

# Approximating the dynamics of active cells in a diffusive medium by ODEs – Homogenization with Localization

Johannes Müller\*, Hannes Uecker†

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## Abstract

Bacteria may change their behavior depending on the population density. Here we study a dynamical model in which cells of radius  $R$  within a diffusive medium communicate with each other via diffusion of a signalling substance produced by the cells. The model consists of an initial boundary value problem for a parabolic PDE describing the exterior concentration  $u$  of the signalling substance, coupled with  $N$  ODEs for the masses  $a_i$  of the substance within each cell. We show that for small  $R$  the model can be approximated by a hierarchy of models, namely first a system of  $N$  coupled delay ODEs, and in a second step by  $N$  coupled ODEs. We give some illustrations of the dynamics of the approximate model.

## 1 Introduction

In recent years it became more and more clear that bacteria are not solitary individuals that only interact via competition for resources, but are social creatures. Bacteria communicate by sophisticated mechanisms with members of their own as well as with members of different species. This communication can be performed by means of small signaling molecules which are released into the environment. The concentration of the molecules at the location of a cell depends on the combination of several factors, of which the density of cells producing the signaling molecules is the most prominent: the cell is – up to a certain degree – able to measure the cell density. This kind of communication is usually called quorum sensing (QS) [FWG94]. Often enough, a certain action is started by a cell population if a certain cell density is reached. E.g., cells start to luminesce (*Vibrio fischeri*), or start to build a biofilm (*Pseudomonas aeruginosa*).

Further features influencing this type of information exchange are the diffusion coefficient in the medium the cell is located in and the geometry of the space surrounding the cell. If the cell is inside some small bounded impermeable container, the molecules cannot diffuse away and will accumulate, while the concentration of signaling molecules in an open sea will diffuse away. This aspect is called diffusion sensing (DS) [Red02]. QS and DS are only extreme cases of a more general concept, namely local efficiency sensing [HKM<sup>+</sup>07]: the ultimate aim for a cell is homeostasis and reproduction, and in order to realize this aim it is of advantage to know how large the molecular concentration of an exudate will be. Exoenzymes, released in the environment are effective only if they reach a certain density. For the cell it is of no importance if this concentration is reached because the molecules cannot diffuse away (DS), or if it is high because a large population produces the exoenzymes (QS). As exoenzymes are expensive to

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\*Centre for Mathematical Sciences, Technical University Munich, Boltzmannstr. 3, D-85748 Garching/Munich, johannes.mueller@mytum.de

†Institut für Mathematik, Universität Oldenburg, D-26111 Oldenburg, hannes.uecker@uni-oldenburg.de

produce, the cells use small, cheap molecules as proxies to check what would happen if they would produce these exoenzymes.

Often enough, the cellular signaling pathway is rather complex and incorporates positive feedback, or the interaction of multiple species of signaling molecules. The reason for this complexity is still under discussion. A positive feedback loop, leading to a highly increased production of the signaling molecule if the threshold is reached, may ensure a synchronized action among a heterogeneous cell population [DK01, WKK<sup>+</sup>04]. However, a positive feedback may also lead to an increased sensitivity on population level, using stochastic effects [MKH08]. Multiple species of signaling molecules can be interpreted as a radio with several radio channels; one idea is that one channel is used for the intra- the other for the interspecies communication. Even reactions of plants and animals on signaling molecules are reported. Our picture of the bacterial world changes – we find more and more individuals communicating in a complex manner.

In order to understand this communication, experiments on single cell level are performed. The data are often obtained by confocal laser scanning microscopy: cells are tagged with reporter constructs that luminesce in different colors indicating different states of a cell. In this way, location and state of a cell is determined. It is hard to use classical spatially structured population models to interpret these data. These models usually describe cell densities. The data, on the other hand, express the state of single cells. Another approach chosen in [MKH<sup>+</sup>06] is to keep the cells as single, extended objects with a spatially homogeneous interior. I.e., the pathway within each cell is formulated as an ordinary differential equation, describing the total mass of certain molecule species within the cell.

The cells communicate with their environment via the cell membrane. In the extracellular space, we find a parabolic equation describing the diffusion and (possible) absorption of the signaling molecules. As we assume only abiotic processes in the extracellular space, this submodel assumes a rather simple, linear form. However, as we have a system of nonlinear ODE's coupled by a linear PDE defined on a region with little holes (the cells), it is not easy to handle this model. Analytical solutions are not available in the case of several cells, and numerical schemes require a fine discretization around the tiny holes, leading to high computational costs. Equations of this type attracted a high degree of interest in the framework of homogenization [CD99]: if one chooses the appropriate measure for averaging, it is possible to get rid of single cells and to recover an equation that is homogeneous in space (the holes are gone), and describes cell densities only.

This theory, however, is in our case of limited use, as we wish to keep the single cells as individuals and do not want to approximate the individual based model by a classical cell density model. In the stationary case, the paper [MKH<sup>+</sup>06] choses another approach: the cell radius is shrunk to zero, leading to a homogeneous equation for the signaling substance. The cells however, appear as delta peaks on the right hand side, where the coefficients couple with the ODE's describing the dynamics of the states within the corresponding cells. In case of the homogeneous space, this PDE can be solved explicitly, such that the stationary points of the system can be computed as the solution of a finite dimensional algebraic equation.

The present work extends this and presents a solution to the problem how to handle models of cell interaction with the environment and cell to cell communication in non-equilibrium situations. We first investigate the case of one single cell thoroughly, present approximate models, and approximation theorems indicating that for long times the solutions of original and approximate models are close to each other. Depending on the desired order of approximation, the approximate models take the form of an ODE or of a delay differential equation (DDE). For  $N \geq 2$  cells, we get systems of DDEs, which can only be approximated consistently by ODEs by assuming a scaling of distances between the cells in the radius.

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## 2 Model, approximate models, and approximation results

We consider  $N$  cells that communicate via diffusible signaling substances. In the extracellular space, the spatio-temporal dynamics of these substances are well described by linear diffusion equations. Within the cells, the spatial structure is less important, and an ODE represents appropriately the dynamics of the internal state of a cell. The extracellular field and the internal state communicate via boundary conditions (in- and outflow).

The cells are described as balls  $\Omega_i = \{x \in \mathbb{R}^3 : \|x - x_i\| \leq R\}$  with radius  $R$  in  $\mathbb{R}^3$ , the total mass of the signaling substance within each cell is denoted by  $a_i = a_i(t) \in \mathbb{R}$ , and the exterior is denoted by  $\Omega = \mathbb{R}^3 \setminus \bigcup_{i=1}^N \Omega_i$ . The model then takes the form [MKH<sup>+</sup>06] of an initial boundary value problem for the diffusion equation for the exterior concentration  $u$  of the signalling substance, coupled with  $N$  ODEs for the  $a_i$ ,  $i = 1, \dots, N$ , namely

$$u_t = D\Delta u \text{ in } \Omega, \quad u(x, 0) = u_0(x), \quad (1a)$$

$$B_i u = \frac{d_2}{R^2} a_i(t) \text{ on } \partial\Omega, \quad \text{where } B_i u := \left[ D \frac{\partial}{\partial \nu} u + \frac{d_1}{R} u \right] \Big|_{\partial\Omega_i}, \quad (1b)$$

$$a'_i = f(a_i(t)) + \int_{\partial\Omega_i} \left( \frac{d_1 u}{R} - \frac{d_2 a_i(t)}{R^2} \right) do, \quad a_i(0) = a_{i0}. \quad (1c)$$

Here  $D > 0$  is a diffusion coefficient,  $d_1, d_2 > 0$  are inflow/outflow constants representing permeability of the cell wall, and  $\nu$  denotes the outer normal of  $\Omega$ . Clearly, (1c) can be rewritten as

$$a'_i = f(a_i(t)) - 4\pi d_2 a_i + \int_{\partial\Omega_i} \frac{d_1 u}{R} do.$$

We are interested in the limit  $R \rightarrow 0$ , and the factors  $\frac{1}{R}$  and  $\frac{1}{R^2}$  in (1c) are due to scaling. The efflux of  $a_i$  is proportional to the surface area of the cell which is  $4\pi R^2$ , hence efflux is scaled by  $1/R^2$ . For  $R \rightarrow 0$  each cell should act as a point source, i.e.,  $u \sim 1/\|x - x_i\|$ , hence the influx by  $u$  is proportional to  $R^{-1} 4\pi R^2 = 4\pi R$ , and we therefore scale it by  $1/R$ , see [MKH<sup>+</sup>06] for more details.

The internal production rate of signaling molecules  $a$  in each cell is modelled by a function  $f$ , for instance of the form

$$f(a) = \alpha_0 + \frac{\beta_0 a^n}{a_{\text{thresh}}^n + a^n} - \gamma_c a. \quad (2)$$

Thus, depending on the choice of  $\alpha_0, \beta_0, a_{\text{thresh}}, \gamma_c > 0$ , the problem  $a' = f(a)$  may have up to three positive stationary states. It is straightforward to generalize the model to, e.g., the case of more complex ODE's where the state of a cell is described by a vector of different chemicals, and the case where  $u$  is a vector of concentration, (and hence  $d_1, d_2, D$  are suitable tensors). Also,  $f$  as well as  $d_1, d_2$  may also vary from cell to cell.

As already said, computationally the model (1) has the disadvantage to be expensive for numerical schemes, since cells appear as little holes in the three dimensional space, which forces a rather fine discretization around the cells leading to high computational costs. In any case, it is desirable to draw as many analytical conclusions as possible. If  $f(\cdot)$  is monotone, the theory of monotone dynamical systems allows to draw some conclusions about stationary states and  $\omega$ -limit sets (see [MKH<sup>+</sup>06]), but the detailed transients cannot be revealed by this method. We

use the fact that cells are often scattered at distances large in comparison with their radius and investigate the limit  $R \rightarrow 0$ . However, in contrast to [MKH<sup>+</sup>06], for the validity of the simplest reduction to coupled ODEs in case  $N \geq 2$  we shall also assume that  $\|x_i - x_j\| = \mathcal{O}(R^\eta)$  for some  $0 < \eta < 1$ .

Our assumptions are summarized as:  $D, d_1, d_2 > 0$ ,  $f \in C^1(\mathbb{R})$ , and

$$\text{there exist } C_1, C_2 > 0 \text{ such that } |f(a)| \leq C_1 + C_2|a| \text{ for all } a \geq 0. \quad (3)$$

Additionally, reasonable models have  $f(a) \leq C_1 - C_2a$  for  $a \geq 0$ , but we shall not use such an assumption. In the following  $C > 0$  denotes various constants that may depend on  $D, d_1, d_2$  and the choice of  $f$ , but not on  $R$ .

## 2.1 A single cell

Let  $N = 1$  and  $x_1 = 0$ . Our goal is to show that under some natural conditions the dynamics of  $a(t) := a_1(t)$  can be well approximated by solutions of the ODE

$$b' = f(b) - Mb, \quad b(0) = a_0, \quad (4)$$

where the rate

$$M = \frac{4\pi D d_2}{d_1 + D} \quad (5)$$

turns out to be a fundamental quantity for (1). It describes the efflux rate out of the cell in (4). One may interpret this model as an compartmental model, describing the signaling substance within one cell. The loss rate of signaling substance is  $M$ . This is, a stochastic Poisson process that corresponds to this compartmental model predicts the mean time a particle stays within the cell to be  $1/M$  (see e.g. [VHL<sup>+</sup>06]). The interpretation for the original model is that  $1/M$  is the mean total residence time of a particle within the cell for a small cell radius, when we take into account that a particle may re-enter several times until it eventually diffuses away. For  $N \geq 2$  cells and assuming some scaling of distances we similarly to (4) find a system of  $N$  ODEs, see (31) below.

To justify (4) we first of all need local existence for (1). Here we opt for  $L^2(\Omega)$  based theory; however, using  $\frac{d_1}{R} \int_{\partial\Omega} \frac{1}{R} do = 4\pi d_1$ , (1) has stationary solutions of the form

$$u(x) = \frac{d_2}{D + d_1} a_s \psi(\|x\|), \quad \text{with } \psi(r) = r^{-1} \text{ and } f(a_s) - M a_s = 0. \quad (6)$$

Thus, the fundamental solution  $\psi$ , i.e.,  $\Delta\psi = -4\pi\delta_0$  is not  $L^p(\Omega)$ . Therefore we fix some constants  $0 < \rho_1 < \rho_2$ ,  $\mathcal{O}(1)$  with respect to  $R$ , and a nonincreasing smooth cutoff function  $\chi$  with

$$\chi(\rho) \equiv 1 \text{ for } \rho \leq \rho_1, \quad \chi(\rho) \equiv 0 \text{ for } \rho \geq \rho_2,$$

and define

$$\psi_c(r) = \psi(r)\chi(r).$$

Then clearly  $\psi_c \in H^m(\Omega)$  for all  $m \geq 0$ , and for all  $m_0 \geq 0$  there exists a  $C_\psi$  such that

$$\|\psi_c\|_{H^m} \leq C_\psi \text{ for } 0 \leq m \leq m_0. \quad (7)$$

In particular, using  $\Delta\psi = \frac{1}{r^2} \partial_r(r^2 \partial_r \psi)$  and  $\int_\Omega f dx = \int_R^\infty r^2 f dr$  for radial functions we find  $\|\Delta\psi_c\|_{L^2}^2 = \int_{\rho_1}^{\rho_2} \chi''^2 dr = \mathcal{O}(1)$ .

We now transform (1) to a system with zero Robin boundary conditions. Letting

$$u(x, t) = \alpha(t)\psi_c(r) + v(x, t), \quad (8)$$

where here and henceforth

$$\alpha(t) = \frac{d_2 a(t)}{D + d_1} = \frac{M}{4\pi D} a(t),$$

(1) takes the form

$$\partial_t v = D\Delta v - \alpha' \psi_c + \alpha D\Delta \psi_c, \quad v_0 = u_0 - \alpha(0)\psi_c, \quad (9a)$$

$$Bv = 0, \quad (9b)$$

$$a' = f(a) - Ma + \int_{\partial\Omega} \frac{d_1}{R} v do, \quad (9c)$$

and given  $v_0 \in H^1(\Omega)$  we can rather conveniently show local existence for (9). For

$$E(t) := \frac{1}{2} \left[ \int_{\Omega} v^2 + D|\nabla v|^2 dx + a^2(t) + \frac{d_1}{R} \int_{\partial\Omega} v^2 do \right]$$

we obtain, setting

$$h = -\alpha' \psi_c + \alpha D\Delta \psi_c$$

and using integration by parts,

$$\begin{aligned} \frac{d}{dt} E &= aa' + \int_{\Omega} v \partial_t v - (D\Delta v) \partial_t v dx + \int_{\partial\Omega} v_t D \partial_\nu v do + \frac{d}{dt} \frac{d_1}{2R} \int_{\partial\Omega} v^2 do, \\ &= aa' + \int_{\Omega} -D|\nabla v|^2 + hv - D^2|\Delta v|^2 - D\Delta v h dx + \int_{\partial\Omega} v D \partial_\nu v do, \end{aligned} \quad (10)$$

where the last two terms in the first line add to zero since  $D\partial_\nu v = -d_1 v/R$ . The last term equals  $-\frac{d_1}{R} \int_{\partial\Omega} v^2 do$  and is thus non-positive. Next, using (7),

$$\left| \int h v dx \right| \leq \int \delta v^2 + \frac{1}{4\delta} h^2 dx \leq \int \delta v^2 dx + \frac{C}{4\delta} (a^2 + a'^2),$$

and since  $\|v\|_{L^1(\partial\Omega)} \leq \sqrt{4\pi R} \|v\|_{L^2(\partial\Omega)} \leq C\sqrt{4\pi R} \|v\|_{H^1(\Omega)}$  we have  $a'^2 \leq (f(a) - Ma)^2 + C(d_1 \|v\|_{H^1})^2$  and thus

$$\left| \int h v dx \right| \leq \delta \|v\|_{L^2}^2 + \frac{1}{4\delta} (C_4 + C_5 a^2).$$

Similarly,  $|\int D\Delta v h dx| \leq D^2 \|\Delta v\|_{L^2}^2 + C(C_4 + C_5 a^2)$ , and the first term can be absorbed by the third in (10). Finally,  $aa' \leq C_6 + C_7 a^2 + C_8 \|v\|_{H^1}^2$ , and altogether

$$\frac{d}{dt} E \leq C_9 + C_{10} E, \quad \text{hence} \quad E(t) \leq e^{C_{10}t} E_0 + \frac{C_9}{C_{10}} (e^{C_{10}t} - 1)$$

by Gronwall's lemma. Combining this a priori estimate with, e.g., a standard Galerkin method, see, e.g., [Eva98, §7.1], or [Sal08, §9.1, §9.2], in particular §9.2.8 for the Cauchy-Robin problem, we obtain local existence for (1). We set

$$H_{\text{Rob}}^2(\Omega) := \{v \in H^2(\Omega) : Bv = 0\}.$$

**Theorem 2.1** *Let  $a_0 \geq 0$  and  $v_0 \in H^1(\Omega)$ . For any  $t_1 > 0$  there exists a unique local weak solution  $(v, a)$  of (9) with  $v \in L^2([0, t_1], H^2_{\text{Rob}}(\Omega)) \cap H^1([0, t_1], L^2(\Omega))$ ,  $a \in C^1([0, t_1], \mathbb{R}_+)$ . In particular,  $v \in C([0, t_1], H^1(\Omega))$ , and there exists a  $C_3 > 0$  such*

$$\sup_{0 \leq t \leq t_1} (\|v(\cdot, t)\|_{H^1} + |a(t)|) \leq C_3. \quad (11)$$

**Remark 2.2** a) Since  $\|v\|_{L^1(\partial\Omega)} \leq C\sqrt{4\pi R}\|v\|_{H^1(\Omega)}$  we also obtain  $\|a\|_{C^1} \leq CC_3$  from (11), (9c). b) For higher regularity we need more regular data and some compatibility conditions. For instance  $v_0 \in H^2_{\text{Rob}}(\Omega)$  implies  $v \in L^2([0, t_1], H^3(\Omega) \cap H^2_{\text{Rob}}(\Omega)) \cap H^1([0, t_1], H^1(\Omega))$ , hence also  $v \in C([0, t_1], H^2_{\text{Rob}}(\Omega))$ . Moreover, then also  $t \mapsto \int_{\partial\Omega} \frac{d_1}{R} v do \in H^1([0, t_1], \mathbb{R})$  in (9) and therefore  $a \in C^{1,1/2}([0, t_1], \mathbb{R})$ . This observation is important when considering higher order approximations, see Theorem 2.6.

For simplicity, in the following we shall in fact assume that

$$v_0 = 0, \quad \text{i.e. } u_0 = \alpha(0)\psi_c. \quad (12)$$

An interpretation is as follows: up to  $t = 0$  the cell is in state  $a_0$  but inactive, and thus  $u$  can adapt to the associated stationary solution, in an  $\mathcal{O}(1)$  neighborhood of the cell, cf. (6). At  $t = 0$  the cell then switches on its dynamics.

Going through the proof of Theorem 2.4 below we find that for our purposes (12) can at least be relaxed to

$$u_0 = \alpha(0)\psi_c + v_0 \text{ with } v_0 \in H^1(\Omega), \|v_0\|_{H^1} = \mathcal{O}(1). \quad (13)$$

The simplest way to fulfill any compatibility conditions is of course to assume  $a_0 = u_0 = 0$ .

c) Note that (9c) formally yields (4) if we have  $\|v\|_{L^\infty(\partial\Omega)} = \mathcal{O}(1)$ . Thus, (8), (9) also contain the heuristics for (4).  $\downarrow$

We provide a hierarchy of approximations of the full model (1), which, using  $a(t) := a_1(t)$ , we rewrite as

$$a'(t) = f(a(t)) - 4\pi d_2 a(t) + (T_R a)(t), \quad (14)$$

where the operator  $T_R a$  is defined as follows, which makes sense due to Theorem 2.1 and Sobolev traces.

**Definition 2.3** *Let  $u \in L^2_{\text{loc}}(\mathbb{R}_+, H^2(\Omega))$  denote the solution of (1a), (1b) for given  $a \in C^1(\mathbb{R}_+)$  and define*

$$T_R : C^1(\mathbb{R}_+) \rightarrow L^2_{\text{loc}}(\mathbb{R}_+), \quad (T_R a)(t) = \frac{1}{R} \int_{\partial\Omega} u(t, x) do.$$

The key idea is to approximate  $u$  in (1) by a diffusion equation with a delta source representing the cell. This yields an approximation of  $T_R$  by an operator  $\widehat{T}_R$  which incorporates a distributed delay. In Appendix A we prove the following result.

**Theorem 2.4** *Assume the compatibility conditions (12). Let  $a$  be the solution of (14) and  $b$  the solution of*

$$b'(t) = f(b(t)) - 4\pi d_2 b + d_1 (\widehat{T}_R M b)(t), \quad b(0) = a_0, \quad (15)$$

where we recall that  $M = \frac{4\pi D d_2}{d_1 + D}$ , and  $\widehat{T}_R$  is defined by

$$(\widehat{T}_R b)(t) = 4\pi R \int_0^t \frac{1}{(4\pi D \tau)^{3/2}} e^{-R^2/4D\tau} b(t - \tau) d\tau. \quad (16)$$

For all  $t_1 > 0$  there exist  $R_0 > 0$  and  $C_e > 0$  such that for  $0 < R < R_0$  we have

$$\sup_{0 \leq t \leq t_1} |a(t) - b(t)| \leq C_e R \|a\|_{C^{0,1/2}}. \quad (17)$$

The solutions  $a$  of (14) and  $b =: b_R$  of (15) depend on  $R$ . Next, by Arzela–Ascoli we find (see Appendix A for the details) that  $b_R \rightarrow b$  as  $R \rightarrow 0$ , where  $b$  satisfies (4). Taking into account that  $\widehat{T}_R f \rightarrow \frac{1}{D} f$ , cf. (49), we obtain the following corollary.

**Corollary 2.5** *Assume (12). For all  $t_1 > 0$  there exist  $R_0 > 0$  and  $C_e > 0$  such that for all  $0 < R < R_0$  and with  $b$  the solution of (4), i.e.,  $b' = f(b) - Mb$ , we have*

$$\sup_{0 \leq t \leq t_1} |a(t) - b(t)| \leq C_e R \|a\|_{C^1}. \quad (18)$$

The approximation in Theorem 2.4 can be improved by introducing higher order delays. For simplicity we restrict to the case  $a_0 = 0$  and  $u_0 = 0$ . In Appendix A.4 we prove

**Theorem 2.6** *Let  $a$  be the solution of (14) with  $a_0 = 0$  and  $u_0 = 0$ , and  $c$  be the solution of*

$$c'(t) = f(c(t)) - 4\pi d_2 c + d_1 (\widehat{T}_R M c_{\text{del}})(t), \quad c(0) = 0, \quad (19)$$

where

$$c_{\text{del}}(t) = (S_R c)(t) := 2c(t) - \frac{\pi}{d_1 + D} \int_0^t c(t - \sigma) \frac{4D}{R^2} \phi(R^2/(4D\sigma)) d\sigma, \quad (20)$$

$$\phi(\tau) = \pi^{-3/2} \tau^{3/2} e^{-\tau} (d_1 + 2D\tau). \quad (21)$$

For all  $t_1 > 0$  there exist  $R_0 > 0$  and  $C_e > 0$  such that for all  $0 < R < R_0$  we have

$$\sup_{0 \leq t \leq t_1} |a(t) - c(t)| \leq C_e R^2 \|a\|_{C^{1,1/2}}. \quad (22)$$

**Remark 2.7** Thus, (20) is the somewhat complicated formula making precise the intuitive idea to take the history into account to higher order. The calculations in Appendix A, see in particular Lemma A.3, show that for  $a \in C_b^1(\mathbb{R}^+)$  and  $t_1 > 0$  we of course have

$$-4\pi d_2 c(t) + d_1 (\widehat{T}_R c_{\text{del}})(t) = -4\pi d_2 c(t) + d_1 (\widehat{T}_R M c)(t) + \mathcal{O}(R) = -M c(t) + \mathcal{O}(R), \quad (23)$$

uniformly in  $0 \leq t \leq t_1$ , i.e., (19) agrees with (4) to  $\mathcal{O}(R)$ . ]

## 2.2 $N \geq 2$ cells

By Corollary 2.5, the interaction of a small cell with the medium can be explicitly calculated, up to a small error. As expected, the interaction of a single cell with the exterior is always damping ( $M > 0$ ), i.e. there is a net outflow of signaling substance from the cell.

If there are several cells then we may also expect a net inflow due to the information exchange between the cells. The goal is again to find simple approximate solutions for  $a_i$  of (1c). To acknowledge the communication between cells the communication terms must not be dominated

by the error terms. In a naive approximation both are of order  $\mathcal{O}(R)$ . Thus, we either need to rescale the model s.t. the communication scales with  $R^{1-\eta}$ , or to improve the approximation s.t. the error term scales with  $R^\beta$ ,  $\beta > 1$ . We discuss both possibilities.

The basic setting parallels that of the single cell scenario. Again we start with a local existence theorem, transforming (1) to a system with zero Robin boundary conditions. We first let  $\delta_{ij} = \|x_i - x_j\| = \mathcal{O}(1)$ , choose  $0 < \rho_1 < \rho_2 = \mathcal{O}(1)$  in such a way that  $\rho_2 < \min\{\delta_{ij}\}$  and define

$$\psi_c(x, t) = \sum_{i=1}^N \frac{d_2 a_i(t)}{d_1 + D} \frac{\chi(\|x - x_i\|)}{\|x - x_i\|} \Big|_{\Omega}. \quad (24)$$

Then again  $\|\psi_c\|_{H^m} \leq C_\psi$  for  $m \leq m_0$ , and setting  $u(x, t) = \psi_c(x, t) + v(x, t)$  we obtain

$$\partial_t v = D\Delta v - \partial_t \psi_c(x, t), \quad B_i v = 0, \quad v_0(x) = u_0(x) - \psi_c(x, 0), \quad (25a)$$

$$a'_i(t) = f(a_i(t)) - M a_i + \int_{\partial\Omega_i} \frac{d_1 v}{R} do, \quad a_i(0) = a_{i0}. \quad (25b)$$

Using the energy

$$E = \frac{1}{2} \left[ \int_{\Omega} v^2 + |\nabla v|^2 dx + \sum_{i=1}^N \left( a_i^2 + \frac{d_1}{R} \int_{\partial\Omega_i} v^2 do \right) \right],$$

existence of solutions to (25) is now a straightforward adaption of Theorem 2.1, and also Remark 2.2 transfers in an obvious way to the case of  $N$  cells.

**Theorem 2.8** *Let  $a_0 = (a_1, \dots, a_N)|_{t=0} \geq 0$  and  $v_0 \in H^1(\Omega)$ . For any  $t_1 > 0$  there exists a unique local weak solution  $v \in L^2([0, t_1], H^2_{\text{Rob}}(\Omega)) \cap H^1([0, t_1], L^2(\Omega))$ ,  $a \in C^1([0, t_1], \mathbb{R}_+^N)$  of (25). In particular,  $v \in C([0, t_1], H^1(\Omega))$  and*

$$\sup_{0 \leq t \leq t_1} (\|v(\cdot, t)\|_{H^1} + \|a(t)\|) \leq C_3. \quad (26)$$

To motivate an approximate ODE model for (1), alternatively to (24) we define

$$\tilde{\psi}_c(x, t) := \chi(r) \sum_{i=1}^N \frac{\alpha_i(t) + R\beta_i(t)}{\|x - x_i\|}, \quad \alpha_i(t) := \frac{d_2}{d_1 + D} a_i(t), \quad \beta_i(t) := -\frac{d_2 d_1}{(d_1 + D)^2} \sum_{j \neq i} \frac{a_j(t)}{\delta_{ij}}, \quad (27)$$

where now  $\rho_1 > 0$  is chosen large enough such that all cells are contained in  $B_{\rho_1/2}(0)$ . This yields, for  $v = u - \tilde{\psi}_c$ ,

$$\partial_t v = D\Delta v - \partial_t \tilde{\psi}_c(x, t), \quad B_i v = h_i(x, t), \quad v_0(x) = u_0(x) - \tilde{\psi}_c(x, 0), \quad (28a)$$

$$a'_i(t) = f(a_i(t)) - 4\pi d_1 a_i + \int_{\partial\Omega_i} \frac{d_1 \tilde{\psi}_c}{R} do + \int_{\partial\Omega_i} \frac{d_1 v}{R} do, \quad a_i(0) = a_{i0}, \quad (28b)$$

with  $\|h_i(x, t)\|_{L^\infty} \leq C\|a(t)\|$ . This last estimate is straightforward but quite lengthy, and therefore we omit the details, see [MKH<sup>+</sup>06, Lemma 10] for a similar construction in the stationary case. Now, similar to Remark 2.2c), heuristically plugging  $v \equiv 0$  into (28b) we find, replacing  $a_i$  by  $b_i$ , and solving the integral,

$$b'_i = f(b_i) - M b_i + R \frac{d_1 M}{d_1 + D} \sum_{j \neq i} \frac{b_j}{\delta_{ij}}. \quad (29)$$



The first goal would be to show that solutions  $b_i$  of (29) approximate solutions  $a_i$  of (1c) up to an  $\mathcal{O}(R)$  error. However, for  $\delta_{ij} = \mathcal{O}(1)$  the communication terms  $R \frac{d_1 M}{d_1 + D} \sum_{j \neq i} b_j / \delta_{ij}$  in (29) are then of the same order as the error and could be dropped. Thus we either need to reduce the error, or, by an additional scaling of some parameters, increase the order of the communication terms. First we assume that

$$\|x_i - x_j\| = \delta_{ij} = R^{2\eta} \tilde{\delta}_{ij} \text{ with } 0 < \eta < 1/2 \text{ and } \tilde{\delta}_{ij} = \mathcal{O}(1), \quad (30)$$

to find the approximate model

$$b'_i = f(b_i) - M b_i + R^{1-2\eta} \frac{d_1 M}{d_1 + D} \sum_{j \neq i} \frac{b_j}{\tilde{\delta}_{ij}}. \quad (31)$$

**Remark 2.9** The simple proof of Theorem 2.8 sketched above has the disadvantage that it cannot easily be adapted to the scaling (30): if we change (24) to

$$\psi_c(x, t) = \sum_{i=1}^N \frac{d_2 a_i(t)}{d_1 + D} \frac{\chi(R^{-2\eta} \|x - x_i\|)}{\|x - x_i\|^2} \Big|_{\Omega},$$

then  $\|\psi_c\|_{L^2}^2 = \mathcal{O}(\|a\|^2 R^{2\eta})$  but  $\|\Delta \psi_c\|_{L^2}^2 = \mathcal{O}\left(|a|^2 \int_{R^\eta \rho_1}^{R^\eta \rho_2} R^{-2\eta} \chi''^2(r) dr\right) = \mathcal{O}(R^{-\eta} |a|^2)$  which leads to the a priori estimate  $E(t) \leq C e^{CR^{-2\eta} t} E_0 + C(e^{CR^{-2\eta} t} - 1)$ . Therefore, to find  $\mathcal{O}(1)$  bounded solutions of (1) on an  $\mathcal{O}(1)$  time scale we need to refine the proof. One possibility is to derive a priori estimates for (28), which again is lengthy but straightforward, and yields (26) even under the scaling (30).  $\square$

The basic idea to justify (31) is to introduce a delta source for each cell. This leads to the delayed ODE system

$$b'_i = f(b_i) - 4\pi d_2 b_i + \frac{d_1}{R} \int_{\partial \Omega_i} \left( \int_0^t \sum_{j=1}^N (4\pi D(t-\tau))^{-3/2} e^{-\|x-x_j\|^2/4D(t-\tau)} \tilde{b}_{j,app}(\tau) d\tau \right) d\sigma, \quad (32a)$$

$$\tilde{b}_{i,app} = M b_i(t) - R^{1-2\eta} \frac{d_1 M}{d_1 + D} \sum_{j \neq i} \frac{b_j(t)}{\tilde{\delta}_{i,j}}, \quad i = 1, \dots, N, \quad (32b)$$

and again we first prove an estimate for the error between  $a$  and the solution  $b$  of (32).

**Theorem 2.10** *Let  $v_0 \in H^1(\Omega)$ ,  $a_0 \in \mathbb{R}_+^n$ . For all  $t_1 > 0$  there exist  $R_0 > 0$  and  $C_e > 0$  such that for all  $0 < R < R_0$  we have*

$$\sup_{0 \leq t \leq t_1} |a(t) - b(t)| \leq C_e R \|a\|_{C^{0,1/2}}, \quad (33)$$

where  $(u, a)$  solves (1) with  $a = (a_1, \dots, a_N) \in C^1$ , and  $b = (b_1, \dots, b_N)$  is the solution of (32).

Denoting the solution of (32) by  $b^{(R)}$  we find  $b^{(R)} \rightarrow b$  as  $R \rightarrow 0$  where  $b$  solves (31):

**Corollary 2.11** *Let  $v_0 \in H^1(\Omega)$ ,  $a_0 \in \mathbb{R}_+^n$ . For all  $t_1 > 0$  there exist  $R_0 > 0$  and  $C_e > 0$  such that for all  $0 < R < R_0$  we have*

$$\sup_{0 \leq t \leq t_1} |a(t) - b(t)| \leq C_e R \|a\|_{C^1}, \quad (34)$$

where  $b = (b_1, \dots, b_N)$  is the solution of (31).

Instead of scaling the distances between cells we may improve the approximation to decrease the error term, – for the price of a more complex equation. To be precise, consider

$$c'_i = f(c_i) - 4\pi d_2 c_i + d_1 \widehat{T}_R c_{i,del}^0(t) - \frac{Rd_1}{\sqrt{4D}} \left( (\widehat{T}_R c_{i,del}^1)(t) + \frac{\pi}{D} \sum_{j \neq i} (I_{1,0}^{i,j} c_{j,del}^0)(t) \right), \quad (35a)$$

$$c_{i,del}^0(t) = MS_R(a_i)(t), \quad c_{i,del}^1(t) = \frac{\pi d_1}{d_1 + D} \sum_{j \neq i} (S_R \circ I_{1,0}^{i,j})(c_{j,del}^0)(t), \quad (35b)$$

where  $S_R f(t) = 2f(t) - \frac{\pi}{d_1 + D} \int_0^t f(t - \sigma) \frac{4D}{R^2} \phi(R^2/(4D\sigma)) d\sigma$  with  $\phi(\tau) = \pi^{-3/2} \tau^{3/2} e^{-\tau} (d_1 + 2D\tau)$  and  $\widehat{T}_R f(t) = 4\pi R \int_0^t f(t - \tau) (4D\pi\tau)^{-3/2} e^{-\frac{R^2}{4D\tau}} d\tau$  as before, cf. (16) and (20), and

$$(I_{1,0}^{i,j} f)(t) = \int_0^t f(t - \tau) \pi^{-3/2} \tau^{-3/2} e^{-\frac{\|x_i - x_j\|^2}{4D\tau}} d\tau$$

are the pertinent interaction terms. This yields (see Appendix B for the proof):

**Theorem 2.12** *Let  $a = (a_1, \dots, a_N)$  be the solution from (1) with  $a_0 = 0$  and  $u_0 = 0$ , and let  $c = (c_1, \dots, c_N)$  denote the solution of (35). For all  $t_1 > 0$  there exist  $R_0 > 0$  and  $C_e > 0$  such that for all  $0 < R < R_0$  we have*

$$\sup_{0 \leq t \leq t_1} |a(t) - c(t)| \leq C_e R^2 \|a\|_{C^{1,1/2}}. \quad (36)$$

The last approximation does not require a rescaling of the distances but this conclusion is paid for by a complex delay model. Most likely, this model is too clumsy to be of practical use. However, we will make clear by heuristic arguments in the next section that many of the operators incorporating a delay can be simplified under certain circumstances. The ODE system (31) may lead to considerable wrong time scales as the traveling time between cells is not taken into account. The DDE model (35), however, also takes the history of one cell into account in order to consistently approximate the self-interaction. It is plausible that this is not necessary, such that the DDE model (38) will be proposed as a kind of compromise. This is much simpler than (35), though it considers the delay due to diffusion between different cells.

### 3 Illustrations and conclusions

#### 3.1 Comparison between approximation by ordinary differential equations and delay equations

We derived a variety of approximations, of which that by ODEs and that by DDEs are the most interesting: ODEs are simple to handle and to analyze, while the DDE models are more complicated but give an error bound of second order. In this paragraph, we address the question which approximation should be applied in a given situation. If we consider more than one cell with  $\mathcal{O}(1)$  distances, then clearly the DDE model is preferential, as the error in the ODE is of the same order as the communication terms. The stationary states of both approximations agree; in all cases of practical importance we do not expect that the dynamics of ODE and DDE model are qualitatively different, e.g. one model will oscillate while the other will not. What we do expect is that the time scales at which these stationary states are approached differ; the

DDE is expected to react slower than the ODE. In order to check this conjecture, we first focus on one cell only, and subsequently consider the case of several interacting cells.

In the case of one cell only, the difference between the two models is the term describing the net outflow of substance out of a cell,

$$-bM \quad \text{in case of the ODE,} \quad -4\pi d_2 c + d_1 M \widehat{T}_R^i S_R c \quad \text{in case of the DDE,}$$

where we again denote the solution of the ODE by  $b$ , and that of the DDE by  $c$ . In cases of practical relevance, the time scale of the reaction  $f(\cdot)$  is similar to or slower than the mean resident time  $1/M$ , i.e., the ODE solution will vary on a time scale  $1/M$ . In the DDE, for a constant function  $c(t) \equiv c_0$  we know that

$$-4\pi d_2 c_0 + d_1 M \widehat{T}_R^i S_R c_0 \rightarrow -M c_0.$$

If this convergence is fast in comparison with  $1/M$ , the solution  $b(t)$  can be considered as quasi-stationary, and

$$-4\pi d_2 b(t) + d_1 M \widehat{T}_R^i S_R b(t) \approx -M b(t).$$

Therefore, given a rapid convergence of the delay operator, the solution  $b(t)$  of the ODE solves approximately the DDE. This is the key insight to exploit.

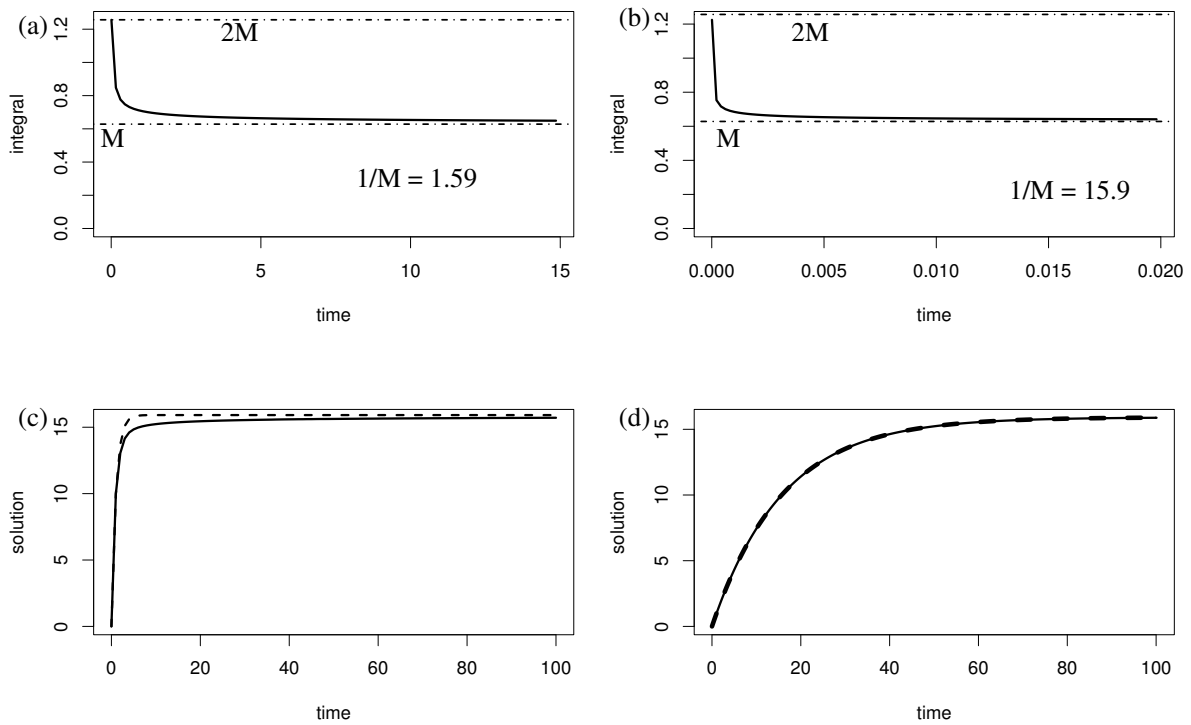


Figure 1: Comparison between ODE and DDE in case of one cell. Upper panels: comparison between  $4\pi d_2 f - d_1 M \widehat{T}_R^i S_R f$  and  $Mf$  in case that  $f(t) \equiv 1$ . Lower panels: Solution of DDE (solid lines) and ODE (dashed line). In panel (d) the two solutions lie on top of each other. Parameters are the same for (a), (c) resp. (b), (d), see Tab. 1.

In Fig. 1 we consider two cases. The upper panels show  $4\pi d_2 f(t) - d_1 M \widehat{T}_R^i S_R f$  for  $f \equiv 1$ . In (a) we find convergence to  $M$  on the time scale defined by  $1/M$ , while in (b) convergence is much faster than  $1/M$ . Thus for (a) we expect the solutions to be different for DDE and ODE, while for (b) we predict the solutions of ODE and DDE to be indistinguishable. This is confirmed by the numerical simulation (Fig. 1 (c) and (d)).

	Fig. 1 (a), (c)	Fig. 1 (b), (d)
$R$	0.01	0.01
$D$	0.0005	1
$d_1$	0.0005	1
$d_2$	0.1	0.1
$a$	10	10
$1/M$	1.59	15.9

Table 1: Parameter used for the simulations in Fig. 1.

In the same spirit as above, for the DDE (35) for several cells we compare the time scale at which the delay terms converge to a constant. The most interesting term is  $I_{0,1}^{i,j}$  as this operator is the one that describes the diffusion between cells. And indeed, numerical observations show that this operator is the one which by far converges most slowly, at least for parameters interesting for cell-cell communication as stated in Tab. 2. All other operators become constant as fast as in the one-cell-example. This observation does not allow to remove all delay terms, but to simplify the DDE considerably: the delays  $S_R$  and  $\widehat{T}_R$  can be replaced by appropriate constants, and only  $I_{1,0}^{i,j}$  stays an integral operator. Thus, (35) simplifies to

$$e'_i = f(e_i) - Me_i + R \frac{d_1 M^2}{d_2} \sum_{j \neq i} \int_0^t \frac{1}{(4D\pi\tau)^{3/2}} e^{-\frac{\|x_i - x_j\|^2}{4D\tau}} e_j(t - \tau) d\tau. \quad (37)$$

One (minor) problem in this equation is that for the derivation of (35) we assume  $u|_{t=0} = 0$ . This can be relaxed to a class of nonzero initial conditions for  $u$  by prescribing a history  $e_i(t)$  for  $t_0 < t < 0$ . Given  $e_i$ , a distribution  $u_0 = u|_{t=0}$  of particles traveling between the cells at time zero can be calculated from (1a,b), or better approximated by the auxiliary system (40a), cf. Lemma A.3, and afterwards arguments similar to Lemma A.4, Lemma A.5 give estimates on  $\sup_{0 \leq t \leq t_1} |a(t) - e(t)|$ . Due to the  $\tau^{-3/2}$  decay of the memory as  $\tau \rightarrow \infty$  it is clear that for  $L^\infty$ -histories we may take  $t_0 \rightarrow -\infty$  to arrive at

$$e'_i = f(e_i) - Me_i + R \frac{d_1 M^2}{d_2} \sum_{j \neq i} \int_0^\infty \frac{1}{(4D\pi\tau)^{3/2}} e^{-\frac{\|x_i - x_j\|^2}{4D\tau}} e_j(t - \tau) d\tau, \quad (38)$$

with the upper limit of the integral as the only difference to (37).

Although still a DDE model, (38) is simple enough to allow for practical applications. To check the differences between (29) and (38) we consider a spatial setup of 27 cells, arranged at a cubic grid (see also Fig. 3 (a)). We use the parameters for cell-cell communication given in Tab. 2, only the nonlinearity in  $f(\cdot)$  is removed, i.e. we set  $\beta = 0$ . This is, to isolate the behaviour of the delay operators we only consider a linear model. We focus on the central cell, named ‘‘cell 1’’ in Fig. 3(a). The distance  $L$  between neighboring cells is taken to 40  $\mu\text{m}$ , which is a realistic length scale. In the right panel of Fig. 2 a comparison between the ODE model the simplified DDE model and the trajectory for one single cell is presented. We find the ODE model to quickly approach the equilibrium. The simple DDE model behaves for the very first time interval as the solution of a solitary cell; only after about 0.5 s to 1 s the solution slowly increases as signaling molecules start to arrive. After a considerable delay, the DDE model approaches the stationary solution of the ODE model. The difference of the single cell solution and the solution of the central cell within a cube of  $3^3$  cells seems not to be large; however, we will see below that this difference is exactly what the cells focus on, and nonlinearities amplify the difference. Thus, the effect we find here is able to alter the time scales of the dynamics significantly.

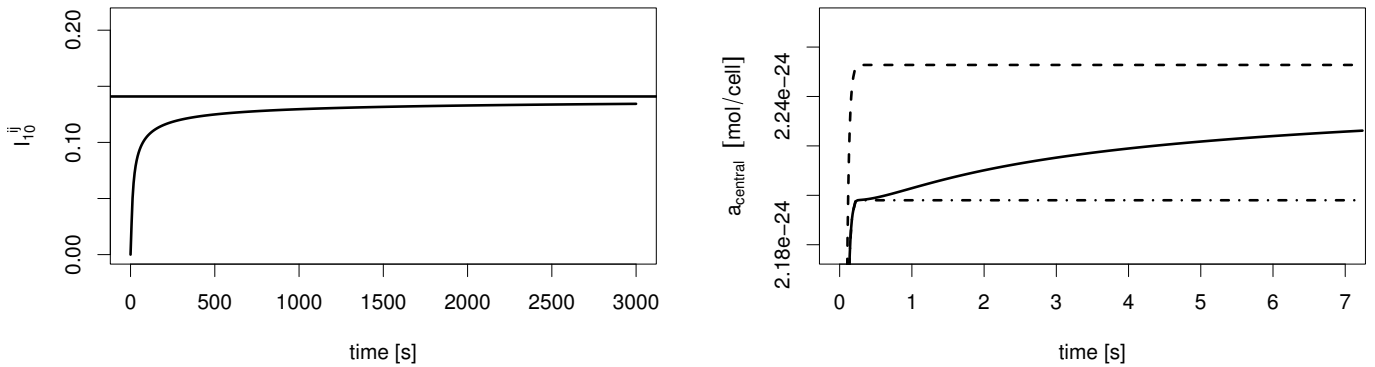


Figure 2: Left: The convergence of the operator  $I_{1,0}^{i,j}$  responsible for cell-cell-communication. Right: trajectory for one cell in a given spatial configuration (see text). Solid line: simple DDE model, dashed line: ODE model, dotted-dashed line: ODE model for a single cell. In all three models zero initial conditions are used but only a narrow interval on the  $y$ -axes is plotted. The distance is  $\delta_{i,j} = 40\mu\text{m}$ , model parameters as in Tab. 2, only  $\beta = 0$ .

### 3.2 Application to quorum sensing

Many major questions concerning quorum sensing are rather basic: what is this pathway good for? Is this really quorum sensing (i.e. communication), or diffusion sensing, or local efficiency sensing or something completely different? If it is communication, why did this communication evolve, why is it evolutionarily stable? These questions are closely related to the behavior of one or several cells in a given geometry.

In the present section we focus on *quorum* sensing, which is perhaps the best investigated mode of bacterial communication. It is of interest to obtain information about the necessary number or cell density that constitutes a quorum. This definitely depends on the diffusion coefficient and the geometry of the cell distribution. In order to demonstrate the applicability of our theory, we consider a colony of 27 cells, arranged in a cubic pattern. The parameter values describing the behavior of the bacteria are assumed to resemble the behavior of *Pseudomonas putida*. These bacteria basically possess a resting and an activated state, depending on the concentration of signaling substance. In the activated state the bacteria show an increased production rate of signaling substance. Models of ordinary differential equations, describing a homogeneous population of bacteria of this type can be e.g. found in [DK01, MKH<sup>+</sup>06]. For simulations, we use the simplified DDE model (38). The parameters chosen for the simulations are partially obtained by the analysis of batch experiments [FKR<sup>+</sup>09], partially chosen *ad hoc*. The production rates, threshold, and the Hill coefficient are rather well known. How to choose the permeabilities  $d_1$  and  $d_2$  is not this clear. Here, these parameters are selected in such a way that a clear threshold behavior can be observed. For the history of  $e_i(t)$ ,  $t \leq 0$ , we assume that  $e_i$  are constant.

Results of the simulation are presented in Fig. 3. We follow the mass of signalling substance in the central cell and in a corner cell, where we use two different initial conditions: one is zero, and one is rather large. If the distance between two neighboring cells is small ( $L = 3\mu\text{m}$ ), the cells become activated no matter where the cells start from. If we increase the distance, we find a bistable regime ( $L = 25\mu\text{m}$ ), while all cells go to the resting state for large distances between two cells ( $L = 50\mu\text{m}$ ). The range of distances where activated cells are possible is comparable with that observed in batch culture experiments (approximately  $10^7$  cells per ml, corresponding

parameter	value	paper
$\alpha_0$	$6.4 \cdot 10^{-23}$ mol/sec	[FKR <sup>+</sup> 09]
$\beta_0$	$10 \alpha_0$	[FKR <sup>+</sup> 09]
$V_c$	Volume of a cylinder of 1 $\mu\text{m}$ length and 0.5 $\mu\text{m}$ diameter	
$R$	0.36 $\mu\text{m}$ (a ball with volume $V_c$ ).	
$D$	$3 \cdot 10^{-10} \text{m}^2/\text{s}$	[Hors <sup>+</sup> 07]
$d_2$	2.7/s	
$d_1$	$8.085 \cdot 10^{-11} \text{m}^2/\text{s}$	
$\tau$	70 n mol/l $\simeq 1.37 \cdot 10^{-23}$ mol/cell	[FKR <sup>+</sup> 09]
$n$	2.5	[FKR <sup>+</sup> 09]

Table 2: Parameter values used in simulations. The cell volume is chosen in such a way that it resembles the size of a bacterium; literature supporting a parameter is indicated; parameters  $d_1$  and  $d_2$  are chosen *ad hoc*, see text.

to 40  $\mu\text{m}$  distance).

As expected, the position of a cell matters: the mass of signalling substances in the central cell is always above that of the corner cell. This central cell may act as a trigger, which becomes activated first and then activates the other cells, and the activation mechanism of a colony works as follows: the broad mass (also the cells in the border region of a colony) contribute to the concentration of signaling substance in the center. In the center, eventually the first cells become supercritical and increase the output of signaling substances. This, in turn, activates the other cells: a front of activation runs from the center to the outer region, until the complete colony is activated. In this way, a synchronized action can be archived. For appropriate parameters, especially a large Hill coefficient, it is also possible to find stationary solutions where the central cells are activated but the outer are not. However, these configurations are only possible for rather small parameter ranges, see also [AP<sup>+</sup>09]. A more likely source of variable behavior within one colony is either a different sensitivity of the regulated genes within one species, or stochastic effects. There is experimental support for both sources of variability.

Looking at the simulations, a further conclusion can be drawn: in experiments, the time to activation (transition from subcritical to supercritical state) is on the order of hours rather than seconds like in our simulation. This is a hint that the factor determining the time scale is not the biophysics (time constant implied by the diffusion rate and the geometry) but the biochemistry, which agrees with the considerations presented in [MKH08], where the authors analyze the reason why cells are able to react on minimal amount of signaling molecules in a reliable way. They show that a low pass filter, biochemically realized by receptor molecules that form long living complexes with the signaling molecules, allow the cell a reliable measurement of very low concentrations of signaling molecules. This measurement necessarily takes a longer time, typically on the order of ten minutes. Also transcription and translation needs time. Thus, the time scale of the biochemical pathway necessarily is much slower than the time scale implied by the communication distance. This is an indication that several papers (also from the first author of the present paper) are valid only for the analysis of stationary states, as they assume that large parts of the pathway are fast and can be thus approximated by much simpler models (Hill functions) using singular perturbation theory.

The simplification of complex models via singular perturbation theory may be an appealing theoretical approach allowing a reduction of parameters and complexity but may not be based on true biochemical time scales. For a realistic dynamic description, models need to be slightly

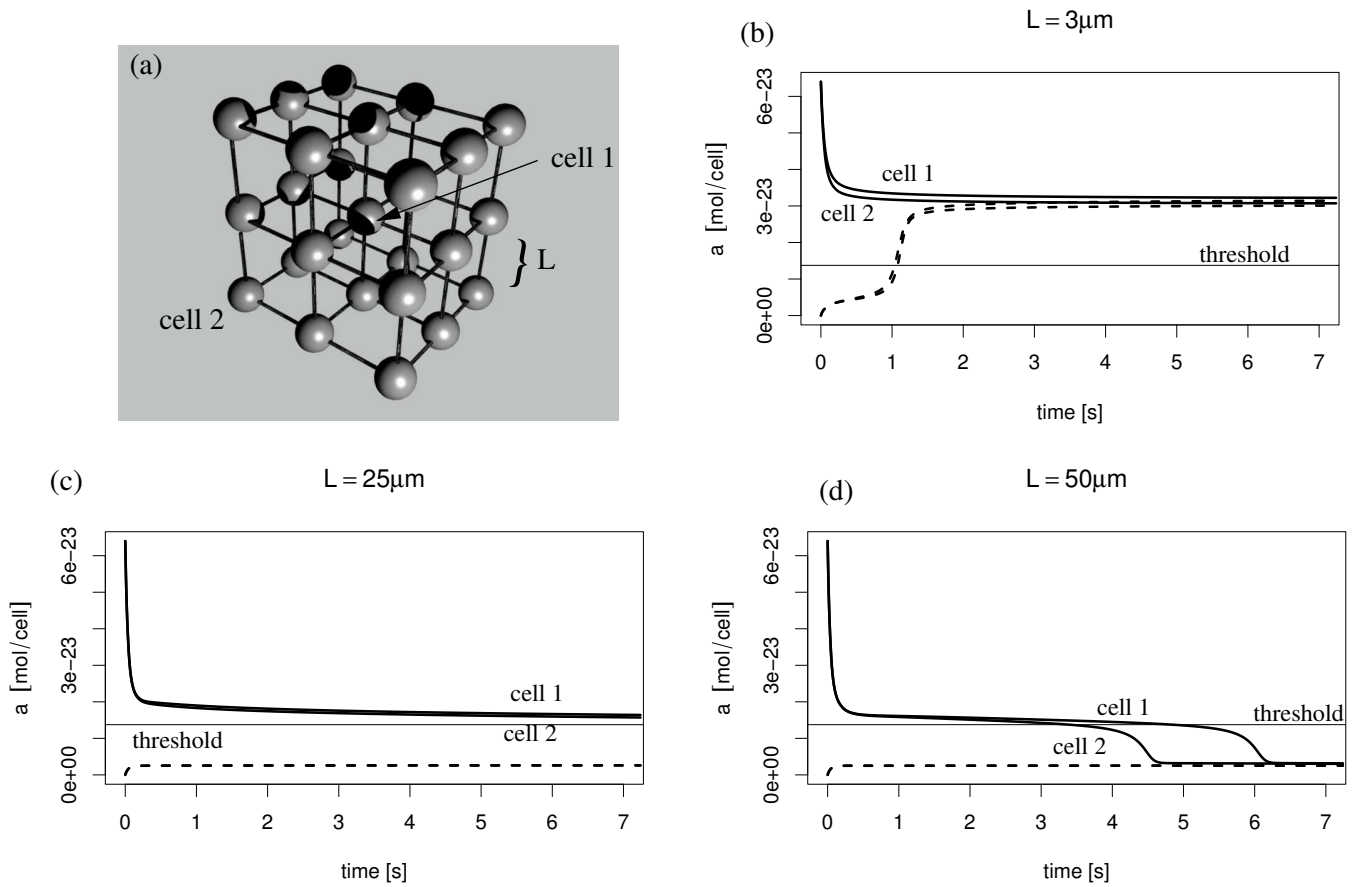


Figure 3: (a) A cubic colony of 27 cells. (b)-(d) presents the dynamics of the signaling molecules for the central cell and a cell in a corner of the colony for distances of  $L = 3\mu\text{m}$ ,  $L = 25\mu\text{m}$ , and  $L = 50\mu\text{m}$ . The solid lines displays the dynamics for a large initial value, while the dotted line presents the dynamics for zero initial conditions. The horizontal bar indicates the threshold concentration. In (c), (d) the two solutions for zero initial conditions lie on top of each other.

more complex. In models that do not address single cell data but results of batch experiments, this difficulty is often hidden by the growth of the population. From the analysis of the signaling aspect, this growth is a non-autonomous, external input which creates a slow time scale. If the population growth is taken as a reference time scale, the pathways of the cells altogether can be (approximately) assumed to be in a quasi-steady state. If, for example, we study the response to a rapid change in the environment (e.g. wash out of the supernatant), then the models should be more sophisticated in order to meet the appropriate timing. A further discussion is needed whether the usual approach for batch experiments may hide some central aspect in the signaling pathway not fully comprehended or acknowledged by the modelling community.

## A Proof of approximation results: One cell

### A.1 The idea

We want to approximate a solution  $a$  of (1) with  $N = 1$ , i.e.,

$$u_t = D\Delta u \text{ in } \Omega, \quad u(\cdot, 0) = u_0 = \frac{d_2}{D + d_1} a_0 \psi_c|_{\Omega}, \quad Bu = \frac{d_2}{R^2} a \text{ on } \partial\Omega, \quad (39a)$$

$$a' = f(a) - 4\pi d_2 a + \int_{\partial\Omega} \frac{d_1 u}{R} do, \quad a(0) = a_0, \quad (39b)$$

by a solution  $b$  of (4), i.e.,  $b' = f(b) - Mb$ ,  $b(0) = a_0$ . For  $u_0$  we assume the compatibility conditions (12). The main idea is to consider the auxiliary problem

$$p_t = D\Delta p + \tilde{b}(t)\delta_0(x), \quad p(\cdot, 0) = \frac{d_2}{D + d_1} a_0 \psi_c(\cdot), \quad (40a)$$

$$b' = f(b) - 4\pi d_2 b + \int_{\partial\Omega} \frac{d_1 p}{R} do, \quad b(0) = a_0. \quad (40b)$$

and to calculate a suitable  $\tilde{b}$ . Since (40a) can be explicitly solved to leading order, the ODE (40b) for  $b$  can then be written as

$$b'(t) = f(b(t)) - 4\pi d_2 b(t) + d_1(\widehat{T}_R \tilde{b})(t) + r(t) \quad (41)$$

with  $\widehat{T}_R$  defined in (16), and small  $r$  due to the initial conditions in (40a). The main step is to derive a priori estimates for the difference between  $T_R a$  and  $\widehat{T}_R \tilde{b}$ , which, to lowest order, lead to the optimal choice  $\tilde{b} = Mb$ . With the notation  $b_R$  for the solution of (41) we then show that  $b_R \rightarrow b$  where  $b$  solves (4) and thus prove Corollary 2.5.

### A.2 The auxiliary problem

We compare solutions of (39) with solutions of (40). As already said, it turns out that in lowest order  $\tilde{b}(t) = Mb(t)$  is optimal, but first we keep  $\tilde{b}$  free. To simplify notation we introduce

$$\rho = R^2/(4D)$$

and define

$$(F_{\rho,k}f)(t) := \frac{1}{\rho} \int_0^t f(t-\tau)(\rho/\tau)^{k/2} e^{-\rho/\tau} d\tau = \int_{\rho/t}^{\infty} f(t-\rho/\zeta) \zeta^{k/2-2} e^{-\zeta} d\zeta,$$

$$(K_{\rho}f)(t) := d_1 \pi^{-3/2} (F_{\rho,3}f)(t) + 2D \pi^{-3/2} (F_{\rho,5}f)(t).$$



**Lemma A.1** Let  $w(x, t) = u(x, t) - p(x, t)|_\Omega$ . Then  $w(x, t)$  satisfies

$$w_t = D\Delta w \text{ in } \Omega, \quad w(x, 0) = 0, \quad Bw = -g(x, t) \text{ on } \partial\Omega, \quad (42)$$

where

$$g(x, t) = \frac{1}{16D^2} \frac{1}{\rho} \left\{ (K_\rho[\tilde{b} - 4\pi D\alpha_0])(t) - 4D d_2(a(t) - a_0) \right\} + \frac{1}{R} g_2(x, t),$$

and  $\|g_2\|_\infty = \mathcal{O}(1)$ .

**Proof.** We have  $Bw = Bu - Bp = \frac{d_2}{R^2} a - Bp =: -g(x, t)$ . The leading order terms of  $p$  can be calculated explicitly. For  $\tilde{p} = p - \alpha_0\psi_c$ , where we recall  $\alpha(t) = \frac{d_2}{D+d_1} a(t) = \frac{M}{4\pi D} a(t)$ , we find

$$\tilde{p}_t = D\Delta\tilde{p} + \hat{c}\delta_0 + \alpha_0 h, \quad \tilde{p}_0 = 0. \quad (43)$$

Here  $\hat{c} = \tilde{b} - 4\pi D\alpha_0$ , using  $D\Delta\psi_c = -4\pi D\delta_0 + h$  with  $\|h\|_{H^2} \leq C$ , cf. (7). Letting

$$k(x, t) = \frac{1}{(4\pi Dt)^{3/2}} e^{-x^2/(4Dt)},$$

we obtain, since  $\tilde{p}(0) = 0$ ,

$$\tilde{p}(x, t) = \int_0^t \int_{\mathbb{R}^3} k(x-y, t-\tau) [\hat{c}(\tau)\delta_0(y) + \alpha_0 h(y, \tau)] dy d\tau = \int_0^t k(x, t-\tau) \hat{c}(\tau) d\tau + p_2(x, t)$$

with  $\|p_2(\cdot, t)\|_{H^2} \leq C\alpha_0$ , and in particular  $\|p_2\|_{L^\infty(\partial\Omega)} \leq C\alpha_0$ . Thus

$$p(x, t) = p_1(x, t) + p_2(x, t) = \int_0^t k(x, t-\tau) \hat{c}(\tau) d\tau + \alpha_0\psi_c + p_2(x, t). \quad (44)$$

Therefore,

$$g(x, t) = \frac{1}{R} \int_0^t (\tilde{b}(\tau) - 4\pi D\alpha_0) [d_1 k(R, t-\tau) - RDk_x(R, t-\tau)] d\tau - \frac{d_2(a(t) - a_0)}{R^2} + \frac{1}{R} g_2$$

with  $\|g_2(\cdot, t)\|_{L^\infty(\partial\Omega)} \leq C\alpha_0$ . The integral kernels read

$$\begin{aligned} \frac{d_1}{R} k(R, t) &= \frac{d_1}{R(4\pi Dt)^{3/2}} e^{-R^2/(4Dt)} = \frac{d_1}{16D^2} \frac{1}{R^4/(4D)^2(\pi t 4D/R)^{3/2}} e^{-\rho/t} \\ &= \frac{d_1}{16D^2} \frac{1}{\rho^2} \pi^{-3/2} (\rho/t)^{3/2} e^{-\rho/t} \\ Dk_x(R, t) &= \frac{1}{(4\pi Dt)^{3/2}} e^{-R^2/(4Dt)} \frac{2DR}{4Dt} = \frac{2D}{R(4\pi Dt)^{3/2}} e^{-R^2/(4Dt)} \frac{R^2}{4Dt} \\ &= \frac{2D}{16D^2} \frac{1}{\rho^2} \pi^{-3/2} (\rho/t)^{5/2} e^{-\rho/t}, \end{aligned}$$

and thus

$$\begin{aligned} g(x, t) &= \frac{1}{16D^2} \frac{1}{\rho} (K_\rho[\tilde{b} - 4\pi D\alpha_0])(t) - \frac{4D}{R^2} d_2(a(t) - a_0) + \frac{1}{R} g_2(x, t) \\ &= \frac{1}{16D^2} \frac{1}{\rho} \left\{ (K_\rho[\tilde{b} - 4\pi D\alpha_0])(t) - 4D d_2(a(t) - a_0) \right\} + \frac{1}{R} g_2(x, t). \quad \square \end{aligned}$$

**Lemma A.2** For solutions  $w$  of (42) we have

$$\|w\|_{L^2(\Omega)}^2 \leq \frac{2R}{d_1} \int_0^t \int_{\partial\Omega} g^2(x, \tau) d\sigma d\tau, \quad (45)$$

$$\|w\|_{L^2([0,t], H^1(\Omega))}^2 \leq \frac{2R}{d_1 D} \left( \int_0^t \int_{\partial\Omega} g^2(x, \tau) d\sigma d\tau + D \int_0^t \int_0^\tau \int_{\partial\Omega} g^2(x, \sigma) d\sigma d\sigma d\tau \right). \quad (46)$$

**Proof.** We have the a priori estimate

$$\begin{aligned} D \int_{\Omega} |\nabla w|^2 dx + \frac{d}{dt} \frac{1}{2} \int_{\Omega} w^2(x, t) dx &= D \int_{\Omega} |\nabla w|^2 dx + D \int_{\Omega} w \Delta w dx \\ &= D \left[ \int_{\Omega} |\nabla w|^2 dx - \int_{\Omega} |\nabla w|^2 dx + \int_{\partial\Omega} w \partial_\nu w d\sigma \right] = - \int_{\partial\Omega} w \left[ \frac{d_1}{R} w + g(x, t) \right] d\sigma \\ &\leq - \frac{d_1}{R} \int_{\partial\Omega} w^2 d\sigma + \frac{d_1}{R} \int_{\partial\Omega} w^2 d\sigma + \frac{R}{d_1} \int_{\partial\Omega} g^2(x, t) d\sigma = \frac{R}{d_1} \int_{\partial\Omega} g^2(x, t) d\sigma. \end{aligned}$$

Integrating over time we find (45), and integrating a second time w.r.t. time yields (46).  $\square$

By (43), the key step to minimize the right hand sides in (45),(46) for given  $a$ , is to approximately solve for  $f$  the integral equation

$$(K_\rho f)(t) := d_1 \pi^{-3/2} (F_{\rho,3} f)(t) + 2D \pi^{-3/2} (F_{\rho,5} f)(t) \stackrel{!}{=} 4D d_2 \hat{a}(t) \quad (47)$$

with  $\hat{a}(t) = a(t) - a_0$ , and  $f = \tilde{b} + 4\pi D \alpha_0$ . Formally, for  $\tau > 0$

$$\lim_{\rho \rightarrow 0} (F_{\rho,k} f)(\tau) = \Gamma(k/2 - 1) f(\tau) =: (F_{0,k} f)(\tau).$$

With  $\Gamma(1/2) = \sqrt{\pi}$  and  $\Gamma(3/2) = \sqrt{\pi}/2$ , we may write

$$\lim_{\rho \rightarrow 0} (K_\rho f) = \pi^{-1} (d_1 + D) f(\tau) =: (K_0 f)(\tau).$$

In order to establish this equation not only formally we define the residual

$$(\mathcal{R}_\rho f)(\tau) := (K_\rho f)(\tau) - (K_0 f)(\tau).$$

**Lemma A.3** Let  $f \in C^{0,1/2}(\mathbb{R}_+)$ ,  $f(0) = 0$ . Then for all  $t_1 > 0$  there exists a  $C > 0$  such that

$$\|\mathcal{R}_\rho f\|_{C^0[0,t_1]} \leq C \|f\|_{C^{0,1/2}[0,t_1]} \rho^{1/2}.$$

**Proof.** We have

$$\begin{aligned} (F_{\rho,k} f)(\tau) - (F_{0,k} f)(\tau) &= \frac{1}{\rho} \int_0^\tau (f(\tau - x) - f(\tau)) (\rho/x)^{k/2} e^{-\rho/x} dx + \frac{f(\tau)}{\rho} \int_\tau^\infty (\rho/x)^{k/2} e^{-\rho/x} dx \\ &= \int_{\rho/\tau}^\infty [f(\tau - \rho/\zeta) - f(\tau)] \zeta^{k/2-2} e^{-\zeta} d\zeta + f(\tau) \int_0^{\rho/\tau} \zeta^{k/2-2} e^{-\zeta} d\zeta \\ &= \rho^\alpha \int_{\rho/\tau}^\infty \frac{f(\tau - \rho/\zeta) - f(\tau)}{|(\tau - \rho/\zeta) - \tau|^\alpha} \zeta^{k/2-2-\alpha} e^{-\zeta} d\zeta + f(\tau) \int_0^{\rho/\tau} \zeta^{k/2-2} e^{-\zeta} d\zeta \end{aligned}$$

for  $\alpha \in (0, 1)$ . Thus, with  $A = \pi^{-3/2}d_1$  and  $B = 2\pi^{-3/2}D$ ,

$$\begin{aligned} |(K_\rho f)(\tau) - (K_0 f)(\tau)| &\leq \left| \rho^{\alpha_1} A \int_{\rho/\tau}^{\infty} \frac{f(\tau - \rho/\zeta) - f(\tau)}{|(\tau - \rho/\zeta) - \tau|^{\alpha_1}} \zeta^{3/2-2-\alpha_1} e^{-\zeta} dy \right| \\ &\quad + \left| \rho^{\alpha_2} B \int_{\rho/\tau}^{\infty} \frac{f(\tau - \rho/\zeta) - f(\tau)}{|(\tau - \rho/\zeta) - \tau|^{\alpha_2}} \zeta^{5/2-2-\alpha_2} e^{-\zeta} dy \right| \\ &\quad + \left| f(\tau) \int_0^{\rho/\tau} (A\zeta^{3/2-2} + B\zeta^{5/2-2}) e^{-\zeta} d\zeta \right| \\ &=: I_1(\tau) + I_2(\tau) + I_3(\tau). \end{aligned}$$

Select  $\alpha_1 \in (0, 1/2)$ . We find by partial integration

$$\begin{aligned} I_1(\tau) &\leq \rho^{\alpha_1} A \int_{\rho/\tau}^{\infty} \frac{|f(\tau - \rho/\zeta) - f(\tau)|}{|(\tau - \rho/\zeta) - \tau|^{\alpha_1}} \zeta^{3/2-2-\alpha_1} e^{-\zeta} d\zeta \leq \rho^{\alpha_1} A \|f\|_{C^{0,\alpha_1}[0,\tau]} \left( \int_{\rho/\tau}^{\infty} \zeta^{-1/2-\alpha_1} e^{-\zeta} d\zeta \right) \\ &= \rho^{\alpha_1} A \|f\|_{C^{0,\alpha_1}[0,\tau]} \left( \frac{-1}{(1/2 - \alpha_1)} (\rho/\tau)^{1/2-\alpha_1} e^{-\rho/\tau} + \frac{1}{(1/2 - \alpha_1)} \int_{\rho/\tau}^{\infty} \zeta^{1/2-\alpha_1} e^{-\zeta} d\zeta \right) \\ &\leq \rho^{\alpha_1} C \|f\|_{C^{0,\alpha_1}[0,\tau]} (\rho/\tau)^{1/2-\alpha_1} = \rho^{1/2} C \|f\|_{C^{0,\alpha_1}[0,\tau]} / \tau^{1/2-\alpha_1} \leq \rho^{1/2} C \|f\|_{C^{0,1/2}[0,\tau]}. \end{aligned}$$

In  $I_2$  we may directly choose  $\alpha_2 = 1/2$ , and obtain  $I_2(\tau) \leq \rho^{1/2} B \|f\|_{C^{0,1/2}} \Gamma(3/2 - 1/2)$ . Last,

$$\begin{aligned} I_3(\tau) &\leq |f(\tau)| \int_0^{\rho/\tau} (A\zeta^{-1/2} + B\zeta^{1/2}) e^{-\zeta} d\zeta \\ &= |f(\tau)| \left( \int_0^{\rho/\tau} (A + B/2) \zeta^{-1/2} e^{-\zeta} d\zeta - B(\rho/\tau)^{1/2} e^{-\rho/\tau} \right) \\ &\leq |f(\tau)| \int_0^{\rho/\tau} (A + B/2) \zeta^{-1/2} d\zeta - B(\rho/\tau)^{1/2} e^{-\rho/\tau} \leq \rho^{1/2} \frac{f(\tau)}{\tau^{1/2}} C \leq C \rho^{1/2} \|f\|_{C^{0,1/2}} \end{aligned}$$

where we used in the last step that  $f(0) = 0$ . □

**Lemma A.4** For all  $t_1 > 0$  there exists a  $C > 0$  such that if  $\tilde{b}(t) = M a(t)$  then

$$\int_0^t \int_{\partial\Omega} g^2(x, \tau) d\sigma d\tau \leq Ct (1 + \|a\|_{C^{0,1/2}}^2) \text{ for } t \leq t_1. \quad (48)$$

**Proof.** First note that without suitable choice of  $\tilde{b}$ , e.g., for  $\tilde{b} \equiv 0$  and  $a \not\equiv 0$ , we obviously have  $\int_0^t \int_{\partial\Omega} g^2(x, \tau) d\sigma d\tau \sim R^{-2}$ . Denote

$$\tilde{a}(t) := a(t) - a_0$$

such that  $\hat{c}(t) := \tilde{b} - 4\pi D \alpha_0 = \hat{a}$ . Then, since  $\tilde{a}(0) = 0$ , we have, for  $|x| = R$ , and using  $\rho = R^2/(4D)$ ,

$$\begin{aligned} \int_0^t g^2(x, \tau) d\tau &= \int_0^t \left[ \frac{1}{R^4} \int_0^\tau \hat{a}(\tau - \sigma) \phi\left(\frac{R^2}{4D\sigma}\right) d\sigma - \frac{d_2}{R^2} \tilde{a}(\tau) + \frac{1}{R} g_2(x, \tau) \right]^2 d\tau \\ &= \int_0^t \left[ \frac{1}{\rho} \frac{1}{4D} (K_\rho \hat{a}(\tau) - 4D d_2 \tilde{a}(\tau)) + \frac{1}{R} g_2(x, t) \right]^2 d\tau \\ &\leq \frac{1}{\rho^2} \frac{1}{16D^2} \int_0^t |(K_\rho \hat{a})(\tau) - 4D d_2 \tilde{a}(\tau)|^2 d\tau + \frac{1}{R^2} \int_0^t g_2^2(x, \tau) d\tau. \end{aligned}$$

Thus, choosing  $\hat{a} = M\tilde{a}(t)$  the first integrand can be estimated, for each  $\tau$ , as

$$|(K_\rho \hat{a}) - 4Dd_2\tilde{a}| = |K_\rho \hat{a} - K_0 \hat{a}| \leq \|\mathcal{R}\hat{a}\|_{C^0} \leq C\rho^{1/2} \|\hat{a}\|_{C^{0,1/2}} \leq CR^2(1 + \|a\|_{C^{0,1/2}}).$$

Moreover,  $\frac{1}{R^2} \int_0^t g_2^2(x, \tau) d\tau \leq CtR^{-2}$ , thus

$$\int_0^t g^2(x, \tau) d\tau \leq CtR^{-2}(1 + \|a\|_{C^{0,1/2}}^2),$$

and integrating over  $\partial\Omega$  now yields the result.  $\square$

To compare solutions of the full problem (39) and the auxiliary problem (40) we finally need to estimate the differences of the traces of  $u$  and  $p$  on  $\partial\Omega$ . For this we start with some explicit calculations involving  $\widehat{T}_R$ . For  $b \in C^1(\mathbb{R}_+)$ , let  $p = p_1 + p_2$  be the solution of

$$\partial_t p = D\Delta p + M b(t)\delta_0, \quad p_0 = \alpha_0\psi,$$

i.e.,  $p_1(x, t) = \int_0^t k(x, t - \tau)(Mb(\tau) - 4\pi D\alpha_0) d\tau + \alpha_0\psi_c$ , cf. (44), such that

$$(\widehat{T}_R Mb)(t) = \frac{1}{R} \int_{\partial\Omega} p_1(x, t) do.$$

We find

$$\begin{aligned} (\widehat{T}_R Mb)(t) &= \frac{1}{R} \int_{\partial\Omega} \int_0^t \frac{1}{(4\pi D(t - \tau))^{3/2}} e^{-x^2/(4D(t - \tau))} (Mb(\tau) - 4\pi D\alpha_0) d\tau do + 4\pi\alpha_0 \\ &= 4\pi R \int_0^t \frac{1}{(4\pi D(t - \tau))^{3/2}} e^{-R^2/(4D(t - \tau))} (Mb(\tau) - 4\pi D\alpha_0) d\tau + 4\pi\alpha_0 \\ &= \frac{1}{\sqrt{\pi D}} \int_{R^2/4Dt}^\infty \xi^{-1/2} e^{-\xi} (Mb(t - R^2/(4D\xi)) - 4\pi D\alpha_0) d\xi + 4\pi\alpha_0. \end{aligned}$$

Moreover, using

$$\int_{R^2/4Dt}^\infty \xi^{-1/2} e^{-\xi} d\xi = \Gamma(1/2) - \int_0^{R^2/4Dt} \xi^{-1/2} e^{-\xi} d\xi$$

and  $Mb(0) = 4\pi D\alpha_0$  we obtain

$$\begin{aligned} &\left| (\widehat{T}_R Mb)(t) - \frac{M}{D} b(t) \right| \\ &= \left| \frac{M}{\sqrt{\pi D}} \left[ (b(t) - 4\pi D\alpha_0) \int_0^{R^2/4Dt} \xi^{-1/2} e^{-\xi} d\xi + \int_{R^2/4Dt}^\infty \xi^{-1/2} e^{-\xi} (b(t - \frac{R^2}{4D\xi}) - b(t)) d\xi \right] \right| \\ &\leq C \|b'\|_{C^0} \int_0^{R^2/4Dt} \xi^{-1/2} e^{-\xi} d\xi + CR^2 \|b'\|_{C^0} \int_{R^2/4Dt}^\infty \xi^{-3/2} e^{-\xi} d\xi \\ &\leq CR\sqrt{t} \|b'\|_{C^0} \end{aligned} \tag{49}$$

Finally, for  $a, b \in C^0$  we have

$$\|\widehat{T}_R a - \widehat{T}_R b\|_{L^\infty(0, t_1)} \leq C \|a - b\|_{L^\infty(0, t_1)}. \tag{50}$$

Setting  $\zeta = a - b$  and assuming w.l.o.g.  $a_0 = b_0$  this follows from

$$\begin{aligned} \|\widehat{T}_R a - \widehat{T}_R b\|_{L^\infty(0, t_1)} &= \frac{1}{R} \sup_{t \in (0, t_1)} \int_{\partial\Omega} \int_0^t \frac{1}{(4\pi D(t - \tau))^{3/2}} e^{-x^2/(4D(t - \tau))} \zeta(\tau) d\tau do \\ &\leq 4\pi \|\zeta\|_{L^\infty(0, t_1)} R \sup_{t \in (0, t_1)} \int_0^t \frac{1}{(4\pi D(t - \tau))^{3/2}} e^{-R^2/(4D(t - \tau))} d\tau \\ &\leq C \|\zeta\|_{L^\infty(0, t_1)} \sup_{t \in (0, t_1)} \int_{R^2/(4Dt)}^\infty \xi^{-1/2} e^{-\xi} d\xi \leq C \|\zeta\|_{L^\infty(0, t_1)} \Gamma(1/2) = C \|\zeta\|_{L^\infty(0, T)}. \end{aligned}$$

**Lemma A.5** For  $a, b$  as above we have  $\|T_R a - \widehat{T}_R M a\|_{L^1(0, t_1)} \leq C R t_1 (1 + \|a\|_{C^{0,1/2}})$ .

**Proof.** We have

$$(T_R a)(t) - (\widehat{T}_R M a)(t) = \frac{1}{R} \int_{\partial\Omega} u(x, t) - p_1(x, t) do = \frac{1}{R} \int_{\partial\Omega} w(x, t) + p_2(x, t) do,$$

with  $\|p_2\|_{L^\infty(\partial\Omega)} \leq C$ , cf. Lemma A.1. Next, reasoning like in Lemma A.2 we have

$$\begin{aligned} 0 &\leq D \int_0^t \int_{\Omega} |\nabla w|^2 dx d\tau + \frac{1}{2} \int_{\Omega} w^2(x, t) dx \\ &= - \int_0^t \frac{d_1}{R} \int_{\partial\Omega} w^2 do - \int_{\partial\Omega} [R^{-1/2} d_1^{1/2} w][g(x, t) R^{1/2} d_1^{-1/2}] do d\tau \\ &\leq - \frac{d_1}{2R} \int_0^t \int_{\partial\Omega} w^2 do d\tau + \frac{R}{2d_1} \int_0^t \int_{\partial\Omega} g^2(x, t) do d\tau \end{aligned}$$

and hence

$$\int_0^t \int_{\partial\Omega} w^2 do d\tau \leq \frac{R^2}{d_1^2} \int_0^t \int_{\partial\Omega} g^2 do d\tau.$$

Thus

$$\begin{aligned} \|T_R a - \widehat{T}_R M a\|_{L^1(0, t_1)} &\leq \frac{1}{R} \int_0^{t_1} \left| \int_{\partial\Omega} w(x, \tau) do \right| d\tau + C R t_1 \\ &\leq \frac{1}{R} \int_0^{t_1} \left( \int_{\partial\Omega} 1^2 do \right)^{1/2} \left( \int_{\partial\Omega} w^2(x, \tau) do \right)^{1/2} d\tau + C R t_1 \leq C \int_0^{t_1} \left( \int_{\partial\Omega} w^2(x, \tau) do \right)^{1/2} d\tau + C R t_1 \\ &\leq \sqrt{t_1} C \left( \int_0^{t_1} \int_{\partial\Omega} w^2(x, \tau) do \right)^{1/2} d\tau + C R t_1 \leq C R \sqrt{t_1} \left( \int_0^{t_1} \int_{\partial\Omega} g^2(x, \tau) do d\tau \right)^{1/2} + C R t_1 \end{aligned}$$

and the result now follows from Lemma A.4.  $\square$

### A.3 The full problem

**Proof of Theorem 2.4.** Let  $a, b$  be the solutions of (14), (15), respectively. We write the ODEs for  $a$  resp.  $b$  as

$$\begin{aligned} a'(t) &= f(a(t)) - 4\pi d_2 a(t) + d_1 (T_R a)(t), & a(0) &= a_0, \\ b'(t) &= f(b(t)) - 4\pi d_2 b(t) + d_1 (\widehat{T}_R M b)(t), & b(0) &= a_0, \end{aligned}$$

where we know that

$$\begin{aligned} \|T_R a - \widehat{T}_R M a\|_{L^1(0, t_1)} &\leq C R t_1 (1 + \|a\|_{C^{0,1/2}}), \\ \|\widehat{T}_R a - \widehat{T}_R b\|_{L^\infty(0, t_1)} &\leq C_2 \|a - b\|_{L^\infty(0, t_1)}. \end{aligned}$$

For  $\zeta = a - b$  we obtain

$$\begin{aligned} |\zeta(t)| &= \left| \zeta(0) + \int_0^t \zeta' d\tau \right| \\ &\leq \int_0^t \left[ |f(a) - f(b)| + 4\pi d_2 |a - b| + d_1 |T_R a - \widehat{T}_R M a| + d_1 |\widehat{T}_R M a - \widehat{T}_R M b| \right] d\tau \\ &\leq d_1 \|T_R M a - \widehat{T}_R M a\|_{L^1} + C \int_0^t \eta d\tau \leq C R t (1 + \|a\|_{C^{0,1/2}}) + C \int_0^t \eta d\tau \end{aligned}$$

where  $\eta(\tau) = \sup_{0 \leq \sigma \leq \tau} \zeta(\sigma)$ . In particular,  $\eta(t) \leq CRt(1 + \|a\|_{C^{0,1/2}}) + C \int_0^t \eta(\tau) d\tau$ , and Gronwall's inequality yields the result.  $\square$

**Proof of Corollary 2.5.** The solutions  $a, b$  of (14), (15) depend on  $R$  and thus henceforth in particular  $b$  is denoted by  $b_R$ . From Theorem 2.4 we have  $b_R(t) = a(t) + Rc_R(t)$  with  $\|c_R(t)\|_{C^0} \leq C$  and  $a \in C^0([0, t_1])$  uniformly bounded by Theorem 2.1 and also equicontinuous since also  $\|a\|_{C^1} \leq C$  independent of  $R$ . Therefore,  $(b_R)_{0 < R < R_0}$  is also uniformly bounded and equicontinuous, and thus by Arzela–Ascoli we have  $b_R \rightarrow b \in C^0([0, t_1])$  as  $R \rightarrow 0$ , at least for a subsequence. It remains to show that  $b$  fulfills (4).

Equation (15) for  $b_R$  is equivalent to

$$b_R(t) = b_R(0) + \int_0^t h_R(b_R)(\tau) d\tau$$

with  $h_R(b_R)(\tau) = f(b_R(\tau)) - 4\pi d_2 b_R(\tau) + d_1(\widehat{T}_R M b_R)(\tau)$ . We show that

$$\int_0^t h_R(b_R)(\tau) d\tau \rightarrow \int_0^t h(b(\tau)) d\tau \text{ for } R \rightarrow 0$$

with  $h(b(\tau)) = f(b(\tau)) - Mb = f(b(\tau)) - 4\pi d_2 b(\tau) + d_1 \frac{M}{D} b(\tau)$ . For the first two terms in  $h_R(b_R)$  we have uniform convergence  $|f(b_R(\tau)) - 4\pi d_2 b_R(\tau) - f(b(\tau)) - 4\pi d_2 b(\tau)| \leq C\|b_R - b\|_{C^0} \leq CR$ . Finally, using (49), and setting  $b_R = b + Re_R$  with  $\|e_R\|_{C^0} \leq C$  and  $e_R(0) = 0$  we also find

$$\int_0^t \left| (\widehat{T}_R M b_R)(\tau) - \frac{M}{D} b(\tau) \right| d\tau \leq \int_0^t \left| (\widehat{T}_R M b)(\tau) - \frac{M}{D} b(\tau) \right| + R \left| (\widehat{T}_R e_R)(\tau) \right| d\tau \leq CR\|b\|_{C^1} \quad (51)$$

uniformly in  $0 \leq t \leq t_1$ .  $\square$

#### A.4 Improved Approximation with delay

In Lemma A.3 we showed that, for  $f(0) = 0$ ,

$$\|R_\rho f\|_{C^0} \leq C\rho^{1/2}\|f\|_{C^{0,1/2}[0,t_1]}, \quad (52)$$

with the residual  $R_\rho f$  defined by

$$R_\rho f = K_\rho f - K_0 f$$

where we recall  $(K_\rho f)(t) = d_1 \pi^{-3/2} (F_{\rho,3} f)(t) + 2D \pi^{-3/2} (F_{\rho,5} f)(t)$ ,  $K_0 f(t) = \pi^{-1} (d_1 + D) f(t)$ . This was used in Lemma A.4 to construct and estimate the approximation  $\tilde{b}(t) = Ma(t)$  of the solution  $b$  of the integral equation

$$K_\rho b = 4Dd_2 a. \quad (53)$$

The purpose of this appendix is to find the improved approximation  $b_{\text{del}}$  of (53), i.e., to prove Theorem 2.6. From  $K_\rho \rightarrow K_0$  we may use, for  $\rho$  sufficiently small, a formal Neumann's series

$$\begin{aligned} K_\rho^{-1} &= K_0^{-1} (\text{Id} - (\text{Id} - K_0^{-1} K_\rho))^{-1} = K_0^{-1} (2\text{Id} - K_0^{-1} K_\rho + \mathcal{O}((\text{Id} - K_0^{-1} K_\rho)^2)) \\ &= 2K_0^{-1} \text{Id} - K_0^{-2} K_\rho + \mathcal{O}(K_0^{-1} (\text{Id} - K_0^{-1} K_\rho)^2). \end{aligned} \quad (54)$$

The problem with this formula is the loss of regularity in (52). To iterate, i.e., to estimate the second order terms  $K_0^{-2} (K_0 - K_\rho)^2$  in (54), we need a  $C^{0,1/2}$ -bound for  $\mathcal{R}_\rho f$ .

**Lemma A.6** *Let  $f \in C^{1,1/2}(\mathbb{R}_+)$ ,  $f(0) = 0$ . Then*

$$\|\mathcal{R}_\rho f\|_{C^{0,1/2}[0,t_1]} \leq C\|f\|_{C^{1,1/2}[0,t_1]} \rho^{1/2}. \quad (55)$$

We postpone the proof to the end of the section and first show that we obtain an improved approximation of  $a$ .

**Corollary A.7** *Let  $a \in C^{1,1/2}$  with  $a(0) = 0$ . Defining*

$$b_{\text{del}}(t) = ((2K_0^{-1} - K_0^{-2}K_\rho)4Dd_2a)(t) = 2Mb(t) - \frac{\pi M}{d_1 + D} \int_0^t b(t - \sigma) \frac{4D}{R^2} \phi(R^2/(4D\sigma)) d\sigma \quad (56)$$

we find

$$\|(K_\rho b_{\text{del}})(\tau) - 4Dd_2a(\tau)\|_{C^0} \leq C\rho \|a\|_{C^{1,1/2}}.$$

**Proof.** This follows from combining Lemma A.3 and Lemma A.6, i.e.,

$$\begin{aligned} (\sqrt{\pi}(A + 2B))^2 |K_\rho b_{\text{del}} - a| &= (\sqrt{\pi}(A + B/2))^2 \left| \frac{-K_\rho K_\rho a}{\pi(A + B/2)^2} + \frac{2K_\rho a}{\sqrt{\pi}(A + B/2)} - a \right| \\ &= |-K_\rho(K_\rho a - \sqrt{\pi}(A + B/2)a + \sqrt{\pi}(A + B/2)(K_\rho a - \sqrt{\pi}(A + B/2)a)| \\ &= |R_\rho(R_\rho a)| \leq C\rho^{1/2} \|R_\rho a\|_{C^{0,1/2}} \leq C\rho \|a\|_{C^{1,1/2}}. \quad \square \end{aligned}$$

**Proof of Theorem 2.6.** We now compare the solution  $a$  of (14) for  $a_0 = 0$  and  $u_0 = 0$  with the solution of the delayed ODE

$$b'(t) = f(b(t)) - 4\pi d_2 b + d_1(\widehat{T}_R b_{\text{del}})(t), \quad b(0) = 0. \quad (57)$$

Since  $a \in C^{1,1/2}([0, t_1])$ , see Remark 2.2, and as

$$g(x, t) = \frac{1}{R^4} \int_0^t b(\tau) \phi(R^2/(4D(t - \tau))) d\tau - \frac{d_2 a(t)}{R^2} = \frac{1}{4DR^2} [K_{R^2/(4D)} b_{\text{del}}(t) - 4Dd_2 a(t)],$$

we find

$$\begin{aligned} \int_0^t \int_{\partial\Omega} g^2(x, \tau) d\sigma &\leq \frac{1}{16D^2 R^4} \int_0^t \int_{\partial\Omega} [K_{R^2/(4D)} b_{\text{del}}(t) - 4Dd_2 a(t)]^2 dt \\ &\leq \frac{1}{16D^2 R^4} \int_0^t \int_{\partial\Omega} [C\|a\|_{C^{1,1/2}} R^2/(4D)]^2 dt = CtR^2 \|a\|_{C^{1,1/2}}^2, \end{aligned}$$

and the remainder of the proof works as the one of Theorem 2.4.  $\square$

It remains to give the somewhat lengthy

**Proof of Lemma A.6.** We claim that  $\|\mathcal{R}_\rho f\|_{C^{0,1/2}} = \|K_\rho f - K_0 f\|_{C^{0,1/2}} \leq C\rho^{1/2} \|f\|_{C^{1,1/2}}$  where

$$(\mathcal{R}_\rho f)(\tau) = (F_{\rho,3} f)(\tau) + F_{\rho,3} f(\tau) - (F_{0,3} f(\tau) + F_{0,5} f(\tau)).$$

For  $k = 3, 5$  we split

$$\begin{aligned} &|\tau_2 - \tau_1|^{-1/2} \left[ (F_{\rho,k} f)(\tau_1) - (F_{\rho,k} f)(\tau_2) - (F_{0,k} f(\tau_1) - F_{0,k} f(\tau_2)) \right] \\ &= |\tau_2 - \tau_1|^{-1/2} \left( \int_{\rho/\tau_1}^\infty [f(\tau_1 - \rho/\zeta) - f(\tau_1)] \zeta^{k/2-2} e^{-\zeta} dy + f(\tau_1) \int_0^{\rho/\tau_1} \zeta^{k/2-2} e^{-\zeta} d\zeta \right) \\ &\quad - |\tau_2 - \tau_1|^{-1/2} \left( \int_{\rho/\tau_2}^\infty [f(\tau_2 - \rho/\zeta) - f(\tau_2)] \zeta^{k/2-2} e^{-\zeta} dy + f(\tau_2) \int_0^{\rho/\tau_2} \zeta^{k/2-2} e^{-\zeta} d\zeta \right) \\ &= T_{1,k} + T_{2,k} + T_{3,k} + T_{4,k}, \end{aligned}$$

where  $0 < \tau_1 < \tau_2 < t_1$  and

$$\begin{aligned} T_{1,k} &= |\tau_2 - \tau_1|^{-1/2} \int_{\rho/\tau_1}^{\infty} [f(\tau_1 - \rho/\zeta) - f(\tau_2 - \rho/\zeta) - f(\tau_1) + f(\tau_2)] \zeta^{k/2-2} e^{-\zeta} d\zeta, \\ T_{2,k} &= |\tau_2 - \tau_1|^{-1/2} \int_{\rho/\tau_2}^{\rho/\tau_1} [f(\tau_2 - \rho/\zeta) + f(\tau_2)] \zeta^{k/2-2} e^{-\zeta} d\zeta, \\ T_{3,k} &= |\tau_2 - \tau_1|^{-1/2} f(\tau_1) \int_{\rho/\tau_2}^{\rho/\tau_1} \zeta^{k/2-2} e^{-\zeta} d\zeta, \\ T_{4,k} &= |\tau_2 - \tau_1|^{-1/2} [f(\tau_1) - f(\tau_2)] \int_0^{\rho/\tau_2} \zeta^{k/2-2} e^{-\zeta} d\zeta. \end{aligned}$$

In the following we estimate term by term, always assuming  $0 < \tau_1 < \tau_2 < t_1$ . The critical terms are  $T_{1,k}$  which yield  $\|f\|_{C^{1,1/2}}$  on the right hand side of (55), while the estimates for all other  $T_{i,k}$  involve only  $\|f\|_{C^1}$ .

**a) ad  $T_{1,k}$ .** We have

$$\begin{aligned} T_{1,k} &= \int_{\rho/\tau_1}^{\infty} \left( \int_0^{\rho/\zeta} \frac{|f'(\tau_2 - x) - f'(\tau_1 - x)|}{\sqrt{|\tau_2 - \tau_1|}} dx \right) \zeta^{k/2-2} e^{-\zeta} d\zeta \\ &\leq \rho \int_{\rho/\tau_1}^{\infty} \|f'\|_{C^{0,1/2}} \zeta^{k/2-3} e^{-\zeta} d\zeta \leq C\rho^{1/2} \|f\|_{C^{1,1/2}}, \end{aligned}$$

where for  $k = 3$  we used

$$\int_{\rho/\tau_1}^{\infty} \zeta^{3/2-3} e^{-\zeta} d\zeta = \int_{\rho/\tau_1}^1 \zeta^{3/2-3} e^{-\zeta} d\zeta + \int_1^{\infty} \zeta^{3/2-3} e^{-\zeta} d\zeta \leq 2\rho^{-1/2} \tau_1^{1/2} + C.$$

while for  $k = 5$  we integrate by parts.

**b) ad  $T_{3,k}$ .** For  $k = 3$  we have

$$\begin{aligned} |T_{3,3}| &= \frac{|f(\tau_1)|}{\sqrt{\tau_2 - \tau_1}} \int_{\rho/\tau_2}^{\rho/\tau_1} \zeta^{-1/2} e^{-\zeta} d\zeta \leq \frac{|f(\tau_1)|}{\sqrt{\tau_2 - \tau_1}} \int_{\rho/\tau_2}^{\rho/\tau_1} \zeta^{-1/2} d\zeta \\ &= |f(\tau_1)| 2\rho^{1/2} \left( \frac{1}{\sqrt{\tau_1}} - \frac{1}{\sqrt{\tau_2}} \right) \frac{1}{\sqrt{\tau_2 - \tau_1}} = 2\rho^{1/2} \frac{|f(\tau_1)|}{\sqrt{\tau_1 \tau_2}} \frac{\sqrt{\tau_2} - \sqrt{\tau_1}}{\sqrt{\tau_2 - \tau_1}} \\ &\leq 2\rho^{1/2} \frac{|f(\tau_1)|}{\tau_1} \frac{(\sqrt{\tau_2} - \sqrt{\tau_1})(\sqrt{\tau_1} + \sqrt{\tau_2})}{\sqrt{\tau_2 - \tau_1}(\sqrt{\tau_1} + \sqrt{\tau_2})} = 2\rho^{1/2} \frac{|f(\tau_1)|}{\tau_1} \frac{\sqrt{\tau_2} - \sqrt{\tau_1}}{\sqrt{\tau_1} + \sqrt{\tau_2}}. \end{aligned}$$

Now,  $f(\tau_1)/\tau_1 = f'(\theta)$  for some  $\theta \in (0, \tau_1)$  as  $f(0) = 0$ , and thus  $|f(\tau_1)/\tau_1| \leq \|f\|_{C^1}$ . The second factor  $\sqrt{\tau_2} - \sqrt{\tau_1}/(\sqrt{\tau_1} + \sqrt{\tau_2}) = 1$  for  $\tau_1 = 0$  and is monotonously decreasing in  $\tau_1$ , thus bounded on  $0 < \tau_1 < \tau_2$ . Hence  $|T_{3,3}| \leq C\rho^{1/2} \|f\|_{C^1}$

For  $k = 5$  we use integration by parts to find

$$\begin{aligned} |T_{3,5}| &= \frac{|f(\tau_1)|}{\sqrt{\tau_2 - \tau_1}} \int_{\rho/\tau_2}^{\rho/\tau_1} \zeta^{1/2} e^{-\zeta} d\zeta \\ &\leq \frac{|f(\tau_1)|}{\sqrt{\tau_2 - \tau_1}} \frac{1}{2} \left[ - \left( \frac{\rho}{\tau_1} \right)^{1/2} e^{-\rho/\tau_1} + \left( \frac{\rho}{\tau_2} \right)^{1/2} e^{-\rho/\tau_2} + \int_{\rho/\tau_2}^{\rho/\tau_1} \zeta^{-1/2} e^{-\zeta} d\zeta \right]. \end{aligned}$$



From  $k = 3$  we already know that  $|f(\tau_1)| \int_{\rho/\tau_2}^{\rho/\tau_1} \zeta^{-1/2} e^{-\zeta} d\zeta / \sqrt{\tau_2 - \tau_1} \leq C\sqrt{\rho} \|f\|_{C^1}$ , and it remains to estimate the remaining part

$$\begin{aligned} \frac{|f(\tau_1)|}{\sqrt{\tau_2 - \tau_1}} \frac{1}{2} \left[ - \left( \frac{\rho}{\tau_1} \right)^{1/2} e^{-\rho/\tau_1} + \left( \frac{\rho}{\tau_2} \right)^{1/2} e^{-\rho/\tau_2} \right] &= \frac{\sqrt{\rho} |f(\tau_1)|}{2} \frac{-\sqrt{\tau_2} e^{-\rho/\tau_1} - \sqrt{\tau_1} e^{-\rho/\tau_2}}{\sqrt{\tau_1 \tau_2} \sqrt{\tau_2 - \tau_1}} \\ &= \frac{\sqrt{\rho} |f(\tau_1)|}{2} \frac{\sqrt{\tau_1} - \sqrt{\tau_2}}{\sqrt{\tau_1 \tau_2} \sqrt{\tau_2 - \tau_1}} e^{-\rho/\tau_1} + \frac{\sqrt{\rho} |f(\tau_1)|}{2} \frac{\sqrt{\tau_1} e^{-\rho/\tau_2} - e^{-\rho/\tau_1}}{\sqrt{\tau_1 \tau_2} \sqrt{\tau_2 - \tau_1}}. \end{aligned}$$

The first term in the last sum is again known from case  $k = 3$ . Concerning the second we have  $|f(\tau_1)|/\sqrt{\tau_1 \tau_2} \leq \|f\|_{C^1}$  as before, and it remains to show that  $\sqrt{\tau_1} \frac{e^{-\rho/\tau_2} - e^{-\rho/\tau_1}}{\sqrt{\tau_2 - \tau_1}}$  is bounded. With  $x = \tau_1/\tau_2 \in (0, 1)$  and  $z = \rho/\tau_2 \in \mathbb{R}_+$  we have

$$\sqrt{\tau_1} \frac{e^{-\rho/\tau_2} - e^{-\rho/\tau_1}}{\sqrt{\tau_2 - \tau_1}} = \sqrt{\tau_1/\tau_2} \frac{e^{-\rho/\tau_2} - e^{-(\rho/\tau_2)(\tau_2/\tau_1)}}{\sqrt{1 - \tau_1/\tau_2}} = \sqrt{x} \frac{e^{-z} - e^{-z/x}}{\sqrt{1 - x}} = h_1(x, z).$$

We fix  $x_0 \in (0, 1)$  and compute  $z_0 = z_0(x_0) = -x_0 \ln(x_0)/(1 - x_0)$  which maximizes  $h_1(x_0, \cdot)$ . This defines

$$h_2(x) = \sqrt{x} \frac{e^{\frac{x \ln(x)}{1-x}} - e^{\frac{x \ln(x)}{x(1-x)}}}{\sqrt{1-x}} = \sqrt{x} e^{\frac{\ln(x)}{1-x}} \frac{1/x - 1}{\sqrt{1-x}} = \frac{e^{\frac{\ln(x)}{1-x}}}{\sqrt{x}} \sqrt{1-x} = x^{1/(1-x)-1/2} \sqrt{1-x},$$

which on  $[0, 1]$  is bounded by  $x^{1/2}(1-x)^{1/2} \leq 1/2$ . Altogether,  $|T_{3,k}| \leq C\rho^{1/2} \|f\|_{C^1}$ .

**c) ad  $T_{2,k}$ .** For  $k = 3$  we have

$$|T_{2,3}| \leq \frac{\rho \|f'\|_{C^0}}{\sqrt{\tau_2 - \tau_1}} \int_{\rho/\tau_2}^{\rho/\tau_1} \zeta^{3/2-3} d\zeta \leq \rho^{1/2} \|f'\|_{C^0} \frac{\sqrt{\tau_2} - \sqrt{\tau_1}}{\sqrt{\tau_2 - \tau_1}}.$$

The last factor equals  $\frac{\sqrt{\tau_2} - \sqrt{\tau_1}}{\sqrt{\tau_1} + \sqrt{\tau_2}}$  and is therefore bounded as in **b)**. Thus  $|T_{2,3}| \leq C\rho^{1/2} \|f\|_{C^1}$ .

Also  $|T_{2,5}| \leq C\rho^{1/2} \|f\|_{C^1}$  by a similar estimate.

**d) ad  $T_{4,k}$ .** Here  $|T_{4,3}| \leq \|f'\|_{C^0} \sqrt{\tau_2 - \tau_1} \int_0^{\rho/\tau_2} \zeta^{3/2-2} d\zeta \leq C\rho^{1/2} \|f\|_{C^1}$ , and integrating by parts for  $k = 5$  yields a similar result.  $\square$

## B Proof of approximation results: several cells

The basic idea for  $N \geq 2$  cells is to introduce a delta source for each cell, i.e., to consider

$$p_t = D\Delta p + \sum_{i=1}^N \tilde{b}_i(t) \delta_{x_i}(x), \quad p|_{t=0} = \psi_c|_{t=0}, \quad (58a)$$

$$b'_i = f(b_i) - 4\pi d_2 b_i + \int_{\partial\Omega_i} \frac{d_1}{R} p d\sigma, \quad b_i(0) = a_{i0}, \quad i = 1, \dots, N, \quad (58b)$$

with  $\psi_c(x, t) = \sum_{i=1}^N \frac{d_2 a_i(t)}{d_1 + D} \frac{\chi(\|x - x_i\|)}{\|x - x_i\|} \Big|_{\Omega}$ , cf. (24). The ODEs (58b) can then be rewritten as

$$b'_i = f(b_i) - 4\pi d_2 b_i + d_1 (\widehat{T}_R^i \tilde{b})(t) + r, \quad (59)$$

$$(\widehat{T}_R^i \tilde{b})(t) = \frac{1}{R} \int_{\partial\Omega_i} p(x, t) d\sigma = \frac{1}{R} \int_{\partial\Omega_i} \left( \int_0^t \sum_j \frac{1}{(4\pi D(t-\tau))^{3/2}} e^{-\|x-x_j\|^2/4D(t-\tau)} \tilde{b}_j(\tau) d\tau \right) d\sigma, \quad (60)$$

with  $r$  due to the initial conditions, i.e.,  $r \equiv 0$  if  $\psi_c|_{t=0} = 0$ . The proof Theorem 2.10 again consists of two parts: first, given  $a := (a_1(t), \dots, a_N(t))$ , we need a good choice of  $\tilde{b} := (\tilde{b}_1, \dots, \tilde{b}_N)$  to control the difference between the solution  $p$  of (58) and the outer field  $u(x, t)$  on the boundary  $\partial\Omega$ ; see Lemma B.4. Second, the communication terms  $\int_{\partial\Omega_i} \frac{d_1}{R} p \, do$  are to be replaced by functionals of  $\tilde{b}$ ; see Lemma B.6. The proofs parallel that for one cell; most computations are straight forward (though often tedious) generalization of the one-cell-case. We only sketch the differences, and start with the scaled case  $\|x_i - x_j\| = \delta_{ij} = R^{2\eta} \tilde{\delta}_{ij}$ .

Using explicit heat kernel calculations we first obtain the following generalization of Lemma A.1.

**Lemma B.1** *Let  $w(x, t) = u(x, t) - p(x, t)|_{\Omega}$ . Then  $w(x, t)$  satisfies*

$$w_t = D\Delta w \text{ in } \Omega, \quad w(0, x) = 0, \quad B_i w = -g_i(x, t) \text{ on } \partial\Omega_i, \quad (61)$$

where

$$\begin{aligned} g_i(x, t) &= \frac{1}{16D^2} \frac{1}{\rho} \left\{ (K_\rho[\tilde{b}_i - 4\pi D\alpha_{i0}])(t) - 4D d_2(a_i(t) - a_{i0}) \right\} \\ &\quad + \sum_{j \neq i} \left\{ \frac{d_1}{16D^2} \rho^{-1/2-\eta} (H_{1,\rho}^j \tilde{b}_j)(x, t) - 2D(4D)^{4-2\eta} \rho^{-\eta/2} (H_{2,\rho}^{i,j} \tilde{b}_j)(x, t) \right\} \\ &\quad + \rho^{-1/2} g_2^i(x, t), \end{aligned}$$

with

$$\begin{aligned} (H_{1,\rho}^j f)(x, t) &= \rho^\eta \pi^{-3/2} \int_0^t f(t-\tau) \tau^{-3/2} e^{-\|x-x_j\|^2/(4D\tau)} \, d\tau, \\ (H_{2,\rho}^{i,j} f)(x, t) &= \rho^{\eta-1/2} \pi^{-3/2} \int_0^t f(t-\tau) \tau^{-5/2} e^{-\|x-x_j\|^2/(4D\tau)} \, d\tau \langle x - x_i, x - x_j \rangle, \end{aligned}$$

and  $\|g_2^i\|_\infty = \mathcal{O}(1)$ .

**Remark B.2** The reason for splitting off  $\rho^{-1/2-\eta}$  respectively  $\rho^{-\eta/2}$  from  $H_{1,\rho}^j f$  and  $H_{2,\rho}^{i,j} f$  is that this way both terms are of order  $\rho^0$ . For  $H_{1,\rho}^j f$  we show this explicitly in Lemma B.7 below, while for  $H_{2,\rho}^{i,j} f$  we may estimate, using  $\|x - x_i\| = \mathcal{O}(\rho^{1/2})$  and  $\|x_i - x_j\| = \mathcal{O}(\rho^{\eta/2})$ ,

$$\|H_{2,\rho}^{i,j} f\|_{C^0} \leq C \rho^{3\eta/2} \|f\|_{C^0} \int_0^t \tau^{-5/2} e^{-\rho^\eta/\tau} \leq C \|f\|_{C^0} \Gamma(3/2).$$

Thus, the second interaction term  $H_{2,\rho}^{i,j} \tilde{b}_j$  can be neglected, while the first interaction term has to be taken into account, also if we scale the distances of cells  $\|x_i - x_j\|$  by  $\rho^\eta$ ,  $\eta \in (0, 1/2)$ .

## B.1 Low order approximation

Let  $\delta_{ij} = R^{2\eta} \tilde{\delta}_{ij}$ . Similarly to  $K_\rho$  in Lemma A.3, the interaction delay terms  $H_{1,\rho}^j f$  may be approximated by undelayed terms as  $\rho \rightarrow 0$ . Also the proof parallels that of Lemma A.3.

**Lemma B.3** *Assume  $\eta \in (0, 1/2)$  and  $f \in C^{0,1/2}[0, t]$ . There exists a  $C > 0$  such that for all  $x \in \partial\Omega_i$  and  $j \neq i$*

$$\|H_{1,\rho}^j f(x, \cdot) - H_{1,0}^{i,j} f(\cdot)\|_{C^0} \leq C \rho^\eta \|f\|_{C^{0,1/2}[0,t]}, \text{ where } H_{1,0}^{i,j} f(t) := \frac{(4D)^{1/2-\eta}}{\pi \tilde{\delta}_{i,j}} f(t).$$

We now transfer Lemma A.4 and explain the (to this order) optimal choice  $\tilde{b}_i$ .

**Lemma B.4** *Let  $\eta \in (0, 1/2)$ . For all  $t_1 > 0$  there exists a  $C > 0$  such that if*

$$\tilde{b}_i(t) = Ma_i(t) - (4D\rho)^{1/2-\eta} \frac{d_1 M}{d_1 + D} \sum_{j \neq i} \frac{a_j(t)}{\tilde{\delta}_{i,j}}, \quad (62)$$

then for  $i = 1, \dots, N$  and  $t \leq t_1$

$$\int_0^t \int_{\partial\Omega_i} g_i^2(x, \tau) d\omega d\tau \leq Ct(1 + \|a\|_{C^{0,1/2}}^2).$$

**Proof.** We know that

$$\begin{aligned} \int_0^t g_i(x, \tau)^2 d\tau &= \frac{1}{(16D^2)^2} \int_0^t \left\{ \frac{1}{\rho} \left[ (K_\rho[\tilde{b}_i - 4\pi D\alpha_{i0}])(\tau) - 4D d_2(a_i(\tau) - a_{i0}) \right. \right. \\ &\quad \left. \left. + \sum_{j \neq i} d_1 \rho^{1/2-\eta} (H_{1,\rho}^j \tilde{b}_j)(x, \tau) \right] + \mathcal{O}(\rho^{-1/2}) \right\}^2 d\tau \\ &\leq \left( \frac{1}{16D^2} \right)^2 \rho^{-2} I_{i,\rho}(x, t) + Ct\rho^{-1}, \end{aligned}$$

with

$$I_{i,\rho}(x, t) = \int_0^t \left[ (K_\rho[\tilde{b}_i - 4\pi D\alpha_{i0}])(\tau) - 4D d_2(a_i(\tau) - a_{i0}) + \sum_{j \neq i} d_1 \rho^{1/2-\eta} (H_{1,\rho}^j \tilde{b}_j)(x, \tau) \right]^2 d\tau$$

The aim is to select  $\tilde{b}_i$  in such a way that  $I_{i,\rho} = \mathcal{O}(\rho)$ . We know that, for  $x \in \partial\Omega_i$ ,

$$|K_\rho f - K_0 f| \leq C\rho^{1/2} \|f\|_{C^{0,1/2}}, \quad |H_{1,\rho}^j f - H_{1,0}^j f| \leq C\rho^\eta \|f\|_{C^{0,1/2}}$$

where  $K_0 f = \frac{d_1 + D}{\pi} f$  and  $H_{1,0}^j f = \frac{(4D)^{1/2-\eta}}{\pi \tilde{\delta}_{i,j}} f$ . Thus, if we define  $I_0$  by

$$\begin{aligned} I_{i,0}(t) &= \int_0^t \left[ (K_0[\tilde{b}_i - 4\pi D\alpha_{i0}])(\tau) - 4D d_2(a_i(\tau) - a_{i0}) + \sum_{j \neq i} d_1 \rho^{1/2-\eta} (H_{1,0}^j \tilde{b}_j)(\tau) \right]^2 d\tau \\ &= \int_0^t \left[ \frac{d_1 + D}{\pi} [\tilde{b}_i(t) - 4\pi D\alpha_{i0}] - 4D d_2(a_i(t) - a_{i0}) + \sum_{j \neq i} (4D\rho)^{1/2-\eta} \frac{d_1}{\pi \tilde{\delta}_{i,j}} \tilde{b}_j(t) \right]^2 dt, \end{aligned}$$

then  $|I_\rho - I_0| \leq C\rho \|\tilde{b}_i\|_{C^{0,1/2}}$ , using  $\alpha_{i0} = \frac{M}{4\pi D} a_{i0}$ . It is sufficient to choose  $\tilde{b}_i$ , such that  $I_0 = \mathcal{O}(\rho)$ . Defining  $\tilde{b}_i = Ma_i + \rho^{1/2-\eta} B_i$  and solving for  $B_i$  at  $\mathcal{O}(\rho^{1/2-\eta})$  yields (62).  $\square$

Given  $a_i(t)$  we have an approximation  $p$  of  $u$  such that  $g_i = (Bu - Bp)|_{\Omega_i}$  is  $\mathcal{O}(1)$ . Next we control the inflow into the cell by a lemma paralleling Lemma A.5; we skip the proof.

**Lemma B.5** *Given  $a = (a_1, \dots, a_N)$ , let  $\tilde{b}_i$  be defined by (62). Let  $T_{i,R}a = \frac{1}{R} \int_{\partial\Omega_i} u(t, x)$  and  $\widehat{T}_{i,R}\tilde{b} = \frac{1}{R} \int_{\partial\Omega_i} p_1(t, x)$  where  $p_1$  is the solution of (58) with zero initial data, as in (44) for  $N = 1$ . There exists a  $C > 0$  such that*

$$\|T_{i,R}a - \widehat{T}_{i,R}\tilde{b}\|_{L^1(0,t_1)} \leq C\rho^{1/2}(1 + \|a\|_{C^{0,1/2}}^2).$$

The Lipschitz-continuity of  $\widehat{T}_R^i$  can be shown similarly like that of  $\widehat{T}_R$ , and the proof of Theorem 2.10, i.e., the justification of the delayed ODE system (32), now follows from Gronwall's inequality, exactly as in the proof of Theorem 2.4, replacing  $\rho$  by  $R^2/(4D)$  to obtain  $\tilde{b}_i(t) = Ma_i(t) - R^{1-2\eta} \frac{d_1 M}{d_1 + D} \sum_{j \neq i} \frac{a_j(t)}{\tilde{\delta}_{i,j}}$ .

In order to obtain an ODE from (32) we approximate the delays

$$C_{ij}(t) := \frac{1}{R} \int_{\partial\Omega_i} \int_0^t \frac{1}{(4\pi D(t-\tau))^{3/2}} e^{-\|x-x_j\|^2/4D(t-\tau)} \tilde{b}_j(\tau) d\tau do.$$

**Lemma B.6** *There exists a  $C > 0$  such that*

$$\left| C_{ii}(t) - \frac{\tilde{b}_i(t)}{D} \right| \leq CRt^{1/2} \|\tilde{b}'\|_{C^0}, \text{ and, for } i \neq j, \left| R^{-(1-2\eta)} C_{ij} - \frac{\tilde{b}_j(t)}{D\tilde{\delta}_{ij}} \right| \leq CRt^{1/2} \|\tilde{b}'\|_{C^0}.$$

**Proof.** The first estimate has been already derived in (49). Recalling  $\|x_i - x_j\| = \delta_{ij} = \tilde{\delta}_{ij} R^{2\eta}$  we obtain for  $j \neq i$

$$\begin{aligned} R^{-(1-2\eta)} C_{ij} &= R^{-(1-2\eta)} \frac{1}{R} \int_{\partial\Omega_i} \int_0^t \frac{1}{(4\pi D(t-\tau))^{3/2}} e^{-\|x-x_j\|^2/4D(t-\tau)} \tilde{b}_j(\tau) d\tau do \\ &= 4\pi R^{2\eta} \int_0^t (4\pi D\tau)^{-3/2} e^{-(\delta_{ij} + \mathcal{O}(R))^2/4D\tau} \tilde{b}_j(t-\tau) d\tau \\ &= \frac{R^{2\eta}}{D\pi^{1/2}(\delta_{ij} + \mathcal{O}(R))} \int_{(\delta_{ij} + \mathcal{O}(R))/4Dt}^\infty \xi^{-1/2} e^{-\xi} \tilde{b}_j(t - (\delta_{ij} + \mathcal{O}(R))^2/4D\xi) d\xi \\ &\rightarrow \frac{1}{D\pi^{1/2}\tilde{\delta}_{ij}} \Gamma(1/2) \tilde{b}_j(t) = \frac{1}{D\tilde{\delta}_{ij}} \tilde{b}_j(t) \quad \text{as } R \rightarrow 0, \end{aligned}$$

as in (49). □

Similar to (51), this last estimate is used in the proof of Corollary 2.11, that is, the justification of the approximate system (31), i.e.,

$$b'_i = f(b_i) - 4\pi d_2 b_i + d_1 \sum_{i=1}^N C_{ij} = f(b_i) - Mb_i + R^{1-2\eta} \frac{d_1 M}{d_1 + D} \sum_{j \neq i} \frac{1}{D\tilde{\delta}_{ij}} b_j, \quad (63)$$

where in the second equality we dropped the  $\mathcal{O}(R)$  resp.  $\mathcal{O}(R^{2-2\eta})$  terms from Lemma B.6.

## B.2 Improved Approximation

We now do not scale the distances between cells ( $\eta = 0$ ), and aim at an error bound of order  $R^2$ . For simplicity we again assume zero initial conditions, s.t.  $\alpha_{i0} = a_{i0} = 0$  and consequently  $g_{i,2} = 0$  in Lemma B.1. The analysis proceeds similar to that before; the pertinent approximation of  $H_{1,\rho}^j$ , however, is different.

**Lemma B.7** *There exists a  $C > 0$  such that  $\|H_{1,\rho}^j f - I_{1,0}^{i,j} f\|_{C^0} \leq C\rho^{1/2} \|f\|_{C^0[0,t]}$  for  $x \in \partial\Omega_i$ , where*

$$I_{1,0}^{i,j} f := \int_0^t f(t-\tau) \pi^{-3/2} \tau^{-3/2} e^{-\frac{\|x_i-x_j\|^2}{4D\tau}} d\tau. \quad (64)$$

**Proof.** For  $x \in \partial\Omega_i$ ,

$$\begin{aligned} \|H_{1,\rho}^j f - I_{1,0}^{i,j} f\|_{C^0[0,t]} &= \sup_{t_1 \in [0,t]} \left| \int_0^{t_1} f(t_1 - \tau) \pi^{-3/2} \tau^{-3/2} \left( e^{-\frac{\|x_i - x_j\|^2}{4D\tau}} - e^{-\frac{\|x - x_j\|^2}{4D\tau}} \right) d\tau \right| \\ &\leq C \|f\|_{C^0[0,t]} \int_0^\infty \tau^{-3/2} \left| e^{-\frac{\|x_i - x_j\|^2}{4D\tau}} - e^{-\frac{\|x - x_j\|^2}{4D\tau}} \right| d\tau \\ &\leq C \|f\|_{C^0[0,t]} \left( \int_0^{1/\sqrt{\rho}} \zeta^{-1/2} \left| e^{-\zeta} - e^{-\frac{\|x - x_j\|^2}{\|x_i - x_j\|^2} \zeta} \right| d\zeta + \int_{1/\sqrt{\rho}}^\infty \zeta^{-1/2} \left| e^{-\zeta} - e^{-\frac{\|x - x_j\|^2}{\|x_i - x_j\|^2} \zeta} \right| d\zeta \right) \end{aligned}$$

Now, as  $\| \|x - x_j\| - \|x_i - x_j\| \| \leq C\rho$ ,

$$\begin{aligned} T_1 &:= \int_{1/\sqrt{\rho}}^\infty \zeta^{-1/2} \left| e^{-\zeta} - e^{-\frac{\|x - x_j\|^2}{\|x_i - x_j\|^2} \zeta} \right| d\zeta = \int_{1/\sqrt{\rho}}^\infty \zeta^{-1/2} e^{-\zeta/2} \left| e^{-\zeta/2} - e^{-\left(\frac{\|x - x_j\|^2}{\|x_i - x_j\|^2} - \frac{1}{2}\right)\zeta} \right| d\zeta \\ &\leq 2\sqrt{\rho} \rho^{-1/2} \int_{1/\sqrt{\rho}}^\infty \zeta^{-1/2} e^{-\zeta/2} d\zeta \leq C\sqrt{\rho} \end{aligned}$$

by l'Hospital's rule. Similarly,

$$T_2 := \int_0^{1/\sqrt{\rho}} \zeta^{-1/2} \left| e^{-\zeta} - e^{-\frac{\|x - x_j\|^2}{\|x_i - x_j\|^2} \zeta} \right| d\zeta \leq C\rho^{1/2} \int_0^{1/\sqrt{\rho}} \zeta^{-1/2} e^{-\zeta} d\tau,$$

using  $\left| \left( \frac{\|x - x_j\|^2}{\|x_i - x_j\|^2} - 1 \right) \zeta \right| \leq C\rho\rho^{-1/2} = C\rho^{1/2}$  for  $0 \leq \zeta \leq 1/\sqrt{\rho}$ .  $\square$

Lemma B.4 is slightly modified in order to define the appropriate approximation.

**Lemma B.8** For all  $t_1 > 0$  there exists a  $C > 0$  such that if

$$\begin{aligned} \tilde{c}_{i,del}^0(t) &= M(2I - K_0^{-1}K_\rho)(a_i)(t) \\ \tilde{c}_{i,del}^1(t) &= \frac{\pi d_1}{d_1 + D} \sum_{j \neq i} ((2I - K_0^{-1}K_\rho) \circ I_{1,0}^{i,j})(\tilde{c}_{j,del}^0)(t) \\ \tilde{c}_{i,del}(t) &= \tilde{c}_{i,del}^0(t) - \rho^{1/2} \tilde{c}_{i,del}^1(t) \end{aligned}$$

then, replacing  $\tilde{b}_j$  by  $\tilde{c}_{j,del}$  in the definition of  $g(x, t)$ , for  $i = i, \dots, N$  and  $t \leq t_1$

$$\int_0^t \int_{\partial\Omega_i} g_i^2(x, \tau) d\omega d\tau \leq C\rho^{1/2} t (1 + \|a\|_{C^{1,1/2}}^2).$$

**Proof.** We start off as in the proof of Lemma B.4, and find that ( $a_{i,0} = 0$ ,  $u_0 = 0$ )

$$\int_0^t g_i(x, \tau)^2 d\tau \leq \left( \frac{1}{(4D)^2} \right)^2 \frac{1}{\rho^2} I_{i,\rho}$$

where  $I_{i,\rho}$  assumes the form ( $\eta = 0$ ,  $a_{i,0} = 0$ ,  $u_0 = 0$  and replacing  $\tilde{b}_j$  by  $\tilde{c}_j$ )

$$I_{i,\rho}(x, t) = \int_0^t \left[ (K_\rho \tilde{c}_i)(\tau) - 4D d_2 a_i(\tau) + \sum_{j \neq i} d_1 \rho^{1/2} (H_{1,\rho}^j \tilde{c}_j)(x, \tau) \right]^2 d\tau$$

We aim at a choice of  $\tilde{c}_i$  that leads to  $I_{i,\rho} = \mathcal{O}(\rho^2)$ . As we know from Corollary A.7 that the integral equation  $K_\rho \tilde{c}_i = 4D d_2 a_i$  is solved up to order  $\rho$  by the choice  $\tilde{c}_{i,del}^0(t) = M(2I - K_0^{-1}K_\rho)(a_i)(t)$ , we plug in the ansatz  $\tilde{c}_{i,del}(t) = \tilde{c}_{i,del}^0(t) - \rho^{1/2}B_i(t)$  to obtain

$$\begin{aligned} I_{i,\rho}(x,t) &= \int_0^t \left[ (K_\rho \tilde{c}_i^0)(\tau) - 4D d_2 a_i(\tau) - \rho^{1/2} K_\rho B_i(\tau) + \sum_{j \neq i} d_1 \rho^{1/2} (H_{1,\rho}^j \tilde{c}_j^0)(x,\tau) + \mathcal{O}(\rho) \right]^2 d\tau \\ &= \int_0^t \left[ -\rho^{1/2} \left( K_\rho B_i(\tau) + \sum_{j \neq i} d_1 (I_{1,0}^{i,j} \tilde{c}_j^0)(\tau) \right) + \sum_{j \neq i} d_1 \rho^{1/2} ((H_{1,\rho}^j - I H_{1,0}^{i,j}) \tilde{c}_j^0)(x,\tau) + \mathcal{O}(\rho) \right]^2 d\tau \end{aligned}$$

The natural choice for  $B_i$  that guarantees the necessary approximation order reads

$$B_i = \frac{\pi d_1}{d_1 + D} (2I - K_0^{-1}K_\rho) \sum_{j \neq i} (I_{1,0}^{i,j} \tilde{c}_j^0)(\tau).$$

As for  $x \in \partial\Omega_i$  we know  $\|(H_{1,\rho}^j - I_{1,0}^{i,j})f\|_{C^0} \leq C\rho^{1/2}\|f\|_{C^0}$ , we find  $I_{i,\rho} = \mathcal{O}(\rho^2)$ . □

This lemma implies

$$\|T_R^i a - \widehat{T}_R^i \tilde{c}_{del}\|_{L^1(0,t_1)} \leq C\rho(1 + \|a\|_{C^{1+1/2}(0,t_1)}^2),$$

and as  $\widehat{T}_R^i$  is Lipschitz-continuous, Gronwall's lemma yields the approximation theorem as before, i.e., the solution  $\tilde{c}_{i,del}$  of

$$\tilde{c}'_{i,del} = f(\tilde{c}_{i,del}) - 4\pi d_2 \tilde{c}_{i,del} + \widehat{T}_R^i \tilde{c}_{del} \quad (65)$$

approximates  $a(t)$  up to an error of  $\mathcal{O}(\rho) = \mathcal{O}(R^2)$ . In order to finish the proof of Theorem 2.12 it only remains to compute explicitly an approximation of

$$\begin{aligned} \widehat{T}_R^i \tilde{c}_{i,del} &= R^{-1} (4D\pi)^{-3/2} \int_{\partial\Omega_i} \int_0^t \tau^{-3/2} \sum_{j=1}^N e^{-\|x-x_j\|^2/(4D\tau)} \tilde{c}_{j,del}(t-\tau) d\tau d\omega \\ &= \sum_{j \neq i} \rho^{-1/2} (4D)^{-2} \int_{\partial\Omega_i} (H_{1,\rho}^j \tilde{c}_{i,del})(t,x) d\omega + \widehat{T}_R^i \tilde{c}_{i,del}(t) \end{aligned}$$

where, of course we take  $\eta = 0$  in the definition of  $H_{1,\rho}^j$ . Lemma B.7 indicates that in case  $j \neq i$  and  $x \in \partial\Omega_i$  we have the estimate  $\|(H_{1,\rho}^j f)(t,x) - (I_{1,0}^{i,j} f)(t)\|_{C^0} \leq C\rho^{1/2}\|f\|_{C^0}$ . Hence,

$$\widehat{T}_R^i \tilde{c}_{i,del} = \widehat{T}_R^i \tilde{c}_{i,del}(t) + \frac{\pi}{D} \sum_{j \neq i} \rho^{1/2} (I_{1,0}^{i,j} \tilde{c}_{j,del})(t) + \mathcal{O}(\rho).$$

If we take into account that  $\tilde{c}_{i,del}(t) = \tilde{c}_{i,del}^0(t) - \rho^{1/2} \tilde{c}_{i,del}^1(t)$ , we find

$$\widehat{T}_R^i \tilde{c}_{i,del} = \widehat{T}_R^i \tilde{c}_{i,del}^0(t) + \rho^{1/2} \left( \frac{\pi}{D} \sum_{j \neq i} (I_{1,0}^{i,j} \tilde{c}_{j,del}^0)(t) - (\widehat{T}_R^i \tilde{c}_{i,del}^1)(t) \right) + \mathcal{O}(\rho).$$

Thus we may replace  $\widehat{T}_R^i \tilde{c}_{i,del}$  by this expression in (65) without increasing the approximation error and this completes the proof of Theorem 2.12.

**Remark B.9** In order to find stationary solutions of (35) we consider a constant function  $c(t) \equiv f_0$  as input into the pertinent delays and consider the limit  $t \rightarrow \infty$ . We either already proved, or it is possible to prove with similar methods, that

$$\begin{aligned} \tilde{c}_{i,del}^0(t) = M(2I - K_0^{-1}K_\rho)f_0 &\rightarrow Mf_0 \\ I_{1,0}^{i,j}f &\rightarrow f_0 \frac{\sqrt{4D}}{\pi\delta_{ij}} \\ \frac{\pi d_1}{d_1 + D} \sum_{j \neq i} ((2I - K_0^{-1}K_\rho) \circ I_{1,0}^{i,j})(c_{j,del}^0)(t) &\rightarrow M \frac{d_1\sqrt{4D}}{(d_1 + D)\delta_{ij}} f_0 \\ \widehat{T}_R &\rightarrow f_0/D. \end{aligned}$$

Therefore, the stationary solutions of the DDE (35) and the ODE (31) agree (up to the scaling of the cell distances in the ODE case). ]

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