# A REACTION-DIFFUSION SYSTEM MODELLING ASYMMETRIC STEM-CELL DIVISION: EXISTENCE, UNIQUENESS, NUMERICAL SIMULATION AND RIGOROUS QUASI-STEADY-STATE APPROXIMATION

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Abstract. During asymmetric stem cell division so-called cell-fate determinants are localised and become inherited into only one of the two daughter cells. In Drosophila SOP precursor cells, this biological mechanism is centred around the phosphorylation of a key protein call Lgl (Lethal giant larvae).

In this paper, we present a surface-volume reaction diffusion system, which models the localisation of Lgl within the cell cytoplasm and on the cell cortex. We prove well-posedness of global solutions as well as regularity of the solutions. Moreover, we rigorously perform a fast reaction limit to a reduced quasi-steady-state approximation system, when phosphorylated Lgl is instantaneously expelled from the cortex.

## 1. Introduction

In stem cells undergoing asymmetric cell division, particular proteins (so-called cell-fate determinants) are localised at the cortex of only one of the two daughter cells during mitosis. These cell-fate determinants trigger in the following the differentiation of one daughter cell into specific tissue while the other daughter cell remains a stem cell.

In Drosophila, SOP stem cells provide a well-studied biological example model of asymmetric stem cell division, see e.g. [25, 23, 24] and the references therein. The mechanism of asymmetric cell division in SOP stem cells operates around a key protein called Lgl (Lethal giant larvae), which exists in two conformational states: a non-phosphorylated form which regulates the localisation of the cell-fate-determinants in the membrane of one daughter cell, and a phosphorylated form which is inactive.

In this paper, we shall present and study a mathematical model system describing the evolution of Lgl in its non-phosphorylated and phosphorylated conformations both in the cytoplasm (i.e. in the cell volume) and at the cortex (i.e. the surface/membrane of the cell). More precisely, we shall denote by $L(t,x)$ and $P(t,x)$ the cytoplasmic concentrations of non-phosphorylated and phosphorylated Lgl within the bounded cell domain $\Omega \subset \mathbb{R}^n$, while $l(t,x)$ and $p(t,x)$ denote the cortical concentrations of the non-phosphorylated and phosphorylated Lgl at the boundary $\Gamma := \partial\Omega$, which is assumed sufficiently smooth (e.g. $C^{2+\alpha}$ with $\alpha > 0$).

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The reaction kinetics between the species $L$, $P$, $l$ and $p$ are depicted in Figure 1 and summarise the following processes: i) a reversible reaction between $L$ and $P$ with rates $\alpha$ and $\beta$ on the domain $\Omega$, ii) a reversible exchange between $L$ and $l$ at the boundary $\Gamma$ with rates $\lambda$ and $\gamma$, iii) an irreversible phosphorylation of $l$-Lgl into $p$-Lgl at the boundary $\Gamma$ with rate $\sigma$ and iv) an irreversible release of $p$-Lgl from the boundary $\Gamma$ into the domain $\Omega$ with rate $\xi$. We emphasise that these processes jointly conserve the total mass of Lgl (see the conservation law (1.4) below).

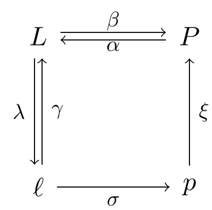



FIGURE 1. The reaction dynamics of $L, P, l$ and $p$

We propose in the following a continuum model of partial differential equations, which describe the reactions and the diffusion processes of these species both on the domain $\Omega$ and on its surface $\Gamma$. The choice of a continuum model is based on the biological observation that protein concentrations in SOP cells are rather large and that stochastic effects in the concentrations can thus be neglected, see [25].

Moreover in SOP cells, the phosphorylation of Lgl occurs at the boundary $\Gamma$ by means of an atypical protein kinase aPKC, which is pre-located at a sub-part $\Gamma_2 \subset \Gamma$. We shall thus assume that $\Gamma$ is the union of two disjoint subsets $\Gamma = \Gamma_1 \cup \Gamma_2$, in which $\Gamma_2$ is connected has a smooth boundary $\partial\Gamma_2$. In case that $\Gamma_1 = \emptyset$, then $\Gamma_2 \equiv \Gamma$ is a surface in $\mathbb{R}^n$ without boundary.

Altogether we consider the following equations for the volume concentrations $L$ and $P$:

$$\begin{cases} L_t - d_L \Delta L = \alpha P - \beta L, & x \in \Omega, \quad t > 0, \\ P_t - d_P \Delta P = -\alpha P + \beta L, & x \in \Omega, \quad t > 0, \\ L(0,x) = L_0(x), \quad P(0,x) = P_0(x), & x \in \Omega, \end{cases} \tag{1.1}$$

where $\Delta$ denotes the Laplacian on the domain $\Omega$, $d_L$, $d_P$ are positive volume-diffusion coefficients, $\alpha$, $\beta$ are positive and constant reaction rates, and $L_0(x)$ and $P_0(x)$ are given initial concentrations.

The volume concentrations $L$ and $P$ are connected to the surface concentrations $l$ and $p$ in terms of Robin- and Neumann boundary conditions

$$\begin{cases} d_L \frac{\partial L}{\partial \nu} = -\lambda L + \gamma l, & x \in \Gamma, \quad t > 0, \\ d_P \frac{\partial P}{\partial \nu} = \chi_{\Gamma_2} \xi p, & x \in \Gamma, \quad t > 0, \end{cases} \tag{1.2}$$

where $\nu(x)$ denotes the unit normal outward vector at $x \in \Gamma$, $\gamma$, $\lambda$, and $\xi$ are positive and constant reaction rates and $\chi_{\Gamma_2}$ denotes the characteristic function localising the aPKC-active part of the boundary $\Gamma_2$, i.e. $\chi_{\Gamma_2}(x) = 1$ if $x \in \Gamma_2$ and $\chi_{\Gamma_2}(x) = 0$ otherwise.

Thirdly, the surface concentrations $l$ and $p$ satisfy

$$\begin{cases} l_t - d_l \Delta_\Gamma l = \lambda L - (\gamma + \sigma \chi_{\Gamma_2}) l, & x \in \Gamma, \quad t > 0, \\ p_t - d_p \Delta_{\Gamma_2} p = \sigma l - \xi p, & x \in \Gamma_2, \quad t > 0, \\ d_p \frac{\partial p}{\partial \nu_{\Gamma_2}} = 0, & x \in \partial \Gamma_2, \\ l(0,x) = l_0(x), & x \in \Gamma, \\ p(0,x) = p_0(x), & x \in \Gamma_2, \end{cases} \tag{1.3}$$

where $\Delta_\Gamma$ and $\Delta_{\Gamma_2}$ are Laplace-Beltrami operators (see e.g. [20]) acting on the surfaces $\Gamma$ and $\Gamma_2$, respectively, $d_l$, $d_p$ are non-negative surface-diffusion coefficients and $\sigma > 0$ is the positive and constant phosphorylation rate.

The considered evolution process conserves the total mass of Lgl, which is expressed in the following conservation law:

$$\int_\Omega (L(t,x) + P(t,x))\, dx + \int_\Gamma l(t,x)\, dS + \int_{\Gamma_2} p(t,x)\, dS = M_0 > 0, \qquad \forall t > 0 \tag{1.4}$$

where $M_0$ is the initial mass, which is assumed to be positive,

$$M_0 := \int_\Omega (L_0(x) + P_0(x))\, dx + \int_\Gamma l_0(x)\, dS + \int_{\Gamma_2} p_0(x)\, dS > 0.$$

The aims of this paper are the following: In Section 2, we first study the well-posedness of system (1.1)–(1.3) and the regularity of solutions. The well-posedness will be shown by splitting the system and applying two nested fixed point arguments, which also entail the non-negativity of the solutions subject to non-negative initial data.

We remark, that although the system is linear, the existence and uniqueness of a solution is not trivial due to i) the system character, ii) the mixed boundary conditions and iii) the presence of surface diffusion. Previous related results can be found, for instance, in [26], where the authors used the fixed point method to prove the well-posedness for a linear elliptic volume-surface reaction-diffusion system arising in the analysis of finite element methods. In [27], the authors obtained well-posedness for a simpler parabolic system in a disk using radial symmetric solutions. The well-posedness for a volume-surface reaction-diffusion system of two equations with arbitrary nonlinear boundary reaction terms was proven in [1] by constructing solutions via converging sequences of upper and lower solutions.

Next, in Section 3, we present a suitable finite element method (FEM) discretisation of the model system (1.1)–(1.3) and discuss some numerical test cases, which illustrate the system behavior. In this part, we also discuss the relation between diffusion and reaction terms both in cytoplasm and cell cortex.

The final major part of this paper is done in Section 4. We consider the quasi-steady-state approximation (QSSA) of the system (1.1)–(1.3), which occurs when considering the limit $\xi \to +\infty$ for the expulsion rate of cortical phosphorylated Lgl. The QSSA thus leads to a reduced system, where the expulsion of Lgl from the cortex is modeled instantaneously and the cortical concentration $p$ of phosphorylated Lgl no longer needs to be considered. QSSAs of reactive systems occur commonly in chemical engineering and although applying a QSSA has been routinely done by chemical engineers since a long time, the mathematical theory is usually missing. Recent however, a lot of mathematical attention has been paid to rigorously prove QSSA approximations (see e.g. [3, 4, 5, 6, 8, 9] and references therein).

In this paper, the biological model suggests that the expulsion rate $\xi$ from cortical $p$-Lgl to cytoplasmic $P$-Lgl is much faster than the others reaction rates. We shall thus prove rigorously the QSSA for the system (1.1)–(1.3) towards a reduced QSSA system (see Section 4). The proof is based on a duality argument, which was already successfully applied to a nonlinear system in [5], yet without surface-volume coupling. We thus require appropriate *a priori* estimates in order to deal with the volume-surface reactions. We remark that we are currently only able to prove the QSSA if no surface diffusion terms are present. The QSSA for the system (1.1)–(1.3) with surface diffusion terms poses technique difficulties, which remain an open problem so far.

## 2. Well-posedness of the system (1.1)–(1.3)

In this section, we will first prove existence and uniqueness of weak solutions to the system (1.1)–(1.3) via an alternative fixed point argument (or a localised method).

Roughly speaking, the idea is as follows: In the system (1.1)–(1.3), we first fix $l \equiv l_1$ and $p \equiv p_1$ and (1.1)–(1.2) becomes a linear reaction diffusion system on the domain $\Omega$ with mixed Robin and Neumann boundary conditions. By solving this system, we get a unique solution $(L_1, P_1)$, which is non-negative for non-negative initial data. Next, by inserting the solution $(L_1, P_1)$ into (1.3), we obtain a new pair of boundary concentrations $(l_2, p_2)$, which we reinsert into (1.1)–(1.2) to get an updated solution $(L_2, P_2)$. By iterating this process, we construct a sequence of pairs of functions $\{(l_1, p_1), (l_2, p_2), \ldots\}$. By *a priori* estimates derived in Theorem 2.4, we prove that the sequence converges $(l_n, p_n) \to (l^*, p^*)$. Finally, inserting $(l^*, p^*)$ into (1.1)–(1.2) yields $(L^*, P^*)$ and it is then easy to verify that $(L^*, P^*, l^*, p^*)$ is a solution to the system (1.1)–(1.3), which is in fact unique.

We will then show that the weak solution is actually a strong solution for any positive time. This is done thanks to the linearity of the system and the smoothing effects of parabolic equations.

**Notations:** Throughout the paper, we will denote by $(\cdot, \cdot)_\Omega$ and $\|\cdot\|_\Omega$ the inner product and its induced norm in $L^2(\Omega)$. Analogously, we will denote the inner products and norms in $L^2(\Gamma), L^2(\Gamma_1)$ and $L^2(\Gamma_2)$ (e.g. the norm in $L^2(\Gamma)$ is denoted by $\|\cdot\|_\Gamma$). The tangent gradients on $\Gamma$ and $\Gamma_2$ corresponding to the metric induced from $\mathbb{R}^n$ are denoted by $\nabla_\Gamma$ and $\nabla_{\Gamma_2}$, respectively.

Moreover, for a function $u \in C([0,T]; L^p(\Omega))$, we shall use the notation $u \geq 0$ to denote that $u(t,x) \geq 0$ for all $t \in [0,T]$ and for a.e. $x \in \Omega$.

**Definition 2.1** (Weak Solutions).
*A weak solution $(L, P, l, p)$ of system (1.1)–(1.3) on $(0,T)$ satisfies*

$$
\begin{aligned}
L, P &\in C([0,T]; L^2(\Omega)) \cap L^2(0,T; H^1(\Omega)),\\
l &\in C([0,T]; L^2(\Gamma)) \cap L^2(0,T; H^1(\Gamma)),\\
p &\in C([0,T]; L^2(\Gamma_2)) \cap L^2(0,T; H^1(\Gamma_2)).
\end{aligned}
$$

*Moreover, for all test functions* $\varphi \in C^1([0,T];H^1(\Omega))$, $\psi \in C^1([0,T];H^1(\Gamma))$ *and* $\psi_2 \in C^1([0,T];H^1(\Gamma_2))$ *with* $\varphi(T) = \psi(T) = \psi_2(T) = 0$, *we have*

$$-\int_0^T (L, \partial_t\varphi)_\Omega \, dt + d_L \int_0^T (\nabla L, \nabla\varphi)_\Omega \, dt - \int_0^T (\gamma l - \lambda L, \varphi)_\Gamma \, dt$$
$$= (L_0, \varphi(0))_\Omega + \int_0^T (\alpha P - \beta L, \varphi)_\Omega \, dt, \quad (2.1)$$

$$-\int_0^T (P, \partial_t\varphi)_\Omega \, dt + d_P \int_0^T (\nabla P, \nabla\varphi)_\Omega \, dt - \int_0^T (\xi p, \varphi)_{\Gamma_2} \, dt$$
$$= (P_0, \varphi(0))_\Omega + \int_0^T (-\alpha P + \beta L, \varphi)_\Omega \, dt, \quad (2.2)$$

$$-\int_0^T (l, \partial_t\psi)_\Gamma \, dt + d_l \int_0^T (\nabla_\Gamma l, \nabla_\Gamma\psi)_\Gamma \, dt$$
$$= (l_0, \psi(0))_\Gamma + \int_0^T (\lambda L - (\gamma + \sigma\chi_{\Gamma_2}) l, \psi)_\Gamma \, dt, \quad (2.3)$$

$$-\int_0^T (p, \partial_t\psi_2)_{\Gamma_2} \, dt + d_p \int_0^T (\nabla_{\Gamma_2} p, \nabla_{\Gamma_2}\psi_2)_{\Gamma_2} \, dt$$
$$= (p_0, \psi_2(0))_{\Gamma_2} + \int_0^T (\sigma l - \xi p, \psi_2)_{\Gamma_2} \, dt. \quad (2.4)$$

Next, we recall a result on the existence of solutions to parabolic equations with inhomogeneous Robin boundary condition:

**Theorem 2.1** (Inhomogeneous Parabolic Robin Problem, [10, 11, 19])**.**
*Let* $c \in \mathbb{R}$, $d > 0$ *and* $\beta \geq 0$. *Consider the following equation*

$$\begin{cases} u_t(t,x) - d\Delta u(t,x) + cu(t,x) = f(t,x), & x \in \Omega, \quad t > 0 \\ d\frac{\partial u(t,x)}{\partial \nu} + \beta u(t,x) = g(t,x), & x \in \Gamma, \quad t > 0 \\ u(0,x) = u_0(x), & x \in \Omega, \end{cases} \quad (2.5)$$

*subject to initial data* $u_0 \in L^2(\Omega)$ *and inhomogeneities* $f \in L^2(0,T;L^2(\Omega))$ *and* $g \in L^2(0,T;L^2(\Gamma))$.

*Then, for* $T > 0$ *is arbitrary, the problem* (2.5) *has a unique weak solution* $u \in C([0,T];L^2(\Omega)) \cap L^2(0,T;H^1(\Omega))$. *Moreover, if* $u_0 \geq 0$ *and* $f(t) \geq 0$, $g(t) \geq 0$ *for all* $t \in [0,T]$, *then* $u(t) \geq 0$ *for all* $t \in [0,T]$.

The following non-negativity Lemma is stated for the convenience of the reader:

**Lemma 2.2** (Non-negativity of Fixed Point)**.**
*Let* $A : C([0,T];L^p(\Omega)) \to C([0,T];L^p(\Omega))$ *with* $p \geq 1$ *be a contraction mapping satisfying* $Au \geq 0$ *whenever* $u \geq 0$.

*Then, the unique fixed point* $u^*$ *of* $A$ *is nonnegative.*

*Proof.* Choose a function $u_1 \in C([0,T];L^p(\Omega))$ such that $u_1 \geq 0$. Define the sequence $\{u_n\}_{n\geq1}$ as $u_{n+1} := Au_n$ for all $n \geq 1$. By the assumption on $A$, we have that $u_n \geq 0$ for all $n \geq 1$. Since $A$ is a contraction mapping, by standard arguments, we have $u_n \to u^*$ in $C([0,T];L^p(\Omega))$ and thus,

$$u_n(t,x) \to u^*(t,x) \text{ for all } t \in [0,T] \text{ and for a.e. } x \in \Omega.$$

Therefore, $u^* \geq 0$. □

The following intermediate result proves the existence of a unique weak solution to the system (1.1)–(1.2) for given $(l,p)$:

**Proposition 2.3** (Existence of the volume sub-system for given surface terms)**.** *Let $g_L \in L^2(0,T;L^2(\Gamma))$ and $g_P \in L^2(0,T;L^2(\Gamma_2))$ be given.*

*Then, for any $(L_0,P_0) \in L^2(\Omega) \times L^2(\Omega)$, the following system*

$$\begin{cases} L_t - d_L\Delta L = \alpha P - \beta L, & x \in \Omega, \quad t > 0, \\ P_t - d_P\Delta P = -\alpha P + \beta L, & x \in \Omega, \quad t > 0, \\ d_L\frac{\partial L}{\partial \nu} + \lambda L = g_L, & x \in \Gamma, \quad t > 0, \\ d_P\frac{\partial P}{\partial \nu} = \chi_{\Gamma_2} g_P, & x \in \Gamma, \quad t > 0, \\ L(0,x) = L_0(x), \ P(0,x) = P_0(x), & x \in \Omega. \end{cases} \tag{2.6}$$

*has a unique weak solution $(L^*,P^*) \in (C([0,T];L^2(\Omega)) \cap L^2(0,T;H^1(\Omega)))^2$ for all $T > 0$. Moreover, if $g_L, g_P, L_0, P_0 \geq 0$, then $L(t) \geq 0$ and $P(t) \geq 0$ for all $t \in [0,T]$.*

*Proof.* Let $X = C([0,T];L^2(\Omega))$ be equipped with the supremum norm $\|u\|_X = \sup\{\|u(t)\|_\Omega : t \in [0,T]\}$. We introduce $S \subset X$ as

$$S = \{u \in X : u(0) = P_0 \in L^2(\Omega)\},$$

and observe that $S$ a closed subset of $X$. For any given $P_1 \in S$, we first consider the problem

$$\begin{cases} L_t - d_L\Delta L = \alpha P_1 - \beta L, & x \in \Omega, \quad t > 0, \\ d_L\frac{\partial L}{\partial \nu} + \lambda L = g_L, & x \in \Gamma, \quad t > 0, \\ L(0,x) = L_0(x), & x \in \Omega. \end{cases} \tag{2.7}$$

Thanks to Theorem 2.1, there exists a unique weak solution $L_1 \in X$ to (2.7). By applying Theorem 2.1 again, the following equation

$$\begin{cases} P_t - d_P\Delta P = -\alpha P + \beta L_1, & x \in \Omega, \quad t > 0, \\ d_P\frac{\partial P}{\partial \nu} = \chi_{\Gamma_2} g_P, & x \in \Gamma, \quad t > 0, \\ P(0,x) = P_0(x), & x \in \Omega \end{cases} \tag{2.8}$$

has a unique weak solution $P_2 \in S \subset X$, since obviously $P_2(0) = P_0$.

Next, we define the mapping $A : S \to S$ by $AP_1 := P_2$. We will show that $A$ is a contraction mapping for sufficiently small $T > 0$. We consider two different images $P_2 = AP_1$ and $\tilde{P}_2 = A\tilde{P}_1$ and denote by $L_1$ and $\tilde{L}_1$ the solutions of (2.7) with respect to $P_1$ and $\tilde{P}_1$, respectively. By denoting $W := P_2 - \tilde{P}_2$ and $V := L_1 - \tilde{L}_1$, we have

$$\begin{cases} V_t - d_L\Delta V = \alpha(P_1 - \tilde{P}_1) - \beta V, & x \in \Omega, \quad t > 0, \\ d_L\frac{\partial V}{\partial \nu} + \lambda V = 0, & x \in \Gamma, \quad t > 0, \\ V(0,x) = 0, & x \in \Omega, \end{cases} \tag{2.9}$$

and

$$\begin{cases} W_t - d_P \Delta W = -\alpha W + \beta V, & x \in \Omega, \quad t > 0, \\ d_P \frac{\partial W}{\partial \nu} = 0, & x \in \Gamma, \quad t > 0, \\ W(0,x) = 0, & x \in \Omega. \end{cases} \tag{2.10}$$

By multiplying (2.9) with $V$ and integrating over $\Omega$, we obtain

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}\|V\|_\Omega^2 + d_L\|\nabla V\|_\Omega^2 + \lambda\|V\|_\Gamma^2 &= \alpha \int_\Omega (P_1 - \tilde{P}_1)V\,dx - \beta\|V\|_\Omega^2 \\ &\le -\frac{\beta}{2}\|V\|_\Omega^2 + \frac{\alpha^2}{2\beta}\|P_1 - \tilde{P}_1\|_\Omega^2, \end{aligned} \tag{2.11}$$

and thus

$$\frac{d}{dt}\|V\|_\Omega^2 + 2d_L\|\nabla V\|_\Omega^2 + 2\lambda\|V\|_\Gamma^2 + \beta\|V\|_\Omega^2 \le \frac{\alpha^2}{\beta}\|P_1 - \tilde{P}_1\|_\Omega^2. \tag{2.12}$$

Then, by integration (2.12) over $(0,t)$ with $V(0) = 0$ yields for all $t \in [0,T]$,

$$\beta \int_0^t \|V(s)\|_\Omega^2\,ds \le \frac{\alpha^2}{\beta}\int_0^t \|P_1(s) - \tilde{P}_1(s)\|_\Omega^2\,ds \le \frac{\alpha^2}{\beta}T\|P_1 - \tilde{P}_1\|_X^2. \tag{2.13}$$

Similar, we multiply (2.10) with $W$ and integrate over $L^2(\Omega)$ to get

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}\|W\|_\Omega^2 + d_P\|\nabla W\|_\Omega^2 &= -\alpha\|W\|_\Omega^2 + \beta\int_\Omega WV\,dx \\ &\le -\frac{\alpha}{2}\|W\|_\Omega^2 + \frac{\beta^2}{2\alpha}\|V\|_\Omega^2. \end{aligned} \tag{2.14}$$

Therefore,

$$\frac{d}{dt}\|W\|_\Omega^2 + 2d_P\|\nabla W\|_\Omega^2 + \alpha\|W\|_\Omega^2 \le \frac{\beta^2}{\alpha}\|V\|_\Omega^2. \tag{2.15}$$

We integrate (2.15) over $(0,t)$ with $W(0) = 0$ and use then (2.13) to find for all $t \in (0,T)$ that

$$\|W(t)\|_\Omega^2 \le \frac{\beta^2}{\alpha}\int_0^t \|V(s)\|_\Omega^2 ds \le \alpha T\|P_1 - \tilde{P}_1\|_X^2. \tag{2.16}$$

Thus,

$$\|AP_1 - A\tilde{P}_1\|_X^2 = \sup_{t\in[0,T]} \|W(t)\|_\Omega^2 \le \alpha T\|P_1 - \tilde{P}_1\|_X^2. \tag{2.17}$$

Hence, by choosing $0 < T < 1/\alpha$, the mapping $A : S \to S$ is a contraction. By Banach's Fixed Point Theorem, there exists a unique fixed point $P^* \in S$ of $A$. We then denote by $L^*$ the unique solution of (2.7) for given $P_1 = P^*$. The pair $(L^*, P^*)$ is then a weak solution to the system (2.6). To prove the uniqueness, we assume that $(\bar{L}, \bar{P})$ shall be another solution of the system (2.6). Then, $\bar{P}$ must be a fixed point of $A$. Hence $\bar{P} = P^*$ and thus $\bar{L} = L^*$.

It remains to show the non-negativity of $L^*$ and $P^*$. We shall first show that $P^* \ge 0$. Thanks to Lemma 2.2, it is sufficient to show that if $P_1 \ge 0$ then $P_2 = AP_1 \ge 0$. Indeed, with $P_1 \ge 0$ and $g_L \ge 0$, we can apply Theorem 2.1 to equation (2.7) to have $L_1 \ge 0$ where $L_1$ is the solution of (2.7) with respect to $P_1$. Since now $L_1 \ge 0$, we conclude from (2.8) that $P_2 \ge 0$. The non-negativity of $L^*$ follows then immediately from (2.7) and Theorem 2.1. □

The following existence result follows the idea outlined in the beginning of this Section and proves the local existence of a unique weak solution to the system (1.1)–(1.3).

**Theorem 2.4** (Local Existence and Uniqueness of Weak Solutions)**.** *Consider* $(L_0, P_0, l_0, p_0) \in L^2(\Omega) \times L^2(\Omega) \times L^2(\Gamma) \times L^2(\Gamma_2)$ *and* $\alpha, \beta, \lambda, \gamma, \sigma, \xi > 0$.

*Then, there exists a* $T > 0$ *such that the system* (1.1)–(1.3) *has a unique weak solution* $(L, P, l, p)$ *on* $[0, T]$*. Moreover, if* $L_0, P_0, l_0$ *and* $p_0$ *is non-negative, then* $L(t), P(t), l(t), p(t)$ *are non-negative for all* $t \in [0, T]$*.*

*Proof.* Let $T > 0$ be chosen later. We denote by $X_1 = C([0,T]; L^2(\Gamma))$, $X_2 = C([0,T]; L^2(\Gamma_2))$ and $X = X_1 \times X_2$ and define

$$S = \{(u, v) \in X : u(0) = l_0 \text{ and } v(0) = p_0\}.$$

It is obvious that $S$ is a closed subset of $X$. For any $(l_1, p_1) \in S$, we consider the system (1.1)–(1.2) with $(l_1, p_1)$ in place of $(g_L, g_P)$, that is

$$\begin{cases} L_t - d_L \Delta L = \alpha P - \beta L, & x \in \Omega, \quad t > 0, \\ P_t - d_P \Delta P = -\alpha P + \beta L, & x \in \Omega, \quad t > 0, \\ d_L \frac{\partial L}{\partial \nu} = -\lambda L + \gamma l_1, & x \in \Gamma, \quad t > 0, \\ d_P \frac{\partial P}{\partial \nu} = \chi_{\Gamma_2} \xi p_1, & x \in \Gamma, \quad t > 0, \\ L(0,x) = L_0(x), \ P(0,x) = P_0(x), & x \in \Omega. \end{cases} \tag{2.18}$$

By Proposition 2.3, there exists a unique solution $(L_1, P_1)$ to (2.18) with $L_1, P_1 \in C([0,T]; L^2(\Omega)) \cap L^2(0,T; H^1(\Omega))$. We remark that $L|_\Gamma \in L^2(0,T; L^2(\Gamma))$ and $P|_{\Gamma_2} \in L^2(0,T; L^2(\Gamma_2))$ due to the Trace Theorem (see e.g. [18, Theorem 1, page 258]). Inserting $L_1|_\Gamma$ into the first two equations in (1.3), we have

$$\begin{cases} l_t - d_l \Delta_\Gamma l = \lambda L_1 - (\gamma + \chi_{\Gamma_2}\sigma) l, & x \in \Gamma, \quad t > 0, \\ l(0,x) = l_0(x), & x \in \Gamma. \end{cases} \tag{2.19}$$

Since $\Gamma = \partial\Omega$ is a smooth manifold without boundary, we can apply the theory of linear parabolic equation on smooth manifold (see e.g. [22, Section 6.1]) to get the unique weak solution $l_2 \in C([0,T]; L^2(\Gamma)) \cap L^2(0,T; H^1(\Gamma))$.

Similarly, the same theory in [22, Section 6.1]) applies to the homogeneous Neumann-problem

$$\begin{cases} p_t - d_p \Delta_{\Gamma_2} p = \sigma l_2 - \xi p, & x \in \Gamma_2, \quad t > 0, \\ d_p \frac{\partial p}{\partial \nu_{\Gamma_2}} = 0, & x \in \partial\Gamma_2, \quad t > 0, \\ p(0,x) = p_0(x), & x \in \Gamma_2. \end{cases} \tag{2.20}$$

Hence, (2.20) has a unique weak solution $p_2 \in C([0,T]; L^2(\Gamma_2)) \cap L^2(0,T; H^1(\Gamma_2))$. Note that clearly $(l_2, p_2) \in S$ since $l_2(0,x) = l_0(x)$ for $x \in \Gamma$ and $p_2(0,x) = p_0(x)$ for $x \in \Gamma_2$.

We can therefore define a mapping $A : S \to S$ as $A(l_1, p_1) = (l_2, p_2)$. In the following we shall prove that $A$ is a contraction mapping. We consider two images

$$A(l_1, p_1) = (l_2, p_2), \qquad \text{and} \qquad A(\tilde{l}_1, \tilde{p}_1) = (\tilde{l}_2, \tilde{p}_2).$$

Moreover, we shall denote

$$\hat{l} := \tilde{l}_2 - l_2, \qquad \hat{p} := \tilde{p}_2 - p_2, \qquad \hat{L} := \tilde{L}_1 - L_1, \qquad \hat{P} := \tilde{P}_1 - P_1,$$

where $(L_1, P_1)$ and $(\tilde{L}_1, \tilde{P}_1)$ are the solutions of (2.18) subject to $(l_1, p_1)$ and $(\tilde{l}_1, \tilde{p}_1)$, respectively. Then, we obtain the following system for $(\hat{L}, \hat{P})$

$$\begin{cases} \hat{L}_t - d_L \Delta \hat{L} = \alpha \hat{P} - \beta \hat{L}, & x \in \Omega, \quad t > 0, \\ \hat{P}_t - d_P \Delta \hat{P} = -\alpha \hat{P} + \beta \hat{L}, & x \in \Omega, \quad t > 0, \\ \hat{L}(0,x) = 0, \ \hat{P}(0,x) = 0 & x \in \Omega, \end{cases} \tag{2.21}$$

with boundary conditions

$$\begin{cases} d_L \frac{\partial \hat{L}}{\partial \nu} + \lambda \hat{L} = \gamma(\tilde{l}_1 - l_1), & x \in \Gamma, \quad t > 0, \\ d_P \frac{\partial \hat{P}}{\partial \nu} = \chi_{\Gamma_2} \xi (\tilde{p}_1 - p_1), & x \in \Gamma, \quad t > 0, \end{cases} \tag{2.22}$$

and a system for $(\hat{l}, \hat{p})$

$$\begin{cases} \hat{l}_t - d_l \Delta_\Gamma \hat{l} + (\gamma + \sigma \chi_{\Gamma_2}) \hat{l} = \lambda \hat{L}, & x \in \Gamma, \quad t > 0, \\ \hat{p}_t - d_p \Delta_{\Gamma_2} \hat{p} + \xi \hat{p} = \sigma \hat{l}, & x \in \Gamma_2, \quad t > 0, \\ d_p \frac{\partial p}{\partial \nu_{\Gamma_2}} = 0, & x \in \partial \Gamma_2, \quad t > 0, \\ \hat{l}(0,x) = 0, & x \in \Gamma, \\ \hat{p}(0,x) = 0, & x \in \Gamma_2. \end{cases} \tag{2.23}$$

Multiplication of the first equation in (2.23) with $\hat{l}$ yields

$$\frac{1}{2} \frac{d}{dt} \|\hat{l}\|_\Gamma^2 + d_l \|\nabla_\Gamma \hat{l}\|_\Gamma^2 + \gamma \|\hat{l}\|_\Gamma^2 + \sigma \|\hat{l}\|_{\Gamma_2}^2 = \lambda \int_\Gamma \hat{L} \hat{l} \, dS \le \gamma \|\hat{l}\|_\Gamma^2 + \frac{\lambda^2}{4\gamma} \|\hat{L}\|_\Gamma^2. \tag{2.24}$$

Thus, for all $t \in [0, T]$,

$$\|\hat{l}(t)\|_\Gamma^2 \le \frac{\lambda^2}{2\gamma^2} \int_0^t \|\hat{L}(s)\|_\Gamma^2 \, ds, \tag{2.25}$$

thanks to $\hat{l}(0,x) = 0$. By multiplying the second equation in (2.23) with $\hat{p}$ and integrating over $L^2(\Gamma_2)$, we get

$$\begin{aligned} \frac{1}{2} \frac{d}{dt} \|\hat{p}\|_{\Gamma_2}^2 + d_p \|\nabla_{\Gamma_2} \hat{p}\|_{\Gamma_2}^2 + \xi \|\hat{p}\|_{\Gamma_2}^2 = \sigma \int_{\Gamma_2} \hat{l} \hat{p} \, dS &\le \xi \|\hat{p}\|_{\Gamma_2}^2 + \frac{\sigma^2}{4\xi} \|\hat{l}\|_{\Gamma_2}^2 \\ &\le \xi \|\hat{p}\|_{\Gamma_2}^2 + \frac{\sigma^2}{4\xi} \|\hat{l}\|_\Gamma^2. \end{aligned} \tag{2.26}$$

Integration of (2.26) over $(0, t)$ yields with (2.25)

$$\begin{aligned} \|\hat{p}(t)\|_{\Gamma_2}^2 &\le \frac{\sigma^2}{2\xi^2} \int_0^t \|\hat{l}(s)\|_\Gamma^2 \, ds \le \frac{\lambda^2 \sigma^2}{4\gamma^2 \xi^2} \int_0^t \int_0^s \|\hat{L}(r)\|_\Gamma^2 \, dr ds \\ &\le \frac{\lambda^2 \sigma^2}{4\gamma^2 \xi^2} T \int_0^t \|\hat{L}(s)\|_\Gamma^2 \, ds. \end{aligned} \tag{2.27}$$

Given the bounds (2.25) and (2.27), we are left to estimate the term $\int_0^t \|\hat{L}(s)\|_\Gamma^2 ds$. In order to proceed, we recall the Trace Theorem

$$\int_\Gamma |f|^2 dS \le C_P \|f\|_{H^1(\Omega)}^2 = C_P (\|f\|_\Omega^2 + \|\nabla f\|_\Omega^2) \text{ for all } f \in H^1(\Omega),$$

for a constant $C_P > 0$.

Then, by testing the two equations in (2.21) with $\beta\hat{L}$ and $\alpha\hat{P}$, respectively, and by integrating and adding the result, we estimate with Young's inequality

$$\begin{aligned}
&\frac{d}{dt}\left(\frac{\beta}{2}\|\hat{L}\|_\Omega^2+\frac{\alpha}{2}\|\hat{P}\|_\Omega^2\right)+d_L\beta\|\nabla\hat{L}\|_\Omega^2+d_P\alpha\|\nabla\hat{P}\|_\Omega^2\\
&\quad=\beta\int_\Gamma\hat{L}\Big(d_L\frac{\partial\hat{L}}{\partial\nu}\Big)\,dS+\alpha\int_\Gamma\hat{P}\Big(d_P\frac{\partial\hat{P}}{\partial\nu}\Big)\,dS-\int_\Omega(\alpha\hat{P}-\beta\hat{L})^2\,dx\\
&\quad\le\beta\int_\Gamma\hat{L}\Big(\gamma(\tilde{l}_1-l_1)-\lambda\hat{L}\Big)\,dS+\alpha\int_{\Gamma_2}\hat{P}\Big(\xi(\tilde{p}_1-p_1)\Big)\,dS\\
&\quad\le-\frac{\beta\lambda}{2}\|\hat{L}\|_\Gamma^2+\frac{\beta\gamma^2}{2\lambda}\|\tilde{l}_1-l_1\|_\Gamma^2+\frac{\alpha d_P}{C_P}\|\hat{P}\|_\Gamma^2+\frac{\alpha C_P\xi^2}{4d_P}\|\tilde{p}_1-p_1\|_{\Gamma_2}^2\\
&\quad\le-\frac{\beta\lambda}{2}\|\hat{L}\|_\Gamma^2+d_P\alpha\Big(\|\hat{P}\|_\Omega^2+\|\nabla\hat{P}\|_\Omega^2\Big)+k\Big(\|\tilde{l}_1-l_1\|_{X_1}^2+\|\tilde{p}_1-p_1\|_{X_2}^2\Big),
\end{aligned}\tag{2.28}$$

where $k:=\max\{\frac{\beta\gamma^2}{2\lambda},\frac{C_P\alpha\xi^2}{4d_P}\}$ and we have used the Trace Theorem. Thus,

$$\begin{aligned}
&\frac{d}{dt}\Big(\beta\|\hat{L}\|_\Omega^2+\alpha\|\hat{P}\|_\Omega^2\Big)+\beta\lambda\|\hat{L}\|_\Gamma^2\\
&\qquad\qquad\le 2d_P\alpha\|\hat{P}\|_\Omega^2+2k\Big(\|\tilde{l}_1-l_1\|_{X_1}^2+\|\tilde{p}_1-p_1\|_{X_2}^2\Big).
\end{aligned}\tag{2.29}$$

By integrating (2.29) over $(0,t)$, we observe in particular that

$$\alpha\|\hat{P}(t)\|_\Omega^2\le 2kT\Big(\|\tilde{l}_1-l_1\|_{X_1}^2+\|\tilde{p}_1-p_1\|_{X_2}^2\Big)+2d_P\alpha\int_0^t\|\hat{P}(s)\|_\Omega^2\,ds.\tag{2.30}$$

Thus, Gronwall's Lemma implies for all $t\in[0,T]$

$$\|\hat{P}(t)\|_\Omega^2\le\frac{2kT}{\alpha}\Big(\|\tilde{l}_1-l_1\|_{X_1}^2+\|\tilde{p}_1-p_1\|_{X_2}^2\Big)e^{2d_PT}\tag{2.31}$$

Reinsert (2.31) into (2.29) yields

$$\begin{aligned}
&\frac{d}{dt}\Big(\beta\|\hat{L}\|_\Omega^2+\alpha\|\hat{P}\|_\Omega^2\Big)+\beta\lambda\|\hat{L}\|_\Gamma^2\\
&\qquad\qquad\le 2k(2d_PTe^{2d_PT}+1)\Big(\|\tilde{l}_1-l_1\|_{X_1}^2+\|\tilde{p}_1-p_1\|_{X_2}^2\Big).
\end{aligned}\tag{2.32}$$

Next, we integrate (2.32) over $(0,t)$ and recall $\hat{L}(0)=0=\hat{P}(0)$ to find

$$\beta\lambda\int_0^t\|\hat{L}(s)\|_\Gamma^2ds\le 2kT(2d_PTe^{2d_PT}+1)\Big(\|\tilde{l}_1-l_1\|_{X_1}^2+\|\tilde{p}_1-p_1\|_{X_2}^2\Big).\tag{2.33}$$

Altogether from (2.25), (2.27) and (2.33), we get now for all $t\in[0,T]$

$$\begin{aligned}
\|\hat{l}(t)\|_\Gamma^2+\|\hat{p}(t)\|_{\Gamma_2}^2&\le\left(\frac{\lambda^2}{2\gamma}+\frac{\lambda^2\sigma^2}{4\gamma\xi}T\right)\int_0^t\|\hat{L}(s)\|_\Gamma^2ds\\
&\le\left(\frac{\lambda^2}{2\gamma}+\frac{\lambda^2\sigma^2}{4\gamma\xi}T\right)\frac{2kT}{\beta\lambda}\big(2d_PTe^{2d_PT}+1\big)\Big(\|\tilde{l}_1-l_1\|_{X_1}^2+\|\tilde{p}_1-p_1\|_{X_2}^2\Big).
\end{aligned}\tag{2.34}$$

Thus,

$$\begin{aligned}
\|\tilde{l}_2-l_2\|_{X_1}^2+\|\tilde{p}_2-p_2\|_{X_2}^2&=\|\hat{l}\|_{X_1}^2+\|\hat{p}\|_{X_2}^2=\sup_{t\in[0,t]}\|\hat{l}(t)\|_\Gamma^2+\sup_{t\in[0,T]}\|\hat{p}(t)\|_{\Gamma_2}^2\\
&\le\left(\frac{\lambda^2}{2\gamma}+\frac{\lambda^2\sigma^2}{4\gamma\xi}T\right)\frac{2kT}{\beta\lambda}\big(2d_PTe^{2d_PT}+1\big)\Big(\|\tilde{l}_1-l_1\|_{X_1}^2+\|\tilde{p}_1-p_1\|_{X_2}^2\Big).
\end{aligned}\tag{2.35}$$

Hence, by choosing $T$ is small enough, we have

$$\left(\frac{\lambda^2}{2\gamma} + \frac{\lambda^2\sigma^2}{4\gamma\xi}T\right)\frac{2k}{\beta\lambda}T(2d_P T e^{2d_P T} + 1) < 1,$$

and the mapping $A : S \to S$ is a contraction. Hence, there exists a unique fixed point $(l^*, p^*)$ of $A$. By solving system (2.18) subject to $(l^*, p^*)$, we obtain a unique solution $(L^*, P^*)$. It is easy to verify that $(L^*, P^*, l^*, p^*)$ is a solution to the system (1.1)–(1.3) on $[0, T]$. Concerning uniqueness, consider another solution $(\bar{L}, \bar{P}, \bar{l}, \bar{p})$ of the system. Then, $(\bar{l}, \bar{p})$ must be a fixed point of $A$. Hence, $(\bar{l}, \bar{p}) = (l^*, p^*)$ and thus $(\bar{L}, \bar{P}) = (L^*, P^*)$.

It remains to prove the non-negativity of the solution $(L^*, P^*, l^*, p^*)$. It is obvious to see that Lemma 2.2 is still true if we replace $C([0,T]; L^p(\Omega))$ by $X = C([0,T]; L^2(\Gamma)) \times C([0,T]; L^2(\Gamma_2))$. Thus, it is enough to show that if $l_1 \geq 0, p_1 \geq 0$ then $l_2 \geq 0, p_2 \geq 0$, where $(l_2, p_2) = A(l_1, p_1)$. Now, for $l_1 \geq 0, p_1 \geq 0$, by using Proposition 2.3, we obtain from (2.18) that $L_1 \geq 0$ and $P_1 \geq 0$. Then, from (1.3) we find that $l_2 \geq 0$ and $p_2 \geq 0$. Thus, Lemma 2.2 proves that $l^* \geq 0$ and $p^* \geq 0$. Since $(L^*, P^*)$ is the solution of system (1.1)–(1.2) subject to $(l^*, p^*)$, we have $L^* \geq 0$ and $P^* \geq 0$. This completes the proof. □

From the weak formulation, it follows by a standard argument that the unique weak solution of system (1.1)–(1.3) conserves the total mass as long as the solution exists, that is, for all $t \in [0, T_{max})$ where $T_{max} \leq +\infty$ is the maximal time of existence:

$$\begin{aligned}\forall t \in [0, T_{max}) :\ M_0 &= \int_\Omega \big(L(t,x) + P(t,x)\big)\,dx + \int_\Gamma l(t,x)\,dS + \int_{\Gamma_2} p(t,x)\,dS \\ &= \int_\Omega \Big(L_0(x) + P_0(x)\Big)\,dx + \int_\Gamma l_0(x)\,dS + \int_{\Gamma_2} p_0(x)\,dS. \qquad (2.36)\end{aligned}$$

For non-negative solutions, the conservation law (2.36) implies further that the $L^1$-norm of the solution is uniformly bounded in time:

$$\forall t \in [0, T_{max}) : \quad \|L(t)\|_{L^1(\Omega)} + \|P(t)\|_{L^1(\Omega)} + \|l(t)\|_{L^1(\Gamma)} + \|p(t)\|_{L^1(\Gamma_2)} = M_0. \qquad (2.37)$$

Nevertheless, global existence in $L^2$ for the system (1.1)–(1.3) is not trivial even though it is linear and global existence is certainly expected. The (technical) difficulties arise from the coupled Robin boundary conditions as well as from the surface diffusion terms. In the sequel, we will show that the unique local weak solution in $L^2$ can be globally extended and is even uniformly-in-time bounded in $L^2$. In the proof, we shall need the following Gagliardo-Nirenberg and Trace inequalities:

**Lemma 2.5** (Interpolation Inequalities)**.**
*Under the assumption on the domain $\Omega$, there exists a constant $C > 0$ such that*

$$\|u\|_\Omega \leq C\|u\|_{L^1(\Omega)}^{2/(n+2)}\|u\|_{H^1(\Omega)}^{n/(n+2)} \qquad (2.38)$$

*for all functions $u \in H^1(\Omega)$.*

*Moreover, basing on (2.38), there exists for any $\varepsilon > 0$ a constant $C_\varepsilon > 0$ such that*

$$\|u\|_\Omega^2 \leq \varepsilon\|\nabla u\|_\Omega^2 + C_\varepsilon\|u\|_{L^1(\Omega)}^2, \quad \textit{and} \quad \|u\|_\Gamma^2 \leq \varepsilon\|\nabla u\|_\Omega^2 + C_\varepsilon\|u\|_{L^1(\Omega)}^2, \qquad (2.39)$$

*for all $u \in H^1(\Omega)$.*

*Proof.* The Gagliardo-Nirenberg inequality (2.38) is well known and can be found e.g. in [2, Theorem 1.3, Page 18] or [20].

Using 2.38, and noting that $\|u\|^2_{H^1(\Omega)} = \|u\|^2_\Omega + \|\nabla u\|^2_\Omega$, we have

$$\begin{aligned}\|u\|^2_\Omega &\le C\|u\|^{4/(n+2)}_{L^1(\Omega)} \left(\|u\|^2_\Omega + \|\nabla u\|^2_\Omega\right)^{n/(n+2)} \\ &\le C_\varepsilon \|u\|^2_{L^1(\Omega)} + \frac{\varepsilon}{\varepsilon+1}\left(\|u\|^2_\Omega + \|\nabla u\|^2_\Omega\right),\end{aligned}$$

by Young's inequality and thus

$$\|u\|^2_\Omega \le C_\varepsilon \|u\|^2_{L^1(\Omega)} + \varepsilon\|\nabla u\|^2_\Omega.$$

For the second inequality, we use then the modified Trace inequality ([21, Theorem 1.5.1.10]) to estimate

$$\|u\|^2_\Gamma \le \frac{\varepsilon}{2}\|\nabla u\|^2_\Omega + C_\varepsilon\|u\|^2_\Omega \le \varepsilon\|\nabla u\|^2_\Omega + C_\varepsilon \|u\|^2_{L^1(\Omega)}.$$

□

**Theorem 2.6** (Global Existence and Uniqueness of Weak Solutions)**.**
*Consider initial data* $(L_0, P_0, l_0, p_0) \in L^2(\Omega)\times L^2(\Omega)\times L^2(\Gamma)\times L^2(\Gamma_2)$ *and assume* $\alpha, \beta, \lambda, \gamma, \sigma, \xi > 0$. *Then, the unique solution to system* (1.1)–(1.3) *exists globally in time.*

*Assume additionally that the initial data* $(L_0, P_0, l_0, p_0) \ge 0$ *are non-negative. Then, there exists a constant* $C$*, which depends only on the domain, the initial data, the reaction rates and the diffusion rates such that*

$$\forall t \ge 0: \qquad \|L(t)\|^2_\Omega + \|P(t)\|^2_\Omega + \|l(t)\|^2_\Gamma + \|p(t)\|^2_{\Gamma_2} \le C,$$

*i.e. the global solutions to system* (1.1)–(1.3) *are bounded uniformly-in-time.*

*Proof.* We shall consider the case of non-negative initial data (and thus solutions) and prove uniform boundedness in time. The proof the existence of global solutions to general $L^2$ initial data follows by a similar argument when replacing the below $L^1$-interpolation and $L^1$-bound (2.37) by analog estimates in $L^2$ and a Gronwall argument, which yields global existence yet without uniform-in-time boundedness.

We consider the functional

$$\mathcal{H}(t) = \frac{1}{2}\Big(\|L(t)\|^2_\Omega + \|P(t)\|^2_\Omega + \sigma\|l(t)\|^2_\Gamma + \xi\|p(t)\|^2_\Omega\Big).$$

By calculating the time derivative of $\mathcal{H}$ along solutions of system (1.1)–(1.3), we get

$$\begin{aligned}\frac{d\mathcal{H}}{dt} =& - d_L\|\nabla L\|^2_\Omega - d_P\|\nabla P\|^2_\Omega - \beta\|L\|^2_\Omega - \alpha\|P\|^2_\Omega - \lambda\|L\|^2_\Gamma \\ &+ (\alpha+\beta)(L,P)_\Omega + (\lambda\sigma+\gamma)(L,l)_\Gamma + \xi(P,p)_{\Gamma_2} \\ &- \gamma\sigma\|l\|^2_\Gamma - \sigma^2\|l\|^2_{\Gamma_2} - \xi^2\|p\|^2_{\Gamma_2} + \sigma\xi(p,l)_{\Gamma_2}.\end{aligned} \tag{2.40}$$

By Cauchy's inequality and (2.39), we have the following estimates

$$\begin{aligned}(\alpha+\beta)(L,P)_\Omega &\le \frac{\alpha+\beta}{2}(\|L\|^2_\Omega + \|P\|^2_\Omega) \\ &\le \frac{d_L}{4}\|\nabla L\|^2_\Omega + \frac{d_P}{2}\|\nabla P\|^2_\Omega + C\|L\|^2_{L^1(\Omega)} + C\|P\|^2_{L^1(\Omega)},\end{aligned} \tag{2.41}$$

and

$$\begin{aligned}(\lambda\sigma+\gamma)(L,l)_\Gamma &\le \frac{\gamma\sigma}{2}\|l\|_\Gamma^2 + \frac{(\lambda\sigma+\gamma)^2}{2\gamma\sigma}\|L\|_\Gamma^2 \\ &\le \frac{\gamma\sigma}{2}\|l\|_\Gamma^2 + \frac{d_L}{4}\|\nabla L\|_\Omega^2 + C\|L\|_{L^1(\Omega)}^2,\end{aligned} \tag{2.42}$$

and

$$\begin{aligned}\xi(P,p)_{\Gamma_2} &\le \frac{\xi^2}{4}\|p\|_{\Gamma_2}^2 + \|P\|_\Gamma^2 \\ &\le \frac{\xi^2}{4}\|p\|_{\Gamma_2}^2 + \frac{d_P}{4}\|\nabla P\|_\Omega^2 + C\|P\|_{L^1(\Omega)}^2,\end{aligned} \tag{2.43}$$

and

$$\sigma\xi(p,l)_{\Gamma_2} \le \sigma^2\|l\|_{\Gamma_2}^2 + \frac{\xi^2}{4}\|p\|_{\Gamma_2}^2. \tag{2.44}$$

Inserting (2.41)–(2.44) into (2.40) yields

$$\begin{aligned}\frac{d\mathcal{H}}{dt} \le &- \frac{d_L}{2}\|\nabla L\|_\Omega^2 - \frac{d_P}{2}\|\nabla P\|_\Omega^2 - \beta\|L\|_\Omega^2 - \alpha\|P\|_\Omega^2 \\ &- \frac{\gamma\sigma}{2}\|l\|_\Gamma^2 - \frac{\xi^2}{2}\|p\|_{\Gamma_2}^2 + C(\|L\|_{L^1(\Omega)}^2 + \|P\|_{L^1(\Omega)}^2).\end{aligned}$$

By defining $\eta := \min\{\beta, \alpha, \frac{\gamma}{2}, \frac{\xi}{4}\}$ and by using $\|L\|_{L^1(\Omega)} \le M$ and $\|P\|_{L^1(\Omega)} \le M$ (thanks to the $L^1$-bound (2.37)), we have

$$\frac{d\mathcal{H}}{dt} + \eta\mathcal{H} + \frac{\xi^2}{4}\|p\|_{\Gamma_2}^2 \le C. \tag{2.45}$$

By Gronwall's inequality, we obtain in particular

$$\mathcal{H}(t) \le e^{-\eta t}\mathcal{H}(0) + C,$$

or equivalently,

$$\begin{aligned}&\|L(t)\|_\Omega^2 + \|P(t)\|_\Omega^2 + \sigma\|l(t)\|_\Gamma^2 + \xi\|p(t)\|_{\Gamma_2}^2 \\ &\qquad \le e^{-\eta t}\left(\|L_0\|_\Omega^2 + \|P_0\|_\Omega^2 + \sigma\|l_0\|_\Gamma^2 + \xi\|p_0\|_{\Gamma_2}^2\right) + C,\end{aligned}$$

which completes the proof. □

To study the regularity of solutions to (1.1)–(1.3), we need the following Lemma:

**Lemma 2.7** (Regularity of Parabolic Equations on Manifolds, [22, Chapter 6])**.** *Let $M$ be a smooth Riemann manifold, $f \in L^2(0,T;L^2(M))$, $g \in L^2(0,T;L^2(\partial M))$ and $u_0 \in L^2(M)$. Then, any weak solution $u$ to*

$$\begin{cases} u_t - d_u\Delta_M u = f, & x \in M, \quad t > 0, \\ \mathcal{B}(u) = g, & x \in \partial M, \quad t > 0, \\ u(0) = u_0, \end{cases}$$

*where $\mathcal{B}$ denotes either a Dirichlet, Neumann or Robin boundary operator, satisfies*

$$u \in L^2(I; H^2(M)) \cap W^{1,1}(I; L^2(M)),$$

*where $I = [t_0, T]$ with all $0 < t_0 < T < +\infty$.*

**Theorem 2.8** (Strong Solutions). *For any $I = [t_0, T]$ with $0 < t_0 < T < +\infty$, the weak solution $(L, P, l, p)$ to* (1.1)–(1.3) *satisfies*

$$L, P \in L^2(I; H^2(\Omega)) \cap W^{1,1}(I; L^2(\Omega)),$$

$$l \in L^2(I; H^2(\Gamma)) \cap W^{1,1}(I; L^2(\Gamma))$$

*and*

$$p \in L^2(I; H^2(\Gamma_2)) \cap W^{1,1}(I; L^2(\Gamma_2)).$$

*Thus, $(L, P, l, p)$ is in fact a strong solution, which satisfies the system* (1.1)–(1.3) *in $L^2$ for almost every $t \in I$.*

*Proof.* We consider, for example, the equation of $L$:

$$\begin{cases} L_t - d_L \Delta L = -\beta L + \alpha P, & x \in \Omega, \quad t > 0, \\ d_L \partial L/\partial\nu = -\lambda L + \gamma l, & x \in \Gamma, \quad t > 0, \\ L(0, x) = L_0. \end{cases}$$

Then, by applying Lemma 2.7 with $f = -\beta L + \alpha P \in L^2(0, T; L^2(\Omega))$ and $g = -\lambda L + \gamma l \in L^2(0, T; L^2(\Gamma))$, we conclude

$$L \in L^2(I; H^2(\Omega)) \cap W^{1,1}(I; L^2(\Omega)).$$

The regularity for $P, l$ and $p$ follows in a similar way. □

## 3. Numerical discretisation and qualitative discussions

In this section, we first present a basic numerical finite element scheme for system (1.1)–(1.3). As a prototypical example, we consider the particular case when $\Omega \subset \mathbb{R}^2$ is the unit ball and the active boundary part is located at $\Gamma_2 = \{(1, \theta) : \pi \leq \theta \leq 3\pi/2\}$.

The test cases discussed in the Section 3.3 serve to illustrate in particular i) the role of surface diffusion in the model system (1.1)–(1.3) and ii) to investigate the behaviour of the system subject to changes in the release rate $\xi$ of cortical Lgl into the cytoplasm, i.e. $p \xrightarrow{\xi} P$.

### 3.1. Time-discretisation.

We apply a first order implicit Euler scheme as time discretisation, which is well known to be stable for such linear problems (see e.g. [16]). More precisely, for a given time step $h$, we shall denote by $L_n(x) := L(nh, x)$ and $L_{n+1}(x) := L((n + 1)h, x)$, respectively and analog for $P, l$ and $p$. Thus, we have for $n \geq 0$ the following iteration of semi-discretised systems :

$$\begin{cases} -hd_L \Delta L_{n+1} + (1 + h\beta) L_{n+1} - h\alpha P_{n+1} = L_n, & x \in \Omega, \\ -hd_P \Delta P_{n+1} + (1 + h\alpha) P_{n+1} - h\beta L_{n+1} = P_n, & x \in \Omega, \\ -hd_l \Delta_\Gamma l_{n+1} + (1 + h(\gamma + \sigma\chi_{\Gamma_2})) l_{n+1} - h\lambda L_{n+1} = l_n, & x \in \Gamma, \\ -hd_p \Delta_{\Gamma_2} p_{n+1} + (1 + h\xi) p_{n+1} - h\sigma l_{n+1} = p_n, & x \in \Gamma_2, \end{cases} \tag{3.1}$$

with boundary condition

$$\begin{cases} d_L \partial L_{n+1}/\partial\nu = -\lambda L_{n+1} + \gamma l_{n+1}, & x \in \Gamma, \\ d_P \partial P_{n+1}/\partial\nu = \xi \chi_{\Gamma_2} p_{n+1}, & x \in \Gamma, \\ d_p \partial p_{n+1}/\partial\nu_{\Gamma_2} = 0, & x \in \partial\Gamma_2. \end{cases} \tag{3.2}$$

3.2. **Space-discretisation.** We use a standard finite element method for space discretisation of the cell volume. More precisely, the domain $\Omega$ is approximated by a triangulation mesh $\mathcal{T}_\eta$ where $\eta$ is the maximum diameter of the triangles. We will use as basis functions the space of continuous, piecewise linear functions on triangles. Although finite element methods are well known for linear reaction-diffusion problems on bounded domains, we ought to remark the following three points specific to this work by addressing surface diffusion as well as the active and nonactive parts of the boundary:

- The boundary $\Gamma$ is approximated by a polygon $\partial\mathcal{T}_\eta$. This choice makes the discretisation procedure easy to implement since we only have to discretise the domain once. Moreover, such a discretisation was already successfully applied for a linear elliptic system featuring mixed volume-surface diffusion in [26], where also an error analysis was carried out.
- The triangulation is made such that the boundary $\partial\Gamma_2$, which are just two points $(-1,0)$ and $(0,-1)$ in the considered case $\Omega \subset \mathbb{R}^2$, coincides with the vertices of one or more triangles. Moreover, since the coefficients of the equations for $P$ and $l$ are discontinuous at the boundary points $\partial\Gamma_2$, we shall significantly refine the mesh in the proximity of these two points as can be seen in Figure 2. The refinement was done by an adaptive strategy implemented in the function "adaptmesh" in Matlab using two point sources at $(-1,0)$ and $(0,-1)$. We remark that, for the sake of clarity, the mesh given in Figure 2, which is obtained after one mesh refinement, has approximately 4000 elements. Later in this paper, to produce high resolution pictures, we will use a mesh created by five mesh refinements, which contains about 65000 elements.

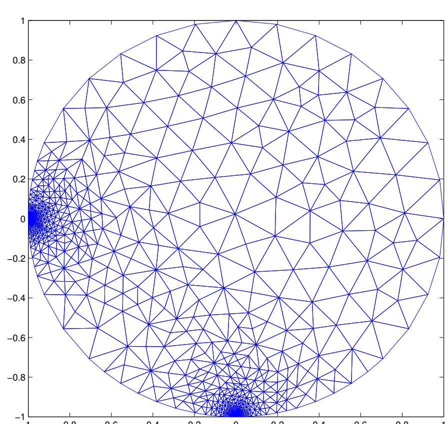



FIGURE 2. Triangulation mesh and refinement in the proximity of $\partial\Gamma_2$, i.e. the points $(-1,0)$ and $(0,-1)$, which are discontinuity points of the system.

- The Laplace-Beltrami operator $\Delta_\Gamma$ and $\Delta_{\Gamma_2}$ on the boundary, which represent the surface diffusion, $\Gamma$ can be approximated by the Laplace-Beltrami operator on $\partial\mathcal{T}_\eta$. By choosing a polygon as approximation of the boundary $\Gamma$, the operator $\Delta_\Gamma$ can itself be approximated by an operator $\Delta_{\partial\mathcal{T}_\eta}$, see e.g. [26]. Because $\partial\mathcal{T}_\eta$ is a union of disjoint segments, the operator $\Delta_{\partial\mathcal{T}_\eta}$ can be split to act on each segment separately. Moreover, since we use a weak/variational problem formulation, we only have to compute the tangential gradient of affine basis functions on the approximating segments and remark that in this case the tangential gradient coincides with the directional derivative. As illustrating example, consider a segment $AB$ and the basis function $\varphi : AB \to [0,1]$ such that $\varphi(A) = 1$ and $\varphi(B) = 0$ then

$$\nabla_{\overrightarrow{AB}}\varphi = -\frac{1}{|\overrightarrow{AB}|}$$

where $\nabla_{\overrightarrow{AB}}\varphi$ denotes the tangential derivative of $\varphi$ along the direction $\overrightarrow{AB}$.

Note that in the case of a circle or a sphere, we could alternatively use spherical coordinates to discretise the Laplace-Beltrami operator (see e.g. [27]). However, the above discretisation has the advantage to work for any sufficiently smooth domain $\Omega$, which can be well approximated by linear segments.

3.3. **Discussion of the numerical results.** The following numerical examples shall highlight certain qualitative features of the model system (1.1)–(1.3). Due to the lack of in-vivo or in-vitro parameters, which are in general unknown for SOP precursor cells, we shall use what we believe to be generic system parameters i.e. typical reaction- and diffusion rates, for which the model exhibits the expected behaviour. Thus, the aim of the following can only be a *discussion of interesting qualitative features* and not a quantitative simulation of Lgl localisation in SOP precursor cell.

As a generic parameters, we use the following reaction rates:

$$\alpha = 1, \qquad \beta = 2, \qquad \gamma = 2, \qquad \lambda = 4, \qquad \sigma = 3, \tag{3.3}$$

the following volume diffusion rates:

$$d_L = 0.01, \quad d_P = 0.02, \tag{3.4}$$

and the following constant initial concentrations:

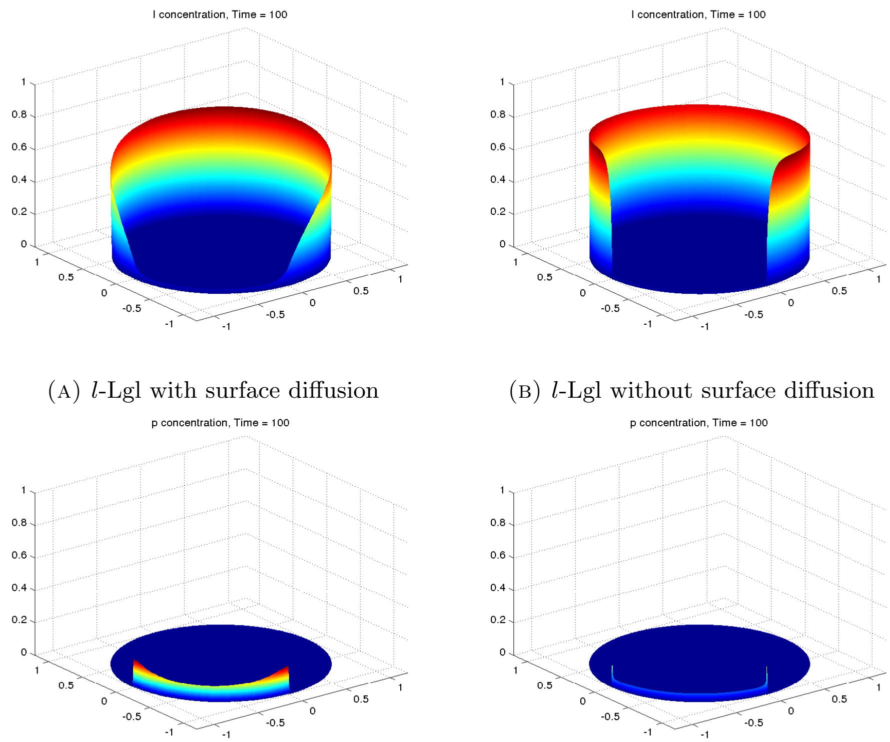
$$L_0(x,y) \equiv 0.8, \qquad P_0(x,y) \equiv 0.6, \qquad l_0(x,y) \equiv 0.3, \qquad p_0(x,y) \equiv 0.4. \tag{3.5}$$

The value of $\xi$ will be chosen differently during the discussion of the numerical examples. The same is true for the surface diffusion rates $d_l$ and $d_p$, which shall be specified later.

3.3.1. *The effects of surface diffusion.* The first two numerical test examples shall illustrate the role of surface diffusion by comparing the numerical stationary state solutions of the system for two cases: i) with surface diffusion rates $d_l = 0.02$, $d_p = 0.04$ and ii) without surface diffusion, i.e. $d_l = d_p = 0$.

Figure 3 plots the resulting numerically stationary state concentrations of non-phosphorylated cortical Lgl $l$ and phosphorylated cortical Lgl $p$ (for the generic parameters (3.3), (3.4) and the initial data (3.5)).

In the case with surface diffusion, Figure 3a shows a smoothly decaying profile of $l$ around the boundary points $\partial\Gamma_2$, i.e. around the points $(-1,0)$ and $(0,-1)$, where the lower concentration of $l$ on $\Gamma_2$ is the result of $l$ being converted into $p$.




(A) $l$-Lgl with surface diffusion

(B) $l$-Lgl without surface diffusion

(C) $p$-Lgl with surface diffusion

(D) $p$-Lgl without surface diffusion

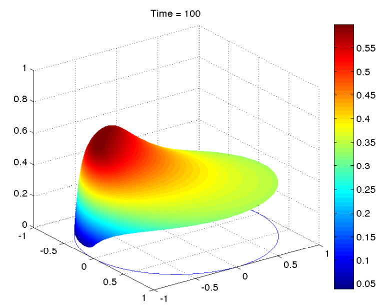
FIGURE 3. Comparison of the numerical stationary states of $l$ and $p$ with surface diffusion rates $d_l = 0.02$, $d_p = 0.04$ (Figs. (A) and (C)) and without surface diffusion $d_l = d_p = 0$ (Figs. (B) and (D)) for the parameters (3.3), (3.4) and initial data (3.5).

The corresponding numerical steady state concentration of $p$ on $\Gamma_2$ is plotted in Figure 3c. The increase of $p$ towards the points $(-1, 0)$ and $(0, -1)$ corresponds to the increasing values of $l$ over and beyond these boundary points.

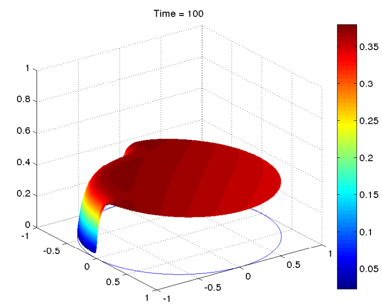
As comparision, the Figures 3b and 3d show the numerical stationary state concentrations of $l$ and $p$ without surface diffusion. Due to the absence of surface diffusion, Figure 3b depicts a significantly sharper profile of $l$ around the boundary points $\partial\Gamma_2$. However, the profile in $l$ is still smooth and so is the corresponding profile of the stationary state concentration of $p$ on $\Gamma_2$, which is shown in 3d using a very highly refined mesh to eliminate potential numerical artefacts. In our understanding, these sharp yet smooth profiles of $l$ and $p$ are the combined effect of the volume diffusion of $L$ and $P$ and the reversible reactions between $L$ and $l$, which transfer a diffusive effect from the volume $\Omega$ onto the boundary $\Gamma$.

Figure 4 plots the volume concentrations $L$ and $P$ corresponding to Figure 3. In the case with surface diffusion, Figure 4a shows very interestingly and somewhat surprisingly a "hump" in the numerical stationary state concentration of $L$ near the active boundary part $\Gamma_2$. This "hump" is not visible in Figure 4b in the case without surface diffusion. The corresponding volume concentrations of $P$ in the

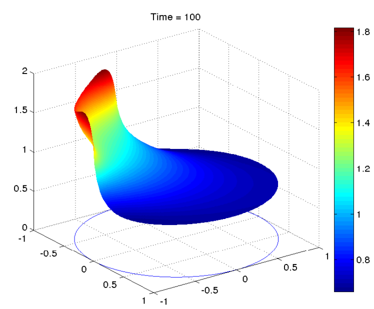
Figures 4c (with diffusion) and 4d (without diffusion) allow to explain this "hump" as the effect of surface diffusion leading to a significant additional transport of $l$-Lgl (compared to the case without surface diffusion) along $\Gamma$ to the active boundary part $\Gamma_2$, where $l$-Lgl becomes phosphorylated into $p$-Lgl, which is subsequently released from the cortex and thus results into a much higher concentration of $P$ along $\Gamma_2$ as depicted in 4c. The "hump" in $L$ is then the consequence of the reversible reaction between $L$ and $P$ and the volume diffusion of $L$.



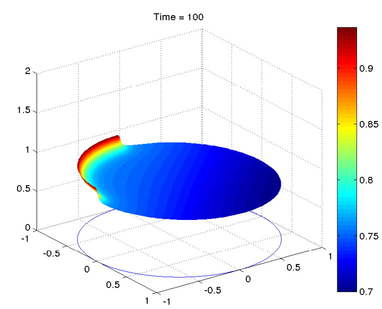

(A) $L$-Lgl with surface diffusion




(B) $L$-Lgl without surface diffusion




(C) $P$-Lgl with surface diffusion




(D) $P$-Lgl without surface diffusion

FIGURE 4. Concentrations of the numerical stationary state of $L$ and $P$ with surface diffusion rates $d_l = 0.02, d_p = 0.4$ (Figure (A) and (C)) and without surface diffusion $d_l = d_p = 0$ (Figure (B) and (D)) for the parameters (3.3), (3.4) and initial data (3.5).

**Remark 3.1.** *We remark that while Figures 3 and 4 cannot be viewed as simulation of Lgl localisation in a real SOP cell, the qualitative behaviour may nevertheless suggest that surface diffusion might play a non-negligible role in real SOP cells and may help, to explain, in particular, an experimentally observed gap between aPKC localisation and the localisation of cell-fate determining proteins, which are derived from the localisation of Lgl, see* [23].

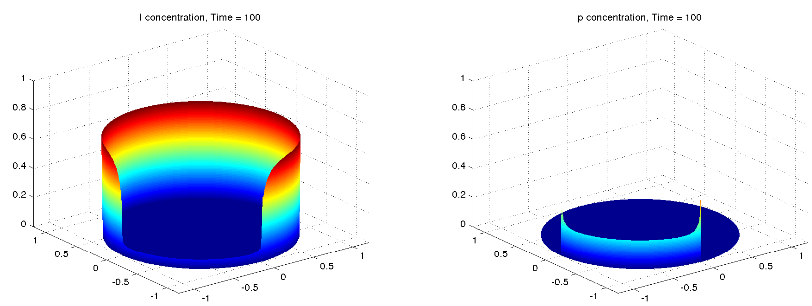
In the following Figure 5, we investigate further the case without surface diffusion by increasing the volume diffusion rate $d_L$ ten-folds compare to (3.4). More precisely, we set $d_l = d_p = 0$, $d_L = 0.1$ and $d_P = 0.02$.

Figure 5a shows the effects of the increased volume diffusion $d_L = 0.1$. It leads to a certain widening and flatening of the profile of $l$-Lgl over the boundary points of

$\Gamma_2$. This profile of $l$ is less steeper than the profile of $l$ in Figure 3b without surface diffusion but still steeper than the profile of $l$ in Figure 3a with surface diffusion. Thus, the observed effect is consistent and confirms the above explanation that the profile of $l$ and $p$ in cases without surface diffusion are a combined effect of volume diffusion $d_L$ and the reversible reaction of $L \rightleftharpoons l$: An increased volume diffusion $d_L$ leads thus to an increased diffusive effect at the surface $\Gamma$.

The corresponding stationary state profile of $p$-Lgl plotted in Figure 5b shows that also the profiles of $p$-Lgl near the boundary points of $\Gamma_2$ are widened, yet still steeper that the profiles of $p$ in Figure 3c with surface diffusion.

The increase of volume diffusion rate $d_L$ does not only affect to profile of $p$ and $l$ around $\Gamma_2$ as discussed above but also changes the absolute value of stationary states of $p$ and $l$ on $\Gamma_2$. More precisely, by comparing Figure 5a and Figure 3b (or Figure 5b and Figure 3d) we see that the absolute value of $p$ and $l$ on $\Gamma_2$ in the case $d_L = 0.1$ are higher than that in the case $d_L = 0.01$.




(A) $l$-Lgl without surface diffusion with big volume diffusion rate $d_L = 0.1$

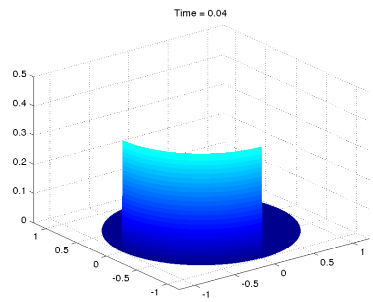
(B) $p$-Lgl without surface diffusion with big volume diffusion rate $d_L = 0.1$

FIGURE 5. Concentrations of the numerical stationary state of $l$-Lgl and $p$-Lgl without surface diffusion with ten-fold volume-diffusion rate $d_L = 0.1$, $d_P = 0.02$ and $d_l = d_p = 0$ and initial data (3.5).

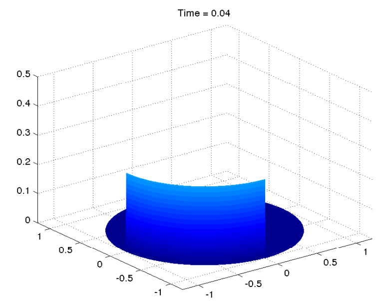
3.3.2. *Asymptotic decay of $p$ for large $\xi$*. In SOP cells, the reaction $p \xrightarrow{\xi} P$ of cortical Lgl $p$ to cytoplasmic Lgl $P$ is suggested to be significantly faster than the other reactions. That means that the expulsion rates $\xi$ is expected to be much larger than the generic reaction rates in (3.3). We are thus interested to study the qualitative behaviour for increasing reaction rates $\xi$ while keeping the reaction rates (3.3) fixed.

Intuitively, one expects that when $\xi$ becomes larger and larger, the concentration of $p$-Lgl will decay to zero since the $p$-Lgl is released more and more rapidly to $P$-Lgl.

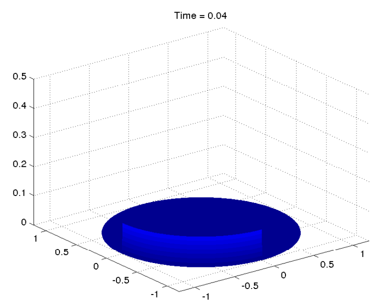
In Figure 6, we compare $p(t,x)$ on $\Gamma_2$ at an early time $t = 0.04$ for four different values of $\xi$ being $10, 20, 50$ and $100$. The numerical results show how a larger reaction rate $\xi$ leads to a decay of $p \searrow 0$ on $\Gamma_2$. This happens already at the very small time $t = 0.04$ and even more so for larger times (data not shown). Observing this fact suggests that the system (1.1)–(1.3) for large $\xi$ may be well



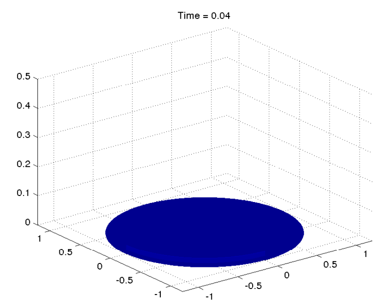

(A) $\xi = 10$




(B) $\xi = 20$




(C) $\xi = 50$




(D) $\xi = 100$

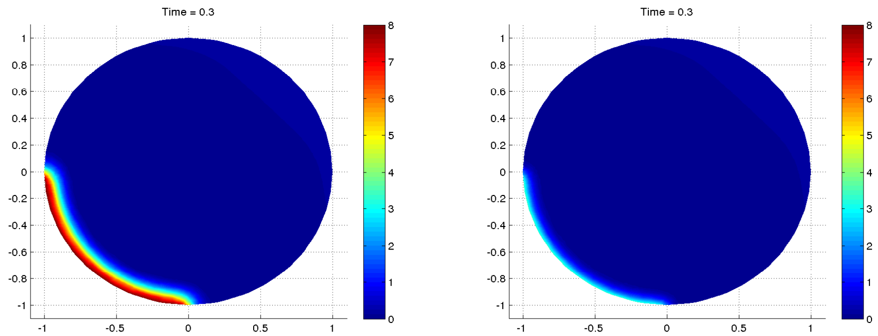
FIGURE 6. Comparison of $p$ for $\xi = 10, 20, 50, 100$ at time $t = 0.04$ and for the generic parameters (3.3), (3.4) and initial data (3.5).

approximated by a reduced quasi-steady-state approximation (QSSA) without $p$, which is formally obtained by letting $\xi \to +\infty$. This QSSA will be rigorously performed in the following Section 4.

3.3.3. *Initial-boundary layers in $P$ for large $\xi$.* The following Figures 7 and 8 continue to numerically investigate the system behaviour for small and large $\xi$, i.e. for slow and fast release of cortical $p$. Note that, in this part, we consider the case of no surface diffusion $d_l = d_p = 0$.

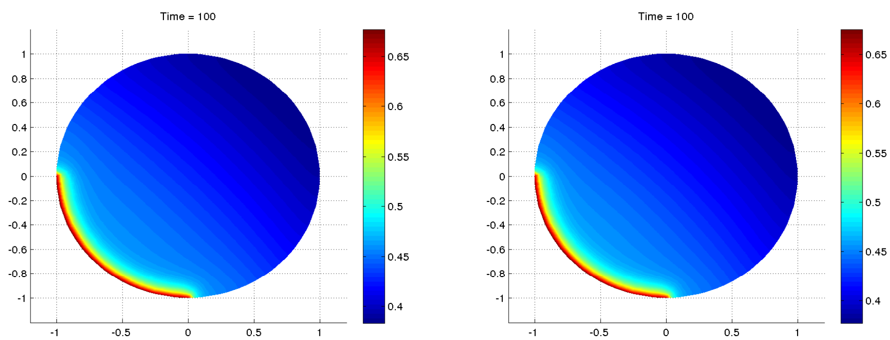
Figure 7 compares the cytoplasmic concentration of phosphorylated $P$-Lgl for two values $\xi = 1000$ and $\xi = 1$ at the smallish time $t = 0.3$ and for the specified, constant initial data (3.5). In particular, Figure 7a illustrates that the fast reaction $p \xrightarrow{\xi} P$ for $\xi = 1000$ leads to much larger values of $P$ near the boundary $\Gamma_2$ as compare to $\xi = 1$. We thus observe the formation of an initial-boundary layer near $\Gamma_2$ in Figure 7a compared to Figure 7b, which plots $P$ being formed by the slow reaction with $\xi = 1$.

Finally, Figure 8 plots the numerical steady state concentrations of $P$ for $\xi = 1000$ and $\xi = 1$ at the time $t = 100$. We observe that the stationary states appear to be identical and that the boundary layer in Figure 7 is indeed an initial-boundary layer for large $\xi$ and no longer present in the stationary states, which features much lower values of $P$ near the boundary $\Gamma_2$. In fact, we will demonstrate in Remark 4.1 in Section 4, that the stationary states of system (1.1)–(1.3) without boundary




(A) $\xi = 1000$ (B) $\xi = 1$

FIGURE 7. Initial-boundary layer in $P$ for $\xi = 1000$ and $\xi = 1$ at time $t = 0.3$ and for the generic parameters (3.3), (3.4), $d_l = d_p = 0$ and initial data (3.5).




(A) $\xi = 1000$ (B) $\xi = 1$

FIGURE 8. Common numerical stationary state concentrations of $P$ for $\xi = 1000$ and $\xi = 1$ at the time $t = 100$ and for the generic parameters (3.3), (3.4), $d_l = d_p = 0$ and initial data (3.5).

diffusion terms *do not depend on the rate* $\xi$ and are unique for fixed total initial mass in the mass conservation law (2.36). Thus, Figure 8 plots indeed that same stationary state.

## 4. Quasi-Steady-State Approximation

In this section, we study the Quasi-Steady-State Approximation (QSSA) for the system (1.1)–(1.3) as $\xi \to +\infty$. The limit $\xi \to +\infty$ can be interpreted as the instantaneous release of phosphorylated Lgl from the cell cortex into the cell cytoplasm. For technical reasons (see Lemma 4.1 and Remark 4.2), we shall restrict our analysis to the case without boundary diffusion, i.e. $d_l = 0 = d_p$. The QSSA for system (1.1)–(1.3) with surface diffusion constitutes currently an open problem.

Quasi-Steady-State Approximations for (bio)chemical reaction systems have long been studied in terms of asymptotic expansions, but it was not until recently that rigorous results were obtained for the corresponding fast-reaction limits (see e.g. [3, 4, 5, 6, 8, 9] and references therein).

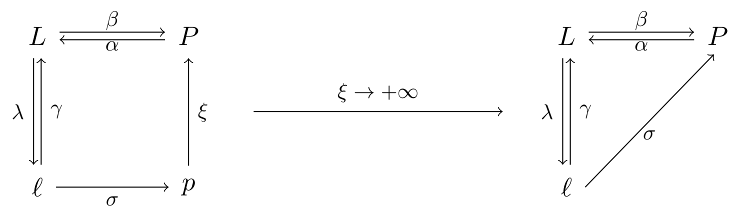



FIGURE 9. The original system (left) and the reduced QSSA system (right)

The QSSA we shall study in this Section can be illustrated as the passage of the left reaction diagram towards the right reaction diagram in Figure 9. Without the surface diffusion terms, the system (1.1)–(1.3) rewrites as

$$\begin{cases} L_t - d_L \Delta L = -\beta L + \alpha P, & x \in \Omega, \quad t > 0, \\ d_L \frac{\partial L}{\partial \nu} + \lambda L = \gamma l, & x \in \Gamma, \quad t > 0, \\ L(0,x) = L_0(x), & x \in \Omega, \end{cases} \tag{4.1}$$

$$\begin{cases} P_t - d_P \Delta P = \beta L - \alpha P, & x \in \Omega, \quad t > 0, \\ d_P \frac{\partial P}{\partial \nu} = \chi_{\Gamma_2} \xi p, & x \in \Gamma, \quad t > 0, \\ P(0,x) = P_0(x), & x \in \Omega, \end{cases} \tag{4.2}$$

$$\begin{cases} l_t = \lambda L - (\gamma + \chi_{\Gamma_2} \sigma) l, & x \in \Gamma, \quad t > 0, \\ p_t = \sigma l - \xi p, & x \in \Gamma_2, \quad t > 0, \\ l(0,x) = l_0(x), & x \in \Gamma, \\ p(0,x) = p_0(x), & x \in \Gamma_2. \end{cases} \tag{4.3}$$

Intuitively and according to the numerical example Fig. 6, we expect from the second equation in (4.3) that in the limit $\xi \to +\infty$ the concentration $p(t,x)$ of phosphorylated Lgl on the boundary $\Gamma_2$ tends to zero for any positive time since all the $p$-Lgl on the active part of the cell cortex part is instantaneously released into the cytoplasm and becomes $P$-Lgl.

However, if the initial $p$-Lgl concentration is non-zero, i.e. $p_0(x) \neq 0$, an initial layer at $t = 0$ will be forming in the limit $\xi \to +\infty$, which expresses the transfer of initial mass of $p_0$ into $P_0$ (see also Figure 7 for a numerical example).

Thus, the expected limiting system has the following form:

$$\begin{cases} L_t - d_L \Delta L = -\beta L + \alpha P, & x \in \Omega, \quad t > 0, \\ d_L \frac{\partial L}{\partial \nu} = -\lambda L + \gamma l, & x \in \Gamma, \quad t > 0, \\ L(0,x) = L_0(x), & x \in \Omega, \end{cases} \tag{4.4}$$

$$\begin{cases} P_t - d_P \Delta P = \beta L - \alpha P, & x \in \Omega, \quad t > 0, \\ d_P \frac{\partial P}{\partial \nu} = \chi_{\Gamma_2} \sigma l, & x \in \Gamma, \quad t > 0, \\ P(0,x) = P_0(x) + P^*(x), & x \in \Omega, \end{cases} \tag{4.5}$$

and

$$\begin{cases} l_t = \lambda L - (\gamma + \sigma\chi_{\Gamma_2})l, & x \in \Gamma, \quad t > 0, \\ l(0,x) = l_0(x), & x \in \Gamma, \end{cases} \tag{4.6}$$

where we emphasise that $P^*$ is the unique function in $L^2(\Omega)$, which satisfies

$$\int_\Omega P^* \varphi \, dx = \int_{\Gamma_2} p_0 \varphi \, dS, \qquad \forall \varphi \in H^1(\Omega). \tag{4.7}$$

Note that the system (4.4)–(4.6) corresponds to the reaction dynamics represented by the right diagram in Figure 9.

**Remark 4.1** (Common Stationary States of Full System and QSSA)**.**
*We point out that the system* (4.1)*–*(4.3) *and the QSSA system* (4.4)*–*(4.6) *with condition* (4.7) *share the same stationary state* $(L_\infty, P_\infty, l_\infty)$*. This is a consequence of the fact that the systems* (4.1)*–*(4.3) *and* (4.4)*–*(4.6) *satisfying the same stationary state system (see* (4.8) *below) and that condition* (4.7) *ensure identical initial total mass.*

*Indeed, it follows from* (4.3) *that* $\xi p_\infty = \sigma l_\infty$ *and* $\lambda L_\infty = (\gamma + \sigma\chi_{\Gamma_2})l_\infty$*. Inserting these two relations into* (4.1)*–*(4.2) *yields the stationary state system*

$$\begin{cases} -d_L \Delta L_\infty = -\beta L_\infty + \alpha P_\infty, & x \in \Omega, \\ -d_P \Delta P_\infty = \beta L_\infty - \alpha P_\infty, & x \in \Omega, \\ d_L \frac{\partial L_\infty}{\partial \nu} = -\frac{\sigma\lambda}{\gamma+\sigma} L_\infty, & x \in \Gamma_2, \\ d_L \frac{\partial L_\infty}{\partial \nu} = 0, & x \in \Gamma \setminus \Gamma_2, \\ d_P \frac{\partial P_\infty}{\partial \nu} = \frac{\sigma\lambda}{\gamma+\sigma} L_\infty, & x \in \Gamma_2, \\ d_P \frac{\partial P_\infty}{\partial \nu} = 0, & x \in \Gamma \setminus \Gamma_2, \end{cases} \tag{4.8}$$

*which is also the stationary state system of the QSSA system* (4.4)*–*(4.6)*. In fact, by solving* (4.8) *the stationary concentration* $l_\infty$ *and* $p_\infty$ *are afterwards calculated from* $L_\infty$ *and* $P_\infty$ *for both systems* (4.1)*–*(4.3) *and* (4.4)*–*(4.6)*.*

*Moreover, the stationary state system* (4.8) *can be solved by observing that*

$$\begin{cases} -\Delta(d_L L_\infty + d_P P_\infty) = 0, & x \in \Omega, \\ \frac{\partial}{\partial \nu}\big(d_L L_\infty + d_P P_\infty\big) = 0, & x \in \Gamma. \end{cases} \tag{4.9}$$

*Thus, the sum* $d_L L_\infty + d_P P_\infty = C$ *equals a constant* $C$ *for all* $x \in \Omega$ *and the stationary state concentrations* $L_\infty$ *or* $P_\infty$*, respectively are obtained by solving an inhomogeneous linear elliptic boundary value problem with mixed Neumann/Robin boundary data. For instance, the equilibrium concentration* $L_\infty$ *satisfies*

$$\begin{cases} -d_L \Delta L_\infty + \big(\beta + \alpha \frac{d_L}{d_P}\big) L_\infty = \alpha \frac{C}{d_P}, & x \in \Omega, \\ d_L \frac{\partial L_\infty}{\partial \nu} = -\frac{\sigma\lambda}{\gamma+\sigma} L_\infty, & x \in \Gamma_2, \\ d_L \frac{\partial L_\infty}{\partial \nu} = 0, & x \in \Gamma \setminus \Gamma_2, \end{cases} \tag{4.10}$$

*The stationary state* $L_\infty$ *is unique for fixed constants* $C$*, since the difference* $\hat{L}_\infty$ *of two such steady state solutions satisfies a homogeneous version of* (4.10) *with* $C = 0$*, which has only the trivial solution. Indeed, when testing* (4.10) *for* $C = 0$ *with* $\hat{L}_\infty$*, we see that any solution* $\hat{L}_\infty$ *has to satisfy*

$$d_L \int_\Omega \big|\nabla \hat{L}_\infty\big|^2 dx + \frac{\sigma\lambda}{\gamma + \sigma} \int_{\Gamma_2} \hat{L}_\infty^2 \, dS + \left(\beta + \alpha \frac{d_L}{d_P}\right) \int_\Omega \hat{L}_\infty^2 \, dx = 0,$$

*which implies* $\hat{L}_\infty = 0$.

*Moreover, the constant* $C$ *is itself determined by the conserved initial total mass. As a consequence, since the system* (4.1)–(4.3) *and its QSSA system*(4.4)–(4.6) *with the condition* (4.7) *share by construction the same initial total mass, the corresponding stationary states are identical.*

In the following, we will show that solutions to (4.1)–(4.3) converge towards solutions of the QSSA system (4.4)–(4.6) as $\xi \to +\infty$.

We will denote by $C$ a generic constant, which only depends on the initial data, all diffusion and reaction rates, yet with the *explicit exception of the reaction rate* $\xi$. Moreover, $C_T$ is such a constant, which additionally depends on the time interval size $T > 0$. For any given $T > 0$ and $q \geq 1$, we shall denote

$$\Omega_T := [0,T] \times \Omega, \qquad \Gamma_T := [0,T] \times \Gamma, \qquad \Gamma_{2T} := [0,T] \times \Gamma_2.$$

The spaces $L^q(\Omega_T)$, $L^q(\Gamma_T)$ or $L^q(\Gamma_{2T})$ will be extensively used with usual norms, for example,

$$\|f\|_{L^2(\Omega_T)} = \left( \int_0^T \|f(t)\|^2_{L^2(\Omega)} dt \right)^{1/2}.$$

The following Lemma provides some crucial *a priori* estimates, which will allow to pass to the limit $\xi \to +\infty$.

**Lemma 4.1** (Uniform in $\xi$ Boundedness of Solutions to the Original System)**.** *For any* $T > 0$*, the solution* $(L, P, l, p)$ *to system* (4.1)–(4.3) *satisfies the following estimates:*

$$\|L\|_{L^2(\Omega_T)} + \|P\|_{L^2(\Omega_T)} + \|l\|_{L^2(\Gamma_T)} \leq C_T, \tag{4.11}$$

*and*

$$\|L\|_{L^2(0,T;H^1(\Omega))} \leq C_T. \tag{4.12}$$

*Proof.* By setting $Z = L + P$ and $W = d_L L + d_P P$, we get from the non-negativity of $L$ and $P$ that

$$0 < \min\{d_L, d_P\} \leq \frac{W}{Z} \leq \max\{d_L, d_P\} < +\infty.$$

It follows from (4.1)–(4.2) that

$$\begin{cases} Z_t - \Delta W = 0, & x \in \Omega, \quad t > 0, \\ \frac{\partial W}{\partial \nu} = -\lambda L + \gamma l + \chi_{\Gamma_2} \xi p, & x \in \Gamma, \quad t > 0. \end{cases} \tag{4.13}$$

We integrate the first equation in (4.13) over $(0, t)$ and take then the inner product with $W(t)$ in $L^2(\Omega)$ to get

$$\int_\Omega W(t)[Z(t) - Z(0)]\, dx + \int_\Omega \nabla W(t) \cdot \nabla \int_0^t W(s)\, ds dx$$
$$= \int_\Gamma W(t) \int_0^t (-\lambda L + \gamma l + \chi_{\Gamma_2} \xi p)\, ds dS. \tag{4.14}$$

In order to estimate the right hand side of (4.14), we observe from (4.3) that

$$-\lambda L + \gamma l + \chi_{\Gamma_2} \xi p = -(l + \chi_{\Gamma_2} p)_t. \tag{4.15}$$

Thus, from (4.14) and (4.15), we have

$$\int_\Omega W(t)[Z(t)-Z(0)]\,dx + \int_\Omega \nabla W(t)\cdot\nabla\int_0^t W(s)\,dsdx = -\int_\Gamma W(t)[l(t)-l(0)]\,dS - \int_{\Gamma_2} W(t)[p(t)-p(0)]\,dS. \quad (4.16)$$

In the following, we shall denote by $\phi(t,x) := \int_0^t W(s,x)ds$, which implies $\partial_t\phi(t) = W(t)$. Therefore, we calculate

$$\int_\Omega \nabla W(t)\cdot\nabla\int_0^t W(s)\,dsdx = \int_\Omega \nabla\partial_t\phi(t)\cdot\nabla\phi(t)\,dx = \frac{1}{2}\int_\Omega \frac{\partial}{\partial t}|\nabla\phi(t)|^2\,dx.$$

As a consequence, integration of (4.16) in $t$ over $(0,T)$ yields

$$\int_{\Omega_T} WZ\,dsdx + \int_{\Gamma_T} Wl\,dsdS + \int_{\Gamma_{2T}} Wp\,dsdS + \frac{1}{2}\int_\Omega \big|\nabla\phi(T)\big|^2\,dx = \int_{\Omega_T} WZ(0)\,dsdx + \int_{\Gamma_T} Wl(0)\,dsdS + \int_{\Gamma_{2T}} Wp(0)\,dsdS, \quad (4.17)$$

where we have uses that $\int_0^T\int_\Omega \frac{\partial}{\partial t}|\nabla\phi(t)|^2\,dxdt = \int_\Omega \big|\nabla\phi(T)\big|^2 dx$ since $\phi(0)=0$.

Next, by Young's inequality, we have

$$\|\phi(T)\|_\Omega^2 = \int_\Omega\left|\int_0^T W(s,x)ds\right|^2 dx \le T\int_\Omega\int_0^T |W(s,x)|^2\,dsdx = T\|W\|^2_{L^2(\Omega_T)}.$$

Considering the right hand side of (4.17), we estimate in the following by Cauchy's, Young's and a Trace inequality that

$$\int_{\Omega_T} WZ(0)\,dsdx \le \sqrt{T}\|W\|_{L^2(\Omega_T)}\|Z(0)\|_\Omega, \quad (4.18)$$

and

$$\begin{aligned}\int_{\Gamma_T} Wl(0)\,dsdS &= (\phi(T),l(0))_\Gamma \le \|l(0)\|_\Gamma\|\phi(T)\|_\Gamma \\ &\le \|l(0)\|_\Gamma(C\|\nabla\phi(T)\|_\Omega + \|\phi(T)\|_\Omega) \\ &\le \frac{1}{8}\|\nabla\phi(T)\|^2_\Omega + C\|l(0)\|^2_\Gamma + \sqrt{T}\|l(0)\|_\Gamma\|W\|_{L^2(\Omega_T)},\end{aligned} \quad (4.19)$$

and similarly,

$$\int_{\Gamma_{2T}} Wp(0)\,dsdS \le \frac{1}{8}\|\nabla\phi(T)\|^2_\Omega + C\|p(0)\|^2_{\Gamma_2} + \sqrt{T}\|p(0)\|_{\Gamma_2}\|W\|_{L^2(\Omega_T)}. \quad (4.20)$$

Hence, by the non-negativity of $L,P,l,p$, we obtain from (4.17)–(4.20)

$$\int_{\Omega_T} WZ\,dsdx + \frac{1}{4}\int_\Omega\big|\nabla\phi(T)\big|^2\,dx \le \sqrt{T}(\|Z(0)\|_\Omega + \|l(0)\|_\Gamma + \|p(0)\|_{\Gamma_2})\|W\|_{L^2(\Omega_T)} + C(\|l(0)\|^2_\Gamma + \|p(0)\|^2_{\Gamma_2}) \quad (4.21)$$

It follows then from $W \le \max\{d_L, d_P\}Z$ that

$$\|W\|^2_{L^2(\Omega_T)} \le \max\{d_L,d_P\}\int_{\Omega_T} WZ\,dsdx \le C_T\|W\|_{L^2(\Omega_T)} + C, \quad (4.22)$$

and the linearity of the right hand side implies by Young's inequality that

$$\|W\|_{L^2(\Omega_T)} \le C_T. \tag{4.23}$$

Therefore, by the non-negativity of $L$ and $P$ and by keeping in mind that $W = d_L L + d_P P$, we conclude that

$$\|L\|_{L^2(\Omega_T)} + \|P\|_{L^2(\Omega_T)} \le C_T. \tag{4.24}$$

Next, by testing (4.1) with $L$, we estimate

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}\|L\|_\Omega^2 + d_L\|\nabla L\|_\Omega^2 &= -\beta\|L\|_\Omega^2 + \alpha\int_\Omega LP\,dx - \lambda\|L\|_\Gamma^2 + \gamma\int_\Gamma Ll\,dS \\ &\le C\|P\|_\Omega^2 + C\|l\|_\Gamma^2 - \frac{\lambda}{2}\|L\|_\Gamma^2. \end{aligned} \tag{4.25}$$

On the other hand, we get from (4.3)

$$\frac{1}{2}\frac{d}{dt}\|l\|_\Gamma^2 = -\gamma\|l\|_\Gamma^2 - \sigma\|l\|_{\Gamma_2}^2 + \lambda\int_\Gamma Ll\,dS \le C\|l\|_\Gamma^2 + \frac{\lambda}{2}\|L\|_\Gamma^2. \tag{4.26}$$

Summing (4.25) and (4.26) yields

$$\frac{d}{dt}(\|L\|_\Omega^2 + \|l\|_\Gamma^2) + 2d_L\|\nabla L\|_\Omega^2 \le C\|P\|_\Omega^2 + C\|l\|_\Gamma^2. \tag{4.27}$$

Therefore, by $\|L\|_{L^2(\Omega_T)} + \|P\|_{L^2(\Omega_T)} \le C_T$, we conclude that

$$\|\nabla L\|_{L^2(\Omega_T)} \le C_T$$

and

$$\|l\|_{L^2(\Gamma_T)} \le C_T\, e^{CT} \le C_T. \tag{4.28}$$

This finishes the proof. □

**Remark 4.2.** *The proof applied in Lemma 4.1 fails when trying to include one of the surface diffusion terms $\Delta_\Gamma l$ or $\Delta_{\Gamma_2} p$ because in these cases, the formulation* (4.17) *would have additional terms $\int_\Gamma \nabla_\Gamma W(t)\cdot\nabla\int_0^t l(s)\,dsdS$ or $\int_{\Gamma_2}\nabla_{\Gamma_2}W(t)\cdot\nabla_{\Gamma_2}\int_0^t p(s)\,dsdS$, for which we do not know a sign or suitable a priori estimates. The problem of the QSSA for system* (1.1)–(1.3) *with surface diffusion remains open for future work.*

From now on, we always denote the solution to (4.1)–(4.3) by $(L^\xi, P^\xi, l^\xi, p^\xi)$ in order to emphasise the dependency on the reaction rate $\xi$.

In the next Lemma, we will show that the concentration $p^\xi$ of the phosphorylated Lgl on the active boundary $\Gamma_2$ tends to zero as $\xi \to +\infty$ in $L^2(\Gamma_{2T})$. Since $p^\xi(0) = p_0 \in L^2(\Gamma_2)$, we cannot expect that $p^\xi \to 0$ in $C([0,T]; L^2(\Gamma_2))$. Nevertheless, we will be able to show that $p^\xi \to 0$ in $C((0,T]; L^2(\Gamma_2))$.

**Lemma 4.2.** *For any $T > 0$, we have*

$$p^\xi \xrightarrow{\xi\to+\infty} 0 \quad \text{in} \quad L^2(\Gamma_{2T}) \cap C((0,T]; L^2(\Gamma_2)).$$

*Proof.* By multiplying the equation (4.3) of $p^\xi$, i.e. $\partial_t p^\xi + \xi p^\xi = \sigma l^\xi$ with $\xi p^\xi$ and integrating over $\Gamma_2$, we estimate

$$\frac{\xi}{2}\frac{d}{dt}\|p\|_{\Gamma_2}^2 + \xi^2\|p^\xi\|_{\Gamma_2}^2 = (\sigma l^\xi, \xi p^\xi)_{\Gamma_2} \le \frac{\sigma^2}{2}\|l^\xi\|_{\Gamma_2}^2 + \frac{\xi^2}{2}\|p^\xi\|_{\Gamma_2}^2.$$

Therefore,

$$\xi \frac{d}{dt}\|p^\xi\|_{\Gamma_2}^2 + \xi^2\|p^\xi\|_{\Gamma_2}^2 \le \sigma^2\|l^\xi\|_{\Gamma_2}^2 \le \sigma^2\|l^\xi\|_{\Gamma}^2,$$

and integration over $(0,T)$ yields

$$\frac{1}{\xi}\|p^\xi(T)\|_{\Gamma_2}^2 + \int_0^T \|p^\xi(s)\|_{\Gamma_2}^2\, ds \le \frac{1}{\xi}\|p_0\|_{\Gamma_2}^2 + \frac{\sigma^2}{\xi^2}\int_0^T \|l^\xi(s)\|_{\Gamma}^2\, ds. \tag{4.29}$$

This implies that $\|p^\xi\|_{\Gamma_{2T}}^2 = O(\xi^{-1})$ and $p^\xi \to 0$ in $L^2(\Gamma_{2T})$ as $\xi \to +\infty$ since $\{l^\xi\}_{\xi>0}$ is uniformly bounded in $L^2(\Gamma_T)$ according to Lemma 4.1.

From (4.3), we also have similar

$$\frac{d}{dt}\|p^\xi\|_{\Gamma_2}^2 + 2\xi\|p^\xi\|_{\Gamma_2}^2 = 2\sigma(l^\xi, p^\xi)_{\Gamma_2}.$$

Hence, for any fixed $0 < t_0 \le t \le T$, we have

$$\begin{aligned}
\|p^\xi(t)\|_{\Gamma_2}^2 &\le e^{-2\xi t}\|p_0\|_{\Gamma_2}^2 + 2\sigma e^{-2\xi t}\int_0^t e^{2\xi s}(l^\xi, p^\xi)_{\Gamma_2} ds \\
&\le e^{-2\xi t_0}\|p_0\|_{\Gamma_2}^2 + 2\sigma\int_0^T (l^\xi, p^\xi)_{\Gamma_2}\, ds \\
&\le e^{-2\xi t_0}\|p_0\|_{\Gamma_2}^2 + 2\sigma\|l^\xi\|_{L^2(\Gamma_T)}\|p^\xi\|_{L^2(\Gamma_{2T})}.
\end{aligned}$$

In the limit $\xi \to +\infty$ and by using $\|p^\xi\|_{\Gamma_{2T}} \to 0$ and $\{l^\xi\}_{\xi>0}$ is bounded in $L^2(\Gamma_T)$, we have thus $p^\xi \to 0$ in $C([t_0,T]; L^2(\Gamma_2))$ for all $t_0 > 0$. □

**Lemma 4.3.** *There exists $L \in L^2(\Omega_T)$ and $l \in L^2(\Gamma_T)$ such that, when $\xi \to +\infty$*

$$L^\xi \xrightarrow{\xi\to+\infty} L \quad \textit{in} \quad L^2(\Omega_T) \tag{4.30}$$

*and*

$$l^\xi \xrightarrow{\xi\to+\infty} l \quad \textit{in} \quad L^2(\Gamma_T). \tag{4.31}$$

*Proof.* By Lemma 4.1, we have that $\{L^\xi\}_{\xi>0}$ is bounded in $L^2(0,T;H^1(\Omega))$. Thus, by using (4.1), we have $\{\partial_t L^\xi\}_{\xi>0}$ is bounded in $L^2(0,T;H^{-1}(\Omega))$ and the Aubin-Lions compactness lemma implies that $\{L^\xi\}_{\xi>0}$ is precompact in $L^2(\Omega_T)$. Thus,

$$L^\xi \xrightarrow{\xi\to+\infty} L \quad \text{in} \quad L^2(\Omega_T)$$

for some $L \in L^2(\Omega_T)$ and up to a subsequence. By using that $\{L^\xi\}_{\xi>0}$ is bounded in $L^2(0,T;H^1(\Omega))$ and by a standard Trace Theorem (see e.g. [20]), we have $\{L^\xi|_\Gamma\}_{\xi>0}$ is also bounded in $L^2(0,T;H^{1/2}(\Gamma))$. Therefore, it follows from

$$l_t^\xi = \lambda L^\xi - (\gamma + \sigma\chi_{\Gamma_2})l^\xi$$

that $\{l^\xi\}_{\xi>0}$ is bounded in $L^2(0,T;H^{1/2}(\Gamma))$ and $\{l_t^\xi\}_{\xi>0}$ is bounded in $L^2(\Gamma_T)$. Using again the Aubin-Lions compactness lemma, we have

$$l^\xi \xrightarrow{\xi\to+\infty} l \quad \text{in} \quad L^2(\Gamma_T)$$

for some $l \in L^2(\Gamma_T)$ and up to a subsequence. □

By Lemma 4.3, we have so far established the strong convergence of $L^\xi, l^\xi$ and $p^\xi$ in $L^2(\Omega_T)$, $L^2(\Gamma_T)$ and $L^2(\Gamma_{2T})$, respectively.

The convergence of $P^\xi$ constitutes a more difficult problem due to the singularity of the boundary flux $d_P\partial P^\xi/\partial\nu = \chi_{\Gamma_2}\xi p^\xi$. As an example to illustrate the, we may attempt a similar approach like in Lemma 4.1, which succeeded in proving the bound (4.12): By testing with $P^\xi$

$$\begin{cases} P^\xi_t - d_P \Delta P^\xi = \beta L^\xi - \alpha P^\xi, \\ d_P \frac{\partial P^\xi}{\partial \nu} = \chi_{\Gamma_2} \xi p^\xi, \end{cases}$$

we get after direct computations that

$$\|P^\xi(T)\|^2_\Omega + d_P \int_0^T \|\nabla P^\xi\|^2_\Omega \, ds = \|P_0\|^2_\Omega + \int_0^T (\beta L^\xi - \alpha P^\xi, P^\xi)_\Omega \, ds + \xi \int_0^T (P^\xi, p^\xi)_{\Gamma_2} \, ds. \quad (4.32)$$

Due to the boundedness of $L^\xi, P^\xi$ in $L^2(\Omega_T)$, we would need the uniform boundedness of $\xi \int_0^T (P^\xi, p^\xi)_{\Gamma_2} ds$ in order to prove a uniform control of the left hand side of (4.32). A uniform bound on right hand side of (2.5) seems thus to requires a uniform bound of $\xi \|p^\xi\|_{L^2(\Gamma_{2T})}$ or equivalently $\|p^\xi\|_{L^2(\Gamma_{2T})} \to 0$ when $\xi \to +\infty$ with the rate $1/\xi$. However, Lemma 4.2 implies only the decay rate of $\|p^\xi\|_{\Gamma_{2T}} = O(1/\sqrt{\xi})$.

However, we notice that (4.3) implies

$$\begin{aligned} \xi \|p^\xi\|_{L^1(\Gamma_{2T})} &= \int_0^T \int_{\Gamma_2} \xi p^\xi(t) \, dS dt = \int_0^T \int_{\Gamma_2} (\sigma l^\xi - \partial_t p^\xi) \, dS dt \\ &= \|p_0\|_{L^1(\Gamma_2)} - \|p^\xi(T)\|_{L^1(\Gamma_2)} + \sigma \int_0^T \|l^\xi\|_{L^1(\Gamma_2)} dt \\ &\le \|p_0\|_{L^1(\Gamma_2)} + C\sigma \|l^\xi\|_{L^2(\Gamma_T)} \le C_T. \end{aligned} \quad (4.33)$$

and the uniform $L^1$-bound (4.33) will be used in Lemma 4.5 below to obtain the compactness of $\{P^\xi\}_{\xi>0}$ in $L^1(\Omega_T)$ and even in $L^1(0,T; W^{1,1}(\Omega))$. The proof of Lemma 4.5 is based on Lemma 4.4, which is similar to results given in [7] and [5], yet for homogeneous boundary conditions. The proof of Lemma 4.4 is based on a duality argument and will given in the Appendix of the sake of completeness.

**Remark 4.3.** *We conjecture that it should actually be possible for solutions of system* (4.4)–(4.6) *to prove the boundedness of $P^\xi_{\xi>0}$ in $L^2(0,T;H^1(\Omega))$ uniformly in $\xi$ and hence the convergence of $P^\xi$ in $L^2(\Omega_T)$ (thus improving Lemma 4.5 and Theorem 4.6 below). Unfortunately, the singularity of boundary flux $\chi_{\Gamma_2}\xi p^\xi$ as $\xi \to +\infty$ prevents currently to establish such an $L^2$-control in the same manner as for $L^\xi$.*

*More precisely, eq.* (4.32) *suggest that it is necessary (or at least sufficient) to show $\|p^\xi\|_{\Gamma_{2T}} = O(1/\xi)$ as $\xi \to +\infty$. While estimate* (4.29) *implies at first only $\|p^\xi\|_{\Gamma_{2T}} = O(1/\sqrt{\xi})$, it also allows to improve this rate for positive times via an iterative procedure: By considering the time interval $(0, 1/3)$, for instance, eq.* (4.29) *implies that exists a time $\theta_1 \in (0, 1/3)$, such that*

$$\|p^\xi(s)\|^2_{\Gamma_2}(\theta_1) \le O(\xi^{\alpha_1}), \qquad \text{for} \quad \alpha_1 > -1.$$

*Otherwise, eq.* (4.29) *would yield the following contradiction as $\xi \to +\infty$*

$$O(\xi^{\alpha_1}) \le \xi^{-1} \|p_0\|^2_{\Gamma_2} + \xi^{-2} C_T, \quad (4.34)$$

*where $C_T$ is given in* (4.28).

*Next, by regarding* (4.29) *on the time-interval* $(\theta_1, 2/3)$*, we obtain similar that there exists a time* $\theta_2 < 2/3$ *such that*

$$\|p^\xi(s)\|^2_{\Gamma_2}(\theta_2) \le O(\xi^{\alpha_2}), \qquad \textit{for} \quad \alpha_2 > \alpha_1 - 1 > -2,$$

*and an final iteration on the time-interval* $(\theta_2, 1)$ *yields a time* $\theta_3 < 1$ *such that*

$$\|p^\xi(s)\|^2_{\Gamma_2}(\theta_3) \le O(\xi^{\alpha_3}), \qquad \textit{for} \quad \alpha_3 > \max\{\alpha_2 - 1, -2\} > -2.$$

*We are thus only able to prove that* $\|p^\xi\|_{L^2([1,T]\times\Gamma)} = O(\xi^\beta)$ *for any* $\beta > -1$*, but we* do not recover *the critical rate* $\beta = -1$*, which would be needed for the boundedness of* $P^\xi_{\xi>0}$ *in* $L^2(0,T;H^1(\Omega))$ *uniformly in* $\xi$*.*

*In fact, we* would be able to recover the critical rate $\beta = -1$ *(at least for large enough times) if we could improve the exponentially growing bound of* $\|l(t)\|_{L^2(\Gamma_T)}$ *as shown in* (4.28) *to a uniform-in-time bound* $\|l(t) - l_\infty\|_{L^2(\Gamma_T)} \le C$*. Such a uniform* $L^2$*-bound would allow to set* $\alpha_3 = -2$ *and still get a contradiction like in* (4.34) *at least after for large enough times* $T > 0$*:*

$$T\,O(\xi^{-2}) \le O(\xi^{\alpha_2 - 1}) + \xi^{-2}C.$$

*Thus, we emphasise that proving the boundedness of* $P^\xi_{\xi>0}$ *in* $L^2(0,T;H^1(\Omega))$ *uniformly in* $\xi$ *seems to be linked to proving that solutions of* (4.4)–(4.6) *converge to a bounded stationary state in a sufficiently good norm such as e.g.* $\|l(t) - l_\infty\|_{L^2(\Gamma_T)} \le C$*. However, proving such a convergence to equilibrium (which was successfully done via entropy methods, for instance, in* [12, 13, 14, 15] *for reaction-diffusion systems or in* [1] *for a nonlinear surface-volume reaction-diffusion system of two equations) is a difficult problem for systems like* (4.4)–(4.6) *and currently under investigation as work in progress.*

**Lemma 4.4.** *The mapping* $\mathfrak{T} : (w_0, \Theta, g) \to (w, \nabla w)$*, where* $w$ *is the solution of*

$$\begin{cases} w_t - d_P \Delta w = \Theta, & x \in \Omega, \quad t > 0, \\ d_P \partial w/\partial \nu = g, & x \in \Gamma, \quad t > 0, \\ w(0,\cdot) = w_0, & x \in \Omega, \end{cases} \tag{4.35}$$

*is compact from* $L^1(\Omega) \times L^1(\Omega_T) \times L^1(\Gamma_T)$ *into* $L^1(\Omega_T) \times (L^1(\Omega_T))^N$*.*

Applying Lemma 4.4 to $w = P^\xi$, $\Theta = \beta L^\xi - \alpha P^\xi$ and $g = \chi_{\Gamma_2}\xi p^\xi$ leads to

**Lemma 4.5.** *The sequence* $\{P^\xi\}_{\xi>0}$ *is pre-compact in* $L^1(0,T;W^{1,1}(\Omega))$*. In other words, there exists* $P \in L^1(0,T;W^{1,1}(\Omega))$ *such that up to a subsequence*

$$P^\xi \xrightarrow{\xi\to+\infty} P \quad \textit{strongly in} \quad L^1(0,T;W^{1,1}(\Omega)) \quad \textit{and weakly in} \quad L^2(\Omega_T),$$

*due to Lemma 4.1.*

**Remark 4.4.** *The proof of Lemma 4.4 as stated in the Appendix shows actually that the mapping* $\mathfrak{T}$ *is indeed compact from* $L^1(\Omega)\times L^1(\Omega_T)\times L^1(\Gamma_T)$ *into* $L^r(\Omega_T)\times (L^s(\Omega_T))^N$ *for any* $r < \frac{N+2}{N}$ *and* $s < \frac{N+2}{N+1}$*. Thus, depending on the space dimension* $N$*, the convergence in Lemma 4.5 could be somewhat improved.*

The following Theorem is the main result of this section.

**Theorem 4.6** (Convergence of the QSSA)**.**
*For any* $(L_0, P_0, l_0, p_0) \in L^2(\Omega) \times L^2(\Omega) \times L^2(\Gamma) \times L^2(\Gamma_2)$ *and any* $T > 0$*, we have*

$$L^\xi \xrightarrow{\xi\to+\infty} L \quad \textit{strongly in} \quad L^2(\Omega_T) \quad \textit{and weakly in} \quad L^2(0,T;H^1(\Omega)),$$

$$P^\xi \xrightarrow{\xi\to+\infty} P \quad \textit{strongly in} \quad L^1(0,T;W^{1,1}(\Omega)) \quad \textit{and weakly in} \quad L^2(\Omega_T),$$

$$l^\xi \xrightarrow{\xi\to+\infty} l \quad \textit{strongly in} \quad L^2(\Gamma_T),$$

*and*

$$p^\xi \xrightarrow{\xi\to+\infty} 0 \quad \textit{strongly in} \quad L^2(\Gamma_{2T}) \cap C((0,T];L^2(\Gamma_2)),$$

*up to a subsequence, where $(L,P,l)$ is the unique weak solution to (4.4)–(4.6).*

**Remark 4.5.** *The well-posedness of system (4.4)–(4.6) can be shown in the same way as for system (1.1)–(1.3) in Section 2.*

*Proof.* All the limits are already proven in the Lemmata 4.2, 4.3 and 4.5. It remains to show that the limit $(L,P,l)$ in Lemma 4.3 is the unique solution of system (4.4)–(4.6). Indeed, by testing

$$\begin{cases} L^\xi_t - d_L\Delta L^\xi = -\beta L^\xi + \alpha P^\xi, & x\in\Omega, \quad t>0,\\ d_L\frac{\partial L^\xi}{\partial\nu} = -\lambda L^\xi + \gamma l^\xi, & x\in\Gamma, \quad t>0,\\ L^\xi(0,x) = L_0(x), & x\in\Omega, \end{cases}$$

with $\varphi\in C^1([0,T];H^1(\Omega))$, $\varphi(T)=0$ and by integration over $\Omega_T$, we have

$$\begin{aligned} &-\int_0^T (L^\xi,\varphi_t)_\Omega\,ds + d_L\int_0^T(\nabla L^\xi,\nabla\varphi)_\Omega\,ds\\ &\quad= (L_0,\varphi(0))_\Omega + \int_0^T(-\lambda L^\xi+\gamma l^\xi,\varphi)_\Gamma\,ds + \int_0^T(-\beta L^\xi+\alpha P^\xi,\varphi)_\Omega\,ds. \end{aligned} \tag{4.36}$$

Since $L^\xi\to L$ and $P^\xi \rightharpoonup P$ in $L^2(\Omega_T)$ as $\xi\to+\infty$, we have

$$-\int_0^T (L^\xi,\varphi_t)_\Omega\,ds \xrightarrow{\xi\to+\infty} -\int_0^T(L,\varphi_t)_\Omega\,ds \tag{4.37}$$

and

$$\int_0^T(-\beta L^\xi+\alpha P^\xi,\varphi)_\Omega\,ds \xrightarrow{\xi\to+\infty} \int_0^T(-\beta L+\alpha P,\varphi)_\Omega\,ds. \tag{4.38}$$

By Lemma 4.1, $\{L^\xi\}_{\xi>0}$ is bounded in $L^2(0,T;H^1(\Omega))$ and together with (4.30), we get

$$L^\xi \rightharpoonup L \quad \text{in} \quad L^2(0,T;H^1(\Omega)) \tag{4.39}$$

up to a subsequence. Thus,

$$d_L\int_0^T(\nabla L^\xi,\nabla\varphi^\xi)_\Omega ds \xrightarrow{\xi\to+\infty} d_L\int_0^T(\nabla L,\nabla\varphi)_\Omega ds. \tag{4.40}$$

By using the Trace Theorem and (4.39), we have

$$L^\xi \rightharpoonup L \quad \text{in} \quad L^2(\Gamma_T).$$

In combination with (4.31), this yields

$$\int_0^T(-\lambda L^\xi+\gamma l^\xi,\varphi)_\Gamma ds \xrightarrow{\xi\to+\infty} \int_0^T(-\lambda L+\gamma l,\varphi)_\Gamma ds. \tag{4.41}$$

From (4.37)–(4.41), we can pass to the limit in (4.36) as $\xi \to +\infty$ and obtain

$$-\int_0^T (L, \varphi_t)_\Omega \, ds + d_L \int_0^T (\nabla L, \nabla \varphi)_\Omega \, ds$$
$$= (L_0, \varphi(0))_\Omega + \int_0^T (-\lambda L + \gamma l, \varphi)_\Gamma \, ds + \int_0^T (-\beta L + \alpha P, \varphi)_\Omega \, ds \quad (4.42)$$

or equivalently that $L$ is a weak solution of

$$\begin{cases} L_t - d_L \Delta L = -\beta L + \alpha P, & x \in \Omega, \quad t > 0, \\ d_L \frac{\partial L}{\partial \nu} = -\lambda L + \gamma l, & x \in \Gamma, \quad t > 0, \\ L(0, x) = L_0(x), & x \in \Omega. \end{cases} \quad (4.43)$$

Next, by taking the inner product of

$$p_t^\xi = \sigma l^\xi - \xi p^\xi$$

with test-functions $\psi \in C^1(0, T; L^2(\Gamma_2))$ satisfying $\psi(T) = 0$, we get

$$-\int_0^T (p^\xi, \psi_t)_{\Gamma_2} \, ds = (p_0, \psi(0))_{\Gamma_2} + \int_0^T (\sigma l^\xi, \psi)_{\Gamma_2} \, ds - \int_0^T (\xi p^\xi, \psi)_{\Gamma_2} \, ds. \quad (4.44)$$

In order to pass to the limit $\xi \to +\infty$ in (4.44), we apply Lemma 4.2 and Lemma 4.3 and obtain

$$\lim_{\xi \to +\infty} \int_0^T (\xi p^\xi, \psi)_{\Gamma_2} ds = (p_0, \psi(0))_{\Gamma_2} + \int_0^T (\sigma l, \psi)_{\Gamma_2} ds. \quad (4.45)$$

In the following, we consider equation for $P^\xi$ in the weak form, i.e.

$$-\int_0^T (P^\xi, \varphi_t)_\Omega \, ds + d_L \int_0^T (\nabla P^\xi, \nabla \varphi)_\Omega \, ds$$
$$= (P_0, \varphi(0))_\Omega + \int_0^T (\xi p^\xi, \varphi)_{\Gamma_2} \, ds + \int_0^T (\beta L^\xi - \alpha P^\xi, \varphi)_\Omega \, ds \quad (4.46)$$

for test-functions $\varphi \in C^1(0, T; C^1(\Omega))$ with $\varphi(T) = 0$. The following limits

$$-\int_0^T (P^\xi, \varphi_t)_\Omega \, ds \xrightarrow{\xi \to +\infty} -\int_0^T (P, \varphi_t)_\Omega \, ds, \quad (4.47)$$

$$d_L \int_0^T (\nabla P^\xi, \nabla \varphi)_\Omega \, ds \xrightarrow{\xi \to +\infty} d_L \int_0^T (\nabla P, \nabla \varphi)_\Omega \, ds \quad (4.48)$$

and

$$\int_0^T (\beta L^\xi - \alpha P^\xi, \varphi)_\Omega \, ds \xrightarrow{\xi \to +\infty} \int_0^T (\beta L - \alpha P, \varphi)_\Omega \, ds \quad (4.49)$$

are due to $L^\xi \to L$ and $P^\xi \to P$ in $L^1(0, T; W^{1,1}(\Omega))$. Pass to the limit $\xi \to +\infty$ in (4.46), we obtain with (4.45), (4.47), (4.48) and (4.49)

$$-\int_0^T (P, \varphi_t)_\Omega \, ds + d_L \int_0^T (\nabla P, \nabla \varphi)_\Omega \, ds$$
$$= (P_0, \varphi(0))_\Omega + (p_0, \varphi(0))_{\Gamma_2} + \int_0^T (\sigma l, \varphi)_{\Gamma_2} \, ds + \int_0^T (\beta L - \alpha P, \varphi)_\Omega \, ds$$
$$= (P_0 + P^*, \varphi(0))_\Omega + \int_0^T (\sigma l, \varphi)_{\Gamma_2} \, ds + \int_0^T (\beta L - \alpha P, \varphi)_\Omega \, ds, \quad (4.50)$$

where we have use (4.7). This means that $P$ is a weak solution of

$$\begin{cases} P_t - d_L\Delta P = \beta L - \alpha P, & x \in \Omega, \quad t > 0, \\ d_L\frac{\partial P}{\partial \nu} = \chi_{\Gamma_2}\sigma l, & x \in \Gamma, \quad t > 0, \\ P(0,x) = P_0(x) + P^*(x), & x \in \Omega. \end{cases} \tag{4.51}$$

Finally, by taking test-function $\psi \in C^1([0,T];L^2(\Gamma))$ with $\psi(T) = 0$ for

$$l^\xi_t = \lambda L^\xi - (\gamma + \chi_{\Gamma_2}\sigma)l^\xi,$$

we get

$$-\int_0^T (l^\xi, \psi_t)_\Gamma\, ds = (l_0, \psi(0))_\Gamma + \int_0^T (\lambda L^\xi, \psi)_\Gamma\, ds + \int_0^T [(\gamma l^\xi, \psi)_\Gamma + (\sigma l^\xi, \psi)_{\Gamma_2}]\, ds. \tag{4.52}$$

We use $L^\xi \rightharpoonup L$ and $l^\xi \rightharpoonup l$ in $L^2(\Gamma_T)$ to pass the limit $\xi \to +\infty$ in (4.52) and obtain

$$-\int_0^T (l, \psi_t)_\Gamma\, ds = (l_0, \psi(0))_\Gamma + \int_0^T (\lambda L, \psi)_\Gamma\, ds + \int_0^T [(\gamma l, \psi)_\Gamma + (\sigma l, \psi)_{\Gamma_2}]\, ds \tag{4.53}$$

or equivalently $l$ is a weak solution of

$$\begin{cases} l_t = \lambda L - (\gamma + \chi_{\Gamma_2}\sigma)l, & x \in \Gamma, \quad t > 0, \\ l(0,x) = l_0(x), & x \in \Gamma. \end{cases} \tag{4.54}$$

In conclusion, from (4.43), (4.51) and (4.54), $(L, P, l)$ is the unique weak solution to the system (4.4)–(4.6), where the well-posedness of weak solutions to (4.4)–(4.6) follows in the same way as for the full system (1.1)–(1.3) as shown in Section 2. □

## 5. Appendix

**The proof of Lemma 4.4, cf.** [5, 7]**.**

*Proof.* The prove of the Lemma is based on a duality argument. We shall denote by

$$\mathfrak{T}^* : (\Phi_i)_{0\le i\le N} \in C_0^\infty(\Omega) \times (C_0^\infty(\Omega_T))^N \to (z(0), z, z|_{\partial\Omega})$$

the adjoint operator $\mathfrak{T}^*$ of $\mathfrak{T}$, where $z$ is the solution of

$$\begin{cases} -z_t - d_P\Delta z = \Phi_0 - \sum_{1\le i\le N} \partial_{x_i}\Phi_i, \\ d_P\partial z/\partial\nu = 0, \\ z(T) = 0. \end{cases} \tag{5.1}$$

The adjointness can be checked by integration by parts: For $\Phi = (\Phi_i)_{1\le i\le N}$

$$\begin{aligned} \langle \mathfrak{T}^*(\Phi_0, \Phi), (w_0, \Theta, g)\rangle &= \langle (z(0), z, z|_\Gamma), (w_0, \Theta, g)\rangle \\ &= \int_\Omega z(0)w_0 + \int_{\Omega_T} z\Theta + \int_{\Gamma_T} zg \\ &= \int_\Omega z(0)w_0 + \int_{\Omega_T} z(w_t - d_P\Delta w) + \int_{\Gamma_T} zg \\ &= -\int_{\Omega_T} wz_t + d_P\int_{\Omega_T} \nabla w\nabla z \end{aligned}$$

by using (4.35) and after integration by parts. Further, with $\partial z/\partial\nu = 0$, we continue

$$\begin{aligned}\langle \mathfrak{T}^*(\Phi_0,\Phi),(w_0,\Theta,g)\rangle &= \int_{\Omega_T} -w(z_t + d_P\Delta z)\\ &= \int_{\Omega_T} -w(-\Phi_0 + \nabla\cdot\Phi)\\ &= \int_{\Omega_T} (\Phi_0 w + \Phi\nabla w) = \langle(\Phi_0,\Phi),(w_0,\nabla w)\rangle\\ &= \langle(\Phi_0,\Phi),\mathfrak{T}(w_0,\Theta,g)\rangle.\end{aligned}$$

It is well-known (see e.g. [17]) that for $p > N/2+1$, $q > N+2$ and $X = L^p(\Omega_T)\times(L^q(\Omega_T))^N$, the solution $z$ to (5.1) satisfies for a small enough $\alpha > 0$

$$\|z\|_{C^\alpha(\Omega_T)} \le \kappa\|(\Phi_0,\Phi)\|_X,$$

where $\kappa$ does not depend on $\Phi_0,\Phi$. Thus, due to the dense embedding $C_0^\infty\times(C_0^\infty(\Omega_T))^N \hookrightarrow L^p(\Omega)\times(L^q(\Omega_T))^N$, we can uniquely extend $\mathfrak{T}^*$ to a continuous operator from $X$ into $C^\alpha(\Omega)\times C^\alpha(\Omega_T)$ and consequently to a compact operator from $X$ into $L^\infty(\Omega)\times L^\infty(\Omega_T)\times L^\infty(\Gamma_T)$. It implies that $\mathfrak{T}$ can be defined as a compact operator from $L^1(\Omega)\times L^1(\Omega_T)\times L^1(\Gamma_T)$ into $X' = L^r(\Omega_T)\times(L^s(\Omega_T))^N$ for all $r < (N+2)/N$ and $s < (N+2)/(N+1)$. By taking $r = s = 1$, we can complete the proof. □

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