Journal of Computational and Applied Mathematics 438 (2024) 115570

Contents lists available at ScienceDirect

Journal of Computational and Applied Mathematics

journal homepage: www.elsevier.com/locate/cam

A coupled stochastic differential reaction–diffusion system for angiogenesis ☆

Markus Fellner, Ansgar Jüngel *

Institute of Analysis and Scientific Computing, Vienna University of Technology, Wiedner Hauptstraße 8–10, 1040 Wien, Austria

ARTICLE INFO

Article history:
Received 15 November 2022
Received in revised form 5 September 2023

MSC:
34F05
35K57
35R60
92C17
92C37

Keywords:
Angiogenesis
Stochastic differential equations
Reaction–diffusion equations
Tip cell movement
Existence analysis

ABSTRACT

A coupled system of nonlinear mixed-type equations modeling early stages of angiogenesis is analyzed in a bounded domain. The system consists of stochastic differential equations describing the movement of the positions of the tip and stalk endothelial cells, due to chemotaxis, durotaxis, and random motion; ordinary differential equations for the volume fractions of the extracellular fluid, basement membrane, and fibrin matrix; and reaction–diffusion equations for the concentrations of several proteins involved in the angiogenesis process. The drift terms of the stochastic differential equations involve the gradients of the volume fractions and the concentrations, and the diffusivities in the reaction–diffusion equations depend nonlocally on the volume fractions, making the system highly nonlinear. The existence of a unique solution to this system is proved by using fixed-point arguments and Hölder regularity theory. Numerical experiments in two space dimensions illustrate the onset of formation of vessels.

1. Introduction

Angiogenesis is the process of expanding existing blood vessel networks by sprouting and branching. Its mathematical modeling is important to understand, for instance, wound healing, inflammation, and tumor growth. In this paper, we analyze a variant of the off-lattice cell-based model suggested in [1] that is used to simulate the early stages of angiogenesis. The model takes into account the dynamics of the tip (leading) endothelial cells by solving stochastic differential equations, the influence of various proteins triggering the cell dynamics by solving reaction–diffusion equations, and the change of some components of the extracellular matrix into extracellular fluid by solving ordinary differential equations. Up to our knowledge, this is the first analysis of the model of [1].

Angiogenesis is mainly triggered by local tissue hypoxia (low oxygen level in the tissue), which activates the production of the signal protein vascular endothelial growth factor (VEGF). Endothelial cells, which form a barrier between vessels and tissues, reached by the VEGF signal initiate the angiogenic program. These cells break out of the vessel wall, degrade the basement membrane (a thin sheet-like structure separating the endothelial cells from the underlying tissue), proliferate, and invade the surrounding tissue while still connected with the vessel network. The angiogenic program specifies the activated endothelial cells into tip cells (cells at the front of the vascular sprouts) and stalk cells (highly proliferating cells). The tip cells lead the sprout towards the source of VEGF, while the stalk cells proliferate to follow the tip cells supporting sprout elongation; see Fig. 1.

☆ The authors acknowledge partial support from the Austrian Science Fund (FWF), grants P33010, W1245, and F65. This work has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme, ERC Advanced Grant no. 101018153.

* Corresponding author.
E-mail addresses: markus.fellner@tuwien.ac.at (M. Fellner), juengel@tuwien.ac.at (A. Jüngel).

https://doi.org/10.1016/j.cam.2023.115570
0377-0427/

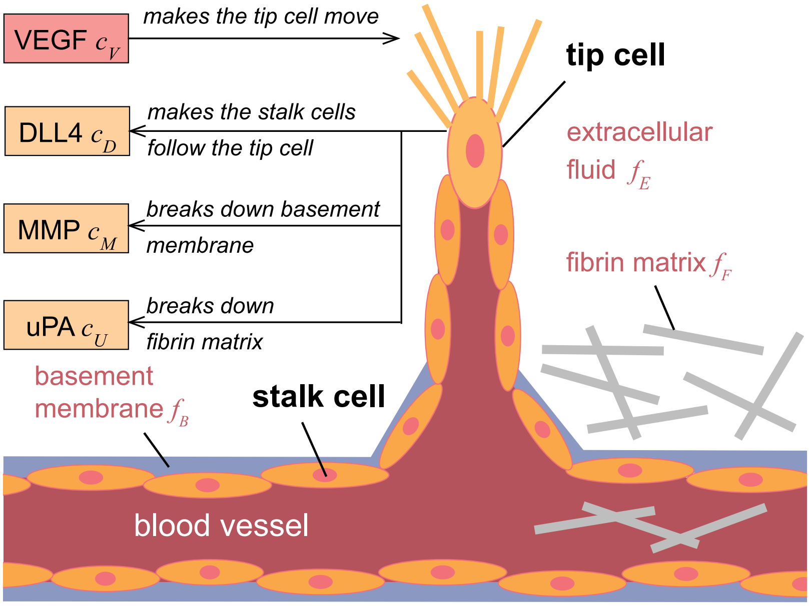

Fig. 1. Schematic model of sprout formation in a blood vessel corresponding to an in-vitro experiment described in [1]. Tip cells are activated by VEGF and they segrete the proteins DLL4, MMP, and uPA. The vessels are embedded in the fibrin matrix, which acts as a substrate and is surrounded by extracellular fluid. The basement membrane is the top layer of the matrix and separates it from the extracellular fluid.

Following [1], the tip cells segrete the proteins delta-like ligand 4 (DLL4), matrix metalloproteinase (MMP), and urokinase plasminogen activator (uPA). The chemokine DLL4 makes the stalk cells follow the tip cells, MMP breaks down the basement membrane, and uPA degrades the fibrin matrix such that cells can move into the matrix. There are many other molecular mechanisms and mediators in the angiogenesis process; see, e.g., [2,3] for details.

1.1. Model equations

The unknowns are

- the positions $X_1^k(t)$ of the kth tip cell and $X_2^k(t)$ of the kth stalk cell;
- the volume fractions of the basement membrane $f_B(x,t)$, the extracellular fluid $f_E(x,t)$, and the fibrin matrix $f_F(x,t)$;
- the concentrations of the proteins VEGF $c_V(x,t)$, DLL4 $c_D(x,t)$, MMP $c_M(x,t)$, and uPA $c_U(x,t)$,

where $t \geq 0$ is the time and $x \in \mathcal{D} \subset \mathbb{R}^3$ the spatial variable. All unknowns depend additionally on the stochastic variable $\omega \in \Omega$, where Ω is the set of events. We assume that the mixture of basement membrane, extracellular fluid, and fibrin matrix is saturated, i.e., the volume fractions f_B, f_E, and f_F sum up to one. We introduce the vectors $X_i = (X_i^k)_{k=1,\ldots,N_i}$ for $i = 1, 2$, $f = (f_B, f_E, f_F)$, and $c = (c_V, c_D, c_M, c_U)$.

Stochastic differential equations

The tip cells move according to chemotaxis force, driven by the gradient of the VEGF concentration, the durotaxis force, driven by the gradient of the solid fraction $f_S := f_B + f_F$, and random motion modeling uncertainties. The dynamics of $X_i^k(t)$ is assumed to be governed by the stochastic differential equations (SDEs), understood in the Itô sense,

$$dX_i^k(t) = g_i[c,f](X_i^k,t)dt + \sigma_i(X_i^k)dW_i^k(t), \quad t > 0, \quad X_i^k(0) = X_i^0, \tag{1}$$

where $i = 1, 2$, $k = 1, \ldots, N_i$ for $N_i \in \mathbb{N}$, $W_i^k(t)$ are Wiener processes, and the drift terms

$$\begin{aligned} g_1[c,f](X_1,t) &:= \alpha_0 M_1(f_S(X_1), X_1)z_1 + \gamma(f_S(X_1))\nabla c_V(X_1) + \lambda(f_S(X_1))\nabla f_S(X_1), \\ g_2[c,f](X_2,t) &:= \alpha_0 M_2(f_S(X_2), X_2)z_2 + \gamma(f_S(X_2))\nabla c_D(X_2) + \lambda(f_S(X_2))\nabla f_S(X_2), \end{aligned} \tag{2}$$

(we omitted the argument t for f_S and X_i on the right-hand side) include a constant $\alpha_0 > 0$, the strain energy M_i, the direction of movement determined by the strain energy density z_i, the chemotaxis force ∇c_V in the direction of VEGF (tip cells) and ∇c_D in the direction of DLL4 (stalk cells), and the migration as a result of the durotaxis force ∇f_S. We refer to [1] for a motivation of the specific choice (2). In this paper, we allow for general drift terms by imposing suitable Lipschitz continuity conditions; see Assumption (A4) below. In the numerical experiments, we choose the functions M_i, γ, and λ as in Appendix C.

Ordinary differential equations

The proteins MMP and uPA degrade the basement membrane and fibrin matrix, respectively, while enhancing the extracellular fluid component. Therefore, the volume fractions f_B, f_E, and f_F are determined by the ordinary differential equations (ODEs)

$$\begin{aligned} \frac{\mathrm{d}f_B}{\mathrm{d}t} &= -s_B c_M f_B, \quad t > 0, \quad f_B(0) = f_B^0, \\ \frac{\mathrm{d}f_F}{\mathrm{d}t} &= -s_F c_U f_F, \quad t > 0, \quad f_F(0) = f_F^0, \\ \frac{\mathrm{d}f_E}{\mathrm{d}t} &= s_B c_M f_B + s_F c_U f_F, \quad t > 0, \quad f_E(0) = 1 - f_B^0 - f_F^0, \end{aligned} \tag{3}$$

where $s_B, s_F > 0$ are some rate constants. Note that the last differential equation is redundant because of the volume-filling condition $f_B + f_E + f_F = 1$. Clearly, Eqs. (3) can be solved explicitly, giving for $(x, t) \in \mathcal{D} \times (0, T)$ and pathwise in Ω (we omit the argument ω),

$$\begin{aligned} f_B(x,t) &= f_B^0(x) \exp\left(-s_B \int_0^t c_M(x,s)\mathrm{d}s\right), \\ f_F(x,t) &= f_F^0(x) \exp\left(-s_F \int_0^t c_U(x,s)\mathrm{d}s\right). \end{aligned} \tag{4}$$

Reaction–diffusion equations

The mass concentrations are modeled by reaction–diffusion equations, describing the consumption and production of the proteins:

$$\begin{aligned} &\partial_t c_V - \mathrm{div}(D_V(f)\nabla c_V) + \alpha_V(x,t)c_V = 0 \quad \text{in } \mathcal{D},\ t > 0, \\ &\partial_t c_D - \mathrm{div}(D_D(f)\nabla c_D) + \beta_D(x,t)c_D = \alpha_D(x,t)c_V \quad \text{in } \mathcal{D},\ t > 0, \\ &\partial_t c_M - \mathrm{div}(D_M(f)\nabla c_M) + s_M f_B c_M = \alpha_M(x,t)c_V \quad \text{in } \mathcal{D},\ t > 0, \\ &\partial_t c_U - \mathrm{div}(D_U(f)\nabla c_U) + s_U f_F c_U = \alpha_U(x,t)c_V \quad \text{in } \mathcal{D},\ t > 0, \end{aligned} \tag{5}$$

with initial and no-flux boundary conditions

$$c_j(0) = c_j^0 \quad \text{in } \mathcal{D}, \quad \nabla c_j \cdot \nu = 0 \quad \text{on } \partial\mathcal{D},\ j = V, D, M, U, \tag{6}$$

where the rate terms are given by $\alpha_V = s_V \widetilde{\alpha}_V$, $\alpha_j = r_j \widetilde{\alpha}_j$ for $j = D, M, U$, $\beta_D = s_D \widetilde{\beta}_D$, and

$$\widetilde{\alpha}_j(x,t) = \sum_{k=1}^{N_1} V_j^k(X_1^k(t) - x), \quad \widetilde{\beta}_D(x,t) = \sum_{k=1}^{N_2} V_D^k(X_2^k(t) - x), \tag{7}$$

for $j = V, D, M, U$ and $V_j^k : \mathbb{R}^3 \to \mathbb{R}$ are nonnegative smooth potentials approximating the delta distribution. The parameters r_j and s_j are positive. In [1], the rate terms are given by delta distributions instead of smooth potentials. We assume smooth potentials because of regularity issues, but they can be given by delta-like functions as long as they are smooth. Indeed, we need $C^{1+\delta}(\overline{\mathcal{D}})$ solutions c_j to solve the SDEs (1), and this regularity is not possible when the source terms of (5) include delta distributions. As the number of the proteins is typically much larger than the number of tip cells, the stochastic fluctuations in the concentrations are expected to be much smaller than those associated with the tip cells, which justifies the macroscopic approach using reaction–diffusion equations for the concentrations.

In Eq. (5) for c_V, the term $\alpha_V c_V$ models the consumption of VEGF along the trajectory of the tip cells. The protein DLL4 is regenerated from conversion of VEGF, modeled by $\alpha_D c_V$ along the trajectories of the tip cells, and consumed by the stalk cells, modeled by $\beta_D c_D$ along the trajectories of the stalk cells. In Eq. (5) for c_M, the term $s_M f_B c_M$ describes the decay of the MMP concentration with rate $s_B > 0$ as a result of the breakdown of the basement membrane, and $\alpha_M c_V$ models the production of MMP due to conversion from VEGF. Similarly, $s_U f_F c_U$ describes the decay of the uPA concentration, which breaks down the fibrin matrix, and the protein uPA is regenerated, leading to the term $\alpha_U c_V$.

The diffusivities are given by the mixing rule

$$D_j(f) = D_j^B f_B + D_j^E f_E + D_j^F f_F, \quad j = V, D, M, U,$$

where $D_j^i > 0$ for $i = B, E, F$. Then

$$0 < \min\{D_j^B, D_j^E, D_j^F\} \le D_j(f) \le \max\{D_j^B, D_j^E, D_j^F\}, \tag{8}$$

and Eqs. (5) are uniformly parabolic. Note, however, that Eqs. (5) are nonlocal and quasilinear, since the diffusivities are determined by the time integrals of c_M or c_U; see (4).

Various biological phenomena are not modeled by our equations. For instance, we do not include the initiation of sprouting from preexisting parental vessels, the branching from a tip cell, and anastomosis (interconnection between blood vessels). Moreover, in contrast to [1], we do not allow for the transition between the phenotypes "tip cell" and "stalk cell" to simplify the presentation. On the other hand, we may include further angiogenesis-related proteins, if the associated reaction–diffusion equations are of the structure (5).

1.2. State of the art

There are several approaches in the literature to model angiogenesis, mostly in the context of tumor growth. Cellular automata models divide the computational domain into a discrete set of lattice points, and endothelial cells move in a discrete way. Such models are quite flexible, and intra-cellular adherence can be easily implemented, but their numerical solution is computationally expensive when the numbers of cells or molecules are large [4]. In individual-based off-lattice models, the cells are treated as discrete entities, and their movement is not restricted to any lattice points [5]. Continuum-scale models consider cell densities whose dynamics is described by partial differential equations; see, e.g., [6] for wound healing and [7] for angiogenesis. Chemotaxis can be modeled in this approach by Keller–Segel-type equations, which admit global weak solutions in two space dimensions without blowup [8]. A hybrid approach was investigated in [9], where the blood vessel network is implemented on a lattice, tip cells are moving in a lattice-free way, and other cells are modeled macroscopically as densities. An off-lattice cell-based approach was chosen in [1], which is the basis of the present paper. The novelty of [1] is the distinction of tip and stalk cells and the inclusion of proteins segregated by the tip cells.

In other models, stochastic effects have been included. In [10], the movement of the tip cells is modeled by a SDE, with a deterministic part describing chemotaxis, and a stochastic part modeling random motion. The mean-field limit in a stochastic many-particle system, leading to reaction–diffusion equations, was performed in [11,12]. We also refer to the reviews [13,14] on further modeling approaches of angiogenesis.

Numerical simulations of a coupled SDE-PDE model for the movement of the tip cells and the dynamics of the tumor angiogenesis factor, fibronectin (a protein of the extracellular matrix), and matrix degrading enzymes were presented in [15]. Other SDE-PDE models in the literature are concerned with the proton dynamics in a tumor [16], acid-mediated tumor invasion [17], and viscoelastic fluids [18]. However, only the works [16,17] treat a genuine coupling between SDEs and PDEs. While the model in [17] also includes a cross-diffusion term in the equation for the cancer cells, we have simpler reaction–diffusion equations but with nonlocal diffusivities. The model of [16] also includes nonlocal terms, but there are different from ours. Up to our knowledge, the mathematical analysis of system (1), (3)–(6) is new.

1.3. Assumptions and main result

Let $(\Omega,\mathcal{F},(\mathcal{F}_t)_{t\ge0},\mathbb{P})$ be a stochastic basis with a complete and right-continuous filtration, and let $(W_i^k(t))_{t\ge0}$ for $i=1,2$, $k=1,\ldots,N_i$ be independent standard Wiener processes on $\mathbb{R}^3$ relative to $(\mathcal{F}_t)_{t\ge0}$. We write $L^p(\Omega,\mathcal{F};B)$ for the set of all $\mathcal{F}$-measurable random variables with values in a Banach space B, for which the L^p norm is finite. Furthermore, let $\mathcal{D}\subset\mathbb{R}^3$ be a bounded domain with boundary $\partial\mathcal{D}\in C^3$ (needed to obtain parabolic regularity; see Theorem 19). We set $Q_T=\mathcal{D}\times(0,T)$.

We write $C^{k+\delta}(\overline{\mathcal{D}})$ with $k\in\mathbb{N}_0$, $\delta\in(0,1)$ for the space of C^k functions u such that the kth derivative $\mathrm{D}^k u$ is Hölder continuous of index δ. The space of Lipschitz continuous functions on $\overline{\mathcal{D}}$ is denoted by $C^{0,1}(\overline{\mathcal{D}})$. For notational convenience, we do not distinguish between the spaces $C^{k+\delta}(\overline{\mathcal{D}};\mathbb{R}^n)$ and $C^{k+\delta}(\overline{\mathcal{D}})$. Furthermore, we usually drop the dependence on the variable $\omega\in\Omega$ in the ODEs and PDEs, which hold pathwise $\mathbb{P}$-a.s. Accordingly, we write c instead of $c(\omega,\cdot,\cdot)$ and $c(t)$ instead of $c(\omega,\cdot,t)$. Finally, we write "a.s". instead of "$\mathbb{P}$-a.s.".

As we deal with stochastic processes depending also on the space variable x, we use the following definition of a progressively measurable process: We call a stochastic process $X:\Omega\times\mathcal{D}\times[0,T]\to\mathbb{R}$ *progressively measurable* with respect to a filtration $(\mathcal{F}_t)_{t\ge0}$, if X is an $\mathcal{F}_t\times\mathcal{B}(\mathcal{D})\times\mathcal{B}([0,t])$-measurable random variable for all $t\in[0,T]$. Here, $\mathcal{B}(G)$ denotes the Borel-σ algebra of the corresponding topological space G.

We impose the following assumptions:

(A1) Initial data: $X_i^0\in L^4(\Omega,\mathcal{F}_0)$ satisfies $X_i^0\in\mathcal{D}$ a.s. $(i=1,2)$, $c^0\in L^\infty(\Omega,\mathcal{F}_0;C^{2+\delta_0}(\overline{\mathcal{D}}))$, $f^0\in L^\infty(\Omega,\mathcal{F}_0;C^{1+\delta_0}(\overline{\mathcal{D}}))$ for some $0<\delta_0<1$; $c_j^0\ge0$ $(j=V,D,M,U)$, $f_i^0\ge0$ $(i=B,E,F)$, and $f_B^0+f_E^0+f_F^0=1$ in $\mathcal{D}$ a.s.; $\nabla c_j^0\cdot\nu=0$ on $\partial\mathcal{D}$ a.s.

(A2) Diffusion: $\sigma_i:\Omega\times\mathcal{D}\times[0,T]\to\mathbb{R}$ $(i=1,2)$ is progressively measurable, satisfies $\sigma_i=0$ on $\partial\mathcal{D}$ a.s., and there exists a constant $L>0$ such that for all $x,y\in\mathcal{D}$, $t\in[0,T]$, and $\omega\in\Omega$,
$$\big|\sigma_i(\omega,x,t)-\sigma_i(\omega,y,t)\big|\le L\big|x-y\big|,\quad \big|\sigma_i(\omega,x,t)\big|\le L\big(1+\big|x\big|\big).$$

(A3) Drift: $g_i(x,y,p,q):\mathbb{R}\times\mathbb{R}\times\mathbb{R}^3\times\mathbb{R}^3\to\mathbb{R}^3$ is measurable and $g_i(c,f,\nabla c,\nabla f)$=0 for $x\in\partial\mathcal{D}$, $t\in[0,T]$ if (c,f) is a solution to (4)–(6). We write $g_i[c,f]$ instead of $g_i(c,f,\nabla c,\nabla f)$ to shorten the notation.

(A4) Lipschitz continuity for g_i: For $c,c',f,f'\in C^1(\overline{\mathcal{D}}\times[0,T])$, there exists $L_1>0$ such that for $(x,t)\in\overline{\mathcal{D}}\times[0,T]$ and $i=1,2$,
$$\begin{aligned}\big|g_i[c,f](x,t)-g_i[c',f'](x,t)\big|&\le L_1\big(1+\|c\|_{L^\infty(0,t;C^1(\overline{\mathcal{D}}))}+\|f\|_{L^\infty(0,t;C^1(\overline{\mathcal{D}}))}\big)\\&\quad\times\big(\|c(t)-c'(t)\|_{C^1(\overline{\mathcal{D}})}+\|f(t)-f'(t)\|_{C^1(\overline{\mathcal{D}})}\big).\end{aligned}$$

Furthermore, for $c, f \in L^\infty(0,T;W^{2,\infty}(\mathcal{D}))$, there exists $L_2 > 0$ such that for $(x,t), (x',t) \in \overline{\mathcal{D}} \times [0,T]$ and $i = 1, 2$,

$$\left|g_i[c,f](x,t) - g_i[c,f](x',t)\right| \le L_2\big(1 + \|c\|_{L^\infty(0,T;W^{2,\infty}(\mathcal{D}))} + \|f\|_{L^\infty(0,T;W^{2,\infty}(\mathcal{D}))}\big) \times |x - x'|.$$

(A5) Potentials: $V_j^k \in C^{0,1}(\mathbb{R}^3)$ for $j = V, D, M, U$, $k = 1, \dots, N_i$ are nonnegative functions.

Let us discuss these assumptions. Since we need $C^{1+\delta}$ solutions (c, f) to obtain Hölder continuous coefficients of the SDEs (which ensures their solvability), we need some regularity conditions on the initial data in Assumption (A1). Accordingly, $\nabla c_j^0 \cdot \nu = 0$ on $\partial\mathcal{D}$ is a compatibility condition needed for such a regularity result. In Assumption (A1), we impose the volume-filling condition initially, $f_B^0 + f_E^0 + f_F^0 = 1$ in $\mathcal{D}$. Eqs. (3) then show that this condition is satisfied for all time. The conditions $\sigma_i = 0$ and $g_i[c,f] = 0$ on $\partial\mathcal{D}$ in Assumptions (A2) and (A3), respectively, guarantee that the tip and stalk cells do not leave the domain $\mathcal{D}$. The conditions on σ_i in Assumption (A2) and the Lipschitz continuity of $g_i[c,f]$ in Assumption (A4) are standard hypotheses to apply existence results for (1). Note that $g_i[c,f]$ in example (2) satisfies Assumption (A4). As g_i is assumed to be measurable by Assumption (A3), $g_i[c,f]$ is progressively measurable if c and f are. Assumption (A5) is a simplification to ensure the parabolic regularity results needed, in turn, for the solvability of (1).

Under these assumptions, the solution to (1) will turn out to be an element of the following metric space for some $R > 0$:

$$Y_R(0,T;\mathcal{D}) := \big\{X \in C^{1/2}([0,T];L^4(\Omega)) : \|X\|_{C^{1/2}([0,T];L^4(\Omega))} \le R, \; X(t) \text{ is } \mathcal{F}_t\text{-measurable}, \; X(t) \in \overline{\mathcal{D}} \text{ a.s. for all } t \in [0,T]\big\}, \tag{9}$$

equipped with the standard norm of $C^0([0,T];L^4(\Omega))$.

Theorem 1 (*Global Existence and Uniqueness*)**.** *Let Assumptions (A1)–(A5) hold. Then there exist a unique solution (f, c, X) to (4)–(7), (1) and some constant $R > 0$ such that*

- *$f = (f_B, f_E, f_F)$ solves (3) pathwise a.s. in the sense of (4), where $f_i \in C^0([0,T];\, L^2(\mathcal{D})) \cap L^\infty(Q_T)$;*
- *$c = (c_V, c_D, c_M, c_U)$ is a classical solution to (5)–(6) pathwise a.s.;*
- *c, ∇c, f and ∇f are progressive measurably;*
- *$X_i^k \in Y_R(0,T;\mathcal{D})$ is a strong solution to (1) for $i = 1, 2$, $k = 1, \dots, N_i$.*

A strong solution (X_1, X_2) to (1) means that $(X_i^k(t))_{t\ge 0}$ is an a.s. continuous $(\mathcal{F}_t)$-adapted process such that for all $t \in [0,T]$,

$$X_i^k(t) = X_i^0 + \int_0^t g_i[c,f](X_i^k(s), s)\mathrm{d}s + \int_0^t \sigma_i(X_i^k(s))\mathrm{d}W_i^k(s) \quad a.s. \tag{10}$$

1.4. Strategy of the proof

The proof of Theorem 1 is based on a variant of Banach's fixed-point theorem [19, Theorem 2.4] yielding global solutions. Let $\widetilde{X}$ be a stochastic process with a.s. Hölder continuous paths and values in $\mathcal{D}$ a.s. More precisely, $\widetilde{X}_i^k \in Y_R(0,T;\mathcal{D})$, defined in (9). Then α_j and β_j are Hölder continuous in $\overline{\mathcal{D}} \times [0,T]$ a.s. as a function of $\widetilde{X}$. As a first step, we prove some uniform regularity results and a priori estimates for solutions to the linearized problem of (5), which are independent of the path $t \mapsto X(\omega, t)$. Moser's iteration method shows that the weak solution is in fact bounded, and a general regularity result for evolution equations yields $\partial_t c \in L^2(Q_T)$. Then, interpreting (the linearized) equations of the form (5) as elliptic equations with right-hand side $\partial_t c \in L^2(Q_T)$, we conclude the Hölder continuity of $c(t)$ for any fixed $t \in (0,T)$. Thus, the diffusivities are Hölder continuous, and we infer $C^{1+\delta}(\overline{\mathcal{D}})$ and $W^{2,\infty}(\mathcal{D})$ solutions c via a bootstrap-type argument for solutions to the original nonlinear problem (5). Second, we show the existence of a classical solution to (5) by an application of the fixed-point theorem of Schauder and the existence and regularity results of Ladyženskaya et al. [20].

In the third step, we solve the SDEs (1). The functions (c, f) have Hölder continuous gradients, and we show that (c, f) and $(\nabla c, \nabla f)$ are progressively measurable. Therefore, together with Assumption (A4), the conditions of the existence theorem of [21, Theorem 3.1.1] are satisfied, and we obtain a solution X to (1) in the sense (10).

Fourth, we define fixed-point operator $\Phi : \widetilde{X} \mapsto X$ on $Y_R(0,T;\mathcal{D})$, which can be written as the concatenation

$$\Phi : \widetilde{X} \mapsto (\alpha, \beta_D) \mapsto (c, f) \mapsto X,$$

where $\alpha = (\alpha_V, \alpha_D, \alpha_M, \alpha_U)$. It remains to show that Φ is a self-mapping and a contraction, which is possible for a sufficiently large $R > 0$. In fact, we show that for any $n \in \mathbb{N}$,

$$\sup_{0<s<t} \left(\mathbb{E}|\Phi^n(X(t)) - \Phi^n(X'(t))|^4\right)^{1/4} \le c_n \sup_{0<s<t} \left(\mathbb{E}|X(t) - X'(t)|^4\right)^{1/4}$$

for all $X, X' \in Y_R(0,T;\mathcal{D})$, where $c_n \to 0$ as $n \to \infty$. It follows from the variant of Banach's fixed-point theorem in [19, Theorem 2.4] that Φ has a unique fixed point, which gives a unique solution (X, c, f) to (1), (3)–(7).

The paper is organized as follows. In Section 2, the existence of a unique classical solution to the reaction–diffusion Eqs. (5)–(6) and some stability results are proved. The progressive measurability of the solutions to (3) and (5) as well as the solvability of the SDEs (1) is verified in Section 3. Based on these results, Theorem 1 is proved in Section 4. Some numerical experiments are illustrated in Section 5, showing stalk cells following the tip cells and forming a premature sprout. Appendix A summarizes some regularity results for elliptic and parabolic equations used in this work, Appendix B contains some auxiliary results, and Appendix C collects the numerical values of the various parameters used in the numerical experiments.

2. Solution of the reaction–diffusion equations

We show first some a priori estimates, prove then the existence of classical solutions to (5)–(6) and finally the uniqueness of solutions.

2.1. A priori estimates

The existence theory for SDEs requires some regularity for the solution c to (5), and in particular uniform estimates are needed. We consider first the linear system

$$\begin{aligned}
&\partial_t c_V - \operatorname{div}(D_V(\widehat{f})\nabla c_V) + \alpha_V(x,t)c_V = 0,\\
&\partial_t c_D - \operatorname{div}(D_D(\widehat{f})\nabla c_D) + \beta_D(x,t)c_D = \alpha_D(x,t)c_V,\\
&\partial_t c_M - \operatorname{div}(D_M(\widehat{f})\nabla c_M) + s_M\widehat{f}_B c_M = \alpha_M(x,t)c_V,\\
&\partial_t c_U - \operatorname{div}(D_U(\widehat{f})\nabla c_U) + s_U\widehat{f}_F c_U = \alpha_U(x,t)c_V,
\end{aligned} \tag{11}$$

where $\widehat{f}$ is calculated from (4), given some a.e. nonnegative function $\widehat{c} \in L^2(0,T;C^\delta(\overline{\mathcal{D}}))$, and it fulfills the volume-filling condition $\widehat{f}_B + \widehat{f}_F + \widehat{f}_E = 1$. Note that the bounds in (8) still hold and that $0 \le \widehat{f} \le 1$ a.e. Therefore, the following Lemmas 2 and 3 do not depend on the choice of $\widehat{c}$ and δ. We will hence omit the dependency of the diffusion coefficients D_j on $\widehat{f}$ in this case.

We prove L^∞ bounds for the solution c to (11). We suppose that Assumptions (A1)–(A5) hold throughout this section.

Lemma 2. *Let c be a weak solution to (6), (11). Then $c \in L^\infty(Q_T)$, it holds for all $0 < t < T$ that $\|c_V(t)\|_{L^\infty(\mathcal{D})} \le \|c_V^0\|_{L^\infty(\mathcal{D})}$,*

$$\|c_j(t)\|_{L^\infty(\mathcal{D})} \le e^t\big(\|c_j^0\|_{L^\infty(\mathcal{D})} + \|\alpha_j\|_{L^\infty(0,T;L^\infty(\mathcal{D}))}\|c_V^0\|_{L^\infty(\mathcal{D})}\big), \quad j = D, M, U,$$

and $c_j(t) \ge 0$ a.e. for $t > 0$ and $j \in \{V, D, M, U\}$.

Proof. First, we use $(c_V - K)^+ := \max\{0, c_V - K\}$ with $K := \|c_V^0\|_{L^\infty(\mathcal{D})}$ as a test function in the weak formulation of Eq. (5) for c_V:

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_{\mathcal{D}}[(c_V - K)^+]^2\mathrm{d}x + \int_{\mathcal{D}} D_V|\nabla(c_V - K)^+|^2\mathrm{d}x = -\int_{\mathcal{D}}\alpha_V c_V (c_V - K)^+\mathrm{d}x \le 0.$$

We conclude that $c_V(t) \le K$ in $\mathcal{D}$ for $t > 0$.

Second, we show that c_D is bounded. For this, set $M(t) = M_0 e^t$, where $M_0 = \|c_D^0\|_{L^\infty(\mathcal{D})} + \|\alpha_D\|_{L^\infty(0,T;L^\infty(\mathcal{D}))}\|c_V^0\|_{L^\infty(\mathcal{D})}$. Then $(c_D(0) - M)^+ = 0$ and, choosing $(c_D - M)^+$ as a test function in the weak formulation of Eq. (5) for c_D,

$$\begin{aligned}
&\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_{\mathcal{D}}[(c_D - M)^+]^2\mathrm{d}x + \int_{\mathcal{D}} D_D|\nabla(c_D - M)^+|^2\mathrm{d}x\\
&\quad = -\int_{\mathcal{D}}\partial_t M(c_D - M)^+\mathrm{d}x + \int_{\mathcal{D}}(\alpha_D c_V - \beta_D c_D)(c_D - M)^+\mathrm{d}x\\
&\quad \le \int_{\mathcal{D}}\big(-M_0 + \|\alpha_D\|_{L^\infty(0,T;L^\infty(\mathcal{D}))}\|c_V^0\|_{L^\infty(\mathcal{D})}\big)(c_D - M)^+\mathrm{d}x \le 0,
\end{aligned}$$

where we used $\beta_D \ge 0$, and the last inequality follows from the choice of M_0. This shows that $c_D(t) \le M_0 e^t$ in $\mathcal{D}$, $t > 0$. The bounds for c_M and c_U are shown in an analogous way.

The nonnegativity of c_D and then of c_j, $j \in \{D, M, U\}$ follows by using $c_j^- := \min\{0, c_j\}$ as a test function in the weak formulation of (11) and using the nonnegativity of the coefficients α_j and β_D. □

Next, we prove that the solution $c(t)$ is Hölder continuous.

Lemma 3. *Let c be a weak solution to (6), (11). We suppose that there exists $\Lambda > 0$ such that for a.e. $0 < t < T$,*

$$\|\alpha_j(t)\|_{L^\infty(\mathcal{D})} + \|\beta_D(t)\|_{L^\infty(\mathcal{D})} \le \Lambda, \quad j = V, D, M, U. \tag{12}$$

Then there exists $\delta > 0$ such that for $0 < t < T$,

$$\|\partial_t c\|_{L^2(Q_T)} \le C_2, \quad \|c(t)\|_{C^\delta(\overline{\mathcal{D}})} \le C_\delta\big(\|c(t)\|_{L^2(\mathcal{D})} + \|\partial_t c(t)\|_{L^2(\mathcal{D})}\big), \tag{13}$$

where $C_2 > 0$ depends on the $L^2(\mathcal{D})$ norm of c^0, the $L^\infty(\mathcal{D})$ norm of f^0, and Λ, and δ, C_δ depend on the lower and upper bounds (8) for D_j and Λ.

Proof. The $L^2(Q_T)$ bound for $\partial_t c$ follows immediately from Theorem 16 in Appendix A. The Hölder estimate follows from [22, Prop. 3.6]. Indeed, we interpret Eq. (5) for c_V,

$$\operatorname{div}(D_V\nabla c_V) + \alpha_V c_V = -\partial_t c_V \in L^2(\mathcal{D}) \quad \text{for } t \in (0,T)$$

as an elliptic equation with bounded diffusion coefficient D_V and right-hand side in $L^p(\mathcal{D})$ with $p > d/2$. By [22, Prop. 3.6], there exists $\delta > 0$ such that $c_V(t) \in C^\delta(\mathcal{D})$ and

$$\|c_V(t)\|_{C^\delta(\mathcal{D})} \le C\big(\|c_V\|_{L^2(\mathcal{D})} + \|\partial_t c_V\|_{L^p(\mathcal{D})}\big).$$

The result follows by observing that $d \le 3$ implies that $p < 2$. The dependency of δ and C_δ on the data follows from [23, Theorem 8.24], which is the essential result needed in the proof of [22, Prop. 3.6]. The regularity for the other concentrations is proved in a similar way. □

Lemma 4. *Let $\widehat{c}(t) \in L^2(0,T;C^\delta(\overline{\mathcal{D}}))$ with $\delta > 0$ as in Lemma 3, satisfying estimate (13), and let c be a weak solution to (6), (11). Furthermore, let $c_j^0 \in C^{1+\delta}(\overline{\mathcal{D}})$ be such that $\nabla c_j^0 \cdot \nu = 0$ on $\partial\mathcal{D}$, α_j, $\beta_j \in C^0(\overline{\mathcal{D}} \times [0,T])$ satisfying (12), and $f_j^0 \in C^\delta(\overline{\mathcal{D}})$ for $j = V, D, M, U$, where $\delta > 0$ is as in Lemma 3 or smaller. Then $c \in C^{1+\delta,(1+\delta)/2}(\overline{\mathcal{D}} \times [0,T])$ and there exists $C_{1+\delta} > 0$ such that*

$$\|c\|_{C^{1+\delta,(1+\delta)/2}(\overline{\mathcal{D}}\times[0,T])} \le C_{1+\delta},$$

where $C_{1+\delta} > 0$ depends only on T, Λ, C_δ, $\|f_0\|_{C^\delta(\mathcal{D})}$, $\|c_0\|_{C^{1+\delta}(\mathcal{D})}$, the L^∞ bound proven in Lemma 2, and the lower and upper bounds (8) for D_j.

The space $C^{1+\delta,(1+\delta)/2}(\overline{\mathcal{D}} \times [0,T])$ consists of all functions being $C^{1+\delta}$ in space and $C^{(1+\delta)/2}$ in time; see Appendix A for a precise definition.

Proof. We know from Lemma 3 that $c(t)$ is Hölder continuous in $\overline{\mathcal{D}}$ for a.e. $t \in (0,T)$. We claim that $\widehat{f}$ is Hölder continuous in $\overline{\mathcal{D}} \times [0,T]$. Let $x, y \in \overline{\mathcal{D}}$ and $\tau, t \in [0,T]$. We assume without loss of generality that $\tau < t$. The Lipschitz continuity of $z \mapsto \exp(-z)$ implies, using the explicit formula for f_B, that

$$\begin{aligned}
|\widehat{f}_B(x,t) - \widehat{f}_B(y,t)| &\le |f_B^0(x) - f_B^0(y)| + s_B\int_0^t |\widehat{c}_M(x,s) - \widehat{c}_M(y,s)|ds, \\
&\le \|f_B^0\|_{C^\delta(\overline{\mathcal{D}})}|x-y|^\delta + s_B C_\delta\big(\|\widehat{c}_M\|_{L^1(0,t;L^2(\mathcal{D}))} + \|\partial_t\widehat{c}_M\|_{L^1(0,t;L^2(\mathcal{D}))}\big)|x-y|^\delta, \\
|\widehat{f}_B(x,t) - \widehat{f}_B(x,\tau)| &\le |f_B^0(x)|s_B\int_\tau^t |\widehat{c}_M(x,s)|ds \\
&\le \|f_B^0\|_{C^\delta(\overline{\mathcal{D}})} s_B\|\widehat{c}_M\|_{L^\infty(Q_T)}T^{1-\delta/2}|t-\tau|^{\delta/2},
\end{aligned}$$

where we also used Lemma 3. Similar estimates hold for $\widehat{f}_E$ and $\widehat{f}_F$. Thus, the assumptions of Theorem 17 in Appendix A are fulfilled, yielding the statement. □

As solutions to (5)–(6) are also solutions to (6), (11) with the choice $\widehat{c} = c$, we can use the previous lemmas to prove the following uniform bound in $L^\infty(0,T;W^{2,\infty}(\mathcal{D}))$ for solutions c to (5).

Lemma 5. *Let the assumptions of Lemma 4 hold and let additionally $c_0 \in W^{2,\infty}(\mathcal{D})$ and $\alpha_j, \beta_D \ge 0$, $j \in \{V,D,M,U\}$. Then every weak solution c to (5)–(6), with f given by (4), is an element of $L^\infty(0,T;W^{2,\infty}(\mathcal{D}))$, and there exists a constant $C > 0$ such that*

$$\|c\|_{L^\infty(0,T;W^{2,\infty}(\mathcal{D}))} \le C,$$

where C depends on $\|f_0\|_{W^{1,\infty}(\mathcal{D})}$, $\|c_0\|_{W^{2,\infty}(\mathcal{D})}$, and has otherwise the same dependencies as $C_{1+\delta}$ in Lemma 4.

Proof. We deduce from Lemma 3 that $c \in L^2(0,T;C^\delta(\overline{\mathcal{D}}))$ and c satisfies (13). Then Lemma 4 implies that $c \in C^{1+\delta,(1+\delta)/2}(\overline{\mathcal{D}} \times [0,T])$ with $\|c\|_{C^{1+\delta,(1+\delta)/2}(\overline{\mathcal{D}}\times[0,T])} \le C_{1+\delta}$. Taking into account the explicit representation (4) of f, the regularity of c carries over to f. Let now $V \subset \mathbb{R}^3$ be a fixed bounded and open set satisfying $\mathcal{D} \Subset V$. We can extend c to a function $\widetilde{c} \in W^{1,\infty}(\mathbb{R}^3)$ with compact support in V such that [24, Section 5.4, Theorem 1]

$$\|\widetilde{c}\|_{W^{1,\infty}(\mathbb{R}^3)} \le C(V)\|c\|_{W^{1,\infty}(\mathcal{D})} \le C(V)C_{1+\delta}, \tag{14}$$

where $C(V)$ only depends on the choice of V. By [24, Section 5.8, Theorem 4], c is Lipschitz continuous, and due to (14), the Lipschitz coefficient is bounded by $C(V)C_{1+\delta}$ (see the first part of the proof of [24, Section 5.8, Theorem 4]). We conclude that, for $x, y \in \mathcal{D}$ and $0 < \zeta < 1$,

$$\frac{|c(x)-c(y)|}{|x-y|^\zeta} = |x-y|^{1-\zeta}\frac{|c(x)-c(y)|}{|x-y|} \le \max\Big\{1, \sup_{x',y'\in\mathcal{D}}|x'-y'|\Big\}C(V)C_{1+\delta}.$$

The map c is hence Hölder continuous of index ζ and its Hölder norm can be bounded independently of ζ. Repeating the proof of Lemma 4, we can show the existence of a constant $K(C_{1+\delta}, \Lambda, V)$ such that

$$\|c\|_{C^{1+\zeta,(1+\zeta)/2}(\overline{\mathcal{D}}\times[0,T])} \le K(C_{1+\delta}, \Lambda, V),$$

where $K(C_{1+\delta}, \Lambda, V)$ is again independent of ζ, see [25, Theorem 1.2]. Applying Lemma 20 for $f = \partial c/\partial x_i$ together with Rademacher's theorem completes the proof. $\square$

Remark 6. All the results proven in Lemmas 2–5 may depend on the L^∞ bound of the processes α, β, but they do not depend on the Hölder norm of index δ and therefore not on the process (X_1, X_2) itself as long as $X_i(\omega, t) \in \overline{\mathcal{D}}$ for $i = 1, 2$ a.s.

2.2. Existence

We show the existence of solutions to the reaction–diffusion and ordinary differential equations.

Theorem 7 (*Existence*). *Let $c_j^0 \in C^{2+\delta}(\overline{\mathcal{D}})$ be such that $\nabla c_j^0 \cdot \nu = 0$ on $\partial\mathcal{D}$, let $\alpha_j, \beta_j \in C^{\delta,\delta/2}(\overline{\mathcal{D}} \times [0,T])$ be nonnegative and satisfy (12), and let $f_j^0 \in C^{1+\delta}(\overline{\mathcal{D}})$ for $j = V, D, M, U$, where $\delta > 0$ is as in Lemma 4 or smaller. Then there exists a pair (c, f) such that $c \in C^{2+\delta,1+\delta/2}(\overline{\mathcal{D}} \times [0,T])$ is a classical solution to (5)–(6) and f is given by (4).*

Proof. Let $\widehat{c} \in C^{1+\delta',(1+\delta')/2}(\overline{\mathcal{D}}\times[0,T]) \cap H^1(0,T; L^2(\mathcal{D}))$ for some $0 < \delta' < \delta$ and let $\widehat{c}$ satisfy (13). Furthermore, let $(\widehat{f}_B, \widehat{f}_F)$ be given by (4) with c_j replaced by $\widehat{c}$, and $\widehat{f}_E$ is defined by the volume-filling condition $\widehat{f}_B + \widehat{f}_E + \widehat{f}_F = 1$. By Theorem 19 in Appendix A, the linear system (11), together with (6), has a classical solution c which satisfies the estimate

$$\begin{aligned}\|c\|_{C^{2+\delta',(2+\delta')/2}(\overline{\mathcal{D}}\times[0,T])} &\le K_0(\widehat{f},\alpha,\beta)\big(\|c_0\|_{C^{2+\delta',(2+\delta')/2}(\overline{\mathcal{D}}\times[0,T])} \\ &\quad + \|c_V\|_{C^{2+\delta',(2+\delta')/2}(\overline{\mathcal{D}}\times[0,T])}\big) \\ &\le K(\widehat{f},\alpha,\beta)\|c_0\|_{C^{2+\delta',(2+\delta')/2}(\overline{\mathcal{D}}\times[0,T])}.\end{aligned} \tag{15}$$

We deduce from Lemma 4 that $\|c\|_{C^{1+\delta,(1+\delta)/2}(\overline{\mathcal{D}}\times[0,T])} \le C_{1+\delta}$, where $C_{1+\delta}$ is independent of $\widehat{f}$ and the choice of $\widehat{c}$.

We define now the fixed-point operator. Let

$$\begin{aligned} f\widehat{c} \in W := \big\{&u \in C^{1+\delta,(1+\delta)/2}(\overline{\mathcal{D}} \times [0,T]) \cap H^1(0,T; L^2(\mathcal{D})) : \\ &\|u\|_{C^{1+\delta,(1+\delta)/2}(\overline{\mathcal{D}}\times[0,T])} \le C_{1+\delta}, \quad u \text{satisfies (13)}\big\}.\end{aligned}$$

Then the operator $\Gamma : W \to W$, mapping $\widehat{c}$ to the solution c to (5)–(6) is well-defined. Furthermore, by estimate (15), it holds that

$$\|\Gamma(\widehat{c})\|_{C^{2+\delta',(2+\delta')/2}(\bar{\mathcal{D}}\times[0,T])} \le K_1(\alpha,\beta)\|c_0\|_{C^{2+\delta',(2+\delta')/2}(\bar{\mathcal{D}}\times[0,T])}, \tag{16}$$

where the constant K_1 does not depend on $\widehat{f}$ thanks to the uniform bound $C_{1+\delta}$ in W. Given two elements $\widehat{c}_1, \widehat{c}_2 \in W$, we set $\Gamma(\widehat{c}_i) = c_i$ and define $u := c_{1,V} - c_{2,V}$. Then u satisfies

$$\begin{aligned}&\partial_t u - \operatorname{div}(D_V(\widehat{f}_1)\nabla u) + \alpha_V u = \operatorname{div}\big((D(\widehat{f}_1) - D(\widehat{f}_2))\nabla c_2\big), \quad \text{in } \mathcal{D}\times(0,T], \\ &u(0) = 0 \quad \text{in } \mathcal{D}, \quad \nabla u\cdot\nu = 0 \quad \text{in } \partial\mathcal{D}\times[0,T],\end{aligned}$$

where $\widehat{f}_i$ is the corresponding solution to (3) associated with $\widehat{c}_i$. By Theorem 19 and estimate (16), $u = c_{1,V} - c_{2,V}$ satisfies the inequality

$$\begin{aligned}&||c_{1,V} - c_{2,V}||_{C^{2+\delta',(2+\delta')/2}(\overline{\mathcal{D}}\times[0,T])} \\ &\quad \le K_2(\widehat{f}_1,\alpha)\|c_2\|_{C^{2+\delta',(2+\delta')/2}(\overline{\mathcal{D}}\times[0,T])}\|\widehat{f}_1 - \widehat{f}_2\|_{C^{1+\delta',(1+\delta')/2}(\overline{\mathcal{D}}\times[0,T])} \\ &\quad \le K_2(\widehat{f}_1,\alpha)K_3(\alpha,\beta,c^0)\|\widehat{c}_1 - \widehat{c}_2\|_{C^{1+\delta',(1+\delta')/2}(\overline{\mathcal{D}}\times[0,T])},\end{aligned}$$

where we also used (4). We obtain similar estimates for the other components $c_{1,i} - c_{2,i}$, $i = D, M, U$. From these inequalities, we directly infer the continuity of Γ in the norm $\|\cdot\|_{C^{1+\delta',(1+\delta')/2}(\overline{\mathcal{D}}\times[0,T])}$. Since W is compactly embedded in $C^{1+\delta',(1+\delta')/2}(\overline{\mathcal{D}} \times [0,T])$, using $\delta' < \delta$, we conclude from Schauder's fixed-point theorem that there exists a fixed point c for Γ and hence a solution to (5)–(6). $\square$

2.3. Stability and uniqueness

The stability results are used for the solution of the SDEs; they also imply the uniqueness of solutions. We start with a stability estimate in the norms of $L^\infty(0,T;L^2(\mathcal{D}))$ and $L^2(0,T;H^1(\mathcal{D}))$. Let Assumptions (A1)–(A5) hold.

Lemma 8. *Let c_i for $i=1,2$ be weak solutions to (5)–(6) with the same initial data (c^0,f^0) but possibly different coefficients α_i and β_i. Then there exists $C>0$, which is independent of c_i, such that for all $t\in[0,T]$,*

$$\begin{aligned}&\|(c_1-c_2)(t)\|_{L^2(\mathcal{D})}+\|c_1-c_2\|_{L^2(0,t;H^1(\mathcal{D}))}\le h(t),\quad \text{where}\\ &h(t):=C\big(\|\alpha_1-\alpha_2\|_{L^2(Q_T)}+\|\beta_1-\beta_2\|_{L^2(Q_T)}\big).\end{aligned}$$

Proof. We first consider c_V. We take the difference of the equations satisfied by $c_{1,V}-c_{2,V}$ and take the test function $c_{1,V}-c_{2,V}$ in its weak formulation. This leads to

$$\begin{aligned}\frac12\frac{\mathrm{d}}{\mathrm{d}t}\int_{\mathcal{D}}(c_{1,V}-c_{2,V})^2\mathrm{d}x&+\int_{\mathcal{D}}D_V(f_1)|\nabla(c_{1,V}-c_{2,V})|^2\mathrm{d}x+\int_{\mathcal{D}}\alpha_{1,V}(c_{1,V}-c_{2,V})^2\mathrm{d}x\\ &=\int_{\mathcal{D}}(D_V(f_1)-D_V(f_2))\nabla c_{2,V}\cdot\nabla(c_{1,V}-c_{2,V})\mathrm{d}x\\ &\quad+\int_{\mathcal{D}}(\alpha_{1,V}-\alpha_{2,V})c_{2,V}(c_{1,V}-c_{2,V})\mathrm{d}x.\end{aligned}$$

Let $\varepsilon:=\min\{D_j^i: j=V,D,M,U,\ i=B,E,F\}>0$. Using Young's inequality and the estimate $\|(f_1-f_2)(t)\|_{L^2(\mathcal{D})}\le C\|c_1-c_2\|_{L^1(0,T;L^2(\mathcal{D}))}$ from Lemma 21, we find that

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}&\|c_{1,V}-c_{2,V}\|^2_{L^2(\mathcal{D})}+\frac{\varepsilon}{2}\|\nabla(c_{1,V}-c_{2,V})\|^2_{L^2(\mathcal{D})}\\ &\le C(\varepsilon)\|\nabla c_{2,V}\|^2_{L^\infty(Q_T)}\|D_V(f_1)-D_V(f_2)\|^2_{L^2(\mathcal{D})}\\ &\quad+\|c_{2,V}\|^2_{L^\infty(Q_T)}\|\alpha_{1,V}-\alpha_{2,V}\|^2_{L^2(\mathcal{D})}+\|c_{1,V}-c_{2,V}\|^2_{L^2(\mathcal{D})}\\ &\le C\|c_1-c_2\|^2_{L^2(\mathcal{D})}+C\|\alpha_{1,V}-\alpha_{2,V}\|^2_{L^2(\mathcal{D})}.\end{aligned}$$

The estimates for $c_{1,j}-c_{2,j}$ with $j=D,M,V$ are similar. This gives

$$\frac{\mathrm{d}}{\mathrm{d}t}\|c_1-c_2\|^2_{L^2(\mathcal{D})}+\frac{\varepsilon}{2}\|\nabla(c_1-c_2)\|^2_{L^2(\mathcal{D})}\le Ch(t)^2+C\|c_1-c_2\|^2_{L^2(\mathcal{D})}.$$

An application of Gronwall's lemma finishes the proof. □

A stability estimate can also be proved with respect to the $H^2(\mathcal{D})$ norm.

Lemma 9. *Let c_i for $i=1,2$ be weak solutions to (5)–(6) with the same initial data (c^0,f^0) but possibly different coefficients α_i and β_i. Then there exists $C>0$ such that for all $t\in[0,T]$,*

$$\begin{aligned}||\partial_t(c_1-c_2)||_{L^2(Q_T)}&+\|c_1-c_2\|_{L^\infty(0,T;H^1(\mathcal{D}))}+\|c_1-c_2\|_{L^2(0,T;H^2(\mathcal{D}))}\\ &\le C\big(\|\alpha_1-\alpha_2\|_{L^2(Q_T)}+\|\beta_1-\beta_2\|_{L^2(Q_T)}\big),\end{aligned}$$

where $C>0$ depends on $\|c_1\|_{L^\infty(0,T;W^{2,\infty}(\mathcal{D}))}$.

Proof. The difference $u:=c_{1,V}-c_{2,V}$ is the solution to the linear problem

$$\begin{aligned}&\partial_t u-\operatorname{div}(D_V(f_1)\nabla u)=g(x,t)\quad\text{in }\mathcal{D},\ t>0,\\ &\nabla u\cdot\nu=0\quad\text{on }\partial\mathcal{D},\quad u(0)=0\quad\text{in }\mathcal{D},\end{aligned}\tag{17}$$

where, by Lemma 5, the right-hand side

$$g:=-\operatorname{div}\big((D_V(f_1)-D_V(f_2))\nabla c_{2,V}\big)+\alpha_{1,V}(c_{1,V}-c_{2,V})+(\alpha_{1,V}-\alpha_{2,V})c_{2,V}\tag{18}$$

is an element of $L^2(Q_T)$. Since the diffusion coefficient is bounded, we can apply Theorem 16 in Appendix A to conclude that

$$\|u\|_{L^\infty(0,T;H^1(\mathcal{D}))}+\|\partial_t u\|_{L^2(Q_T)}\le C\|g\|_{L^2(Q_T)}.$$

For the estimate of the right-hand side, we recall from Lemma 21 that

$$\|\nabla(f_1-f_2)\|_{L^2(Q_T)}\le C\|c_1-c_2\|_{L^1(0,T;H^1(\mathcal{D}))}.$$

Then, using the linearity of D_V and the estimate for $c_{2,V}$ from Lemma 5, we infer that

$$\begin{aligned}\|g\|_{L^2(Q_T)} &\le C\|\nabla(f_1-f_2)\|_{L^2(Q_T)}\|\nabla c_{2,V}\|_{L^\infty(Q_T)} + C\|f_1-f_2\|_{L^2(Q_T)}\|\Delta c_{2,V}\|_{L^\infty(Q_T)} \\ &\quad + \|\alpha_{1,V}\|_{L^\infty(Q_T)}\|u\|_{L^2(Q_T)} + \|\alpha_{1,V}-\alpha_{2,V}\|_{L^2(Q_T)}\|c_{2,V}\|_{L^\infty(Q_T)} \\ &\le C\big(\|c_1-c_2\|_{L^2(0,T;H^1(\mathcal{D}))} + \|\alpha_{1,V}-\alpha_{2,V}\|_{L^2(Q_T)}\big).\end{aligned}$$

The difference $c_1 - c_2$ in the $L^2(0,T;H^1(\mathcal{D}))$ norm can be estimated according to Lemma 8. Therefore,

$$\|u\|_{L^\infty(0,T;H^1(\mathcal{D}))} + \|\partial_t u\|_{L^2(Q_T)} \le C\big(\|\alpha_1-\alpha_2\|_{L^2(Q_T)} + \|\beta_1-\beta_2\|_{L^2(Q_T)}\big). \tag{19}$$

Similar estimates can be derived for the differences $c_{1,j} - c_{2,j}$ ($j = D, M, U$).

To estimate u in the $L^2(0,T;H^2(\mathcal{D}))$ norm, we use the inequality

$$\|u\|_{H^2(\mathcal{D})} \le C\big(\|\Delta u\|_{L^2(\mathcal{D})} + \|u\|_{L^2(\mathcal{D})}\big).$$

Thus, it remains to consider Δu. We deduce from

$$\begin{aligned}D_V(f_1)\Delta u &= \operatorname{div}\big(D_V(f_1)\nabla c_{1,V} - D_V(f_2)\nabla c_{2,V}\big) - \nabla(D_V(f_1)-D_V(f_2))\cdot\nabla c_{2,V} \\ &\quad - (D_V(f_1)-D_V(f_2))\Delta c_{2,V} - \nabla D_V(f_1)\cdot\nabla(c_{1,V}-c_{2,V}) \\ &= \partial_t u - \alpha_{1,V}u - (\alpha_{1,V}-\alpha_{2,V})c_{2,V} - \nabla(D_V(f_1)-D_V(f_2))\cdot\nabla c_{2,V} \\ &\quad - (D_V(f_1)-D_V(f_2))\Delta c_{2,V} - \nabla D_V(f_1)\cdot\nabla u\end{aligned}$$

and $\|\nabla(D_V(f_1)-D_V(f_2))\|_{L^2(Q_T)} \le C\|c_1-c_2\|_{L^2(0,T;H^1(\mathcal{D}))}$ (see Lemma 21) that

$$\|\Delta u\|_{L^2(Q_T)} \le C\big(\|\alpha_1-\alpha_2\|_{L^2(Q_T)} + \|\beta_1-\beta_2\|_{L^2(Q_T)} + \|u\|_{L^2(0,T;H^1(\mathcal{D}))}\big).$$

We infer from (19) and related inequalities for $c_{1,j} - c_{2,j}$ that

$$\|\Delta(c_1-c_2)\|_{L^2(Q_T)} \le C\big(\|\alpha_1-\alpha_2\|_{L^2(Q_T)} + \|\beta_1-\beta_2\|_{L^2(Q_T)}\big),$$

which concludes the proof. □

Lemma 10. *Let c_i for $i = 1, 2$ be weak solutions to (5)–(6) with the same initial data (f^0, c^0) but possibly different coefficients α_i and β_i. Then there exists $C > 0$ such that for all $t \in [0,T]$,*

$$\|c_1-c_2\|_{L^4(0,T;W^{2,4}(\mathcal{D}))} \le C\big(\|\alpha_1-\alpha_2\|_{L^4(Q_T)} + \|\beta_1-\beta_2\|_{L^4(Q_T)}\big).$$

Proof. Let $u = c_{1,V} - c_{2,V}$ be the solution to (17). Since $g \in L^4(Q_T)$ by Lemma 5 (recall definition (18) of g), Theorem 18 in Appendix A shows that $u \in L^4(0,T;W^{2,4}(\mathcal{D})) \cap H^1(0,T;L^4(\mathcal{D}))$ and, because of $\nabla c_{2,V} \in L^\infty(0,T;W^{1,\infty}(\mathcal{D}))$,

$$\begin{aligned}||c_{1,V}-c_{2,V}||_{L^4(0,T;W^{2,4}(\mathcal{D}))} &\le C\|g\|_{L^4(Q_T)} \\ &\le C\big(\|c_1-c_2\|_{L^1(0,T;W^{1,4}(\mathcal{D}))} + \|c_{1,V}-c_{2,V}\|_{L^4(Q_T)} + \|\alpha_{1,V}-\alpha_{2,V}\|_{L^4(Q_T)}\big).\end{aligned}$$

The first and second terms on the right-hand side can be estimated by using the embedding $H^2(\mathcal{D}) \hookrightarrow W^{1,4}(\mathcal{D})$ and Lemma 9:

$$\begin{aligned}\|c_1-c_2\|_{L^1(0,T;W^{1,4}(\mathcal{D}))} &\le C\|c_1-c_2\|_{L^2(0,T;H^2(\mathcal{D}))} \\ &\le C\big(\|\alpha_1-\alpha_2\|_{L^2(Q_T)} + \|\beta_1-\beta_2\|_{L^2(Q_T)}\big), \\ \|c_{1,V}-c_{2,V}\|_{L^4(Q_T)} &\le C\|c_{1,V}-c_{2,V}\|_{L^4(0,T;H^1(\mathcal{D}))} \\ &\le C\big(\|\alpha_1-\alpha_2\|_{L^2(Q_T)} + \|\beta_1-\beta_2\|_{L^2(Q_T)}\big).\end{aligned}$$

This gives

$$\|c_{1,V}-c_{2,V}\|_{L^4(0,T;W^{2,4}(\mathcal{D}))} \le C\big(\|\alpha_1-\alpha_2\|_{L^4(Q_T)} + \|\beta_1-\beta_2\|_{L^2(Q_T)}\big).$$

The estimates for $c_{1,j} - c_{2,j}$ ($j = D, M, U$) are similar. □

3. Solution of the stochastic differential equations

Let α, β be given by (7). We first study the measurability of (c, f).

Lemma 11. *Let $f^0 \in L^\infty(\Omega; C^{1+\delta}(\overline{\mathcal{D}}))$ and $c^0 \in L^\infty(\Omega; W^{2,\infty}(\mathcal{D}))$ be such that $\nabla c_j^0 \cdot \nu = 0$ on $\partial\mathcal{D}$, $j = V, D, M, U$. Furthermore, let (c, f) be a pathwise solution to (3), (5)–(6) and let (X_1, X_2) in (7) be adapted stochastic processes with Hölder continuous paths (with Hölder index δ) almost surely. Then f, ∇f are measurable as maps from $(\Omega\times\mathcal{D}\times[0,t], \mathcal{F}_t\times\mathcal{B}(\mathcal{D})\times\mathcal{B}([0,t]))$ to $\mathcal{B}(\mathbb{R}^3)/\mathcal{B}(\mathbb{R}^{3\times3})$, and c, ∇c are measurable as maps from $(\Omega\times\mathcal{D}\times[0,t], \mathcal{F}_t\times\mathcal{B}(\mathcal{D})\times\mathcal{B}([0,t]))$ to $\mathcal{B}(\mathbb{R}^4)/\mathcal{B}(\mathbb{R}^{4\times3})$ for all $t \in [0,T]$. In particular, these functions are progressively measurable.*

Proof. Since f_j can be represented as a function depending on the time integral of c, it is sufficient to show the measurability of c_j. The continuity of the potentials defining α_j and β_j in (7) shows that α_j and β_j are processes with càdlàg paths almost surely. By approximating the initial data c^0, f^0 and the processes α_j, β_j by suitable simple processes, which are adapted to the filtration by construction, we can obtain the $\mathcal{F}_t$-measurability of $c_j(t) : \Omega \to C^1(\overline{\mathcal{D}})$ for $t \in [0, T]$. We conclude from Lemma 8 and the compactness of $W^{2,\infty}(\mathcal{D}) \subset C^{1+\delta}(\overline{\mathcal{D}})$ in $C^1(\overline{\mathcal{D}})$ the measurability of c_j as the limit of measurable functions. For details of this construction, we refer to [17, Section 3.3].

It is known that càdlàg processes $Y_t : \Omega \times [0, T] \to H$ with $H = \mathbb{R}^n$, which are adapted to the filtration, are progressively measurable [26, Prop. 1.13]. If the filtration is complete, this holds also true for processes having càdlàg paths almost surely. A straightforward modification of the proof of [26, Prop. 1.13], utilizing [27, Theorem 4.2.2], shows that this holds for arbitrary Banach spaces H. The estimate $\|c_j(t) - c_j(s)\|_{C^1(\overline{\mathcal{D}})} \le C|t - s|^\delta$, which follows from Lemma 4, implies that $c_j(t)$ has almost surely continuous paths and consequently, $c_j(t)$ is progressively measurable. To be precise, this yields the measurability of c_j as a function from $(\Omega \times [0, t], \mathcal{F}_t \times \mathcal{B}([0, t]))$ to $(C^1(\overline{\mathcal{D}}), \mathcal{B}(C^1(\overline{\mathcal{D}})))$ for every $t \in [0, T]$.

The function $(c, x) \mapsto c(x)$, $C^1(\overline{\mathcal{D}}) \times \overline{\mathcal{D}} \to \mathbb{R}^4$, is continuous and hence, it is measurable as a mapping from $(C^1(\overline{\mathcal{D}}) \times \bar{\mathcal{D}}, \mathcal{B}(C^1(\overline{\mathcal{D}})) \times \mathcal{B}(\bar{\mathcal{D}}))$ to $(\mathbb{R}^4, \mathcal{B}(\mathbb{R}^4))$. Now, we can write $c(\omega, x, t)$ as the concatenation

$$(\omega, x, t) \mapsto (c(\omega, \cdot, t), x) \mapsto c(\omega, x, t), \quad \Omega \times \overline{\mathcal{D}} \times [0, T] \to C^1(\overline{\mathcal{D}}) \times \overline{\mathcal{D}} \to \mathbb{R}^4,$$

of measurable functions, which yields the measurability of c. In a similar way, we can prove the measurability of $\partial c_j/\partial x_i$ for $i = 1, 2, 3$ by considering the continuous mapping $(c, x) \mapsto (\partial c/\partial x_i)(x)$. □

Lemma 12. *Let Assumptions (A1)–(A5) and the assumptions of Lemma 11 hold. Then there exists a unique, progressively measurable solution (X_i^k) to (1) such that $X_i^k(t) \in \overline{\mathcal{D}}$ a.s. for every $t \in [0, T]$, $i = 1, 2$.*

Proof. We extend the coefficients g_i and σ_i by setting them to zero outside of $\mathcal{D}$. The extended coefficients are still uniformly Lipschitz continuous. We infer from Lemma 11 that g_i is progressively measurable. Thus, by [28, Theorem 32.3], there exists a strong solution to (1).

It remains to show that $X_i^k(t) \in \overline{\mathcal{D}}$ a.s. Let ϕ be a smooth test function satisfying $\operatorname{supp}\phi \subset \mathcal{D}^c$. We obtain from Itô's lemma that

$$d\phi(X_i^k) = \nabla\phi(X_i^k) \cdot g_i[c, f](X_i^k, t)dt + \frac{1}{2}\sigma_i(X_i^k)^2 \Delta\phi(X_i^k)dt + \nabla\phi(X_i^k) \cdot \sigma_i(X_i^k)dW_i^k. \tag{20}$$

If $X_i^k(t) \in \mathcal{D}$, we have $\phi(X_i^k) = 0$. If $X_i^k(t) \in \mathcal{D}^c$ then $g_i[c, f](X_i^k(t), t) = 0$ by Assumption (A3) and $\sigma_i(X_i^k(t)) = 0$ by Assumption (A2). Eq. (20) then shows that $\phi(X_i^k(t)) = \phi(X_i^0) = 0$ and $X_i^k(t) \in \overline{(\operatorname{supp}\phi)^c}$ a.s. Since ϕ with $\operatorname{supp}\phi \subset \mathcal{D}^c$ was arbitrary, we conclude that $X_i^k(t) \in \overline{\mathcal{D}}$ a.s. for $t \in (0, T)$. □

4. Proof of Theorem 1

The fixed-point operator is defined as a function that maps $\widetilde{X} \mapsto (\alpha, \beta_D) \mapsto (c, f) \mapsto X$, where (α, β_D) is defined in (7) with X replaced by $\widetilde{X}$. To define its domain, we need some preparations.

Lemma 13. *The space $Y_R(0, T; \mathcal{D})$, defined in (9), is complete. Furthermore, any $X \in Y_R(0, T; \mathcal{D})$ has a progressively measurable modification with almost surely Hölder continuous paths.*

Proof. Let (X_n) be a Cauchy sequence in $Y_R(0, T; \mathcal{D})$ and let $\varepsilon > 0$. Then there exists $N \in \mathbb{N}$ such that for all $n, m \ge N$,

$$\|X_n(t) - X_m(t)\|_{L^4(\Omega)} \le \|X_n - X_m\|_{C^0([0,T];L^4(\Omega))} < \varepsilon.$$

For any $t \in [0, T]$, $(X_n(t))$ is a Cauchy sequence in $L^4(\Omega)$. Consequently, $X_n(t) \to X(t)$ in $L^4(\Omega)$, where $X(t) \in L^4(\Omega)$ is $\mathcal{F}_t$-measurable. Furthermore, there exists a subsequence of $(X_n(t))$ (not relabeled) that converges pointwise to $X(t)$ a.s., proving that $X(t) \in \overline{\mathcal{D}}$ a.s. The definition of the Hölder norm implies that $\|X_n(t) - X_n(s)\|_{L^4(\Omega)} \le R|t - s|^{1/2}$ for all $s, t \in [0, T]$. This gives in the limit $n \to \infty$ that $\|X(t) - X(s)\|_{L^4(\Omega)} \le R|t - s|^{1/2}$ and consequently $X \in C^{1/2}(0, T; L^4(\mathcal{D}))$. We conclude that $X \in Y_R(0, T; \mathcal{D})$. By the Kolmogorov continuity criterium, (a modification of) X has almost surely Hölder continuous paths. As $X(t)$ is an adapted process with respect to the filtration $\mathcal{F}_t$, X is progressively measurable. □

Lemma 14. *Let $(\widetilde{X}_1, \widetilde{X}_2) \in Y_R(0, T; \mathcal{D})$ for some $R > 0$, and let (c, f) be a solution to (3), (5)–(6), where α, β are given by (7) with X replaced by $\widetilde{X}$. Then, for fixed initial datum (X_1^0, X_2^0), there exists $R_0 > 0$ not depending on R such that the solution (X_1, X_2) to (1) satisfies $(X_1, X_2) \in Y_{R_0}(0, T; \mathcal{D})$.*

Proof. According to Lemma 5, c is bounded in the $L^\infty(0, T; W^{2,\infty}(\mathcal{D}))$ norm by a constant that is independent of R. Then, by Lemma 12, there exists a unique solution (X_1, X_2) to (1). Since $X_i^k(t) \in \overline{\mathcal{D}}$ a.s., c, ∇c, f, ∇f are bounded uniformly in R, i.e., there exists $K = K(c^0, f^0) > 0$, which is independent of R, such that $|g_i[c,f](X_i^k(t),t)| \le K$ a.s. Thus, for $s,t \in [0,T]$, using the Burkholder–Davis–Gundy inequality,

$$\begin{aligned}\mathbb{E}|X_i^k(t) - X_i^k(s)|^4 &\le C(K)|t-s|^4 + C\mathbb{E}\bigg(\int_s^t \sigma(X_i^k(s))\mathrm{d}W_i^k(s)\bigg)^4 \\ &\le C(K)|t-s|^4 + C\mathbb{E}\bigg(\int_s^t \sigma(X_i^k(s))^2\mathrm{d}s\bigg)^2 \\ &\le C(K)\big(|t-s|^2 + \|\sigma\|^4_{L^\infty(\mathcal{D})}\big)|t-s|^2 \le C(K,T,\sigma,\mathcal{D})|t-s|^2.\end{aligned}$$

The lemma follows after choosing $R_0 := \max\{C(K,T,\sigma,\mathcal{D})^{1/4}, (K\sqrt{T} + C\|\sigma\|_{L^\infty(\mathcal{D})})\sqrt{T} + \|X_0\|_{L^4(\Omega)}\}$. □

The previous lemma shows that the fixed-point operator $\Phi : Y_{R_0}(0,T;\mathcal{D}) \to Y_{R_0}(0,T;\mathcal{D})$, $\widetilde{X} \mapsto X$, is well defined. We need to verify that Φ is a contraction. We first prove an auxiliary result.

Lemma 15. *Let (c,f) and (c',f') be progressively measurable solutions to (3)–(6), where α, β are given by (7) with X replaced by $\widetilde{X}$, $\widetilde{X}' \in Y_R(0,T;\mathcal{D})$ for some $R > 0$, respectively. Then the associated solutions X and X' to (1) satisfy*

$$\mathbb{E}|X(t) - X'(t)|^4 \le Ct\int_0^t \mathbb{E}\|c(s) - c'(s)\|^4_{C^1(\overline{\mathcal{D}})}\mathrm{d}s,$$

where the constant $C > 0$ does not depend on R, (c,f), or (c',f').

Proof. The Itô integral representation of $X(t) - X'(t)$ gives

$$\begin{aligned}\mathbb{E}|X_i^k(t) - (X')_i^k(t)|^4 &\le C\mathbb{E}\bigg(\int_0^t \big(g_i[c,f](X_i^k(s),s) - g_i[c',f']((X')_i^k(s),s)\big)\mathrm{d}s\bigg)^4 \\ &\quad + C\mathbb{E}\bigg(\int_0^t \big(\sigma(X_i^k(s)) - \sigma((X')_i^k(s))\big)\mathrm{d}W_i^k(s)\bigg)^4 =: I_1 + I_2.\end{aligned} \tag{21}$$

It follows from Assumption (A4) and the explicit representation (4) that

$$\begin{aligned}I_1 &\le C\mathbb{E}\bigg|\int_0^t \big(g_i[c,f](X_i^k(s),s) - g_i[c',f'](X_i^k(s),s)\big)\mathrm{d}s\bigg|^4 \\ &\quad + \mathbb{E}\bigg|\int_0^t \big(g_i[c',f'](X_i^k(s),s) - g_i[c',f']((X')_i^k(s),s)\big)\mathrm{d}s\bigg|^4 \\ &\le L_1^4\mathbb{E}\big(1 + \|c\|_{L^\infty(0,T;C^1(\overline{\mathcal{D}}))}\big)^4\bigg(\int_0^t \|c(s) - c'(s)\|_{C^1(\overline{\mathcal{D}})}\mathrm{d}s\bigg)^4 \\ &\quad + L_2^4\mathbb{E}\big(1 + \|c'\|_{L^\infty(0,T;W^{2,\infty}(\mathcal{D}))}\big)^4\bigg(\int_0^t |X(s) - X'(s)|\mathrm{d}s\bigg)^4.\end{aligned}$$

Furthermore, by the Burkholder–Davis–Gundy inequality and the Lipschitz continuity of σ,

$$I_2 \le C\mathbb{E}\bigg(\int_0^t \big(\sigma(X_i^k(s)) - \sigma((X')_i^k(s))\big)^2\mathrm{d}s\bigg)^2 \le C\mathbb{E}\bigg(\int_0^t |X(s) - X'(s)|^2\mathrm{d}s\bigg)^2.$$

We insert these estimates into (21) and use Hölder's inequality:

$$\begin{aligned}\mathbb{E}|X(t) - X'(t)|^4 &\le Ct^3\mathbb{E}\int_0^t \|c(s) - c'(s)\|^4_{C^1(\overline{\mathcal{D}})}\mathrm{d}s \\ &\quad + Ct^3\mathbb{E}\int_0^t |X(s) - X'(s)|^4\mathrm{d}s + Ct\mathbb{E}\int_0^t |X(s) - X'(s)|^4\mathrm{d}s.\end{aligned}$$

Then Gronwall's lemma concludes the proof. □

We prove now that $\Phi : Y_{R_0}(0,T;\mathcal{D}) \to Y_{R_0}(0,T;\mathcal{D})$, $\widetilde{X} \mapsto X$, is a contraction. By Lemmas 10 and 15, we have

$$\begin{aligned}\mathbb{E}|\Phi(X(t)) - \Phi(X'(t))|^4 &\le Ct\int_0^t \mathbb{E}\|c(s) - c'(s)\|^4_{C^1(\overline{\mathcal{D}})}\mathrm{d}s \\ &\le Ct\mathbb{E}\big(\|\alpha - \alpha'\|^4_{L^4(Q_T)} + \|\beta - \beta'\|^4_{L^4(Q_T)}\big) \\ &\le Ct\mathbb{E}\|X - X'\|^4_{L^4(0,t,L^4(\mathcal{D}))} = Ct\int_0^t \mathbb{E}|X(s) - X'(s)|^4\mathrm{d}s.\end{aligned}$$

We iterate this inequality to find after n times that

$$\begin{aligned}\mathbb{E}|\Phi^n(X(t))-\Phi^n(X'(t))|^4 &\le (Ct)^n\int_0^t\int_0^{s_1}\cdots\int_0^{s_{n-1}}\mathbb{E}|X(s_n)-X'(s_n)|^4\mathrm{d}s_n\cdots\mathrm{d}s_1\\ &\le (Ct)^n\frac{t^n}{n!}\sup_{0<s<t}\mathbb{E}|X(s)-X'(s)|^4.\end{aligned}$$

We conclude that

$$\sup_{0<s<T}\big(\mathbb{E}|\Phi^n(X(t))-\Phi^n(X'(t))|^4\big)^{1/4}\le\frac{(CT^2)^{n/4}}{(n!)^{1/4}}\sup_{0<s<T}\big(\mathbb{E}|X(s)-X'(s)|^4\big)^{1/4}.$$

The sequence $(CT^2)^{n/4}/(n!)^{1/4}$ converges to zero as $n\to\infty$. Hence, there exists $n\in\mathbb{N}$ such that Φ^n is a contraction. By the variant [19, Theorem 2.4] of Banach's fixed-point theorem, Φ has a fixed point, proving Theorem 1.

5. Numerical experiments

We illustrate the dynamics of the tip and stalk cells in the two-dimensional ball $\mathcal{D}=B_R(0)$ around the origin with radius $R=500$ (in units of μm) for one path $t\mapsto X(\omega,t)$. Let $h=10$ be the space step size and introduce the grid points $x_{ij}=((k-i)h,(k-j)h)\in\mathbb{R}^2$, where $i,j=0,\ldots,2k$ and $k=R/h$. The time step size equals $\tau=1$ (in units of seconds).

The stochastic differential Eqs. (1) are discretized by using the Euler–Maruyama scheme

$$(\widetilde{X}_i^k)^{(n+1)}=(\widetilde{X}_i^k)^{(n)}+g_i[c^n,f^n]\big((\widetilde{X}_i^k)^{(n)},t\big)\tau+\sigma_i\big((\widetilde{X}_i^k)^{(n)}\big)\sqrt{\tau}\mathcal{N},$$

with initial datum $(\widetilde{X}_i^k)^{(0)}=(X_0)_i^k$, where $\mathcal{N}$ is standard normally distributed and c^n, f^n are approximations of c, f obtained by linear interpolation of the values c_{ij}^n (see below). The nonlinearity g_i is chosen as in (2) with M, γ, and λ given in Appendix C. Furthermore, α_0 and z are taken as in [29, formulas (10) and (14)]. Compared to [1], we neglect the contribution of the Hertz contact mechanics regarding z to guarantee the boundary condition $g_i[c,f](\cdot,t)=0$ on $\partial\mathcal{D}$. We choose the continuous radially symmetric stochastic diffusion

$$\sigma(x)=\begin{cases}0 & \text{for } |x|\ge R,\\ (1/R)\sqrt{(R/10)^2-[R/10-(R-|x|)^2]} & \text{for } 9R/10<|x|<R,\\ 1/10 & \text{for } |x|\le 9R/10.\end{cases}$$

The solutions (4) to the ordinary differential Eqs. (3) are written iteratively as

$$f_B(x,(n+1)\tau)=f_B(x,n\tau)\exp\bigg(-s_B\int_0^\tau c_M(x,s+n\tau)\mathrm{d}s\bigg),\quad n\in\mathbb{N},$$

and similarly for f_F. The integral is approximated by the trapezoid rule

$$\int_0^\tau c_M(x,s+n\tau)\mathrm{d}s\approx\frac{\tau}{2}(c_{M,ij}^n+c_{M,ij}^{n+1}),$$

where $c_{M,ij}^n$ approximates $c_M(x_{ij},n\tau)$. We set $f_{ij}^n:=(f_B,f_E,f_F)(x_{ij},n\tau)$.

Finally, we discretize the reaction–diffusion Eqs. (5) using the forward Euler method and the central finite-difference scheme

$$\operatorname{div}(D_V(f)\nabla c_V)\approx\frac{1}{h}\big(J_{i+1/2,j}-J_{i-1/2,j}+J_{i,j+1/2}-J_{i,j-1/2}\big),$$

where

$$\begin{aligned}J_{i+1/2,j}&=\frac{1}{2h}(D_V(f_{i+1,j}^n)+D_V(f_{ij}^n))(c_{i+1,j}^{n+1}-c_{ij}^{n+1}),\\ J_{i,j+1/2}&=\frac{1}{2h}(D_V(f_{i,j+1}^n)+D_V(f_{ij}^n))(c_{i,j+1}^{n+1}-c_{ij}^{n+1}).\end{aligned}$$

Notice that we obtain a semi-implicit scheme. The resulting linear system of equations is implemented in the Python-based software environment *SciPy* using sparse matrices and solved by using the `spsolve` function from the `scipy.sparse.linalg` package.

The potentials V_j^k, used in (5), are given by

$$V_j^k(x)=\frac{1}{IR_m^2}\exp\bigg(-\frac{R_m^2}{R_m^2-|x|^2}\bigg),\quad x\in\mathcal{D},\ j=D,M,U,V,$$

where $R_m=12.5$, and $I>0$ is a normalization constant to ensure that $\int_{\mathbb{R}^2}V_j^k(x)\mathrm{d}x=1$.

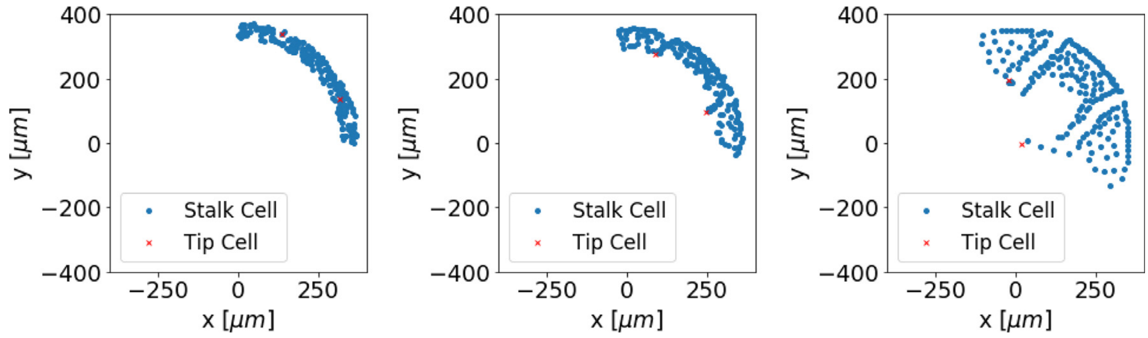

Fig. 2. Positions of two tip cells (red crosses) and 200 stalk cells (blue dots) at times $T = 0\,\mathrm{s}$, $T = 400\,\mathrm{s}$, and $T = 1600\,\mathrm{s}$.

It remains to define the initial conditions. The initial positions of the endothelial cells $X_i^{0,k}$ ($i = 1, 2$, $k = 1, \ldots, N_i$) are given by

$$X_i^{0,k} = \begin{pmatrix} r\sin\phi \\ r\cos\phi \end{pmatrix},$$

where (r, ϕ) is uniformly drawn from the set $[0.65R, 0.75R]\times[0, \pi/2] = [325, 375]\times[0, \pi/2]$. The initial volume fractions are

$$f_F^0(x) = \begin{cases} 0 & \text{for } |x| \geq R_f, \\ 0.4(1-\cos(\frac{\pi}{0.3R_f}(R_f - |x|))) & \text{for } 0.7R_f < |x| < R_f, \\ 0.8 & \text{for } |x| \leq 0.7R_f, \end{cases}$$

where $R_f = 0.95R = 475$, as well as $f_B^0 = 0.2f_F^0$ and $f_E^0 = 1 - f_B^0 - f_F^0$. We choose the initial VEGF concentration

$$c_V^0(x) = 0.1\exp\left(-\frac{R_c}{\sqrt{R_c^2 - |x|^2}}\right)1_{B_{R_c}}(x),$$

which is concentrated at the origin, and assume that the concentrations of the remaining proteins vanish, $c_D^0 = c_M^0 = c_U^0 = 0$ in $\mathcal{D}$, as they are segregated by the tip cells.

We choose $N_1 = 2$ tip cells and $N_2 = 200$ stalk cells. Fig. 2 shows the positions of the tip and stalk cells at different times 2 for one trajectory. The tip cells segregate the DLL4 protein, and the stalk cells detect the local increase of the DLL4 concentration, such that they follow the corresponding tip cell. This effect is slightly more pronounced for the tip cell that starts in an environment with a dense stalk cell population. The position of this tip cell is closer to the origin than the other tip cell with a higher VEGF concentration, leading to a relatively high production of DLL4 proteins. The stalk cells, which do not follow a tip cell, are primarily influenced by the stiffness gradient $\nabla(f_B + f_F)$ and the strain energy density M, which incorporates contact mechanics, resulting to a spreading of these cells.

The protein concentrations are shown in Fig. 3. As the diffusion coefficient for VEGF is much larger than the reaction rate s_V, the concentration of the VEGF protein becomes uniform in the large-time limit. The DLL4, MMP, and uPA proteins are produced by the tip cells and hence follow their paths. The corresponding concentrations increase with the availability of VEGF and decrease due to consumption by the stalk cells or by getting exhausted from breaking down the fibrin matrix or the boundary membrane. Since the diffusion is slow, the changes in the concentration are local up to time $T = 1600\,\mathrm{s}$.

We present the volume fractions of the basement membrane, fibrin matrix, and extracellular fluid in Fig. 4. The membrane and fibrin matrix are degraded by the MMP and uPA proteins, thus increasing the volume fraction of the extracellular fluid. As both proteins are produced by the tip cells, the degradation follows their paths.

Summarizing, we see that the model successfully describes the formation of premature sprouts. The experiments from [1] for dermal endothelial cells show that the in vitro angiogenesis sprouting qualitatively well agrees with the numerical tests. Clearly, the proposed system of equations models only a very small number of biological processes, chemical reactions, and signal proteins, and more realistic results can be only expected after taking into account more biological modeling details. Still, the onset of vessel formation is well illustrated by our simple model.

Data availability

No data was used for the research described in the article.

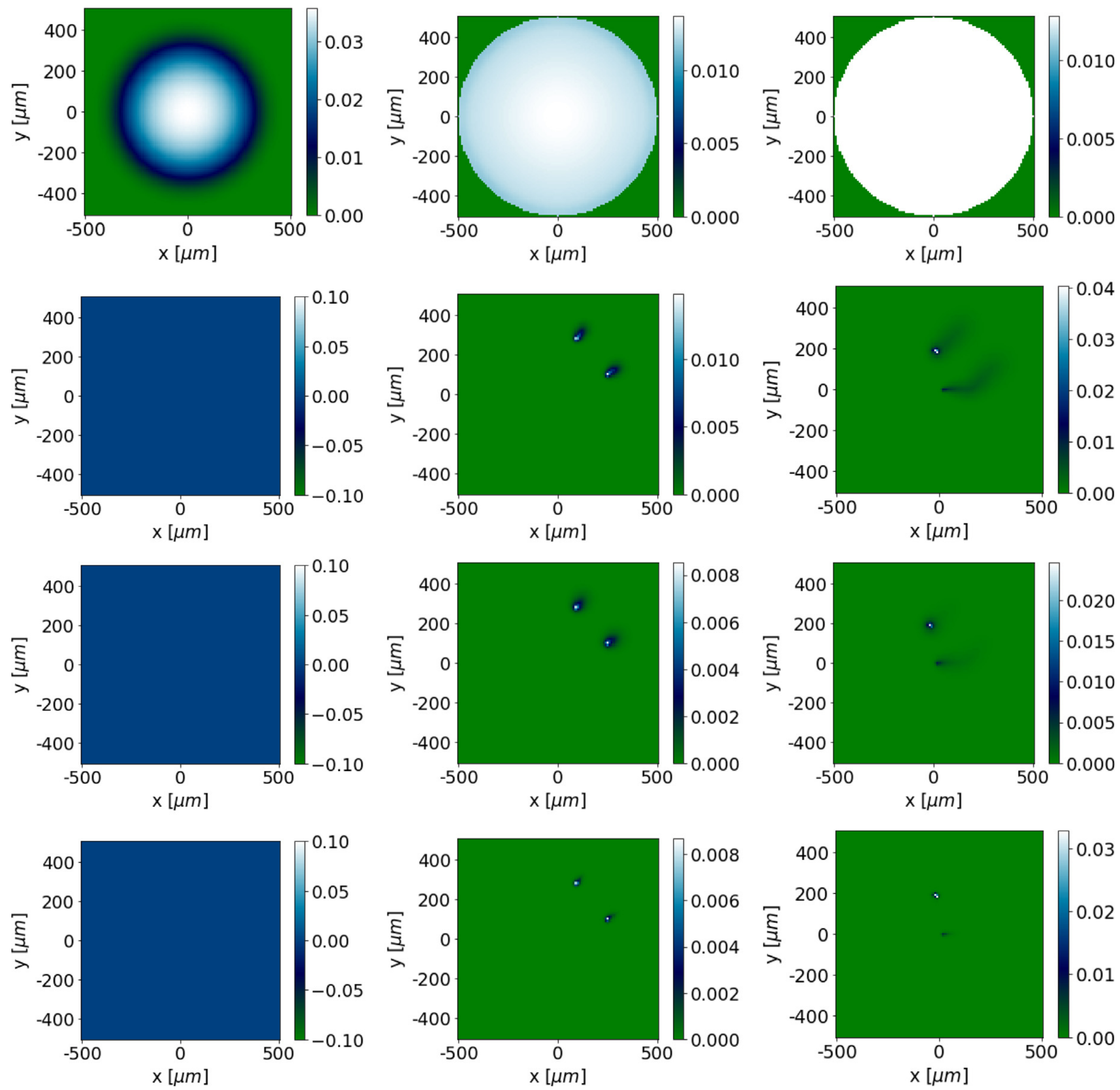

Fig. 3. Concentrations of the proteins VEGF (first row), DLL4 (second row), MMP (third row), and uPA (last row) at times $T = 0\,$s (left column), $T = 400\,$s (middle column), and $T = 1600\,$s (right column).

Appendix A. Regularity results for elliptic and parabolic equations

Let $\mathcal{D} \subset \mathbb{R}^m$ ($m \geq 1$) be a bounded domain.
The following regularity results hold for the parabolic problem

$$\begin{aligned} &\partial_t u - \operatorname{div}(a(x,t)\nabla u) = f \text{ in } \mathcal{D},\ t > 0, \\ &a(x,t)\nabla u \cdot \nu = 0 \text{ on } \partial\mathcal{D}, \quad u(0) = u^0 \text{ in } \mathcal{D}. \end{aligned} \tag{22}$$

Theorem 16 *([30], Section II.3, Theorem 3.3)***.** *Let $a \in L^\infty(Q_T)$ be such that $a(x,t) \geq a_0 > 0$ for all $(x,t) \in \overline{\mathcal{D}} \times [0,T]$, $f \in L^2(Q_T)$, and $u^0 \in H^1(\mathcal{D})$. Then there exists a unique weak solution to (22) such that $u \in C^0([0,T]; H^1(\mathcal{D}))$, $\partial_t u \in L^2(Q_T)$, and there exists a constant $C > 0$, not depending on a, u, u^0, or f, such that*

$$\|u\|_{L^\infty(0,T;H^1(\mathcal{D}))} + \|\partial_t u\|_{L^2(Q_T)} \leq C\big(\|f\|_{L^2(Q_T)} + \|u^0\|_{H^1(\mathcal{D})}\big).$$

Proof. The a priori estimate is a consequence of the proof of [30, Theorem 3.3]. $\square$

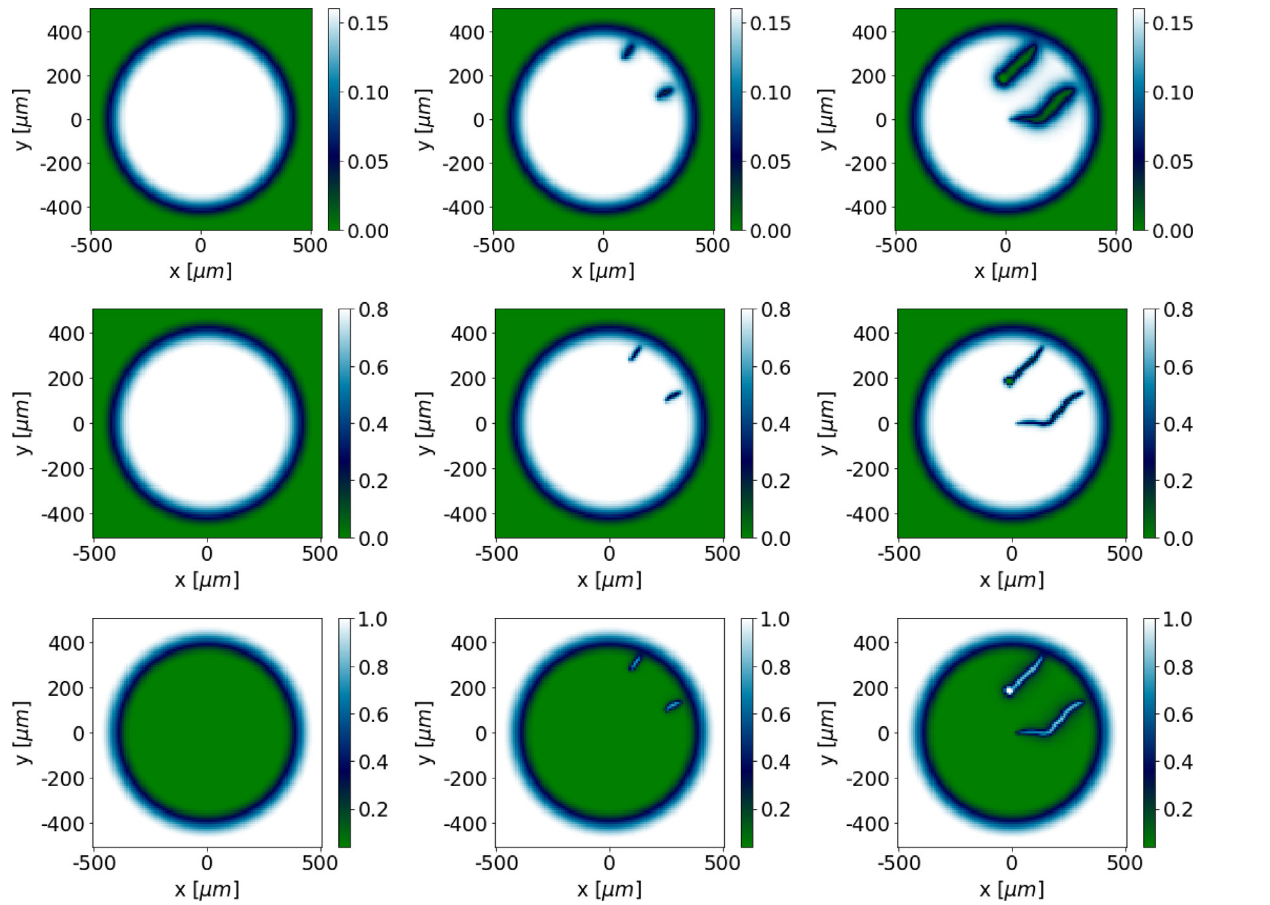

Fig. 4. Volume fractions of the basement membrane (first row), fibrin matrix (second row), and extracellular fluid (last row) at times $T = 0\,\mathrm{s}$ (left column), $T = 400\,\mathrm{s}$ (middle column), and $T = 1600\,\mathrm{s}$ (right column).

Let $\alpha, \beta \in (0, 1]$. The space $C^{\alpha,\beta}(\overline{\mathcal{D}} \times [0, T])$ consists of all functions $u : \overline{\mathcal{D}} \times [0, T] \to \mathbb{R}$ such that there exists $C > 0$ such that for all $(x, t), y, s) \in \overline{\mathcal{D}} \times [0, T]$,

$$|u(x, t) - u(y, s)| \le C(|x - y|^\alpha + |s - t|^\beta) \quad \text{for all } (x, t),\ (y, s) \in \overline{\mathcal{D}} \times [0, T].$$

The space $C^{k+\beta}(\overline{\mathcal{D}})$ is the space of all functions $u \in C^k(\overline{\mathcal{D}})$ such that $\mathrm{D}^k u$ is Hölder continuous with index $\beta > 0$.

Theorem 17 (*[25], Theorem 1.2*)**.** *Let $\beta \in (0, 1)$, $\partial\mathcal{D} \in C^{1+\beta}$, $a \in C^{\beta,\beta/2}(\overline{\mathcal{D}} \times [0, T])$ be such that $a(x, t) \ge a_0 > 0$ for all $(x, t) \in \overline{\mathcal{D}} \times [0, T]$, $f \in L^\infty(0, T; L^\infty(\mathcal{D}))$, and $u^0 \in C^{1+\beta}(\overline{\mathcal{D}})$ be such that $a(x, t)\nabla u_0 \cdot \nu = 0$ on $\partial\mathcal{D}$. Furthermore, let $u \in C^0([0, T]; L^2(\mathcal{D})) \cap L^2(0, T; H^1(\mathcal{D}))$ be a weak solution to (22). Then there exists a constant $C_\beta > 0$, only depending on the data, such that*

$$\|u\|_{C^{1+\beta,(1+\beta)/2}(\overline{\mathcal{D}}\times[0,T])} \le C_\beta.$$

Theorem 18 (*[20], Section IV.9, Theorem 9.1*)**.** *Let $\partial\mathcal{D} \in C^2$, $q > 3$, $T > 0$, $a \in C^0(\overline{\mathcal{D}} \times [0, T])$ be such that $a(x, t) \ge a_0 > 0$ for all $(x, t) \in \overline{\mathcal{D}} \times [0, T]$, $f \in L^q(0, T; L^q(\mathcal{D}))$, $u^0 \in W^{2,q}(\mathcal{D})$ be such that $a(x, t)\nabla u^0 \cdot \nu = 0$ on $\partial\mathcal{D}$. Then there exists a unique strong solution $u \in L^q(0, T; W^{2,q}(\mathcal{D}))$ to (22) satisfying $\partial_t u \in L^q(0, T; L^q(\mathcal{D}))$, and there exists a constant $C > 0$, not depending on u, f, or u_0, such that*

$$\|u\|_{L^q(0,T;W^{2,q}(\mathcal{D}))} + \|\partial_t u\|_{L^q(0,T;L^q(\mathcal{D}))} \le C\big(\|f\|_{L^q(0,T;L^q(\mathcal{D}))} + \|u_0\|_{W^{2,q}(\mathcal{D})}\big).$$

Theorem 19 (*[20], Section V.5, Theorem 5.4*)**.** *Let $\beta \in (0, 1)$, $\partial\mathcal{D} \in C^{2+\beta}$, $T > 0$, $a_{ij}, b_i, c \in C^{\beta,\beta/2}(\overline{\mathcal{D}} \times [0, T])$ be such that $a_{ij}(x, t) \ge a_0 > 0$ for all $(x, t) \in \overline{\mathcal{D}} \times [0, T]$ for $i, j = 1, \ldots, m$, $f \in C^{\beta,\beta/2}(\overline{\mathcal{D}} \times [0, T])$, and $u^0 \in C^{2+\beta}(\overline{\mathcal{D}})$ be such that*

$\nabla u_0 \cdot \nu = 0$ on $\partial\mathcal{D}$. Then there exists a unique classical solution $u \in C^{2+\beta,1+\beta}(\overline{\mathcal{D}} \times [0,T])$ to

$$\partial_t u - \sum_{i,j=1}^m a_{ij}(x,t)\frac{\partial^2 u}{\partial x_i \partial x_j} + b(x,t)\cdot\nabla u + c(x,t)u = f \quad \text{in } \mathcal{D},\ t > 0,$$
$$\nabla u \cdot \nu = 0 \quad \text{on } \partial\mathcal{D},\ t > 0, \quad u(0) = u^0 \quad \text{in } \mathcal{D},$$

and there exists a constant $C > 0$, not depending on u, f, or u_0, such that

$$\|u\|_{C^{2+\beta,1+\beta}(\overline{\mathcal{D}}\times[0,T])} \le C\big(\|f\|_{C^{\beta;\beta/2}(\overline{\mathcal{D}}\times[0,T])} + \|u_0\|_{C^{2+\beta}(\overline{\mathcal{D}})}\big).$$

Appendix B. Auxiliary results

We collect some auxiliary results used in the paper.

Lemma 20. *Let $\Omega \subset \mathbb{R}^d$ be an open set and let $f \in C^\delta(\Omega)$ for every $0 < \delta < 1$. If the Hölder norm of f can be bounded uniformly, i.e., there exists a $C^* > 0$ such that $\|f\|_{C^\delta(\Omega)} \le C^*$ for all $0 < \delta < 1$, then f is a Lipschitz continuous function on Ω.*

Proof. Since we have not found a reference in the literature, we provide the short proof. Let $x, y \in \Omega$ with $x \neq y$. Then there exists $0 < \delta < 1$ such that $|x-y|^{1-\delta} \ge 1/2$. With this choice of δ, we compute

$$\frac{|f(x)-f(y)|}{|x-y|} = \frac{|f(x)-f(y)|}{|x-y|^\delta}\frac{1}{|x-y|^{1-\delta}} \le 2C^*.$$

As C^* does not depend on δ and $x, y \in \Omega$ are arbitrary, we infer that f is Lipschitz continuous with Lipschitz constant $L \le 2C^*$. □

Lemma 21. *Let $u_1, u_2 \in L^\infty(0,T;W^{k,\infty}(\mathcal{D}))$ with $k \in \mathbb{N}_0$, $g_1^0, g_2^0 \in W^{k,\infty}(\mathcal{D})$, and let $g_1, g_2 \in C^0([0,T];W^{k,\infty}(\mathcal{D}))$ be the unique solutions to*

$$\frac{\mathrm{d}g_i}{\mathrm{d}t} = -u_i g_i, \quad 0 < t < T, \quad g_i(0) = g_i^0 \quad \text{a.e. in } \mathcal{D},\ i = 1,2.$$

Then there exists $C > 0$, only depending on T, the $L^\infty(0,T;W^{k,\infty}(\mathcal{D}))$ norm of u_i, and the $W^{k,\infty}(\mathcal{D})$ norm of g_i^0, such that for $p > 1$,

$$\max_{[0,T]}\|g_1 - g_2\|_{W^{k,p}(\mathcal{D})} \le C\big(\|g_1^0 - g_2^0\|_{W^{k,p}(\mathcal{D})} + \|u_1 - u_2\|_{L^1(0,T;W^{k,p}(\mathcal{D}))}\big).$$

Proof. The regularity of g_i follows from the explicit formula and the regularity for g_i^0 and u_i. Furthermore, taking the $W^{k,p}(\mathcal{D})$ norm of

$$g_1(t) - g_2(t) = g_1^0 - g_2^0 - \int_0^t \big(u_1(g_1 - g_2) + (u_1 - u_2)g_2\big)\mathrm{d}x,$$

the result follows from the regularity $u_1 \in L^\infty(0,T;W^{k,\infty}(\mathcal{D}))$ and $g_2 \in W^{k,\infty}(\mathcal{D})$. □

Appendix C. Model parameters and constants

The model parameters and constants are taken from [1]. For the convenience of the reader, we collect here the expressions:

$$\alpha_0 = \frac{b_i R_c^3}{F_i \mu},$$
$$\gamma(x,t) = \frac{0.1 b_i F_i (1 - f_E(x,t))}{\rho_B f_B(x,t) + \rho_F f_F(x,t) + \rho_E f_E(x,t)},$$
$$\lambda(x,t) = \frac{4^3 b_i F_i \widetilde{\lambda}}{30}(1 - f_E(x,t))\left(\frac{1}{2} - f_E(x,t)\right) f_E(x,t),$$
$$M_i^k(x,t) = \sum_{j=1}^2 \sum_{\ell=1}^{N_j} \frac{F_i^2}{20\pi^2 R_c^4}(1 - f_E(x,t))\exp\left(\frac{-|X_i^k - X_j^\ell|}{R_c}\right) - \frac{2\sqrt{2}}{\pi}\left(\frac{\max\{0, R_c - 0.5|X_i^k - X_j^\ell|\}}{R_c}\right)^{5/2},$$

$$v_i^k = \sum_{j=1}^{2}\sum_{\ell=1}^{N_j} \frac{F_i^2}{20\pi^2 R_c^4}(1 - f_E(x,t))\exp\left(\frac{-|X_i^k - X_j^\ell|}{R_c}\right),$$
$$z_i^k = \frac{v_i^k}{|v_i^k|}.$$

The parameters are chosen as in the following table; see [1, Appendix].

	Value	Unit		Value	Unit		Value	Unit
b_i	0.02	s^{-1}	D_V^E	10	$\mu m^2 s^{-1}$	r_D	10	$\mu m^3 s^{-1}$
F_i	1000	nN	D_D^B	0.51	$\mu m^2 s^{-1}$	r_M	10	$\mu m^3 s^{-1}$
μ	0.2	–	D_D^F	1.02	$\mu m^2 s^{-1}$	r_U	10	$\mu m^3 s^{-1}$
$\widetilde{\lambda}$	15	–	D_D^E	0.051	$\mu m^2 s^{-1}$	s_V	0.024	$\mu m^3 s^{-1}$
R_c	11.25	μm	D_M^B	1.23	$\mu m^2 s^{-1}$	s_D	0.024	$\mu m^3 s^{-1}$
ρ_B	$1.06 \cdot 10^{-3}$	$ng\mu m^{-3}$	D_M^F	2.46	$\mu m^2 s^{-1}$	s_M	0.024	s^{-1}
ρ_F	$1.06 \cdot 10^{-3}$	$ng\mu m^{-3}$	D_M^E	0.123	$\mu m^2 s^{-1}$	s_U	0.024	s^{-1}
ρ_E	$0.9933 \cdot 10^{-3}$	$ng\mu m^{-3}$	D_U^B	0.53	$\mu m^2 s^{-1}$	s_B	1.21	$\mu m^3 ng^{-1} s^{-1}$
D_V^B	100	$\mu m^2 s^{-1}$	D_U^F	1.06	$\mu m^2 s^{-1}$	s_F	1.21	$\mu m^3 ng^{-1} s^{-1}$
D_V^F	200	$\mu m^2 s^{-1}$	D_U^E	0.053	$\mu m^2 s^{-1}$			

References

[1] F. Bookholt, H. Monsuur, S. Gibbs, F. Vermolen, Mathematical modelling of angiogenesis using continuous cell-based models, Biomech. Model. Mechanobiol. 15 (2016) 1577–1600.
[2] R. Blanco, H. Gerhardt, VEGF and notch in tip and stalk cell selection, Cold Spring Harb. Perspect. Med. 3 (2013) a006569.
[3] A. Ucuzian, A. Gassman, A. East, H. Greisler, Molecular mediators of angiogenesis, J. Burn Care Res. 31 (158) (2010).
[4] F. Graner, J. Glazier, Simulation of biological cell sorting using a two-dimensional extended potts model, Phys. Rev. Lett. 69 (1992) 2013–2016.
[5] H. Byrne, D. Drasdo, Individual-based and continuum models of growthing cell populations: a comparison, J. Math. Biol. 58 (2009) 657–687.
[6] N. Britton, M. Chaplain, A qualitative analysis of some models of tissue growth, Math. Biosci. 113 (1993) 77–89.
[7] E. Gaffney, K. Pugh, P. Maini, Investigating a simple model for cutaneous wound healing angiogenesis, J. Math. Biol. 45 (2002) 337–374.
[8] L. Corrias, B. Perthame, H. Zaag, Global solutions of some chemotaxis and angiogenesis systems in high space dimensions, Milan J. Math. 72 (2004) 1–28.
[9] A. Carlier, L. Geris, K. Bentley, G. Carmeliet, P. Carmeliet, H. van Oosterwyck, MOSAIC: a multiscale model of osteogenesis and sprouting angiogenesis with lateral inhibition of endothelial cells, PLoS Comput. Biol. 8 (2012) e1002724.
[10] C. Stokes, D. Lauffenburger, Analysis of the roles of microvessel endothelial cell random motility and chemotaxis in angiogenesis, J. Theoret. Biol. 152 (1991) 377–403.
[11] V. Capasso, F. Flandoli, On the mean field approximation of a stochastic model of tumour-induced angiogenesis, Eur. J. Appl. Math. 30 (2019) 619–658.
[12] F. Spill, P. Guerrero, T. Alarcon, P. Maini, H. Byrne, Mesoscopic and continuum modelling of angiogenesis, J. Math. Biol. 70 (2015) 485–532.
[13] M. Chaplain, S. McDougall, A. Anderson, Mathematical modeling of tumor-induced angiogenesis, Ann. Rev. Biomed. Eng. 8 (2006) 233–257.
[14] S. Pierce, Computational and mathematical modeling of angiogenesis, Microcirculation 15 (2008) 739–751.
[15] V. Capasso, D. Morale, Stochastic modelling of tumour-induced angiogenesis, J. Math. Biol. 58 (2009) 219–233.
[16] P. Kloeden, S. Sonner, C. Surulescu, A nonlocal sample dependence SDE-PDE system modeling proton dynamics in a tumor, Discrete Contin. Dyn. Syst. Ser. B 21 (2016) 2233–2254.
[17] S. Hiremath, C. Surulescu, A. Zhigun, S. Sonner, On a coupled SDE-PDE system modeling acid-mediated tumor invasion, Discrete Contin. Dyn. Syst. Ser. B 23 (2018) 2339–2369.
[18] B. Jourdain, C. Le Bris, T. Lelièvre, Coupling PDEs and SDEs: the illustrative example of the multiscale simulation of viscoelastic flows, in: B. Engquist, O. Runborg, P. Lötstedt (Eds.), Multiscale Methods in Science and Engineering, in: Lect. Notes Comput. Sci. Eng., vol. 44, Springer, Berlin, 2005, pp. 149–168.
[19] A. Latif, Banach contraction principle and its generalizations, in: S. Almezel, Q.H. Ansari, M.A. Khamsi (Eds.), Topics in Fixed Point Theory, Springer, Cham, 2014, pp. 33–64.
[20] O.A. Ladyženskaja, V.A. Solonnikov, N.N. Ural'ceva, Linear and Quasi-Linear Equations of Parabolic Type, Amer. Math. Soc., Providence, 1968.
[21] W. Liu, M. Röckner, Stochastic Partial Differential Equations: An Introduction, Springer, Cham, 2015.
[22] R. Nittka, Regularity of solutions of linear second order elliptic and parabolic boundary value problems on Lipschitz domains, J. Differential Equations 251 (2011) 860–880.
[23] D. Gilbarg, N. Trudinger, Elliptic Partial Differential Equations of Second Order, Springer, Berlin, 1998.
[24] L. Evans, Partial Differential Equations, second ed., Amer. Math. Soc., Providence, 2010.
[25] G. Lieberman, Hölder continuity of the gradient of solutions of uniformly parabolic equations with conormal boundary conditions, Ann. Mat. Pura Appl. 148 (1987) 77–99.
[26] J. Karatzas, S. Shreve, Brownian Motion and Stochastic Calculus, second ed., Springer, New York, 1991.
[27] R.M. Dudley, Real Analysis and Probability, second ed., Cambridge University Press, Cambridge, 2002.
[28] O. Kallenberg, Foundations of Modern Probability, thied ed., Springer, Cham, 2021.
[29] F. Vermolen, A. Gefen, A semi-stochastic cell-based formalism to model the dynamics of migration of cells in colonies, Biomech. Model. Mechanobiol. 11 (2012) 183–195.
[30] R. Temam, Infinite-Dimensional Dynamical Systems in Mechanics and Physics, second ed., Springer, New York, 1997.