell-cell attraction and repulsion shape the emergent cellular aggregation patterns, which are a key component of the metastatic process. Performing a linear stability analysis, we identify parameter regions corresponding to ADI. These regions are confirmed by numerical simulations, which also reveal different types of aggregation patterns and these patterns are significantly affected by $\text{Ca}^{2+}$. Our study demonstrates that the maximal cell density decreases with calcium concentration, while the frequencies of the calcium oscillations and the cell density oscillations are approximately equal in many cases. Furthermore, as the calcium levels increase the speed of the travelling fronts increases, which is related to a higher cancer invasion potential. These novel insights provide a step forward in the design of new cancer treatments that may rely on controlling the dynamics of cellular calcium.

Keywords Cancer cells · Non-local model of cancer · Calcium · Cell-cell adhesion · Travelling wave · Aggregation patterns · Adhesion-driven instability · Oscillatory signalling pathway
Mathematics Subject Classification (2000) MSC 35B36 · MSC 35Q92 · MSC 35R09 · MSC 70K50 · MSC 92C15 · MSC 92C17 · MSC 92-08

1 Introduction

Cell-cell adhesion and cellular proliferation are fundamental features of multicellular organisms, along with cell division, migration and apoptosis. These processes are orchestrated and coordinated by a multitude of cellular signalling pathways (Alberts et al, 2000). When these signalling cascades are disturbed, numerous pathologies ensue, including cancer. Amongst the many molecular changes that characterise cancer, alterations of intracellular calcium (Ca\textsuperscript{2+}) signalling have been identified as a crucial driver (Colomer and Means, 2007). In particular, Ca\textsuperscript{2+} has been reported as a key factor in cellular proliferation (Roderick and Cook, 2008; Shapovalov et al, 2013) and in cellular adhesion (Weinberg, 2013). Here, we formulate and analyse for the first time a model that describes the evolution of a cancer cell density incorporating the effects of Ca\textsuperscript{2+} in the adhesion and proliferation processes.

Rising levels of intracellular Ca\textsuperscript{2+} have been shown to increase the proliferation of cancer cells in various cancer types such as breast and prostate cancer, melanoma, hepatocellular and non-small-cell lung carcinoma (Prevarskaya et al, 2014, 2018). Experiments (Simpson and Arnold, 1986; Taylor and Simpson, 1992) have shown that increasing extracellular Ca\textsuperscript{2+} levels increased intracellular calcium Ca\textsuperscript{2+} levels, which increased the cell number and the DNA synthetic ability of cell lines.

Cellular adhesion is mediated through cadherins, which are transmembrane proteins and belong to the class of calcium-dependent cell adhesion molecules (CAMs) (Weinberg, 2013). As an example, consider epithelial cells, which bind to each other by linking the extracellular domains of E-cadherins (Morales et al, 2002). The cytosolic domain of E-cadherin binds to β-catenin, which in turn binds to the cytoskeleton. Changes in the function of β-catenin result in the loss of the ability of E-cadherin to sustain sufficient cell-cell adhesion (Makena and Rao, 2020; Wijnhoven et al, 2000), while alterations in any type of cadherin expression may affect cell adhesion and signal transduction (Cavallaro et al, 2002). Intracellular Ca\textsuperscript{2+} directly impacts on the dynamics of both cadherins and catenins (Ko et al, 2001). Moreover, Hills et al (2012) have shown that activation of extracellular Ca\textsuperscript{2+}-sensing receptors leads to an increase in E-cadherin expression and an increase in the binding of β-catenin. In cancer, disrupted cell-cell adhesion due to abnormal expression of cadherins and their associated catenins has been linked to metastasis (Morales et al, 2002). For instance, Byers et al, 1995; Cavallaro and Christofori, 2004 have shown a reduced expression of cadherins in various cancer types, including melanoma, prostate, breast cancer, invasive carcinomas and carcinoma cell lines, and cancers of epithelial origin, when Ca\textsuperscript{2+} levels are increased. This results in a reduced force between cells and consequently to cell migration. These results are in line with findings that show that altering CAM function in metastatic cancer cells blocked their ability to invade healthy tissue and move to secondary sites (Kotteas et al, 2014; Naik et al, 2008; Slack-Davis et al, 2009; Zhu et al, 1992). Taken together, the combined changes in cell-cell adhesion and the increase in the proliferation rate and their dependence on Ca\textsuperscript{2+} are important mechanisms in cancer and enhance the formation of cancer cell clusters/aggregations that can migrate in a collective manner, a process critical for cancer progression (Friedl et al, 2004; Glimsky et al, 2003; Knútsdóttir et al, 2014).

Ca\textsuperscript{2+} signalling uses an extensive molecular repertoire of signalling components termed the Ca\textsuperscript{2+} signalling “toolkit” (Berridge et al, 2000). A key feature of Ca\textsuperscript{2+} signalling is Ca\textsuperscript{2+} release from the Endoplasmic Reticulum (ER) to the cytosol through inositol-1,4,5-trisphosphate (InsP\textsubscript{3}) receptors (InsP\textsubscript{3}Rs). Together with Ca\textsuperscript{2+} resequestration from the cytosol through sarco-endoplasmic Ca\textsuperscript{2+} ATPase (SERCA) pumps, a process known as calcium-induced-calcium release can give rise to intracellular Ca\textsuperscript{2+} oscillations (Berridge and Galione, 1988; Berridge et al, 2000; Parekh, 2011; Dupont and Combettes, 2016; Thul et al, 2008; Dupont et al, 2011a, 2016b; Schuster et al, 2002; Uhlén and Fritz, 2010; Powell et al, 2020; Sneyd et al, 2017). In addition, Ca\textsuperscript{2+} can spread across a population of cells, forming an intercellular Ca\textsuperscript{2+} wave (Bereiter-Hahn et al, 2007).
Mathematical models of intracellular $\text{Ca}^{2+}$ oscillations vary substantially in their complexity, ranging from two coupled nonlinear ordinary differential equations (ODEs) to three-dimensional hybrid partial differential equations (PDEs) — see Dupont et al (2016a), Falcke et al (2018) for recent perspectives. In the present study, we employ the model developed in Atri et al (1993), which for simplicity we will call the ‘Atri model’. The Atri model is a so-called ‘minimal’ model consisting of only two ODEs that can generate non-linear relaxation oscillations at constant $\text{InsP}_3$ concentrations (Dupont et al, 2016b; Keener and Sneyd, 2009a,b). Importantly, the Atri model most consistently described hormone-induced $\text{Ca}^{2+}$ oscillations in HeLa cells (an immortal cell line derived from cervical cancer cells), compared to seven other minimal models for intracellular $\text{Ca}^{2+}$ oscillations (Estrada et al, 2016). In addition, the mathematical structure of the Atri model allows us to determine analytically the parameter range sustaining calcium oscillations and other bifurcations of the system — see Atri et al (1993), Kaouri et al (2019). Despite its simplicity, the Atri model generates prototypical $\text{Ca}^{2+}$ signals such as $\text{Ca}^{2+}$ oscillations and action potentials which correspond to periodic wave trains and solitary pulses, respectively, when $\text{Ca}^{2+}$ diffusion is taken into account. The Atri model is, hence, sufficient for our modelling framework since our focus is on studying cancer cell movement with $\text{Ca}^{2+}$ signals as input.

We base our model for the cancer cell density on previously published work (Armstrong et al (2006); Bitsouni et al (2017, 2018); Bitsouni and Eftimie (2018); Chaplain et al (2011); Dyson et al (2016); Domschke et al (2014); Eftimie et al (2017); Gerisch and Chaplain (2008); Gerisch and Painter (2010); Green et al (2010); Hillen and Buttenschön (2019); Painter et al (2015); Shuttleworth and Trucu (2019); Szymańska et al (2009)). These models include nonlinear PDEs with reaction terms for cell growth/proliferation and a non-local advection term, describing cell-cell adhesion. The latter is expressed as an integral term that describes how a cell at position $\mathbf{x}$ adheres to other cells at position $\mathbf{x} \pm \mathbf{s}$, for some $\mathbf{s} > 0$ within the cell’s sensing radius (Armstrong et al, 2006). In the present work, both the rate of cell proliferation and the strength of adhesion are taken to be $\text{Ca}^{2+}$-dependent. It is worth noting that additional molecular components and processes could be included. For instance, integrins and TGF-$\beta$ proteins are explicitly represented in (Bitsouni et al, 2018; Engwer et al, 2017) and (Bitsouni et al, 2017; Eftimie et al, 2017), respectively. Moreover, collagen-controlled cell-matrix adhesion, where $\text{Ca}^{2+}$ is considered as constant, has been developed in (Shuttleworth and Trucu, 2019), while (Ramis-Conde et al, 2008, 2009) studied cadherin-dependent cellular adhesion in an individual-cell-based multiscale model. However, since our study explores the impact of intracellular $\text{Ca}^{2+}$ on cancer cell movement, we focus on diffusion, cell-cell adhesion and proliferation, the core components of cancer cell behaviour.

The structure of the paper is as follows. In Section 2, we formulate a new model that captures the crucial role of $\text{Ca}^{2+}$ signalling in cancer by incorporating $\text{Ca}^{2+}$-dependent adhesion and proliferation effects. In Section 3, we perform a linear stability analysis and show the ability of the model to generate ADIs and hence cell aggregations. In Section 4, we solve the model numerically. We present various types of aggregation patterns, as well as travelling wave patterns. Taken together, our work provides new insights into the connection between $\text{Ca}^{2+}$ signalling and cancer cell movement, and suggests a mechanistic approach that can contribute to developing $\text{Ca}^{2+}$-transport-targeting tools for cancer diagnosis and treatment (Prevarskaya et al, 2013, 2014).
2 A non-local model for calcium signalling in cancer

We denote by \( u(x,t) \) the cancer cell density, by \( c(x,t) \) the cytosolic Ca\(^{2+}\) concentration and \( h(x,t) \) is the fraction of InsP\(_3\)Rs on the ER that have not been inactivated by Ca\(^{2+}\). Then the model takes the form

\[
\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + J_{ER} - J_{pump}, \tag{2.1a}
\]

\[
\tau_p \frac{\partial h}{\partial t} = \frac{k_3^2}{k_3^2 + c^2} - h, \tag{2.1b}
\]

\[
\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} - \frac{\partial}{\partial x} \left( uF[c,u] + f(c,u) \right), \tag{2.1c}
\]

where

\[ J_{ER} = kf\mu([\text{InsP}_3])h \frac{bk_1 + c}{k_1 + c} \quad \text{and} \quad J_{pump} = \frac{\gamma c}{k_\gamma + c}. \]

Equations (2.1a) and (2.1b) are the spatially extended Atri model for Ca\(^{2+}\) signalling. In equation (2.1a) the term \( J_{ER} \) is the flux of Ca\(^{2+}\) from the ER into the cytosol through InsP\(_3\)Rs, where the constant \( k_f \) is the calcium flux when all InsP\(_3\)Rs are open and activated, \( b \) is a basal current through the InsP\(_3\)Rs, and \( \mu([\text{InsP}_3]) = [\text{InsP}_3]/(k_\mu + [\text{InsP}_3]) \) is the fraction of the InsP\(_3\)Rs that have InsP\(_3\) bound and is an increasing function of [InsP\(_3\)]. In the spatially clamped Atri model relaxation oscillations can be sustained at constant [InsP\(_3\)], and \( \mu \) is a bifurcation parameter (see Atri et al. (1993); Kaouri et al. (2019) for representative bifurcation diagrams). \( J_{pump} \) is the Ca\(^{2+}\) flux through the SERCA pumps where \( \gamma \) is the maximal pump rate and \( k_\gamma \) is the Ca\(^{2+}\) concentration at which the pump rate is at half-maximum. In equation (2.1b) the time constant \( \tau_p > 1 \) represents the slower time-scale of the inactivation of the InsP\(_3\)R by Ca\(^{2+}\) compared to its activation (Atri et al. 1993, Dupont et al. 2016b). Equations (2.1c) is a non-local, non-linear PDE for the cell density that combines diffusion, cell-cell adhesion (advection) and proliferation (see Domschke et al. (2014) and references therein). All parameter values can be found in Tables 1 and 2.

2.1 Effect of Ca\(^{2+}\) on cell proliferation

The role of Ca\(^{2+}\) signals in the proliferation of cancer cells is cancer type specific due to differences in the behaviour of the Ca\(^{2+}\)-conducting channels and pumps (Monteith et al. 2017). Here, we assume that Ca\(^{2+}\) enhances the proliferation rate since it has been shown that InsP\(_3\)Rs are upregulated in cancer (Monteith et al. 2007, 2017), leading to an enhanced proliferation and survival in all types of cancer (Cárdenas et al. 2016; Prevarskaya et al. 2018; Rezuchova et al. 2019; Tsunoda et al. 2005). Moreover, assuming that cancer cells proliferate in a logistic manner (to describe the observed slow-down in tumour growth following the loss of nutrients (Laird 1964)), we choose the growth function \( f(c,u) \) as

\[
f(c,u) = r_1 \left( 1 + g(c) \right) u \left( 1 - \frac{u}{k_u} \right), \tag{2.2}
\]

where \( r_1 \) is the basal growth rate of \( u \) and \( k_u \) is the carrying capacity. The Ca\(^{2+}\)-dependent function \( g(c) \) describes the enhanced proliferation of cancer cells that is associated with a major re-arrangement of Ca\(^{2+}\) pumps, Na\(^+\)/Ca\(^{2+}\) exchangers and Ca\(^{2+}\) channels (Capio et al. 2007; Simpson and Arnold 1986, Taylor and Simpson 1992); we assume that it is given by

\[
g(c) = \frac{r_2 c^2}{r_3 + c^2}, \tag{2.3}
\]

i.e. it saturates as \( c \) increases and vanishes at \( c = 0 \).
2.2 Effect of Ca\(^{2+}\) on cell-cell adhesion

Cancer cells often show a decrease in cell-cell adhesion compared to healthy cells, which correlates with tumour invasion and metastasis (Cavallaro and Christofori, 2001; Makena and Rao, 2020). When adhesive bonds are formed and broken a cell-cell adhesion-mediated directed cancer cell migration occurs as a result of cellular attraction and repulsion. The cell-cell adhesion forces are created through the binding of adhesive molecules such as cadherins (Byers et al, 1995; Kim et al, 2011; Panorchan et al, 2006), see Section 1. Thus, we consider a calcium-dependent adhesion term in a bounded domain \( \Omega = [0, R_s] \) in the cell density equation (2.1c) where the non-local cell-cell interactions are described by a function that depends on cell density and Ca\(^{2+}\),

\[
F[c, u] = \frac{S(c(x,t))}{R_s} \int_0^{R_s} K_{int}(r) \left( u(x+r,t) - u(x-r,t) \right) dr,
\]

where \( K_{int} \in L^\infty(\Omega) \) is the interaction kernel between cancer cells, with \( \partial_r K_{int} \in L^\infty(\Omega) \), and \( S(c) \) the adhesion strength function, which depends on Ca\(^{2+}\), \( R_s > 0 \) is the cell sensing ‘radius’, i.e. the maximum range over which a cell can detect surrounding cells (Armstrong et al, 2006). Here, we assume that \( R_s \) equals five times the length of an average cell (Armstrong et al, 2006; Gerisch and Chaplain, 2008). Biologically this represents the extent of the cell’s protrusions, e.g. filopodia. We define an attraction-repulsion kernel (see Eftimie et al, 2007, 2017) as

\[
K_{int}(x) = q_a K_a(x) - q_r K_r(x),
\]

with \( q_a \) and \( q_r \) describing the magnitude of attractive and repulsive interactions, respectively, and \( K_a(x) \) and \( K_r(x) \) denoting the spatial range over which these interactions take place. We will take the kernel to be attractive at medium/long ranges (i.e. at the edges of the cell) ensuring cell cohesion, and repulsive at very short ranges (i.e. over the cell surface) to represent cell volume-exclusion effects and thus prevent unrealistically high cell densities (Palachanis et al, 2015). Throughout the rest of this study, we consider Gaussian attraction and repulsion kernel (Eftimie et al, 2007) so that

\[
K_{int}(x) = \frac{q_a}{\sqrt{2\pi m_a^2}} e^{-\frac{(x-s_a)^2}{2m_a^2}} - \frac{q_r}{\sqrt{2\pi m_r^2}} e^{-\frac{(x-s_r)^2}{2m_r^2}},
\]

where \( s_a \) and \( s_r \) represent the location of maximal attraction and repulsion, respectively, with \( s_r < s_a < R_s \). The constants \( m_j = s_j/8, j = a, r \), represent the widths of the interaction kernels, respectively. They are chosen such that the support of more than 98% of the mass of the kernels is inside the interval \([0, \infty)\).

As discussed in Section 1, expression of Ca\(^{2+}\)-dependent cell-cell adhesion molecules is reduced in several human cancer types when Ca\(^{2+}\) levels are increased (Byers et al, 1995; Cavallaro and Christofori, 2004), which leads to a decreased adhesive force between the cells. A biologically realistic choice for the adhesion strength function is thus

\[
S(c) = s^* \left( 1 - \frac{a_1 c}{a_2 + c} \right)
\]

an inverse Hill function for \( c \) that tends to zero for large \( c \) values. We estimated the parameters \( a_1, a_2 \) and \( s^* \) so that the adhesive force exhibits a biologically sensible response to Ca\(^{2+}\) variations (for parameter values see Table 2).
2.3 Non-dimensionalized model

To non-dimensionalize the model (2.1), we define the following quantities:

\[
\tilde{t} = \frac{t}{\tau_h}, \quad \tilde{x} = \frac{x}{L_0}, \quad \tilde{c} = \frac{c}{k_1}, \quad \tilde{u} = \frac{u}{k_u}, \quad \tilde{R}_s = \frac{R_s}{L_0}, \quad \tilde{q}_a = k_u q_a, \quad \tilde{q}_r = k_u q_r,
\]

\[
\tilde{S}(\tilde{c}) = \frac{\tau_h}{\tau_m^2} S(k_1 \tilde{c}).
\]

The length scale, \( L_0 \), is defined as the typical cell size/diameter of an average cancer cell. Cancer cells can be smaller or bigger than healthy cells depending on several factors including the cancer type. HeLa cells, for example, are around 40 \( \mu \)m in diameter, while they measure 20 \( \mu \)m in their naturally compressed state (Boulter et al. 2006; Puck et al. 1956). Generally, the average cancer cell diameter is between 20 – 30 \( \mu \)m (Ha and Bhagavan. 2011). Here, we choose \( L_0 = 20 \mu m \), while we set the time scale as \( \tau_h = 2s \) (Kaouri et al. 2019).

In addition, we rescale the cell density with the cell carrying capacity, \( k_u \), taken to be \( 6.7 \cdot 10^4 \) cell/volume (Gerisch and Chaplain 2008). We obtain the dimensionless parameters:

\[
\tilde{D}_c = \frac{D_c \tau_h}{L_0^2}, \quad K_1 = \frac{k_f \tau_h}{k_1}, \quad \Gamma = \frac{\gamma \tau_h}{k_1}, \quad K = \frac{k_r}{k_1}, \quad K_2 = \frac{k_r}{k_1},
\]

\[
\tilde{D}_a = \frac{D_a \tau_h}{L_0^2}, \quad \tilde{r}_1 = r_1 \tau_h, \quad \tilde{r}_3 = \frac{r_3}{k_1^2},
\]

We also briefly discuss the choice of the diffusion coefficients. It has been shown in (Allbritton et al. 1992) that the diffusion coefficient of free cytosolic Ca\(^{2+}\) is \( 2.23 \cdot 10^{-6} \) cm\(^2\) s\(^{-1}\). The action of omnipresent Ca\(^{2+}\) buffers can be subsumed into an effective Ca\(^{2+}\) diffusion coefficient, which we here set to \( D_c = 0.2 \cdot 10^{-6} \) cm\(^2\) s\(^{-1}\). Assuming that the delay of Ca\(^{2+}\) propagation through gap junctions joining cells is negligible, we arrive at \( \tilde{D}_c = 0.1 \). The diffusion coefficient of cancer cells is in the range of \( 10^{-11} - 10^{-9} \) cm\(^2\) s\(^{-1}\) (Bray 1992; Chaplain and Lolas 2006; Franssen et al. 2019). This corresponds to dimensionless values of \( \tilde{D}_a \) between \( 5 \cdot 10^{-6} - 5 \cdot 10^{-3} \).

As in (Domschke et al. 2014), we introduce the dimensionless functions \( \tilde{K}_{a,r} (\tilde{r}) = L_0 K_{a,r} (L_0 \tilde{r}) = L_0 K_{a,r} (r) \) so that

\[
\tilde{K}_{\text{int}} (\tilde{r}) = L_0 k_u (q_a K_a (r) - q_r K_r (r)).
\]

Therefore, we have for the non-local term

\[
F [c, u] (x, t) =
\]

\[
= \frac{L_0}{\tau_h \tilde{R}_s} \tilde{S}(\tilde{c}) \tilde{q}_a \int_0^{\tilde{R}_s} \left( \tilde{K}_a (\tilde{r}) - \frac{\tilde{q}_r}{\tilde{q}_a} \tilde{K}_r (\tilde{r}) \right) (\tilde{u} (\tilde{x} + \tilde{r}, \tilde{t}) - \tilde{u} (\tilde{x} - \tilde{r}, \tilde{t})) \, d\tilde{r}
\]

\[
= \frac{L_0}{\tau_h \tilde{R}_s} \tilde{s}^* \tilde{q}_a \tilde{F} \tilde{F} [\tilde{c}, \tilde{u}] (\tilde{x}, \tilde{t}) = F_0 \tilde{F} \tilde{F} [\tilde{c}, \tilde{u}],
\]

where \( F_0 = L_0 \tilde{s}^* \tilde{q}_a / (\tau_h \tilde{R}_s) \) is the typical cancer cell speed.

Clark and Vignjevic (2015) showed that cancer cell speeds cannot exceed 10 \( \mu \)m/min. We consider the typical cancer cell speed, \( F_0 \), to vary between 1 \( \mu \)m/min and 10 \( \mu \)m/min to account for various cancer types which are characterised by slower or faster cells (e.g. for A375M2 human melanoma the speed ranges between 0.5 – 10 \( \mu \)m/min, and for MDA-MB-231 breast cancer it ranges between 0.4 – 4.2 \( \mu \)m/min). We find that the ratio \( \tau_h F_0 / L_0 \) is in the range

\[
0.0017 \leq \frac{\tau_h}{L_0} F_0 \leq 0.017,
\]

leading to

\[
0.008 \leq \tilde{s}^* \tilde{q}_a \leq 0.08. \tag{2.6}
\]
This provides bounds for the value of \( \tilde{s} \tilde{q} \) we are going to choose in Sections 3 and 4.

After dropping the tildes for notational convenience, we obtain the following non-dimensional system:

\[
\begin{align*}
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + \mu K_1 h \frac{b + c}{1 + c} - \frac{\Gamma_c}{K + c}, \\
\frac{\partial h}{\partial t} &= 1 + \frac{c}{2} - h, \\
\frac{\partial u}{\partial t} &= D_u \frac{\partial^2 u}{\partial x^2} - \frac{\tau_c}{L_0} F_0 \left( \frac{\partial}{\partial x} (u(F[c, u])) + r_1 \left( 1 + \frac{r_2 c^2}{r_3 + c^2} \right) u (1 - u) \right).
\end{align*}
\]

(2.7a) (2.7b) (2.7c)

Although \( D_u = 0.0025 \), which corresponds to a large diffusion value, the behaviour of cancer cells is still advection-dominated. This directed, advective movement of cancer cells results from the aforementioned cell-cell adhesion forces and from an elevated macrophage density near highly mutated cancer cells (Lin et al., 2006), which decreases the random movement of the cancer cells (Goswami et al., 2005; Hagemann et al., 2005).

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Table 1: Model parameters, dimensional values, non-dimensional values and relevant references.

| Param. | Description | Dim. value | Non-dim. value | Reference |
|--------|-------------|------------|----------------|-----------|
| \( D_c \) | Diffusion coefficient of Ca\(^{2+} \) | 20\( \mu m^2 s^{-1} \) | 0.1 | Atri et al (1993); Höfer et al (2001); Wilkins and Sneyd (1998) |
| \( b \) | Fraction of activated InsP\(_3\)Rs receptors when \( [Ca^{2+}] = 0 \) | - | 0.111 | Atri et al. (1993) |
| \( k_1 \) | \( K_m \) (Michaelis constant) for activation of InsP\(_3\)Rs receptors by Ca\(^{2+} \) | 0.7\( \mu M \) | 1 | Atri et al. (1993); Kaouri et al (2019) |
| \( k_f \) | Ca\(^{2+} \) flux when all InsP\(_3\)Rs receptors are open and activated | 16.2\( \mu M s^{-1} \) | \( K_1 = 324/7 \) | Atri et al. (1993); Kaouri et al (2019) |
| \( k_\mu \) | \( K_m \) (Michaelis constant) for binding of InsP\(_3\) to its receptor | 0.7\( \mu M \) | 1 | Atri et al. (1993); Kaouri et al (2019) |
| \( \gamma \) | Maximum rate of pumping of ER Ca\(^{2+} \) | 2\( \mu M s^{-1} \) | \( \Gamma = 40/7 \) | Atri et al. (1993) |
| \( k_\gamma \) | \( [Ca^{2+}] \) at which the rate of Ca\(^{2+} \) pumping from the cytosol is at half-maximum | 0.1\( \mu M \) | \( K = 1/7 \) | Atri et al. (1993); Kaouri et al (2019) |
| \( k_2 \) | \( K_m \) (Michaelis constant) for inactivation of InsP\(_3\) receptors by Ca\(^{2+} \) | 0.7\( \mu M \) | \( K_2 = 1 \) | Atri et al. (1993); Kaouri et al (2019) |
| \( D_u \) | Diffusion coefficient of cancer cells | 0.5\( \mu m^2 s^{-1} \) | 0.0025 | Bray (1992); Chaplain and Lolas (2006); Enderling et al. (2006); Franssen et al (2019) |
| \( R_s \) | Sensing radius | 100\( \mu m \) | 5 | Armstrong et al (2006); Gerisch and Chaplain (2008) |
Table 1 – *Continued from previous page*

| Param. | Description | Dim. value | Non-dim. value | Reference |
|--------|-------------|------------|----------------|-----------|
| $k_u$  | Carrying capacity of the cancer cell population | $6.7 \times 10^7$ cells/cm$^3$ | 1 | Gerisch and Chaplain (2008) |
| $r_1$  | Growth rate of the cancer cell population | 7 days (doubling time) | 0.1 | Cunningham and You (2015); Morani et al (2014); Panetta et al (2000) |

Table 2: Estimated model parameters, non-dimensional values and relevant references.

| Param. | Description | Non-dim. value | Reference |
|--------|-------------|----------------|-----------|
| $q_a$  | Magnitude of attraction | $0 - 0.44$ | Guided by linear stability analysis (Section 3.2) and the range [2.6], based on Clark and Vignjevic (2015) |
| $q_r$  | Magnitude of repulsion | $0 - 0.44$ | Guided by linear stability analysis (Section 3.2) |
| $s_a$  | Attraction range | 1 | Bitsouni and Eftimie (2018) |
| $s_r$  | Repulsion range | $0.25$ | Bitsouni et al (2017, 2018); Bitsouni and Eftimie (2018) |
| $m_a$  | Width of attraction kernel | $1/8$ | Bitsouni and Eftimie (2018) |
| $m_r$  | Width of repulsion kernel | $1/32$ | Bitsouni et al (2017, 2018); Bitsouni and Eftimie (2018) |
| $s^\star$ | Magnitude of cell-cell adhesion forces of the cancer cell population | 1 | Armstrong et al (2006); Bitsouni et al (2017, 2018); Gerisch and Chaplain (2008) |
| $a_1$  | Lowest value of cell-cell strength due to increase in $[Ca^{2+}]$ | 0.5 | Estimated |
| $a_2$  | Half-minimum ($K_m$) $[Ca^{2+}]$ | 0.5 | Estimated |
| $r_2$  | Largest reaction value at saturating $[Ca^{2+}]$ | 1.6 | Simpson and Arnold (1986); Taylor and Simpson (1992) |
| $r_3$  | Half-maximal $[Ca^{2+}]$ | 4 | Simpson and Arnold (1986); Taylor and Simpson (1992) |
3 Analytical results

3.1 Existence of solution

The existence of a unique global-in-time classical solution of the model (2.1) can be proven using the theory of semigroups [Henry 1981], within the framework of ODEs. The proof of the theorem follows the same steps as [Bitsouni et al 2017; Chaplain et al 2011].

3.2 Linear stability analysis

In our model an instability of a spatially homogeneous state can arise when advection effects increase; we will call this an advection-driven instability (ADI). The loss of stability leads to spatial patterns, which biologically correspond to cell aggregations [Keller and Segel 1970].

In this section, we linearise the model (2.7) and investigate the conditions for ADIs. The spatially homogeneous steady states \((c^*, h^*, u^*)\) of the system (2.7) are given by

\[
\left( c^*, \frac{1}{1 + c^*}, 0 \right) \text{ and } \left( c^*, \frac{1}{1 + c^*}, 1 \right),
\]

with \(c^* \geq 0\) determined by the solution of the quartic equation

\[
c^*^4 + c^*^3 + \left( 1 - \frac{K_1}{T} \right) c^*^2 + \left( 1 - \frac{K_1}{T} \left( K + b \right) \right) c^* - \frac{K_1}{T} Kb = 0.
\]

We seek conditions for a steady state \((c^*, h^*, u^*)\) to become unstable due to ADI. We thus consider small perturbations to the steady state, \((\bar{c}, \bar{h}, \bar{u})\), such that

\[
c(x, t) = c^* + \bar{c}(x, t),\ h(x, t) = h^* + \bar{h}(x, t),\ u(x, t) = u^* + \bar{u}(x, t).
\]

Substituting these into (2.7), linearising around the spatially uniform steady state, and using the notation \(\bar{y} = (\bar{c}, \bar{h}, \bar{u})\), we obtain

\[
\frac{\partial \bar{y}}{\partial t} = D \frac{\partial^2 \bar{y}}{\partial x^2} - \frac{\partial J_a}{\partial x} + J_r \bar{y},
\]

where \(D\) is a diagonal matrix with entries \((D_c, 0, D_u)\) and \(J_a = (0, 0, \alpha)\), with

\[
\alpha = \frac{u^*}{R_s} S(c^*) \int_0^{R_s} K_{\text{int}}(r) (\bar{u}(x + r, t) - \bar{u}(x - r, t)) \, dr,
\]

and

\[
J_r = \begin{bmatrix}
J_2(c^*, h^*) & 0 & 0 \\
0 & 0 & 0 \\
(r_1 u^* (1 - u^*) - 2 r_2 c^* c^* r_3 + c^*^2) & r_1 (1 - 2 u^*) & \left( 1 + \frac{r_2 c^*^2}{r_3 + c^*^2} \right)
\end{bmatrix},
\]

where

\[
J_2 = \begin{bmatrix}
\mu K_1 h \left( 1 - \frac{b}{1 + c^*} \right) - \frac{\Gamma K}{(1 + c^*)^2} & \mu K_1 \left( \frac{b + c^*}{1 + c^*} \right) \\
\mu K_1 \left( \frac{b + c^*}{1 + c^*} \right) & \mu K_1 \left( \frac{b + c^*}{1 + c^*} \right) - 1
\end{bmatrix},
\]

is the Jacobian of the linearised Atri model. We seek solutions of the form \(\bar{y} = we^{i\xi x + \lambda t}\), where \(w = (A_c, A_h, A_u)\) with \(|A_c|, |A_h|, |A_u| \ll 1\). The wave number and frequency of the perturbations are denoted by \(\xi\) and \(\lambda\), respectively. We then find

\[
\lambda w = (J_d + J_r) w,
\]
regions for positive 
models may achieve higher
model exhibits limit cycles and action potentials, respectively (see Fig. 4).
µ of which stable relaxation oscillations (limit cycles) exist. Action potentials also appear for a very small range
detail in (Atri et al, 1993; Kaouri et al, 2019). Hopf bifurcations occur at µ = 0.289 and µ = 0.495, between
which stable relaxation oscillations (limit cycles) exist. Action potentials also appear for a very small range
of µ. Including diffusion leads to the emergence of periodic wave trains and solitary pulses when the Atri
model exhibits limit cycles and action potentials, respectively (see Fig. 4).

with

\[ J_d = \begin{bmatrix}
-D_u \xi^2 & 0 & 0 \\
0 & 0 & 0 \\
0 & -D_u \xi^2 + 2 \xi u^* \bar{K}_{\text{int}}(\xi) S(\xi^*) / R_s \\
\end{bmatrix} \]

where \( \bar{K}_{\text{int}}(\xi) = \int_0^{R_s} K_{\text{int}}(r) \sin(\xi r) \, dr \) is the Fourier sine transform of \( K_{\text{int}}(r) \).

Since the cell density equation (2.7e) is not coupled to the Atri equations (2.7a) and (2.7b), the matrix 
\( M = J_d + J_r \) has a block structure and the eigenvalues of \( M \) are split into those of the (linearised) Atri model 
and that of the (linearised) cancer cell density equation. Hence, to identify ADIs we only need to study the 
linear stability of the cell density equation, i.e. the eigenvalue (dispersion relation)

\[ \lambda_u (\xi, c^*) = -D_u \xi^2 + \frac{2 \xi u^*}{R} S(c^*) \bar{K}_{\text{int}}(\xi) + r_1 (1 - 2u^*) \left( 1 + \frac{r_2 c^*}{r_3 + c^*} \right), \]

which for the Gaussian attraction and repulsion kernels given in (2.4) becomes

\[ \lambda_u (\xi, c^*) = -D_u \xi^2 + \frac{2 \xi u^*}{R} S(c^*) \left( e^{- (\xi a^2)^2} \sin(\xi s_a) - \frac{q_r}{q_a} e^{- (\xi c^*)^2} \sin(\xi s_r) \right) + r_1 (1 - 2u^*) \left( 1 + \frac{r_2 c^*}{r_3 + c^*} \right). \] 

(3.2)

Solutions with \( \lambda_u > 0 \) are unstable and grow exponentially in time, corresponding to pattern formation and cell aggregation in the non-linear system (Murray 2003; Painter et al 2015). For \( u^* = 0 \) and \( \xi = 0 \), we obtain

\[ \lambda_u^0 (0, c^*) = r_1 \left( 1 + \frac{r_2 c^*}{r_3 + c^*} \right) > 0, \]

In contrast, for \( u^* = 1 \) and \( \xi = 0 \), we find

\[ \lambda_u^1 (0, c^*) = -r_1 \left( 1 + \frac{r_2 c^*}{r_3 + c^*} \right) < 0. \]

Here, we use the superscript to indicate the value of \( u^* \). Note that \( \lambda_u^0 (\xi, 0) \) and \( \lambda_u^1 (\xi, 0) \) are the eigenvalues of the linearised Fisher’s equation when \( q_a = q_r = 0 \). For positive \( q_a \) and \( q_r \) and no calcium, \( \lambda_u^1 (\xi, 0) \) becomes positive for some \( \xi > 0 \) when the advection strength increases sufficiently. To identify the threshold values of \( q_a \) and \( q_r \), we present the non-negative contour plots of \( \lambda_u^1 (\xi, 0) \) in Fig. 1, where negative values are mapped
to zero for better visualisation. In Figs. 1(a)–1(d) we set \( q_a = 0.14, q_a = 0.22, q_a = 0.33 \) and \( q_a = 0.44 \), respectively, while \( q_r \) varies from 0 to 0.44. We observe extended regions with \( \lambda_u^1 > 0 \), which indicate pattern formation in the nonlinear system via ADI. In Figs. 1(b)–1(d) we observe disjoint parameter regions, which grow larger as \( q_a \) increases. Note that we do not need to plot for larger values of \( \xi \) since \( \lambda_u^1 (\xi, 0) \) tends to \( -\infty \) as \( \xi \) tends to \( \infty \).

We next establish the effect of Ca\(^{2+}\) on ADI. In Fig. 2 we display contour plots corresponding to non-
negative values of \( \lambda_u^1 (\xi, c^*) \), for nine different combinations of \( q_a \) and \( q_r \): (0.14, 0.01), (0.16, 0.01), (0.22, 0.01), (0.33, 0.01), (0.01, 0.22), (0.14, 0.22), (0.22, 0.22), (0.33, 0.33) and (0.44, 0.44). We observe that the ADI regions vanish at sufficiently large values of \( c^* \) for all figures except Figs. 2(d)–2(h) and 2(i). Note that we choose \( 0 \leq c^* \leq 2.3 \) since 2.3 is the maximum value of the steady state of the Atri model; other Ca\(^{2+}\) models may achieve higher \( c^* \) levels but we expect a qualitatively similar behaviour. Also, as \( c^* \) increases the range of \( \xi \) in the ADI regions decreases. In Figs. 2(c)–2(d) and 2(h) and 2(i) we observe disjoint parameter regions for positive \( \lambda_u^1 (\xi, c^*) \).

The stability of the spatially homogeneous Atri model (determined by the matrix \( J_2 \)) has been covered in
detail in (Atri et al 1993; Kaouri et al 2019). Hopf bifurcations occur at \( \mu = 0.289 \) and \( \mu = 0.495 \), between
which stable relaxation oscillations (limit cycles) exist. Action potentials also appear for a very small range
of \( \mu \). Including diffusion leads to the emergence of periodic wave trains and solitary pulses when the Atri
model exhibits limit cycles and action potentials, respectively (see Fig. 4).
Fig. 1: The contours of non-negative $\lambda_1^u(\xi, 0)$, dispersion relation of the linearised cell density equation, for $c^* = 0$, $u^* = 1$, which enclose parameter regions corresponding to adhesion-driven instabilities, for: (a) $q_a = 0.14$ (b) $q_a = 0.22$ (c) $q_a = 0.33$ (d) $q_a = 0.44$. In (a)–(d) $q_r$ varies from 0 to 0.44, respectively. The remaining parameter values are given in Tables 1 and 2. Negative values of $\lambda_1^u(\xi, 0)$ have been set to zero for better visualisation.
Fig. 2: Contour plots of the dispersion relation $\lambda^*_1(\xi, c^*)$ as $c^*$ varies for: (a) $q_a = 0.14$, $q_r = 0.01; (b) q_a = 0.16$, $q_r = 0.01; (c) q_a = 0.22$, $q_r = 0.01; (d) q_a = 0.33$, $q_r = 0.01; (e) q_a = 0.01$, $q_r = 0.22; (f) q_a = 0.14$, $q_r = 0.22; (g) q_a = 0.22$, $q_r = 0.22; (h) q_a = 0.33$, $q_r = 0.33; (i) q_a = 0.44$, $q_r = 0.44$. All other parameter values are given in Tables 1 and 2. Negative values of $\lambda^*_1(\xi, 0)$ have been set to zero for better visualisation.
4 Numerical simulations

In this section we numerically solve model (2.7) using a method-of-lines approach. The domain \([0, L]\) is discretized into a cell-centered grid with uniform length \(h = 1/N\), where \(N = 100\) is the number of grid cells per unit length. All simulations are performed with \(L = 120\) and with periodic boundary conditions. The diffusion terms are discretized using a second order centered difference scheme. The advection term is discretized using a third order upwind scheme, augmented with a flux-limiting scheme to ensure the solution’s positivity. The non-local term in equation (2.7c) presents challenges regarding its efficient and accurate evaluation. Here we employ the scheme based on the Fast Fourier Transform introduced in (Gerisch, 2010), using the trapezoidal rule to pre-compute the integration weights. The resulting system of ODEs is integrated using the ROWMAP integrator introduced in Weiner et al (1996). We use the implementation provided in (Weiner et al, 1996). The integrator (written in Fortran) was wrapped using f2py into a scipy integrate class (Virtanen et al, 2019). The spatial discretisation (right hand side of ODE) is implemented using NumPy. The integrator’s error tolerance is set to \(v_{tol} = 10^{-7}\). For the full details of the numerical methods we refer to (Gerisch, 2001; Hundsdorfer and Verwer, 2003).

4.1 Adhesion-driven instability, pattern formation and cell aggregations

Each term in the cancer cell density equation (2.7c) critically affects the behaviour of cancer cells. Thus, below we examine the effect of each term in turn and compare the results with those of the linear stability analysis in the absence of \(\text{Ca}^{2+}\), in Section 3.2. We explore a wide range of values for \(q_a\) (magnitude of attraction) and \(q_r\) (magnitude of repulsion), guided by Fig. 1. For \(q_a\) we also take into account the range of \(q_a\) reported in (2.6)), based on measurements of the speed of cancer cell movement. No experimental evidence was found for \(q_r\) and we consider the same range as for \(q_a\). We thus examine several possible scenarios and identify various types of patterns and aggregations.

In Fig. 3(a) we plot the cell density for non-zero diffusion and advection but zero proliferation; this represents cells with very slow doubling time. We take \(q_a = 0.22, q_r = 0.01\), i.e. attraction much larger than repulsion. We see that the cancer cells form a single stationary pulse. In Fig. 3(b), we add proliferation, but take zero adhesion (Fisher’s equation). The cancer cells exhibit a travelling front that propagates in opposite directions at a constant speed, as expected (Murray, 2003). In Fig. 3(c) we include diffusion, advection and proliferation, with \(q_a = 0.14\) and \(q_r = 0.01\). We still see a Fisher-like travelling front, consistently with Fig. 1(a) which predicts no ADI for these choices of \(q_a\) and \(q_r\).

In Fig. 3(d), we further increase the strength of attraction to \(q_a = 0.22\) while keeping \(q_r = 0.01\), and a pattern emerges behind the travelling front due to ADI, as predicted by Fig. 1(b). It is a “mixed” pattern, featuring merging and emerging peaks; some cancer cells form stationary pulses, while others organise into travelling pulses. This behaviour can be explained by the strong attractive forces that make cells form large aggregations. This type of pattern has been identified in previous work (see Andasari et al (2011); Bitsouni et al (2017); Hillen and Painter (2009); Loy and Preziosi (2019); Eftimie et al (2017); Wang and Hillen (2007)).

In Fig. 3(e), we lower attraction to \(q_a = 0.14\) and increase the magnitude of repulsion to \(q_r = 0.22\); the Fisher-like front persists and the pattern behind it now exhibits thin spikes. This can be explained by

1 http://www.mathematik.uni-halle.de/wissenschaftliches_rechnen/forschung/software/
Fig. 3: Cancer cell density, $u(x,t)$, for no Ca$^{2+}$ effect ($a_1 = a_2 = r_2 = r_3 = 0$), governed by equation (2.7c). The initial conditions are given in (4.1c). (a) $q_a = 0.22, q_r = 0.01$, no proliferation; (b) $q_a = 0, q_r = 0$; (c) $q_a = 0.14, q_r = 0.01$; (d) $q_a = 0.22, q_r = 0.01$; (e) $q_a = 0.14, q_r = 0.22$; (f) $q_a = 0.22, q_r = 0.22$. All other parameter values as in Tables 1 and 2.
the strong repulsive forces leading to a larger number of smaller aggregations than those in the case where attraction is larger than repulsion, as in Fig. 3(d). This behaviour again agrees with the linear stability analysis (see Fig. 1(b)). Finally, in Fig. 3(f) we take equal attraction and repulsion, $q_r = q_a = 0.22$. The pattern is similar to that in Fig. 3(e). Note: in order to see the more detailed features of the Figures the reader is encouraged to follow the electronic version of the paper.

### 4.2 Calcium Signals

Here, we investigate the behaviour of the spatially extended Atri model (2.7a) and (2.7b). The four panels in Fig. 4 display the behaviour of the $Ca^{2+}$ concentration as we increase $\mu$, which is equivalent to increasing the InsP$_3$ concentration. For $\mu = 0.1$, for which the spatially clamped Atri model possesses a linearly stable fixed point (Atri et al., 1993; Kaouri et al., 2019). Fig. 4(a) illustrates that the initial Gaussian condition decays to the steady state, setting the InsP$_3$ concentration as we increase $\mu$. In Fig. 4(b), while a value of $\mu$ between the two Hopf bifurcations results in a periodic wave train (Keener and Sneyd, 2009a,b); in Fig. 4(c) we take, as an example, $\mu = 0.3$. Finally, for larger values of $\mu$ the Atri model is linearly stable again and we find a similar pattern to Fig. 4(a), in that the initial condition decays to this fixed point (Atri et al., 1993; Kaouri et al., 2019). Fig. 4(d) illustrates that the initial Gaussian condition decays to this fixed point. Setting $\mu = 0.288$ leads to a solitary travelling pulse (Fig. 4(b)), while a value of $\mu$ between the two Hopf bifurcations results in a periodic wave train (Keener and Sneyd, 2009a,b); in Fig. 4(c) we take, as an example, $\mu = 0.3$. Finally, for larger values of $\mu$ the Atri model is linearly stable again and we find a similar pattern to Fig. 4(a), in that the initial condition decays to the steady state, but in a periodic manner. In Fig. 4(d) we take $\mu = 0.6$ as an example of the latter case. These four types of $Ca^{2+}$ signals emerge in almost all $Ca^{2+}$ models. Here, we use them as input to the cancer cell density equation (2.7c).

### 4.3 The Effect of $Ca^{2+}$ on the Cell Density

We now examine the effect of the $Ca^{2+}$ signals on the cancer cell density. We fix the attraction and repulsion magnitudes, $q_a$ and $q_r$, and vary $\mu$. Fig. 5 (top panel) ($q_a = 0.14, q_r = 0.01$) shows a Fisher-like travelling front in all Figs. (a)–(d), irrespective of the InsP$_3$ and $Ca^{2+}$ levels; this is consistent with the linear stability analysis that predicts no ADI. These results are in line with Fig. 2(a). In contrast, when we increase $q_a$ to 0.22 in Fig. 5(bottom panel) small InsP$_3$ concentrations ($\mu = 0.1$ and $\mu = 0.3$, respectively) induce a pattern, due to ADI. As we increase the InsP$_3$ concentration, the pattern vanishes, as illustrated in Figs. 5(c’) and 5(d’) which are for $\mu = 0.45$ and $\mu = 0.6$, respectively. These results are in line with Fig. 2(c).

In Figs. 6 we see that for larger values of $q_a$ ($q_a = 0.33, q_r = 0.01$) patterns emerge behind the Fisher-like front for all values of $\mu$. This is consistent with the linear stability analysis — see Fig. 2(d). For small values of $\mu$, $\mu = 0.1$ and $\mu = 0.3$ in Figs. 6(a) and 6(b), respectively, the cancer cells exhibit merging and emerging peaks; cells move towards each other forming new aggregations of new cells and of cells that broke off from existing aggregations and in the long-term dynamics stationary pulses are also formed. (Bitsouni et al., 2017). For larger values of $\mu$, and consequently larger values of $Ca^{2+}$ (see Figs. 6(c) and 6(d)) the patterns are thin stripes (stationary pulses).

In Figs. 5 and 6 attraction dominates over repulsion. In Fig. 7 we plot the cancer cell density when repulsion is stronger than attraction ($q_a = 0.14, q_r = 0.22$). For small values of the InsP$_3$ concentration ($\mu = 0.1, \mu = 0.3$), Figs. 7(a), (b) exhibit thin-stripe patterns via ADI (stationary pulses). As we increase $\mu$, patterns vanish — see Figs. 7(c) and 7(d), respectively for $\mu = 0.45$ and $\mu = 0.6$. These results are consistent with Fig. 2(f). Finally, for large and equal values of $q_a$ and $q_r$, Figs. 2(g) and 2(h) predict that ADI patterns exist for all $Ca^{2+}$ concentrations within the physiological range of the Atri model. This is confirmed in Fig. 8 where we observe ADI patterns for any InsP$_3$ (and $Ca^{2+}$) level when $q_a = q_r = 0.33$.

Above, we have established the emergence and disappearance of patterns as $Ca^{2+}$ varies. Furthermore, below we will summarise the effect of $Ca^{2+}$ on three important characteristics of the solution: the wave speed of the Fisher-like front, and also the amplitude and frequency of the cancer cell density.
Fig. 4: Patterns of the Ca$^{2+}$ concentration, $c(x,t)$, generated by the Atri model (2.7a)-(2.7b) for (a) $\mu = 0.1$ ($c^* = 0.016$), (b) $\mu = 0.288$ ($c^* = 0.177$), (c) $\mu = 0.3$ and (d) $\mu = 0.5$ ($c^* = 1.332$). The initial conditions are given in (4.1a)-(4.1b). The remaining parameter values are given in Tables 1 and 2. Note that although we report $c^*$ for all $\mu$ when Ca$^{2+}$ is oscillatory the steady state is linearly unstable.

Wave speed: In Figs. 5-8 we see that as $\mu$ increases (fixed $q_a$ and $q_r$) the speed of the travelling front increases. This can be linked to a higher invasion and hence metastatic potential of the cancer cells. On the other hand, for fixed $\mu$ the wave speed does not change much as $q_a$ and/or $q_r$ vary.

Amplitude: Comparing Figs. 5 and 6 we see that the maximal cell density increases as $q_a$, the attraction magnitude, increases from 0.14 to 0.33. Also, comparing Figs. 6 and 8 we see a significant increase in the maximal cell density as $q_r$ increases from 0.01 to 0.33 (and $q_a$ fixed to 0.33). The same effect is observed when comparing Fig. 5, top panel with Fig. 7 where again $q_r$ increases from 0.01 to 0.33 (while $q_a$ is fixed to 0.14.). For fixed $q_a$ and $q_r$ as $\mu$ increases the maximal cell density decreases, as we can see in Figs. 5-8.

Frequency: Moreover, we investigate how Ca$^{2+}$ signalling affects the temporal frequency of cancer cell density oscillations. In Fig. 9 we fix $x = 55$ and plot $c(x,t)$ and $u(x,t)$ for two choices; at the top panel we have $q_a = 0.22$, $q_r = 0.01$ (attraction much larger than repulsion) and in the bottom panel we have $q_a = 0.14$, $q_r = 0.22$ (attraction comparable to repulsion). From the frequency bifurcation diagram of the Atri model...
Fig. 5: Cancer cell density, \( u(x,t) \), governed by equation (2.7c), as \( q_a \) increases (top panel for \( q_a = 0.14 \) and bottom panel for \( q_a = 0.22 \)); \( q_r = 0.01 \). The initial conditions are given by (4.1). For (a), (a') \( \mu = 0.1 \), \( c^* = 0.016 \) (non-oscillatory \( \text{Ca}^{2+} \); (b), (b') \( \mu = 0.3 \), \( c^* = 0.556 \), oscillatory \( \text{Ca}^{2+} \); (c), (c') \( \mu = 0.45 \), \( c^* = 1.195 \), oscillatory \( \text{Ca}^{2+} \); (d), (d') \( \mu = 0.6 \), \( c^* = 1.5712 \) (non-oscillatory \( \text{Ca}^{2+} \)). The rest of model parameters are given in Tables 1 and 2. As predicted from the linear stability analysis (see Fig. 2(b)), when \( q_a \) increases ADI emerges for small values of \( \mu \). Note that although we report \( c^* \) for all \( \mu \) when \( \text{Ca}^{2+} \) is oscillatory the steady state is linearly unstable.
Fig. 6: Cancer cell density, $u(x,t)$, governed by equation (2.7c), for $q_a = 0.33$, $q_r = 0.01$. The initial conditions are given by (4.1). (a) $\mu = 0.1$, $c^* = 0.016$ (non-oscillatory Ca$^{2+}$); (b) $\mu = 0.3$, $c^* = 0.556$ (oscillatory Ca$^{2+}$); (c) $\mu = 0.45$, $c^* = 1.105$ (oscillatory Ca$^{2+}$); (d) $\mu = 0.6$, $c^* = 1.5712$ (non-oscillatory Ca$^{2+}$). The rest of model parameters are given in Tables 1 and 2. Note that although we report $c^*$ for all $\mu$ when Ca$^{2+}$ is oscillatory the steady state is linearly unstable (see Fig. 2 in Kaouri et al. (2019)) we choose four values of $\mu$ that sufficiently ‘sample’ the variation of the frequency as $\mu$ increases. We see that the frequency of Ca$^{2+}$ oscillations is approximately equal to the frequency of cell density oscillations, if the cell density is oscillatory. We have verified this observation by also computing the frequency spectra for $t \in (1900, 2000)$ (the time interval has been chosen to ensure that solutions converged to steady state). For other choices of $q_a$ and $q_r$, the effect of Ca$^{2+}$ oscillations on the cell density is similar, and thus other figures are not included for brevity.

5 Summary, conclusions and further work

Since cell proliferation and cell-cell adhesion, which play a critical role in invasion and cancer metastasis, are Ca$^{2+}$-dependent, here we have developed and analysed a new model for Ca$^{2+}$ signalling in cancer. The Ca$^{2+}$ dynamics have been described by the spatially extended Atri model (Atri et al. 1993), which consists of a reaction-diffusion equation for the Ca$^{2+}$ concentration, coupled with an ODE for the fraction of InsP$_3$ receptors on the ER that have not been inactivated by Ca$^{2+}$. This model, although simple enough, generates
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Fig. 7: Cancer cell density, $u(x,t)$, governed by equation (2.7c), for $q_a = 0.14$ and $q_r = 0.22$. The initial conditions are given in (4.1). (a) $\mu = 0.1$, $c^* = 0.016$ (non-oscillatory Ca$^{2+}$); (b) $\mu = 0.3$, $c^* = 0.556$ (oscillatory Ca$^{2+}$); (c) $\mu = 0.45$, $c^* = 1.195$ (oscillatory Ca$^{2+}$); (d) $\mu = 0.6$, $c^* = 1.5712$ (non-oscillatory Ca$^{2+}$). The rest of model parameters are given in Tables 1 and 2.

Note that although we report $c^*$ for all $\mu$ when Ca$^{2+}$ is oscillatory the steady state is linearly unstable.

four ‘prototypical’ Ca$^{2+}$ signals as many other excitable Ca$^{2+}$ models; periodic wavetrains (which correspond to limit cycles in the spatially clamped Atri model), solitary pulses (which correspond to action potentials), decaying wavetrains and solutions decreasing monotonically with time. The cancer cell density evolution is described by a non-local PDE that incorporates diffusion, cell-cell adhesion (advection) and proliferation. We have modelled the dependence of the adhesion and proliferation terms on the Ca$^{2+}$ dynamics, motivated by experimental evidence, and we have considered cancer types where the adhesion strength decreases with Ca$^{2+}$ [Byers et al. 1995, Cavallaro and Christofori 2004], while proliferation increases with Ca$^{2+}$ [Cárdenas et al. 2016, Prevarskaya et al. 2018, Rezuchova et al. 2019, Tsunoda et al. 2005]. The model, assumptions and parameter values are presented in Section 2. As much as possible, the model parameters were chosen from experimental studies (see Tables 1 and 2).

In Section 3 we linearised the model (2.7) and determined the parameter range for which an adhesion-driven instability (ADI) forms, while varying systematically the magnitudes of cell-cell attraction and repulsion, $q_a$ and $q_r$, respectively. In the absence of Ca$^{2+}$ (Fig. 1) we showed that ADIs may arise for sufficiently large values of either $q_a$ and $q_r$ (or both). ADIs correspond to cell aggregations which are critical for cancer
invasion and metastasis. Then, in Fig. 2 we investigated the effect of Ca$^{2+}$ on the cell aggregations and found that they change qualitatively and eventually vanish as the Ca$^{2+}$ level increases.

In Section 4 we solved the full non-linear model (2.7) numerically and systematically investigated a range of attraction and repulsion magnitudes, guided by the linear stability analysis. Firstly, we validated numerically the results of the linear analysis in the absence of Ca$^{2+}$ (Fig. 3). We subsequently examined the effect of four types of Ca$^{2+}$ signals on the cancer cell density, paying special attention to the periodic wave trains (Figs. 5-8). We found that as Ca$^{2+}$ levels increase the maximal cell density decreases due to the decreased cell-cell adhesion strength preventing the formation of clusters of high density levels. Moreover, as Ca$^{2+}$ levels increase the speed of the travelling wave fronts increases which is linked to a faster spread of cancer. An other important result from our numerical investigations is that the frequency of Ca$^{2+}$ oscillations is approximately equal to the frequency of the cancer cell density oscillations, when the cell density is oscillatory. Moreover, cellular aggregations vanish for sufficiently large Ca$^{2+}$ levels, as it was predicted by the linear analysis. Our results demonstrate that accounting for the dependence of cell-cell adhesion and proliferation on Ca$^{2+}$ signalling we can reveal the conditions for which cancer cell aggregations appear as
Mathematical model of cancer and calcium

Fig. 9: Cancer cell density and Ca$^{2+}$ oscillations. Each plot shows a cross-section (i.e. $u(t) = u(55,t)$) of a solution of model (2.7) with initial conditions given in (4.1) for selected increasing values of $\mu$. (Top) $q_a = 0$, $q_r = 0.22$. (Bottom) $q_a = 0.22$, $q_r = 0.01$. The rest of model parameters are given in Tables 1 and 2. The cell density $u(55,t)$ picks up the oscillations in the Ca$^{2+}$ concentration. Indeed the frequencies (computed using the Fourier transform) match.
Ca$^{2+}$ varies. This allows us to study the dependence of the cancer invasion potential on Ca$^{2+}$ and paves the ways for new therapies based on controlling Ca$^{2+}$.

Our model provides a general framework for cancer cell movement under the effect of any oscillatory signalling pathway dynamics and paves the way for treatments that are based on controlling these pathways, and in particular Ca$^{2+}$ signalling. It, however, has various limitations which outline avenues for future work. The assumption that the adhesion strength function is decreasing with Ca$^{2+}$ is not appropriate for all cancer types; an increase of cell-cell adhesion with Ca$^{2+}$ has been observed in some cancers. Additionally, the repulsion magnitude has been taken over a wide range since there is no experimental evidence supporting its value. New experiments could investigate this. Another limitation of the model is that it includes cell–cell interactions; it would be useful to incorporate the interaction of the cancer cells with the extracellular matrix (ECM) in future work as this would allow to study cancer invasion in more detail. Additionally, the way cell-ECM interactions are dependent on Ca$^{2+}$ could be also modelled. Finally, the delay of the Ca$^{2+}$ waves in the gap junctions between cells has been considered negligible; a cell-based model accounting for these gap junctions could be developed. Moreover, as we are now equipped with the insights generated by the one-dimensional geometry, we plan to develop the model to two and three dimensions.

A main focus of this study was to unravel the impact of the cellular Ca$^{2+}$ signalling on the behaviour of cancer cells. As such, a key component of our model is the description of the cellular Ca$^{2+}$ dynamics. We chose the Atri model as a typical representative for a minimal framework that captures essential features of the dynamics of the cellular Ca$^{2+}$ concentration such as Ca$^{2+}$ oscillations. This naturally raises the question about how robust our results are with respect to the Ca$^{2+}$ model that we employed. The answer to this question combines two main lines of argument: the specific model for the InsP$_3$R and whether Ca$^{2+}$ oscillations are deterministic or stochastic. For the first point, we note that there exist a substantial number of InsP$_3$R models, see e.g. Atri et al. [1993], De Young and Keizer [1992], Li et al. [1994], Li and Rinzel [1994b], Meyer and Stryer [1988], Sneyd and Dufour [2002], Siekmann et al. [2012], Sneyd and Falcke [2005], Shuai et al. [2007], Ullah et al. [2012]. While they differ in their complexity, the overall range of the Ca$^{2+}$ concentration and the frequency of the Ca$^{2+}$ oscillations are comparable amongst them. Consequentially, exchanging the Atri model for any of the other InsP$_3$R models will most probably not change our conclusions. A more contentious point is whether Ca$^{2+}$ oscillations should be described within a deterministic or stochastic framework. Both approaches have been used extensively to date as e.g. in [Dupont et al. 2011b], Falcke et al. [2018], Gaspers et al. [2014], Kummer et al. [2000], Li and Rinzel [1994a], Politi et al. [2006], Powell et al. [2020], Shuai and Jung [2002], Skupin et al. [2008], Sneyd et al. [2017], Sun et al. [2017], Tang et al. [1996], Thul et al. [2009], Thul and Falcke [2007, 2006, 2004a,b], Thurley et al. [2011], Tilnaaite et al. [2017], Thul [2014], Thurley et al. [2012, 2015], Tsaneva-Atanasova et al. [2005], Voorslujs et al. [2019], Weinberg and Smith [2014], Wieder et al. [2015] — see also the book by [Dupont et al. 2016b] for a detailed discussion. As this study is the first to explore the role of Ca$^{2+}$ in a mathematical model of cancer cell propagation, we opted for a deterministic approach. This provides us with a baseline against which we can test future models in which the Ca$^{2+}$ dynamics will be described stochastically.

Acknowledgements The authors would like to thank Dr. A. Athenodorou for his valuable technical support. VB acknowledges support from the European Union’s H2020 Research and Innovation Action under Grant Agreement No 741657 (SciShops.eu). AB was partially supported by an NSERC (Natural Sciences and Engineering Research Council) post-doctoral fellowship, and is grateful to the Pacific Institute for Mathematical Sciences for providing space and resources for AB’s postdoctoral research.

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